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Dual or Multi-Targeting Inhibitors: The Next Generation Anticancer Agents

Nulgumnalli Manjunathaiah Raghavendra[1,*], Divya Pingili[2,3], Sundeep Kadasi[4], Akhila Mettu[5], S.V.U.M. Prasad[3]

[1]Center for Technological Development in Health, National Institute of Science and Technology on Innovation on Neglected Diseases, Fiocruz, Rio de Janeiro, Brazil
[2]Sri Venkateshwara College of Pharmacy, Osmania University, Hyderabad, India
[3]Department of Pharmacy, Jawaharlal Nehru Technological University, Kakinada, India
[4]Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Osmania University, Hyderabad, India
[5]Department of Pharmaceutical Chemistry, Gokaraju Rangaraju College of Pharmacy, Osmania University, Hyderabad, India

Correspondence Author:
N.M. Raghavendra,
Researcher,
Center for Technological Development in Health (CDTS),
Fundação Oswaldo Cruz (Fiocruz),
Av. Brasil 4036, Prédio da Expansão, 8° Andar, Sala 814, Manguinhos, 21040-361
Rio de Janeiro, RJ, Brazil.
E-mail: nmraghav@cdts.fiocruz.br

Abstract

Dual-targeting/Multi-targeting of oncoproteins by a single drug molecule represents an efficient, logical and alternative approach to drug combinations. An increasing interest in this approach is indicated by a steady upsurge in the number of articles on targeting dual/multi proteins published in the last 5 years. Combining different inhibitors that destiny specific single target is the standard treatment for cancer. A new generation of dual or multi-targeting drugs is emerging, where a single chemical entity can act on multiple molecular targets. Dual/Multi-targeting agents are beneficial for solving limited efficiencies, poor safety and resistant profiles of an individual target. Designing dual/multi-target inhibitors with predefined biological profiles present a challenge. The latest advances in bioinformatic tools and the availability of detailed structural information of target proteins have shown a way of discovering multi-targeting molecules. This neoteric artifice that amalgamates the molecular docking of small molecules with protein-based common pharmacophore to design multi-targeting inhibitors is gaining great importance in anticancer drug discovery. Current review focus on the discoveries of dual targeting agents in cancer therapy using rational, computational, proteomic, bioinformatics and polypharmacological approach that enables the discovery and rational design of effective and safe multi-target anticancer agents.

Key Words: Dual-targeting; multi-targeting; proteomics; bioinformatics; polypharmacology.

1. INTRODUCTION

Cancer disease is characterized by the multiple molecular lesions and functional redundancy of many signaling pathways affected by abnormal mutations [1-2]. Efficient targeting of tumor pathways needs the detailed understanding of molecular alterations that lead to the formation and maintenance of malignant phenotype of cancer cells. Uncovering the complex signaling pathways modulated by all the oncoproteins would aid in the discovery and development of more effective and less toxic anticancer treatments [3-5].

Anticancer drug discovery has been strongly focused on the development of drugs intended to act against a specific target with high potency and selectivity. Clinical experience including the discoveries of drug resistance in cancer chemotherapy has disclosed that single targeting might not always produce the desired biological effect, even if the target is inactivated or inhibited [6-8]. The reason is the development of resistance either by self-modification of the target through mutation or by the adoption of new pathways by a cancer cell, for the growth and multiplication. The approach of identifying and targeting a single oncoprotein has not produced a successful treatment and may not be sufficient to achieve durable remission in patients [9]. Therefore, modulation of the biological network is recognized to be beneficial.

Currently, there are two contrasting strategies to design the multi-targeting therapeutics. Combination drug therapy is the first strategy by creating an additive or synergistic effect of multiple drugs acting on separate targets. There are many successful treatments with the combination therapies, for example, preclinical evidence of increased apoptosis and delayed resistance to serine/threonine-protein kinase B-Raf [10,11] has led the FDA to approve the combination of dabrafenib (BRAF inhibitor) plus trametinib (MEK inhibitor) for the treatment of metastatic melanoma with BRAF mutations [12,13]. Combination therapy with both RAF inhibitor (vemurafenib) and MEK inhibitor (cobimetinib) has been found to be promising in phase III clinical trials against BRAF mutated melanoma [14]. Another example of successful combined therapy is the use of palbociclib and letrozole in the treatment of advanced breast cancer [15]. Inhibition of multiple pathways by the combination of different drugs (topotecan, cyclophosphamide, doxorubicin, and vincristine) was successfully reported for the treatment of small-cell lung cancer [16]. One of the most common regimens, known as "AC", combines adriamycin and cyclophosphamide; sometimes docetaxel, is also included, and the regime is then known as "AC-T" is practiced worldwide for the treatment of breast cancer [17].

The second strategy is to design and develop multiple-targeting drugs to effectively block the multiple oncogenic pathways synergistically [8,18]. The approach of multi-targeting therapeutics involves discovering a single agent that can act on two or more targets simultaneously. For example, US Food and drug administration (FDA) has approved lenvima (lenvatinib) as a receptor tyrosine kinase inhibitor that inhibits the kinase activities of vascular endothelial growth factor (VEGF) receptors VEGFR1, VEGFR2 and VEGFR3 [19]. Cabozantinib, marketed under the trade name cabometyx was approved by FDA as a small molecule dual-targeting inhibitor of the tyrosine kinases c-Met and VEGFR2; and has been shown to reduce tumor growth, metastasis, and angiogenesis [20].

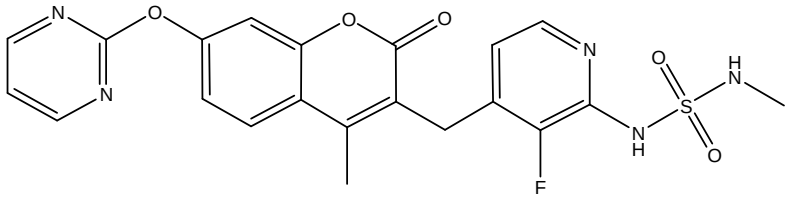
2. DUAL TARGETING LIGANDS

2.1. Inhibitors of BRAF and MEK

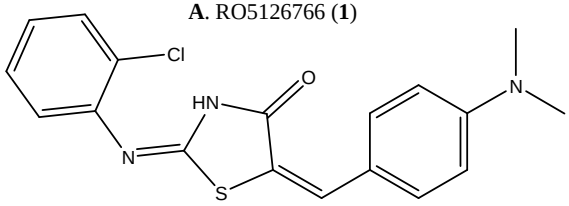
BRAF somatic mutation, particularly $BRAF^{V600E}$ is a common oncogenic mutation among several tumors, and it drives the tumorogenesis through constitutive activation of downstream mitogen-activated protein kinase (MAPK) signaling [21]. Selective BRAF inhibitors such as vemurafenib (zelboraf) and dabrafenib (tafinlar) as single agents were approved by the FDA for the treatment of BRAF-mutated unresectable or metastatic melanoma [22,23]. But selective and single targeted BRAF inhibition acquired resistance by reactivation of the MAPK pathway and/or increased Phosphoinositide 3-kinases (PI3K)/serine-threonine kinase (AKT) signal transduction cascade [24,25]. MEK is a member of the MAPK signaling cascade that is activated in melanoma [26]. When MEK is inhibited, cell proliferation is blocked and apoptosis is induced. Several MEK inhibitors including trametinib were found to be effective in the treatment of advanced melanoma [26-28] until the discovery of amplification of BRAF as a mechanism of acquired MEK inhibitor resistance [29]. Inhibition of BRAF has been shown to reverse resistance to the MEK inhibitor AZD6244 in colorectal cancer cell lines [11,30]. To overcome the BRAF resistance associated with MEK inhibitor, RO5126766 (1, **Fig**. **1A**) was discovered as a dual MEK/RAF inhibitor that allosterically inhibits BRAF, CRAF, and MEK in a panel of tumor cells including melanoma with a BRAF or Neuroblastoma rat sarcoma (NRAS) mutation [31]. RO5126766 induced G1 cell cycle arrest in two melanoma cell lines with the $BRAF^{V600E}$ or NRAS mutation. It was also more effective than an MEK inhibitor in NRAS or Kirsten rat sarcoma (KRAS) mutated cells. The IC_{50} values of RO5126766 were found to be in <50 nm against 6 cancer cell lines. RO5126766 was also found to be successful in first-in-human, phase I dose-escalation study of the safety, pharmacokinetics, and pharmacodynamics clinical trial investigation as the dual MEK/RAF inhibitor [32].

2.2. Inhibitors of HSP90 and Tubulin

Recent evidence suggests that having a single molecule that simultaneously inhibits heat shock protein 90 (HSP90) and one or more of its client proteins could improve efficacy [33]. Tubulins, the client proteins of HSP90 are important for diverse cellular functions, including chromosome segregation during cell division, intracellular transport, development and maintenance of cell shape, cell motility, and distribution of molecules on the cell membranes [34]. Tubulin is also a prime cancer drug target as the tubulin-binding drugs kill cancerous cells by inhibiting microtubule dynamics, which are required for DNA segregation and therefore cell division [35,36]. Moulick et. al. described an affinity-based proteomics approach combined with bioinformatics for the characterization of HSP90 complexes interacting with specific small molecules in chronic myeloid leukemia [37]. They provided evidence that PU-H7155, a known HSP90 inhibitor, preferentially targets tumor-enriched HSP90 complexes and affinity captures HSP90-dependent oncogenic client proteins. This strategy may be useful for identifying targets for both combination therapies and multi-target inhibitor design. In another study, MDG892, a small molecule able to interact with both HSP90 and tubulin targets was discovered through combined ligand and structure based virtual screening including docking and pharmacophore modeling [38]. Similarly, compound 2-(2-Chlorophenylimino)-5-(4-dimethylamino-benzylidene) thiazo-lidin-4-one (CDBT) (2, **Fig. 1B**) targeting HSP90 and tubulin were discovered through phenotypic screening including cell proliferation and cell binding assays [39]. CDBT shows the excellent inhibitory potential against the proliferation of non-small cell lung cancer cells H460 and H322 without any toxicity to the normal fibroblast cells NHFB and WI-38. CDBT targets both microtubule and HSP90 concurrently with significant affinities than colchicine (a microtubule inhibitor) and 17-DMAG (Hsp90 inhibitor). Indeed, CDBT blocks the microtubule formation, decreases cancer-essential proteins CRAF-1, ERBB2 and phosphorylated AKT, and causes G2/M arrest and apoptosis. Binding assay of nanoparticle-bound CBDT was done against HSP90 and Tubulin and the target protein identification was carried out using MALDI-TOF MS.



A. RO5126766 (**1**)



B. CDBT (**2**)

Fig. 1. A. RO5126766 (1, BRAF and MEK dual inhibitor); **B.** CDBT (2, HSP90 and Tubulin dual inhibitor).

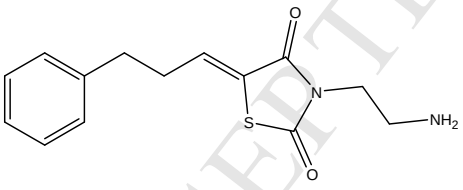
2.3. Inhibitors of ERK and PI3K/Akt

Extracellular receptor kinase (ERK) pathway is the main pathway of controlling the cell proliferation and preventing apoptosis [40]. Aberrant activation of ERK leads to tumorogenesis in several types of cancer such as melanoma, breast cancers, ovarian cancers and human leukemia's [41,42]. There are many examples of ERK inhibitors in literature, all of them are having significant anticancer properties but not devoid of resistance [28,43]. The PI3K/AKT/mTOR pathway is another signaling pathway, which regulates the cell cycle including cellular quiescence and proliferation [44]. PI3K activation by growth factors and cytokines phosphorylates and activates AKT, localizing it in the plasma membrane [45]. AKT further triggers several downstream effects such as activating CREB transcription factor, inhibiting p27, localizing FOX proteins in the cytoplasm, activating mammalian target of rapamycin (mTOR) which can affect transcription of p70, etc [46-48]. In many cancers, this pathway is overactive, thus reducing the apoptosis and enhancing oncogenesis. [44,49]. The ERK and PI3K/Akt pathways are interlinked and there is a considerable evidence of frequent activation of the Raf/MEK/ERK and PI3K/Akt cascades in advanced human prostate cancer [50]. With the hypothesis of designing dual targeting ERK and PI3K/Akt inhibitors, Li et al. successfully developed a thiazolidine-2, 4-dione analog (3, **Fig. 2A**) as a dual inhibitor [51]. The lead compound having thiazolidine-2,4-dione scaffold was found to inhibit the cancer cell proliferation, induce apoptosis and arrest cell growth at G_0/G_1 phase; the dual inhibition of Raf/MEK/ERK and PI3K/Akt pathways was demonstrated by Western Blot analysis. The lead compound inhibited the phosphorylation of ERK at 10 μM and phosphorylation of AKT at 25 μM concentration. It was also found that thiazolidine-2,4-

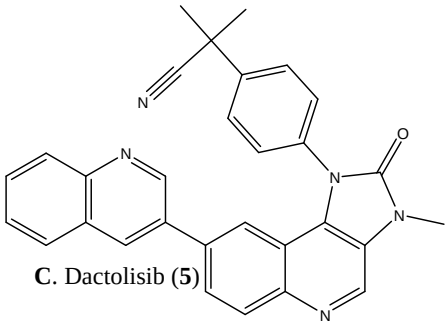
dione lead compound inhibited the cell proliferation through both apoptotic and necrotic pathways.

2.4. Inhibitors of PI3k and mTOR

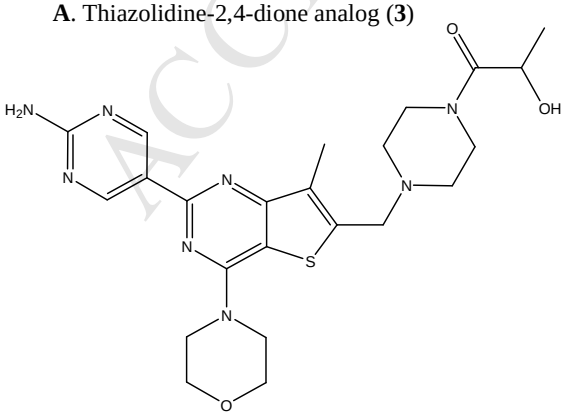
The PI3K family of enzymes is comprised of 15 lipid kinases classified into four different classes with distinct substrate specificities, expression patterns and modes of regulation [52]. The class I PI3Kα and mTOR have emerged as the potential targets for cancer therapeutics [53]. The kinase domain of mTOR is homologous to the p110R catalytic subunit of the class I PI3Kα [54]. With this knowledge of structural homology between PI3Kα and mTOR proteins and an idea of dual inhibiting PI3Kα and mTOR for effective stoppage of PI3k/Akt/mTOR pathway; Knight et al. discovered a quinolinyl analog (Apitolisib/GSK2126458/GDC-0980) as PI3K and mTOR dual inhibitor (4, **Fig. 2B**) [55]. Apitolisib effectively inhibits PI3Kα with IC_{50} of picomolar range and mTOR with IC_{50} of subnanomolar range, it also exhibited excellent *in vivo* anticancer activity by sustained pharmacodynamic effects at very low circulating drug levels [56-58]. Heterocyclic compounds having quinoline, quinoxaline and pyridyl benzothiazolyl moieties were also discovered to have dual PI3k/mTOR inhibiting properties [59,60]. Schrauwen et al. reported the discovery of dual inhibiting properties of dactolisib (BEZ235) (5, **Fig. 2C**) against pan-PI3K and mTOR proteins in endometrial carcinoma [61,62]. BEZ235 is presently under clinical trials against breast and pancreatic neuroendocrine tumors.



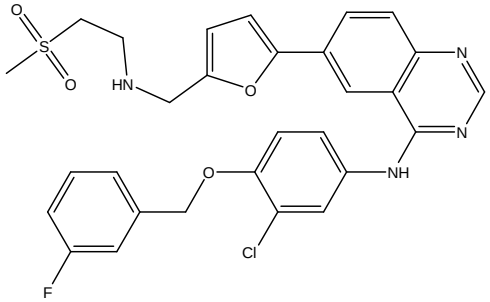
A. Thiazolidine-2,4-dione analog (**3**)



C. Dactolisib (**5**)



B. Apitolisib (**4**)



D. Lapatinib (**6**)

Fig. 2. A. Thiazolidine-2,4-dione analog (3, ERK and PI3K/AKT dual inhibitor); **B**. Apitolisib (4, PI3K and mTOR dual inhibitor); **C**. Dactolisib (5, PI3K and mTOR dual inhibitor); **D**. Lapatinib (6, HER2 and EGFR dual inhibitor).

2.5. Inhibitors of EGFR and human epidermal growth factor receptor 2 (HER2)

The epidermal growth factor receptor (EGFR), a member of the ErbB family of receptors, has four similar receptor tyrosine kinases: EGFR (ErbB-1), HER2/c-neu (ErbB-2), Her3 (ErbB-3) and Her4 (ErbB-4). Over-expression of EGFR has been shown to play an important role in the development and progression of certain aggressive types of breast cancer [63]. In recent years, EGFR and HER2 proteins have become important biomarkers and the targets of therapy for approximately 30% of breast cancer patients [64]. Many people have explored the SAR studies on the 6-furanylquinazoline series to optimize the dual inhibition of EGFR (ErbB-1) and HER2 (ErbB-2) receptors [65,66]. Aryl group attached at the third position was found to be crucial for the dual targeting properties. Groups such as phenylsulfonylphenyl, N1-benzylindazolyl, benzyloxyphenyl, benzyloxyaniline were also investigated [67]. The halogen substitution on the benzyloxyanilino group was the key to improve the enzyme/cell ratio of activity, with 4-(3-fluorobenzyloxy)-3-chloroanilino providing the most promising cellular efficacy. Lapatinib (6, **Fig. 2D**) having 6-furanyl-4-(4-benzyloxyanilino)-quinazoline scaffold afforded the necessary drug-like properties and dual ErbB-2/ErbB-1 tyrosine kinase inhibition. Lapatinib and their analogs were identified having their anline moieties buried inside the ATP binding pocket of ErbB family receptors [68,69]. Lapatinib was approved in 2007 in combination with capecitabine or letrozole in patients with metastatic breast cancer that over-express the HER2 receptor; recently phase II study as a dual inhibitor of EGFR and HER2 tyrosine kinase in patients with castration-resistant prostate cancer was also reported [70,71]. Irreversible inhibitors (Neratinib/HKI-27212 and Afatinib/BIBW-299213) and reversible inhibitors (AEE-78814 and BMS-59962615) have also been tested in clinical trials. Ishikawa et al. reported a compound belonging to pyrrolo [3,2-d]pyrimidine scaffold showed the potent HER2 and EGFR (HER1) inhibitory activities as well as tumor growth inhibitory activity [71]. The anticancer compound, vandetanib (ZD6474), targets on both EGFR-1 and VEGFR-2 tyrosine kinase and has been entered into clinical trials in combination with docetaxel, pemetrexed and erlotinib [72]. Cha et al. reported the discovery of a novel HER1/HER2 dual tyrosine kinase inhibitor, N(4)-(3-chlorophenyl)-5-(oxazol-2-yl)pyrimidine-4,6-diamines for the treatment of HER1 selective inhibitor-resistant non-small cell lung cancer [73].

2.6. Inhibitors of BCR-ABL with HSP90

The Philadelphia chromosome is a specific genetic abnormality in the chromosome 22 of leukemia cells. This chromosome is defective and has a fusion gene called BCR-ABL1, which codes for an active hybrid oncoprotein leading to oncogenesis [74]. The BCR-ABL kinase inhibitor imatinib is a standard treatment for Ph+ leukemia and has been shown to induce a complete hematologic and cytogenetic response in most patients with chronic myelogenous leukemia [75]. Although promising in the clinical results, imatinib treatment leads to the resistance in leukemia and clinical relapse due to the mutations of the BCR-ABL kinase domain [76-79]. Gorre and colleagues [80] reported that BCR-ABL point mutants were found sensitive to the HSP90 inhibitors geldanamycin (GA) and 17-allylaminogeldanamycin (17-AAG). Moreover, Peng and colleagues [81] reported that IPI-504, an HSP90 inhibitor, had a dramatic inhibitory effect on these LSCs. This result indicates that the inhibition of HSP90 can effectively reduce the survival and proliferation of LSCs. Curcumin is a multi-targeted anticancer agent targeting BCR-ABL, EFGR, HER2 and tumor necrosis factor; but the major drawback of reduced bioavailability has reduced its clinical application [82]. In an effort to identify the new inhibitors that are safe for humans and to overcome the resistance to tyrosine kinase inhibitors, such as nilotinib and dasatinib; caused by BCR-ABL mutations and LSCs, Wu et al. used structure-based drug design to develop synthetic libraries of curcumin analogs having dual targeting properties. Using a docking model, they identified C086, as a potent novel inhibitor binding to both BCR-ABL kinases and HSP90 (7, **Fig. 3A**), which is useful especially with BCR-ABL-induced leukemia resistant to tyrosine kinase inhibitors [83]. C086 demonstrated the binding interaction to HSP90 and inhibit the ATPase activity in CML cells, causing the subsequent degradation of HSP90 client proteins (BCR-ABL and BRAF) in K562 cells [83].

2.7. Inhibitors of BCR-ABL with Src

Proto-oncogene tyrosine-protein kinase (Src) is the prototypical member of a family of kinases (Src Family Kinases) that modulate multiple intracellular signal transduction pathways involved in cell growth, differentiation, migration, and survival [84]. The protein sequence of ABL kinase is homologous with most Src family kinases. Many researchers took the advantage of this and discovered BCR-ABL kinase inhibitors that target both Src and ABL kinases such as dasatinib, bosutinib, AP23464, PD166326, AZD0530, and CGP70630 [85]. Dasatinib (Sprycel) and Bosutinib (Bosulif), which inhibits both BCR-ABL and Src tyrosine kinase are approved for the treatment of CML and Philadelphia chromosome-positive acute lymphoblastic leukemia (8, **Fig. 3B** and 9, **Fig. 3C**) [86,87]. Wang et al. in a

similar line, found a way to overcome the resistance caused by BCR-ABL mutations of imatinib, by discovering series of 9-arenethenyl purines possessing a trans double bond; many of these compounds have the dual inhibitory activity on BCR-ABL and Src tyrosine kinase and their potency is 10-fold greater than imatinib [88]. In a new discovery, azaacridine analogs were designed to fit the binding sites of Src including EGFR, and were developed successfully as the dual targeting anticancer compounds [89].

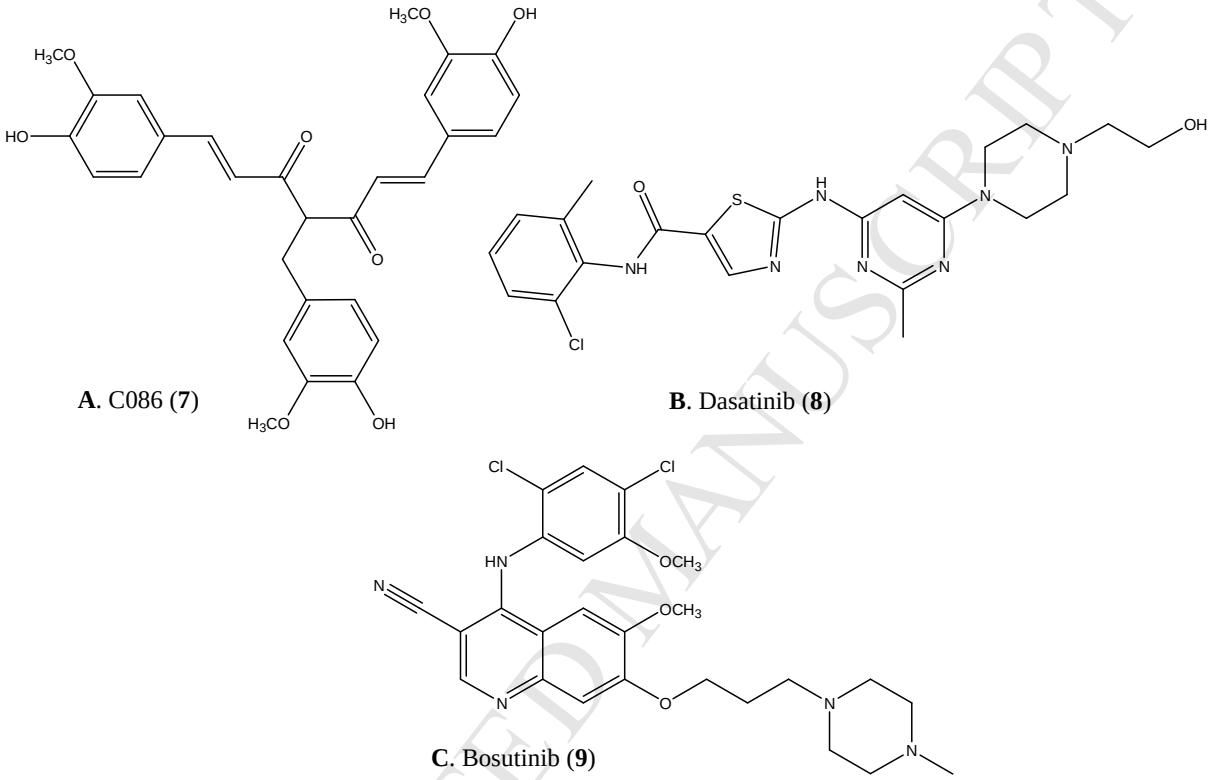
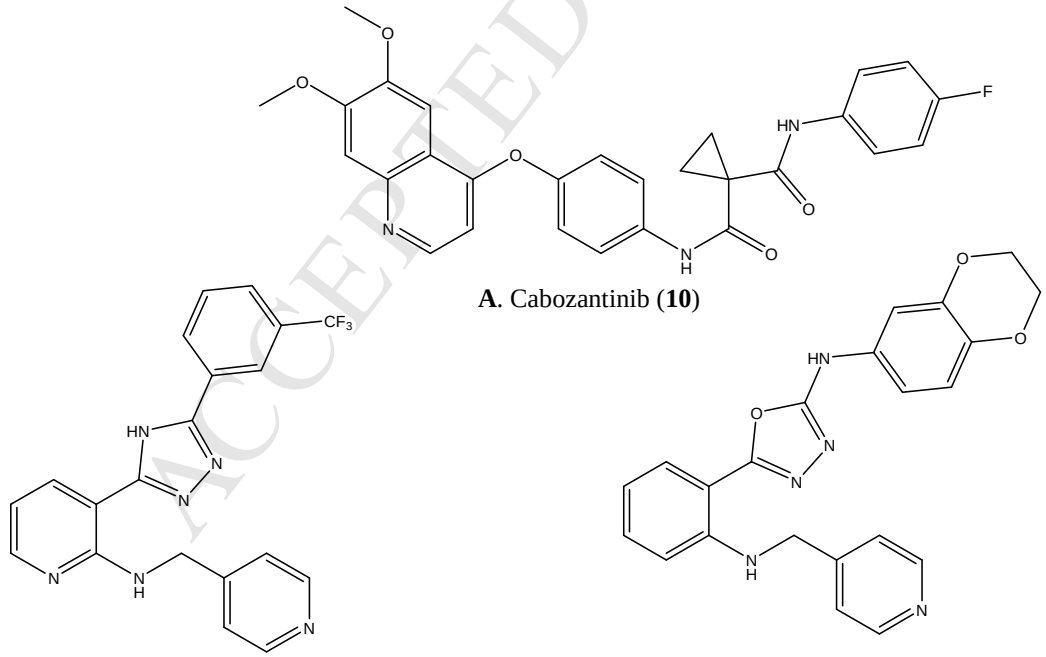


Fig. 3. A. C086 (7, BCR-ABL and HSP90 dual inhibitor); **B.** Dasatinib (8, BCR-ABL and HSP90 dual inhibitor); **C.** Bosutinib (9, BCR-ABL and Src dual inhibitor).

2.8. Inhibitors of VEGFR and C-Met/Tubulin

Angiogenesis occurs in response to cues from the tumor, inducing the formation of blood vessels from the surrounding vasculature to deliver nutrients to the tumor. VEGF is considered as the predominant growth factor required for the angiogenesis by invading endothelial cells. The tyrosine-protein kinase Met (c-Met) with its ligand hepatocyte growth factor has been shown to synergistically collaborate with vascular endothelial growth factor receptor-2 (VEGFR-2), resulting in angiogenesis and promoting the development and progression of various human cancers [90]. Compounds that simultaneously target c-Met and VEGFR-2 may be superior to either c-Met selective or VEGFR-2 selective inhibitor as they can produce the synergistic anticancer effect [91]. In clinical trials, cabozantinib was reported to be effective in response to many tumor types [92]. Cabozantinib (10, **Fig. 4A**), an approved drug for the treatment of medullary thyroid cancer, is a highly potent c-Met and

VEGFR-2 inhibitor, and also has inhibitory properties against oncoproteins such as RET, KIT, AXL, and FLT3 [76,92,93]. On the basis of SAR studies of carbozantinib, Zhan et al. designed and developed anilinopyrimidine scaffold having a cyclopropane-1,1-dicarboxamide moiety, which potently inhibited both c-Met and VEGFR-2 with enzymatic IC_{50} values of 8.8 and 16 nM, respectively [94]. Indenoisoquinolone derivatives having dual inhibition of VEGFR-2 and estrogen receptor were reported to have the best anticancer properties and fewer drawbacks against malignant breast cancer MDA-MB-231 cells [95]. The microtubules are essential for many biological processes such as maintenance of cell shape, protein trafficking, cell division, etc. The predominant mode of action of microtubule inhibitors is the disruption of mitotic spindle formation during cell division, leading to the mitotic arrest and subsequent apoptosis of cancer cells. A drug that inhibits tubulin and has antiangiogenic properties by inhibiting VEGF results in the synergistic effect on tumor growth inhibition. In this approach, 5-membered heterocyclic scaffolds (11, **Fig. 4B** and 12, **Fig. 4C**) were designed and developed as dual inhibitors of VEGF and tubulin polymerization [96]. Recently, DNA intercalating properties of the platinum complex were hybridized in tubulin inhibitor combretastatin, which lead to the discovery of dual targeting combretastatin analogs with the ability to inhibit tubulin polymerization and intercalate DNA [97].



A. Cabozantinib (**10**)

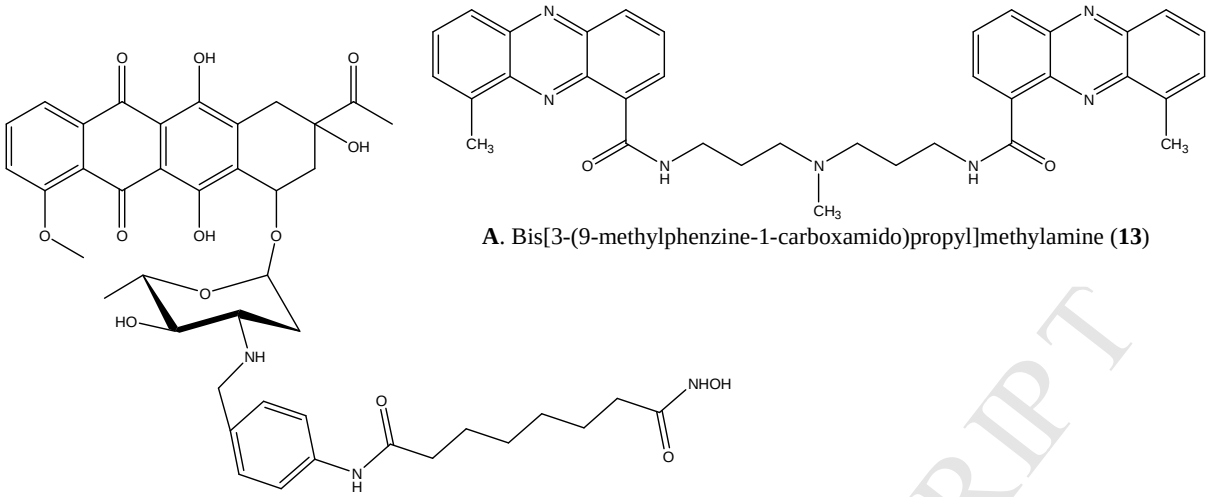
B. Bis-aryl-substituted triazole analog (**11**)

C. Bis-aryl-substituted oxadiazole analog (**12**)

Fig. 4. A. Cabozantinib (10, C-Met and VEGFR dual inhibitor); **B.** Bis-aryl-substituted triazole analog (11, VEGFR and tubulin dual inhibitor); **C**. Bis-aryl-substituted oxadiazole scaffold (12, VEGFR and tubulin dual inhibitor).

2.9. Inhibitors of Topoisomerase (Topo) and Histone deacetylase (HDAC)

DNA replication is the biological process of forming two similar units of DNA from one original DNA molecule. During metastasis, topoisomerase enzymes work continuously to make sure that DNA replication happens without a problem. Topo I and II helps in the DNA replication through excision and relegation mechanisms and are considered as the validated targets for many small molecule inhibitors including clinically useful anthracyclines such as doxorubicin and topotecan [98]. Inhibition of both topo I and II would synergistically inhibit the DNA replication causing cancer cell death. In this direction, a novel compound was discovered named as DACA, is a tricyclic carboxamide-based cytotoxic agent that binds to the DNA by intercalation and stimulates DNA cleavage by inhibition of both topo I and II. But the phase II study of DACA was not successful due to the lack of objective response, although therapy in patients with advanced ovarian cancer was well tolerated [99]. But the failure of DACA in phase II clinical trial lead to the discovery of bis(phenazine-1-carboxamides) (13, **Fig. 5A**) as the potent dual inhibitors of topo I and II proteins [100]. The most potent compound bis[3-(9-methylphenazine-1-carboxamido)propyl]methylamine was shown to inhibit topo I and topo II at concentrations of 1 and 5 μM respectively; it was also more efficient than DACA in lung carcinoma. HDACs are the proteins that remove the acetyl groups from N-acetyl lysine on proteins including histone, p53, E2F, α-tubulin, and HSP90; this process important for DNA expression and cell growth [101-104]. HDAC inhibitors, that induce hyperacetylation of histone proteins complexed with DNA could increase the accessibility of DNA within chromatin and consequently potentiate the anticancer activities of topo inhibitors [105,106]. Encouraged by this link between topo and HDAC, Guerrant et al. discovered the dual-targeting of histone deacetylase and topo II with novel bifunctional inhibitors (14, **Fig. 5B**) [107,108]. These dual-targeting agents were inspired from suberoylanilide hydroxamic acid (HDAC inhibitor) and daunorubicin (topo II inhibitor).



A. Bis[3-(9-methylphenzine-1-carboxamido)propyl]methylamine (**13**)

B. Daunorubicin-N-benzyl-4-amino-8-oxooctahydroxamic A (**14**)

Fig. 5. A. Bis[3-(9-methylphenazine-1-carboxamido)propyl]methylamine (13, Topo I and II dual inhibitor); **B.** Daunorubicin-N-benzyl-4-amino-8-oxooctahydroxamic acid (14, Topo II and HDAC dual inhibitor).

2.10. Inhibitors of Inosine monophosphate dehydrogenase (IMPDH) and HDACs

IMPDH, a key nicotinamide adenine dinucleotide (NAD)-dependent enzyme in the *de novo* synthesis of purine nucleotides. They induce differentiation due to depletion of guanine nucleotides affecting DNA and RNA replication, which leads to the oncogenesis [109-111]. Mycophenolic acid (MPA), is a potent inhibitor of IMPDH (Ki = 10 nM), binds at the NAD binding domain of the enzyme and is used worldwide in the organ transplantation as an immunosuppressant [112]. Recently, numerous studies have shown its importance in the cancer treatment [113,114]. Suberoylanilide hydroxamic acid (SAHA), recently got an approval as a HDAC inhibitor for the treatment of cutaneous T cell lymphoma [115]. MPA's structure consists of an aromatic moiety and a linker (essential for IMPDH inhibition); however, it does not contain a zinc binding group (required for HDAC inhibition) (15, **Fig. 6A**). With this SAR in mind, Chen et al. designed the dual inhibitors by structurally modifying the parent compound without compromising their initial activity while simultaneously enhancing their activity against a second target. They replaced the carboxylic group of MPA with a hydroxamic acid moiety and synthesized hydroxamic acid analog (MAHA) (16, **Fig. 6B**). Further, they also modified SAHA (17, **Fig. 6C**) by the addition of groups known to interact with IMPDH and prepared SAHA analog (SAHA14) (18, **Fig. 6D**). Both compounds MAHA and SAHA14 were found to act as the novel dual inhibitors of IMPDH and HDACs [116] and are more potent anticancer agents than parent drugs. A similar group also developed many cinnamic hydroxamic acid analogs as a new type of dual inhibitors of IMPDH and HDAC [117]. The poly (ADP-ribose) polymerase (PARP) proteins are a kind of proteins that can modulate certain cellular processes such as DNA damage

response, cell cycle regulation, and cell death; their over expression is found to be one of the reason for carcinogenesis [118]. Hybridization strategy was adopted to design and develop novel analogs of the olaparib as promising anticancer agents having the dual inhibitory properties against PARP and HDACs [119]. In another recent study, using hybridization approach researchers have modified the chlorambucil structure into a new dual targeting compound against HDACs proteins while retaining the alkylating action on DNA [120].

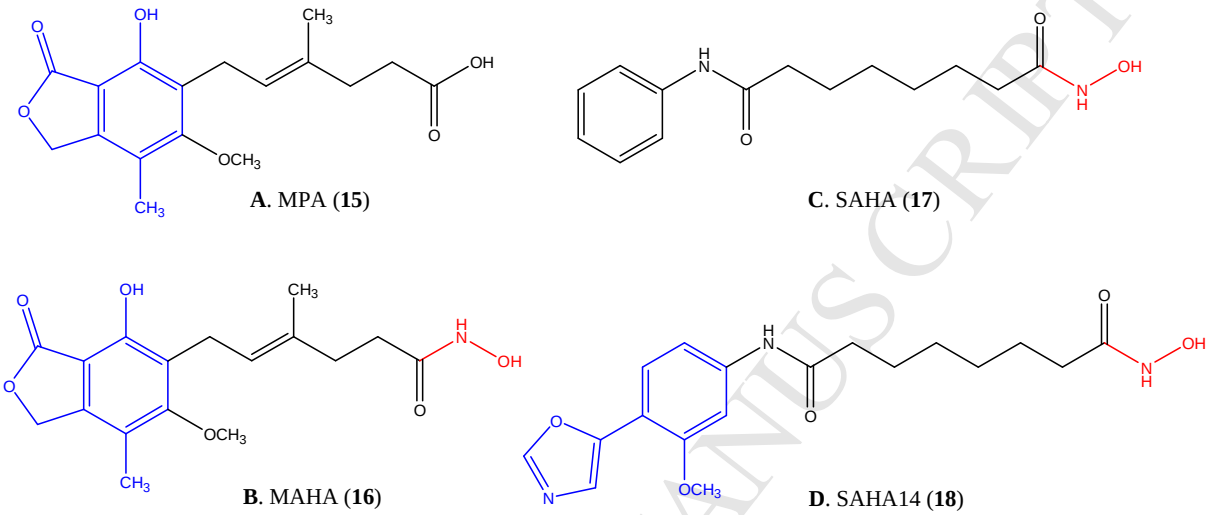


Fig. 6A-D. MPA (15) is an IMPDH inhibitor, SAHA (17) is a HDAC inhibitor; MAHA (16) and SAHA14 (18) are the two new lead optimized compounds having moieties of both MPA and SAHA and are reported as the dual inhibitors of IMPDH and HDACs.

2.11. Inhibitors of TGFβ-Activated Kinase 1 (TAK1) and Mitogen-Activated Protein Kinase Kinase Kinase Kinase 2 (MAP4K2)

There are approximately 518 kinases encoded in the human genome, dysregulation of kinase activity results in many pathologies including cancer. TAK1 regulates the signaling of multiple cytokine receptors and plays an important role in the inflammatory signaling pathways [121,122]. The TAK1 inhibitors have been discovered to have significant anti-inflammatory and anticancer activity [123-125]. The role of MAP4K2 is reported as a regulator of NF-Kb signaling leading to carcinogenesis [126]. Tan et al. developed a pharmacophore model (pyrrolo[2,3-b]pyridine analog, 19, **Fig. 7A**) that defined the structural features needed to access type II binding conformation (**Fig. 7 A-E**). These compounds possess a 1H-pyrrolo[2,3-b]pyridine scaffold (20-23, **Fig. 8A-D**) as the hinge-interacting "head" motif, a 1,3-benzoic acid linker motif inspired by imatinib and a 3-trifluormethylbenzamide "tail" motif inspired by sorafenib/nilotinib [127]. This pharmacophore model search resulted in the identification of potent dual TAK1 and

MAP4K2 inhibitors, which possessed good pharmacological and pharmacokinetic properties required for a successful anticancer agent.

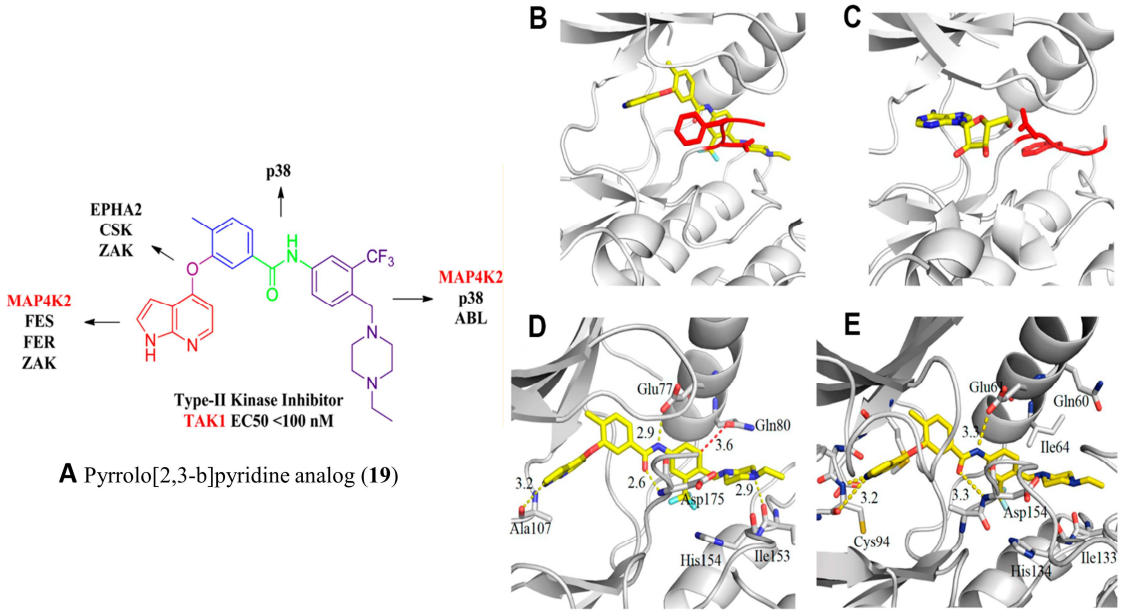
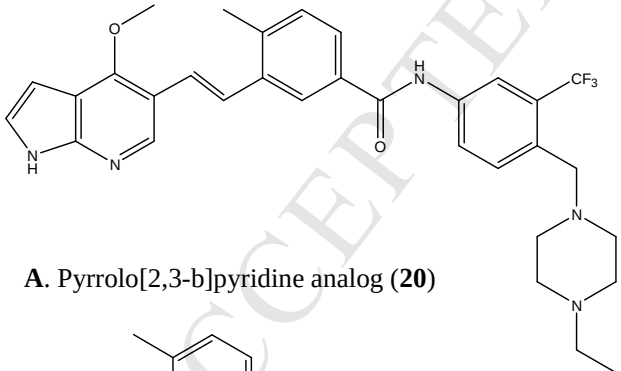
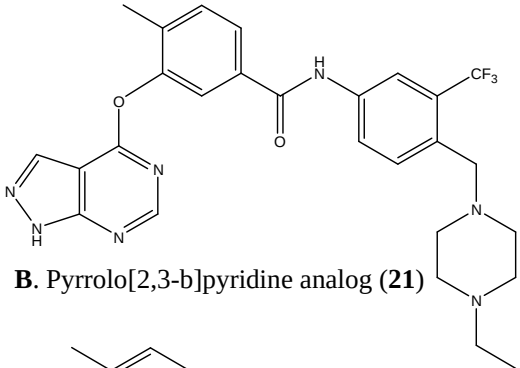


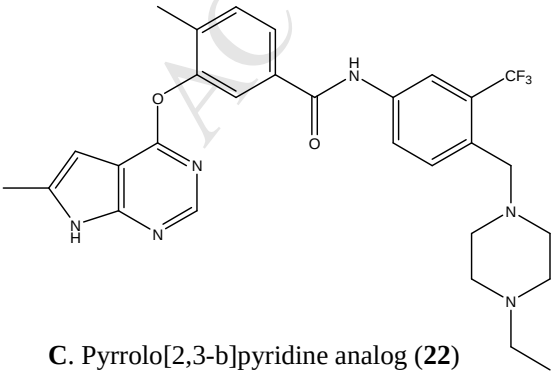
Fig. 7. A. 4-substituted 1H-pyrrolo[2,3-b]pyridine analog (19) is a type II inhibitor of TAK1 and MAP4K2; **B.** Binding of the ligand to the active site of TAK1–TAB1 results in the DFG-out conformation characterized by type II inhibitors; **C.** The structure of adenosine bound to the active site of TAK1–TAB1 (PDB ID 2EVA) is provided for comparison and shows the DFG-in conformation, The DFG motif is highlighted in red. **D.** Key interactions of a ligand with TAK1; **E.** Molecular model of the binding mode of MAP4K2 with a ligand. Reprinted with permission from [127]. Copyright (2017) American Chemical Society.



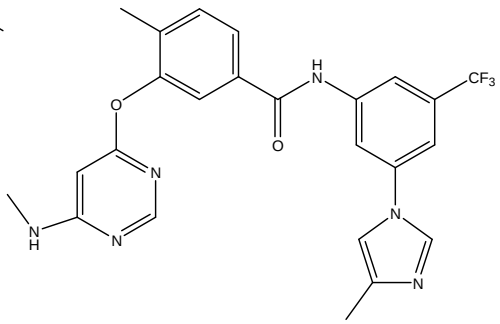
A. Pyrrolo[2,3-b]pyridine analog (**20**)



B. Pyrrolo[2,3-b]pyridine analog (**21**)



C. Pyrrolo[2,3-b]pyridine analog (**22**)



D. Pyrrolo[2,3-b]pyridine analog (**23**)

Fig. 8A-D. Chemical structures of heterocyclic lead compounds (20-23) as the potent dual TAK1 and MAP4K2 inhibitors.

2.12. Inhibitors of Dihydrofolate reductase (DHFR) and Thymidylate Synthase (TS)

DHFR, is an enzyme that reduces dihydrofolic acid to tetrahydrofolic acid, is essential for the de novo synthesis of many nucleobases and some certain amino acids [128]. TS is an enzyme that catalyzes the conversion of deoxyuridine monophosphate to thymidine monophosphate by using tetrahydrofolic acid as a cofactor [129]. This is the sole de novo source of thymidine monophosphate, and hence, inhibition of DHFR or TS activity leads to the "thymineless death". Thus, TS and DHFR have long been recognized as the important targets for cancer chemotherapy. There are many examples of DHFR inhibitors mainly methotrexate and TS inhibitors such as 5-fluorouracil used as anticancer agents [130,131]. The pyrimidine ring of methotrexate is considered as important for the potent DHFR inhibitory activity, while a 2-amino-4-oxopyrimidine or 2-methyl-4-oxopyrimidine ring is reported as essential for the potent TS inhibitory activity [130]. Gangjee et al. tried to incorporate these two moieties in a single compound to attain DHFR and TS dual inhibiting activities without pharmacokinetic disadvantages [132]. They developed a new compound N-{2-amino-4-methyl[(pyrrolo[2,3-d]pyrimidin-5-yl)ethyl]benzoyl}-L-glutamic acid (24) as potent dual inhibitor of DHFR and TS. Compound **24** was designed to bind in the "2,4-diamino mode" to DHFR and in the "2-amino-4-methyl mode" to TS, and hence function as a dual inhibitor (24, **Fig. 9**). The binding of compound **24** to DHFR and TS was confirmed by X-ray crystallography and molecular modeling studies. A similar group led by Gangjee further modified the structure and prepared compound **25a** and **25b** as the dual inhibitors of DHFR and TS (**Fig. 9**). Compound **25a** showed GI_{50} values in the nanomolar range against more than 18 human tumor cell lines in the standard NCI preclinical *in vitro* screen [133].

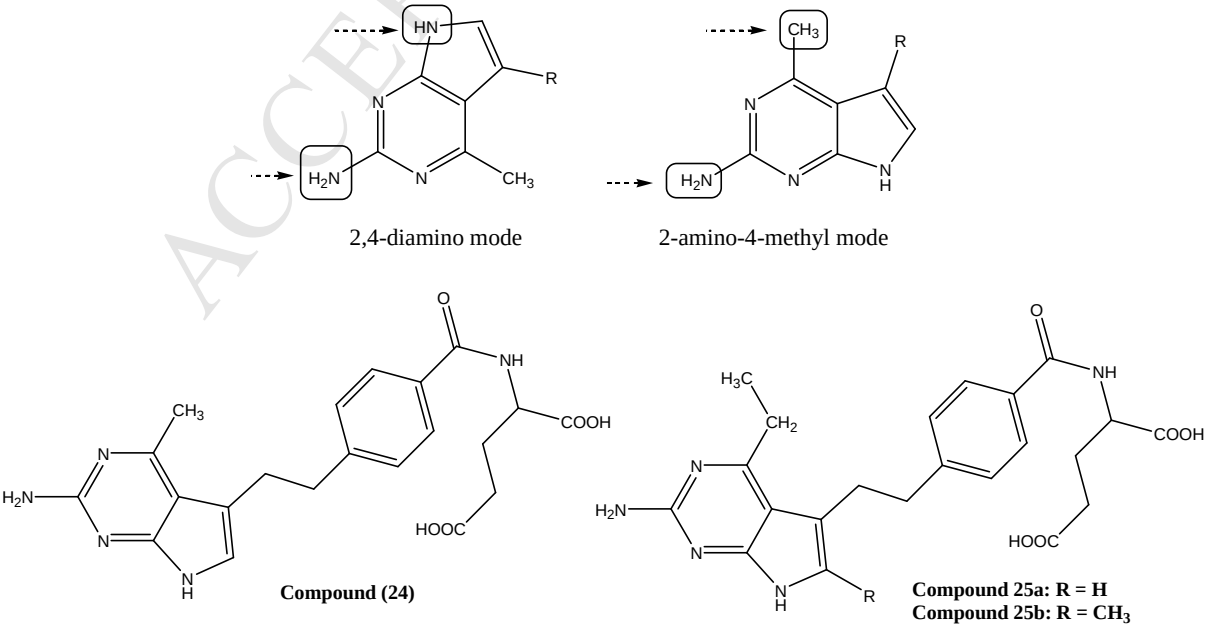
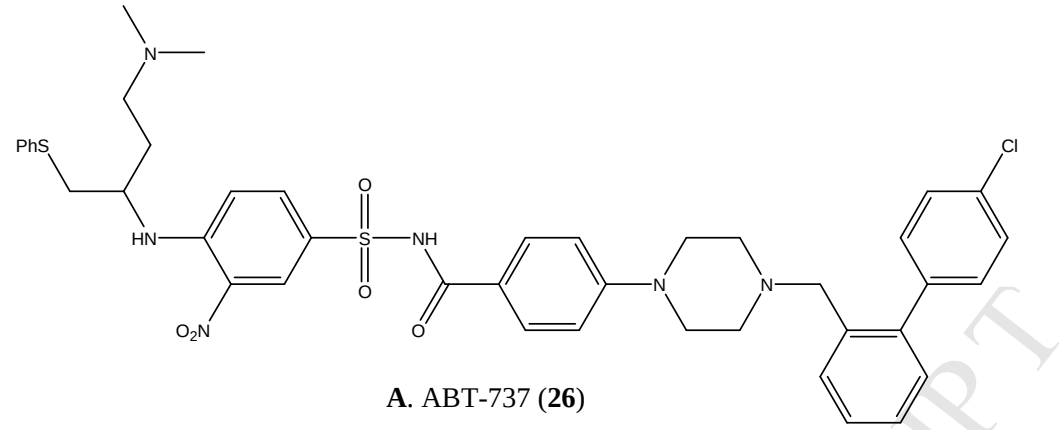


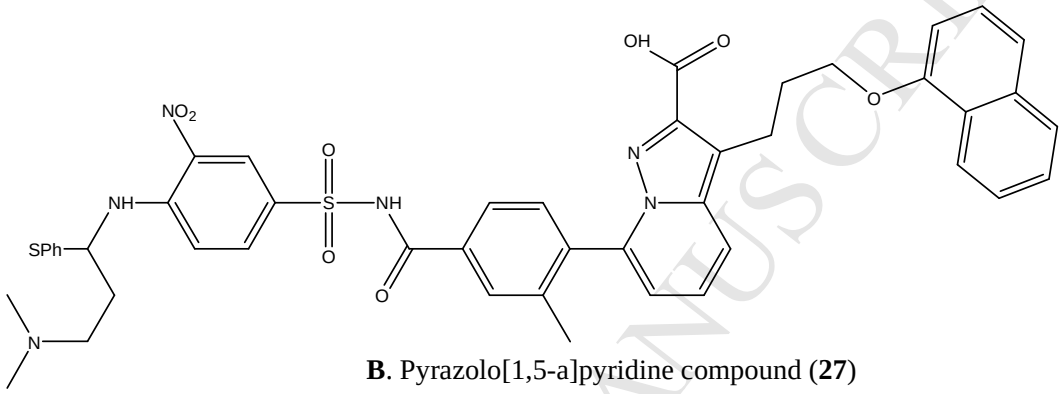
Fig. 9. Rational design of the compounds **24**, **25a** and **25b** having a 2,4-diamino mode for binding to DHFR and 2-amino-4-methyl for TS inhibition.

2.13. Inhibitors of B-cell lymphoma (Bcl) and Induced myeloid leukemia cell differentiation protein (Mcl)

Apoptosis or programmed cell death is a cell suicide mechanism by which multicellular organisms remove damaged or abnormal cells in order to maintain the normal life development and homeostasis [134]. The Bcl-2 a family of proteins is composed of both proapoptotic (prodeath) and antiapoptotic (prosurvival) members that, through a complex series of protein-protein interactions maintain the survival of normal cells and eliminate abnormal cells [135-137]. The apoptotic proteins are categorized into two groups; those that contain three Bcl homology (BH) domains (BH1-BH3) (Bax, Bak) and those that contain a single BH3 domain (BH3-only) (Bad, Bik, Bid, Bim, Hrk, Bmf, Noxa, and Puma). Prosurvival Bcl-2 family members contain four BH domains (BH1-BH4) and include Bcl-2, BclxL, Bcl-w, Mcl-1, and Bcl2-A1. The failure of the programmed cell death systems by antiapoptotic proteins plays a causative role in carcinogenesis as well as in the chemoresistance of tumor cells [138,139]. Bruncko et al. used structure-guided design to exploit a deep hydrophobic binding pocket on the surface of antiapoptotic proteins, and succeeded in developing the dual, subnanomolar inhibitors of Bcl-xL and Bcl-2 [140]. Compound ABT-737 was found to be inhibiting the human follicular lymphoma cell lines (26, **Fig. 10A**). Compound ABT-737 exhibited EC_{50} values of 8 nM and 30 nM in Bcl-2 and Bcl-xL dependent cells, respectively. Tanaka et al. reported the discovery of potent Mcl-1/Bcl-xL dual inhibitors by using a hybridization strategy based on structural analysis of the target proteins, with pyrazolo[1,5-a]pyridine compound (27, **Fig. 10B**) showing IC_{50} values of 0.088 and 0.0037 μM against Mcl-1 and Bcl-xL respectively. [141].



A. ABT-737 (**26**)



B. Pyrazolo[1,5-a]pyridine compound (**27**)

Fig. 10. A. ABT-737 (26, Bcl-2 and Bcl-xL dual inhibitor); **B.** Pyrazolo[1,5-a]pyridine compound (27, Bcl-2 and Bcl-xL dual inhibitor).

2.14. Inhibitors of Thromboxane and Aromatase

Aromatase is a microsomal enzyme consisting of cytochrome P450 heme protein and NADPH cytochrome reductase [142]. Aromatase enzyme synthesizes estrogen and the over expression of aromatase produces excess estrogen, which in turn leads to the formation of breast cancer. Aromatase inhibitors have a significant role in the treatment of breast cancer in women and gynecomastia in men [143,144]. Thromboxane A2 synthase is an enzyme involved in the arachidonic acid metabolism converting prostaglandin H2 into thromboxane A2 [145]. Several tumor tissues contain the elevated concentrations of thromboxane A2 synthase [146]. Prostacyclin, the functional antagonist of thromboxane A2 synthase display antitumoral activity in many metastatic tumors [147]. Coincidently there is a homology between aromatase and thromboxane A2 synthase in the heme-binding region which is closely located to the active site and is considered to be the important region for inhibitor molecules [148]. As there is a homology, there was a possibility of designing ligands, which can antagonize both the proteins and produce synergistic antitumor activity. In view of this, Jacobs et al. discovered the novel imidazole analogs where the heterocyclic nitrogen forms a complex with the heme iron of both the proteins and inhibit them [149].

3. MULTI TARGETING INHIBITORS

The human kinome consists of more than 518 protein kinases and is involved in signal transduction pathways that regulate numerous cellular functions, including proliferation, differentiation, migration, apoptosis, and angiogenesis. Many kinases such as BRAF, BCR-ABL, EML4-ALK, mutant EGFR and tyrosine-protein kinase Kit (c-KIT) are reported to be oncogenic and their inhibition has a significant role in the anticancer treatment [150]. However, it is expected that the most effective kinase inhibitor should act on multiple oncogenic kinases by the synergistic action [151]. In this direction, perhaps sorafenib is the first drug discovered and approved as a multikinase inhibitor drug. Sorafenib (Nexavar, BAY-43006, Bayer Pharma) (28, **Fig. 11A**) was approved as a drug for the treatment of advanced renal cell carcinomas and non-resectable hepatocellular carcinomas [152-154]. Since then, many discoveries highlighted the broad spectrum anticancer properties of sorafenib to its multi-kinase targeting ability including all three members of the Raf family of protein kinases (a-Raf, b-Raf, and c-Raf), as well as Platelet-derived growth factor receptors (PDGFR), VEGF 2/3, and c-Kit kinases [154]. Sorafenib belongs to type II class of kinase inhibitors which binds to the ATP binding pocket in addition to an adjacent hydrophobic pocket that is created when the activation loop, which contains the conserved DFG motif, is in an “out” conformation. In addition to sorafenib, other clinically approved inhibitors such as dovitinib (29, **Fig. 11B**), imatinib (30, **Fig. 11C**), and nilotinib have been crystallographically proven to be the type II inhibitors of kinases such as B-RAF, ABL, c-KIT and p38 kinases [155-158].

Analogs of heterocyclic compounds such as azaindoles, quinazolines, pyrazoles, benzimidazoles, xanthenes, diaryl ureas, azulenes, etc were also discovered as multiple targeting ligands having promising anticancer properties [159-166]. Simultaneous inhibition of multiple kinases together with HSP90 is turning out to be the potential way of inhibiting oncogenesis [167]. Inhibition of HSP90 prevents the multiple checkpoint kinase proteins from being activated, and are reported to have the synergistic action leading to the death of cancer cells [168-170].

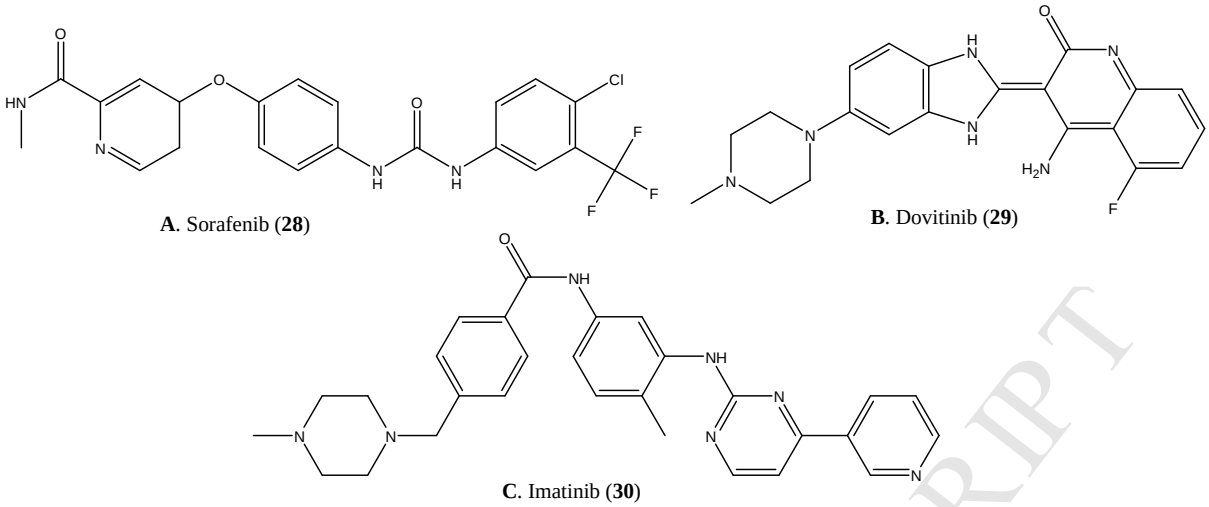


Fig. 11. A. Sorafenib (28, multi-kinase inhibitor); **B.** Dovitinib (29, multi-kinase inhibitor); **C.** Imatinib (30, multi-kinase inhibitor).

4. RATIONAL DESIGN OF DUAL-TARGETING INHIBITORS

Taking into consideration all the aspects highlighted so far, there is a need to design drugs with a multi-target activity profile without any obvious side effects [171,172]. This task, which is challenging, without doubt, involves considering structure−activity relationship profiles of the molecules interacting with different biological targets. Following are the various strategies and approaches used to design and develop the dual targeting inhibitors.

4.1. Pharmacophore modeling

Type I inhibitors are small molecule kinase inhibitors that target the ATP binding site with the kinase assuming a conformation, while Type II inhibitors are the broad class of kinase inhibitors that bind to the hydrophobic pocket adjacent to the ATP binding pocket when the DFG motif is in “out” conformation. Many compounds such as imatinib (30), nilotinib (31), BIRB796 (32), and sorafenib (28) have been crystallographically confirmed to be type II inhibitors (**Fig. 12A**) of kinases including ABL, c-KIT, B-RAF and p38 kinases [156-158,173]. On the basis of these crystal structures, Tan et al. developed a pharmacophore model explaining the optimal structural features needed to access this type II binding conformation (**Fig. 12B**) [127]. The model highlights the importance of a “head” heterocyclic motif that occupies the ATP binding pocket making crucial hydrogen bonds to the kinase hinge segment, a linker moiety that pass the region occupied by the “gatekeeper” residue, a hydrogen bond donor/acceptor motif and a hydrophobic “tail” that occupies the pocket created by the “out” conformation of “DFG” motif [174]. Based on this information a library of type II inhibitors was developed and subsequently screened for kinome-wide selectivity profiling. A library many type II inhibitors were investigated against a panel of over 420 kinases using the KinomeScan methodology. These compounds have a pyrrolo[2,3-

b]pyridine as the hinge-interacting "head" motif, a 1,3-benzoic acid linker motif inspired by imatinib and a 3-trifluormethylbenzamide "tail" motif inspired by sorafenib/nilotinib. Several molecules were found to exhibit inhibitory activities on TAK1 and MAP4K2.

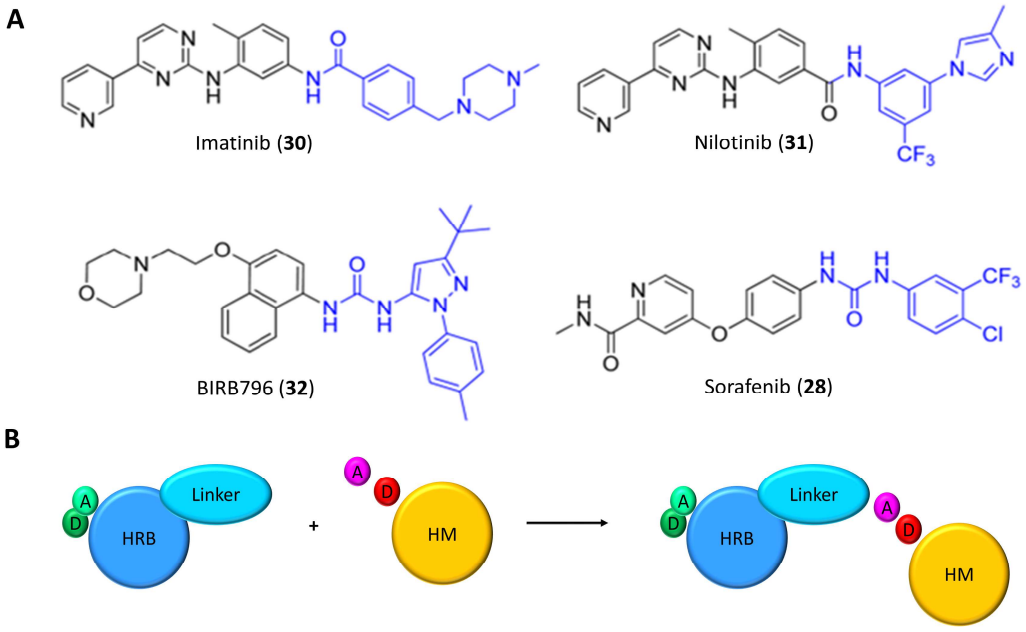


Fig. 12. General pharmacophore model for the rational design of type II inhibitors. **A.** Examples of known type II inhibitors, which can be divided into a "type I" head (black) attached to a "type II" tail (blue); **B.** Schematic representation of the rational design of new type II kinase inhibitors: A, hydrogen bond acceptor; D, hydrogen bond donor; HRB, hinge-region binding; HM, hydrophobic motif. Reprinted with permission from [127]. Copyright (2017) American Chemical Society.

4.2. Hybridization Strategy

To discover potent Mcl-1/Bcl-xL dual inhibitors, Tanaka et al. adopted the hybridization strategy to incorporate the important pharmacophoric groups of two different inhibitors in a single moiety to have dual inhibition property [141]. Co-crystal structure of pyrazolo[1,5-a]pyridine (33) with Mcl-1 (PDB ID 3WIX) and inhibitory activities of this compound was studied. The cocrystal structure showed the binding interactions of compound **33** to the west region of Mcl-1 as well as Bcl-xL. The naphthalene ring was found in a deep cavity of the west region, while the carboxylic acid of the pyrazolopyridine ring was having hydrogen bonds with Arg263 [141]. Similarly, the important binding interactions of Bcl-xL were also studied using the co-crystal structure of compound ABT-737 with Bcl-xL (PDB ID 2YXJ) [175]. The biphenyl moiety of compound ABT-737 interacted with a lipophilic space of the west region, whereas the acylsulfonamide moiety of the compound interacted with another hydrophobic pocket in the east region. Cocrystal structure of ABT-737 with Bcl-xL revealed

that the ring B of compound **34** is located in the solvent region. Compound **33** and compound **34** were found to be a potent Mcl-1 inhibitor and Bcl-xL with IC_{50} of 0.54 and 0.15 µM respectively. Based on these results, Tanaka et al. used hybridization strategy to design novel Mcl-1/Bcl-xL dual inhibitors by connecting ring A in compound **33** and ring B of compound **34** with a suitable linker (**Fig. 13**). Compound **35** amongst the series showed the potent dual inhibitory properties (Mcl-1 IC_{50} = 0.61 µM; and Bcl-xL IC_{50} = 0.0044 µM) (**Fig. 14 A** and **14B**).

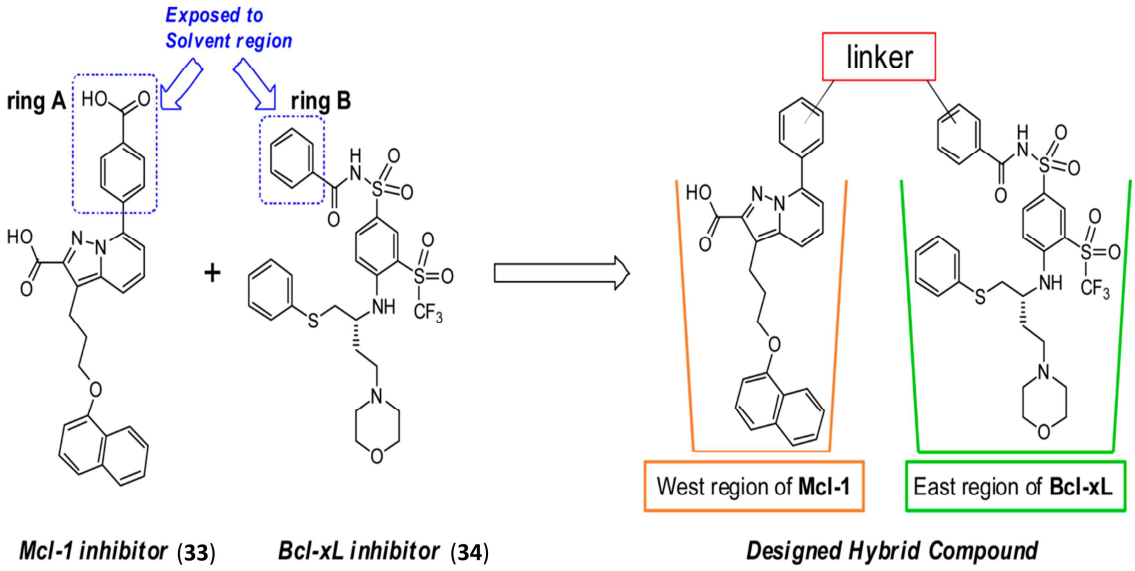


Fig. 13. Hybridization strategy used to design Mcl-1/Bcl-xL dual inhibitors. Reprinted with permission from [141]. Copyright (2017) American Chemical Society.

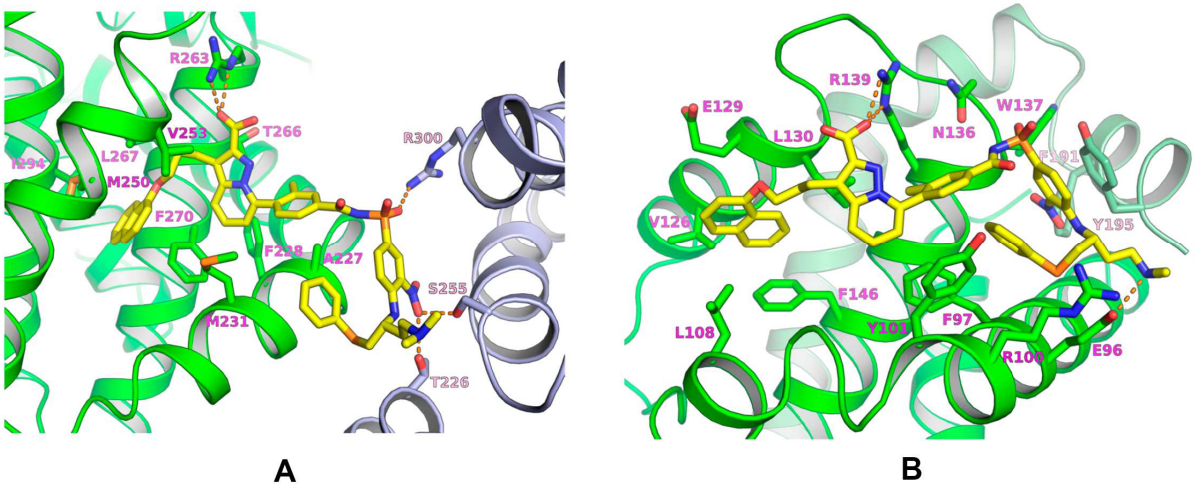


Fig. 14. A. Co-crystal structure of compound **35** with Mcl-1 (PDB ID 3WIY); **B.** Co-crystal structure of compound **35** with Bcl-xL (PDB ID 3WIZ). Reprinted with permission from [141]. Copyright (2017) American Chemical Society.

4.3. Structure based drug design

Bcl-2 having BCL2 gene, regulate the programmed cell death by either inducing or inhibiting the apoptosis [176,177]. Three-dimensional structural information of Bcl-2 protein is well established and is reported to have a bundle of eight to nine α-helices in which two generally lipophilic α-helices form a structural backbone that is enclosed by six to seven amphipathic α-helices [178-181]. The three-dimensional structure of Bcl-xL and Bcl-2 are similar and they fold to form identical active sites [182] with the global root-mean-square deviation of their backbones is only ~1.85 Å. The binding groove is made up of a cleft between the α3 and α4 helices that has a floor composed of the central α5 and α6 helices (**Fig. 15**). Inside the pocket, there are only three differences in primary sequence located at positions 104 (Ala in Bcl-xL, Asp in Bcl-2), 108 (Leu in Bcl-xL, Met in Bcl-2), and 122 (Ser in Bcl-xL, Arg in Bcl-2). With the structural parameters of these proteins in mind, Bruncko et al. designed several lead compounds, which can antagonize the binding site of Bcl-xL and Bcl-2 using molecular docking approach [140]. The NMR derived structures of benzothiazole analog (36, **Fig. 16A**) revealed that it has the structural parameters required enough to bind both the Bcl-2 and Bcl-xL efficiently but in two different conformations (**Fig. 16 B-D**). The compounds developed found to be active against both the proteins in subnanomolar concentration, with the most potent being ABT-737, for which the biological activity has recently been described [183].

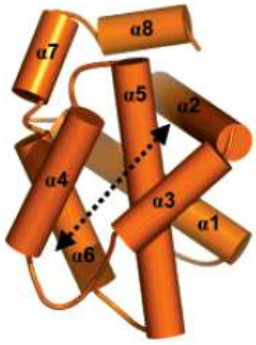


Fig. 15. Generic, cylinder depiction of the three-dimensional structures of Bcl-xL and Bcl-2 proteins with the helices labeled. The dotted line is drawn along the axis of the hydrophobic binding groove formed largely by the α3, α4, and α5 helices. Reprinted with permission from [140]. Copyright (2017) American Chemical Society.

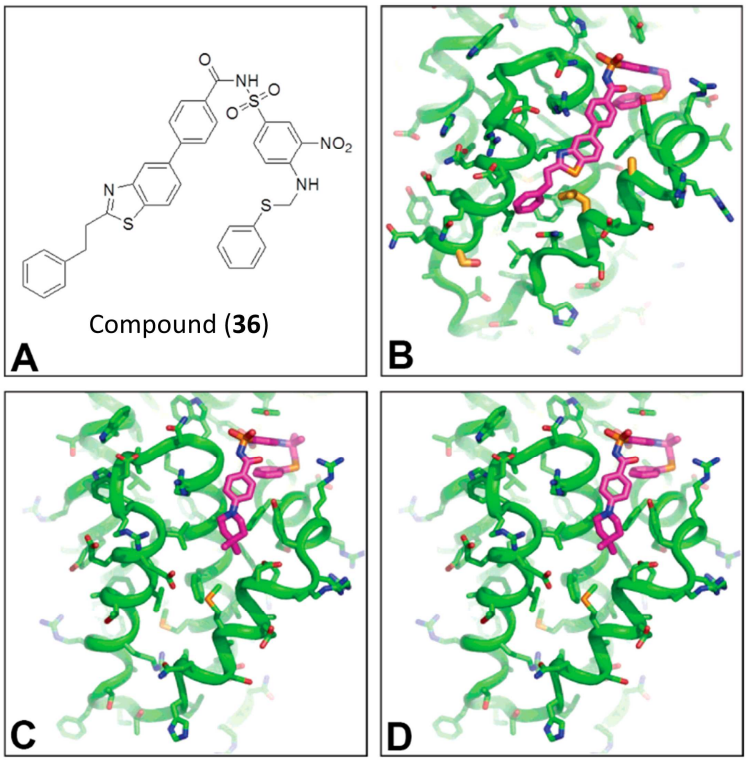


Fig. 16. A. Structure of benzothiazole inhibitor compound **36**; **B.** NMR-derived structure of 3 bound to Bcl-xL. Ala104, Leu108, and Ser122 are highlighted in yellow (PDB ID 2O1Y); **C.** NMR-derived structure of 3 bound to Bcl-2. Asp104, Met108, and Arg122 are highlighted in yellow (PDB ID 2O21); **D.** NMR-derived structure of 1b bound to Bcl-2 (PDB ID 2O22). For all structures, protein backbone and residue side chains are depicted in green with the α3 and α4 helices emphasized. Reprinted with permission from [140]. Copyright (2017) American Chemical Society.

4.4. Polypharmacology

Tyrosine kinases are required for cell growth and proliferation, unfortunately, they are also the sites of frequent oncogenic mutations in neoplasm [184]. Tyrosine kinases activate the lipid kinases of the PI3-K family, including p110α (often mutated kinase in cancer), and mTOR (central regulator of cell growth) [53, 185]. Failure of monotherapy of tyrosine kinase inhibitors was attributed to reactivation of PI3-K signaling [186,187]. Coincidentally, preclinical studies have reported the effectiveness of the combination treatment including inhibitors of these two families [188,189]. Though the protein kinases and PI3-Ks have a diverse sequence of amino acids, they tend to have a homologous hydrophobic pocket in the binding site due to the similar two-lobed architecture displayed by their domains [190]. Hence, targeting both tyrosine kinases and PI3-Ks are considered to be beneficial for the effective anticancer chemotherapy. Based on iterative chemical synthesis, X-ray crystallography, and biochemical profiling, Apsel et al. discovered compounds with promising dual-targeting activity [191]. They screened a library of tyrosine kinase inhibitors

for activity against the PI3-K. This screen yielded two pyrazolopyrimidines, **37** [192] and **38** [193], that inhibit several PI3-Ks at low micromolar concentrations (**Fig. 17A**). SAR studies revealed that substitution of the exocyclic amine (N4) with N-methyl lead to inactivity against PI3-Ks, indicating that this amino group might donate a hydrogen bond (**Fig. 17A**) and at the R2 position, methyl and isopropyl groups were found to be optimal for activity. The pyrazolopyrimidine was already reported as a potential scaffold for tyrosine kinase inhibition [194,195] and was screened against over 200 protein kinases in this study. Based on this data, Apsel et al. further optimized the potency and selectivity of compounds **37** and **38** by iterative synthesis and diversification of the R1 and R2 substituents. Compounds PP121 and PP487 [196] were discovered by this study that can inhibit at nanomolar concentrations both PI3-Ks (e.g. p110α and mTOR) and tyrosine kinases (e.g. Src, ABL, and the VEGF receptor). X-crystallographic studies and biochemical profiling against 15 tyrosine kinases and PI3-Ks confirmed the dual targeting profiles of PP121 and PP487 (**Fig. 17B**).

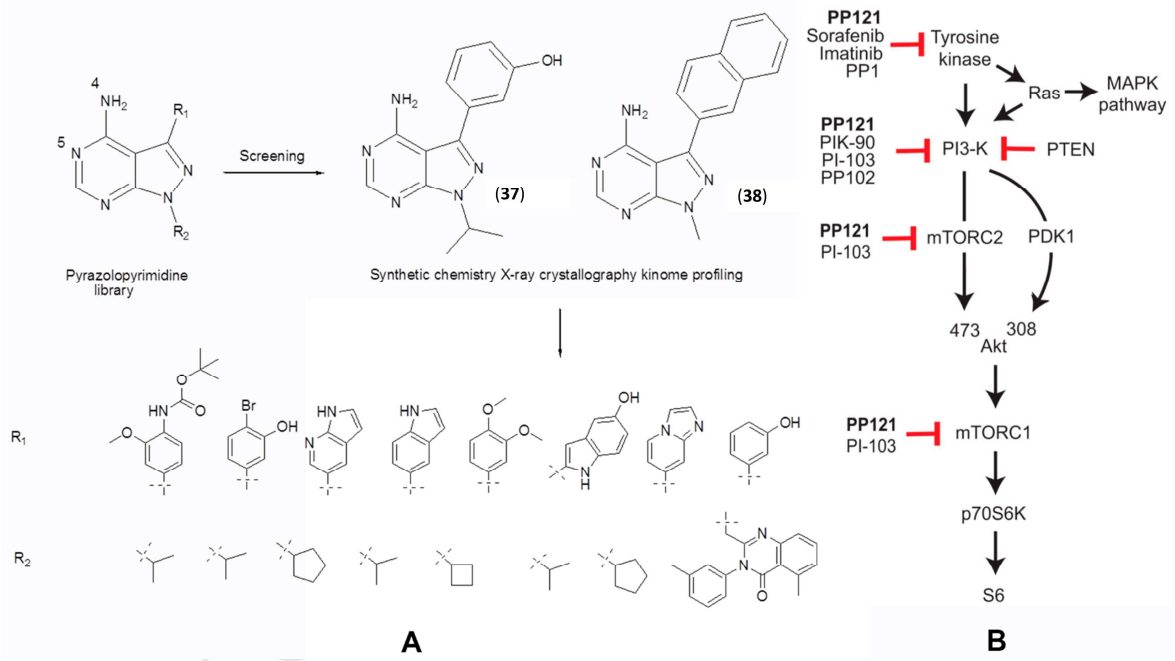


Fig. 17. A. Synthesis of novel Pyrazolopyrimidines (37 and 38); **B.** Schematic of signaling downstream of tyrosine kinases. Not all arrows represent direct physical interactions. Drugs used in this study and their key targets are highlighted. Reprinted by permission from Macmillan Publishers Ltd: [Nat. Chem. Biol.] [191], copyright (2017).

4.5. Activity Landscapes

Activity landscapes are 3D representations of the relationship between structural parameters (2D) and biological activity (1D) of sets of active compounds [197]. Activity landscapes are a kind of topological map, obtained by adding compound potency as a third dimension to an existing two-dimensional projection of a chemical compound. Moving around in the chemical

space plane (e.g. making chemical modifications to an active compound) is accompanied by changes in biological activity, giving rise to landscapes with varying topologies. This approach can be extended from the analysis of the single target activity to multiple targets. The multi-target activity profiles are created by classifying the compounds as weakly (“0”), moderately (“1”), or highly potent (“2”) and are encoded as ternary numbers, e.g., “121” for three or “0112” for four targets. Using this type of format, every compound activity profile is uniquely encoded. In the figure 18A, activity profiles are arranged based on high compound potency against one to three (**Fig. 18A**) targets, which is an essential for the systematic organization of all theoretically possible activity cliffs. The top level in this graph represents activity profiles of compounds that do not have high potency against any target, the second level compounds with high potency against only one target, the third level compounds with high potency against two targets, and so on. The architecture of this approach is based on cliff classification scheme. These landscapes can be conceptualized as graphs, where nodes depict individual compounds and edges activity cliffs. In addition, node proximity indicates molecular similarity (**Fig. 18B**). Modeling of multi-target activity landscapes may provide useful insights into SAR of ligands active on proteins spanning different families. By using this methodology, landscape models can be developed for several compounds having activity against many targets of different families. These landscape models might reveal the single or multi-targeting nature of compounds based on the hierarchical cliff distributions [198].

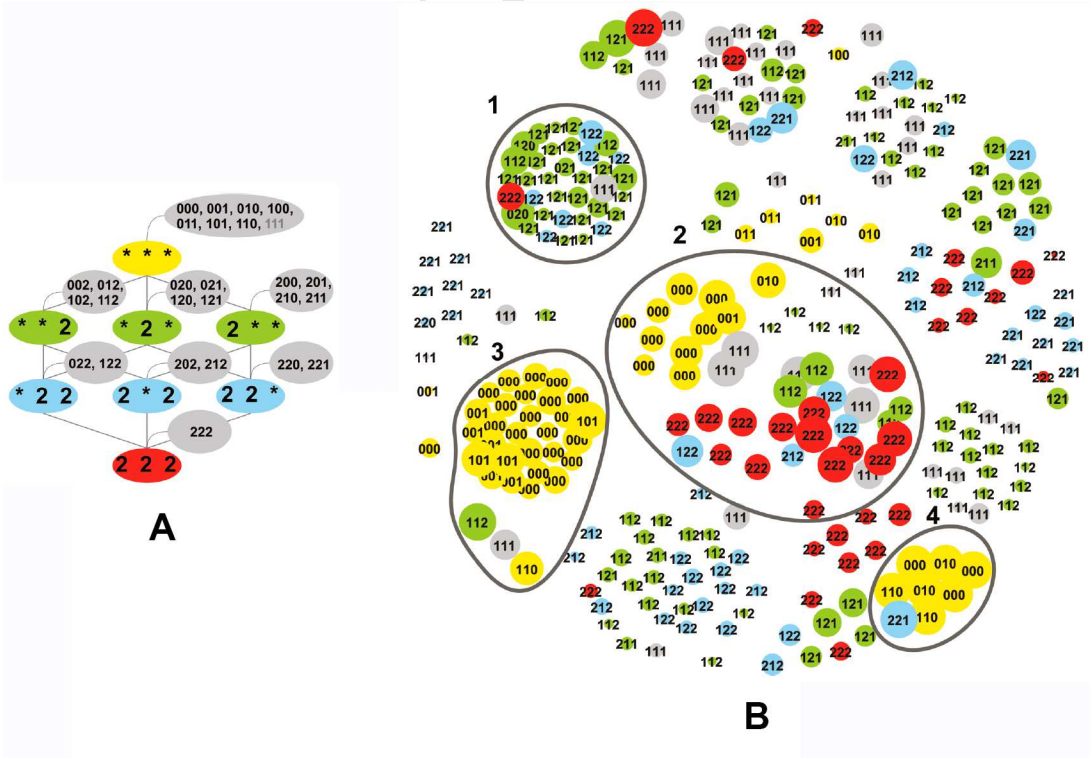


Fig. 18. A. Activity profiles: Shown is the formal organization of activity profiles containing highly potent compounds for three targets. Asterisks indicate ternary digits of either 0 or 1. Sets of all ternary numbers covered by the generic profiles are shown as gray tags. The colors correspond to the node coloring scheme introduced for multi-target activity landscapes. This organization scheme provides a basis for the systematic enumeration of all principally possible single target and multi-target activity cliffs and specification of different activity cliff types using decimal code combinations; **B.** Multi-target graph: Shown is the multi-target activity landscape representation for the multi-targeting compound data set. Selected clusters are encircled and reveal the presence of hierarchical cliff distributions. Reprinted with permission from [198]. Copyright (2017) American Chemical Society.

4.6. Multi-target Virtual ligand screening (VLS)

The VLS represents a fast and efficient alternative to high throughput screening for processing large libraries of compounds [199,200]. In a single-target VLS, every single molecule would be screened against a possible target protein. This type of model is derived from the pharmacophoric and physicochemical descriptors of known ligands or from the binding interactions at the target binding site. Multi-target VLS is an excellent tool to discover molecules having the multi-targeting ability from a diverse group of chemical libraries having compounds of synthetic and natural origin. Several types of chemical libraries are commercially available as a diverse oriented, drug-like, lead-like, peptide-mimetic, natural product-like, targeted against a specific family of biological targets such Kinases, GPCRs, Proteases, PPI, etc from many databases such as ACS Chemworx, Beilstein, Zinc database, etc. In the multi-target VLS, docking may be independently performed on two or more biological targets of interest, and multi-target hits may be identified from compounds located at the top of all the ranked lists [201-203]. Based on the docking scores and the interaction details, the libraries of compounds can be classified into single, dual or multi-target ligands and can be selected for further development (**Fig. 19A**) [200,204]. This approach was effectively used to discover the multi-targeting ability of the naturally occurring limonoid, gedunin. Gedunin is a secondary metabolite of the Meliaceae species *Azadirachta indica* (Neem) and *Carapa guianensis* (andiroba). Multi-target VLS predicts the binding interactions of gedunin with many inflammatory target proteins such as Toll like receptor (TLR) 2, TLR3, Caspase and TLR4/myeloid differentiation factor-2 complex (**Fig. 19B** and **19C**). This discovery of the multi-targeting ability of gedunin was also supported by positive biochemical profiling and *in vitro* and *in vivo* pharmacological assays [205].

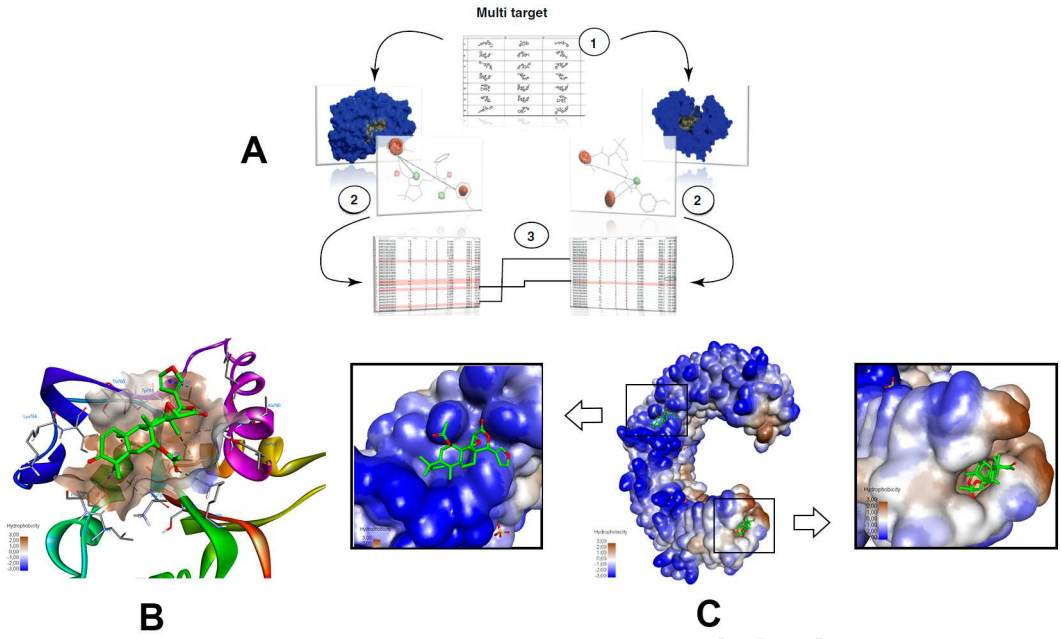


Fig. 19. A. In multi-target VLS the same library of compounds is screened independently against different targets and the overlapping hits proceed to further testing, three main steps involving ligand generation, docking, and scoring; **B**. Binding interaction of gedunin on TLR2 and TLR3. Reprinted from [200,205] with permission from Elsevier, copyright (2017).

4.7. Similarity Ensemble Approach (SEA)

Ligand and structure based virtual screening continue to be proposed as attractive alternatives to more expensive high-throughput screening. In particular, the generation of libraries enriched with molecular structures focused on intended targets is thought to improve the likelihood of identifying the multi-targeting compounds [206,207]. A ligand-based approach named SEA (**Fig. 20**) was introduced by Keiser et al. and successfully applied to identify proteins sharing related ligand sets and discover unknown off-target activities. This approach quantitatively evaluates the chemical similarity of two sets of ligands by measuring the Tanimoto coefficient (Tc) of ligand pairs and by applying a statistical model reminiscent of the BLAST algorithm to normalize chemical similarity scores. SEA helps to find a link for several ligand compounds to their corresponding protein targets in the minimal spanning tree. As these trees are designed based on the chemical similarity, clusters of biologically related proteins could emerge. In this approach, it is possible to analyze the origins and possible significance of both the identified and unknown relationships, and their use for uncovering side effects and the polypharmacology of individual chemical agents. Emetine is an amebicide that inhibits polypeptide chain elongation in parasites [208]. Loperamide is an opioid that is used for relief of diarrhea through action on μ-opioid receptors in the gut [209]. Applying SEA, the authors were able to identify off-target activities for the drug emetine

against α2-adrenergic receptors with a predicted activity range of 400 nM to 1 μM, this predicted off-target activity of emetine is consistent with the known side effects of this drug, which can lead to hypotension, tachycardia, dyspnea, myocarditis and congestive heart failure. Similarly, off-target activities of loperamide against neurokinin NK2 receptor was also predicted with an activity range of 1 to 2 μM, suggesting that loperamide also has a direct action on neurokinin receptors [210]. The off-target activities of emetine and loperamide were also confirmed by pharmacological screening.

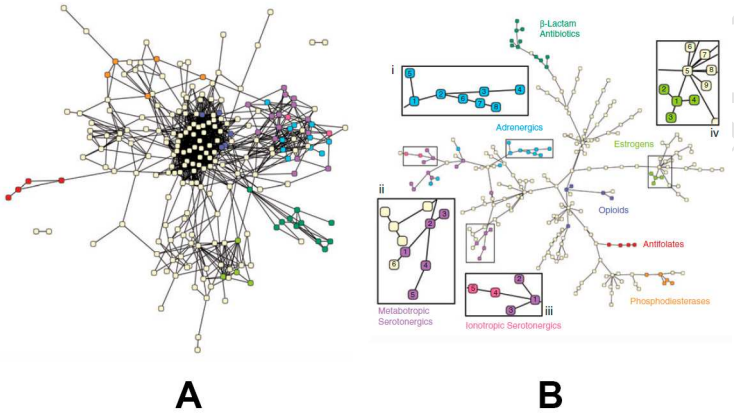


Fig. 20. Similarity maps for 246 enzymes and receptors. **A.** Network view of pharmacological space, in which each node represents a particular target in the MDL drug data report. The nodes are colored for several pharmacologically related targets: antifolates (red), phosphodiesterases (orange), opioids (blue), β-lactam antibiotics (dark green), metabotropic serotonergics (violet), ionotropic serotonergics (pink), adrenergics (cyan) and estrogen modulators (light green); **B.** A tree view of pharmacological space connecting all nodes (protein targets) using only the most significant connections. Reprinted by permission from Macmillan Publishers Ltd: [Nat. Biotechnol.] [210], copyright (2017).

4.8. Quantitative structure activity relationship (QSAR) Approach

Several computational methods or protocols have been proposed to predict the kinase bioactivity profiles for the large-scale compound libraries or screen selective multi-target kinase inhibitors based on quantitative structure activity relationship (QSAR) modeling [211-214]. Target based approaches, especially molecular docking, have already become mainstream for computer-aided drug design when target structures are available. However, the prediction of accurate selectivity by molecular docking has become a difficult task due to highly conserved ATP binding pocket of many kinase enzymes. Chien-Yu Chen employed the Comparative molecular field analysis (CoMFA) and pharmacophore analysis for designing HER2 and HSP90 dual targeting inhibitors [215,216]. Purine based compounds, targeting the biological activities of HER2 and HSP90 are collected as the training set to determine the statistical indexes of CoMFA (**Fig. 21A**). The scaffolds are aligned

stereological to calculate the forcefields around molecules (**Fig. 21 B**). The CoMFA models elicited highly predictive r^2 values for both the targets and their contour maps (**Fig. 22 A-C**) are assembled which indicated bulky favor areas. By 3D-QSAR and pharmacophore analysis, key features required for dual targeting HER2 and HSP90 were discovered. Purines having electronegative and electropositive groups on the benzene ring; distribution of hydrogen bond acceptor on 3-N position and donor on 6-N position were found be important for dual-targeting (HSP90 and HER2) activity.

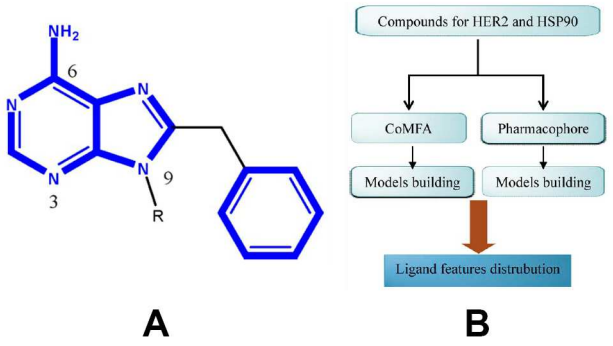


Fig. 21. A. The scaffold of purine-based compounds. The aligned core atom (blue) indicated the selected scaffold for CoMFA model; **B**. Flow chart of CoMFA analysis. Reprinted from [215] with permission from Elsevier, copyright (2017).

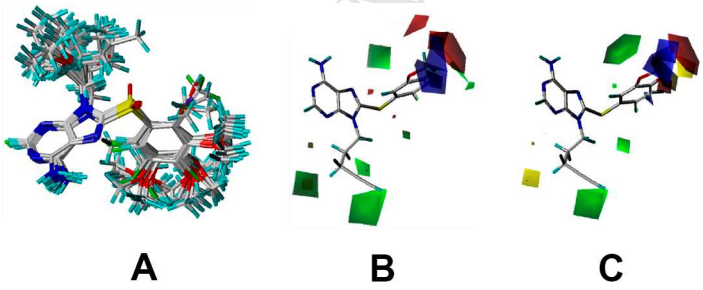


Fig. 22. A. Alignment of compounds for CoMFA statistics; **B.** The steric and electrostatic CoMFA contour maps for HSP90; **C.** The steric and electrostatic CoMFA contour maps for HER2. Reprinted from [215] with permission from Elsevier, copyright (2017).

5. FUTURE PERSPECTIVES

Multi-targeting drugs may represent the valuable complement or even alternative to therapeutic regimens based on drug combinations. Multi-target drugs have therapeutic advantages over single-target drugs because they can show either additive or synergistic effects. Combination therapies usually have complex problems including different bioavailabilities, PKs, metabolisms, and drug-drug interactions. A single administration of a compound having desired multiple biological actions guarantees the simultaneous presence of the molecule at the sites of action and interacts with its multiple targets. Preclinical and clinical development of a drug that can hit multiple targets is far simpler approach than the

development of new combination therapies. In addition, the risk of possible drug-drug interactions would be avoided and the therapeutic regimen could be greatly simplified.

But, a general concern is that excessive promiscuity could lead to adverse reactions caused by interactions with anti-targets. Hence, multi-targeting drug candidates should be designed by trying to optimize activity profiles toward the desired targets while minimizing the risk of the anti-target activity.

To address this issue, efforts made through the integrated approaches involving medicinal chemistry, proteomics, chemical biology, and computational chemistry to explore the complex interlinked molecular signaling pathways would help designing multi-targeting compounds, which can effectively block the desired oncogenic pathways (**Fig. 23**). Promising computational approaches in this field include data mining, ligand and structure based analyses for the identification of target combinations, and virtual screening for the design of multi-targeting ligands. Many compounds discovered through these approaches are in use today and many of them are under clinical trials (**Fig. 24**). It is conceivable that in the near future rational polypharmacology will play an increasingly important role in drug discovery. The combination of different disciplines and expertise (experimental and computational) will likely be a key to success.

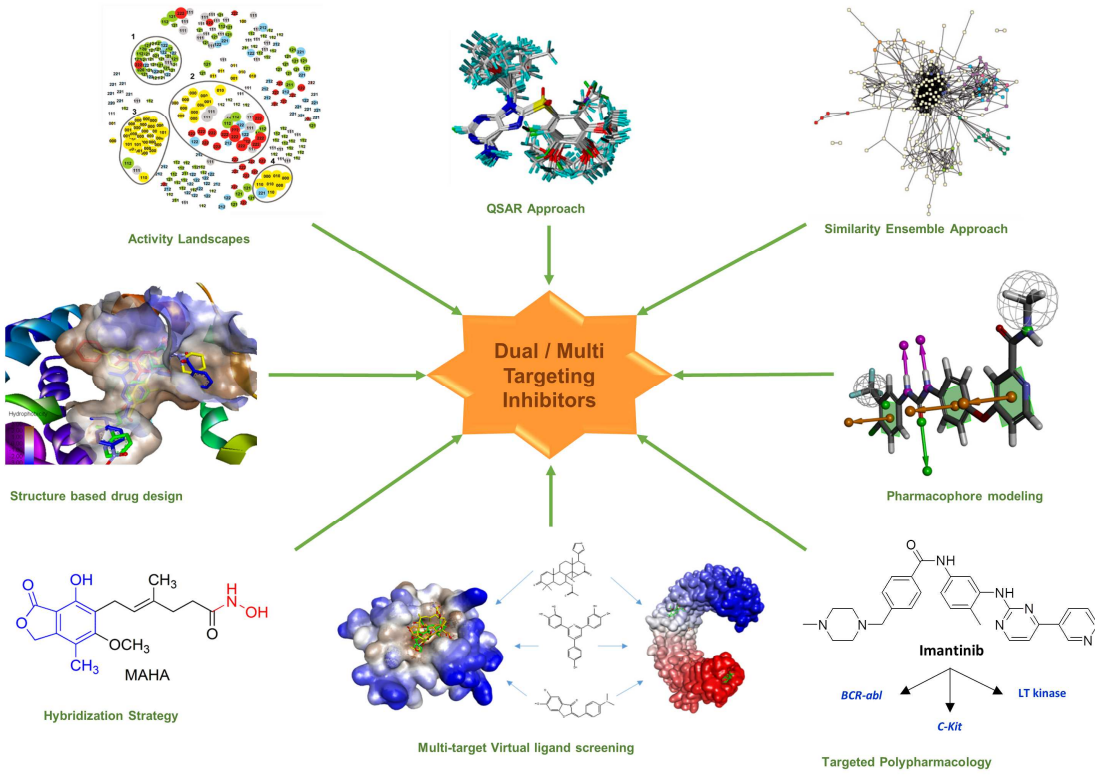


Fig. 23. A representative illustration of the approaches utilized in the discovery of dual/multi-targeting molecules.

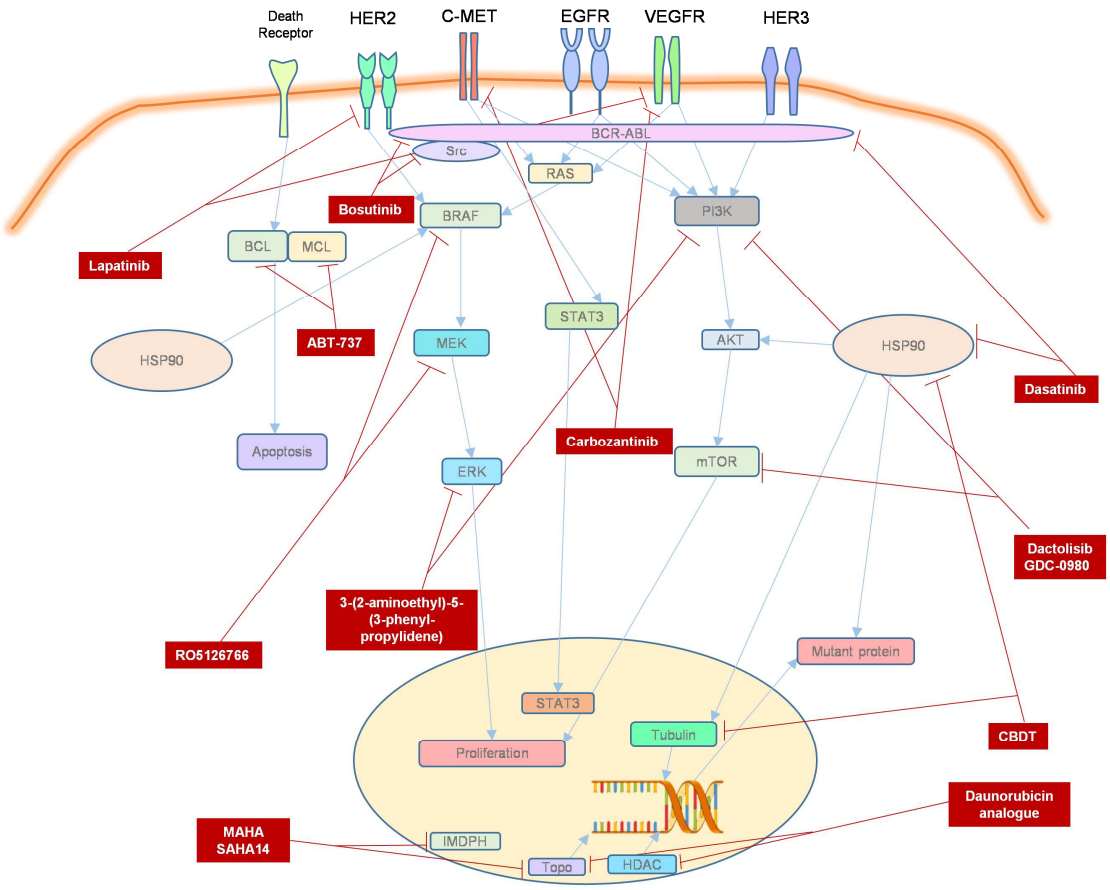


Fig. 24. Representative examples of the dual targeting inhibitors and their molecular targets in the cell signaling pathways of a cancer cell.

CONFLICT OF INTEREST

The authors have declared no conflicts of interest.

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ABBREVIATIONS

BRAF	Serine/threonine-protein kinase B-Raf
MEK	Mitogen-activated protein kinase kinase
FDA	Food and Drug Administration
VEGF	Vascular endothelial growth factor
MAPK	Mitogen-activated protein kinase
ERK	Extracellular receptor kinase
PI3K	Phosphoinositide 3-kinases
AKT	Serine/threonine kinase
NRAS	Neuroblastoma Rat Sarcoma
KRAS	Kirsten Rat Sarcoma
HSP90	Heat shock protein 90
mTOR	Mammalian target of rapamycin
HER2	Human epidermal growth factor receptor 2
BCR	Break point cluster
ABL	Abelson
TK	Tyrosine kinase
Src	Proto-oncogene tyrosine-protein kinase
c-Met	Tyrosine-protein kinase Met
Topo	Topoisomerase
IMPDH	Inosine monophosphate dehydrogenase
HDAC	Histone deacetylase
NAD	Nicotinamide adenine dinucleotide
TAK1	TGFβ-Activated Kinase 1
MAP4K2	Mitogen-Activated Protein Kinase Kinase Kinase Kinase 2
SAHA	Suberoylanilide hydroxamic acid
DHFR	Dihydrofolate reductase
TS	Thymidylate Synthase
Bcl-2	B-cell lymphoma 2
BH	Bcl homology
Mcl	Induced myeloid leukemia cell differentiation protein
c-kit	Tyrosine-protein kinase Kit
PDGFR	Platelet-derived growth factor receptors
VLS	Virtual ligand screening
TLR	Toll like receptor
SEA	Similarity Ensemble Approach
QSAR	Quantitative structure activity relationship
CoMFA	Comparative molecular field analysis

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Dual or Multi-Targeting Inhibitors: The Next Generation Anticancer Agents

Nulgumnalli Manjunathaiah Raghavendra[1,*], Divya Pingili[2,3], Sundeep Kadasi[4], Akhila Mettu[5,] S.V.U.M. Prasad[3]

HIGHLIGHTS

- Discoveries on dual or multi-targeting compounds in the cancer chemotherapy are discussed.
- The strategies employed for the discovery and development of dual or multi-targeting compounds are explained.
- The advantages and efficiency of dual or multi-targeting inhibitors over single-targeted drugs are discussed with examples.
- The need of integrated approach including computational medicinal chemistry, proteomics, bioinformatics and polypharmacology is described.

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In Process Validation of Nevilast-30

Thejovathi B,* Kondal Reddy J, Kondla Usha
Thejovathi B, Associate Professor,
Department of Pharmaceutics,
Vision College of Pharmaceutical Sciences & Research,
RNS Colony, Boduppal, Hyderabad 500092
Corresponding Author: Thejovathi B

Abstract: *Process validation and optimize the manufacturing process and established key process parameters involved in the manufacturing of NEVILSAT – 30 Tablets. The objective of present study was to develop a stable and robust manufacturing process for NEVILAST – 30 Tablets. The process parameters will yield product which meets predetermined quality attributes .The prospective process validation was performed on three consecutive batches. The future scope of the work is to enable the process on commercial production of tablet meeting its predetermined specification and quality attributes after these validation batches. Concurrent process validation is carried out for the NEVILAST 30 -700mg. NEVILAST-30 is indicated for the treatment of Human Immunodeficiency virus Type 1 infected adults and adolescents. The bioavailability of the drug in adults is normally 80-90 %. This fixed combination replaces the three components (lamivudine, stavudine, nevirapine) used separately in similar dosages. Process controls included raw materials inspection, in-process controls and targets for final products. The purpose was to monitor the on-line performance of the manufacturing process and then validate it. Even after the manufacturing process was validated, current good manufacturing practice required a well written procedure for process controls which was established to monitor its performance. The bioavailability of the drug in adults is normally 80-90 %.*

Key Words*: Nevirapine, Lamivudine, Stavudine, Croscarmellose Sodium (Primellose), Croscarmellose Sodium (Primellose), 3batches, Bowl & Lots.*

Date of Submission: 20-04-2019 Date of acceptance: 04-05-2019

I. Introduction

Process validation is establishing documented evidence, which provides a high degree of assurance that a specific process will consistently produce product meeting its predetermined specifications and quality attributes. The concept of validation has expanded through the years to encompasses a wide range of activities from analytical methods used for the quality control of drug substances and drug products & to computerized systems for clinical trials, labeling or process control. The validation simply means, "Assessment of validity" or action of proving effectiveness.

Validation Protocol:

- General information
- Objective
- Background/revalidation activities
- Summary of development and technical transfer (for R&D or another site) activities to justify in process testing and controls any previous validations.
- List of equipment and their qualification status
- Facilities qualification
- Process flow chart
- Manufacturing procedure narrative
- List of critical processing parameters and critical excipients
- Sampling, tests and specifications
- Acceptance criteria

Concurrent process validation is carried out for the product NEVILAST 30 -2.5 mg. Consecutively 3 batches or lots were taken for process validation. All the critical parameters were evaluated for fixing the optimum process parameters. The following is the plan of work designed based on Master Manufacturing Formula

1. Literature Review 2. Preparing process flow chart 3. Preparing the validation protocol
4. Execution of validation 5. Documentation of the same process.

Lamivudine is ananalogue of cytidine. It can inhibit both types of (1 and 2) of HIV reverse transcriptase. Lamivudine enters the cell by passive diffusion. Stavudine inhibits the activity of HIV-1 reverse transcriptase both by competing with natural substrate dGTP and by its incorporation into viral DNA. Nevirapine is a non-nucleoside reverse transcriptase. Nevirapine binds directly to reverse transcriptase (RT) and blocks the RNA-dependent and DNA-dependent DNA polymerase activities by causing a disruption of the enzyme's catalytic site.

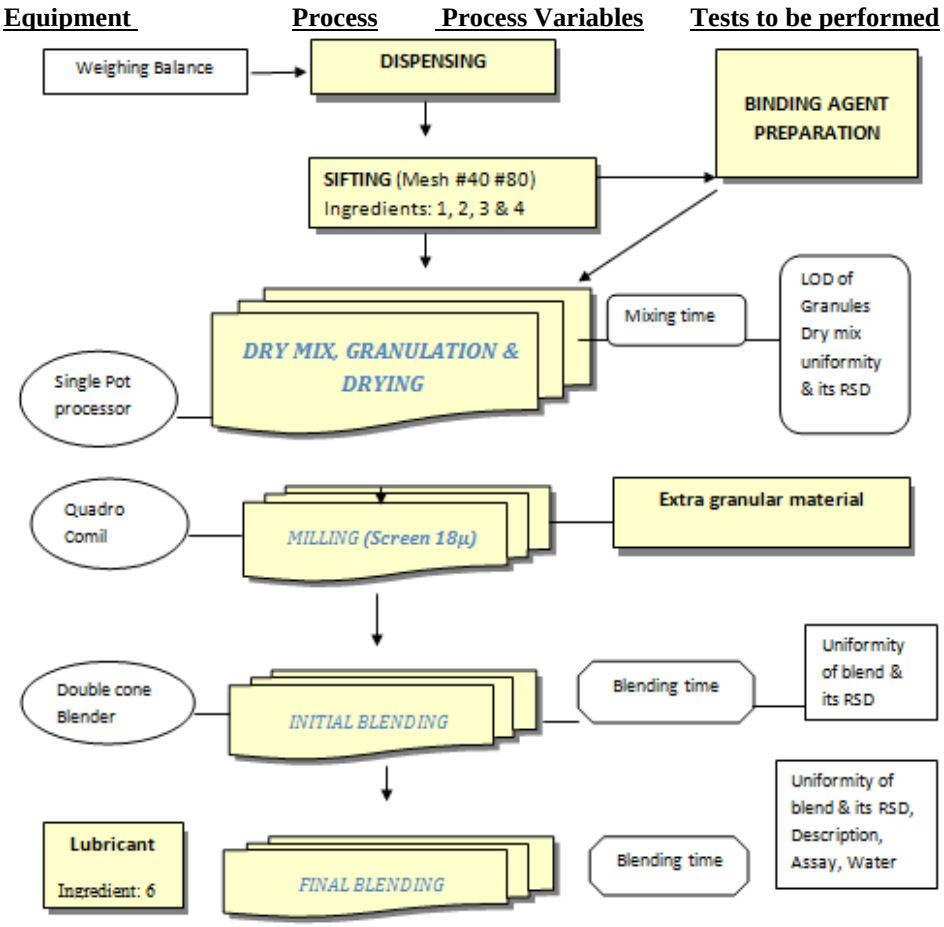
II. Materials and Methods

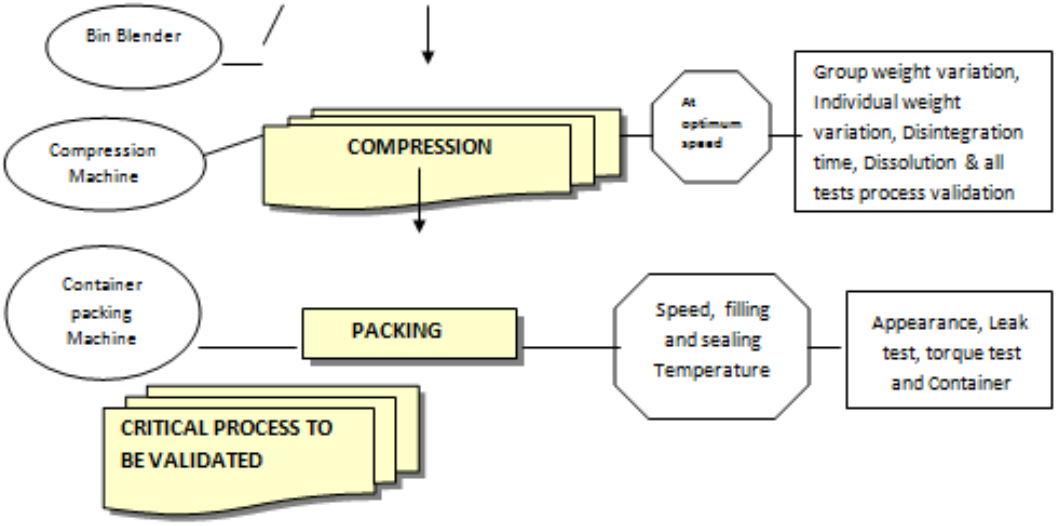
Each tablet of NEVILAST 30- contains 700 mg.

Item code	Item	*Function*	Quantity As Per Tablet(mg)	Quantity As Per Batch(kg)
	Intra Granular Materials			
1	Lamivudine Stavudine Nevirapine	Active ingredient	150 30 200	31.250 6.250 41.666
2	Lactose	Diluent	195.10	41.800
3	Maize Starch	Disintegrant	55.40	11.452
4	Croscarmellose Sodium (Primellose)	Binder	9.00	1.875
5	Povidone (PVPK-30)	Vehicle	17.00	3.542
6	Isopropyl Alcohol	Granulating agent	117. 57	24.494
	Extra Granular Materials			
7	Magnesium Stearate	Lubricant	11.50	7.187
8	Sodium Starch glycollate	Lubricant	19.00	11.875
9	Croscarmellose Sodium	Lubricant	6.00	3.750
10	Colloidal Anhydrous Silica	Lubricant	7.00	4.375
11	Lake Sunset yellow	Coloring agent	4.00	0.833

Validation plan: For batch size: 15 kg (150000 tablets)

Process Flow Chart





Manufacturing procedure

Dispensing

The Following Instructions to be followed during Dispensing

- The Area and Equipment must be cleared by QA before use.
- Follow the Gowning Procedures as per S.O.P.
- Issue only approved Materials.
- Ensure labeling at all stages of Dispensing.
- Check the Accuracy & ensure that Balances are calibrated before use.
- Ensure to fill the details in list of Personnel before starting the Dispensing.
- General Dispensing Instructions
- ✓ Room Temp: NMT 25°C
- ✓ Relative Humidity: NMT 60%

Process instructions

- Follow the Gowning procedure
- The area & Equipment must be cleared by QA before use.
- Check & Ensure that all balances are in calibrated state.
- Ensure that the product is label with all stages of manufacturing.
- Follow the operative instructions & SOP's.
- General manufacturing conditions:
- ✓ Room Temperature: NMT 25°C
- ✓ Relative Humidity: 45±5
- ✓ Pressure Differential: NLT 12.5 Pascal's
- Ensure to fill the details in the list of personnel before executing the batch.
- Ensure that the isolators are showing healthy conditions before starting the operation.
- The recommended process time for manufacturing the finished drug product is within 30 days of
- Start of manufacturing process.
- Record the tare weight of blender before starting of process.

Sifting (Intra Granular Materials)

- Ensure that the Area and Equipment must be cleared by QA before use.
- Check the sieve no's 40&80 before starting.
- Check & ensure that the temperature, RH & DP is within the specified limits.
- Check the integrity of the sieve before and after sifting of material and record the details.
- Sift Lamivudine (31.250Kg), Stavudine(6.250kg), Nevirapine(41.666kg), Croscarmellose Sodium(1.875Kg.) in the process area through 40 mesh and collective double polythene bag and labeled.

Granulation

Equipment must be cleared by QA before use

Dry Mixing

- Load the Sifted material in Single Pot rapid mixer granulator.
- Dry mix the material for 5 minutes at 120±10 Impeller rpm at slow speed and chopper off.

Binder Solution Preparation

Take IsoPropyl Alcohol (IPA), stir IPA (24.494lit) in a vessel to form vortex with out drawing air into liquid ,add steadily povidone(3.542kg) to vortex to get a clear solution.

Wet Granulation

- Start and run the impeller at 120±10 rpm with chopper off, add binder solution to the dry mixed material in the granulator over a period of 3min slowly, while mixing with impeller at slow speed.
- Scrap the impeller and inner walls of the bowl using a scrapper/ spatula. Continue mixing for 2 min with impeller and chopper at slow speed. Check for complete formation of granules.
- Add extra quantity of IPA(if required) and mix until the granulation end point is reach.
- Rake the material for 1 min at impeller fast and chopper slow speed.
- Record the observed parameters at the end of Granulation process.
- ✓ Total Additional Mixing Time-2 min.
- ✓ Total Mixing Time-10 min.

Drying

- Transfer the wet granular mass into a clean prelabeled Fluidized Bed Dryer(FBD) bowl check the integrity of the finger bag before use.
- Start the vacuum pump, start the Thermal resistor and set the temperature at 25 ± 5^{0}C, close the vacuum vent valve provided on the filter assembly, apply vacuum by opening the manual valve, inject air at a pressure of 15 – 20 ltr. Per min.
- Air dry the wet mass in fluid bed dryer to get the final LOD of the granules not more than 3% w/w on IR moisture analyzer.
- Rate the granules intermittently for every 10min.
- Check the LOD after every 10 Min. of drying cycle. Repeat the cycle till the LOD of the granule is within the limit of NMT 3% w/w.
- Unload the dried granules and collect in a double poly bag, weigh and labeled.

Sieving & Milling

- Ensure that the Equipment must be cleared by QA before use.
- Check the integrity of sieve and record details. (same as granulation)
- Check and ensure the temp., RH and DP. within specified limits.
- Sieve the dry granules through mesh #18 (screen size 2mm) on vibrator sifter.
- Mill the oversized dried granules using a multi mil at medium speed in forward direction and finally pass through sieve #18.
- Collect the granules in double polythene bag and labeled.

Sifting (Extra Granular Materials)

- Ensure that the Equipment must be cleared by QA before use.
- Check the integrity of sieve and record details. (same as granulation)
- Check and ensure the temp., RH and DP with in specified limits.
- Sift the extra granular material in the process area (outside isolator & transfer it to the isolator through the pass box before starting the process).
- Sift Magnesium Stearate – 7.187 Kg.
- Sodium Starch – 11.875 Kg.
- Croscarmellose Sodium – 3.750 Kg.
- Colloidal anhydrous silica -- 4.375 Kg
- Through # 40 mesh sieve and collect in double polythene bag and labeled.

Blending

- Ensure that the Equipment must be cleared by QA before use.
- Record the tare weight of Bin Blender.
- Load the granules and sifted ingredients (extra granular materials) into the Double cone blender.
- Blend the materials for 5 minutes at 10 rpm.

- Sift Lake Sunset (0.833 Kg) yellow through sieve #80 using sifter for color blend.
- Send "Request for Analysis" to QA for sampling and onward submission of samples to QC.
- Detoxify the Isolated chamber and remove bin blender from isolator and check the gross weight of bin blender.

Compression

- Ensure that the Equipment must be cleared by QA before use.
- Check and ensure the temp., RH and DP. with in specified limits.
- Set up the tablet compression machine with 12.8 mm round plain flat bevel edged lower and upper punches with correspondence dies.
- Ensure that the blend is approved for Compression.

VALIDATION PROCEDURE

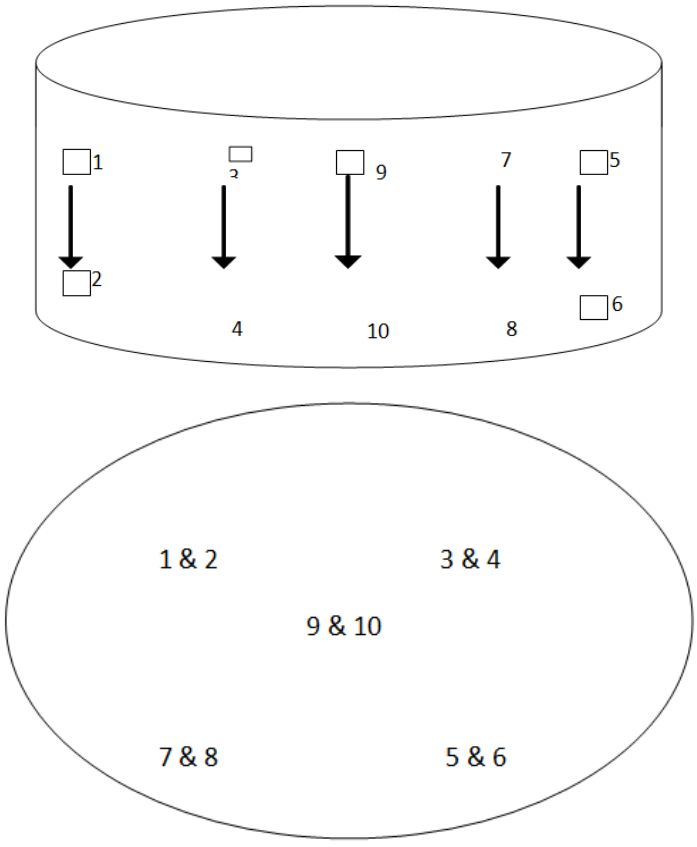
- Three batches of 12.5 Lakhs tablets batch size will be manufactured as described in the Batch manufacturing record.
- Current version of standard operating procedures to be followed
- Record the yield after blending, compression and packing.

Sampling Procedure at different stages

Dry mixing

The drying mixing step involves mixing of active ingredient with other additives using rapid mixer granulator processor. The content uniformity of Nevilast-30 has to be established during validation of dry mixing process. Determination of the content uniformity of the drug has to be done at the end of 5 minutes. The acceptance criteria for the content uniformity are 100 ± **5** % of the theoretical quantity, where as the limit for Relative Standard deviation (RSD) should be NMT± 5.0%. The sample quantity shall be between 639.5 mg to 1918.5 mg. Sampling should be done with sampling rod. Samples to be collected in Poly bags. Collect samples in to three sets. One set of sample is taken for analysis and other sets are kept as a reserve sample. In case of failure results of first sample, use reserve set otherwise discard the reserve samples.

SPP(FBD) sampling location of Dry mix



Sample No.	Location
1 & 2	Upper (left front)
3 & 4	Upper (right front)
5 & 6	Lower (right rear)
7 & 8	Lower (left front)
9 & 10	Upper (Centre)

Table no. 8: Sampling location of Dry mix

Granulation

The granulation is to be performed using SPP. The granulation step involves converting the powder into wet rough mass. The granule strength, bulk density of blend, dissolution, hardness of tablets etc are influenced by mixing time. Binding agent preparation (BAP) is being used for granulation. The granulation end point is critical process and the end point of granulation shall be checked against the amperage readings of Impeller & chopper of the SPP, which gives the co-relation to the granulation end point.

Drying

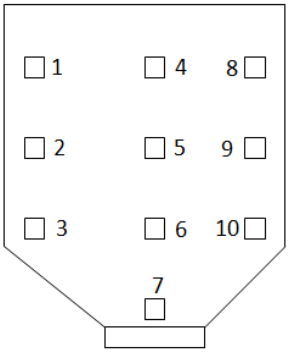
The drying of the wet granules is performed in SPP. The inlet temperature of the SPP is controlled during the process and the outlet temperature is monitored and co-related with the corresponding Loss on drying (LOD) of the granules under drying. The outlet temperature range is established which is required to attained desired LOD of the granules.

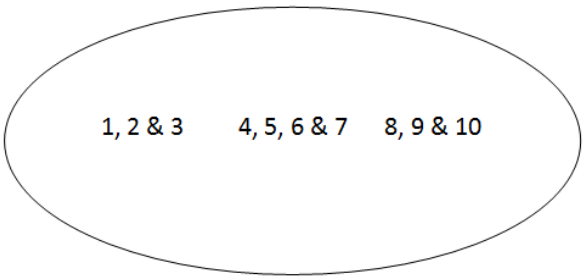
- Draw samples from different positions of the SPP bowl and make pooled Sample and check LOD. Repeat the same at different outlet temperatures.
- Once the LOD of the polled sample meets the desired range, draw samples from five different places in the S bowl and check LOD
- Record the following observations
- Inlet air temperature, outlet temperature for every 10 minutes.
- Check and record LOD of granules at different temperatures and at end of drying process.

Blending

Load the sifted materials in to the Bin blender except Magnesium stearate. Start the blender in inch mode and check for any leakage of material. On ensuring that there is no leakage, blend for 8-10 minutes. Add Magnesium stearate, Sodium starch, Croscarmellose Sodium and Colloidal anhydrous silica gel along with equal quantity of blend from octagonal blender in double polythene bags for proper mixing. Then add this lubricated material to blended material in the blender. Then blend for another 5 minutes and collect the samples from 10 locations. Sample size shall be between 700 mg to 2100 mg. All samples shall be collected in tarred vials. Collect samples in 3 sets .one set of sample is taken for analysis. Other sets are kept as reserved Sample.

Sampling locations in a cone blender





Sample No.	Location
1	Upper (left)
2	Middle (left)
3	Lower (left)
4	Upper (Centre)
5	Middle (Centre)
6	Lower (Centre)
7	Bottom (Centre)
8	Upper (right)
9	Middle (right)
10	Lower (right)

- Sample numbers to be given as 1/1 to 1/10

Check and record the following
- Sieve analysis
- Bulk density
- Content uniformity
- Assay
- LOD/Moisture content

Compression

Compression is to be carried out as per batch manufacturing record using 12.8 mm circular, plain flat, beveled edge with plain surface on upper punches, 12.8 mm circular, beveled edge with plain surface and 8 mm diameter dies set the machine at different speeds of 16, 80 rpm and check the following parameters.
- No. Of stations: 37 station compression machine
- Type of tooling type: 6.8 on lower punch and LET on upper punch
- Speed of machine from 2, 21,500 to 2, 22,000 tablets per hour.

Carry out the testing of content uniformity of physical parameters as mentioned in the below table. The tablets compressed at various set parameters of the specification limits should confirm as per the following:

Standard parameters

S.No.	Parameters	Standards
01	Weight of 20 tablets	14 gm ± 2%
02	Hardness	NLT 4 kp
03	*Thickness*	4.5 mm ± 0.3 mm
04	Friability	NMT 1 % w/w
05	Individual weight variation	700mg ± 2 %

Table no. 9: Standard parameters

Hopper study

To evaluate effects of vibrations during compression on blend uniformity hopper study shall be carried out. Fill the hopper completely run the compression machine. Collect tablets when powder level in the hopper is full, approx, middle hopper and when it is nearing end of the hopper.

Dissolution profile

Check the dissolution profile of 6 tablets at 10 min, 15 min, 20 min, 30 min and 45 min from the pooled sample after the completion of compression.

Note: Dissolution profile on 12 tablets shall be done in 0.1N Hydrochloric acid media, pH 4.5 acetate buffer & pH6.8 phosphate buffer using 900ml media, 50 rpm, paddle, the time points 5, 10,15,30,45 & 60min.

Container packing

Packing is to be done as per batch packing record. Before starting packing operations check the container sealing roller temperature and speed of the machine. After packing check container quality, sealing appearance and leak test.

III. Results

PROCESS VALIDATION REPORT OF TABLET DOSAGE FORMS NEVILAST 30 – 700MG

1. Dispensing

Analysis report of all the raw materials were checked and only approved raw material were used

2. Sifting

Presence of foreign particles and final and hard lumps were observed and no such materials were observed.

3. Dry mixing

Fixed Parameters

Rapid mixer Granulator rpm	: 19-21 RPM
Rapid mixer Granulator Type & Capacity	: SSPM, 400 liters
Variables Considered for Study	: Mixing Time
Time Interval Studied	: 5 minutes
Measured Response	: Description, Blend uniformity
Acceptance Criteria	: Not less than 90 % and not more

than 110 % of the label claim.

Dry mixing – blend uniformity samples (colorless layer)

DRY MIXING BLEND UNIFORMITY SAMPLES (% w/w)																	
Sampling Point Location	**Specification/ Acceptance Criteria**	**Batch No.**															
		XXXX									**YYY**			**ZZZ**			
A.R. No.	-------	**Lot-I**			**Lot-II**			**Lot-III**			**Lot-I**			**Lot-I**			
		L	**S**	**N**	**L**	**S**	**N**	**L**	**S**	**N**	**L**	**S**	**N**	**L**	**S**	**N**	
1	**90% - 110% With RSD< 5.0%**	92.4	101.4	95.0	91.29	104.59	94.69	99.92	106.59	100.21	102.95	102.01	103.18	97.58	94.73	101.12	
2		94.0	98.7	97.3	95.16	94.62	97.16	93.49	96.14	94.49	100.59	97.09	100.31	98.29	97.91	100.86	
3		94.4	99.2	97.6	94.16	98.62	97.50	105.46	108.32	106.72	100.03	97.95	100.09	98.71	95.92	101.10	
4		93.3	100.4	96.7	93.96	98.58	97.57	100.06	106.71	100.35	100.28	106.82	100.19	98.64	95.00	100.14	
5		93.4	98.9	96.4	93.76	99.20	97.06	102.09	98.76	100.70	100.63	95.34	99.28	98.27	99.78	100.64	
6		93.4	100.6	96.8	93.74	102.35	96.79	94.21	97.18	95.65	101.03	104.69	101.54	98.43	97.24	99.30	
7		94.2	99.1	97.3	90.70	102.97	94.42	97.42	100.07	98.57	100.37	97.30	100.67	98.66	97.92	100.29	
8		93.1	98.7	96.0	95.26	94.97	96.98	98.96	94.01	99.68	101.15	101.08	101.17	97.82	98.44	101.24	
9		92.4	101.6	95.1	99.54	99.27	101.40	101.91	102.24	102.56	102.60	98.57	101.37	101.14	100.02	103.25	
10		93.1	98.7	96.2	95.71	95.54	97.51	103.99	100.45	102.22	98.36	102.61	97.84	97.43	100.32	100.16	
Min.		98.7	95.0	90.7	91.2	94.42	93.49	94.01	94.49	98.36	95.34	97.84	97.84	97.43	94.73	99.3	
Max.		101.6	97.6	99.54	100.59	101.4	105.46	108.32	106.72	102.95	106.82	103.18	101.18	101.14	100.32	103.25	
MEAN		93.0	100.0	97.0	94.3	98.3	97.1	99.8	101.01	100.1	100.8	100.3	100.6	98.5	97.7	100.8	
% RSD		0.7	1.2	0.9	2.6	4.3	2.0	3.9	4.8`	3.5	1.3	3.7	1.4	1.1	2.1	1.0	

Table-13: Dry mixing – blend uniformity samples (colorless layer)

Dry mixing – blend uniformity samples (color layer)

DRY MIXING BLEND UNJIFORMITY SAMPLES (% w/w)																
Sampling Point Location	**Specification/ Acceptance Criteria**	**Batch No.**														
		XXXX									**YYY**			**ZZZ**		
A.R. No.	-------	**Lot-I**			**Lot-II**			**Lot-III**			**Lot-I**			**Lot-I**		
		L	**S**	**N**	**L**	**S**	**N**	**L**	**S**	**N**	**L**	**S**	**N**	**L**	**S**	**N**
1	**90% - 110% With RSD< 5.0%**	95.92	96.14	98.46	94.88	95.50	96.29	99.18	106.33	103.77	100.18	103.18	104.57	100.26	97.20	103.63
2		93.30	94.29	94.97	91.88	91.43	93.87	98.93	101.0	103.55	100.12	103.13	104.71	101.94	101.36	104.34
3		94.74	95.02	97.74	103.53	102.87	105.84	98.65	106.9	102.63	95.70	106.95	99.35	103.12	99.79	105.14
4		91.25	91.04	93.41	93.74	93.80	96.60	98.93	105.73	103.07	99.04	105.91	102.56	104.04	99.71	103.57
5		92.85	93.10	95.23	95.95	96.60	97.80	98.49	107.92	103.26	96.46	104.07	100.53	103.35	104.18	102.56
6		91.87	92.54	93.54	91.78	92.53	93.10	99.68	101.85	103.38	96.34	103.94	100.44	99.91	98.64	100.71
7		97.25	96.75	99.74	97.26	97.53	99.49	99.27	104.59	102.77	99.33	106.20	102.64	103.35	101.81	100.66
8		94.37	95.03	96.14	92.26	9.79	93.81	99.51	105.11	103.69	95.72	106.98	99.31	98.35	101.50	101.49
9		94.53	94.74	97.34	94.04	94.09	96.67	101.37	107.0	103.30	9929	102.31	103.75	100.23	99.03	101.96
10		95.84	95.27	98.07	94.45	93.83	96.06	98.85	100.91	103.07	101.01	104.35	104.39	102.98	99.86	105.09
Min.		91.26	91.04	93.14	91.78	91.43	93.1	98.49	100.91	102.63	95.7	102.31	99.31	98.35	97.2	100.66
Max.		97.25	96.75	99.74	103.53	102.87	105.84	101.37	107.92	103.77	101.01	106.98	104.71	104.04	104.18	105.14
MEAN		94.2	94.4	96.5	95.0	95.1	97.0	99.3	104.8	103.3	98.3	104.7	102.2	101.8	100.3	102.9
% RSD		2.0	1.8	2.2	3.7	3.5	3.8	0.8	2.5	0.4	2.1	1.6	2.1	1.9	2.0	1.6

Table-14: Dry mixing – blend uniformity samples (color layer)

a) Dry mixing – Composite sample (Colorless layer)

Checks	**Specification/ Acceptance Criteria**	**Observations**				
		Batch No.				
		XXX			**YYY**	**ZZZ**
		Lot-I	**Lot-II**	**Lot-III**	**Lot-I**	**Lot-I**
Bulk Density (gm/ml)	For information	0.471	0.496	0.477	0.462	0.497
Tapped Density (gm/ml)	For information	0.730	0.851	0.738	0.707	0.739

Table-15: Dry mixing – Composite sample (Colorless layer)

b) Dry mixing – Composite sample (Color layer)

Checks	**Specification/ Acceptance Criteria**	**Observations**				
		Batch No.				
		XXX			**YYY**	**ZZZ**
		Lot-I	**Lot-II**	**Lot-III**	**Lot-I**	**Lot-I**
Bulk Density (gm/ml)	For information	0.477	0.567	0.593	0.443	0.607
Tapped Density (gm/ml)	For information	0.738	0.692	0.726	0.950	0.743

Table-16: Dry mixing – Composite sample (Color layer)

4. Wet granulation

a) Wet granulation - Composite sample (Colorless layer)

Checks	Specification/ Acceptance Criteria	Observations				
		Batch No.				
		XXX			YYY	ZZZ
		Lot-I	Lot-II	Lot-III	Lot-I	Lot-I
LOD by moisture analyzer in an auto mode at 105ºC (%w/w)	For information	4.2	9.5	7.7	8.9	6.9

Table-17: Wet granulation - Composite sample (Colorless layer)

b) Wet granulation - Composite sample (Color layer)

Checks	Specification/ Acceptance Criteria	Observations				
		Batch No.				
		XXX			YYY	ZZZ
		Lot-I	Lot-II	Lot-III	Lot-I	Lot-I
LOD by moisture analyzer in an auto mode at 105ºC (%w/w)	For information	4.2	9.5	7.7	8.9	6.9

Table-18: Wet granulation - Composite sample (Color layer)

5. Drying

Fixed Parameters

- Fluidized Type & Capacity : CLIT, 120 kg
- Bowel Temperature(^{0}C) : 25±5
- Air Pressure (L/min) : 12-14
- Fluidization : Continuous

Observed parameters

- Product temperature attained during drying : 25-28^{0}C
- Total Drying time (min) : 30
- LOD (%w/w) : NMT 3%

a) Drying Results – Rate of Drying (Colorless layer)

Percentage LOD Results for every 10 minutes (Rate of Drying)												
Checks	Specifications	Time	Observations									
			Batch No.									
			XXX						YYY		ZZZ	
			Lot-I		Lot-II		Lot-III		Lot-I		Lot-I	
			B-I	B-II	B-I	B-II	B-I	B-II	B-I	B-II	B-I	B-II
% LOD	NMT 3.0% w/w	10 min.	---	---	---	---	---	---	---	---	---	---
		20 min.	3.04	4.87	4.39	4.43	4.33	4.48	4.19	4.46	4.24	4.27
		30 min.	2.55	2.63	2.63	2.54	2.57	2.37	2.53	2.31	2.50	2.18

Table-19: Drying Results – Rate of Drying (Colorless layer)

b) Drying Results – Rate of Drying (Color layer)

Percentage LOD Results for every 10 minutes (Rate of Drying)												
Checks	Specifications	Time	Observations									
			Batch No.									
			XXX						YYY		ZZZ	
			Lot-I		Lot-II		Lot-III		Lot-I		Lot-I	
			B-I	B-II	B-I	B-II	B-I	B-II	B-I	B-II	B-I	B-II
% LOD	NMT 3.0% w/w	10 min.	---	---	---	---	---	---	---	---	---	---
		20 min.	3.89	3.77	2.85	3.94	3.44	3.78	3.83	3.77	3.34	3.29
		30 min.	2.03	1.39	1.73	2.81	1.44	1.94	1.87	1.70	1.16	1.73

Table-20: Drying Results – Rate of Drying (Color layer)

c) Drying results (Drying Uniformity) (Colorless layer)

BOWL-I

Percentage LOD results (Drying Uniformity)								
Checks		**Specification**	**Observations**					
Batch Number		---	**Batch No.**					
			XXX			**YYY**	**ZZZ**	
			Lot-I	**Lot-II**	**Lot-III**	**Lot-I**	**Lot-I**	
%LOD of Dried granules (%m/m) after completion of drying	**Location**	**NMT 3.0%**	---	---	---	---	---	
	1		1.2	0.8	1.3	0.9	1.0	
	2		1.3	1.0	1.8	0.6	0.9	
	3		1.2	0.8	1.5	0.5	1.0	
	4		1.2	0.9	1.3	0.2	0.9	
	5		0.5	1.1	1.4	0.4	0.8	
	6		0.6	1.2	1.4	1.1	0.6	

Table-21: Drying results (Drying Uniformity) (Colorless layer)

BOWL-II

Percentage LOD results (Drying Uniformity)							
Checks		**Specification**	**Observations**				
Batch Number		---	**Batch No.**				
			XXX			**YYY**	**ZZZ**
			Lot-I	**Lot-II**	**Lot-III**	**Lot-I**	**Lot-I**
%LOD of Dried granules (%m/m) after completion of drying	**Location**	**NMT 3.0%**	---	---	---	---	---
	1		1.5	1.0	1.2	1.0	0.6
	2		1.3	0.8	1.3	0.9	0.9
	3		1.2	1.0	1.5	0.7	1.2
	4		1.4	1.3	1.1	1.0	1.3
	5		1.2	0.8	1.6	1.2	1.1
	6		0.9	1.1	1.2	1.0	1.2

Table-22: Drying results (Drying Uniformity) (Colorless layer)

d) Drying results (Drying Uniformity) (Color layer)

BOWL-I

Percentage LOD results (Drying Uniformity)								
Checks		**Specification**	**Observations**					
Batch Number		---	**Batch No.**					
			XXX			**YYY**	**ZZZ**	
			Lot-I	**Lot-II**	**Lot-III**	**Lot-I**	**Lot-I**	
%LOD of Dried granules (%m/m) after completion of drying	**Location**	**NMT 3.0%**	---	---	---	---	---	
	1		1.4	1.1	0.4	1.2	0.9	
	2		1.3	1.1	0.5	1.2	0.9	
	3		1.5	1.0	0.1	1.0	0.8	
	4		1.1	1.0	0.6	0.9	0.7	
	5		0.9	1.0	0.5	0.9	0.8	
	6		0.7	0.7	0.5	1.0	0.8	

Table-23: Drying results (Drying Uniformity) (Color layer)

BOWL-II

Percentage LOD results (Drying Uniformity)								
Checks		**Specification**	**Observations**					
Batch Number		---	**Batch No.**					
			XXX			**YYY**	**ZZZ**	
			Lot-I	**Lot-II**	**Lot-III**	**Lot-I**	**Lot-I**	
%LOD of Dried granules (%m/m) after completion of drying	**Location**	**NMT 3.0%**	---	---	---	---	---	
	1		1.0	0.5	0.6	1.3	0.9	
	2		1.1	0.6	0.7	1.2	0.7	
	3		1.6	0.4	0.7	1.3	0.9	
	4		1.2	0.6	0.6	1.2	0.8	
	5		1.0	0.5	1.0	1.2	0.8	
	6		1.0	0.1	0.6	1.0	1.0	

Table-24: Drying results (Drying Uniformity) (Color layer)

e) Drying results - composite sample (Colorless layer)

BOWL-1

Percentage LOD results (Drying Uniformity) – BOWL-I						
Checks	**Specification**	**Observations**				
---	---	**Batch No.**				
		XXX			**YYY**	**ZZZ**
		Lot-I	**Lot-II**	**Lot-III**	**Lot-I**	**Lot-I**
LOD by moisture analyzer in an auto mode at 105ºC (%w/w)	NMT 3.0% w/w	1.7	1.1	1.6	1.0	1.7
Residual solvents analysis (IPA Content)	NMT 5000 ppm	113	329	620	758	711

Table-25: Drying results - composite sample (Colorless layer)

BOWL-2

Percentage LOD results (Drying Uniformity) – BOWL-II						
Checks	**Specification**	**Observations**				
---	---	**Batch No.**				
		XXX			**YYY**	**ZZZ**
		Lot-I	**Lot-II**	**Lot-III**	**Lot-I**	**Lot-I**
LOD by moisture analyzer in an auto mode at 105ºC (%w/w)	NMT 3.0% w/w	1.4	0.8	1.1	1.3	1.8
Residual solvents analysis (IPA Content)	NMT 5000 ppm	138	607	1048	705	587

Table-26: Drying results - composite sample (Colorless layer)

f) Drying results - composite sample (Color layer)

BOWL-1

Percentage LOD results (Drying Uniformity) – BOWL-I						
Checks	**Specification**	**Observations**				
---	---	**Batch No.**				
		XXX			**YYY**	**ZZZ**
		Lot-I	**Lot-II**	**Lot-III**	**Lot-I**	**Lot-I**
LOD by moisture analyzer in an auto mode at 105ºC (%w/w)	NMT 3.0% w/w	1.0	1.9	0.8	1.1	1.5
Residual solvents analysis (IPA Content)	NMT 5000 ppm	348	135	121	352	1974

Table-27: Drying results - composite sample (Color layer)

BOWL-II

Percentage LOD results (Drying Uniformity) – BOWL-II						
Checks	**Specification**	**Observations**				
---	---	**Batch No.**				
		XXX			**YYY**	**ZZZ**
		Lot-I	**Lot-II**	**Lot-III**	**Lot-I**	**Lot-I**
LOD by moisture analyzer in an auto mode at 105ºC (%w/w)	NMT 3.0% w/w	1.5	0.9	0.9	0.9	1.2
Residual solvents analysis (IPA Content)	NMT 5000 ppm	146	109	160	372	1186

Table-28: Drying results - composite sample (Color layer)

6. Sifting / milling dried granules

Fixed Parameters

Equipment : Multimill
Screen Size : 2 mm (2000µ)
Sieve No. : 18

Percentage of Granules Retained & Passed

After milling through Multimill			
%of Granules retained on #18 mesh	4.2	3.5	3.7
%of Granules passed through #80esh	89.5	89.4	90.0

Table-29: Percentage of Granules Retained & Passed

7. Blending

Fixed parameters

Blender rpm : 9 ±1 rpm
Variables considered for study : blending time
Time interval studied : 5 minutes
Acceptance criteria : NLT90 % and not morethan110 % of the label claim
Measured response : Content Uniformity and RSD

a) Lubrication (Colorless layer)

LUBRICATION BLEND UNIFORMITY SAMPLES (% w/w)										
Sampling Point Location	**Specification/ Acceptance Criteria**	**Batch No.**								
		XXXX			**YYY**			**ZZZ**		
A.R.No.	-------	**Lot-I**			**Lot-I**			**Lot-I**		
		L	**S**	**N**	**L**	**S**	**N**	**L**	**S**	**N**
1	**90% - 110% With RSD<5.0%**	92.32	91.03	92.80	97.02	99.33	97.64	92.36	94.76	95.65
2		99.70	95.72	100.44	99.28	99.57	98.92	94.15	97.69	97.60
3		94.54	93.85	94.92	97.44	97.59	97.04	92.37	95.64	95.858
4		92.14	90.35	92.30	98.30	98.78	98.67	90.42	91.62	94.49
5		92.77	91.97	93.16	98.67	98.71	98.32	91.23	92.00	93.88
6		98.59	101.18	100.58	100.43	100.50	100.02	98.83	101.18	99.62
7		96.43	96.74	97.41	98.70	99.26	99.08	97.06	92.19	98.16
8		98.75	97.86	99.52	97.63	97.28	97.24	100.46	99.72	101.92
9		102.38	97.93	101.74	101.56	101.81	101.07	100.24	103.11	103.44
10		100.42	98.44	100.86	96.98	99.30	97.41	101.60	104.26	104.72
Min.		92.14	90.34	92.3	96.98	97.59	97.04	90.42	91.62	93.88
Max.		102.38	101.18	101.74	101.56	101.81	101.07	101.6	104.26	104.72
MEAN		96.8	95.5	97.4	98.6	99.3	98.5	95.9	97.2	98.5

Table-30: Lubrication (Colorless layer)

b) Lubrication - Sample from Containers (Colorless layer)

LUBRICATION BLEND UNIFORMITY SAMPLES (% w/w)										
Sampling Point Location	**Specification/ Acceptance Criteria**	**Batch No.**								
		XXXX			**YYY**			**ZZZ**		
A.R.No.	-------	**Lot-I**			**Lot-I**			**Lot-I**		
		L	**S**	**N**	**L**	**S**	**N**	**L**	**S**	**N**
1	**90% - 110% With RSD<5.0%**	91.40	90.08	92.28	101.90	94.62	99.67	99.90	102.25	104.26
2		94.11	93.29	94.72	101.70	99.74	100.91	97.69	92.76	98.46
3		100.58	102.96	101.91	99.51	102.65	99.97	90.20	93.23	94.17
4		98.47	98.81	99.25	101.23	102.89	101.69	90.24	91.39	94.60
5		100.32	96.26	100.81	99.49	99.16	98.80	96.15	96.79	98.86
6		96.13	94.76	96.80	99.54	99.17	98.83	101.70	100.99	103.17
7		97.78	96.89	98.51	100.83	102.33	101.06	98.27	101.11	101.41
8		95.06	90.72	94.99	99.31	102.54	99.67	98.06	98.97	99.13
9		92.73	91.98	93.25	100.14	92.95	98.0	98.05	100.50	100.17
10		99.98	97.39	100.13	101.27	99.14	100.25	95.43	90.72	96.21
Min.		91.5	90.08	92.28	99.31	92.95	98.0	90.2	90.72	94.17
Max.		100.58	102.96	101.91	101.9	102.89	101.69	101.7	102.25	104.26

MEAN		96.7	95.3	97.3	100.5	99.5	99.9	96.6	96.9	99.0

Table-31: Lubrication - Sample from Containers (Colorless layer)

c) Lubrication - Sample from Containers (Color layer)

LUBRICATION BLEND UNIFORMITY SAMPLES (% w/w)										
Sampling Point Location	**Specification/ Acceptance Criteria**	**Batch No.**								
		XXXX			**YYY**			**ZZZ**		
A.R.No.	-------	**Lot-I**			**Lot-I**			**Lot-I**		
		L	**S**	**N**	**L**	**S**	**N**	**L**	**S**	**N**
1	**90% - 110% With RSD<5.0%**	96.42	103.27	100.46	96.13	103.23	99.99	96.24	98.20	96.10
2		97.68	99.48	101.93	95.01	102.48	99.55	94.26	98.41	95.15
3		96.12	103.73	99.60	98.37	105.87	102.03	96.86	103.89	100.76
4		94.27	100.64	97.85	96.53	104.20	100.73	97.31	103.26	99.65
5		97.14	106.19	101.54	95.91	100.23	98.86	97.20	101.36	99.20
6		94.93	96.93	98.18	95.83	102.46	99.48	97.49	103.52	99.70
7		96.12	101.39	98.14	95.43	102.84	99.54	96.92	103.85	100.45
8		95.86	103.75	99.29	96.23	100.67	99.0	94.36	98.57	95.16
9		98.89	104.53	99.62	95.31	101.77	98.59	97.12	99.19	96.45
10		96.22	98.27	100.23	95.54	102.97	99.72	96.54	100.73	98.71
Min.		94.27	96.93	97.85	95.01	100.23	98.59	94.26	98.2	95.15
Max.		98.89	106.19	101.93	98.37	105.87	102.03	97.49	103.89	100.76
MEAN		96.4	101.8	99.7	96.0	103.0	99.8	96.4	101.1	98.1
% RSD		1.4	2.9	1.4	1.0	1.6	1.0	1.2	2.4	2.2

Table-32: Lubrication - Sample from Containers (Color layer)

d) Lubrication - Sample from Containers (Color layer)

LUBRICATION BLEND UNIFORMITY SAMPLES (% w/w)										
Sampling Point Location	**Specification/ Acceptance Criteria**	**Batch No.**								
		XXXX			**YYY**			**ZZZ**		
A.R.No.	-------	**Lot-I**			**Lot-I**			**Lot-I**		
		L	**S**	**N**	**L**	**S**	**N**	**L**	**S**	**N**
1	**90% - 110% With RSD<5.0%**	92.10	98.56	97.62	94.78	101.79	99014	94.4	104.11	100.78
2		93.22	98.55	98.87	99.78	105.81	103.83	98.75	100.08	99.25
3		92.70	98.23	98.36	96.84	100.87	100.54	95.48	103.10	102.00
4		91.90	98.97	97.88	95.77	98.99	99.33	94.32	104.94	98.80
5		92.59	99.24	99.37	94.25	99.51	98.03	93.49	102.44	100.23
6		91.97	99.32	98.36	94.19	99.35	98.03	94.39	104.86	98.90
7		92.33	99.14	98.54	95.21	98.42	98.78	93.63	102.69	100.47
8		91.07	97.41	96.47	95.76	99.78	99.41	94.39	102.41	101.01
9		91.51	96.77	96.75	94.21	101.04	98.28	98.45	99.79	98.90
10		92.50	99.96	98.70	98.75	104.76	102.87	94.42	104.05	100.77
Min.		91.07	96.77	96.47	94.12	98.42	98.03	93.49	99.79	98.8
Max.		93.22	99.96	99.37	99.78	105.81	103.83	98.75	104.94	102.0
MEAN		92.2	98.6	98.1	96.0	101.0	99.8	95.2	102.9	100.1
% RSD		0.7	1.0	0.9	2.0	2.5	2.0	2.0	1.7	1.1

Table-33: Lubrication - Sample from Containers (Color layer)

Blend pooled sample Results

Parameter	**XXX**	**YYY**	**ZZZ**
Sieve analysis			
1. Retains on # 16	3.94 % w/w	3.96% w/w	3.92 % w/w
2. Retains on # 30	5.783 % w/w	5.661 % w/w	5.714 % w/w
3. Retains on # 40	17.613 % w/w	16.518 % w/w	17.500 % w/w
4. Retains on # 60	34.281 % w/w	34.910 % w/w	35.134 % w/w
5. Retains on # 80	89.15 % w/w	89.42% w/w	90.2 % w/w
6. Retains on # 100	57.320 % w/w	58.921 % w/w	59.222 % w/w
7. Passing through # 100	39.674 % w/w	39.479 % w/w	39.518 % w/w
Untapped density (g/ml)	0.592	0.555	0.576
Tapped density (g/ml)	0.721	0.654	0.696

Angle or repose (°)	30 – 35	30 – 35	30 – 35
Compressibility index (%)	17.910	15.150	17.187
Hausner's ratio	1.218	1.180	1.207

Table-34: Blend pooled sample Results

The water contents and Assay of Blend as follows

Batch No.	Specification	XXX	YYY	ZZZ
Water content (%) (Limit: NMT 4.5%)	NMT 5% w/w	3.6	3.31	3.6
Assay (mg)				
Lamivudine	NLT 90% & NMT 110%	99.3%	100.0%	98.8%
Stavudine		101.6%	101.2%	97.8%
Nevirapine		100%	100.8%	100%

Table-35: The water content and Assay of Blend

8. Compression

Fixed parameters

Number of station : 37

Type of tooling : D type

Variables considered for study : Optimum Speed

MEASURED RESPONSE	ACCEPTANCE CRITERIA
Appearance	Two layered, flat, circular, bevel edged uncoated tablets, one layer with white color and the other layer with Orange color.
Individual weight variation	700 mg ± 2% (686mg-714 mg)
Thickness	4.5 ± 0.30mm (4.2mm – 4.8 mm)
Hardness	Not less than 4.0 Kp
Friability	NMT 1.0% w/w
Disintegration time	NMT 15 minutes
Content Uniformity RSD	90.0% to 110.0% NMT 5.0%
Dissolution	NLT 85.0% in 30 min.

Table-36: Compression parameters

a) Group weight variation

The target speedof the compression machine is 18-20 rpm.The speed is decreased by 3 rpm and the group weight variation is checked.

Approximate sample size **Acceptance criteria**

20 tablets 7.00 gm ± 2% (6.86gms - 7.14gms)

S.No	GROUP WEIGHT VARIATION (grams)		
	XXX	YYY	ZZZ
01	7.0415	7.0355	7.0148
02	7.0157	7.0014	6.9806
03	7.0245	7.0212	7.0180
04	7.0083	7.0009	7.0012
05	7.0232	7.0415	7.0293
06	7.0012	6.9819	6.9913
07	7.0415	7.0325	7.0120
08	6.9809	7.0010	6.9723
09	6.9982	7.0147	6.9969
10	6.9805	7.0134	7.0030
11	7.0169	6.9911	7.0357
12	6.9715	7.0425	7.0013
13	7.0018	7.0230	7.0294
14	7.0432	7.0512	6.9816
15	7.0245	7.0089	7.0207
16	7.0011	7.0320	7.0136
17	7.0537	7.0037	7.0073
18	7.0130	7.0215	7.0231
19	7.0256	7.0534	6.9865
20	7.0431	7.0123	7.0380
Avg	**7.0155**	**7.0192**	**7.0078**

Min	**6.9805**	**6.9911**	**6.9723**
Max	**7.0431**	**7.0534**	**7.0380**

Table-37: Group weight variation

TREND CHART FOR GROUP WEIGHT VARIATION

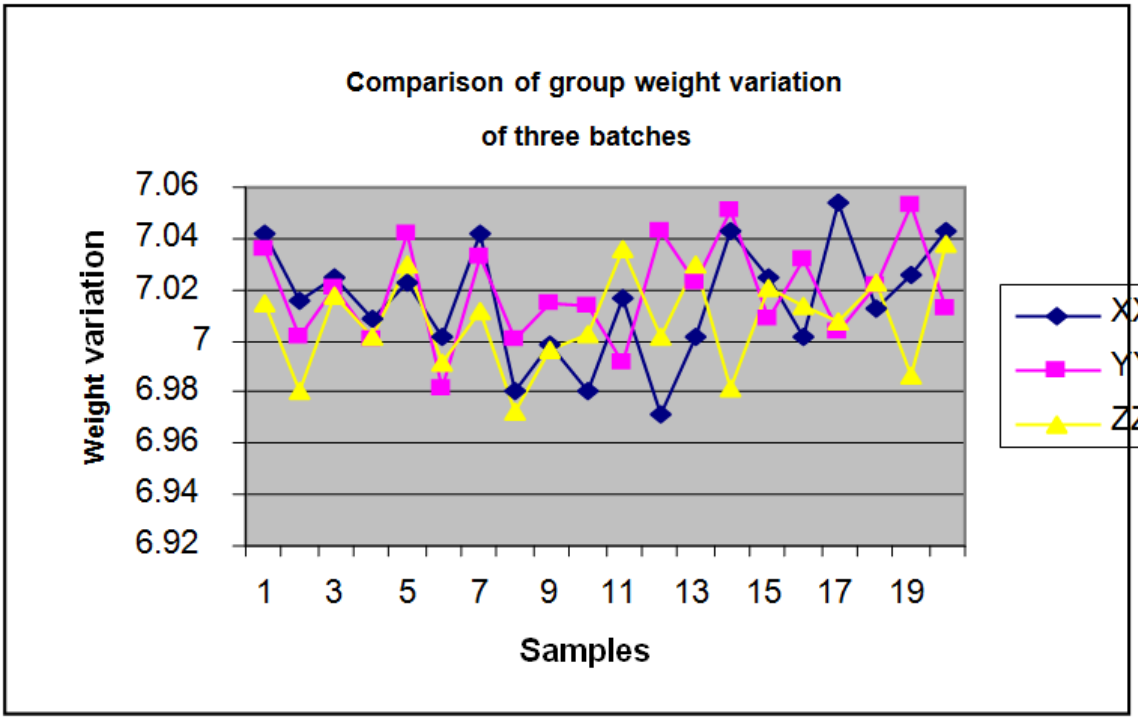


Figure-1

b) Individual weight variation:
Approx. sample size: 20 tablets **Acceptance criteria:** 700mg+/-2 % (686mg -714 mg)

S.No	INDIVIDUAL WEIGHT VARIATION (mg)		
	XXX	YYY	ZZZ
01	702.2	691.3	706.6
02	694.9	690.4	706.9
03	708.3	709.8	702.1
04	698.2	706.7	694.8
05	701.3	711.5	711.7
06	698.3	698.8	703.9
07	699.3	694.7	695.2
08	698.6	706.7	702.5
09	705.4	699.2	696.4
10	709.2	713.0	697.9
11	697.6	698.5	700.9
12	693.8	697.6	698.9
13	690.2	704.9	713.4
14	700.4	705.9	701.4
15	704.6	709.1	703.3
16	694.0	707.7	703.8
17	691.1	710.7	709.3
18	704.2	705.1	689.4
19	703.5	703.5	701.2
20	701.5	689.5	707.2
Avg	**699.83**	**702.73**	**702.34**
Min	**690.2**	**690.4**	**689.4**
Max	**705.4**	**713.0**	**713.4**

Table-38: Individual weight variation

Trend Chart For Individual Weight Variation

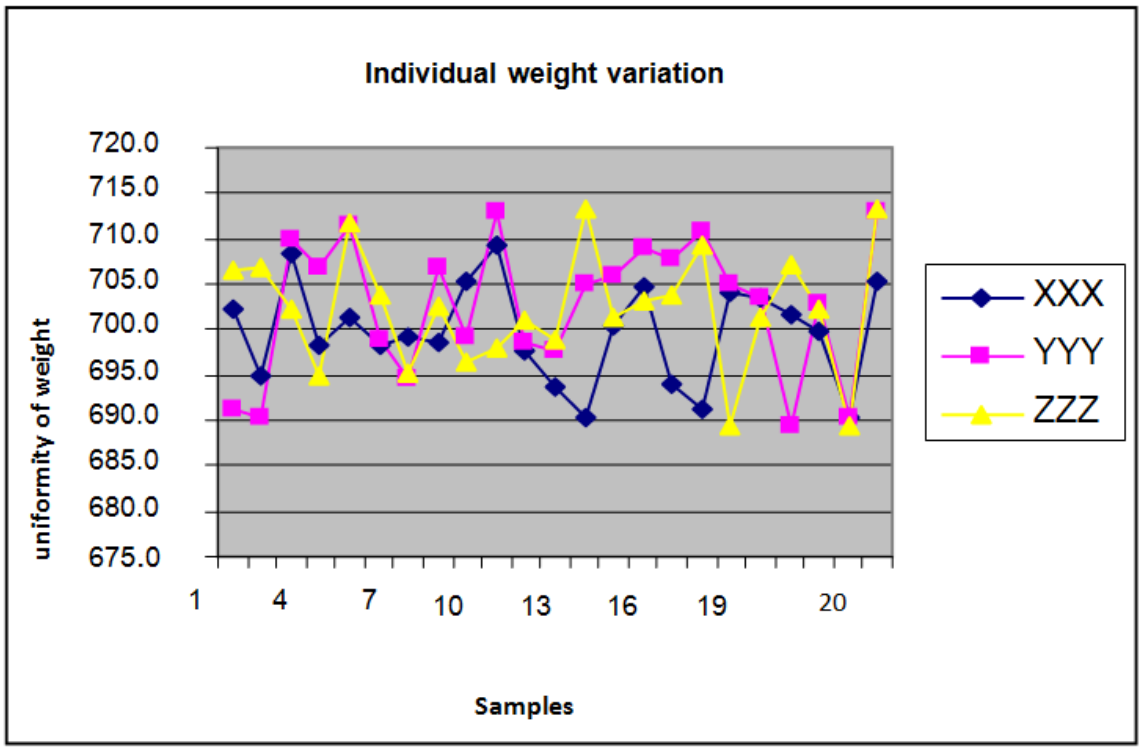


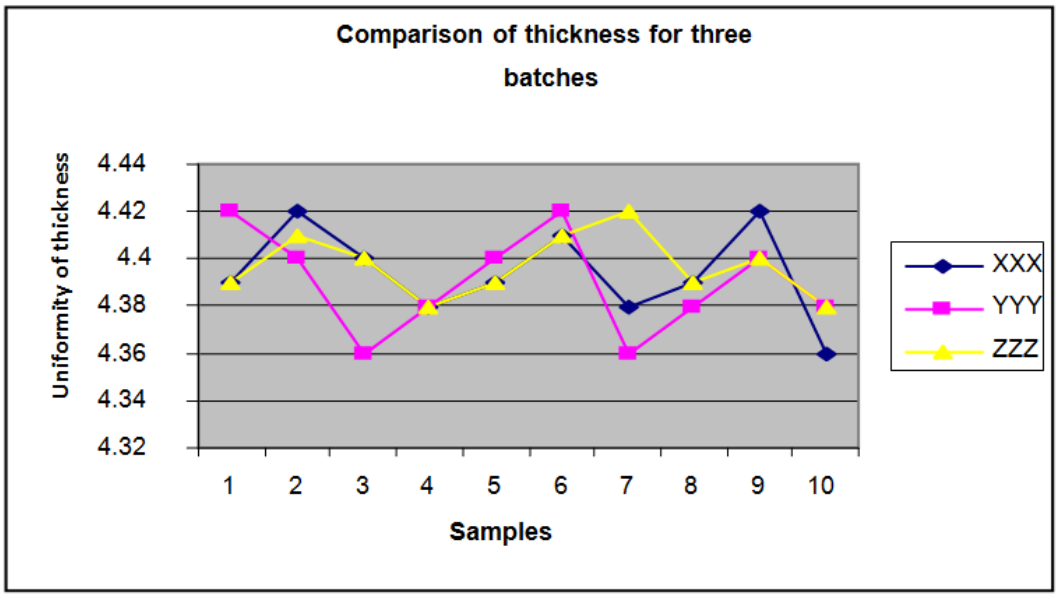
Figure-2

c) Thickness & Hardness studies for three batches

Average Thickness **Acceptance criteria :**
Approx. sample size : 6 Tablets 4.50 mm ± 0.30 mm
Average Hardness **Acceptance criteria**
Approx. sample size : 6 Tablets NLT 4.0 Kp

S.No	Thickness (4.50 mm ± 0.30 mm) Batch number			Hardness (NLT 4.0 Kp) Batch number		
	XXX	YYY	ZZZ	XXX	YYY	ZZZ
01	4.39	4.42	4.39	10.9	12.2	12.8
02	4.42	4.40	4.41	11.2	12.8	11.6
03	4.40	4.36	4.40	12.1	14.5	13.2
04	4.38	4.38	4.38	10.9	13.8	12.8
05	4.39	4.40	4.39	11.6	12.8	11.2
06	4.41	4.42	4.41	12.3	12.2	12.9
07	4.38	4.36	4.42	11.2	13.8	13.2
08	4.39	4.38	4.39	12.9	13.5	12.8
09	4.42	4.40	4.40	11.2	13.5	11.6
10	4.36	4.38	4.38	12.8	13.8	12.2
Avg	**4.39**	**4.39**	**4.39**	**11.71**	**13.29**	**12.43**
Min	**4.36**	**4.36**	**4.38**	**10.9**	**12.2**	**11.2**
Max	**4.42**	**4.42**	**4.42**	**12.8**	**14.5**	**13.2**

Table-39: Thickness & Hardness studies for three batches



Trend chart for thickness

Trend chart for Hardness

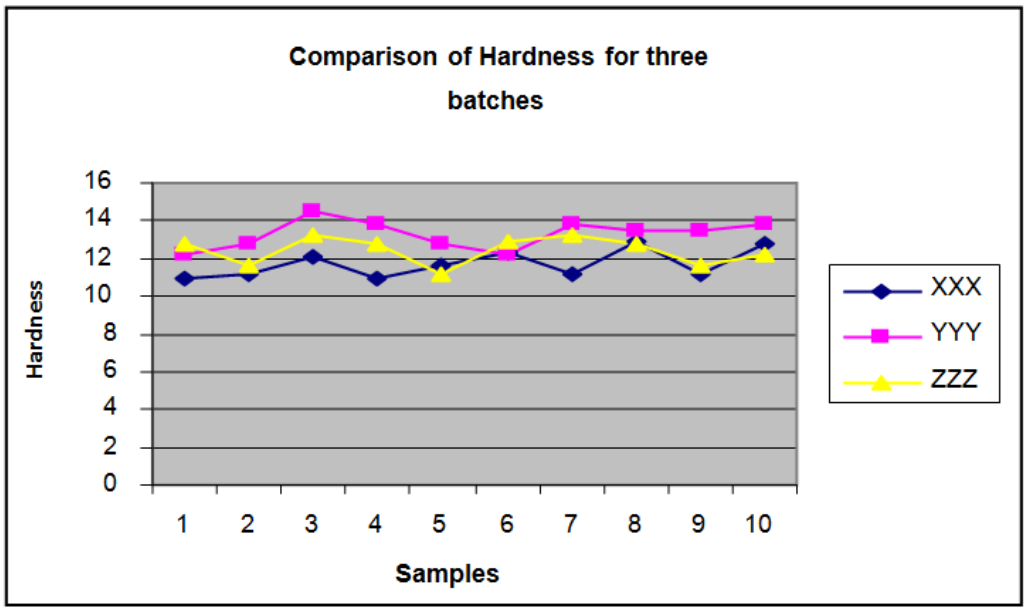


Figure-4

d) Friability:

Approx. sample size : Acceptance criteria: 20 Tablets NMT 1%

Batch no	Friability (%) w/w
XXX	0.16
YYY	0.12
ZZZ	0.21

Table-40: Friability

e) Dissolution and content uniformity studies at different rpm

Dissolution:

Approx. sample size :

3x6 Tablets

Acceptance criteria
NLT 85% in 30 minutes

Content uniformity in %(NEVILAST 30)

S.No.	CONTENT UNIFORMITY STUDIES AT DIFFERENT RPM								
	BATCH NO: XXX								
	12RPM			25 RPM			18 RPM		
	L	S	N	L	S	N	L	S	N
01	101.03	101.37	101.75	97.90	98.34	99.67	100.15	96.93	101.40
02	99.38	99.81	100.36	97.95	98.98	99.36	99.41	96.09	100.35
03	99.55	98.38	100.49	98.04	97.02	99.17	98.49	95.05	99.31
04	102.84	103.31	103.24	98.88	99.94	100.04	99.48	95.08	100.55
05	99.16	100.22	100.49	99.34	98.17	100.18	100.46	95.92	100.18
06	96.81	98.87	99.11	99.62	99.64	100.90	101.34	97.99	102.14
07	97.13	99.23	99.51	100.85	101.00	102.14	99.69	99.73	102.79
08	98.38	98.67	100.03	99.66	100.60	100.66	100.54	97.12	101.44
09	99.32	99.63	100.92	96.07	98.17	98.48	99.91	96.67	100.34
10	97.91	99.03	99.52	95.80	97.85	98.17	10.94	97.65	102.05
Min	**96.81**	**98.38**	**99.11**	**95.80**	**97.02**	**98.17**	**98.49**	**95.05**	**99.31**
Max	**102.84**	**103.31**	**103.24**	**100.85**	**101.00**	**102.14**	**101.34**	**99.73**	**102.79**
Mean	**99.2**	**99.9**	**100.5**	**98.4**	**99.0**	**99.9**	**100**	**96.9**	**101.1**
RSD	**1.8**	**1.5**	**1.2**	**1.6**	**1.3**	**1.2**	**0.8**	**1.3**	**1.1**

Table-41: Content uniformity in %(NEVILAST 30)

Trend chart for content uniformity at different RPM for XXX

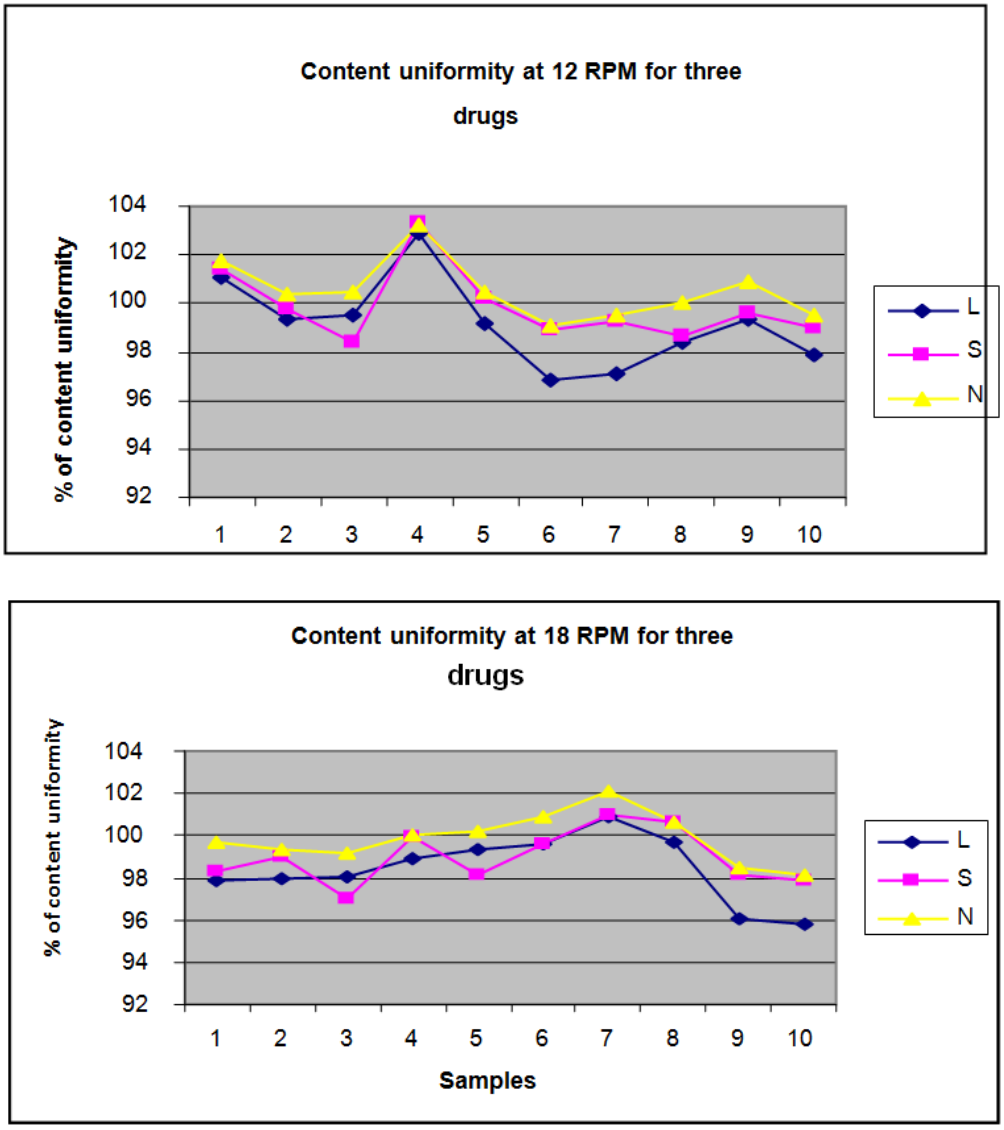


Figure-6

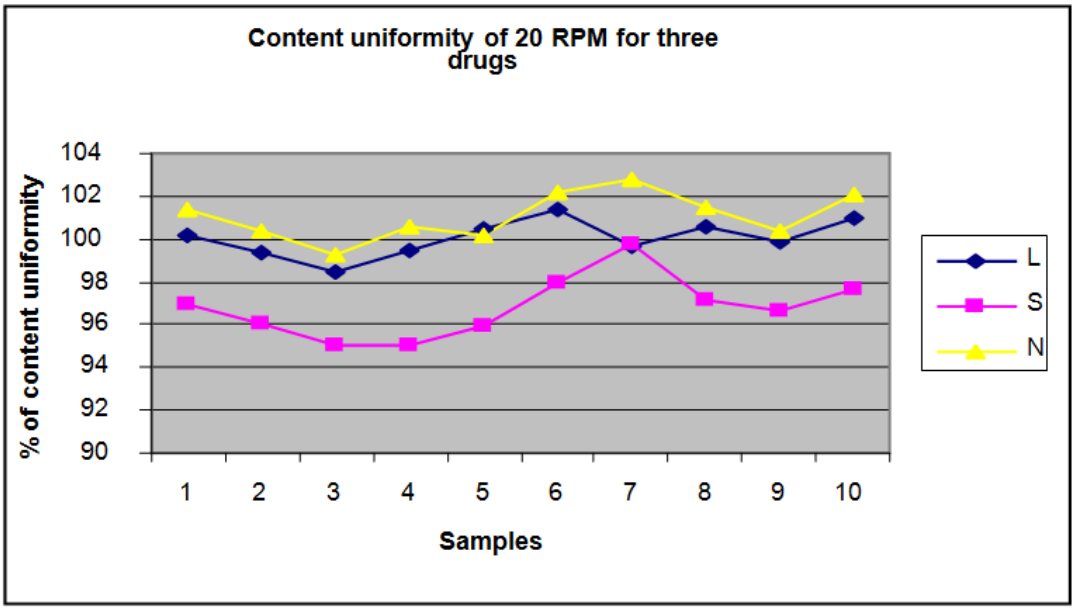


Figure-7

f) Hopper study

The hopper study is conducted at different stages of hopper like full hopper, middle hopper, and end hopper. In this hopper study content uniformity of **NEVILAST 30** are studied.

Full hopper study for three batches

Content uniformity (NEVILAST 30) is NLT 85% in 30 min.

S.No.	Content uniformity results								
	Batch Number								
	XXX			YYY			ZZZ		
	L	S	N	L	S	N	L	S	N
01	98.0	96.2	99.8	97.0	99.2	98.7	98.3	94.9	96.8
02	93.4	93.5	90.7	98.9	101.9	100.8	94.6	95.7	97.7
03	101.8	100.1	103.8	91.4	95.5	89.2	94.6	93.9	95.1
04	95.1	96.1	93.3	100.3	100.5	100.0	98.8	93.5	95.1
05	95.8	92.8	96.9	91.3	95.4	89.1	97.9	95.7	97.6
06	98.1	94.5	99.2	98.7	102.0	100.7	99.3	94.9	96.8
Min	**93.4**	**92.8**	**90.7**	**91.3**	**95.4**	**89.1**	**94.6**	**93.5**	**95.1**
Max	**101.8**	**100.1**	**103.8**	**100.3**	**102.0**	**100.8**	**99.3**	**95.7**	**97.7**

Table-42: Content uniformity (NEVILAST 30) is NLT 85% in 30 min.

Trend chart for content uniformity at Full hopper study

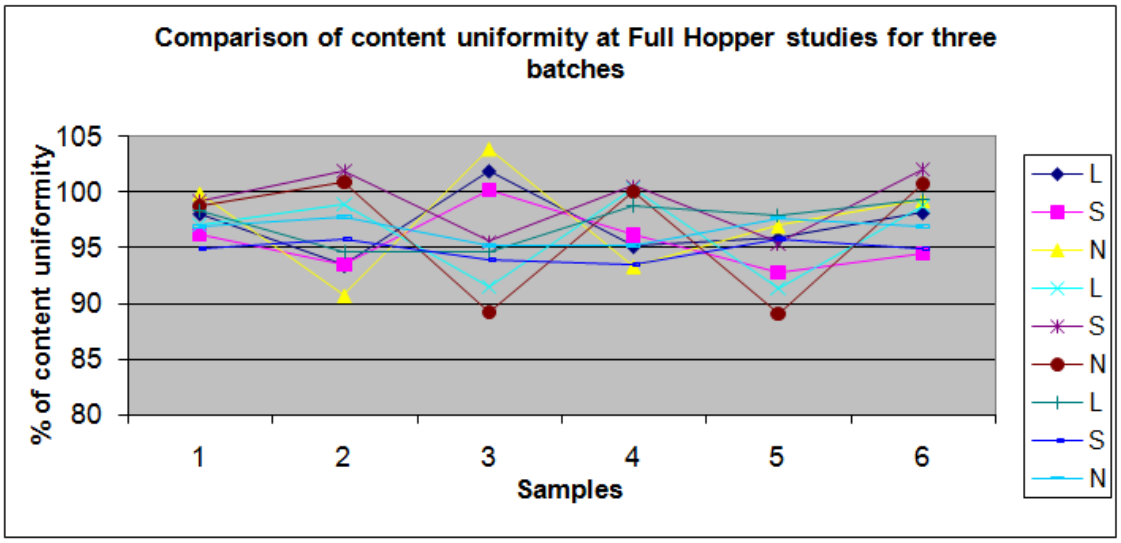


Figure-8

Middle hopper study for three batches
Content uniformity (NEVILAST 30) is NLT 85% in 30 min.

S.No.	Content uniformity results								
	Batch Number								
	XXX			YYY			ZZZ		
	L	S	N	L	S	N	L	S	N
01	98.6	95.0	99.6	87.1	89.2	87.8	100.9	101.6	100.1
02	97.9	96.1	99.8	89.9	93.7	91.0	103.9	104.1	103.1
03	98.1	96.3	100.0	87.1	89.0	87.7	103.7	104.0	102.5
04	96.4	95.3	97.7	94.7	97.3	92.0	96.3	97.0	95.4
05	97.5	96.2	98.0	89.9	93.4	90.8	96.5	97.2	95.7
06	97.5	96.2	98.8	99.9	102.3	97.9	100.9	101.6	100.1
Min	**96.47**	**95.0**	**98.0**	**87.1**	**89.0**	**87.7**	**96.3**	**97.0**	**95.4**
Min	**98.6**	**96.2**	**100.0**	**99.9**	**102.3**	**97.9**	**103.9**	**104.1**	**103.1**

Table-43: Content uniformity (NEVILAST 30) is NLT 85% in 30 min.

Trend chart for content uniformity at Middle Hopper study for three batches

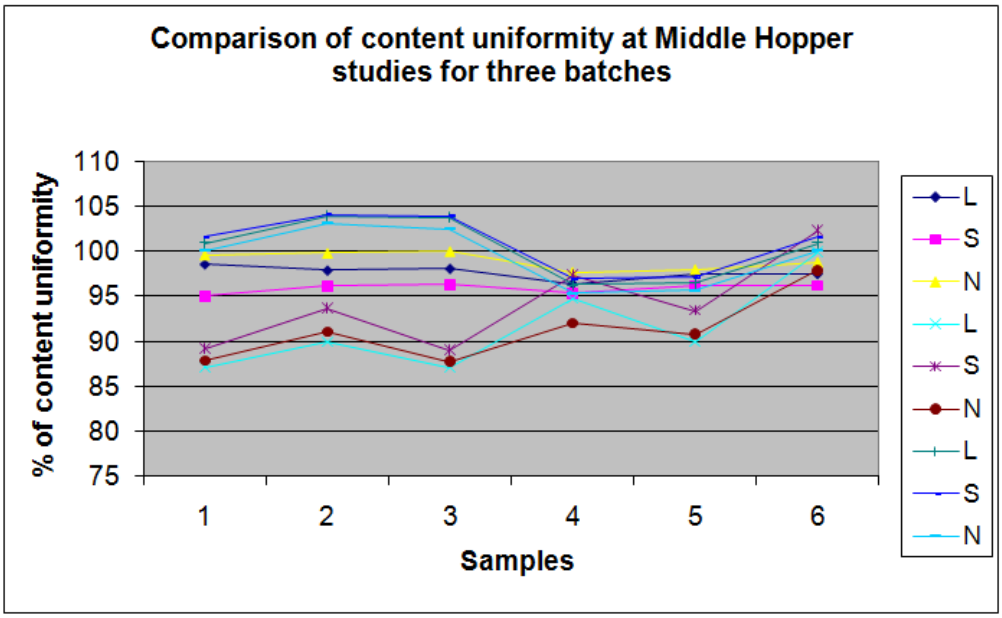


Figure-9

End hopper study for three batches:
Content uniformity (NEVILAST 30) is NLT 85% in 30 min.

S.No.	Content uniformity results								
	Batch Number								
	XXX			YYY			ZZZ		
	L	S	N	L	S	N	L	S	N
01	96.9	95.7	97.4	100.3	100.5	100.0	98.9	98.4	98.2
02	97.9	96.4	98.9	97.5	97.9	95.3	99.0	98.2	98.3
03	94.5	92.7	96.1	101.0	101.6	100.3	105.2	105.8	104.3
04	93.4	92.1	95.3	100.6	101.3	99.8	105.2	105.6	104.4
05	90.5	93.9	93.3	98.7	98.9	99.8	105.3	95.8	98.8
06	87.8	89.4	91.2	98.2	98.4	99.4	98.8	95.4	98.4
Min	**87.8**	**89.4**	**91.2**	**97.5**	**97.9**	**95.3**	**98.8**	**95.4**	**98.2**
Max	**97.9**	**96.4**	**98.9**	**101.0**	**101.6**	**100.3**	**105.3**	**105.8**	**104.4**

Table-44: Content uniformity (NEVILAST 30) is NLT 85% in 30 min.

Trend chart for content uniformity at end Hopper study for three batches

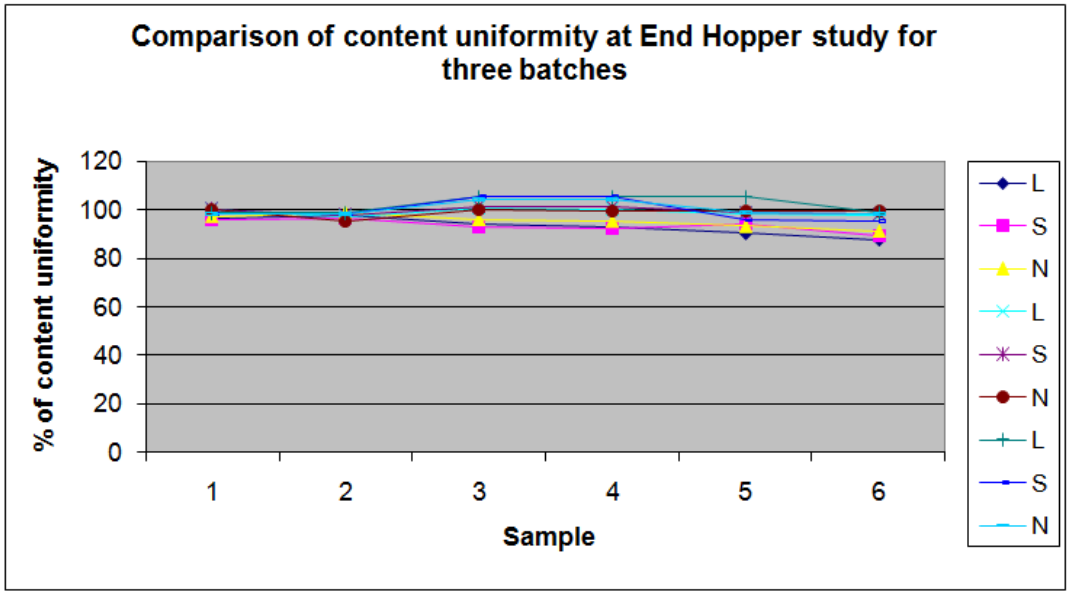


Figure-10

a) Content uniformity, Dissolution of NEVILAST 30 in compressed tablets at different Hardness during compression (Expressed in%)

Low Hardness Tablets: content uniformity in %(NEVILAST-30)

Batch No.	**XXX**					
	Acceptance criteria	**Time(min)**	**MIN.**	**MAX.**	**MEAN**	**%RSD**
A)Lamivudine USP	NLT 85% in 30 minutes	10	65.6	80.4	73.9	8.07
		15	85.5	92.4	89.5	2.65
		20	93.9	98.1	96.7	1.52
		30	97.0	101.2	99.7	1.64
		45	96.2	101.1	98.8	1.91
B)Stavudine USP	NLT 85% in 30 minutes	**Time(min)**	**MIN.**	**MAX.**	**MEAN**	**%RSD**
		10	65.2	80.4	72.5	8.33
		15	87.5	93.9	90.5	2.48
		20	94.7	100.5	98.0	2.08
		30	97.5	102.6	100.7	2.00
		45	97.7	103.7	100.7	2.29
C)Nevirapine USP	NLT 85% in 30 minutes	**Time(min)**	**MIN.**	**MAX.**	**MEAN**	**%RSD**
		10	72.4	82.4	78.3	5.42
		15	87.5	93.1	91.6	2.06
		20	94.7	98.4	96.9	1.23
		30	97.5	100.9	99.3	1.58
		45	97.7	102.4	99.5	1.86

Table -46: Low Hardness Tablets: content uniformity in %(NEVILAST-30)

High Hardness Tablets: Content uniformity in %(NEVILAST 30)

	% of Nevilast 30					
Batch No.	**XXX**					
	Acceptance criteria	**Time(min)**	**MIN.**	**MAX.**	**MEAN**	**%RSD**
A)Lamivudine USP	NLT 85% in 30 minutes	10	65.4	79.2	73.4	7.81
		15	85.2	91.8	88.9	2.59
		20	94.3	98.9	96.6	1.66
		30	85.7	101.0	96.3	5.72
		45	97.2	100.8	99.3	1.54
B)Stavudine	NLT 85% in 30	**Time(min)**	**MIN.**	**MAX.**	**MEAN**	**%RSD**

USP	minutes	10	66.3	77.3	73.7	8.18
		15	88.6	94.8	91.6	2.34
		20	96.1	102.4	99.0	2.32
		30	88.3	104.3	98.6	5.64
		45	99.0	103.7	101.4	1.93
C)Nevirapine USP	NLT 85% in 30 minutes	**Time(min)**	**MIN.**	**MAX.**	**MEAN**	**%RSD**
		10	70.6	81.3	76.9	5.86
		15	87.2	92.5	91.0	2.11
		20	95.3	98.5	96.8	1.50
		30	85.5	101.4	96.3	5.92
		45	97.3	101.3	99.1	1.54

Table-47: High Hardness Tablets: Content uniformity in %(NEVILAST 30)

Dissolution profile of NEVILAST 30:

Batch No.	Dissolution Profile	LAMIVUDINE				STAVUDINE				NEVIRAPINE			
		Min	**Max**	**Mean**	**%RSD**	**Min**	**Max**	**Mean**	**%RSD**	**Min**	**Max**	**Mean**	**%RSD**
XXX	10Min	58.5	83.3	69.0	15.96	57.0	92.2	68.0	16.58	65.1	92.4	72.98	12.17
	15 Min	70.9	94.4	85.0	9.42	69.9	94.7	85.0	9.97	76.3	93.7	86.42	7.15
	20 Min	94.0	98.6	97.0	1.71	93.2	98.0	96.0	1.65	89.8	97.7	95.08	2.72
	30 Min	95.2	102.0	99.0	2.17	93.4	100.1	98.0	2.21	90.4	101.9	97.09	3.59
	45 Min	96.5	106.8	101.0	2.73	95.4	101.5	99.0	2.47	94.7	102.9	99.14	2.79
YYY	10 Min	61.1	89.2	71.0	13.40	62.0	87.7	72.0	11.76	67.1	86.7	74.0	9.73
	15 Min	90.1	95.1	93.0	2.30	92.8	96.3	94.0	1.39	92.2	96.1	94.0	1.41
	20 Min	90.6	99.7	95.0	3.15	90.4	103.0	97.0	4.32	90.7	100.6	96.0	3.77
	30 Min	91.3	99.2	95.0	2.60	90.9	102.0	96.0	3.87	92.3	101.1	96.0	2.83
	45 Min	92.2	99.4	96.0	2.45	91.6	104.6	97.0	4.70	93.2	101.4	97.0	2.83
ZZZ	10 Min	50.3	84.2	69.0	18.26	47.8	81.1	66.0	18.55	55.8	80.7	69.0	12.66
	15 Min	80.2	101.6	91.0	8.08	77.5	97.3	88.0	7.92	79.6	99.9	90.0	7.97
	20 Min	93.0	104.5	98.0	4.29	89.3	100.1	93.0	4.02	92.0	103.7	96.0	4.34
	30 Min	94.3	103.8	98.0	2.33	91.0	98.9	93.0	2.18	25.2	97.6	90.0	22.72
	45 Min	94.3	105.1	99.0	3.39	89.7	98.8	93.0	2.98	93.6	104.3	98.0	3.36

Table-45: Dissolution profile of NEVILAST 30

Acceptance criteria: NLT 85% in 30 min

7. Yield

STAGE	Limit	%Yield								
		XXX			YYY			ZZZ		
		L	S	N	L	S	N	L	S	N
Blending Color less	**98.50 – 100.0%**	99.3	101.6	100.0	99.0	101.2	100.8	98.8	97.8	100.0
Color		99.8	101.9	100.3	100.0	100.5	100.2	98.1	98.9	99.6
Compression	**96-100%**	97.47			98.04			98.12		
Packing	**95-100%**	99.95			99.80			99.85		

Table-48: % Yield of blending, compression, packing

Trend chart for Yield at different stages.

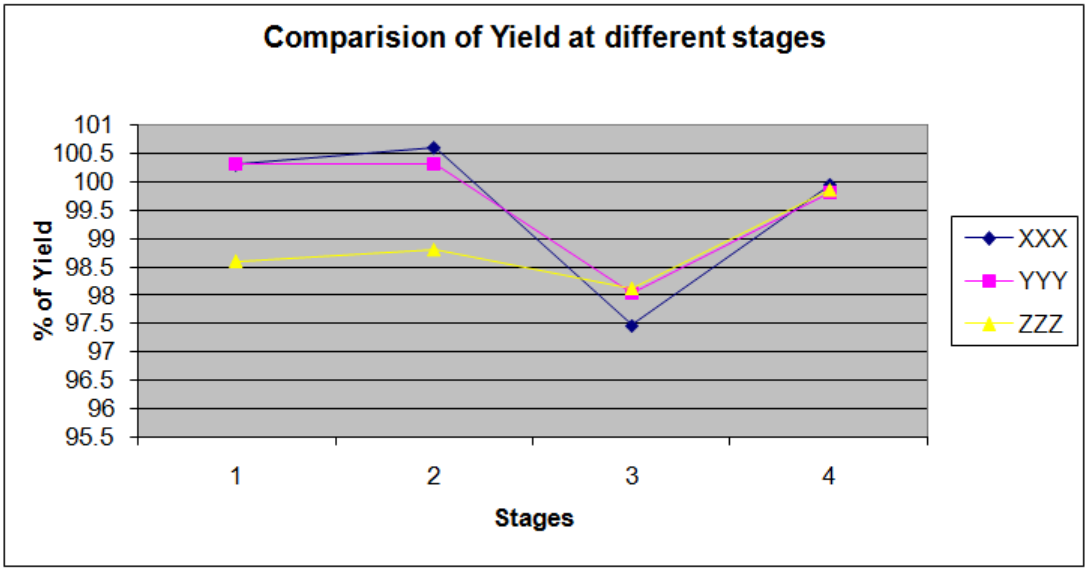


Figure-11

IV. Discussions

PROCESS VALIDATION REPORT OF TABLET DOSAGE FORMS NEVILAST 30 – 700MG

1. Dispensing

As per the analysis report all the raw materials were checked and reported that materials are approved as per specifications for use.

2. Sifting

Presence of foreign particles and hard lumps were observed and such materials are sifted as per specification and reported the material for use.

3. Dry Mixing

After dry mixing blend uniformity of drug for colour & colourless layers of three validation batches as shown in Table-15 & 16 is specified that the results are with in the acceptance criteria.

4. Granulation

Wet granulation: At this stage %LOD for both color and colorless layers of the drug is specified with in the limits of acceptance criteria as per the specification which are mention in Table-17 & 18.

5. Drying

%LOD of the drug of 3lots for both color and colorless layer parts shown in Tables.19-28 for 3three validation batches are specified that the results are with in the acceptance criteria as per specification.

6. Milling

After milling % of granules retained on #16 and #80 mesh in 3lots results are specified that with in the accepted limits. Hence the granulation is similar in three lots.

8. Blending

a) Lubrication

The % of blend uniformity of color and colorless layers of the drug shown in Tables.31-33 for three validation batches are specified with in the limits of acceptance criteria.

b) Blend pooled samples:

Seive analysis, untapped density, tapped density, angle of repose, compressibility index and hausner's ratio shown in Table-19 for three validated batches are specified with in the limits of acceptance criteria.

c) Water content
It is observed that the moisture content of the drug for3 validated batches are with in the acceptance criteria shown in Table-35.

d)Assay
The assay value of lamuvidine, stamudine, nevarupine (NEVILAST-30) in Table-20 are specified with in the limits of acceptance criteria and comparision of trend charts for three batches shown in Figure-1.

9. Compression
a) Group weight variation
The group weight variation is checked for 20 tablets shown in Table-37 for 3 validated batches are within the limits of acceptable criteria and comparision of trend charts for three batches shown in Figure-1.

b) Individual weight variation
It is specified that for each tablet in Table-38 , the individual weight variation are with in the limits of acceptable criteria for three validated batches of the drug and comparision of trend charts for three batches shown in Figure-2.

c) Thickness and Hardness
The checked individual thickness and hardness in Table-39 for 10 tablets are specified with in the limits for 3 validated batches of the drug and comparision of trend charts for three validated batches shown in Figure-3 and 4.

d) Friability
The friability is checked for 20 tablets for 3 validated batches are within the limits of acceptance criteria shown in Table-40.

e) Content uniformity at different RPM
The content uniformity of the drug for 3 validation batches at different RPM i.e., 12, 18, 20rpm are shown in Table-26 well specified and it is in the limits of acceptance.

f) Hopper study
Content uniformity of drug is studied at different levels of the hopper i.e., full, middle and end of the hopper shown in Table-42, 43 and 44 are within the limits of acceptable criteria as per the specification and trend charts for three validated batches shown in Figure-8,9, and 10.

g) Hardness during compression
At different hardness like low and high hardness during compression, it is reported that the content uniformity of the drug for 3 validated batches are specified with in the limits of acceptance criteria. The results were given in table- 46, 47.

h) Dissolution profile:
The dissolution for NEVILAST-30 is shown in TABLE-45. It is reported that the dissolution profile of the drug for three validated batches are specified within the limits of acceptance criteria.

9. Yield
% of yield at different stages of blending, compression and packing are accepted and the results are in tablulated which are specified within the acceptance limits shown in trend chart.

V. Conclusion

This project involves Process validation of NEVILAST-30 which is carried out in Hetero Drugs Ltd. The data provided by trail and executive batches was studied extensively to understand product behaviour and drug verified cessability and available steps of facilities and equipments. These validation batches of commercial scale were taken successfully and setup the inprocess critical parameters for commercial batches.NEVILAST-30 were prepared with in specific for resulting all quality attributes.

The overall successful three consecutive validation batches of NEVILAST-30 verified all predetermined limits and it assure the process to use for production of tablet and it meets the goals. Hence the process is validated.

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Research Article

Neuroprotective And Anti-Alzheimer's Effects Of Plant-Zaga Latifolia

MADHUSUDAN REDDY[1], HARIKIRAN LINGABATHULA[2],RAKESH KUMAR JAT[1]
[1]Department of Pharmacy, Shri Jagdishprasad Jhabarmal Tibrewala University, Jhunjhunu, Rajasthan, India, 333001
[2]Department of Pharmacy, Associate Professor, Princeton College of Pharmacy Narapally, Ghatkesar, Hyderabad
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ABSTRACT:
Neurodegenerative disorder can be described as an irreversible gradual loss of neuronal cell which is essential to perform the normal brain functions and the continuous loss of neuronal cell ultimately leads to brain death. Alzheimer's disease is defined as an irreversible neurological disorder which impairs the cognitive and intellectual function of human brain.
The fresh leaves of Zaga latifolia (ZL) was collected from the local flora in Vellore district, Tamil Nadu India for the Neuroprotective activity of Indian medicinal plants in Alzheimer's disease. The doses (200 mg/kg and 400 mg/kg) of ethanolic extracts of ZL was used for the Neuroprotective activity of Indian medicinal plants in Alzheimer's disease. The tested doses at 200 mg/kg and 400 mg/kg of ethanolic extracts of ZL showed significant neuroprotective behavioral study. These extracts bring back the declined level of brain neurotransmitters like dopamine, glutamate and antioxidant enzymes like catalase, glutathione peroxidase and glutathione reductase.
In vitro neuroprotective activity for ethanolic leaves extracts of Zaga latifolia (ZL) was performed on SH-SY5Y cells. The copper oxide nanoparticles synthesized from the ethanolic leaves extracts of ZL showed very good neuroprotective activity.

Keywords: Neuroprotective, Alzheimer's disease, Zaga latifolia.

INTRODUCTION:

Neurodegenerative disease can be described a disease with an irreversible gradual loss of neuronal cell which is essential to perform the normal brain functions and the continuous loss of neuronal cell ultimately leads to brain death. The neurodegenerative disorder includes Alzheimer's disease, Parkinson's disease, Huntington's disease and Amyotrophic lateral sclerosis (Marcello et al., 2010). The number of dementias affected cases mounts very higher in number in the recent days which is much more than expected and will ascend to over and above sixty five million peoples gets affected by dementia throughout the world before the year 2030 (Korolev, 2014). Dementia is a collective term of medical manifestation characterized by the significant decline in the normal intellectual nature of human brain (Gilman, 2010). Reversible dementia and irreversible dementia are the two major types of dementia. Reversible dementia is also known as pseudo dementia which is caused by the secondary manifestation of any other primary disorders like endocrine or exocrine gland secretion disorders, metabolic disorders, malnutrition or depressions. Alzheimer's disease is defined as an irreversible neurological disorder which impairs the cognitive and intellectual function of human brain. Alzheimer's disease is characterized by a major loss of neuronal cells which disorders the normal function of human brain. At molecular level, Alzheimer's disease is illustrated by the loss of cortical neuronal cells particularly pyramidal cell which is majorly responsible for intellectual and cognitive functions (Mann, 1996; Norfray, 2004). The earlier stage of Alzheimer's disease is characterized by the synaptic dysfunction which is responsible for the transmission of neuronal circuit for normal cognitive functions (Selkoe, 2002). Alzheimer's disease originally affects the neuronal cells of temporal lobe particularly the neuronal cells of hippocampal and entorhinal cortex (Jack et al., 1997).

METHODOLOGY

PREPARATION OF PLANT EXTRACTS

The fresh leaves of Zaga latifolia was washed in running tap water to remove the filth and dust. The hygienic leaves materials were dried over the shadow in a room temperature for about 72 hours. The dried leaves materials were made into

fine particles by using the mechanical grinder. The plant materials were extracted with petroleum ether and ethanol by Soxhlet apparatus for 4 hours and subjected to rotary evaporator to remove the excess solvent. The concentrated petroleum ether and ethanol leaves extract of Zaga latifolia was filtered and collected for further process. The leaf powder of Zaga latifolia (100gm) was successively extracted by Soxhlet apparatus using the petroleum ether and ethanol solvents. The leaves of Zaga latifolia were concentrated in vacuum to afford 7.90gm (7.90%w/w) of dry extract of petroleum ether and 9.60gm (9.60%w/w) of dry extract of ethanol. These extracts were then subjected to preliminary phytochemical tests, in-vitro bioactivity evaluations, neuroprotective pharmacological activity, and this extract is also used to isolate and identify the different phytoconstituents present in selected plants by gas chromatography-mass spectral analysis. These extracts were then subjected to prepare copper oxide nanoparticles.

RESULTS AND DISCUSSION

QUALITATIVE PHYTOCHEMICAL ANALYSIS

Phytochemical screening of the petroleum ether and ethanol leaves extracts of Zaga latifolia (ZLPE and ZLE) by qualitative study showed the presence of phytochemical alkaloids, terpenoids, carbohydrates, proteins, phenolics, anthroquinones, flavonoids, glycosides, saponins and tannins as shown in the Table 1

Table 1: Preliminary phytochemical analysis of AP and OC

S. No	Test name	Procedure	Observation	ZLPE	ZLE
1	Alkaloids	Mayers test	Yellow color	+	+
2	Flavonoids	Lead acetate test	Yellow color	+	+
3	Carbohydrates	Molisch test	Violet ring	+	+
4	Terpenoids	Salkowski's text	Reddish brown	+	+
5	Proteins	Biuret test	Violet color	+	+
6	Saponins	Froth test	Froth making	-	+
7	Anthraquinones	Borntrager's test	Pink color	+	+
8	Tannins	Ferric chloride test	Green color	-	+
9	Steroids	Sulfuric acid test	Green color	+	+
10	Phenols	Lead acetate test	Yellow color	+	+

+ Presence

- Absence

PHYSICOCHEMICAL ANALYSIS OF ZAGA LATIFOLIA

The physico-chemical analysis like total ash, acid insoluble ash, water soluble ash, petroleum ether extractive value, ethyl alcohol extractive value and chloroform extractive value were performed and tabulated as shown in the Table 2 Zaga latifolia (ZL).

Table 2: Physicochemical analysis of leaves of ZL

WHO parameters	Leaves value (%w/w)
Total ash	4.6
Acid insoluble ash	1.23
Water soluble ash	1.65
Petroleum ether extractive value	4.41
Alcohol extractive value	7.27
Chloroform extractive value	1.54

FLUORESCENCE ANALYSIS OF ZAGA LATIFOLIA

The fluorescence analysis for the different leaves were carried out with different chemical reagents to determine the phytochemicals present in it and the results were tabulated as shown in the Table 3 for the leaves of Zaga latifolia (ZL).

Table 3: Fluorescence analysis of leaf powder of zaga latifolia

S. No	Particulars of treatment	Under ordinary light	Under UV light
1	Powder as such	Green	Dark green
2	Powder and Sulphuric acid (1:1)	Yellowish green	Pale green
3	Powder and Nitric acid (1:1)	Greenish yellow	Dark green
4	Powder + NH3	Light green	Dark green
5	Powder + I2	Yellowish green	Green
6	Powder + 5% Ferric chloride	Greenish black	Dark green
7	Powder+ CH3COOH	Greenish yellow	Dark green

DETERMINATION OF TOTAL PHENOLICS CONTENT ZAGA LATIFOLIA

The total phenolics content for the different leaves of Zaga latifolia (ZL) were carried out and tabulated (Mean±SD) as shown in the Table 4. The ethanol extracts of leaves of Zaga latifolia (ZL) have higher phenolics content.

Table 4: Total phenolic content of zaga latifolia

Extracted samples	ZL	
Ethanol	82.49±0.20	
Petroleum ether	64.89±0.28	

DETERMINATION OF TOTAL FLAVONOIDS CONTENT

The total flavonoids content for the different leaves of Zaga latifolia (ZL) were carried out and tabulated (Mean±SD) as shown in the Table 5. The ethanol extracts of leaves of Zaga latifolia (ZL) have higher flavonoids content than the petroleum ether leaves extracts.

Table 5.: Total flavonoid content of ZL and DD

Extracted samples	ZL	
Ethanol	139.54±0.18	
Petroleum ether	74.20±0.86	

DISCUSSION:

The standardization of medicinal plant is very much important to ensure the safetyand quality of medicinal drugs prepared from the plant source. World Health Organization has emphasized the importance of pharmacogenetic analysis of medicinal plants which state that pharmacogenetic analysis is the first and foremost step to ensure the purity, safety and quality of medicinal plant drug materials before commencing any kind of plant materials drug tests.

Zaga latifolia (ZL) have higher phenolic and flavonoids content than the petroleum ether leaves extracts.

It could be concluded that the leaves of Zaga latifolia plant is of phytopharmaceutical significance and this study helps to undertake further studies towards these plants to explore the pharmacological bioactivity profile of Zaga latifolia.

IN VITRO BIOACTIVITY EVALUATIONS

IN VITRO ANTIOXIDANT ACTIVITY

The in vitro antioxidant activity for the petroleum ether and ethanol leaf extracts of Zaga latifolia was performed by DPPH (1, 1- diphenyl-2-picrylhydrazyl) scavenging activity method and the results are tabulated as shown in the Table 6.

The in vitro antioxidant activity is measured by the parameter called IC50 value. The IC50 value is defined as the concentration of the plant extracts required to scavenge 50% of the DPPH radical. The higher antioxidant property is evident by the lower IC50 value and the higher in IC50 value results in the lower antioxidant property (Maisuthisakul et al., 2007).

The ethanol extracts of leaves of Zaga latifolia (ZLE) has higher antioxidant activity than the petroleum ether leaves extract Zaga latifolia (ZLPE).

Table 6: In Vitro Antioxidant Activity of ZL and DD

Extraxt samples	Zaga latifolia (ZL) IC50 ± SD (µg/ml)	
Ethanol extracts	88.12±6.2	
Petroleum ether extracts	116.34±9.2	

Values are expressed in mean ± SD for the four determinations

IN VITRO ANTIDIABETIC ACTIVITY

The in vitro antidiabetic activity of Zaga latifolia and Dalbergia diphaca were performed by alpha-amylase enzyme inhibition method and the results are tabulated as shown in the Table 7. The ethanol extracts of leaves of Zaga latifolia (ZLE) have higher dose dependent antidiabetic activity than the petroleum ether leaves extract of Zaga latifolia (ZLPE).

Table 8: In Vitro Antidiabetic Activity of ZL

Samples	Concentration (µg/ml)	% Inhibition	IC50 (µg/ml)
Acarbose (Standard)	100	34.86 ± 0.3536	339.85 ± 5.9
	200	50.11 ± 0.4805	
	400	60.19 ± 0.3944	
	800	68.33 ± 0.2544	
	1000	74.98 ± 0.4847	
ZLPE	100	25.63 ± 0.3674	687.95 ± 4.97
	200	35.80 ± 0.2691	
	400	39.67 ± 0.3465	
	800	57.94 ± 0.4925	
	1000	63.62 ± 0.4920	
ZLE	100	20.84 ± 0.3864	595.84 ± 4.58
	200	31.95 ± 0.2497	
	400	35.69 ± 0.3847	
	800	52.48 ± 0.4836	

	1000	58.53 ± 0.4658	

Values are expressed in mean ± SEM for the three determinations

IN VITRO ANTI-INFLAMMATORY ACTIVITY

The in vitro anti-inflammatory activity for the petroleum ether and ethanol leaf extracts of Zaga latifolia and Dalbergia diphaca were performed by Human Red Blood Corpuscles membrane stabilizing method and the results are tabulated as shown in the Table 5.10.

Table 9: In Vitro Anti-inflammatory Activity of ZL

Treatment	Absorbance	% Inhibition
Control	0.67 ± 0.43	_
ZLPE	0.48 ± 0.27^{a}	33.97
ZLE	0.32 ± 0.19^{aaa}	57.08
Diclofenac potassium	0.16 ± 0.07^{aaa}	77.41

Values are expressed in mean ± SEM for triplicate experiments. All the data were assessed by student't' test using $^{aaa}P<0.0001$, $^{aa}P<0.001$, $^{a}P<0.05$ values to indicate significant levels compared to control group for the all different extracts at concentration of 1000 mcg/ml.

IN VITRO ANTIMICROBIAL ACTIVITY

The in vitro antimicrobial activity for the petroleum ether and ethanol leaf extracts of Zaga latifolia was performed by agar well diffusion method and the results of in vitro antimicrobial activity for the petroleum ether and ethanol leaf extracts of Zaga latifolia was tabulated as shown in the Table 10. Ethanolic leaves extract Zaga latifolia (ZLE) have higher antimicrobial activity than the petroleum ether leaves extract of Zaga latifolia (ZLPE

The ethanol extracts of leaves of Dalbergia diphaca (DDE) and Zaga latifolia (ZLE) have higher significant ($p<0.0001$) anti- inflammatory activity than the petroleum ether leaves extract of Dalbergia diphaca (DDPE) and Zaga latifolia (ZLPE).

Table 10: In Vitro Antimicrobial Activity of ZL

Organism	Zone of inhibition (mm)		
	Petroleum ether extract	Ethanolic extract	Ampicillin
	Concentration 10mg/ml	Concentration 10mg/ml	Concentration 1mg/ml
	Dose: 0.2ml	Dose: 0.2ml	Dose: 0.2ml

Escherichia coli ATCC 25922	14	17	20
Staphylococcus aureus ATCC 29213	13	16	23
Klebsiela pneumonia ATCC 27738	15	18	22
Pseudomonas aeruginosa ATCC 27853	16	19	21

DISCUSSION

In the current study, the petroleum ether and ethanol leaf extracts of Zaga latifolia was studied for different in-vitro bioactivity evaluations like antidiabetic activity, anti-inflammatory activity, antimicrobial activity and antioxidant activity because the pathological pathway aspects of Alzheimer's disease is very much complex which requires multiple functional drugs like antidiabetic, anti-inflammatory, antimicrobial and antioxidant drugs for the treatment of Alzheimer's disease. The ethanol extracts of leaves of Zaga latifolia (ZLE) have higher antidiabetic activity, anti-inflammatory activity, antimicrobial activity and antioxidant activity than the petroleum ether leaves extract of Zaga latifolia (ZLPE). The different in- vitro bioactivity evaluations proved that the ethanol extracts of leaves of Zaga latifolia (ZLE) have significant pharmacology activity than the petroleum ether extracts of leaves of Zaga latifolia (ZLPE).

PHARMACOLOGICAL ACTIVITY

ACUTE TOXICITY STUDIES

The acute toxicity study for the ethanol leaves extracts of Zaga latifolia (ZL) were studied and tabulated as shown in the Table 11. The ethanol leaves extract of Zaga latifolia (ZL) had not shown up any mortality or any kind of toxic symptoms on mice even at the dosage of 2000 mg/kg body weight through oral route of administration. The guidelines for the acute toxicity studies as per the OECD-423 guidelines suggests that the LD_{50} dosage of above 2000 mg/kg termed as unclassified drugs and ethanol leaves extracts of Zaga latifolia (ZL) were viewed as a secured and non-toxic drug for the other pharmacological studies (Muralidharan et al., 2010). Since the dosage of extracts found to be safe and non-toxic up to 2000 mg/kg, the one-tenth (200 mg/kg) and one-fifth (400mg/kg) dosage of ethanol leaves extracts of Zaga latifolia (ZL) were chosen for the neuroprotective activity study.

Table 11: Individual mortality data of ZL in acute toxicity study

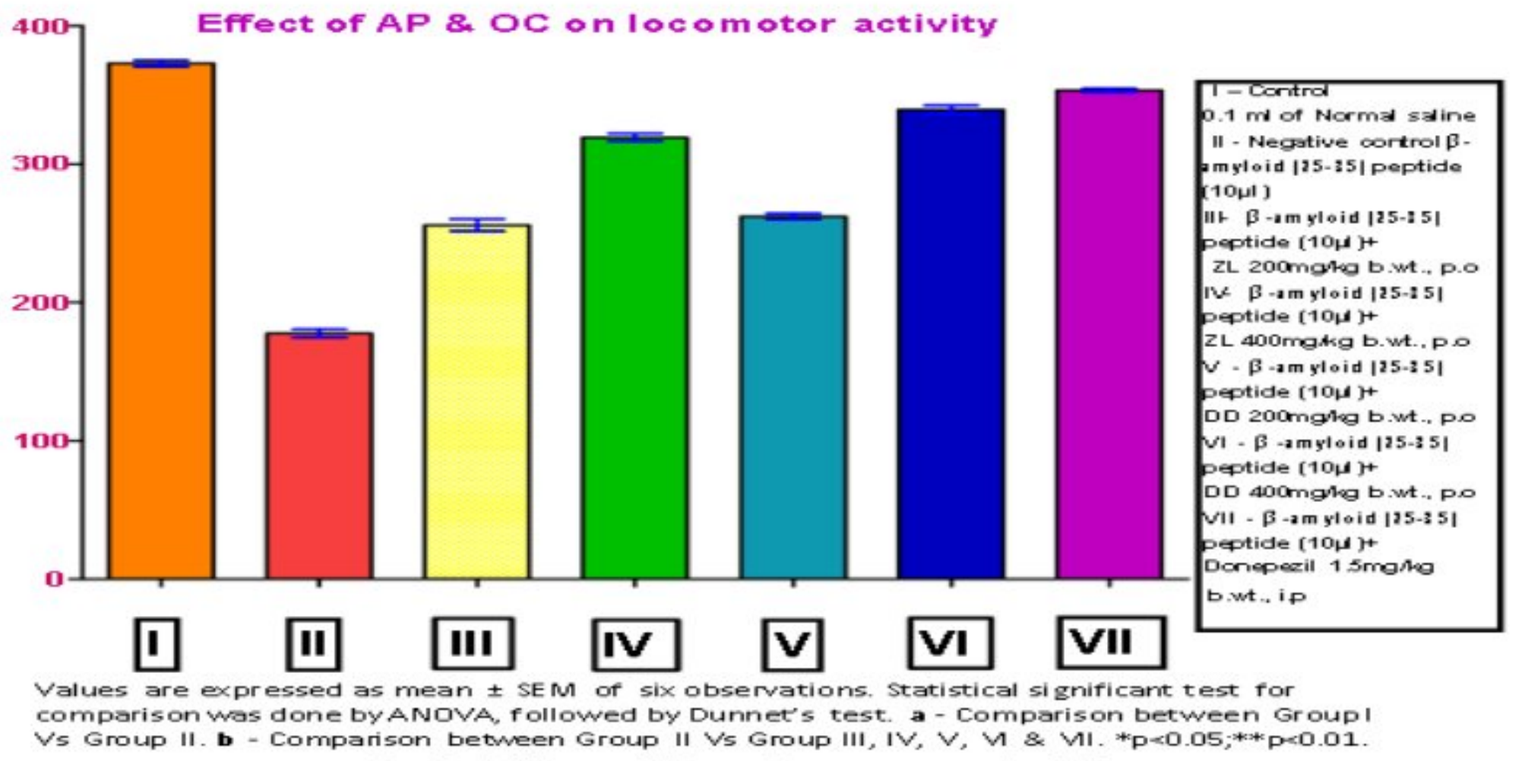
Maximum dose level	Sex	Number of animals died during day of dosing (hr)					Number of animals died during period after dosing (Days)								Deaths
		1/2	1	2	3	4	1	2	3	4	5	6	7	8 - 14	
ZL 2000mg/kg	M/3	0	0	0	0	0	0	0	0	0	0	0	0	0	0/3
	F/3	0	0	0	0	0	0	0	0	0	0	0	0	0	0/3

OPEN FIELD TEST

The open field test for the ethanol leaves extracts of Zaga latifolia (ZL) were studied and the results are tabulated as shown in the Table 12. There is a significant increase in the locomotor activity of ethanol leaves extracts of Dalbergia diphaca (DD) when compared with the locomotor activity of toxic negative control group as shown in the Fig. 1.

Table 12: Effect of ZL and on Locomotor activity

Groups	Treatment	Locomotor activity (Counts/5min)
I	Control 0.1 ml of Normal saline	384.94 ± 3.44
II	Negative control β-amyloid (25-35) peptide (10μL)	189.78 ± 4.39**a
III	β-amyloid (25-35) peptide (10μL)+ ZL 200mg/kg b.wt., p.o	267.94 ± 5.50**b
IV	β-amyloid (25-35) peptide (10μL)+ ZL 400mg/kg b.wt., p.o	329.44 ± 3.71**b
V	β-amyloid (25-35) peptide (10μL)+ DD 200mg/kg b.wt., p.o	274.28 ± 3.42**b
VI	β-amyloid (25-35) peptide (10μL)+ DD 400mg/kg b.wt., p.o	349.44 ± 4.64**b
VII	β-amyloid (25-35) peptide (10μL)+ Donepezil 1.5mg/kg b.wt.,i.p	365.44 ± 2.58**b



Values are expressed as mean ± SEM of six observations. Statistical significant test for comparison was done by ANOVA, followed by Dunnet's test. **a** - Comparison between Group I Vs Group II. **b** - Comparison between Group II Vs Group III, IV, V, VI & VII. *p<0.05;**p<0.01.

Fig.1: Effect of ZL on Locomotor Activity

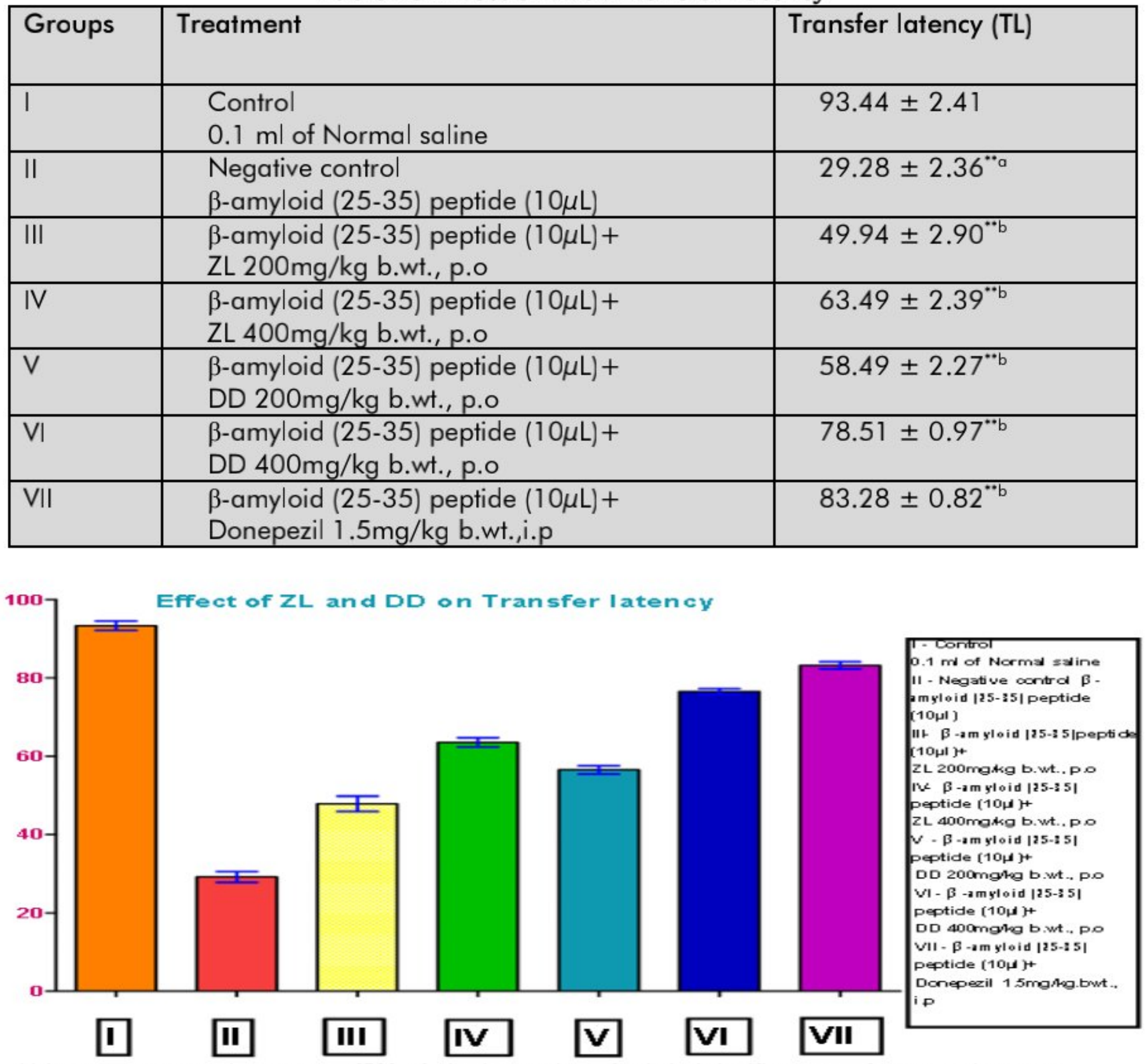
Values are expressed as mean ± SEM of six observations. Statistical significant test for comparison was done by ANOVA, followed by Dunnet's test. a - Comparison between Group I Vs Group II. b - Comparison between Group II Vs Group III, IV, V, VI& VII. *p<0.05;** p<0.01.

ELEVATED PLUS MAZE TEST

The elevated plus maze test for the ethanol leaves extracts of Zaga latifolia (ZL) were studied and the results are tabulated as shown in the Table 13. There is a significant increase in the transfer latency of ethanol leaves extracts of when compared with the transfer latency of toxic negative control group as shown in the Fig. 2.

Table 13: Effect of ZL on Transfer Latency

Groups	Treatment	Transfer latency (TL)
I	Control 0.1 ml of Normal saline	93.44 ± 2.41
II	Negative control β-amyloid (25-35) peptide (10μL)	29.28 ± 2.36**a
III	β-amyloid (25-35) peptide (10μL)+ ZL 200mg/kg b.wt., p.o	49.94 ± 2.90**b
IV	β-amyloid (25-35) peptide (10μL)+ ZL 400mg/kg b.wt., p.o	63.49 ± 2.39**b
V	β-amyloid (25-35) peptide (10μL)+ DD 200mg/kg b.wt., p.o	58.49 ± 2.27**b
VI	β-amyloid (25-35) peptide (10μL)+ DD 400mg/kg b.wt., p.o	78.51 ± 0.97**b
VII	β-amyloid (25-35) peptide (10μL)+ Donepezil 1.5mg/kg b.wt.,i.p	83.28 ± 0.82**b



Values are expressed as mean ± SEM of six observations. Statistical significant test for comparison was done by ANOVA, followed by Dunnet's test. **a** - Comparison between GroupIVs Group II. **b** - Comparison between Group II Vs Group III, IV, V, VI & VII. *p<0.05;**p<0.01.

Fig.2: Effect of ZL on Transfer Latency

ESTIMATION OF ANTIOXIDANT & ACETYLCHOLINESTERASE ENZYME

The antioxidant enzymes like superoxide dismutase, catalase, glutathione peroxidase, glutathione reductase and brain enzyme acetyl cholinesterase (AChE) were estimated for the animals treated with ethanol leaves extracts of Zaga latifolia (ZL) and the results are tabulated as shownin the Table .14.

There is a significant improvement in restoring the decreased level of antioxidant enzymes and the brain enzyme acetyl cholinesterase by the ethanol leaves extracts of Zaga latifolia (ZL) when compared with the other treated groups and toxic negative control group as shown in the Fig. 5.44, Fig. 5.45, Fig. 5.46, Fig 5.47 and Fig 3.

The level of antioxidant enzymes and the brain enzyme acetyl cholinesterase restored by ethanol leaves extracts of Zaga latifolia (ZL).

Table 14: Effect of ZL and DD on Antioxidant & Acetylcholinesterase Enzymes

Groups	Antioxidant enzymes				AchE µmol/min/mg Protein
	SOD U/min/mg Protein	Catalase U/mg Protein	Glutathione peroxidase U/min/mg Protein	Glutathione reductase U/min/mg Protein	
I	7.73±0.25	2.30±0.05	34.73±0.57	36.73±0.63	14.57±0.43
II	2.62±0.13^{**a}	0.83±0.03^{**a}	20.47±0.63^{**a}	20.37±0.67^{**a}	21.27±0.73^{**a}
III	3.73±0.03^{**b}	1.34±0.04^{**b}	23.83±0.67^{**b}	24.63±0.53^{**b}	20.72±0.67^{**b}
IV	5.28±0.07^{**b}	1.93±0.04^{**b}	27.07±0.58^{**b}	27.32±0.35^{**b}	18.47±0.43^{**b}
V	5.12±0.05^{**b}	1.78±0.03^{**b}	25.72±0.73^{**b}	25.73±0.79^{**b}	19.85±0.45^{**b}
VI	6.71±0.06^{**b}	2.26±0.07^{**b}	28.57±0.57^{**b}	30.61±0.47^{**b}	16.26±0.41^{**b}
VII	7.37±0.05^{**b}	2.47±0.05^{**b}	32.62±0.53^{**b}	33.19±0.37^{**b}	14.73±0.35^{**b}

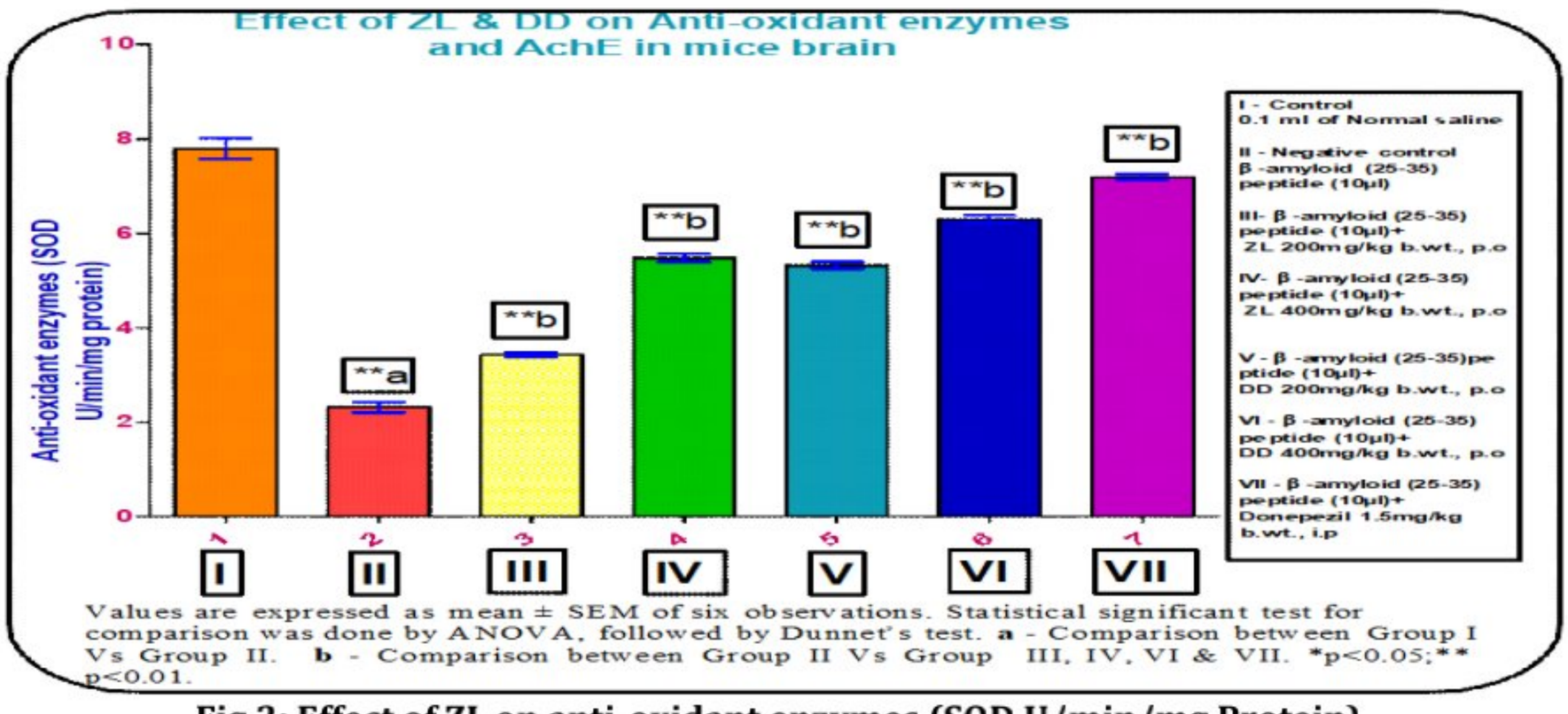


Fig.3: Effect of ZL on anti-oxidant enzymes (SOD U/min/mg Protein)

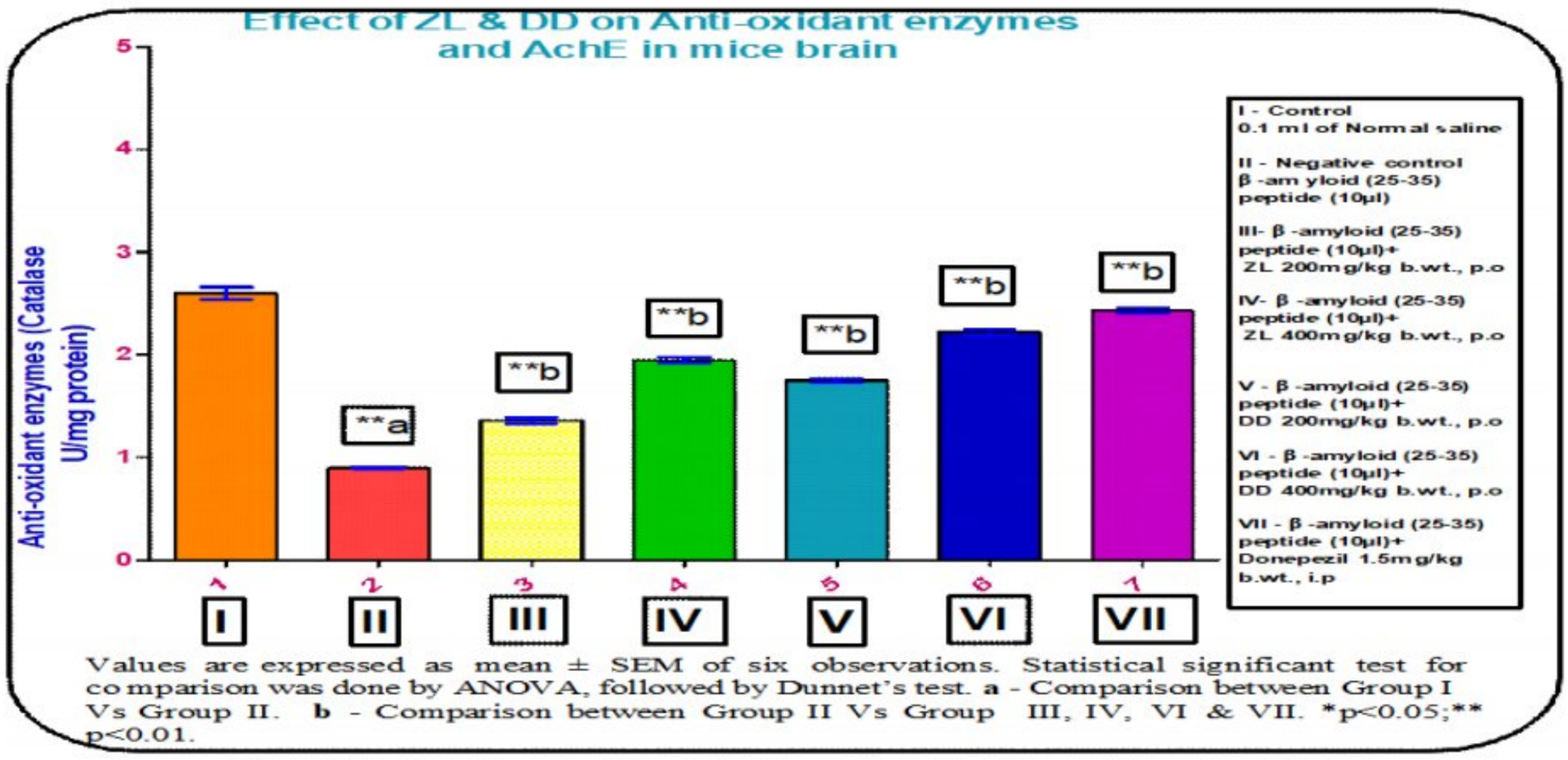


Fig.4: Effect of ZL on anti-oxidant enzymes (Catalase U/mg Protein)

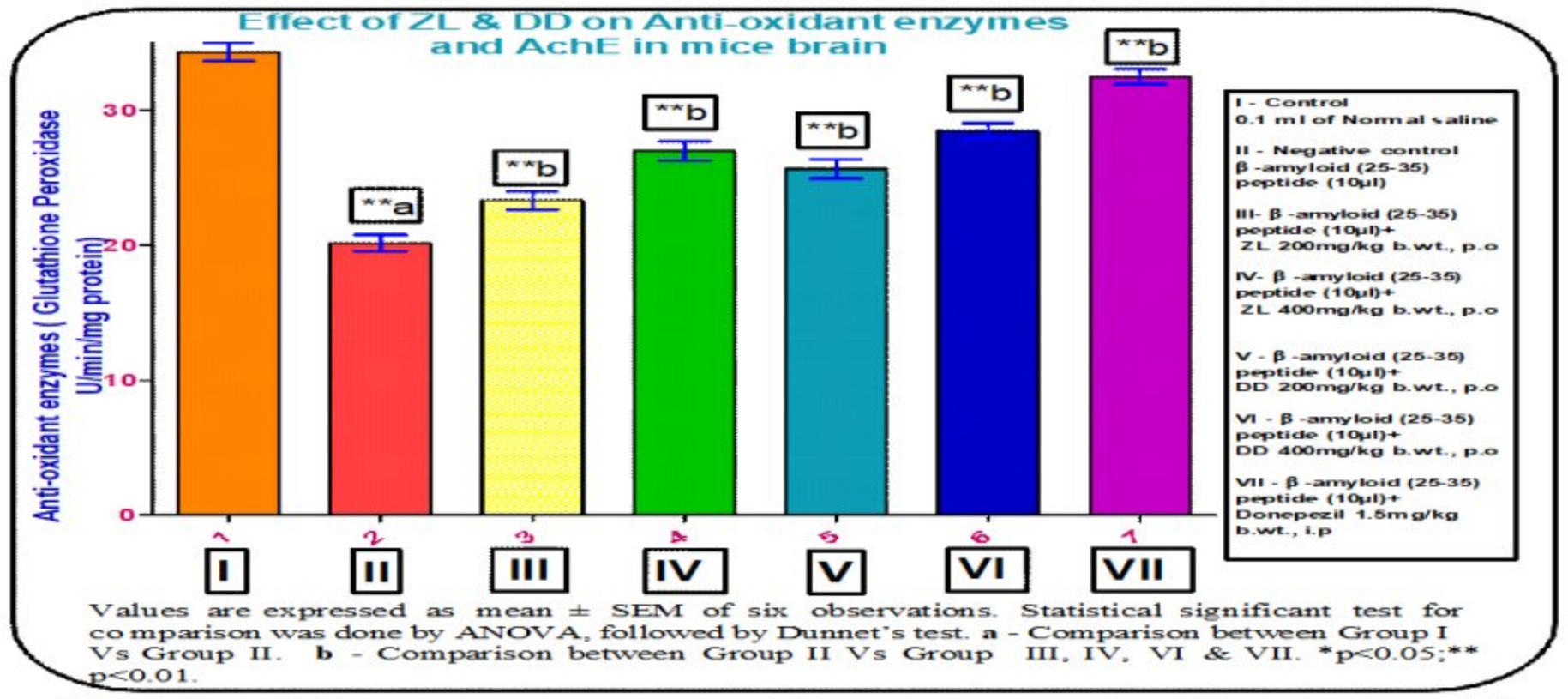


Fig.5: Effect of ZL on anti-oxidant enzymes (Glutathione peroxidase U/min/mg Protein)

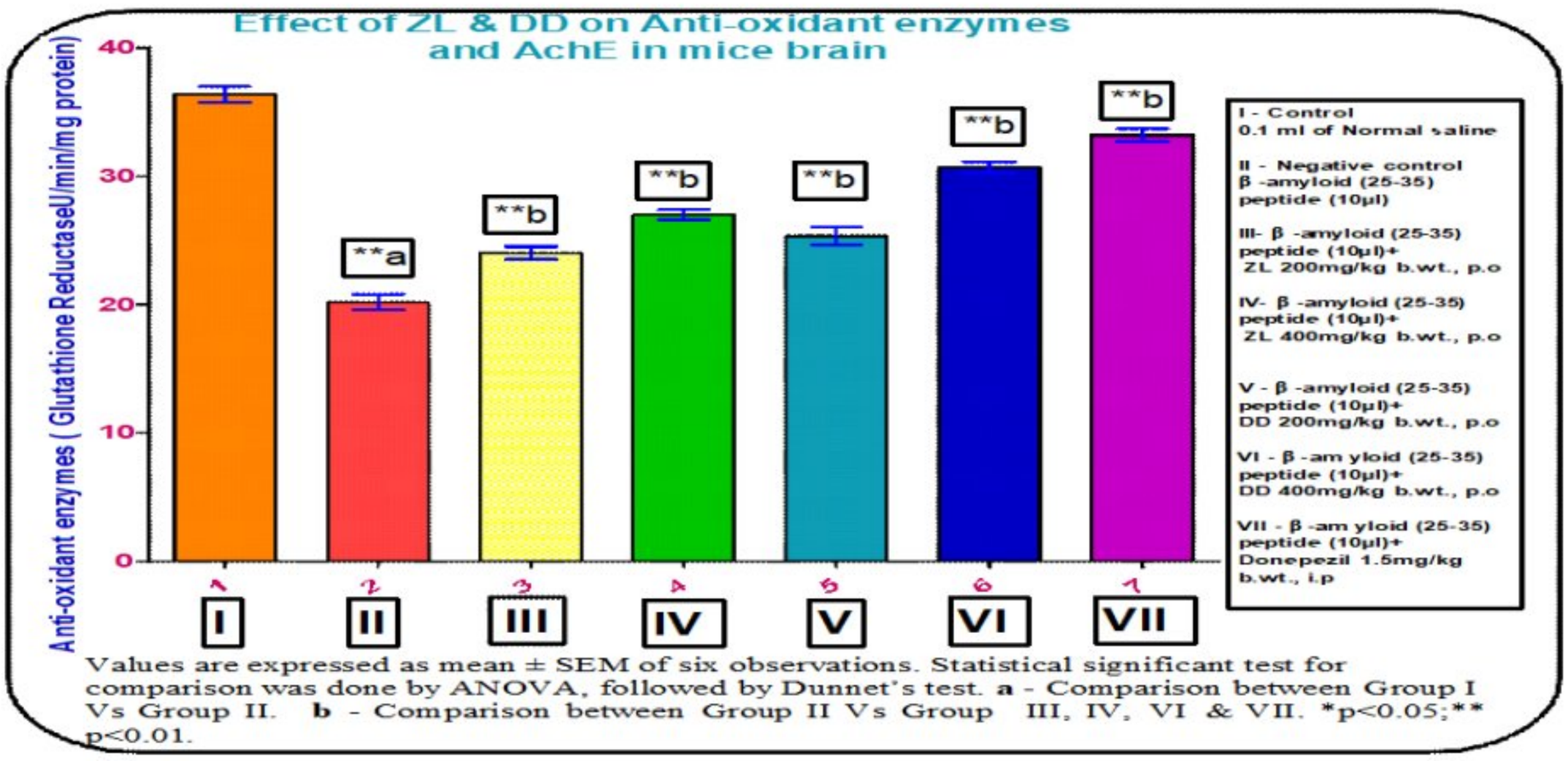


Fig.6: Effect of ZL anti-oxidant enzymes (Glutathione reductase U/min/mg Protein)

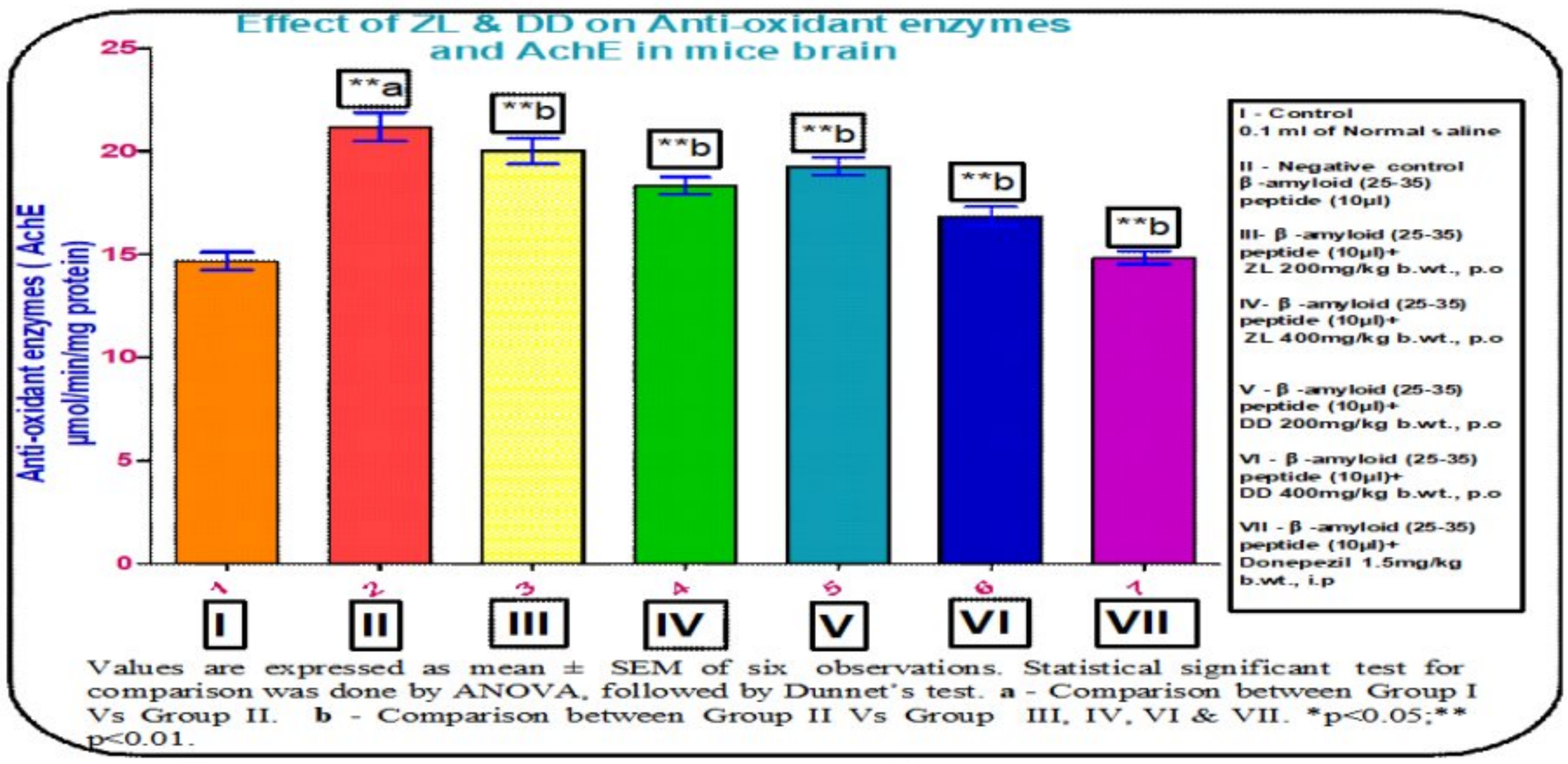


Fig.7: Effect of ZL and DD on Acetylcholinesterase enzyme

SUMMARY AND CONCLUSION

The petroleum ether and ethanol leaf extracts of Zaga latifolia was studied for different in-vitro bioactivity evaluations anti-diabetic activity, anti-inflammatory activity, antimicrobial activity and antioxidant activity because the pathological pathway aspects of Alzheimer's disease is very much complex which requires multiple functional drugs like anti-diabetic, anti-inflammatory, antimicrobial and antioxidant drugs for the treatment of Alzheimer's disease. The ethanol extracts of leaves of Zaga latifolia (ZLE) have higher anti-diabetic activity, anti-inflammatory activity, antimicrobial activity and antioxidant activity than the petroleum ether leaves extracts of Zaga latifolia (ZLPE). The different in-vitro bioactivity evaluations proved that the ethanol extracts of leaves of Zaga latifolia (ZLE) have significant pharmacology activity than the petroleum ether extracts of leaves of and Zaga latifolia (ZLPE).

The ethanol leaves extracts of Zaga latifolia (ZL) had not shown up any mortality or any kind of toxic symptoms on mice even at the dosage of 2000 mg/kg through oral route of administration. Hence, one-tenth (200 mg/kg) and one-fifth (400 mg/kg) dosage were chosen for the neuroprotective activity study. The neuroprotective effect of ethanol extracts of leaves of Zaga latifolia (ZL) on Alzheimer's disease model caused by the β-Amyloid peptide was proved by the in vivo methods through behavioral studies like open field test, elevated plus maze test, water maze task and learned helplessness test. The tested doses at 200 mg/kg and 400 mg/kg of ethanolic extracts of ZL showed significant neuroprotective behavioral study. These extracts bring back the declined level of brain neurotransmitters like dopamine, glutamate and antioxidant enzymes like catalase, glutathione peroxidase and glutathione reductase. Preincubation of ethanol leaves extracts of Zaga latifolia (ZL) with different concentration on human SH-SY5Y neuroblastoma cell lines produced significant neuroprotective activity against the neurotoxicity induced by 6-hydroxydopamine. The in vitro neuroprotective study of the ethanol leaves extracts of ZL have significant neuroprotective activity against the 6-hydroxydopamine on human SH-SY5Y neuroblastoma cell line.

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EXPLORING THE THERAPEUTIC POTENTIAL OF VITEX NEGUNDO: A COMPREHENSIVE REVIEW OF ITS ETHNOMEDICINAL USES AND PHYTO-PHARMACOLOGY AS AN ANTI-INFLAMMATORY HERB

Hariprasad Kadiyam
Asst. Professor, Department of Pharmaceutical Chemistry, Princeton College of Pharmacy, Hyderabad, Telangana, India
G Lavanya
Asst. Professor, Department of Pharmaceutical Chemistry, Princeton College of Pharmacy, Hyderabad, Telangana, India

Abstract - An important medicinal plant with potent anti-inflammatory properties is Vitex negundo. Flavonoids, casticin, chryso-splenol, vitexin, Chrysophenol D, nishindine, and hydrocotylene are the plant's main components. The monoterpenes agnuside, eurostoside, and aucubin are also present. These components contribute to numerous pharmacological activities, including free radical scavenging, hepatoprotective, antioxidant, antinociceptive, and anti-ulcer. The research that has been conducted on this plant over the years into its ethnobotanical claims, ayurvedic properties, chemical constituents, pharmacological activities, analytical studies, and other aspects are discussed in this review.

1 INTRODUCTION

Linn's Vitex negundo (VN). is a member of the Verbenaceae family, more commonly known as Nirgundi. It is a substantial, fragrant shrub; with its typical five-foliate leaf pattern, which can be found in warmer regions of the majority of India and reaches 1500 m in the Western Himalayas. One of the most frequently used plants in Indian medicine is the shrub. It has been claimed to have numerous therapeutic properties. It includes alkaloids, tannins, flavonoids, carbohydrates, and tannins, among other chemical classes. Traditionally, leaves were thought to have sedative and insecticidal properties and were used to cover grain to keep insects away. The leaves' extracts were effective against E. coli and Micrococcus pyogenes var aureus.

It has been hypothesized that the fresh leaves of VN have anti-inflammatory, pain-relieving, antihistamine, membrane-stabilizing, antioxidant, and PG synthesis inhibition properties. This additionally have hostile to ulcer action against piroxicam incited ulcers, most likely by expanding PG levels .Its different dynamic constituents groups different pharmacological exercises.

Ethnobotanical claim: Since antiquity, chasteberry has been used as a female remedy. Roman wives whose husbands were away with the legions spread the aromatic leaves on their couches because one of its properties was to reduce sexual desire. The chasteberry tree was given to it as its name. Chasteberry was used as a food spice in monasteries and was referred to as "Monk's pepper" or "Cloister pepper" due to its alleged ability to increase sexual desire in medieval times. It was also used as a significant European remedy for controlling and regulating the female reproductive system,

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according to tradition. It was once used to make menstruation more regular and treat dysmenorrhea and amenorrhea. It also helped women go through menopause and helped them get pregnant.

Distribution: It originated in India: Jammu and Kashmir, Assam, Bihar, Delhi, Himachal Pradesh, Hubei, Hunan, Jiangsu, Jiangxi, Karnataka, Kerala; States of America: Alabama, Arkansas, Arizona, California, Colorado, Connecticut).

Describe the plant: a medium-sized deciduous shrub that can grow to 3 meters. Drafting 8 is strong. From September to October, it blooms. Insects pollinate the fragrant flowers, which are hermaphrodite (having both male and female organs). The plant can thrive in nutrient-poor soil, prefers light (sandy) and medium (loamy) soils, and it needs well-drained soil. Soils that are alkaline, neutral, or acidic are preferred by the plant. Shade cannot support its growth. It needs soil that is either dry or wet (see Figure 1).

Fig. 1 Leaves and branches of *vitex negundo*

2 PHARMACOLOGICAL STUDIES:

- Human liver cells are shielded from carbon tetrachloride-induced calcium-mediated toxicity by negundoside, an irridoid glycoside extracted from Vitex negundo leaves. Through the inhibition of lipid peroxidation, improved intracellular calcium homeostasis, and inhibition of Calcium dependent proteases, it prevents CYPE1-dependent CCL4 toxicity.
- The anti-oxidant activity of Vitex negundo leaf extract was demonstrated by a decrease in the enzymic antioxidants SOD, CAT, GPX, G6PD, and non-enzymic antioxidants GSH, Vit-C, in complete freund's adjuvant arthritic rats.
- In a cotton pellet granuloma and carrageenan-induced hind paw edema test on albino rats, the anti-inflammatory activity and mechanism of action of Vitex negundo leaf extract were investigated. The study

demonstrated that VN leaf extract prevented plasma MDA (malondialdehyde) levels and oxytocin-induced uterine contractions in rats. This suggests that VN inhibits prostaglandin synthesis and reduces oxidative stress, respectively, to have anti-inflammatory effects against both acute and subacute inflammation.

- The ability of the freeze-dried root extract of Vitex negundo to scavenge the DPPH (1, 1-diphenyl-2-picraylhrazyl) free radical and to prevent hydroxyl radical-mediated damage to deoxyribose was used to investigate the antioxidant activity of the root extract in vitro. While the leaf extract can reduce oxidative stress by reducing lipid peroxidation, it has not altered the activity of endogenous antioxidant enzymes.
- The deffated seeds of Vitex negundo were extracted using chloroform, which produced four triterpenoids with anti-inflammatory properties: 2-beta, 3-alpha-diacetoxy-18-hydroxyoleana-5, 12-dien- 28-oic acid, 3-beta-acetoxyolean-12-en-27-oic acid, 2-alpha, 3-alpha-dihydroxyoleana-5, 12-dien- 28-oic acid
- Portion subordinate histomorphological changes created by VN separate were seen in examples of heart, liver and lung, which showed that the major poisonous attack of VN was on heart. As non-reversible dyspnoea developed, cardiopulmonary arrest was the leading cause of death. Dyspnoea brought on by cardiac toxicity in the form of vascular dilatation and hemorrhage is the leading cause of death.
- The antinociceptive capacity of Vitex negundo linn was investigated through the use of the tail flick test in rats and acetic acid-induced writhing in mice. extract from the leaf that suggests that VN has both central and peripheral analgesic properties. Opioid receptors do not appear to mediate the central analgesic effect.
- It has been hypothesized that the fresh leaves of VN possess anti-inflammatory and pain-relieving properties, which may be mediated through the inhibition of PG synthase, antihistamine, membrane stabilizing, and antioxidant properties. This also has anti-ulcer activity against ulcers caused by piroxicam, possibly by raising PG levels.
- The total polyphenol content of the plant's total methanol extract was standardized. When tested for its anti-inflammatory properties using the carrageenan-induced rat paw edema method, the standardized extract at a dose of 100 mg/kg reduced edema in a manner that was comparable to that of diclofenac sodium (25 mg/kg). The concentrate likewise showed major areas of strength for an extremist searching movement by 1,1-diphenyl-2-picrylhydrazyl technique and caused a critical decrease in the development of thiobarbituric corrosive

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responding substances when assessed for its lipid peroxidation inhibitory movement. The findings strongly suggest that one of the mechanisms underlying its antiinflammatory activity may be radical quenching.

- The minimum inhibitory concentration assay was used to measure the antimicrobial activity. The antimicrobial activity-generating fraction was identified through bioactivity-guided fractionation. The 5-lipoxygenase, 2, 2-diphenyl-1-picrylhydrazyl, and tetrazolium cellular viability assays were used to evaluate the toxicity profile, anti-oxidant activity, and anti-inflammatory activity, respectively. Using the tritiated hypoxanthine incorporation assay, the antimalarial activity of the extracts and isolated compound was also examined against the chloroquine-resistant Gambian FCR-3 strain of Plasmodium falciparum.

3 USES

The entire plant is utilized for therapeutic purposes. Astringent, febrifuge, sedative, tonic, and vemifuge properties make the leaves useful for relieving acute rheumatism joint swelling. Oil made from the leaf juice is applied to sinuses and scrofulous sores, and the juice of the leaves is used to get rid of foetid discharges and worms from ulcers. The dried fruit is used as a vermifuge and to treat angina, colds, coughs, rheumatic conditions, and other conditions.

The fresh berries are ground up into a pulp and used as a tincture to treat paralysis, limb pain, weakness, and other ailments. The root is used to treat colds and rheumatic diseases because it is an expectorant, febrifuge, and tonic. It is believed that the plant as a whole can prevent malaria and treat bacterial dysentery. Antitumor and bactericidal properties have also been demonstrated by the leaf extracts. In grain stores, the leaves are used to repel insects. The leaves' extracts are effective against insects. The new leaves are ignited with grass as a fumigant against mosquitoes. A decoction of the stems is utilized in the treatment of consumes and burns.

4 SAFETY AND TOXICITY:

- Side effects of using *Vitex negundo* are rare. Minor gastrointestinal upset and a mild skin rash with itching have been reported in less than 2% of the women monitored while taking *Vitex negundo.* It is not recommended for use during pregnancy.
- The LD50 was established at 7.58 g/kg, b. w.

5 CONCLUSION

Chemical components and pharmacological studies of Vitex negundo have been thoroughly investigated. Considering the plant's anti-inflammatory, anti-tumor, anti-arthritic, and anti-ulcer activity is crucial. Tissue culture and biotechnology, on the other hand, offer opportunities to increase plant yields of essential chemical constituents. There have been few reports of toxicological and analytical studies. To guarantee the plant's free use, the work could also be carried out in this manner.

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EFFECTIVENESS OF NIFEDIPINE IN MANAGING PRETERM LABOR AMONG SOUTH INDIAN WOMEN: A COMPARATIVE STUDY

Kadasi Sundeep
Assoc. Professor, Department of Pharmaceutical Chemistry, Princeton College of Pharmacy, Hyderabad, Telangana, India
Golla Lavanya
Asst. Professor, Department of Pharmaceutical Chemistry, Princeton College of Pharmacy, Hyderabad, Telangana, India

Abstract- At the CSI Kalyani hospital in Chennai, hydration and bed rest were the first lines of treatment for preterm labor, followed by tocolytics and a nifedipine treatment plan. According to the protocol, 48 patients with singleton pregnancies ranging in age from 28 to 36 weeks were chosen to receive nifedipine. Preterm labor age, gravid status, suppression of preterm labor, pregnancy extension, adverse events, and neonatal outcomes by apgar scores were all found to be comparable in the meta analysis. The findings confirmed that nifedipine is becoming a more popular calcium channel blocker as a safe and potential treatment for preterm labor, particularly when a woman requires a full course of corticosteroids for the maturation of the fetal lung or a transfer to a hospital that can provide neonatal intensive care.
Keywords: Tocolytics, Nifedipine, Preterm labor.

1 INTRODUCTION

Any adverse infant outcome is primarily determined by preterm birth. Numerous studies have demonstrated that using tocolytics during preterm labor significantly extends the delivery time, facilitating the completion of corticosteroids or in utero transfer. Drugs are a big part of making people healthier and making them feel better. However, for them to have the desired effect, they must be safe, effective, and used in a rational manner. Due to the risk of teratogenic effects and physiologic changes caused by pregnancy in the mother, drug treatment during pregnancy is especially concerning. However, it has been demonstrated that human teratogenic drugs only account for less than 1% of all congenital abnormalities.

Due to various chronic diseases and pregnancy-related complications, approximately 8% of pregnant women require ongoing medication. The first calcium channel blockers (CCBs) were developed in the early 1960s to treat angina pectoris. However, since then, the number of indications for CCBs has increased. Angina pectoris, hypertension, supraventricular arrhythmias, subarachnoid hemorrhage, and myocardial infraction are currently treated with calcium channel blockers. CCBs have made their way into obstetrics and gynecology in recent years, particularly in the treatment of preterm labor and preeclampsia5. When compared to betamimetics6,7, their lack of tachyphylaxis and low incidence of side effects account for at least some of their popularity in preterm labor management. The ladies probably going to profit from tocolysis are the individuals who are

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still very preterm, those requiring move to a clinic that can give neonatal serious consideration or the people who have not yet followed through with a full tasks of corticosteroids to advance fetal lung development. As a result, there has been a lot of interest in finding a safe alternative that works just as well, or better, and has fewer side effects in recent years. Numerous medications, including nitric oxide donors (primarily glyceryl trinitrate), ritodrine, magnesium sulfate, atosiban, indomethacin, and nifedipine, are under investigation as tocolytics. Conclusions regarding the impact on neonatal mortality could not be drawn from the insufficient evidence. Whether they have a significant advantage in terms of fetal or neonatal outcome is unknown. There is insufficient evidence to draw reliable conclusions regarding more significant effects on serious neonatal morbidity or prenatal or infant mortality. The ideal tocolytic has not yet been developed, despite extensive research on various pharmacological agents for the treatment of preterm labor. The purpose of this study was to provide the clinical research society with safety data on the maternal and neonatal outcomes of using nifedipine as a tocolytic agent.

2 MATERIAL AND METHODS

Between March 1, 2009 and December 30, 2011, the study was conducted. Eligible participants were women over the age of 18 with singleton pregnancies, a cervical dilatation of no more than 4 centimeters, and intact membranes who were admitted to CSI Kalyani Multi Speciality Hospital for preterm labor between 28 and 36 weeks' gestation. Ultrasonographic examination and the last menstrual period were used to estimate the gestational age. Regular uterine activity, which is defined as regular uterine contractions that occur 4 times per 20 minutes and last 30 seconds each, cervical dilatation of 0–3 cm for nulliparous and 1–3 cm for multiparous, and 50% cervical effacement, were used to diagnose preterm labor. The study was approved by the institutional review board, and prior to enrolling each patient, written informed consent was obtained from each one.

Maternal exclusion criteria included obstetric or medical indication for delivery, documented intrauterine infection, cervical incompetence, known exposure to tocolytic agents during the study pregnancy, and any contraindication to the use of the study medications, such as renal insufficiency, hepatic insufficiency, myasthenia gravis, or preeclampsia. Maternal hypotension, characterized as a pulse <90/50 mm Hg, was likewise cause for rejection. The study did not include any people whose cervical dilatation was less than 4 centimeters.

Nonreassuring fetal status, intrauterine growth restriction, and congenital fetal anomalies were among the fetal exclusion criteria. Before the study was included, a sonogram was taken to check for fetal anomalies, confirm the gestational age, and measure the volume of the amniotic fluid. The patient was given nifedipine with an initial oral loading dose of 30 mg (10 mg sublingual and 20 mg oral) and a maintenance oral dose of 20 mg every 6 hours until tocolysis was achieved after informed consent was obtained. Indomethacin was switched to 25-50 mg every 6

hours, with a maximum daily dose of 200 mg, for 48 hours if there were no uterine contractions within 48 hours. Delivery was considered if membranes ruptured spontaneously within 48 hours of treatment. All of the patients were placed in a head-down position and given an injection of 12 mg of dexamethasone every 12 hours for two doses, followed by weekly injections for the next 36 weeks. Erythromycin was used as antibiotic prophylaxis. In all cases, rest and hydration were used as first-line treatment. Normal saline infusion was given at a rate of 100-150 milliliters per hour after a 200 milliliter initial bolus was given for hydration.

Every woman had her electrocardiogram taken before, during, and after the first 24 hours of drug treatment, as well as every 24 hours up until the seventh day. The oral temperature, heart rate, and pulse of the mother were checked at the screening, before the beginning of the treatment, every 15 minutes for two hours, every eight hours, and every seven days thereafter. Tension in the uterus; were confirmed by external tocodynamometry, which was done every 15 minutes for the first two hours, every hour for the next 22 hours, and twice daily after uterine quiescence. After achieving uterine quiescence, fetal heart rate was measured twice daily after the first two hours, then every 15 minutes for the next 22 hours. Every six hours, clinical signs and symptoms of nifedipine intolerance were checked. The presence of hyperbilirubinemia, umbilical arterial and vein PH values, and a number of neonatal parameters, including weight and apgar score, as well as neonatal complications like infections and hemorrhages, were recorded.

Tocolysis was thought to have occurred when cervical change was absent and uterine activity fell to less than four contractions per hour. Patients could be switched to a different tocolytic regimen if, six hours after admission, they still had uterine activity or their cervical dilatation was greater than 2 centimeters. The study's outcomes included time lost in hours from the beginning of preterm labor to delivery, failure of tocolysis, and recurrence of preterm labor. Tocolytic failure was defined as delivery occurring less than 48 hours after the study agent was initiated. At hospital discharge, each patient was placed on a Tokos Medical Corp., Encino, California, home uterine activity monitor. Twice a day, uterine activity was checked. The research nurses received these data via telephone. Repeat of preterm work was as recently characterized. All oral medications for maintenance were supplied by the pharmacy at the CSI Kalyani Multi Specialty Hospital. From conception to delivery, the outpatient research clinic conducted weekly follow-ups on all patients. Monitor recordings were analyzed and the degree of cervical dilatation was determined at each clinic visit. Tocolytic therapy was initiated once more with nifedipine, which had previously been shown to be effective for that particular patient, in the event that a patient was readmitted due to preterm labor.

All emergent adverse events were measured using SPSS graph pad prism software following the initial and subsequent treatments, and descriptive statistics and qualitative analysis were used to analyze the

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safety and tocolytic outcomes. Additionally, a meta-analysis of tocolysis-related research findings was carried out.

3 CONCLUSION

Tocolytic therapy's current objective, according to meta-analyses, is to delay delivery for at least 48 hours, allowing the mother to be transferred to a tertiary center for delivery, receive corticosteroids, and treat any maternal infection that may be present. These actions have been displayed to decrease neonatal horribleness and mortality and forceful quest for these attainable objectives might be supposed to prompt further upgrades in neonatal result. Nifedipine was found to be more tolerable, to have fewer side effects, and to have better tocolytic efficacy in this study. However, only through a comparison with other tocolytics can the significance be established. It appears likely that Nifedipine will play a larger role in the suppression of preterm labor due to the increasing evidence of its efficacy, safety, and ease of administration.

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OPTIMIZING ROSIGLITAZONE DELIVERY: MICROENCAPSULATION TECHNIQUES FOR CONTROLLED RELEASE

Sangu Jyothi
Asst. Professor, Department of Pharmaceutical Chemistry, Princeton College of Pharmacy, Hyderabad, Telangana, India
Roopani Madhu
Asst. Professor, Department of Pharmaceutical Chemistry, Princeton College of Pharmacy, Hyderabad, Telangana, India

Abstract:
Background: Rosiglitazone belongs to the thiazolidinedione class of drugs. It works by activating the peroxisome proliferator-activated receptors, which lowers blood sugar.
Aim: Rosiglitazone microcapsule design and preparation were the goals of the study.
Methods: Ionic gelation was used to prepare the rosiglitazone microcapsule formulations (F1 through F8) using carbopol – 934, hydroxy propyl methyl cellulose, and sodium carboxy methyl cellulose as rate-controlling polymers in various ratios of 1:1, 1:2, and 1:2.5 (Drug: polymer). FTIR and DSC methods were used to investigate the drug polymer compatibility. Yield, particle size, shape (SEM study), wall thickness, flow property, drug content, loose surface crystal study, swelling index, percentage moisture loss, in vitro drug release and kinetic studies, stability study, and mucoadhesion property were all evaluated for the prepared microcapsules.
Discussions and outcomes: The microcapsules had good flow properties and a small, spherical shape. No such huge physical or synthetic cooperation was happened among medication and polymer. The amount of drugs found to be adequate. F8 produced the highest drug content (84 percent). The drug released from each microcapsule formulation was controlled. When compared to other microcapsule formulations, the microcapsule formulation F8 (0.8 percent Hydroxy propyl cellulose) was found to release the drug at a rate of only 15.003 percent even after 8 hours.
Conclusion: For the safe management of type II diabetes, it could be concluded that the microcapsule formulation F8 is the most optimized formulation.
Keywords: Microcapsules, Rosiglitazone, diabetes, and mucoadhesive.

1 INTRODUCTION

Controlling the rate of drug delivery, maintaining activity duration, and directing drug delivery to a specific tissue are the goals of controlled release drug delivery systems. The drug's residence time at the absorption site is one of the most important aspects of controlled drug release. Enhanced bioavailability, targeted specific delivery to a specific region of the GI tract, maximized absorption rate due to intimate contact with the absorbing membrane, improved drug protection by polymer encapsulation, and longer gut transit time resulting in extended

periods of absorption are all benefits of the development of an effective oral mucoadhesive drug delivery system. The term "microcapsule" refers to a spherical particle whose size ranges from 50 nm to 2 mm and consists of a core substance encased in a polymeric coating. Micro-encapsulation is the process of coating tiny droplets or particles to create small capsules with numerous useful properties. Rosiglitazone belongs to the thiazolidinedione class of drugs. It works by activating the peroxisome proliferator-activated receptors, which lowers blood sugar. Utilizing a variety of mucoadhesive release rate controlling polymers, the study aimed to design, formulate, and prepare rosiglitazone microcapsules with the goals of minimizing the frequency of dosing and minimizing the side effects of rosiglitazone.

2 MATERIALS AND METHOD

The drug Rosiglitazone was obtained as gift sample from Dr. Reddy Lab., Hyderabad. The polymers such are Hydroxy Propyl Methyl Cellulose (HPMC), Hydroxy Propyl Cellulose (HPC) were obtained from Universal Chemical Ltd., Mumbai. All other chemicals and reagents of analytical grade were procured from authorized dealer.

Rosiglitazone microcapsules were made by ionic gelation using carbopol, Hydroxy Propyl Methyl Cellulose (HPMC), Hydroxy Propyl Cellulose (HPC), and Sodium Carboxy Methyl Cellulose (SCMC) in ratios of 1:1, 1:2, and 1:2.5, respectively, for the formulation design. A homogeneous polymer solution was created by dissolving the mucoadhesive polymer (500 mg) and sodium alginate (500 mg) in 32 ml of purified water. To create a smooth, viscous dispersion, the core material, 500 mg of rosiglitazone, was thoroughly mixed into the polymer solution. Using a syringe and needle (gage 20), the resulting solution was extruded drop by drop into 100 milliliters of 4% aqueous calcium chloride solution and stirred at 100 rpm. The microcapsules were separated, washed with water, and dried in an oven at 70°C for 6 hours after being stirred for 15 minutes.

Estimation of the percentage yield the yield was calculated by dividing the weight of the recovered microcapsules by the total weight of the drug and polymer used to prepare that batch by 100.

An IR spectrophotometer (Shimadzu, model 840, Japan) was used to take ambient temperature spectral measurements for the drug polymer interaction study. Using the KBr pressed pellet method, two milligrams of the pure drug, empty microcapsules, and drug-loaded microcapsules were chosen and measured for 100 scans in the range of 4000-400 cm-1.

Surface morphology study using scanning electron microscopy (SEM) The morphological characteristics of the rosiglitazone microcapsule were examined using scanning electron microscopy (Stereo scan S250 MK III, Cambridge, UK). In a gold coating unit, the dried microcapsules were coated with gold at 100 A° in an argon atmosphere. At resolutions of 5 KV X 4000, scanning electron micrographs of microcapsules were observed.

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Measurement of the particle size Xg = 10 [(ni log Xi)/N] was used to calculate the size distribution of the microcapsules using an optical microscope and a calibrated stage micrometer (m). The geometric mean diameter (Xg), the number of particles in the range (ni), the range's midpoint (xi), and the total number of particles (N) are all variables.

Determination of Wall Thickness Hypothetical mean wall thicknesses of the still up in the air by the technique as recommended by Luu et al. utilizing the formula 10: h = r (1-P) d1 / 3 [P d2 + (1-P) d1], where h is the microcapsule's wall thickness in millimeters, r is the arithmetic mean radius in millimeters, d1 is the drug material's density in g/cc, d2 is the polymer material's density in g/cc, and P is the proportion of the medicament Each formulation's wall thickness was measured three times, and the mean and standard deviation are shown.

Drug content estimation Drug stacked microcapsules (100 mg) were powdered and suspended in 100 ml 0.1N HCl arrangement and saved for 24 h. It was blended for 5 min and sifted. At 203 nm, the filtrate's rosiglitazone content was measured spectrophotometrically (UV-visible-1700, Shimadzu, Japan, spectrophotometer).

Loose surface crystals study the rosiglitazone stacked microcapsules arranged by different strategies were assessed by free surface gem study to notice the abundance drug present on the outer layer of microcapsules. 500 mg of microcapsules were shaken for five minutes in 20 ml of double-distilled water from each batch before passing through whatman filter paper. Spectroscopy was used to calculate the percentage of total drug content of the drug lost in the filtrate.

In vitro drug release study a 900 ml volume of 0.1 N HCl was used as the dissolution medium for an in vitro drug release study in a USP XXI peddle-type dissolution test apparatus, and the bath temperature was kept at (371°C) throughout the entire experiment. The pedal speed was changed to 50 rpm. Five milliliters of the sample were removed after a one-hour interval and replaced with five milliliters of fresh medium for Rosiglitazone content analysis using a UV-Visible spectrophotometer at 203 nm. Each release test was conducted in triplicate.

In vitro drug release kinetic study in order to study the exact mechanism of drug release from microcapsules, drug release data was analyzed according to zero order, first order, Higuchi square root and Korsemeyer-Peppas model. The criterion for selecting the most appropriate model was chosen on the basis of goodness of fit test.

Accelerated stability studies were performed according to ICH guidelines. The optimized best formulation was stored in room temperature at (25±1)°C, in oven at (37±1)°C, and at (60±1)°C for a period of 8 weeks. The samples were analyzed for drug content every week by spectrophotometer at 203 nm.

A piece of stomach mucosa measuring less than 2 centimeters was taken from a nearby slaughterhouse for the in vitro wash-off test of mucoadhesion. Adhesive was used to mount it to glass slides. Each wet-rinsed tissue specimen

received approximately one hundred microcapsules, and the support was then hung from the arm of a USP tablet disintegration test machine. The tissue specimen was moved slowly and regularly in the 37°C test fluid taken in the machine's vessel by operating the disintegrating test machine. Toward the finish of each and every one hour up to 10 h the machine was paused and number of microcapsules as yet sticking onto the tissue was counted.

Statistical studies all the values obtained during observation were verified with different statistical methods including one way ANOVA at 5 % level of significance, standard deviation (SD), standard error mean (SEM) and coefficient of variance (CV).

3 CONCLUSION

The microcapsule formulation F8 with 0.8% hydroxyl propyl cellulose is the best optimized formulation because it has maximum encapsulation efficiency and releases the drug in a more controlled manner. As a result, this Rosigltazone microcapsule formulation could be used to safely manage type II diabetes.

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ADVANCEMENTS IN OPHTHALMIC DRUG DELIVERY: A COMPREHENSIVE OVERVIEW

Dr. Sumalatha Reddi
Assoc. Professor, Department of Pharmaceutical Analysis College of Pharmacy, Hyderabad, Telangana, India
Viyyapu Ramesh Naidu
Asst. Professor, Department of Pharmaceutical Analysis College of Pharmacy, Hyderabad, Telangana, India

Abstract - The eye is the body's most distinctive organ. Although a variety of drug delivery systems are used to deliver drugs into the eye, conventional systems have a number of drawbacks. As a result, researchers are looking for new ways to improve contact time, bioavailability, and residence time while also reducing patient discomfort and dose frequency. 90% of all ophthalmic formulations that are currently available are available in conventional dosage forms. The serious issue experienced is quick precorneal drug misfortune. Newer drug delivery systems for ophthalmic administration are the focus of significant research and development efforts with the goal of increasing ocular drug bioavailability. The development of systems that not only prolong the vehicle's contact time at the ocular surface but also slow the drug's elimination is the focus of recent research into ophthalmic drug delivery systems. This includes combining a number of drug delivery technologies. In this audit different new medication conveyance frameworks applied in eye like additions, in-situ gel, liposomes, niosomes, nanoparticles, iontophorosis, corneal safeguards, drug implanted contact focal points, visual wafers and movies and so on, are examined.

1 INTRODUCTION

Any active pharmaceutical ingredient in a dosage form or drug delivery system can be given to a patient via any method of administration. For the purpose of localized ophthalmic therapy, dosage forms are injected into the eye directly. The majority of ocular treatments require the application of ophthalmic active drugs topically to the tissues surrounding the ocular cavity1. When it comes to drug delivery through the eyes, there are a number of different dosage forms that can be utilized.

Eye Physiology: Figure 1 depicts the eye's cross-section. The blood supply and the eye's internal structures are both depicted. The vitreous body, lens, and cornea are all transparent media that lack blood vessels. The aqueous humor transports oxygen and nutrients to these nonvascular tissues. The oxygen tension of the aqueous humor is high, and its osmotic pressure is about the same as that of blood.

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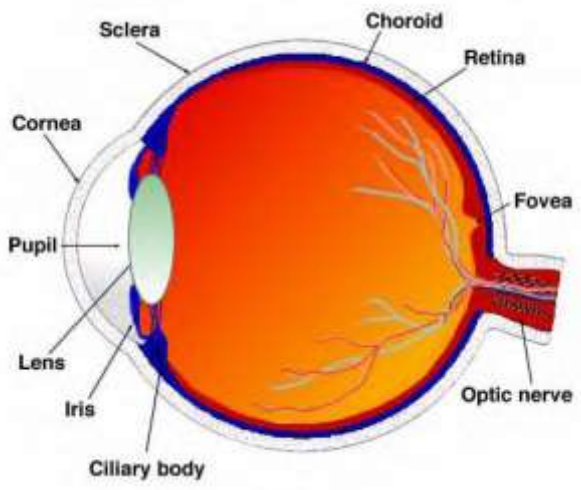

Fig. 1 Cross section of the eye

The cornea also gets some of its oxygen from the air; if oxygen isn't available, the anaerobic metabolism causes an increase in the concentration of lactic acid within the cornea. This can cause enough edema to prevent vision for a short time and cause the cornea to become less transparent. This could happen if a contact lens on the cornea prevents the exchange of oxygen from the air or blocks the capillary blood supply at the limbus.

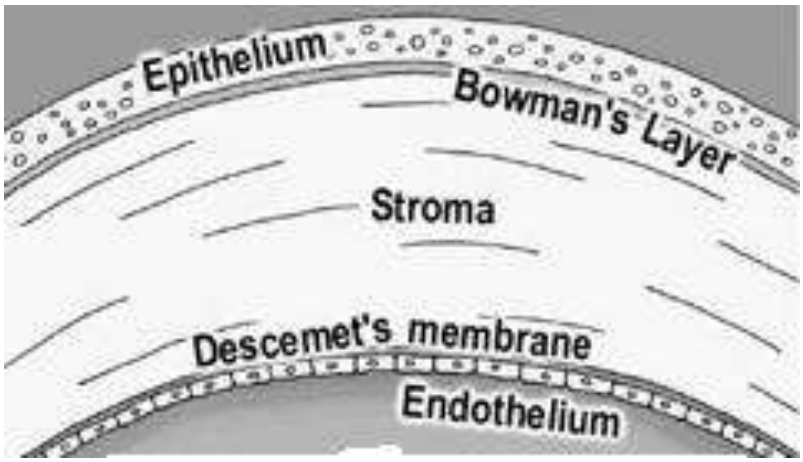

Fig. 2 Section through the through the cornea

A thin epithelial layer that runs parallel to the conjunctiva at the cornea-sclerotic junction covers the cornea; The main part of the cornea is made up of collagen layers that cross each other and are surrounded on both the front and back by elastic laminae. Its posterior surface is covered by an endothelium layer. There are a lot of free nerve endings in the cornea. The tough, fibrous sclera, which is white and opaque, extends posteriorly from the transparent cornea. The eye's constant intra-ocular tension is able to withstand the cornea and sclera.

The four structures that make up the lachrymal apparatus constantly clean and lubricate the eye; naso-lachrymal duct, lachrymal

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sac, lachrymal glands, and canals At a turnover rate of 16% per minute, the lachrymal glands empty the lachrymal fluid onto the upper eyelid's conjunctiva surface. It is swept up by the blinking of the eyelids and washes over the eyeball. The lachrymal sac is compressed by the blinking reflex muscles. The sac expands when these muscles relax, pulling the lachrymal fluid into the lachrymal sacs from the lid edges along the lachrymal canals. The fluid is then pushed down the nasal duct and into the inferior meatus of the nose by gravitational force. As a result, the lachrymal fluid keeps the eyeball from becoming dry and inflamed by constantly irrigating it. How much lachrymal liquid restored by the incessant compulsory squinting developments typically is only adequate to stay up with its vanishing from conjunctiva. Lacrimation, or an excessive production and secretion of lachrymal fluid, can, on the other hand, occur when emotional stress, bright light is shined into the eye, or foreign objects or other irritants enter the eye.

2 VISCOSITY AND OCULAR RESIDENCE

Maintaining acuity is a physiological requirement, which makes it difficult to maintain drug concentrations for long periods of time. This is especially true when it comes to providing a transparent formulation, reducing irritation, and avoiding rapid clearance. Constitution or solvency contemplations limit the grouping of the dynamic to around 2% w/v which likens to a greatest portion of around 500-600 µg in a solitary drop 10. Particulates and ointments can be used to expose the pericorneal area more, but emulsion formulations offer a variety of benefits. If a drug has a high affinity for the oil phase, for instance, in a micro emulsion, it is likely to be cleared before sufficient time has passed for partition from the vehicle to the tissue. Consequently, the depot release is low, though the oil-based formulation may have significant persistence.

3 CONCLUSION AND FUTURE SCOPE

Nanocarrier-based ocular drug delivery technology based on the use of nanoparticles, liposomes, and dendrimers has recently been investigated with the goal of improving frontal ocular drug delivery. It is claimed that these systems have a longer residence time at the ocular surface, minimizing the impact of the body's own natural mechanisms for clearing the eye.

It has been contended that, when joined with controlled drug conveyance, giving medication remedial levels to a delayed time at the site of action ought to be conceivable. In a number of excellent books, the use of nanoparticles and other ocular drug delivery methods has been discussed; The research in this area will undoubtedly gain momentum in the future as well.

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REVOLUTIONIZING DRUG DELIVERY: EXPLORING THE LATEST ADVANCES IN NASAL DRUG ADMINISTRATION TECHNOLOGY

Sagar Gattuvelli
Asst. Professor, Department of Pharmacology Princeton College of Pharmacy, Hyderabad, Telangana, India
M Pavani
Asst. Professor, Department of Pharmacology Princeton College of Pharmacy, Hyderabad, Telangana, India

Abstract - Although the potential of the nose as a route of administration has been known since ancient times, intranasal drug delivery has shown tremendous promise for systemic delivery of therapeutic agents over the past two decades. In many parts of the world, psychotropic and hallucinogenic substances have been snuffed for hundreds of years. The nasal route could be used in place of parenteral delivery due to its dense vasculature and highly permeable structure. Nasal route avoids gut wall enzyme-mediated degradation and hepatic first pass metabolism. The nasal route is simple to use for self-administration without the assistance of medical professionals, and there are no risks of needle stick with nasal administration. Rapid onset of action, a lower risk of overdose, and increased patient compliance are additional benefits of nasal drug delivery systems. However, there are a number of drawbacks to using the nasal route of administration, such as the need for a costly delivery device, dose inaccuracy, the impermeability of the nasal mucosa to drugs that are lipophilic or high molecular weight, and the mucotoxicity that can result from using the formulation for an extended period of time.

1 INTRODUCTION

The nasal drug delivery system is a profitable method for administering both systemic and topical therapies. The nasal cavity's high permeability, high vasculature, and low enzymatic environment make it ideal for systemic drug delivery via the nose with remarkable bioavailability. The nasal's self-administration and lack of invasiveness also draw formulation scientists to the delivery of protein and peptide compounds.

Regardless of the multitude of benefits, the bioavailability of nasally controlled items are impacted by numerous obstructions, for example, physiological, physicochemical and definition boundaries. Passive and active transport pathways 1-2 are followed by nasal absorption. Simple diffusion, facilitated transport, and active transport regulate the absorption mechanism for intramucosal transport.

1.1 Merits:

- Avoidance of hepatic first-pass metabolism
- Absorption rate comparable to that of intravenous medication
- Rapid onset of pharmacological action
- Mode of administration that is user-friendly, painless, and needle-free

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1.2 Demerits:

- Once administered, rapid removal of the therapeutic agent from the site of absorption is difficult
- Pathologic conditions such as cold or allergies may alter significantly the nasal bioavailability

Boosting Nasal Drug Absorption Strategies: Despite its effectiveness for topical, systemic, and central nervous system (CNS) drug delivery, the intranasal route cannot be used for many other medications due to their low nasal bioavailability. In a nutshell, the rapid mucociliary clearance, poor membrane penetration, rapid enzymatic degradation in the nasal cavity, and low drug solubility all limit the bioavailability of drugs administered through the nose.

2 NASAL DRUG DELIVERY TECHNIQUES:

Methods of Delivery: The tendency for anterior versus more uniform distribution achieved by nasal sprays and solutions, for instance, has a significant impact on drug deposition. Although it is likely that more sophisticated presentations will be required for many compounds in development, the straightforward presentation as nasal drops is straightforward, cost-effective, and convenient. Solutions, nasal sprays (solutions and suspensions), gels, and powders are currently the most common delivery methods. Snorting: The success of the procedure probably depends on how the medication is given through the intranasal route. Elicit drug users use a method known as "snorting," in which they take a highly concentrated powder form of a drug like cocaine or heroin and quickly inhale the powder. The powder is deposited on the nasal mucosa as a result, and the drug is quickly absorbed into the bloodstream and brain. In medical therapeutic settings, this method is unlikely to be effective because it requires a skilled and cooperative user.

Utilizing a syringe or dropper, drug delivery as drops: Taking a solubilized medication in its liquid form and dripping a few drops at a time into the nose to allow it to run down onto the nasal mucosa is another method of intranasal drug delivery. This can be done with a syringe or sometimes by using the medication in its packaged form to drip directly into the nose. The majority of generic medications must be extracted from their storage bottle with a syringe in order to use this method. The syringe can then serve as both a dropper and a measuring and dosing instrument.

Spraying or Atomizing Medication Administration: The pharmaceutical industry has recently adopted sprayed or atomized intranasal medication delivery due to improved bioavailability data and issues with usability. A spray tip that breaks up the medication into fine particles as it is sprayed into the nose is combined with a method of measuring a unit dose of medication, such as a syringe or unit dose pump, in this delivery method. It would appear that this method of administration increases the drug's bioavailability and broadens the medication's

distribution throughout the nasal mucosa.

Moreover, the convenience issue makes this nasal showering of drugs far simpler to utilize the patient can have the prescription conveyed from any position (sitting, resting, inclined, on side) and since it just requires one moment to oversee the portion they needn't bother with to be controlled. Last but not least, because the medication is sprayed or atomized into a mist, less of it is likely to escape through the nose and into the surrounding environment. The majority of pharmaceutical nasal medications now come packaged with a spray applicator rather than a dropper for all of these reasons. Additionally, a variety of generic nasal medications can now be administered via syringe-driven or pump-driven spraying devices (atomizers).

Atomized versus nebulized: Systemic drugs can be administered through nebulized medications. Although the lung has a large absorptive surface area, this method of drug delivery has several drawbacks for routine systemic and central nervous system administration. To begin, nebulizers only deliver a small amount of medication to the actual target tissue—the lung—and the rest is lost to the surrounding environment or absorbed by the relatively non-absorptive tissue between the oral opening and the alveoli. The unknown toxicity is even more concerning.

A drug that irritates the mucosa of the nose is not ideal, but it probably isn't all that dangerous if used occasionally. A drug that harms lung tissue is a completely different matter, and doctors should avoid administering a drug to pulmonary tissue until they are certain of its safety. The difference between the time it takes to atomize the same volume (1-2 seconds) and the time it takes to nebulize a medication (many minutes) is, without a doubt, crucial to the majority of the indications for nasal drug delivery discussed on this website. The requirements for the best nasal drug delivery devices include, in conclusion.

Accurate and repeatable dosing

- Consistent delivery to the optimal site of action
- Protection for preservative free formulations in multidose presentations
- Patient independent actuation

3 APPLICATIONS:

- Delivery of non-peptide pharmaceuticals
- Delivery of peptide-based pharmaceuticals
- Delivery of diagnostic drugs

Pharmacies that do not contain peptides: Progesterone, estradiol, propranolol, nitroglycerin, and sodium chromoglyate are examples of drugs that have a high pre-systemic metabolism and can be rapidly absorbed through the nasal mucosa with a systemic bioavailability of about 100%.

Conveyance of peptide-based drugs: Peptides and proteins have a for the most part low oral bioavailability in view of their physico-compound precariousness and weakness to hepato-gastrointestinal first-pass disposal e.g., Insulin, Calcitonin, Pituitary chemicals and so on. For

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such biotechnological products, the nasal route is proving to be the most effective.

3.1 Delivery of Diagnostic:

- Phenol sulfonaphthalein- kidney function
- Secretin- pancreatic disorders
- Pentagastrin- secretory function of gastric acid

4 CONCLUSION

Taking into account the broad premium in nasal medication conveyance and the likely advantages of intranasal organization, it is normal that original nasal items will keep on arriving at the market. They will include novel nasal vaccines that provide enhanced local or systemic infection protection in addition to medications for acute and chronic conditions. It is possible to develop medications that directly target the brain in order to achieve a favorable therapeutic effect in the central nervous system (CNS) with fewer systemic side effects.

However, it was also mentioned that the intranasal route has a few drawbacks that must be overcome in order to create a successful nasal medication. The most crucial factors in nasal drug absorption are physiological conditions and the physicochemical properties of drugs and formulations. Prodrugs, enzymatic inhibitors, absorption enhancers, mucoadhesive drug delivery systems, and new pharmaceutical formulations are some of the most common strategies used today. The relationship between the drug's characteristics, the strategies considered, and the permeation rate is crucial because each drug is a unique case. Nasal drug delivery is becoming more common. However, additional efforts are required to increase this delivery method's popularity and effectiveness.

The special advantages of nasal delivery make it attractive for (i) crisis treatment where rapid onset of action is desired (e.g., pain, migraine, and panic attacks), (ii) systemic delivery of compounds that at present can only be delivered by injection (peptides=pro-Proteins=vaccination), and (iii) direct targeting of the CNS (polar drugs for the treatment of CNS disorders). The nasal route is generating an increasing amount of interest as a route for the administration of

Innovative approaches to overcoming the biological barriers to delivery are being developed so that these opportunities provided by nasal delivery can be fully utilized. Bioadhesive polymers, enzyme inhibitors, penetration enhancers, formulation design, and nasal delivery systems all require an understanding of the biological barriers they seek to overcome. Additionally, appropriate models are required to evaluate new delivery strategies.

These ought to be able to identify any toxic effects of formulations or ingredients, avoiding results that are misleading due to poor experimental design or model selection. Prior to in vivo testing, in vitro optimization should be carried out to fully investigate fundamental concepts and optimize formulations. This will increase the likelihood of success and adhere to the ethical principles of replacement, refinement, and reduction of animal experimentation.

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EXPLORING THE SYNTHESIS STRATEGIES AND PROMISING THERAPEUTIC APPLICATIONS OF PYRIMIDINE DERIVATIVES: A COMPREHENSIVE REVIEW

Zareena Begum Shaik
Asst. Professor, Department of Pharmaceutics, Princeton College of Pharmacy, Hyderabad, Telangana, India
K Bhavani
Asst. Professor, Department of Pharmaceutics, Princeton College of Pharmacy, Hyderabad, Telangana, India

Abstract - The transdermal drug delivery system (TDDS) established itself as an essential component of novel drug delivery systems that utilize a structure as a drug reservoir. Transdermal delivery has become an increasingly accepted method for the administration of both prescription and nonprescription drugs, and a number of drugs have entered the market in this form. The transdermal drug delivery system outperforms traditional drug administration methods in many ways. Ketorolac and tromethamine form a salt known as "ketorolac tromethamine" that is more soluble in water than ketorolac. Nonsteroidal anti-inflammatory medication ketorolac tromethamine is useful for the short-term treatment of moderate to severe pain. The analgesic and anti-inflammatory properties of ketorolac tromethamine are high; administered by mouth. The purpose of this review article is to discuss various aspects of ketorolac administration and its subsequent effects on the human body following administration through a transdermal drug delivery system.

1 INTRODUCTION

The transdermal drug delivery system (TDDS) established itself as an essential component of novel drug delivery systems that utilize a structure as a drug reservoir. Transdermal delivery has become an increasingly accepted method for the administration of both prescription and nonprescription drugs, and a number of drugs have entered the market in this form. The transdermal drug delivery system outperforms traditional drug administration methods in many ways. Ketorolac and tromethamine form a salt known as "ketorolac tromethamine" that is more soluble in water than ketorolac. Nonsteroidal anti-inflammatory medication ketorolac tromethamine is useful for the short-term treatment of moderate to severe pain. The analgesic and anti-inflammatory properties of ketorolac tromethamine are high; administered by mouth. The purpose of this review article is to discuss various aspects of ketorolac administration and its subsequent effects on the human body following administration through a transdermal drug delivery system.

Ketorolac tromethamine drugs entrapped in the form of TDDS: By inhibiting prostaglandin synthesis 14, 15, ketorolac is a nonsteroidal anti-inflammatory drug with potent analgesic and moderate anti-inflammatory effects. The therapeutic effects of ketorolac tromethamine are significantly influenced by their transdermal delivery. A transdermal

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drug delivery system has been studied as an alternative dosage form to eliminate frequent oral dosing regimens and invasive drug therapy like injections.

Notwithstanding the painless treatment and keeping up with the medication blood levels for a lengthy timeframe, the transdermal conveyance framework enjoys a few benefits: It reduces side effects, prevents first-pass metabolism, and makes administration simple. Due to the low skin permeability of the majority of drugs, only a small number of medications can be administered percutaneously despite these benefits. It was discovered that the stratum corneum formed an excellent barrier against skin penetration. Vehicles, penetration enhancers, and electron transport facilitated transdermal systems have all been tested in development as potential solutions to this issue.

Ketorolac tromethamine benefits TDDS: Even though ketorolac was reported to have a 90% oral bioavailability and a very low first-pass metabolism, its short biological half-life (4–6 hours) insisted that many adverse effects, such as pain in the upper abdomen and ulceration in the gastrointestinal tract, should only be taken orally. By that time, the idea of administering ketorolac via transdermal route has already been floated. Using a variety of solution formulations, Yu et al. describe the percutaneous absorption of ketorolac and ketorolac tromethamine in Rhesus monkeys. Propylene glycol and oleic acid and propylene glycol and linoleic acid were found to improve ketorolac and ketorolac tromethamine's percutaneous absorption from vehicles. Within eight hours, high C max values were achieved.

Additional adverse experiences reported occasionally (< 1% in patients taking Ketorolac in clinical trials) include:

1. Body as a Whole: fever, infections, sepsis
2. Cardiovascular: congestive heart failure, palpitation, pallor, tachycardia, syncope
3. Dermatologic: alopecia, photosensitivity, urticaria
4. Gastrointestinal: anorexia, dry mouth, eructation, esophagitis, excessive thirst, gastritis, glossitis, hematemesis, hepatitis, increased appetite, jaundice, melena, rectal bleeding
5. Hemic and Lymphatic: ecchymosis, eosinophilia, epistaxis, leukopenia, thrombocytopenia
6. Metabolic and Nutritional: weight change
7. Nervous System: abnormal dreams, abnormal thinking, anxiety, asthenia, confusion, depression, euphoria, extrapyramidal symptoms, hallucinations, hyperkinesis, inability to concentrate, insomnia, nervousness, paresthesia, somnolence, stupor, tremors, vertigo, malaise
8. Reproductive, female: infertility
9. Respiratory: asthma, cough, dyspnea, pulmonary edema, rhinitis
10. Special Senses: abnormal taste, abnormal vision, blurred vision, hearing loss
11. Urogenital: cystitis, dysuria, hematuria, increased urinary frequency, interstitial nephritis,

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oliguria/polyuria, proteinuria, renal failure, urinary retention.

Fundamental safeguard taken for a patient: Ketorolac may occasionally result in serious (rarely fatal) stomach/intestinal bleeding. Additionally, blood clots have formed as a result of ketorolac-related medications, resulting in serious and even fatal heart attacks and strokes. Ketorolac should not be given to pregnant women, nursing mothers, people with stomach/intestinal problems (such as bleeding ulcers), severe kidney problems, severe water loss (dehydration), or bleeding/ clotting issues. It should not be taken before, during, or after heart bypass surgery or any other surgery. Ketorolac should not be taken in conjunction with other NSAIDs or aspirin in high doses.

2 CONCLUSION

Since the 1800s, the transdermal route has been widely used as a safe and efficient drug delivery method. The transdermal route is increasingly being accepted as a method of drug administration due to recent technological advancements and the capability to apply the medication to the site of action without rupturing the skin membrane. One of the pharmaceutical industry's fastest-growing segments is transdermal drug delivery technologies. Scientists around the world are taking advantage of their potential role in controlled release with a high success rate. As a result, the idea of administering a drug through the transdermal route approaches the successful enhancement of a drug like ketorolac tromethamine. As if its easy availability and low risk of side effects make it a good transdermal drug delivery system for analgesic administration.

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EXPLORING THE THERAPEUTIC POTENTIAL OF POLYOZEILLIN AS AN ANTI-PLATELET AGENT: IN VITRO AND IN VIVO STUDIES

Dr. Kokkula Satyanarayana
Professor, Department of Pharmacognosy, Princeton College of Pharmacy, Hyderabad, Telangana, India
Sunitha Chintala
Assoc. Professor, Department of Pharmacognosy, Princeton College of Pharmacy, Hyderabad, Telangana, India

Abstract - Purpose: In various peripheral vascular diseases, thrombosis and thromboembolic occlusions of blood vessels are a major complication. In the treatment of atherothrombosis, inhibitors of platelet function are recognized as essential tools. As a result, a wide range of vascular diseases came to rely on it as their primary treatment. A major component of the edible mushroom Polyozellus multiplex, polyozellin (POZ), was found to have anti-inflammatory, anti-oxidant, and anti-angiogenesis properties. However, POZ's anti-platelet effect has not yet been examined. Methods: In our review, the counter platelet exercises of POZ were estimated by thrombin-or collagen-actuated platelet accumulation in vitro, adenosine diphosphate (ADP)- prompted platelet conglomeration in vivo, and the clots arrangement in vivo.
Results: POZ really repressed the platelet total not just in vitro utilizing newly secluded human platelets, yet additionally in vivo thrombin or collagen-actuated platelet conglomeration. In vivo pulmonary embolism and arterial thrombosis models, POZ's enhanced anti-thrombotic effect was in line with its in vitro anti-platelet activities.
Conclusion: Based on these findings, POZ may be useful in the development of drug candidates or functional foods for the non-side effect-free treatment of cardiovascular diseases.

1 INTRODUCTION

The blood cells known as platelets are involved in the human body's primary hemostatic mechanism. All of the functions of platelets require their activation, which can begin with an endothelial injury that exposes subendothelial structures to the blood flow. The communication of platelets each other which implies collection has the last reason to deliver a platelet clots that is the essential hemostatic fitting. Anti-platelet agents have also been used clinically in patients who are at risk for brain ischemia, unstable angina, and acute myocardial infarction because platelet aggregation plays a crucial role in the pathophysiology of thrombotic diseases. As a result, it has been established that the relationship between platelets and blood vessels plays a significant role in the onset of thrombosis and cardiovascular diseases. In arterial thrombosis, uncontrolled platelet aggregation is critical and can lead to life-threatening conditions like heart attacks, unstable angina, and re-occlusion following angioplasty. As a result, a potential strategy for treating and preventing these cardiovascular diseases could be to inhibit platelet aggregation.

In Korea and Japan, Polyozellus multiplex (Thelephoraceae) is a wild edible black mushroom. Especially in Korea, this is harvested in the early fall and blanched in boiling water before being eaten. The chemical structures of P. multiplex constituents like kynapsin-12, -13, and -28, thelephoric acid, and polyozellin (POZ) were identified in the previous study. Additionally, the biological activities were evaluated. For instance, the inhibitory effects of kynapcin-12, -13, and -28 on prolyl endopeptidase were discovered. In vitro, members of the human cytochrome

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P450 family were inhibited in a dose- and time-dependent manner by thelephoric acid. Both the lipopolysaccharide (LPS)-induced activation of nuclear factor-B (NF-B) and c-Jun N-terminal kinase (JNK) in the mouse macrophage cell line Raw 264.7 and the anti-cancer effect of POZ on the mouse hepatoma cell line Hepa1c1c7 were inhibited by POZ. In addition, POZ reduced the production of interleukin-8 (IL-8) and matrix metalloproteinase-7 (MMP-7) in the human intestinal epithelial cell line HT-29, which is mediated by tumor necrosis factor (TNF).

However, the anti-coagulant and anti-platelet properties of POZ remain the subject of sporadic reports that require further investigation. Since recent studies suggested that POZ could be an anti-oxidant and an anti-inflammatory agent, it was anticipated that POZ would demonstrate its anti-platelet and anticoagulant properties. In this study, we looked at how POZ affected thrombus formation and platelet aggregation in both in vitro and in vivo models.

2 MATERIALS AND METHODS

2.1 Reagents

Thrombin, collagen, epinephrine, adenosine diphosphate (ADP) were obtained from Sigma (St. Louis, MO).

2.2 Plant Material, Isolation, and Identification Polyozellus multiplex (PM) was collected in September 2001 at Mt. Odaesan in Gangwon-do, Korea, and Prof. Kyung-Sik Song at Kyungpook National University was the one who identified it. At Kyungpook National University's Laboratory of Natural Products Medicine, a voucher specimen (NPM-PM-2001) was deposited. After being refluxed twice with MeOH for three hours on the dried fruiting body of PM (1.0 kg), the extract was filtered and concentrated to dryness using a rotary evaporator (EYELA, Tokyo, Japan). Organic solvents such as benzene, CHCl3, and EtOAc were used to partition the 204.0 g methanolic extract that was suspended in distilled water. The residue (1.2 g) was suspended in 500 mL of MeOH after the EtOAc soluble fraction (2.1 g) was washed with EtOAc (100 mL). The suspension was then centrifuged for five minutes at 3,000 g. The accelerate was disposed of and the supernatant was concentrated. Senshu Pak ODS high performance liquid chromatography (HPLC) was used to further purify the resulting residue. Using MeOH to elute: Compound 1 (512.0 mg) was produced as a dark green powder when H2O = 65:10 and 1% acetic acid were incorporated. The isolated compound's NMR spectral data were compared to those in the reference to determine its chemical structure.

3 ANIMALS AND HUSBANDRY

After a 12-day acclimatization period, male C57BL/6 mice (6 to 7 weeks old, approximately 27g in body weight) purchased from Orient Bio Co. (Sungnam, Korea) were used in this study. Five animals were housed in a polycarbonate cage with a 12:12 hour light/dark cycle and controlled temperatures of 20 to 25 degrees Celsius and 40 to 45 percent humidity. Animals were given a standard diet of rodent pellets and free access to water during acclimatization. In accordance with Kyungpook National University's (IRB No.) Guidelines for the Care and Use of Laboratory Animals, all animals were treated. KNU 2012-13).

Culture in Cells Cambrex Bio Science, Charles City, Iowa, provided the primary HUVECs, which were then cared for as previously described. HUVECs were used in all experiments from passage 3 to passage 5.

Ex vivo clotting time after mice were fasted overnight, POZ (1.8, 44, 8.8, or 17.5 mg/mouse) was given intravenously (i.v.) in Tris-buffered saline (TBS). injection. For the purpose of determining the ex vivo activated partial thromboplastin time (aPTT) and prothrombin time (PT) in vivo one hour after administration, 0.1 milliliters of arterial blood samples were taken out and

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dissolved in 3.8% Na-citrate (1/10, v/v). Using a Thrombotimer (Behnk Elektronik, Norderstedt, Germany), aPTT and PT were determined in accordance with the manufacturer's instructions. Simply put, 100 mL of aPTT assay reagent was added after 100 mL of citrated mouse plasma were incubated for three minutes at 37°C. 100 L of 20 mM CaCl2 was added after a one-minute incubation at 37°C, and the clotting times were recorded. 100 L of citrated mouse plasma were incubated at 37°C for three minutes for the PT assay. After that, 200 L of PT assay reagent that had been pre-incubated for 10 minutes at 37°C was added, and the time it took for the clot to form was recorded.

In vitro platelet aggregation assay Blood from human volunteers was collected through venipuncture and injected into a plastic syringe containing a trisodium citrate solution containing 3.8% (1/9, citrate/blood, v/v). Before the blood was taken, the healthy male volunteers had not taken any drugs for at least seven days. Centrifugation at 150 g for 15 minutes at room temperature (RT) was used to create platelet-rich plasma (PRP). By cell counting with a hemacytometer, the concentration of PRP was adjusted to 3 108 platelets per mL, and it was washed with TBS in the presence of 1 mM CaCl2. After being washed, the platelets were stimulated for 15 minutes at 37°C with either 5 g/mL collagen or 0.1 U/mL thrombin (Sigma) in 0.9% saline for five minutes. An aggregometer (Chronolog, Havertown, PA) was used to measure platelet aggregation. The Institutional Review Board of Kyungpook National University Hospitals (Daegu, Republic of Korea) approved the study protocol (KNUH 2012-01-010).

Animal Model for Arterial Thrombosis The mouse model for FeCl3-induced thrombosis was developed as previously mentioned. POZ (1.8, 44, 8.8, or 17.5 μg/mouse) in TBS was directed by i.v. injection into mice that had been fasting for the previous night. After the mice were anesthetized with 3% isoflurane (Forane®, Choongwae Pharmaceutical, Seoul, Korea), 0.1 mL of 0.1% rhodamine 6G (Sigma) was injected intravenously into them. A cotton thread with a diameter of 0.2 millimeters and a concentration of 0.25 M FeCl3 was applied to the adventitial surface for five minutes after a testicular artery with a diameter of 200 millimeters was carefully exposed. To use saline to clean the wound, the cotton thread was taken off. Afterward, hematoxylin-eosin (HE) staining was used to monitor the size of the testicular artery thrombus. A photosensitive color charge-coupled device camera (L-600;) was used to digitize the microscopic images. Leica). The following categories are used to score the findings: 0 with no thrombus; 1, a small thrombus (50-75 micrometers); 2, a thrombus of medium size (100-150 m); 3, a large (200-300 mm) thrombus The time between the onset of vascular injury and stable occlusion of the testicular artery by a large thrombus was measured as the time from FeCl3-induced endothelial injury.

Acute Thrombosis Caused by Collagen and Epinephrine Following overnight fasting, the mice were divided into 10 groups and given POZ (1.8, 44, 8.8, or 17.5 mg/mouse) via i.v. in TBS. injection. The mixture of 500 g/kg collagen and 50 g/kg epinephrine for acute thrombosis was injected into the mouse tail vein one hour later. To determine whether a mouse had recovered from the acute thrombotic challenge, remained paralyzed, or died, each mouse was carefully observed for 15 minutes. Five distinct experiments were carried out for the purpose of statistical analysis.

4 CONCLUSION

On the freshly isolated human platelets as well as a thrombosis mouse model, the anti-platelet activity of POZ derived from a natural product, P. multiplex, was examined. The results of the cytotoxicity and cell viability tests showed that POZ's

anti-platelet effect was not caused by its cytotoxicity. Through regulation of platelet functions, we anticipate that POZ and P. multiplex could be useful in the development of drug candidates or functional foods for the treatment and prevention of various vascular diseases.

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EXPLORING THE MEDICINAL PROPERTIES OF ACORUS CALAMUS: A COMPREHENSIVE REVIEW OF ITS PHARMACOLOGICAL STUDIES

T Nagaraju
Asst. Professor, Department of Pharmaceutics, Princeton College of Pharmacy, Hyderabad, Telangana, India
Swetha Elishetty
Asst. Professor, Department of Pharmaceutics, Princeton College of Pharmacy, Hyderabad, Telangana, India

Abstract - A semiaquatic, perennial, aromatic herb with a creeping rhizome is Acorus calamus (Araceae), more commonly known as "sweet flag." It is used for domestic consumption and export in Ayurveda, Siddha, Unani, and Homeopathy. It has a wide range of pharmacological effects, including anti-inflammatory, anticonvulsant, analgesic, anticellular, immunosuppressive, and diabetes-fighting effects. Sweet flag is composed of a variety of chemical components, including dipentene, eugenol methyl ether, -asarone, calameone, and others. Additionally, toxic substances exist, resulting in a variety of genotoxicity and mutagenecity.

1 INTRODUCTION

Mother Earth has given humanity and various plants the ability to treat human ailments. This distinguishing feature has been identified since prehistoric times. Additionally, it has been estimated by the World Health Organization (WHO) that traditional medicine is utilized to meet the requirements of 80% of the world's population. Medicinal plants are those that have secondary metabolites and are potential sources of therapeutic drugs due to their extensive chemical list and curative nature. India is the eighth largest country, home to approximately 47,000 plant species. There are over 7500 of these species that are used as medicines.

Plant products are the most common way to treat a wide range of human ailments all over the world. About half of the medicines that are used today in the United States of America come from nature, particularly from various plants. A growing interest in Ayurvedic, Siddha, Unani, and Homeopathic medicines for home use and product purposes can be seen. The global trade in plant-based medicines and goods is growing at an exponential rate; due to the widespread awareness of the harmful effects and toxicity of antibiotic and synthetic drug use over long periods of time (Figure 1).

Figure 1 Dig Acorus calamus.

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1.1 Taxonomy

- Kingdom: Plantae
- Division: Magnoliophyta
- Class: Liliopsida
- Order: Acorales
- Family : Acoraceae
- Genus : Acorus
- Species: calamus/A. aromaticus/ A. calamus var. americanus
- Other species: Acorus gramineus

1.2 Vernacular Names

- English- Sweet Flag
- Ayurvedic- Vacha
- Unani- Bacch
- Hindi- Bajai, Gora-bach, Vasa Bach
- Marathi- Vekhand
- Tamil- Vashambu
- Telugu- Vadaja, Vasa
- Kannada-Baje
- Malayalam-Vayambu
- Sanskrit- Bhutanashini, Jatila1

1.3 Botany

A. calamus is a long-lived plant with a rhizome that crawls and spreads widely, has a sweet scent, is round and hollow, and can be up to 2.5 centimeters thick. The outside of the rhizome is a purplish-brown to light brown color, while the inside is white. A single prominent mid vein, numerous fine tertiary veins on both sides, and slightly raised secondary veins characterize the leaves of A. calamus. It clearly stands out from Acorus americanus because of this. The leaves have a width of 1 cm on average, ranging from 0.7 cm to 1.7 cm. The sympodial leaf of A. calamus is slightly shorter than the vegetative leaf. The margin has a curly or undulating edge. When plants do flower or produce fruit, the flowers are cylindrical, greenish-brown, 3 to 8 cm long, and covered with numerous rounded spikes. The spadix may reach a length of between 4.9 and 8.9 cm during expansion. The small, berry-like fruits have few seeds. Blooms from early to late summer, depending on latitude, in marshy areas up to 2000 meters above sea level in the Himalayas, Manipur, Naga Hills, and some parts of South India.

1.4 Ethanobotany

Sweet banner, or vash or vaj in Arabic, was an old remedy for "consuming water" ascending from the stomach to the throat. It has been viewed as an emmenagogue, an excitant, a stomachic, a diaphoretic, a diuretic, a sharp, and a guide for fart, dizziness, and migraines emerging from dyspepsia. In Spanish, the plant is referred to as acoro and acoro verdadero. Women receive the rhizome for painful menstruation. The medicinally sweet flag has been used as an antihelminthic.

Buboes, carbuncles, deaf ears, itchy eyes, anorexia, and chest and abdomen congestion are all treated with the powdered rhizome. Due to the presence of coumarins, the powdered rhizome is said to be diuretic, expectorant, and a tuberculosis cure [8]. An infusion of the rhizome is used to treat intestinal worms, dysentery, choleric diarrhea, bronchitis, cough, dyspepsia, epilepsy, and dysentery in children. Asthma, dysentery, loss of appetite, catarrh, ague, and hysteria are all alleviated by using the oil as an expectorant. Infants are given the burnt rhizome for colic, diarrhea, teething, and as an emetic.

2 USES

The rhizomes of AC are thought to have sweet-smelling, energizing, unpleasant tonic, emetic, expectorant, emmenagogue, Spanish fly, purgative, diuretic, antispasmodic, carminative, and anthelmintic properties in the Ayurvedic medication system. They are utilized to treat a large number of conditions, including ongoing looseness of the bowels and diarrhea, bronchial catarrh, irregular fevers, tympanitis, colic, otitis media, hack, asthma, glandular and stomach growths, and dysfunctional behaviors like epilepsy, schizophrenia, and memory problems. Additionally, they have traditionally been used to treat flatulent

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colic and chronic dyspepsia. Additionally, they are used to treat rheumatism, eczema, and liver and kidney issues. The skin of the rhizomes is said to prevent blood flow. Ghee preparations, powder, balms, enemas, and pills all contain the rhizomes.

2.1 Chemical Constituents

The oil was found to contain varying concentrations of

1. A-asarone
2. B-asarone
3. C-asarone
4. Calamene, calamenenol, calameone
5. A-pinene
6. B-pinene
7. Camphene, p-cymene, eugenyl acetate, eugenol
8. Isoeugenol
9. Methyl isoeugenol
10. Calamol, azulene
11. Eugenolmethylether, dipentene
12. Methyleugenol
13. Asaronaldehyde
14. Terpinolene
15. 1,8-cineole
16. Camphor
17. A-caryophyllene

Fatty acids like palmitic acid and its ester, heptylic acid, which is an ester of butyric acid, are also present in the oil. Gas chromatography fractionation of the volatile oil led to the isolation of a-asarone and b-asarone, which are the trans- and cis-isomers of 2, 4, 5-trimethoxy-l-propenylbenzene, respectively. The rhizome also contained sitosterol and acoramone, galangin (5, 7-dihydroxytlavanol), cyclobutanolignan acoradin, 2, 4, 5-trimethoxybenzaldehyde, and 2,5-dimethoxybenzoquinone.

3 PHARMACOLOGICAL STUDIES

3.1 Inhibitory Role in ferric Chloride Induced-Epileptogenesis in Rat

Out of the various methods used to induce experimental epileptic models, intracortical administration of ferric chloride (FeCl3) into the sensorimotor cortex induces recurrent seizures and epileptic discharge, similar to human post-traumatic epilepsy, through the generation of free radicals. This study focuses primarily on the behavioral, electroencephalographic, and antioxidant changes in FeCl3-induced rat epileptogenesis. topically administered FeCl3 n(5 L); Wet canine shake conduct, spike wave releases, and cell reinforcement catalyst action, (for example, superoxide dismutase and catalase) altogether expanded when 100 mM) was infused into the sensorimotor cortex of rodents. The cerebral cortex experienced an increase in lipid peroxidation as a result. Calamus acorus (200 mg/kg body weight) p.o. prior treatment diazepam (DZ, 20 mg/kg b.w., for fourteen days), i.p.) The cerebral cortex's levels of lipid peroxidation and superoxide dismutase activity, decreased WDS behavior, and spike wave discharges with single isolated positive waves were all significantly lower than those in the FeCl3-induced epileptic group. This further demonstrates that Acorus calamus has the potential to become an effective medication for epilepsy.

3.2 Analgesic and Anti-Convulsant Studies on Mice

The pain relieving impacts of methanolic concentrate of Acorus calamus roots (MEAC) have been assessed utilizing acidic corrosive instigated Squirming reaction and Rodent caudal submersion technique. While pentylenetetrazol-induced convulsion methods were used to investigate the anticonvulsant effect. In mice, MEAC had a protective effect against pain models when taken orally at 100 and 200 mg/kg. Additionally, the latency time of PTZ-induced seizures in mice was significantly extended by the methanolic extract of Acorus calamus roots. The results show that the analgesic and anticonvulsant properties of Acorus calamus roots are present.

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4 TOXICOLOGY

Based on the discovery of cancerous tumors in laboratory animals treated with the plant, the U.S. Food and Drug Administration declared that the use of sweet flag was unsafe in 1968. Under certain conditions, Acorus calamus can be poisonous, causing digestive disturbances, gastroenteritis, persistent constipation, followed by diarrhea, and blood in the feces. AC may cause normal pregnancy reactions to be disrupted because it is a mild cocarcinogen. The effects of -asarone on chromosomes were examined in cultures of human lymphocytes. The induction of structural chromosome aberrations was significantly influenced by cellular damage and metabolic activation. The results demonstrated the -asarone's capacity to cause Genotoxicity and suggested that only Acorus with a low concentration of -asarone should be used. Salmonella typhimurium mutated concentration-dependently as a result of asarone. A promutagen mixture containing liver S-9 division and NADPH was required for asarone-induced mutagenicity. The mutagenicity of aflatoxin and -asarone was comparable. - It appears that asarone is a positive mutagen. The Salmonella mammalian microsome assay demonstrated -asarone's mutagenic activity in a separate study. In human phytotherapy, this study's findings suggested that only commercial medications devoid of or containing a low amount of -asarone should be used.

5 CONCLUSION

The wetland perennial monocot plant Acorus calamus, also known as the "Sweet Flag," has traditionally been used to treat a variety of ailments, including cough, fever, asthma, bronchitis, and digestive issues like gas, bloating, colic, and poor digestive function. Additionally, the plant's scented leaves and rhizomes are also known as the "Sweet Flag." A number of active components and an essential oil were identified and characterized from the leaves and rhizomes. This article highlights some of its pharmacological activities as well as its toxic effects.

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ASSESSING BRONCHODILATOR ACTIVITY OF SUBSTANCES USING GOAT TRACHEAL MUSCLE PREPARATION

Kadasi Sundeep
Assoc. Professor, Department of Pharmaceutical Chemistry, Princeton College of Pharmacy, Hyderabad, Telangana, India
Hariprasad Kadiyam
Assoc. Professor, Department of Pharmaceutical Chemistry, Princeton College of Pharmacy, Hyderabad, Telangana, India

Abstract- The hyperresponsiveness of the tracheobronchial tree to a variety of stimuli is the hallmark of bronchial asthma, a disease of the airways. Using tracheal or bronchial tissue in an organ bath, conventional methods should be used to begin testing a drug's effect on tracheobronchial smooth muscle. The purpose of this study was to see if goat tracheal muscle preparation could be used to screen for drugs or substances with bronchodilator activity. The trachea of a goat that had just been killed was taken from the slaughterhouse. Before reaching the maximum dose, a series of dose responses were obtained at various histamine doses. Theophylline anhydrous, prepared by dissolving it in warm distilled water, was added to the bath in various doses and allowed to work. Theophylline anhydrous (5X10-3) solution was found to inhibit contraction responses induced by histamine (p 0.001). Preparations of goat tracheal muscle are simpler to handle and prepare, and they appear to be more sensitive than those of guinea pig tracheal chain, with reliable responses. The bronchodilator activity of a wide range of plant extracts and products can be evaluated using this preparation. The goat tracheal preparation is readily available, and the evaluation of substances with bronchodilator properties can be avoided by not sacrificing a large number of laboratory animals.

1 INTRODUCTION

The hyperresponsiveness of the tracheobronchial tree to a variety of stimuli is the hallmark of bronchial asthma, a disease of the airways. These patients have been treated with a plethora of treatments and medications. Although the majority of patients respond well to the treatment that is currently available, 5-10% of patients with severe disease respond poorly. Scientists are currently looking into extracts of herbs and plants that are commonly grown in India for a bronchodilator that is safe, acceptable, effective, and inexpensive. These plants and herbs have been used for centuries to treat bronchial asthma. The best way to make a bronchodilator could be by looking at the extracts of herbs. Using tracheal or bronchial tissue in an organ bath, conventional methods should be used to begin testing a drug's effect on tracheobronchial smooth muscle. This has a few advantages, including the fact that only a small amount of the test material is required and that the effect is directly tested without the interference of nerve reflexes or factors like absorption, metabolism, or excretion. Various researchers have investigated bronchodilator drugs

using a variety of in vitro preparations. The muscle that these researchers used came from large animals. By dividing the trachea into circular rings and connecting the rings in a chain-like fashion with loops of silk thread, a tracheal chain can be made from a smaller laboratory animal like the Guinea pig. However, the trachea itself is extremely short and embedded in the tissue that surrounds it, necessitating extensive dissection. Despite this, a conventional preparation necessitates skill and is not sensitive to many agonists. Goat tracheal muscle preparation, on the other hand, is simpler to handle and prepare. It also appears to be more sensitive than the tracheal chain from guinea pigs.

Histamine's pharmacological effect on tracheobronchial muscle varies by species. Bronchoconstriction is the response of rodents, dogs, and humans. The variations between species and the nature of goat trachea receptors have been the subject of numerous studies.

Some of the authors have determined the normal pharmacological responses of goat tracheal muscle to histamine, 5-HT, acetylcholine, catecholamine, and their known antagonists.

Asthmatics frequently exhibit bronchial hyperactivity in addition to airway inflammation. The amount of histamine required to cause a 20% increase in airway resistance is only 1% to 2% of the concentration that is equally effective in healthy control subjects.

Histamine has a wide range of effects on the airway smooth muscles of different mammals. The nature of the receptors in the goat tracheal muscle has been the subject of research. Because atropine effectively inhibited acetylcholine-induced contractions, it was discovered that the goat trachea contained H1 (excitatory), a small population of H2 (inhibitory), 5-HT, and muscarinic excitatory receptors.

Both the trachea and bronchi respond pharmacologically in the same manner, and histologically, the trachea and bronchi share a type of cartilage and muscle.

The antagonist can be tested against either the spontaneous contraction or the spasmogen-induced contraction, in which a spasm is usually induced with a standard agonist like histamine and an antagonist is added to the bath to help relax the body.

The purpose of this study was to determine whether a goat tracheal chain preparation could be used to test an antagonist against spasmogen-induced contraction of the tracheal muscle activity as a bronchodilator

2 METHODOLOGY

The trachea of a goat that had just been killed was taken from the slaughterhouse and immediately transferred to a thermostat flask containing a cold solution of Krebs's Hansleit at 40 degrees Celsius. The trachea was kept in the refrigerator at 40 degrees Celsius until it was used the following day.

The trachea of a goat was cut transversely between the cartilage segments to produce a number of tracheal muscle rings. The portion of smooth muscle with its tiny ends made of cartilaginous tissue was cut off from the rest of the ring. In order

to suspend the tissue in a 40 ml organ bath containing Kreb's Hansleit solution at 370C and aerated with mixture of oxygen (95%) and carbon dioxide (5%), one end of the trachealis muscle was attached to the bent portion of the tissue holder cum aerator tube and the other to the lever writing on a smoked drum. The lever carried a 0.5gm load. For the purpose of stabilizing the preparation, a preliminary period of thirty minutes was allowed.

The speed of the kymograph was set to 0.1 cm/min. After recording the baseline for five minutes on the smoked cylinder, 0.1 milliliters of agonist histamine were added and allowed to work for five minutes. The kymograph was turned off after five minutes, and the tissue was washed with fresh Kreb's Hansleit solution. Three to four washes were given as needed. Cycles of fifteen minutes were followed, with five minutes allotted for the recovery of the tissue. A series of dose-related responses were obtained with various doses of histamine until the maximum dose was reached. Theophylline anhydrous, prepared by dissolving it in warm distilled water, was added to the bath in varying doses, and it was left to work for three minutes. In the presence of theophylline anhydrous solution, the response to the submaximal dose of histamine was observed. Before and after each addition of theophylline, the heights of contraction caused by histamine were measured and tallied. The contraction's height was reduced by a certain percentage.

3 DISCUSSIONS

A.K. Nagchaudhuri used slightly higher concentrations, but the goat tracheal muscle preparation is more sensitive and can be prepared easily for the study of both agonists and antagonists. These preparations produced consistent results for 8 to 10 hours. A study by Dinesh K et al. also found that the log concentration of theophylline solution added to the bath had a linear relationship with the inhibition of histamine-induced contraction. During the rainy season, while the other seasons were ideal for experiments, it was discovered that the tissue's response was inconsistent.

A drug may have different effects on smaller bronchi and larger bronchi or the trachea. Due to the close anatomical and physiological connection that exists between tracheal and bronchial muscle, the evidence suggests that the trachea and larger bronchi react similarly to drugs.

Concerning kind of hostility among receptor and theophylline, it is vague which doesn't be guaranteed to include receptor occupation and may happen at any step from drug receptor cooperation to the effector framework which brings about a reaction.

To demonstrate that the goat tracheal preparation provides consistent and dependable responses, this study used drugs with demonstrated bronchodilator activity. Similar to how bronchodilator activity can be evaluated, this preparation can be used to screen a variety of plant extracts or products. It is important to note that goat trachea can be easily obtained, avoiding the need to slay a large number of laboratory animals in order to evaluate substances with bronchodilator properties. This study

provides insight into using a cost-effective and straightforward method for drug screening in light of the ban on dissecting laboratory animals and the pressing need to develop alternative approaches to animal experimentation.

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NEONATAL INFECTIONS: CURRENT UNDERSTANDING, DIAGNOSIS, AND MANAGEMENT STRATEGIES

Anumula Narender Reddy
Asst. Professor, Department of Pharmaceutics, Princeton College of Pharmacy, Hyderabad, Telangana, India
A Mallikarjun
Asst. Professor, Department of Pharmaceutics, Princeton College of Pharmacy, Hyderabad, Telangana, India

Abstract - During the first four weeks after birth, or during the neonatal period, diseases of the infant are known as neonatal contaminations. Transplacental movement can reduce neonatal contaminations in utero, during delivery (perinatal), or after birth in a variety of ways. Some neonatal infections are obvious shortly after birth, while others can cause baby blues within the first week or month.

1 NEONATAL SEPSIS

HIV, hepatitis B, and jungle fever are just a few of the contaminations that don't show up until much later in life. Preterm or low-birth-weight infants pose a greater threat of contamination. Respiratory tract diseases that occur in premature infants can last into adolescence or even adulthood, limiting one's ability to participate in routine physical activities, lowering one's level of personal satisfaction, and driving up the cost of human services. In a couple of events, neonatal respiratory parcel defilements might fabricate one's weakness to future respiratory pollutions and combustible responses related to lung contamination.

A type of neonatal infection known as neonatal sepsis refers specifically to the presence of a bacterial circulatory system infection (BSI) in an infant with a fever, such as meningitis, pneumonia, pyelonephritis, or gastroenteritis. The term "sepsis neonatorum" may be used in more established literature to refer to neonatal sepsis. Models concerning hemodynamic deal or respiratory disillusionment are not important clinically in light of the fact that these secondary effects every now and again don't arise in youngsters til' the very end is quick drawing nearer and unavoidable. There are two distinct categories of neonatal sepsis: late-onset sepsis as well as early-onset sepsis LOS refers to the presentation of sepsis after seven days (or 72 hours, depending on the framework used), whereas EOS refers to sepsis appearing within the first seven days of life (although some allude to EOS as occurring within the first 72 hours of life). The leading cause of neonatal death in hospitals and groups in the developing nation is neonatal sepsis.

1.1 Early-onset Infections

Infections that begin early can strike during the first week of life. Most of the time, it shows up on the first day after birth. Typically, this kind of contamination is acquired prior to the birth of the child. Inopportune break of movies and other obstetrical ensnarements can add to the risk of

beginning stage sepsis. The newborn child may be at greater risk because of this complexity if the amniotic layer bursts earlier than 18 hours before delivery. Complexities like rashes, low birth weight, chorioamnionitis, maternal urinary tract infection, and maternal fever raise the risk of early-onset sepsis. Real signs of respiratory distress indicate early sepsis. Pneumonia, hypothermia, or shock are typical of the newborn. Between 30% and 50% of people die.

One explanation for the proximity of the explosive reaction in both the mother and the baby has been provided by recent evidence of the presence of microorganisms in sterile body fluids of the mother and her newborn. Microorganisms were found in the urine of 61 pregnant women who had chorioamnionitis, or an aggravation of the amniotic fluid. Multiple pathogens were frequently available. Even though there was no evidence of pathogens, irritability was still evident in 15% of pregnant women. This may show that there are multiple causes. Between 51% and 62% of pregnant women with chorioamnionitis also experienced placental aggravation.

2 CAUSES

A neonatal infection can be devastating to a family and prompts clinicians to focus on finding a solution. The neonatal emergency unit is where neonatal diseases are treated in industrialized nations. Numerous factors can contribute to neonatal contamination. The reason for compelling microorganisms and a few distinct microbes is much of the time the maternal gastrointestinal and genitourinary parcel. A significant number of these maternal contaminations are unnoticeable to the mother. Sexually transmitted infections, both bacterial and viral, are additional maternal contaminations that may be passed on to the unborn child during pregnancy or during birth. The infant's juvenile resistant structure muddles its ability to fight disease. Microorganisms, infections, and growths are the main causes of neonatal disease. Additionally, the neonate's innate susceptibility may react in ways that can entangle treatment, such as the emergence of explosive chemicals. The ability of the infants to fight off the infection is also impacted by inborn defects in the secure framework.

3 DIAGNOSIS

Because the contamination may pose a significant threat to the infant, the evaluation of tests for neonatal sepsis is crucial. In order to begin treatment as soon as possible, it is urgently necessary to determine whether the infant has sepsis. Analytical tests are used to get a quick indication of the contamination status because confirmation of the finding may require significant investment. These tests don't do very well. While a small number of healthy children will test positive, true cases of contamination may result in negative test results. The child's clinical condition will be the most important factor in determining the test's usefulness. The test will not provide much additional information if the infant is truly extremely drained. Additionally, a clinical examination will suffice if the child appears to be healthy, and a positive test result would not

significantly increase the likelihood that the infant is contaminated. An analytical test is likely to be useful in situations where the clinical picture leaves the doctor uncertain about the contamination status. As a result, the clinical state of the infant must be taken into consideration when evaluating the results of an analytical test.

4 PREVENTION & TREATMENT

In the UK, pregnant women must be routinely screened for HIV, hepatitis B, syphilis, and rubella defenselessness to reduce neonatal contamination. Treatment with a vaginal enemy of microbial wash before birth doesn't neutralize tainting with get-together B streptococcus microorganisms. Necrotizing enter colitis is prevented by breast milk.

Because GBS microorganisms are capable of colonizing the lower regenerative tract in 30% of women, pregnant women typically undergo testing for this pathogen between 35 and 37 weeks of pregnancy. The incidence of neonatal infection is reduced when the mother receives antimicrobial treatment prior to delivery. Penicillin treatment of the mother concludes the process of contamination prevention for the child. Newborn GBS infection mortality has decreased by 80% since this preventative treatment was implemented. Antiviral prophylaxis reduces the likelihood of mothers with symptomatic HSV developing a dynamic, symptomatic case during childbirth and may also lower the risk of contracting HSV during childbirth. The risk of the baby becoming contaminated is reduced during Caesarean birth.

Youngsters, sepsis is difficult to clinically investigate. They may be mildly asymptomatic until a hemodynamic and respiratory breakdown occurs; consequently, if there is even a remote suspicion of sepsis, they are frequently treated with anti-infection agents precisely until societies are sufficiently proven to be negative. A beta-lactam antibiotic (typically ampicillin) in combination with an aminoglycoside (typically gentamicin) or third-generation cephalosporin (typically cefotaxime—ceftriaxone is typically avoided in neonates due to the potential for kernicterus) is a typical anti-toxin regimen in babies with suspected sepsis. The species that are the focus are those that live in the female genitourinary tract and are particularly dangerous to newborns, such as Group B Streptococcus, Escherichia coli, and Listeria monocytogenes. (This is the fundamental reason why ampicillin is used instead of other beta-lactams.) Naturally, neonates are also immune to other common pathogens that can cause meningitis and bacteraemia, such as Streptococcus pneumonia and Neisseria meningitides. Although it is rare, clindamycin is frequently included when anaerobic species are suspected, such as when necrotizing enteric colitis or intestinal puncturing is a concern.

Every year, up to 3.3 million babies die from neonatal contamination, which kills 23.4% of them. Approximately half of deaths caused by sepsis or pneumonia occur during the first week of baby blues. Mortality has decreased in industrialized nations as a result of preventative anti-infection treatment

for pregnant women with B streptococcal infections, early detection of sepsis in the infant, and administration of anti-toxins to the infant. The prevalence of neonatal herpes in North America is estimated to be between 5 and 80 per 100,000 live births. The prevalence of HSV is lower among mothers outside of the United States. The prevalence in the United Kingdom, which is estimated to be 1.6 per 100,000 live births, is significantly lower. 70% to 80% of tainted newborns are born to mothers whose HSV infection history is unknown.

Europe, the Western Pacific, and the Americas are among the regions with low rates of neonatal mortality. These regions also have sepsis rates that range from 9.1 percent to 15.3 percent of the global total of neonatal deaths. This is interesting because asset-poor nations like Nigeria, the Democratic Republic of the Congo, India, Pakistan, and China have a rate of 22.5 to 27.2% of all deaths.

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EXPLORING THE ADVANCEMENTS AND CHALLENGES IN TRANSDERMAL DRUG DELIVERY SYSTEMS: A COMPREHENSIVE REVIEW

Banuvari Sandeep
Asst. Professor, Department of Pharmacology Princeton College of Pharmacy, Hyderabad, Telangana, India
Shireesha Bandirala
Asst. Professor, Department of Pharmacology Princeton College of Pharmacy, Hyderabad, Telangana, India

Abstract - Skin is also utilized for continuous transdermal drug infusion into the circulatory system due to its positioning for drug administration. Matrix dispersion systems, adhesive diffusion controlled systems, and small reservoir systems have been developed for the medication's continuous diffusion and penetration through intact skin surface membranes. Different types of penetration enhancers are used to help the drug diffuse through the skin. The polymers and the drug are distributed within the solvent of matrix dispersion systems, and the solvent is allowed to evaporate, resulting in a solid drug-polymer matrix. The gift study resulted in the creation of matrix type systems. Using the solvent evaporation method, an effort has been made in the gift work to develop a matrix-type transdermal therapeutic system containing Budesonide in various ratios and substance mixtures. Along with the in vitro diffusion studies, a variety of physical evaluations were performed on the patches. The patches containing hydrophilic poly vinyl pyrrolidone, polyehylene glycol as a result of the penetration attention (5%) were thought to be applicable for large-scale manufacturing with a backing layer and an appropriate adhesive membrane on the basis of the results obtained from the in-vitro study and the physical analysis.

1 INTRODUCTION

One of the delivery methods in which the drug is released at a predetermined rate for both local and systemic effects is controlled drug delivery. Controlled drug conveyance goes with drug epitome methods which conveys drug at standard spans for a period from days to months. When compared to conventional medication, these offer a combination of advantages and drawbacks.

The following can be used to categorize controlled drug delivery:

1. Rate-decided drug conveyance frameworks
2. Systems for dissolution-controlled drug delivery Systems for encapsulating drug delivery Controlled diffusion drug delivery systems New drug delivery systems like transdermal delivery, intrauterine delivery, ocular inserts, and sub dermal implants are included in matrix type 1. The advantages of transdermal drug delivery include the ability to deliver drugs through the skin to the systemic circulation at a predetermined rate and to maintain therapeutic concentration for an extended period of time.

2 TRANSDERMAL DRUG DELIVERY

A medicated adhesive pad called a transdermal patch is applied to the skin to deliver a specific dose of medication to a specific area through the skin and into the skin. The primary benefit of the transdermal medication conveyance framework over the other course of organizations like oral, intravenous, sublingual, intramuscular is its controlled arrival of the medication through skin for the most part by a permeable film

covering the drug or through internal heat level which breaks down the slender layers of prescription implanted in the glue. The only drawback is that drugs whose molecules are smaller than those of the skin can only reach the skin. Due to their high penetration rate, transdermal patches' use has been restricted. A special membrane in a transdermal patch controls the rate at which the liquid drug in the reservoir between the patches moves.

Oscine, nicotine, estrogen, vasodilator, and topical anesthetic are among the medications that are applied through skin patches. Thermal and cold patches, nutrient patches, skin care patches (which fall under the therapeutic and cosmetic subcategories), aroma patches, weight loss patches, and patches that measure daylight exposure are examples of non-medicated patch markets. Transdermal drug delivery outperforms conventional drug delivery in many ways.

2.1 Advantages:

The transdermal drug delivery system has the potential to provide the following benefits:

1. keeps away from the "first pass effect".
2. A drug concentration in the blood that is steady and under control.
3. Similar to those of an intravenous infusion.
4. Can halt any further administration that is not required.
5. Delivery of drugs over a long period of time, from a few hours to a week.
6. There is no interference with oral medications, food, drinks, and fluids in the stomach and intestines.
7. Drugs that have a very short half-life, a small therapeutic window, and poor oral absorption reduced inter-patient variability and improved patient compliance.
8. Self-management is possible.
9. Frameworks are painless.
10. Reduces side effects like diarrhea and vomiting.

3 MORPHOLOGY OF SKIN

The epidermis, dermis, and hypodermis are the three primary layers of skin tissue. The body's surface layer is the epidermis and its epithelium. It is a squamous keratinized stratified epithelium that can be found in most parts of the body. In the basal and prickle cell layers, which are the lowest cellular layers, cells divide continuously. One daughter cell migrates to the surface during this process, and the other divides once more. The cells become cornified and form stratum granulosum as they move toward the surface. The stratum corneum and the epidermis' top layer constitute the skin's primary barrier. The keratinized, flattened remains of epidermal cells that were once actively dividing make up the stratum corneum. It acts like a tough, flexible membrane despite being hygroscopic and impermeable to water. Lipids are abundant in the space between the cells. The stratum corneum is about 10M thick, but it can be up to 600M thick on the palms and soles.

Transdermal patches are arranged into five significant sorts in light of its organization and component. The individual type is described in detail below:

- **Drug-in-adhesive with a single layer:** This kind of patch's adhesive not only holds the system to the skin and all of its layers together, but it also lets the drug out. A backing and liner layer surrounds the adhesive.
- **Drug-in-adhesive in multiple layers:** A collection of one or more single-layer drug-in-adhesive is referred to as a multi-layer drug-in-adhesive. These layers are isolated by a film however not in all cases. The remaining layers are used for controlled drug delivery, while one of

the layers is used for immediate drug release. Additionally, a layer of permanent backing and thin liner are used to cover this patch.

- **Storage:** In contrast to the previous types, the reservoir type patch has a separate drug layer that houses the drug in a liquid state as a solution or suspension and is separated from the adhesive layer. With a vinyl acetate rate-controlling membrane on one surface, the drug reservoir is completely enclosed in a shallow compartment embedded in a drug-impermeable metallic plastic laminate. The fix is encircled with support layer. Zero Order is followed by the reservoir patch.
  The Matrix The drug solution or suspension is embedded in a semi-solid matrix that serves as the drug layer in the matrix patch. The drug layer is surrounded by a thin adhesive layer of this type. Monolithic devices are another name for this type.
- **Patch for Vapor:** The adhesive layer of a vapor patch not only adheres all of the layers and the system to the skin, but it also lets out vapor from the patch. The patch is active for five to six hours. Decongestion treatment, sleep aid, and smoking cessation are all applications for this patch.

4 COMPONENTS OF TRANSDERMAL PATCH

There are numerous components in both liquid reservoir patches and matrix patches. Some are type-specific while others are similar across both classes. The following are common elements: 33-5]:

1. Films as Support: Both when using the system and in the transdermal patch, backing films play a crucial role. Skin permeation and tolerance are affected, depending on occlusion or breathability, by the film, which serves to protect the active layer and maintain system stability. The release liner must be completely inert to the ingredients in order to prevent any kind of incompatibility. It should likewise be adaptable, agreeable and should have great proclivity with the glue and fantastic printability. Polypropylene, polyesters, PVC, and nylon are the most frequently used release liners.

2. Liners to Release: The release liners will be covered by a coating that prevents adhesion. The release liner will be removed just prior to the application of TDDS to the skin to protect the system while it is in the package. The patch's stability, safety, and effectiveness are significantly impacted by release liners. The release liners should be selected with care. The patch's easy release will be hindered by an improper release liner, which may also interfere with the active(s) or other components, shortening its shelf life. The most widely recognized films utilized as delivery liners are paper-based, plastic film-based and composite movies. Silicones and fluoro-polymers are the two main types of coating.

3. Adhesives With Pressure Sensitivity: Pressure-sensitive adhesives (PSAs) serve as the matrix that carries the active, such as additives and permeation enhancers, and the means by which the patch adheres to the skin for both types of TDDS. There are three classes in public service announcements: Silicon PSAs, emulsion polymers or hot melts, acrylic in the form of solutions, and rubber-based The patch has several sub-categories that provide the necessary flexibility for each category.

4. Enhancers for penetration: These are the totally unique synthetic substances that have a place with similar family by qualities. They multiply the active ingredient's rate of skin penetration by several times. Because the majority of the actives do not enter the skin through a

relatively small area, this makes a system more feasible. Occasionally, a combination of these components is required to achieve the desired enhancement.

5. Membranes that are semi-permeable or microporous: The role of some matrix-type patches is to regulate the flow of the semi-solid content from the liquid reservoir and to act as a ratelimiting membrane for the systems. Porous membrane is a special type of membrane that is typically used in all liquid transdermal patches. The membrane's capacity is determined by the system's design, the active component's size, and the requirement for a rate-limiting factor to meet the system's release and absorption characteristics. The chemical composition of the membrane plays a major role in determining the rate of permeation.

5 RESULTS

The transdermal drug delivery system is an innovative method of drug administration. Transdermal patches can be used to administer medications that undergo biodegradation, undergo first pass effect, or have drug-drug interactions, as well as medications that have incompatibilities or reactions with gastric contents, food, or beverages, as in the case of oral administration. Due to its patient compliance, simple administration route, and desired therapeutic effect, it is more popular. Different methods for this transdermal drug delivery make it simple to apply to various drug molecules based on their physicochemical properties. Transdermal patches have a number of benefits and drawbacks. It works differently under different circumstances. In general, transdermal patches can be used for a wide range of things, such as contraception, quitting smoking, treating motion sickness, hormonal therapies, sleeping aids, pain medication, antihypertensive medication, and treating overactive baldness. Beyond that, the technology needs to advance, and it should be combined with biotechnology to create many more novel medications.

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ADVANCES IN TARGETED DRUG DELIVERY USING NIOSOMES: A COMPREHENSIVE REVIEW

Dr. Harikiran Lingabathula
Professor, Department of Pharmacology Princeton College of Pharmacy, Hyderabad, Telangana, India
Vaishnavi Munnangi
Asst. Professor, Department of Pharmacology Princeton College of Pharmacy, Hyderabad, Telangana, India

Abstract- Infectious disease treatment and vaccination have undergone a paradigm shift in recent years. Not only have numerous disease-specific biologicals been developed as a result of research in nanobiotechnology, but also significant efforts have been made to efficiently deliver these biologicals. As an alternative to liposomes, non-ionic surfactant vesicles, or niosomes, are currently the subject of extensive research. Liposomes, microspheres, nanotechnology, microemulsions, antibody-loaded drug delivery, magnetic microcapsules, implantable pumps, and niosomes are some of the novel methods used to deliver these drugs. Both niosomes and liposomes have the potential to deliver drugs and boost drug efficacy in comparison to free drug. Liposomes are less efficient and have a lower chemical stability than niosomes do. Niosomes are self-assembling vesicles that are mostly made of cholesterol and synthetic surfactants. Their structure is similar to that of the more widely studied liposomes made from phospholipids derived from biological sources. Niosomes are a new class of novel vesicular systems that are just starting to emerge. The formation of niosomes necessitates the presence of a specific class of amphiphiles and an aqueous solvent. The niosome's role as a drug carrier has been the subject of extensive research in recent years.

Keywords: Nanocarriers, encapsulation, niosomes, liposomes, non-ionic surfactants, and proniosomes.

1 INTRODUCTION

There is currently no drug delivery system that can deliver a drug to a specific site with predictable controlled release kinetics. In 1909, Paul Ehrlich set the stage for the development of targeted delivery by envisioning a drug delivery mechanism that would directly target diseased cells. The goal of targeted drug delivery is to try to concentrate the drug in the tissues that are of interest while decreasing the drug's concentration in the rest of the tissues. Since then, a variety of carriers, such as immune globulins, serum proteins, synthetic polymers, liposomes, microspheres, erythrocytes, and niosomes, have been used to deliver drugs to the target organ or tissue. Liposomes and niosomes are well-documented forms of drug delivery among various carriers. The ability to direct a therapeutic agent precisely to the desired site of action with little or no interaction with non-target tissue is known as drug targeting.

A novel method for delivering drugs, niosomes contain the medication within a vesicle. The

vesicle is made out of a bilayer of non-ionic surface dynamic specialists and subsequently the name niosomes. The niosomes are tiny, and minute in size. The nanometric scale describes their size. They have a number of advantages over liposomes despite being structurally similar to them. Since it has recently been demonstrated that niosomes can be used for both targeted drug delivery and transdermal drug delivery, further research into these structures may lead to the development of novel drug delivery strategies.

2 SALIENT FEATURES OF NIOSOMES

1. Niosomes can entrap solutes in a manner analogous to liposomes.
2. Niosomes are osmotically active and stable.
3. Niosomes possess an infra structure consisting of hydrophobic and hydrophilic mostly together and so also accommodate the drug molecules with a wide range of solubility.
4. Niosomes exhibits flexibility in their structural characteristics (composition, fluidity and size) and can be designed according to the desired situation.
5. Niosomes can improve the performance of the drug molecules.
6. Better availability to the particular site, just by protecting the drug from biological environment.

3 STRUCTURE OF NIOSOMES

The microscopic structures known as niosomes are lamellae. They are composed of cholesterol and a nonionic surfactant of the alkyl or dialkyl polyglycerol ether class, which are then hydrated in aqueous media. The hydrophobic ends of the non-ionic surfactant face each other to form the bilayer, while the hydrophilic ends of the surfactant tend to be oriented so that they face outward. The lamellar structures that are formed when cholesterol and a non-ionic surfactant of the alkyl or dialkyl polyglycerol ether class are combined and then hydrated in aqueous media are better depicted in the figure in this article on niosomes. Noisomes share structural characteristics with liposomes, including the presence of a bilayer.

4 ADVANTAGES OF NIOSOMES

A. The vehicle's suspension is based on water. When compared to oily dosage forms, this ensures a higher level of patient compliance.
B. They have a framework comprising of hydrophilic, amphiphilic and lipophilic moieties together and subsequently can oblige drug particles with an extensive variety of solubilities.
C. The vesicle formulation's characteristics can be altered and controlled. The characteristics of the vesicle can be altered by modifying their composition, size, lamellarity, tapped volume, surface charge, and concentration.
D. The vesicles may release the drug in a controlled manner as a depot.
E. Because they are not ionic, they can reduce drug toxicity.

5 OTHER ADVANTAGES OF NIOSOMES INCLUDE:

A. They are stable and osmotically active, and they also make entrapped drugs more stable.
B. There are no special requirements for handling and storing surfactants.
C. They enhance drug skin penetration and improve poorly absorbed drugs' oral bioavailability5.
D. They can be administered orally, through a parenteral route, or topically.
E. The surfactants are non-immunogenic, biocompatible, and biodegradable.
F. They delay the drug molecules' clearance from the bloodstream, shielding them from the biological environment and limiting their effects to the cells they are intended to treat.
G. To control the rate of drug delivery and administer normal vesicle in an external nonaqueous phase, niosomal dispersion in an aqueous phase can be emulsified in a non-aqueous phase.

6 RATIONALE FOR SITE SPECIFIC DRUG DELIVERY

1) To reach previously inaccessible domains e.g. intracellular site, bacteria, viruses, parasites etc6.
2) Exclusive drug delivery to the specific cells or diseased site in the body.
3) Reduction in the drug dose and side effects.
4) To control the rate and frequency of drug delivery at the pharmacological receptor.
5) To protect the drug and the body from one another until it reaches at the desired site of action.

7 CHARACTERIZATION OF NIOSOMES

1. Entrapment efficiency is determined by complete vesicle disruption using 50% n-propanol or 0.1% Triton X-100 and analyzing the resultant solution using the appropriate assay method for the drug after preparing niosomal dispersion. Unentrapped drug is separated by dialysis, centrifugation, or gel filtration, as described above. Where (Amount of drug entrapped/ total amount of drug) x 100 is the percentage of entrapment efficiency (% EF). Light microscopy, photon correlation microscopy, and freeze fracture electron microscopy can all be used to measure the diameter of niosomes. The vesicle diameter may be increased by fusion of vesicles during the cycle during freeze thawing, which involves keeping the vesicles suspended at –20°C for 24 hours before heating to ambient temperature.
2. In-vitro release the utilization of dialysis tubing is one approach to conducting an in-vitro release rate study. A dialysis sac is washed and absorbed refined water. Pipette the vesicle suspension into a bag made of tubing and seal it. The vesicles are immersed in 200 milliliters of buffer solution in a 250 milliliter beaker with constant shaking at 25 or 37 degrees Celsius. An

appropriate assay method is used to examine the drug content of the buffer at various intervals.

3. Vesicle charge the vesicle surface charge can assume a significant part in the way of behaving of niosomes in vivo and in vivo. When compared to uncharged vesicles, charged niosomes are generally more resistant to aggregation and fusion. Microelectrophoresis can be used to measure the zeta potential of individual niosomes to estimate their surface potential. Using pH-sensitive fluorophores is an alternative strategy. The zeta potential of niosomes has recently been measured by dynamic light scattering.
4. Rigidity and homogeneity of the bilayer Niosome biodistribution and degradation are influenced by the rigidity of the bilayer. It is possible to identify in omogeneity through, which can take place both within the structures of niosomes and between niosomes that are dispersed. techniques like p-NMR, differential scanning calorimetry (DSC), and fourier transform infrared spectroscopy (FT-IR). Recently, the energy of fluorescence resonance.

8 APPLICATIONS OF NIOSOMES

The application of niosomal technology is widely varied and can be used to treat a number of diseases.

1. Niosomes as Drug Carriers

Niosomes have also been used as carriers for iobitridol, a diagnostic agent used for Xray imaging. Topical niosomes may serve as solubilization matrix, as a local depot for sustained release of dermally active compounds, as penetration enhancers, or as rate-limiting membrane barrier for the modulation of systemic absorption of drugs.

2. Targeting of bioactive agents

a. To reticulo-endothelial system (RES)

The cells of RES preferentially take up the vesicles. The uptake of niosomes by the cells is also by circulating serum factors nown as opsonins, which mark them for clearance. Such localized drug accumulation has, however, been exploited in treatment of animal tumors known to metastasize to the liver and spleen and in parasitic infestation of liver.

b. To organs other than RES

It has been suggested that carrier system can be directed to specific sites in the body by use of antibodies. Immunoglobulins seem to bind quite readily to the lipid surface, thus offering a convenient means for targeting of drug carrier. Many cells possess the intrinsic ability to recognize and bind particular carbohydrate determinants and this can be exploited to direct carriers system to particular cells.

3. Anti-neoplastic Treatment

Most antineoplastic drugs cause severe side effects. Niosomes can alter the metabolism; prolong circulation and half life of the drug, thus decreasing the side effects of the drugs. Niosomes, is decreased rate of proliferation of tumor and higher plasma levels accompanied by slower elimination.

4. Leishmaniasis

Leishmaniasis is a disease in which a parasite of the genus Leishmania invades the cells of the liver and spleen. Use of niosomes in tests conducted showed that it was possible to administer higher levels of the drug without the triggering of the side effects, and thus allowed greater efficacy in treatment.

5. Delivery of Peptide Drugs

Oral peptide drug delivery has long been faced with a challenge of bypassing the enzymes which would breakdown the peptide. Use of niosomes to successfully protect the peptides from gastrointestinal peptide breakdown is being investigated. In an invitro study conducted by oral delivery of a vasopressin derivative entrapped in niosomes showed that entrapment of the drug significantly increased the stability of the peptide.

9 CONCLUSION

Due to its stability and affordability, the niosome appears to be a preferred drug delivery method over the liposome. Additionally, niosomes have a lot of potential for drug delivery, particularly for the targeted delivery of anti-cancer and anti-infective agents. Utilizing novel concepts like proniosomes, discomes, and aspasome can enhance the niosome's potential for drug delivery. Additionally, niosomes are a more effective diagnostic imaging and vaccine adjuvant. Therefore, in order to produce a niosomal preparation that is available for purchase in the market, these areas require additional investigation and research. Academics and researchers are generally in agreement with the idea of putting the drug in liposomes or niosomes to better target it at the right tissue. Niosomes are a promising module for drug delivery. Due to their ability to encapsulate a variety of drugs within their multienvironmental structure, they can represent alternative vesicular systems in comparison to liposomes because they share a structure with liposomes. Due to a number of factors, including cost, stability, and others, it is thought that niosomes are better candidates for drug delivery than liposomes. Niosomes can be used to deliver a variety of drugs, including targeting, ophthalmic, topical, and parenteral.

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EXPLORING THE LATEST DEVELOPMENTS IN TABLET COATING TECHNIQUES: A COMPREHENSIVE REVIEW OF CONCEPTS AND ADVANCEMENTS

Thejovathi B
Assoc. Professor, Department of Pharmaceutics, Princeton College of Pharmacy, Hyderabad, Telangana, India
Zareena Begum Shaik
Asst. Professor, Department of Pharmaceutics, Princeton College of Pharmacy, Hyderabad, Telangana, India

Abstract - Tablet covering is quite possibly of the most seasoned drug process actually is presence. Covering is a cycle by which a basically dry, external layer of covering material is applied to the outer layer of a measurement structure to present explicit advantages over uncoated assortment. It involves coating the tablet with sugar or polymeric material. The ability to control the drug's release profile, taste masking, odor masking, physical and chemical protection, and stomach protection are all benefits of tablet coating. Particles, powders, granules, crystals, pellets, and tablets are just a few of the oral solid dosage forms that can be coated. A tacky polymeric film is applied to the tablet surfaces when coating composition is applied to a batch of tablets in a coating pan. Sugar coating, film coating, and enteric coating are three methods for coating tablets. The most recent advancements in coating technologies have eliminated the drawbacks of the older methods of coating. Coating materials are applied directly to the tablet surface without the use of a solvent in these technologies. Considering the product's safety profile, ICH guidelines also recommend avoiding the use of organic solvents in dosage formulations for pharmaceuticals. The fundamental ideas behind tablet coating, the most recent developments, the challenges encountered during the process, their solutions, and the evaluation of the coating are all discussed in this review.

1 INTRODUCTION

The process of applying edible paint to the surface of a pharmaceutical dosage form in order to achieve particular benefits is known as tablet coating. The cost of making tablets goes up as a result of this additional tableting process. Numerous solid dosage forms, including pills, tablets, drug crystals, and pellets, can be coated. A tacky polymeric film covers the tablet surfaces when a coating solution is applied to a batch of tablets in a coating pan. After the tablets have dried, the film eventually forms a dry, non-stick surface. In addition to a number of other non-spray-related parameters, the coating technique requires precise control of the spray pattern, drop size, and nozzle spacing in order to ensure uniform coating material distribution.

1.1 Objectives of Coating

- The following are the goals of tablet coating:
- To cover up the tablet's unpleasant taste, color, or odor.
- To provide the drug with chemical or physical protection.
- To control and support the arrival of the medication from the measurements structure.
- To include another medication that causes incompatibility issues.
- To shield an acid-labile medication from stomach acid.
- Increasing the dosage form's mechanical strength.

1.2 Coating Process

The coating should be uniform and not crack under stress, which is extremely desirable. As a result, a variety of methods for applying the coating to the

tablet surface were developed. Typically, the uncoated tablets are agitated in a pan, fluid bed, or other vessel before the coating solutions are sprayed onto them. A thin film that adheres to each tablet forms as the solution is applied. After that, the coating solution's liquid component is evaporated by blowing air over the tumbling pans' surfaces. The coating can be developed in layers through multiple spraying cycles, or it can be formed in one application. The pharmaceutical industry makes frequent use of rotating coating pans.

1.3 Film Coating

As the glossing over process is extremely tedious and is reliant upon the abilities of the covering administrator, this method has been supplanted by film covering innovation. Spraying a polymer, pigment, and plasticizer solution onto a rotating tablet bed to form a thin, uniform film on the tablet surface is the process. The decision of polymer for the most part relies upon the ideal site of medication discharge (stomach/digestive tract), or on the ideal delivery rate. Hydroxypropyl methyl cellulose (HPMC), methyl hydroxyethyl cellulose, ethylcellulose, and povidone are examples of non-enteric coating polymers. On the other hand, enteric coating polymers like cellulose acetate phthalate, acrylate polymers (Eudragit L& Eudragit S), HPMC phthalate, and others are frequently utilized. The following qualities should be present in an ideal film coating material:

- It ought to be soluble in any suitable solvent.
- It must produce a sophisticated coat.
- It ought to remain stable when exposed to light, heat, or moisture.
- It shouldn't have a bad taste, smell, or color.
- It ought to be pharmacologically inert and non-toxic.
- Coating additives should be compatible with it.

1.4 Organic Film Coating

Liquid coating technology (aqueous based organic based polymer solutions) is currently the technology that is used most frequently to coat solid dosage forms. In liquid coating, a mixture of polymers, pigments, and excipients is dissolved in an organic solvent (for water-insoluble polymers) or water (for water-soluble polymers) to form a solution, or dispersed in water to form a dispersion. The mixture is then sprayed onto the dosage forms in a pan coater (for tablets) and dried by continuously providing heat, typically through hot air, until a dry coating film is created. Because the majority of polymers are soluble in a wide variety of organic solvents, organic solvent-based coatings offer a wide range of useful polymer alternatives. However, there are some drawbacks, such as the fact that they are expensive, toxic, flammable, and pose environmental issues. Considering the product's safety profile, ICH guidelines also recommend avoiding the use of organic solvents in dosage formulations for pharmaceuticals. As a result, formulations coated with an aqueous film are receiving a lot of attention from the pharmaceutical industry right now.

1.5 Aqueous Film Coating

Water has replaced organic solvents as the preferred coating solvent due to all of the aforementioned issues. When compared to coatings that are based on organic materials, their use is on the rise. The coating process becomes more cost-effective by switching from coatings that are based on organic solvents to coatings that are based on water, though upgrading the coating facility may initially require a small investment.

The need for a higher drying capacity (the latent heat of water is 2200 kJ, whereas that of methylene chloride is 550 kJ) necessitates this upgrade. This indicates that compared to an organic solvent, one would require four times more energy.

1.6 Tribo Charging

Tribo charging, in contrast to corona charging guns, uses the principle of friction charging associated with the dielectric properties of solid materials. As a result, there will be no free ions or electrical field between the grounded substance and the spray gun. Electrical forces are only considered to be the repellent forces that exist between the charged particles in tribo charging guns. When charged particles enter the space next to the substrate after spraying, the attraction forces between the grounded substrate and the charged particles cause the particle to deposit on the substrate. Mechanical forces and electrostatic attraction cause charged particles to be uniformly sprayed onto the earth's substrate. Before the electrostatic attraction exceeds the repulsion force of the deposited particles against the coming particles, particles accumulate on the substrate. Finally, once the aforementioned repulsion reaches the same level as the aforementioned attraction, particles cease to adhere to the substrate, and the coating thickness ceases to increase.

Many dry covering strategies have been grown, for example, pressure covering, plasticizer dry covering, heat dry covering and electrostatic dry covering. To achieve coating, these techniques typically permit the application of high hearing stresses, high impaction forces, or higher temperatures. Guest particles may be layered or even embedded onto the host particles' surfaces as a result of the strong mechanical forces and heat generated. Organic and relatively soft, many pharmaceutical and food ingredients are extremely heat-sensitive and susceptible to deformation by strong mechanical forces. As a result, soft coating techniques that are able to attach the guest (the coating material) particles to the host (the material to be coated) particles without significantly affecting the size, shape, or composition of the particles as a result of heat buildup are better suited for such applications. The MAIC devices are capable of coating soft organic host and guest particles without significantly altering the material's shape or size.

2 VACUUM FILM COATING

This innovative coating method makes use of a specialized baffled pan. The pan can be sealed to create a vacuum system because it is hot and has a water jacket on it. Before reaching the desired vacuum level, the tablets are placed in the pan and nitrogen is used to move air out of the pan. The airless spray system is used to apply the coating solution. The vacuum system removes the solvent vapors that have evaporated. With these coating techniques, organic solvents can be used effectively and with high environmental safety.

3 COMPRESSION COATING

Although compression coating isn't widely used, it has advantages when the tablet core needs to be coated for taste masking, delayed or enteric properties, or because it can't handle organic solvents or water. Additionally, the process makes it simple to separate ingredients that are incompatible. A specialized tablet machine is required for this kind of coating.

4 COATED TABLET EVALUATION

The study of the film and the interactions between the tablet and the film are necessary for determining the quality of a tablet coat. The tests listed below can be used.

- The force required to peel the film from the tablet surface is measured using adhesion tests using tensile strength testers.
- A tablet hardness tester is used to measure the coated tablets' diametric crushing strength. The rate of disintegration and dissolution of coated tablets should

also be investigated. Coated tablets can be the subject of stability tests to determine whether changes in temperature and humidity would result in film defects.

- The film's level of protection can be estimated by measuring tablet weight gain and being exposed to high humidity.

5 CONCLUSION

Over the past three decades, remarkable development efforts have been made to ensure and improve the quality of pharmaceutical formulation coatings, including tablet coating.

This technology has seen significant development thanks to advancements in energy consumption, film distribution, drying efficiency, continuous processing, and improved safety profiles. There is a lot of potential for advancements in tablet coating in the future to achieve specific benefits.

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EXPLORING THE PROMISING PROPERTIES OF CURCUMIN FOR CANCER PREVENTION AND TREATMENT

Banuvari Sandeep
Asst. Professor, Department of Pharmaceutics, Princeton College of Pharmacy, Hyderabad, Telangana, India
Kasireddy Swetha Reddy
Asst. Professor, Department of Pharmaceutics, Princeton College of Pharmacy, Hyderabad, Telangana, India

Abstract- Most medications as of now accessible for the therapy of disease have restricted potential since they are extremely poisonous, exceptionally wasteful in treating malignant growth, or profoundly costly and accordingly past the span of the larger part. There must be treatments that don't have these drawbacks. One such substance is curcumin; It is derived from turmeric (Curcuma longa) and has been used to treat a wide range of illnesses in the Orient for thousands of years. Curcumin is a powerful anti-inflammatory agent with strong therapeutic potential against a variety of cancers, according to decades of research. Tumor transformation, proliferation, and metastasis have all been shown to be inhibited by curcumin. It regulates a variety of transcription factors, growth factors, inflammatory cytokines, protein kinases, and other enzymes to carry out these effects. Curcumin has been shown to inhibit angiogenesis and metastasis in rodents and to protect against and treat cancers of the blood, skin, oral cavity, lung, pancreas, and intestinal tract. In preclinical models, curcumin's ability to alter gene transcription and elicit apoptosis is likely to be particularly useful for patients receiving chemotherapy for cancer. The molecular mechanisms by which curcumin mediates its effects against various cancers are the focus of the current review.

1 INTRODUCTION

Phytochemicals are substances that plants naturally produce. The use of phytochemicals derived from dietary components to combat human diseases, particularly cancer, has piqued both public and scientific interest. Plants have been used for medicinal purposes for a long time in India. Turmeric (Curcuma longa L.), a medicinal plant, is a common home remedy for a variety of illnesses in Ayurveda, Siddha, and Unani medicine. The ground-dried rhizome of Curcuma longa Linn., a perennial herb Since the second millennium BC, turmeric, also known as haldi in Hindi and ukon in Japanese, has been used in Asian medicine. In the ancient Hindu text known as the Ayurveda, it is mentioned for its use. Turmeric, when combined with other natural compounds like slaked lime and used topically to treat wounds, inflammation, and tumors, has properties that include aroma, stimulant, and color. In contrast to the maximum daily intake of 1.5 grams in some South East Asian communities, smaller amounts of turmeric are typically used for medicinal purposes. According to the Food and Agriculture Organization of the United Nations, over 2400 metric tons of turmeric are imported annually into the United States for consumer use because of its appeal as a colorant, food preservative, and flavoring.

2 CHEMICAL COMPOSITION OF TURMERIC

Curcuma species contain essential oils like turmerones, atlantones, and zingiberene, curcuminoids like curcumin [1, 7-bis-(4-hydroxy-3-methoxyphenyl)-1, 6-heptadiene-3, 5-dione], and turmerin, a peptide that dissolves in water. Curcuminoids can be characterized as

phenolic compounds got from the underlying foundations of Curcuma spp. (Zingiberaceae). Curcumin (diferuloylmethane) is a low-molecular-weight polyphenol that was first chemically characterized in 1910. It is generally regarded as the most active component of most turmeric preparations and accounts for 2–8% of them. Protein (6.3%), fat (5.1%), minerals (3.5%), carbohydrates (69.4%), and moisture (13.1%) are all found in turmeric.

-phellandrene (1%), sabinene (0.6%), cineol (1%), borneol (0.5%), zingiberene (25%), and sesquiterpines (53%) are found in the 5.8% essential oil produced by steam distillation of rhizomes. The yellow color comes from curcumin (diferuloylmethane), which is composed of curcumin I (94%), curcumin II (6%) and curcumin III (0.3%)6. At 176–177°C, it has a melting point; It is soluble in ethanol, alkali, ketone, acetic acid, and chloroform and forms a reddish-brown salt when exposed to alkali.

3 MECHANISM OF ACTION

Curcumin, the active ingredient in turmeric, has been shown to inhibit the growth of a wide range of tumor cells in numerous animal and in vitro studies. There are numerous hypothesized mechanisms for these anticancer effects.

Effects against proliferation: at high concentrations, apoptosis is induced, proteins that control apoptosis are suppressed, and transcription factors are altered. Concealment of cyclooxygenase-2 (COX-2) and lipooxygenase articulation, which blocks creation of prostaglandins and leukotrienes, separately. suppression of adhesion molecules, which are crucial to tumor metastasis, and suppression of cyclin D1, a proto-oncogene that is overexpressed in many cancers (including breast, esophagus, lung, liver, head and neck, colon, and prostate). suppression of a number of inflammatory cytokines, including TNF. suppression of angiogenesis, which is an essential step in the growth and spread of many cancers. Competition with carcinogens that make use of the cytochrome P450 and aryl hydrocarbon pathways.

4 LABORATORY STUDIES

Curcumin has been shown to inhibit telomerase activity, an important factor in tumorigenesis, and to promote apoptosis in some cancer cell lines. The production of reactive oxygen intermediate is one potential mechanism for the induction of tumor cell death. After extracting curcumin, the oleoresin of turmeric was found to also have antimutagenic properties, which were thought to be mediated through its antioxidant action. Curcumin is the known active principal of turmeric.

Prostaglandin synthesis inhibition may play a role in curcumin's anti-inflammatory properties. Arachidonic acid prostaglandin synthesis is facilitated by two isoenzymes: COX-1 and COX-2, both of which are present in human and rodent colon tumors. Curcumin significantly reduced COX-2 expression in human colon cancer cells and COX-2-deficient cell lines, without altering COX-1 expression, according to Goel et al. Since non-specific inhibition of COX-1 and chronic use of nonsteroidal anti-inflammatory drugs (NSAIDs) can have unfavorable effects on the gastrointestinal and renal systems, this is a significant advantage of curcumins.

Mahady et al. also demonstrated that curcumin prevents gastric and colon cancer in rodents by inhibiting the growth of a group 1 carcinogen called Helicobacter pylori.

5 ANIMAL STUDIES

In animal studies on the prevention and treatment of cancer, curcumin has demonstrated promising results. A diet containing 0.2% curcumin was given to a mouse model of hepatocellular carcinoma (HCC) four days before N-diethylnitrosamine injections and

continued until death. Curcumin-fed mice had a 62% and 81% lower incidence of HCC and tumors, respectively, when compared to controls 42 weeks after injection. Using a mouse model of familial adenomatous polyposis, Mahmoud and colleagues found that mice fed a diet containing 0.1 percent curcumin had 64 percent fewer tumors than controls. Tetrahydrocurcumin, an active metabolite of curcumin, significantly reduced the development of preneoplastic aberrant crypt foci following treatment with 1, 2-dimethylhydrazene dihydrochloride to initiate tumors in comparison to controls in another study using a mouse model of colon carcinogenesis.

Oral curcumin organization has been found to hinder the improvement of artificially prompted malignant growth in creature models of oral, stomach, liver and colon disease. The genetic condition known as familial adenomatous polyposis, which is characterized by the development of numerous colorectal adenomas (polyps) and a high risk for colorectal cancer, is mirrored in ApcMin/+mice by a mutation in the Apc (adenomatous polyposis coli) gene. In ApcMin/+ mice, oral curcumin administration was found to prevent the growth of intestinal adenomas.

6 HUMAN CLINICAL STUDIES

The review article by Aggarwal et al. examining the anticancer effect of turmeric/curcumin reported a study in China by Cheng et al. of 25 patients with one of five high-risk conditions: oral leukoplakia, cervix (high grade cervical intraepithelial neoplasia), skin (squamous carcinoma in situ), or stomach (intestinal metaplasia). The results of the phase I clinical trial in Taiwan examined the effects Arsenic Bowen's disease of the skin, uterine cervical intraepithelial neoplasm (C1N), oral leucoplakia, and stomach intestinal metaplasia have all recently been resected.

In a controlled trial, 16 chronic smokers receiving 1.5 g of turmeric daily for 30 days reduced mutagen excretion from their urine. Mutagen excretion in the controls' urine did not change. Measuring surrogate outcomes, like urinary mutagens, does not necessarily correlate with a decrease in cancer incidence, despite being suggestive. 18 HIV-positive patients received an average daily dose of 2g of curcumin for 127 days as a follow-up to pharmacological research on the effects of curcumin on HIV cell replication. The number of CD4 and CD8 lymphocytes increased significantly.

6.1 Epidemiology

In general, India has much lower cancer rates than Western nations. Overall cancer rates were found to be lowest among Indians in India and Singapore and highest among whites in the US in a report comparing cancer incidence rates among Indians living in India, the US, the UK, and Singapore. Indians living in the US and UK had intermediate cancer rates. Esophagus, colorectal, liver, pancreas, lung, breast, uterine, ovary, prostate, bladder, kidney, renal, brain, and non-Hodgkin lymphoma are among the cancers with the lowest incidence rates in India. Male cancer rates were three times higher for white men in the United States than for Indian men in India and Singapore, and 50 to 75 percent higher for Indian men in the United States and the United Kingdom. The most striking difference was in the prevalence of prostate cancer, which was 20 times higher in white Americans than in Indians. Overall, women's cancer rates were lowest in India and more than 180% higher among white Americans. Indians were found to have a higher prevalence of certain cancers. The occurrence of stomach disease in guys and females was most noteworthy among Indians in Singapore. India had the highest rates of mouth, pharynx, gall bladder, cervix, and male larynx cancer.

7 CONCLUSION

As an alternative to chemotherapy, the use of naturally occurring compounds with high phenolic content has gained widespread acceptance over time. Disease, one of the main sources of death on the planet can now be deferred, stifled or turned around by these polyphenolic mixtures, for example, curcumin. Several additional phytochemicals have also been used as chemopreventives. Curcumin's anticancer, antioxidant, and anti-inflammatory properties are now better understood thanks to extensive research into its molecular mechanisms. Curcumin's non-toxic nature necessitates additional research to establish its chemopreventive potential as the best alternative to harmful chemotherapeutic agents for cancer patients.

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USING CARDIAC MARKERS FOR THE DIAGNOSIS AND MANAGEMENT OF HEART FAILURE: A REVIEW OF CURRENT RESEARCH

Dr. Harikiran Lingabathula
Assoc. Professor, Department of Pharmacology Princeton College of Pharmacy, Hyderabad, Telangana, India
Vaishnavi Munnangi
Asst. Professor, Department of Pharmacology Princeton College of Pharmacy, Hyderabad, Telangana, India

Abstract- The process of diagnosing and treating diseased patients is entering a new era. Coronary illness is the main source of mortality in created nations said as deadly sicknesses everywhere. In this audit, we sum up late writing zeroing in on circling biomarkers that can help the finding of intense cardiovascular breakdown, work with forecast, and guide illness the executives. Indicators of neurohormonal activation (brain natriuretic peptide [BNP] and norepinephrine), markers of myocyte injury and extracellular matrix remodeling, and inflammatory mediators are all examples of putative heart failure biomarkers. Other biomarkers that are still in the early stages of investigation are also briefly discussed. Although cardiac markers are used to predict the increased risk of heart diseases, this review does not cover genomic and echocardiographic biomarkers of heart failure. Instead, it provides the diagnostic, monitoring, and risk of stratification properties of existing and emerging cardiovascular disease (CVD) markers. Troponin, myoglobin, creatine kinase, and C-reactive protein are among the cardiac risk markers for cardiovascular disease that this review focuses on to highlight the clinical value of serial measurement of these markers in heart diseases. The researchers are able to study emerging markers like homocysteine, matrix metaloproteins (MMP), and myeloperoxidase (MPO) using the existing cardiac markers and their potential. Putting cardiac markers in the same time frame as clinical signs and symptoms is critical. This is a significant advantage for point-of-care (POC) testing, particularly in the emergency department (ED), where biochemical markers are readily available.

Keywords: Troponin, Creatine kinase, biomarkers, heart failure, and testing at the point of care.

1 INTRODUCTION

Both randomized trials and population-based studies have described the adverse morbidity and mortality of heart failure patients. Heart failure's poor prognosis has prompted increased efforts to identify the condition earlier and improve risk stratification strategies for management.

Clinical risk factors for heart failure, such as elevated blood pressure, diabetes, renal insufficiency, and coronary heart disease, have been identified by epidemiologic studies. However, it can be difficult to accurately predict heart failure and its outcomes. The diagnostic and prognostic abilities that doctors use on a daily basis may

be further enhanced by using biomarkers. Discoveries into the pathophysiology of cardiac dysfunction and a deeper comprehension of the contributing molecular mechanisms have led to a steady increase in the scientific literature on biomarkers for the diagnosis and prediction of heart failure. Any eligible biomarker must meet the same gold standard as any other diagnostic test or prognostic index: it must provide incremental information beyond what a straightforward clinical assessment can provide. Before a biomarker can be recommended for widespread clinical use, this expectation must be satisfied.

Cardiac Markers: When a heart muscle is damaged as a result of a myocardial infarction, cardiac markers are substances that are released. Cardiovascular marker tests recognize blood synthetics related with myocardial dead tissue (MI), usually known as a coronary failure. The heart muscle can be found in the middle layer of the heart wall, called the myocardium. An interruption in a region's blood supply results in tissue death known as an infarction. A substance that is used as an indicator of a biologic state is called a biomarker. It is a property that can be objectively measured and assessed as a sign of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention." The term "biomarker" encompasses any parameter that describes or reflects a particular biological process. It can include a variety of indices and parameters derived from clinical images, physiological tests, tissue biopsies, and even genetic variants. However, this term is typically used only for blood or urine-based assessments because it leaks into the bloodstream from damaged myocardial cell membranes.

History: In the late 1960s, Total CK was created as a fast, repeatable spectrophotometric test. CK isoenzyme are in this manner portrayed as MM, MB and BB fractions.1970's: CKMB is now measured using a monoclonal antibody assay that is extremely sensitive and found to be elevated in acute MI1. It was felt for a period that quantitative CKMB assurance could be utilized to enzymatically measure the size of an infarct. During reperfusion, the release of additional enzymes has complicated this. Researchers come to the paradoxical conclusion that CKMB assays are also not entirely cardiac-specific as they get more sensitive. It has been determined that skeletal muscle expresses the MB fraction, particularly during the process of muscle regeneration. Due to issues with specificity, myosin light chains were initially isolated and then abandoned. In 19871, trophonin I was first described as a biomarker for AMI; 1989: Troponin T. The current biochemical "gold standard" for ESC/ACC consensus-based acute myocardial infarction diagnosis Other clinical assays for the diagnosis and prognosis of a wide range of cardiac diseases are encouraged by this work. Some notable examples include: C-reactive protein (BNP) was approved by the FDA in November 2000 for the diagnosis of CHF.

Need: In order to start the right treatment, cardiac biomarker tests are ordered to help identify the presence of ACS and cardiac ischemia as soon as possible. Because the treatments and requirements for monitoring are different, it is important to distinguish between heart attacks, angina, heart failure, and other conditions that may have similar signs and symptoms. In order to minimize heart damage and potential complications in the future, prompt medical intervention is essential in cases of heart attacks. The doctor must be able to get cardiac biomarker tests quickly, seven days a week, 24 hours a day. A portion of the tests might be performed at the mark of care (POC) - in the Trauma center or at the individual's bedside. In order to estimate the severity of a heart attack and avoid missing a rise in blood levels, periodic testing of one or more cardiac biomarkers is required. Physicians only use a small number of cardiac biomarker tests on a daily basis. Troponin is currently the biomarker test of choice for detecting heart damage. After irreversible myocardial necrosis, it is thought that the existing markers for myocardial necrosis, such as cardiac Troponin, Creatine kinase-MB, and Myoglobin, are released into the blood. As a result, patients with acute coronary syndromes (ACS) who present to the emergency department (ED) within the first three hours of experiencing chest pain typically receive negative results from these tests. Biomarkers that can be used to diagnose and/or risk stratify ACS patients during their initial ED presentation will be important given the need to make early therapeutic and triage decisions. Several classes of biomarkers that hold promise for early disease detection have been identified through current research in this field. These include tests for acute inflammation and infiltration (such as high sensitivity C-reactive protein and myeloperoxidase), plaque instability (such as pregnancy-associated plasma protein-A and placental growth factor), platelet activation (such as whole blood choline, platelet density, and CD40 ligand), and myocardial ischemia.

2 TYPES OF BIOCHEMICAL MARKERS

2.1 Prognostic Biochemical markers Neurohormones

Norepinephrine In response to HF's characteristic low cardiac output and small arterial volume caused by systolic left ventricular (LV) dysfunction, a complex series of neurohormonal changes occur. Myocardial noradrenalin stores are depleted, sympathetic nervous system activity rises, and beta1-adrenoreceptor desensitization occurs. Myocardial contractility, tachycardia, and arterial vasoconstriction, which increases cardiac afterload, are all negative outcomes of an initial increase in adrenergic activity, which may help maintain cardiac performance in the short term. While only a small amount of circulating norepinephrine originates from the heart8, this hormone's increased release from adrenergic nerve endings and spillover into the plasma are the causes of the elevated concentrations in the blood. Log plasma norepinephrine remained the only independent predictor of mortality in the Vasodilator-Heart Failure II Trial, which examined

several potential predictors of outcome in nearly 750 patients. These potential predictors included baseline LV ejection fraction (EF), peak oxygen consumption during exercise, and cardiothoracic ratio. Plasma norepinephrine and mortality were found to be positively correlated in the placebo group of patients in the Cooperative North Scandinavian Enalapril Survival Study. Patients with LV dysfunction had significantly higher median plasma norepinephrine concentrations than healthy controls in the Studies of Left Ventricular Dysfunction. Plasma norepinephrine concentrations have limited clinical use due to the need for bed rest prior to blood sampling and high-performance liquid chromatography, a time-consuming procedure that is not readily available, despite the robustness of these historical observations.

2.2 Renin, Angiotensin, Aldosterone

The local renin-angiotensin system plays an important role in the pathogenesis of chronic heart failure, and the activity of the circulatory renin-angiotensin-aldosterone system is crucial to maintaining the balance of water and electrolytes and blood volume. In response to renal hypoperfusion and sympathetic activation, the juxta-glomerular cells are primarily responsible for the release of renin. Renin cleaves angiotensinogen into angiotensin I, which is then transformed into angiotensin II by the angiotensin-converting enzyme (ACE), a stimulator of aldosterone production in the adrenal cortex. However, these compensatory mechanisms ultimately increase the preload and afterload in chronic HF patients. Plasma renin and plasma aldosterone concentrations may not rise significantly in mild chronic HF patients, but their activation does predict outcome, albeit perhaps not as accurately as plasma norepinephrine.

3 NATRIURETIC PEPTIDE

Rather than different neurohormones that are raised in persistent HF, ANP and BNP appear to assume versatile counter-administrative parts. Amino acid precursor proteins are used in the production of both hormones. When pro-ANP is released into the bloodstream, it is broken down into the active hormone ANP and Nterminal proANP by atrial storage granules. BNP is released from ventricular myocytes as BNP, the active hormone, and Nterminal proBNP (NT-proBNP), which is regulated during gene expression. Relaxing vascular smooth muscle, dilation of arteries and veins, lowering blood pressure and ventricular preload, and inhibiting sympathetic activity and the renin—angiotensin—aldosterone system appear to be the same effects of ANP and BNP. Additionally, they promote natriuresis and diuresis by increasing glomerular filtration and inhibiting sodium reabsorption by the kidney. Plasma BNP concentrations are currently used as diagnostic and prognostic markers in patients with chronic HF. BNP is more reliable than ANP or N-terminal proANP in the evaluation of chronic HF. The fact that BNP was a better predictor of mortality using multiple variable analysis than NHYA functional class, ANP, norepinephrine, LVEF, or age is especially noteworthy.

4300 Val-HeFT patients had their baseline levels of norepinephrine, BNP, aldosterone, plasma renin activity (PRA), big endothelin (ET)-1, and ET-1 measured. BNP had the strongest correlation with mortality using multiple variable analysis, followed by PRA and norepinephrine. BNP is likewise an indicator of endurance in patients with intensely decompensated HF. In the Intense Decompensated Cardiovascular breakdown Vault, the connection between BNP focus on admission to the medical clinic and in-clinic mortality was direct.

4 CONCLUSION

New sensitive POC assays for cardiac markers and the search for specific biomarkers of cardiac injury will continue to be the primary focus of future research. Standardization of methods and enhancement of analytical sensitivity and specificity will continue to be the primary focuses. The compatibility of the results obtained by various POC assays and those obtained by the central laboratory remains a significant issue. The number of people with heart failure (HF) is rising rapidly, and most of them will not receive treatment from highly specialized medical facilities worldwide. It is hoped that this systematic review will assist in the creation of management strategies that are broadly applicable. BNP and NT-proBNP are currently the biochemical markers with the greatest impact on risk stratification and diagnosis of HF. Study protocols based on multiple markers with the intention of risk stratification, monitoring, or targeting therapy ought to be taken into consideration. Several other new biochemical markers are being studied.

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DEVELOPMENT AND ASSESSMENT OF RANITIDINE HCL FLOATING MATRIX TABLET

Malothu Suresh
Asst. Professor, Department of Pharmaceutics, Princeton College of Pharmacy, Hyderabad, Telangana, India
Thandu Rajini
Asst. Professor, Department of Pharmaceutics, Princeton College of Pharmacy, Hyderabad, Telangana, India

Abstract - Ranitidine HCl is utilized for the H2 receptor bad guy. It is a drug with a limited absorption window, whose solubility decreases with pH and has a short half life of 2 to 3 hours. As a result, the current investigation is focused on the development of floating matrix tablets that, when taken orally, were made to increase the drug's bioavailability and half life by extending the gastric residence time. In 0.1N HCl, ranitidine HCl absorbed the most light at 324 nm wavelength. DSC's studies of drug-polymer compatibility reveal that there is no interaction between certain polymers and the drug. Various formulations were created by combining the direct compression method with the addition of sodium bicarbonate as a gas-generating agent and utilizing release rate-controlling and gel-forming polymers like HPMC K4 M and Polyethylene oxide WSR 303. Swelling studies indicated significant water uptake and contributed to drug release. All formulations had a floating lag time of less than 4 minutes and consistently floated on the dissolution medium for more than 12 hours. Batches F5 and F6 were chosen as the best formulations because they extended drug release for longer than any other developed formulation. Diffusion through polymer relaxation and power law kinetics were identified as the drug release mechanism for the best formulations. During a one-month period of stability testing, the most effective formulations were found to be stable. As a result, the requirements for a floating drug delivery system—floating time, swelling index, and in vitro drug release profile—were met by the best formulations.

Keywords: Floating Matrix tablet, Ranitidine HCl, and the Floating Drug Delivery System.

1 INTRODUCTION

The development of an oral controlled-release drug delivery system faces the real challenge of not only maintaining drug release but also maintaining the dosage form's presence within the gastrointestinal tract (GIT) until the drug is released completely at the desired time. Indeed, gastric drug retention has garnered a lot of attention in recent decades. The fast gastric emptying time of the majority of conventional oral delivery systems has been shown to have some limitations.

divided the dosage forms that are harmful to the stomach into four main categories: I) Drifting frameworks, (ii) Expandable frameworks, (iii) Bioadhesive frameworks and (iv) high thickness frameworks. There are two types of floating systems: (A) bubbly

frameworks, contingent upon the age of carbon dioxide gas upon contact with gastric liquids, and no bubbly frameworks. There are four subtypes of the latter systems, including hydrodynamically balanced systems; microporous compartment frameworks, alginate dab and empty microspheres/microballons. Super-porous hydrogels and magnetic systems were also described. According to Singh and Kim, floating drug delivery is especially important for drugs that: a) primarily affect the stomach; (b) are mostly taken in through the stomach; c) have a low soluble capacity at an alkaline pH; d) have a limited absorption window; (e) and are unstable in the colonic or intestinal environment.

The drug should have an absorption window either in the colon or throughout the gastrointestinal tract with a traditional oral sustained release formulation. Ranitidine has a 50% absolute bioavailability and is only absorbed in the first part of the small intestine. Additionally, ranitidine's low bioavailability from the colon is partially attributable to its metabolism in the colon. These properties of ranitidine hydrochloride don't incline toward the customary way to deal with supported discharge conveyance. Subsequently, clinically OK supported discharge measurement types of ranitidine hydrochloride arranged with regular innovation may not find success.

Improved oral sustained delivery of drugs with an absorption window in a specific region of the gastrointestinal tract can be made possible by the gastro retentive drug delivery systems, which can be retained in the stomach. By continuously releasing the drug prior to the absorption window, these systems ensure maximum bioavailability.

It is additionally revealed that oral treatment of gastric problems with a H2-receptor adversary like ranitidine or famotidine utilized in mix with acid neutralizers advances nearby conveyance of these medications to the receptor of the parietal cell wall. Drugs that reduce acid secretion are also more effective when delivered locally because it increases the bioavailability of the receptor site on the stomach wall. Ranitidine hydrochloride delivery could be improved using this principle to effectively reduce gastric acid secretion at the systemic and local levels.

A few methodologies are right now used to drag out gastric maintenance time. These incorporate drifting medication conveyance frameworks, otherwise called hydrodynamically adjusted frameworks, swelling and growing frameworks, polymeric bioadhesive frameworks, altered shape frameworks, high-thickness frameworks and other postponed gastric purging gadgets. A straightforward and practical strategy for increasing the dosage form's gastric residence time and ensuring sustained drug release is the buoyant preparation principle.

Ranitidine hydrochloride is an antagonist of the histamine H2-receptor. In active duodenal ulcers, gastric ulcers, Zollinger-Ellison syndrome, gastroesophageal reflux disease, and erosive esophagitis, it is frequently prescribed. The suggested grown-up oral dose of ranitidine is

150 mg two times day to day or 300 mg once day to day. 150 mg of ranitidine four times a day is required for the effective treatment of erosive esophagitis. An alternative dose of 300 mg causes plasma fluctuations, whereas the conventional 150 mg dose can inhibit gastric acid secretion for up to 5 hours but not for 10 hours. Consequently, a ranitidine hydrochloride dosage form with sustained release is desirable. A sustained release formulation is also encouraged by the drug's short biological half-life (2.5-3 hours).

2 MATERIALS AND METHODS

2.1 Materials

HPMC K 4 M was obtained from Torrent Pharmaceutical Ltd., and a gift sample of Ranitidine HCl was kindly provided by Torrent Pharmaceutical Ltd. Ahmedabad. Poly Ethylene Oxide WSR 300 was obtained from Torrent Pharmaceutical Ltd. Talc, magnesium stearate, sodium bicarbonate, and microcrystaline cellulose were all obtained from Seva Fine Chemicals in Ahmedabad.

2.2 Drug Release Kinetics of Batch F4 to F6 of Floating Matrix Tablet of Ranitidine HCl

In order to determine the mechanisms of drug release, the data on drug release were fitted to models of zero order (the cumulative amount of drug released versus time), first order (the log percentage of drug unreleased versus time), Higuchi's (the cumulative percentage of drug released versus the square root of time), and Korsmeyer's equation (the log cumulative percentage of drug released versus time). Table 8 provides a summary of the findings. The Higuchi model, which describes drug release as being characterized by diffusion, was found to be the most suitable for the formulations F5 and F6. The release pattern for F19 is zero order.

3 STABILITY STUDY

According to ICH guidelines Q1C, stability studies were conducted on the most satisfactory formulations F4 to F6 for one month at 30 °C/65 % RH and 40 °C/75 % RH. Samples were evaluated at various intervals of 15 days and 30 days. The various physicochemical parameters examined, such as hardness, drug content, and floating properties, as well as the in vitro dissolution pattern, did not significantly alter at any of the sampling points. The stability study batch and the F6 optimized batch did not differ significantly.

4 CONCLUSION

One of the medications that is used to treat peptic ulcers is ranitidine HCl. It has a short half life of 2-3 hours and is an absorption window limited drug whose solubility in the GIT decreases with pH. As a result, the current investigation focuses on the development of floating matrix tablets, which, when taken orally, were intended to increase the drug's bioavailability and half life by extending the gastric residence time. Various formulations were created by combining the direct compression method with the addition of sodium bicarbonate as a gas-generating agent and utilizing release rate-controlling and gel-forming polymers like HPMC and Poly ethylene oxide WSR 303. The

necessary physicochemical parameters, such as hardness, friability, weight variation, drug content, swelling index, and floating properties, were present in the developed floating tablets. Swelling studies indicated significant water uptake, which contributed to drug release and gastroretention. All of the developed matrix tablets floated for up to 12 hours. Ranitidine HCl's initial burst release from the FDDS was observed to be inhibited by the higher viscosity polymer. Since formulation F6 extended the drug release for longer than 12 hours, they were chosen as the best formulations out of all the ones developed. After being stored at 35 °C (65% RH) and 40 °C (75% RH) for a month in stability tests, the formulations that performed the best showed no significant changes in their physicochemical properties, drug content, floatability, or in vitro dissolution pattern.

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AN OVERVIEW OF THE IMPORTANCE OF CARDIAC REHABILITATION IN MANAGING CARDIOVASCULAR DISEASES

Soorammagari Sunayana
Asst. Professor, Department of Pharmacology Princeton College of Pharmacy, Hyderabad, Telangana, India
Vaishnavi Munnangi
Asst. Professor, Department of Pharmacology Princeton College of Pharmacy, Hyderabad, Telangana, India

Abstract - Cardiac rehabilitation (CR) is regarded as a means of controlling and preventing cardiovascular diseases due to the high mortality and morbidity rates associated with them. Outpatient, comprehensive, long-term programs that include medical evaluation, prescribed exercise, cardiac risk factor modification, education, and counseling are typically provided as CR services. Diet and medication management of lipid abnormalities, blood pressure control, diabetes management, and stress management are all examples of this. The fear and anxiety that so many people feel after a heart attack can be lessened with the help of exercise as part of a comprehensive rehabilitation strategy. Cardiovascular fitness can be improved through aerobic exercise training in both healthy individuals and cardiac patients. Cardiovascular rehabilitation improves the patient's exercise capacity, improves quality of life, reduces cardiac risk factors, and prevents and treats cardiovascular disease. Aerobic exercise with an intensity of 60-70 percent of maximum heart rate for 30-60 minutes three to four times per week for four to six weeks increases exercise capacity.

Keywords: Cardiovascular disease and cardiac rehabilitation.

1 INTRODUCTION

1.1 Cardiac Rehabilitation (CR)

The world's leading cause of morbidity and mortality is heart disease. A subspecialty of rehabilitation medicine known as cardiac rehabilitation (CR) focuses on improving cardiac patients' physical function. By attempting to lessen the physiological and psychological toll, cardiac rehabilitation aims to promote secondary prevention, improve both quantity and quality of life by reducing risks of re-infarction, managing symptoms, and allowing clients to regain control of their lives. Outpatient, comprehensive, long-term programs that include medical evaluation, prescribed exercise, cardiac risk factor modification, education, and counseling are typically provided as CR services. Management of lipid abnormalities through diet and medication, control of blood pressure, diabetes management, and stress management are all examples of this.

The process by which patients with cardiac disease, in conjunction with a multidisciplinary team of health professionals, are encouraged and supported to achieve and maintain optimal physical and psychosocial health is known as cardiac rehabilitation (CR). Cardiac rehabilitation (CR) is a secondary

prevention program that consists of structured exercise, comprehensive yoga education, and diet counseling.1 Additionally significant is the involvement of partners and other members of the family who can provide social support2. Participation in CR results in lower morbidity and mortality.

Unfortunately, patients are significantly less likely to participate in these programs.1 Previous research has shown that these programs reduce all-cause and cardiac mortality by 20-25%.3 More recent research has allowed for the analysis of a larger number of patients (8440 in 32 trials) and has shown that these programs reduce total cardiac mortality by up to 31%. In 2001, Pasquali et al. found that participation in CR after MI also increases well-being and decreases disability4. suggested that a variety of factors contribute to the low utilization of cardiac rehabilitation programs, with physician recommendation and referral being regarded as the most important factor for increased utilization. Another factor that has an impact is social support. Yates et al. in 1994 suggested that clients are more likely to adhere to the program than those who do not have family support. King, colleagues, and it has been reported that older people and women frequently lack social support. This is in line with research showing that women, older people, people without jobs, and people with less education are less likely to participate in cardiac rehabilitation. Participation has been suggested to be influenced by convenience factors like transportation accessibility and distance.

2 ORGANIZED REHABILITATION VS HOME PROGRAM

There are a number of advantages to structured rehabilitation that are not available through home programs, and it is more structured and closely monitored. Direct medical supervision of exercise is more important for high-risk patients, such as those who experience angina while exercising, have cardiac rhythm disturbances, a drop in systolic blood pressure while exercising, or are cardiac arrest survivors. Since repetitive coronary episodes are more normal in the weeks or initial not many months after the underlying one, clinical oversight during activity might be more significant during this period than later. Additionally, the presence of a doctor or other medical personnel helps many patients overcome their fear of beginning an exercise program.

A coordinated program might give additional inspiration to proceed. After a heart attack, it is all too common for patients to leave the hospital with the determination to alter their lifestyle, such as to lose weight, quit smoking, start exercising, and so on. The decision typically lasts for a few weeks before the person begins to fall back into old habits as the fear goes away and life returns to its normal routine. If the person is a part of a program that is planned out for them, this is less likely to happen.

3 BENEFITS OF CARDIAC REHABILITATION ON CARDIOVASCULAR DISEASES

Heart Failure

Heart failure affects between 1 and 2 million people in the United States. People with this condition die more frequently as they get older. In

patients with heart failure, exercise training raises the anaerobic threshold, reduces resting and sub maximal exercise heart rates, reduces exercise minute ventilation, and improves peak blood flow to exercising limbs. Subjective symptoms and quality of life scores were also better after exercise training. There has been reported improvement of 18% to 25% in peak oxygen uptake18-19 and 18% to 34% in exercise duration. After two to six months of training, no adverse effects were observed.

3.1 Hyperlipidemia and Ischemic Heart Disease

To determine the effect of cardiac rehabilitation on lipid profile, Toufan and Afrasiabi conducted a study. After heart recovery there is significant effects on working on useful limit, prosperity sensation, return to work and there is decline in serum lipid profiles in coronary patients. Omiya K looked into the effects of a cardiac rehabilitation program on ischemic heart disease. Patients with ischemic heart disease saw improvements in exercise tolerance, quality of life, coronary risk factors, and many other areas as a result of this program.

3.2 Myocardial Infarction

In Myocardial dead tissue there is lacking myocardial perfusion which brings about harm and putrefaction of heart. As a result, coronary blood vessels become obstructed and narrow. Treatment in view of patient's general signs and side effects of coronary deficiency and hemodynamic unsteadiness. Junger and co. exhibited the impact of cardiovascular restoration in patients with myocardial localized necrosis. During the one-year follow-up period after ST elevation myocardial infarction (STEMI) or Non ST elevation myocardial infarction (NSTEMI), a strong association between cardiac rehabilitation and reduced mortality was observed. conducted a prospective randomized controlled trial on the long-term effects of cardiac rehabilitation in patients undergoing PCI or myocardial infarction. After cardiac rehabilitation, patients' quality of life improved.

3.3 Heart Rate

HRV, or heart rate variability, is a useful, noninvasive, and repeatable indicator of how well the autonomic nervous system works. Variable and responsive heart rates are thought to increase survival chances, whereas lower HRV may be linked to poorer cardiovascular health and outcomes. People with diabetes mellitus, chronic heart failure, unstable angina, and myocardial infarction may benefit from a lower HRV's prognostic value. Exercise therapy and other interventions that can raise HRV have also been looked at. By increasing vagal tone and decreasing sympathetic activity, exercise therapy may increase HRV in patients with myocardial infarction, chronic heart failure, and revascularization.

3.4 Blood Pressure

Due to a decrease in total peripheral resistance, exercise causes a gradual rise in systolic blood pressure and a slight drop in diastolic pressure. An increase in both stroke volume and ejection fraction is possible with reduced left ventricle afterload. Because there is a reduction in double product following exercise, there is a

reduction in the risk of myocardial ischemia as a result of the lower systolic blood pressure.

3.5 Diabetes Management

Both diabetes mellitus and impaired fasting glucose are associated with adverse long-term cardiovascular outcomes; improved glycemic control favorably affects cardiovascular morbidity and mortality. Physical activity reduces insulin resistance and glucose intolerance.

3.6 Effect of Cardiac Rehabilitation on Mortality and Cardiovascular Outcomes

Randomized preliminaries recognize two sorts of activity based heart restoration:

i. Only exercise
ii. In addition to psychological and educational interventions, exercise, and typically comprehensive cardiac rehabilitation.

Exercise-only cardiac rehabilitation reduced all-cause mortality by 27%, cardiac death by 31%, and a combined end point of mortality, nonfatal myocardial infarction, and revascularization by 19% in men and women of all ages with previous MI, revascularization, or angina. Over the course of an average of 2.4 years, benefits accrued. There was no effect on nonfatal myocardial infarction alone, and comprehensive cardiac rehabilitation did not appear to add any additional benefit. Post-MI, the majority of subjects were low-risk middle-aged men. Heart transplant recipients; Heart failure and artificial valves were ruled out. There are two potential clarifications for the disappointment of thorough heart restoration to show extra advantage. One is that, even if it is not structured, exercise-only cardiac rehabilitation is likely to include psychological and educational support. Another factor is that the majority of exercise-only trials were carried out prior to the thrombolytic era; whereas the majority of comprehensive trials were only recently published. As a result, the advantages of the comprehensive rehabilitation trial are likely to outweigh those of thrombolysis, preventative medication, and/or revascularization.

4 BENEFITS OF YOGA

Yoga and meditation help the body and limbic system relax, which can lead to feelings of motivation, contentment, energy, and potential. Yoga leads to significant changes in the neurohormonal system, which improves the brain's electrophysiological activity. During meditation, high-resolution brain imaging studies have demonstrated that activity in the frontal and other cortical brain regions decreases, while activity in the limbic brain areas, particularly the hippocampus, which is associated with the stress hormone cortisol, increases. Bremmer et al. demonstrated that patients with post-traumatic stress disorder or depression have smaller hippocampuses, which may be related to higher levels of stress-induced cortisol. Later, they also demonstrated that meditation actually makes the hippocampus bigger.

The parasympathetic nervous system is activated, resulting in a balanced sympathetic-parasympathetic axis, and the

physiological benefits of yoga can be primarily due to a decrease in catecholamine release and activity, lowering blood pressure, heart rate, and respiratory rate. A decrease in urinary homovanillic mandelic acid, an increase in beta-endorphins, and a galvanic skin response (a measure of decreasing sympathetic nervous activity) are additional biochemical alterations associated with yoga practice. In addition, there is a significant decrease in the amount of adrenaline, noradrenaline, dopamine, and aldosterone excreted from the urine, as well as an increase in the amount of cortisol excreted from the urine, as well as a 5-fold increase in plasma arginine vasopressin levels and EEG synchrony. One study was conducted on residents of a yoga retreat. According to Innes et al., who looked at 70 studies, yoga practice has a positive effect on cardiac risk factors like glucose tolerance and insulin sensitivity, lipid profiles, blood pressure, oxidative stress, coagulation, and cardiovagal function. Body mass index, total and LDL cholesterol, fibrinogen, and blood pressure are all reduced by regular yoga practice.

5 CURRENT AWARENESS– PREVALENCE IN INDIA

The number of exercise programs for heart patients with medical supervision has significantly increased in recent years. Outpatient departments or research labs at hospitals or medical centers typically provide many of these programs; Others are provided by organizations or fitness centers. A few specialists fight that there is no requirement for a formal heart restoration program for most of generally safe people, and that such patients can achieve what should be finished on their own after a few educational meetings with a doctor or recovery trained professional.

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A DESCRIPTIVE STUDY ON THE USE OF MULTIPLE ANTIPSYCHOTIC MEDICATIONS IN TREATING PATIENTS WITH RESISTANT SCHIZOPHRENIA

Ajmeera Rajya Laxmi
Asst. Professor, Department of Pharmaceutical Chemistry, Princeton College of Pharmacy, Hyderabad, Telangana, India
Gaddam Swetha Reddy
Asst. Professor, Department of Pharmaceutical Chemistry, Princeton College of Pharmacy, Hyderabad, Telangana, India

Abstract-
Purpose: to find out how frequently and how often patients with resistant schizophrenia in Lebanon use antipsychotic polypharmacy (APP).
Methods: This is a study that looked back from February to May of 2016. The patient records provided the necessary data.
Results: There were 116 patients included. The majority of patients were taking two antipsychotics together. Four of the 29 patients were taking clozapine alone, 18 were taking it with one antipsychotic, and seven were taking it with two. 74 of the 90 patients who experienced side effects while receiving antipsychotic medication were taking a combination. Cardiovascular (11), metabolic (11), anticholinergic (57), extrapyramidal symptoms (25), and blood abnormalities (9) were reported APP events. Three patients were found to be taking a combination that contained either Clozapine or Risperidone—both of which are linked to a frequent risk of side effects on weight gain, glucose level, and lipid profile—and had a BMI greater than 40. In addition, four elderly patients were taking a combination of two or three antipsychotics and a high dose of haloperidol.
Conclusion: Based on the findings of this study, additional efforts should be made to recommend the APP with the fewest side effects.
Keywords: Antipsychotics; Polypharmacy; Resistant; Schizophrenia.

1 INTRODUCTION

Significant clinical issues include treatment resistance and inadequate response to antipsychotic (AP) medication. 20% to 30% of schizophrenia patients are resistant to treatment. The use of combined antipsychotics, usually for people who already have schizophrenia, has been found to be relatively common and consistent in psychiatric services around the world, with a prevalence of up to 50% in some clinical settings. The fact that almost 30% of schizophrenia patients do not respond well to antipsychotic monotherapy lends credence to APP. It is still hard to find the best treatments for people who have schizophrenia. Despite the abundance of antipsychotic medications on the market, patients rarely achieve their therapeutic objectives.

Even though the data are inconclusive, there is a lot more evidence that APP increases the risk of significant pharmacokinetic and pharmacodynamic interactions, chronic side effects, and mortality, which should not be overlooked. The lack of comprehensive research on

APP's long-term effects is a growing cause for concern. Particularly concerning is the possibility of an increase in overall mortality among APP patients. With no clear evidence of differential clinical benefit, APP has also been linked to higher than maximum daily doses, a higher risk of adverse effects, and longer hospital stays. Additionally, treatment compliance may be compromised and costs may rise due to APP.

We are aware that hospital-based data on APP use in Lebanon is either scarce or unavailable. As a result, the goal of this study is to find out which long-term APP is used most frequently in a major Lebanon psychiatric facility and how often it is used in schizophrenic resistant patients. Dose adjustments, the prevention of drug-drug interactions, and anticipated adverse effects from antipsychotic use were all evaluated as part of the secondary objective.

2 METHODOLOGY

2.1 Study Design and Ethical Considerations

The study, which took place in the Psychiatric Hospital of the Cross, Lebanon's largest psychiatric facility, from February 2016 to May 2016, consisted of reviewing the medical records of schizophrenic patients. Because it was an observational study that did not cause any harm to the participants and respected their privacy, the Lebanese International University school of Pharmacy Institutional Review Board and the hospital ethics committee decided not to require approval. Before distributing the questionnaire to each parent, written informed consent was obtained.

Patients over the age of 18 who had resistant schizophrenia and were taking one or more antipsychotics (typical or atypical) were eligible to participate in the study. Patients with schizophrenia who did not respond to treatment were considered to be resistant.

The study did not include people who had mental retardation or other cognitive disorders, had serious side effects from APP treatments in the past, had their first psychotic episode, or had evidence of severe resistance to treatment in the past. Patients who had any change in their antipsychotic prescriptions less than a week prior to the day of the study were excluded in an effort to capture long-term polypharmacy. As a result, patients were required to remain on the same antipsychotic dosage for at least a week. The practice of using chlorpromazine equivalents (CPZeqs), which is strongly linked to polypharmacy, was used to see if there was a prescription for an excessive amount. This was only done with antipsychotics that showed equivalent Chlorpromazine doses. The total of each patient's individual CPZeqs for all oral and intramuscular antipsychotics was then used to calculate CPZeqs.

A high dose of CPZeqs was considered for any patient taking more than 1000mg. The following formula was used to determine the Body Mass Index (BMI): body weight (in kilograms) partitioned by the square of the level (in meters), and ordered by the European Culture of Cardiology (ESC) and the European Atherosclerosis Society (EAS) rules 2011 and WHO: Normal (18.5-24.9),

underweight (18.5), overweight (25.0-29.9), and obese

3 STATISTICAL ANALYSIS

All study variables were subjected to descriptive statistics analysis. The counts and percentages for categorical variables, as well as the mean and standard deviation for continuous measures, are all included in this. The side effects of patients receiving APP and those receiving monotherapy were compared using the Chi square test. All statistical analysis was performed with the statistical software package SPSS version. The significance level was set at p 0.05.

4 CONCLUSION

We presumed that a typical justification for polypharmacy is to accomplish a more fast helpful reaction than with monotherapy. However, it is generally agreed that there is insufficient evidence to support recommending this strategy for use in psychiatric routine clinical practice. In order to determine the most effective antipsychotic combination, larger experimental studies need to be carried out.

In the interim, a prudent APP practice will necessitate a careful selection of products based on prior patient history (including drug treatment history) and interaction liability, valid consent from patients or their representatives, and careful monitoring of clinical outcomes and emerging side effects to prevent the indefinite administration of ineffective and potentially harmful combinations.

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A CRITICAL ASSESSMENT OF PHARMACISTS

Dr. P.Raja Sridhar Rao
Assoc. Professor, Department of Pharmaceutics, Princeton College of Pharmacy, Hyderabad, Telangana, India
G Satheesh
Asst. Professor, Department of Pharmaceutics, Princeton College of Pharmacy, Hyderabad, Telangana, India

1 INTRODUCTION

Pharmacists, also known as scientists (Commonwealth English) or pharmacists (North American and, earlier, Commonwealth English), are experts in medicine who specialize in drug store, the health sciences field that focuses on medication safety and effectiveness. A pharmacist is a member of the social insurance group who is directly involved in providing patient care. In order to comprehend the biochemical instruments and activities of medications, medication uses, remedial components, symptoms, potential medication associations, and checking parameters, pharmacists receive training equivalent to that of a college professor. Life structures, physiology, and pathophysiology are combined with this. Pharmacists translate this particular information for patients, physicians, and other providers of human services.

Different nations require pharmacists to have a Bachelor of Pharmacy, Master of Pharmacy, or Doctor of Pharmacy degree, among other authorization requirements.

The most well-known positions for a pharmacist are those of a group pharmacist (also known as a retail pharmacist, first-line pharmacist, or administering physicist) or a hospital pharmacist. In these positions, pharmacists teach and direct on the proper use and adverse effects of therapeutically endorsed medications and medicines. The profession is subject to professional regulation in numerous nations. Depending on their actual scope of practice, pharmacists may also recommend (also known as a "pharmacist prescriber") and direct certain medications (such as vaccinations) in specific locations. Pharmacists may also practice in a variety of other settings, including the government, the military, the educated community, wholesaling, and examination.

2 NATURE OF THE WORK

As a social insurance specialist, pharmacists were clearly responsible for checking and transporting patients' prescribed medications to specialists. In more recent times, pharmacists serve as educated mediators between a prescriber and a patient and advise patients and providers of medical services regarding the selection, measurements, interactions, and symptoms of pharmaceuticals. To ensure the safe and effective use of a

medication, pharmacists monitor patients' health and development. Pharmacists might try to get more intense; Nevertheless, numerous medications are currently manufactured by pharmaceutical companies in standardized dosage forms and delivery systems. In some places, pharmacists have the authority to prescribe either on their own accord or in collaboration with a primary care physician following a predetermined protocol.

One of the most important areas that pharmacists are currently addressing is one of pharmaceutical care. Pharmaceutical consideration includes assuming direct liability for patients and their ailment states, solutions, and administration of each to improve results. In addition, maturing but more educated and requesting populations, inadequacies in other areas of the social insurance framework, and expanded quantities of medication appear to be driving increased interest for the clinical directing abilities of the pharmacist. Taking pharmaceutical consideration has many benefits, some of which include but are not limited to: reduced medication slips; increased patient acceptance of the medication regimen; better management of chronic diseases, such as hypertension and other risk factors for cardiovascular disease; a strong relationship between the pharmacist and the patient; and less money spent on medical care in the long run.

- Drug specialists are routinely the primary reason for contact for patients with prosperity demand. As a result, pharmacists play a significant role in surveying patients' prescription administration and referring patients to physicians. These parts might integrate, but are not obliged to:
- Specialized checking of ailment states, such as dosing medications in kidney and liver failure
- Compounding medications
- Providing pharmaceutical data
- Providing patients with wellbeing checking and advice, including guidance and treatment of basic diseases and ailment states
- Supervising drug store specialists and other staff
- Oversight of apportioning prescriptions on remedy
- Provision of non-remedy or over-the-counter medications
- Education and advising for patients and other health awareness providers on optimal use of medications.

3 INSTRUCTION AND CREDENTIALING

Drug store instruction, pharmacist authorization, and continuing education vary by country and between districts or territories within countries. A college degree from a drug store school or a related foundation is required for pharmacists in many countries, as are other national or neighborhood credentialing requirements. To obtain a degree in

pharmacy—such as a Doctor of Pharmacy—in many instances, understudies must first complete paraprofessional (undergraduate) coursework. After that, approximately four years of professional studies are required. Pharmacology, pharmacognosy, science, natural science, organic chemistry, pharmaceutical science, microbiology, pharmacy work on (counting medication collaborations, drug checking, Prescription administration), pharmaceutics, drug store law, physiology, life systems, pharmacokinetics, pharmacodynamics, drug conveyance, pharmaceutical consideration, nephrology, hepatology, and exacerbating of prescriptions are among the subjects that pharmacists receive instruction in. An additional educational module might focus on decision-making with an emphasis on research center tests, treatment, and endorsing (choosing the best drug for a given patient).

After graduation, pharmacists are authorized to administer a variety of pharmaceuticals in the areas they have prepared for, either broadly or territorially. Some may require additional concentrated preparation.

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A NEW TYPE OF POLYMER IS CALLED DENDRIMER

G Lavanya
Asst. Professor, Department of Pharmaceutical Chemistry, Princeton College of Pharmacy, Hyderabad, Telangana, India
Hariprasad Kadiyam
Asst. Professor, Department of Pharmaceutical Chemistry, Princeton College of Pharmacy, Hyderabad, Telangana, India

Abstract - Dendrimers are a new class of synthetic macromolecules with a three-dimensional, highly branched architecture at the nanoscale, very little polydispersity, and a lot of functionality. Their potential applications in nanotechnology, pharmaceuticals, and medicinal chemistry are particularly appealing due to these characteristics. Dendritic architecture can be altered in shape, size, polarity, surface properties, and internal structure using synthetic approaches. Most people use nanoparticle drug delivery systems because they can make therapeutic agents more selective and stable. However, the utilization of these nanostructures is constrained by the reticuloendothelial system (RES) uptake, drug leakage, immunogenicity, hemolytic toxicity, cytotoxicity, and hydrophobicity. Surface engineering the dendrimers, such as polyester dendrimers, citric acid dendrimers, arginine dendrimers, glycodendrimers, PEGylated dendrimers, and so on, helps to overcome these drawbacks. The bioactive agents can be easily encapsulated inside the dendrimers, chemically attached (conjugated), or physically adsorbed onto the dendrimer surface to meet the active material's and its therapeutic applications' specific requirements. Dendrimers not only provide a multivalent backbone for drug attachment, but they also give access to a variety of novel polymer architectures that could be useful in drug delivery applications.

Keywords: Dendrimers, Poly (Propylene Imine), Polyamidoamine.

1 INTRODUCTION

A dendrimer is typically referred to as a macromolecule because of its highly branched, three-dimensional structure and high degree of surface functionality and adaptability. Dendrimers have earned the moniker "Polymers of the 21st century" on numerous occasions. Fritz Vogtle and his colleagues introduced dendrimer chemistry for the first time in 1978. He created the initial "cascade molecules." The first family of dendrimers was synthesized by Donald A. Tomalia in 1985.

The Greek words dendron, which means tree, and meros, which means part, are where the word "dendrimer" got its name. At the same time, the synthesis of similar macromolecules was independently reported by Newkome's group. From the Latin word "arbor," which also means a tree, they referred to them as arborols. Dendrimer is the most well-known term, but cascade molecule is also used. Dendrimers have sparked a lot of interest in the fields of chemistry and biology due to their monodisperse and multivalent nature,

particularly for use in drug delivery, gene therapy, and chemotherapy.

2 STRUCTURE

Dendrimers are built from a starting atom, such as nitrogen, to which carbon and other elements are added by a repeating series of chemical reactions that produce a spherical branching structure. As the process repeats, successive layers are added, and the sphere can be expanded to the size required by the investigator. The result is a spherical macromolecular structure whose size is similar to albumin and hemoglobin, but smaller than such multimers as the gigantic IgM antibody complex.

Dendrimers possess three distinguished architectural components, namely

(i) An initiator core.
(ii) Interior layers (generations) composed of repeating units, radically attached to the interior core.
(iii) Exterior (terminal functionality) attached to the outermost interior generations.

3 COMPONENTS OF A DENDRIMER STRUCTURE

1. Generation is the hyper branching that occurs when dendrimers move from the center to the periphery, creating homostructural layers between the focal points (branching points). The generation number is the number of focal points from the core to the dendrimer surface. The term "5th generation dendrimer" refers to a dendrimer with five focal points when moving from the center to the periphery. This term is simply referred to as a G5-dendrimer in this context; for instance, a polypropylene imine of the fifth generation is referred to as a "G5-PPI-" dendrimer. The core portion of the dendrimer is sometimes referred to as generation "zero," or in the terms used in this context, "G0."
2. The homo-structural space between the focal points, or "generation space," is the dendrimer shell. The "outer shell" is the space between the surface and the final outer branching point. Dendrimer interior is the common name for the "inner shells."
3. The last focal point before reaching the dendrimer surface creates a variety of pincers that make up the outer shell of dendrimers. Because the chain splits into two chains at each focal point, the number of pincers in PPI and PAMAM dendrimers is half that of surface groups.
4. End-group the dendrimer's "terminal group" or "surface group" are also common names for this group. "Amino-terminated dendrimers" are dendrimers with amine end groups.

4 TYPES OF DENDRIMERS

1. Pamam Dendrimer

The divergent method uses ammonia or ethylenediamine initiator core reagents to create poly (amidoamine) dendrimers (PAMAM). Products up to generation 10 have been produced, with a molecular weight of over 9,30,000 g/mol (human

hemoglobin's molecular weight is approximately 65,000 g/mol). PAMAM dendrimers can be purchased commercially, typically in the form of methanol solutions. A subclass of PAMAM dendrimers with a tris-aminoethylene-imine core is referred to as "Starburst dendrimers" in the trademark application. The name comes from the star-like pattern that can be seen when looking at the two-dimensional structure of these high-generation dendrimers.

2. Pamamos Dendrimer

The inverted unimolecular micelles known as radially layered poly (amidoamineorganosilicon) dendrimers (PAMAMOS) have exteriors made of hydrophobic organosilicon (OS) and interiors made of hydrophilic, nucleophilic poly (amidoamine) (PAMAM). For creating honeycomb-like networks with nanoscopic PAMAM and OS domains, these dendrimers are extremely useful precursors.

3. The term "Poly (Propylene Imine)"

The propylamine spacer moieties in the oldest known dendrimer type, which was initially developed by Vögtle. The interior of these dendrimers is composed of numerous tertiary tris-propylene amines, and they are typically poly-alkyl amines with primary amines serving as their end groups. PPI dendrimers, which are commercially available up to G5, have numerous applications in biology and material science. As an elective name to PPI, POPAM is at times used to portray this class of dendrimers. The acronym POPAM, which stands for "Poly (Propylene Amine)," is very similar to the acronym PPI. Additionally, these dendrimers are sometimes referred to as "DAB-dendrimers," in which "DAB" stands for the core structure, which typically is based on diamine butane.

4. Tecto Dendrimer

These are made up of a core dendrimer that is surrounded by dendrimers of various steps (each design type) to carry out a function that is necessary for a smart therapeutic nanodevice. Different compounds carry out a variety of tasks, including identifying diseased cells, diagnosing the disease state, delivering drugs, reporting location, and reporting treatment outcomes.

5. Dendrimers

Multiple Functional Groups these dendrimers have multiple functional group copies on their surface.

6. Chiral Dendrimers

The construction of chemically similar but constitutionally distinct branches to the chiral core is the foundation for these dendrimers' chirality.

7. Half breed Dendrimers Direct Polymers

These are half breeds (block or join polymers) of dendritic and straight polymers.

8. Amphiphilic dendrimers

Have two distinct electron-donating and electron-repelling chain end sites built into their structure.

9. Micellar Dendrimers

These are water-soluble hyperbranched polyphenylenes in the form of unimolecular micelles.

10. Multiple Antigen Peptide Dendrimers

This molecule is based on a polylysine skeleton and resembles a dendron. Because of its alkyl amino side-chain, lysine is an excellent monomer for establishing numerous branchingpoints. Since its introduction in 1988 by J. P. Tam, this type of dendrimer has primarily found application in biological research, such as diagnostic and vaccine development.

5 PROPERTIES OF DENDRIMERS

Dendrimers can be precisely controlled during synthesis, whereas the classical polymerization process, which results in linear polymers, is typically random in nature and produces molecules of varying sizes. Contrary to linear polymers, dendrimers are monodisperse macromolecules. Dendrimers outperform conventional linear polymers in terms of their chemical and physical properties due to their molecular architecture. Linear chains appear as flexible coils in solution; Dendrimers, on the other hand, form a tightly packed ball. Their rheological properties are significantly affected by this. Dendrimers of the lower generation, which are large enough to be spherical but do not have a tightly packed surface, have huge surface areas for their volume. In contrast to linear polymers, dendrimer solutions' intrinsic viscosity does not increase linearly with mass; rather, it reaches its peak at a particular generation before beginning to decrease. This is not how linear polymers behave. This is probably because the shape of dendrimers changes with generation, with lower generations adopting a more open planar–elliptical shape and higher generations moving to a more compact spherical shape. High reactivity and high solubility and miscibility are both caused by the abundance of chain ends. The periphery of the dendrimers is thought to have the highest molecular density in the structure of the dendrimers. It has been recommended that back collapsing of the terminal branches prompts a more uniform or even converse thickness profile. Tree-like structures have evolved in nature to maximize the surface area that is exposed, such as to maximize light exposure and the number of leaves on a tree. Similar to dendritic architecture, molecules with very high molecular surface to volume ratios (up to 1000 m2/g) are made with a large proportion of the groups exposed at the surface. Dendrimers typically exhibit high solubility, reactivity, and binding due to the multiple terminal

groups that make it possible for surface groups to interact with the solvent, surfaces, or other molecules simultaneously.

6 CONCLUSION

Because of their unique properties, such as their high degree of branching, multivalency, globular architecture, and well-defined molecular weight, dendrimers offer new scaffolds for drug delivery. As a result, they hold a promising future in a variety of pharmaceutical applications as well as the diagnostic field in the coming years. Poor solubility, bioavailability, and permeability are issues with an increasing number of drugs currently in development. Dendrimers have the potential to be a useful tool for enhancing drug delivery of such hazardous substances. Surface engineering can also solve the biocompatibility and toxicity issues. Dendrimer synthesis has recently been simplified and improved, resulting in a wider range of structures at lower production costs. Dendrimer-based drug delivery systems should become increasingly commercialized in the future, and newer applications of dendrimers will also emerge as research advances.

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EXPLORING THE USE OF HIGH SHEAR GRANULATORS IN TABLET FORMULATION DEVELOPMENT: A CRITICAL ANALYSIS

Roopani Madhu
Asst. Professor, Department of Pharmaceutical Chemistry, Princeton College of Pharmacy, Hyderabad, Telangana, India
Sangu Jyothi
Asst. Professor, Department of Pharmaceutical Chemistry, Princeton College of Pharmacy, Hyderabad, Telangana, India

Abstract - In the production of pharmaceutical finished products, primarily tablets and capsules, granulation is a significant unit operation. In most cases, the granulation process can be carried out using either dry granulation or wet granulation. Wet granulation is considered by many product formulators to be a universally applicable method for tablet production. Wet granulation, which does not rely on the drug's intrinsic properties or the excipients, can produce the final blend of a compression mix that generally requires a good flow, good compactability, uniform drug distribution, and controllable drug release.

1 INTRODUCTION

Fine or coarse particles are transformed into large agglomerates known as granules during the granulation process. As a result, "a process whereby small powder particles are gathered to form larger, multiparticulate entities" can be used to describe granulation. In the production of pharmaceutical finished products, primarily tablets and capsules, granulation is a significant unit operation. The granulation process aims to combine components to produce a high-quality product. Granulation is based on the size enlargement process, which transforms small particles into agglomerates that are physically stronger and larger.

1.1 Reasons for Granulation

1. Make sure that the drug distribution in the product is uniform.
2. Builds thickness of the material
3. Accentuate the compression and flow properties.
4. Reduces environmental contamination and dust
5. Makes the product look better
6. Lower compression pressure and less tooling wear and tear Lower pressure weight, less mileage on tooling

1.2 Choice of Methods for Granulation

In the process of making numerous solid dosage forms, granulation is an essential processing step. In most cases, the granulation process can be carried out using either dry granulation or wet granulation. Each of these two granulation methods has its own set of benefits and drawbacks.

1.3 Wet Granulation

The dry powder blend and granulating fluid are combined during the wet granulation process. The fluid used in the granulation process needs to be

non-toxic and volatile so that it can be removed after drying. Water, isopropanol, and ethanol are the liquids used in the granulation process. You can add these liquids separately or in combination. The granulation liquid can be used alone or with a dissolved adhesive (binders) to ensure that the particles adhere to the granule after it has dried. Because they aid in connecting particles to one another, binding agents play a crucial role in tablet formulation. It is used to make granules out of powder. Binders can be added to granulating fluid either as solids or as a liquid solution, or they can be added as dry powder.

1.4 Dry Granulation

By placing the powder particles under high pressure, the particle size in dry granulation is increased. One type of dry granulation is called "slugging," in which a large tablet (also known as a slug) is made in a heavy-duty tableting press. The other type, "roller compactor," forces the powder between two counter-rotating rolls to produce materials that look like ribbons. In both the cases the slugs or compacts are size decreased utilizing a reasonable processing procedure to deliver granules, which is generally sieved to yield the necessary size part. It is possible to rework the obtained fines material to reduce waste. For APIs that are sensitive to temperature or moisture, dry granulation is an appealing method that can be used in continuous granulation processes. There has been very little advancement in the dry granulation strategy in contrast with wet granulation, aside from one significant development known as pneumatic dry granulation innovation, a creative dry granulation innovation, which produce granules with great flowability and compressibility. Processing time is decreased when the materials and blend are dry granulated. Because the equipment requirements are simplified, the final product costs less. The most significant drawback of dry granulation is the higher percentage of non-compacted or fine products, which may compromise tablet quality.

1.5 Purpose of Wet Granulation

Wet granulation is considered by many product formulators to be a universally applicable method for tablet production. Wet granulation, which does not rely on the drug's intrinsic properties or the excipients, can accomplish the requirements for the final blend of a compression mix—good flow, good compactability, uniform drug distribution, and controllable drug release. Wet granulation is currently the preferred drug product processing method for low dose (high dilution) drugs, as it locks the drug particles into the granules and reduces segregation intensity and content uniformity. High dose drugs, on the other hand, can be manufactured using wet granulation, which has poor flow and compressibility of the active mean.

1.6 Lesser Amount of Liquid Binders Required Compared to Fluid Bed Granulator

Wet granulation therefore has a number of benefits in addition to a number of drawbacks. Granulation Liquid utilized in the cycles can acquire numerous superfluous changes drugs or in excipients;

Because it takes time, requires equipment, energy, labor, and space, it is expensive. Material loss at various processing stages. Stability can be a major concern when it comes to drugs that are sensitive to moisture. Chemical degradation of thermolabile materials can occur as a result of an increase in temperature. Overwetting can result in the formation of large granules. In a QbD development program, the number of quality critical factors that must be studied and controlled increases as a result of the numerous processing steps in wet granulation.

1.7 Types of Wet Granulation

Wet granulation, which includes fluid bed granulation, can be a low or high shear process. Wet granulation has traditionally been a batch process governed by process parameters. In practice, a formulator may not be able to choose which process to use for a product because of equipment availability and the company's choice based on experience. Each process has its own strengths and weaknesses that may be useful for different formulations.

1.8 Low Shear Granulation

This method uses low-speed planetary or trough mixers to granulate the active pharmaceutical ingredient and intra-granular excipients with a binder solution. The resulting wet mass is then screened to form discrete granules and dried in a tray dryer. After being rescreened or milled to the desired size, the dried granules are combined with additional granular excipients, blended, lubricated, and compressed. The openness of the equipment and the need for manual material transfer are the process's primary drawbacks, as are the lengthy drying times, the possibility of soluble components migrating during tray drying, and the general lack of instrumentation for in-process control.

1.9 High Shear Granulation

A high shear granulator has a cylindrical mixing bowl, an impeller with three blades, a chopper, an auxillary chopper, a motor to drive the blades, and a discharge pot. The process that is carried out in a high shear granulator includes the following:

1) Dry mixing of the powder mixture;
2) Adding binder solution or granulating fluid;
3) Wetting of the powder and the nucleation process;
4) Granule growth and Powder densification; and
5) Breaking down the large lumps that are formed.

The impeller that is used for mixing the powder mixture typically rotates at a speed that typically ranges from 100 to 500 rpm and applies high The wet mass is broken up by the high-speed chopper as the granulation process continues at speeds between 1000 and 3000 rpm. When compared to low shear granulation, the combination of impeller and chopper blades results in effective component mixing and a reduced need for water.

2 END POINT DETERMINATION

The important control in the granulation process is to get the required consistency by determining the granulation end point. This is done by keeping an eye on how much

power the impeller motor uses, but many other approaches have also been looked into. The target particle size mean or distribution can be used as the endpoint.

2.1 Traditional Methods for Detecting the end Point

a) Power Consumption: The measurement of the mixer motor's power consumption for scale-up and end-point determination is widely used because it is cost-effective, does not require extensive mixer modifications, and has a strong correlation with granule growth.

b) Impeller Torque: Strain gauges must be installed on the impeller shaft or on the coupling that connects the motor and impeller shaft. A device known as a slip ring is used to send the signal to the stationary data acquisition system because the shaft is rotating.

c) Torque Rheometer: A torque rheometer can be used to evaluate the granulation's rheological properties and provides an off-line measurement of the torque required to rotate the device's blades. The obtained torque values have been referred to as a "measure of wet mass consistency."

d) Reaction Torque: The motor attempts to rotate in the opposite direction as the impeller shaft rotates, but it is unable to do so because it is bolted in place. A reaction torque transducer can be used to measure the tensions in the base of the stationary motor.

2.2 Optimisation in Wet Granulation

Many variables in wet granulation method affects the physical properties of the granules and tablets.

2.3 Apparatus Variables

Apparatus variables such as the size and shape of the bowl, impeller and chopper are dependent on the type of mixer used. The effects of the impeller model in high-speed mixers can be described in terms of volume swept out by the impeller. A high swept volume causes increased densification of the agglomerate and narrow granule size distribution. The size of the Chopper and rotation speed had no effect upon the granule size distribution.

2.4 Process Variables

Mechanical forces exerted by the mixing tools on the moist powder mass control granulation in a high shear granulator. The impeller speed and the wet massing time are the main variables that affect the properties of the granules. The concept of liquid saturation can be used to describe the effect that these two variables have when combined.

Speed of the Impeller: Granules made at a high speed tend to be smaller and more dense. Granules with a lower impeller speed tend to be larger and more porous.

Chopper Speed - Chopper speed significantly affects granule size and thickness however in the event that the chopper is huge, it might go about as an optional impeller.

Method and rate of water addition - The rate of water addition is crucial to the quality of granules. The rate of water addition was chosen to avoid overwetting the powder mass while still being fast enough to accommodate processing times.

Massing Time: The wet mass can typically be kneaded for one to ten minutes. As a result of decreased

disintegrant functionality or the formation of dense granules, prolonged massing times may result in lower dissolution rates.

2.5 Fluidised Bed Granulation

Granulation is the process of transforming a fine powder into larger granules of a particular size and shape. Using a single piece of equipment, fluid bed granulation produces granules by spraying a binder solution onto a fluidized powder bed. Drugs and excipients are loaded into a fluid bed processor, where they are fluidized with air. The granulating fluid is then sprayed into the bed, typically from above, with a steady stream of warm drying air.

1) **Blending:** The drug and excipients are dry mixed with a small volume of fluidizing air to achieve blend homogeneity and warm the dry powders. This is the first of three stages.
2) Granulation, in which the fluidized bed is sprayed with binder solution. Development of granule during this stage relies upon various factors, for example, grinding liquid thickness and drop size and shower rate.
3) Drying, in which the powder bed is fluidized gently until the granules dry before the spraying process is stopped. We can figure out where the end is based on the temperature of the bed.

2.6 Advantages of Fluidised Bed Granulation

A single piece of equipment can be used for both granulation and drying in this contained process, making it less expensive than high shear granulation. Because it produces uniform particles with a specified particle size, loss of drying (LOD), and other required variables, fluid bed granulation enhances the manufacturing process. Because the equipment combines granulation and drying, the process saves money and reduces product storage space. It diminishes material misfortune. Throughout the entire processing, it reduces dust production.

3 CONCLUSION

High-shear granulators are used for blending and granulation in many pharmaceutical industries. Since many years ago, the wet granulation method has been used for tablet production and is universally applicable.

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REVOLUTIONIZING DRUG DELIVERY: AN OVERVIEW OF MOUTH-DISSOLVING FILMS

Boggula Ratnakumari
Asst. Professor, Department of Pharmacognosy, Princeton College of Pharmacy, Hyderabad, Telangana, India
Surendar Angothu
Asst. Professor, Department of Pharmacognosy, Princeton College of Pharmacy, Hyderabad, Telangana, India

Abstract - Mouth Dissolvable Films, or MDFs, originated in the confectionery and oral care industries as breath strips and have since developed into a novel and well-liked form among consumers. MDF that dissolve in one minute when placed in the mouth without chewing or drinking water. Additionally, it is utilized to mask the taste of drugs with a strong bitter taste, which is particularly important for pediatric patients. By allowing the medication to bypass the first-pass metabolism, these drug delivery systems increase bioavailability. The application of both aesthetic and performance characteristics, such as plasticized hydrocolloids, an active pharmaceutical ingredient, and a taste masking agent that are laminated through solvent casting or hot melt extrusion, is necessary for the formulation of oral films. Films with a fine gloss and improved physical properties are produced by solvent casting, which is the method of choice because of its superior thickness uniformity. The thickness, surface pH, folding endurance, disintegration, and dissolution study of oral strips are all evaluated. The evaluation parameter and formulation methodology are discussed in this review.

Keywords: Film for dissolving in the mouth, solvent casting, semisolid casting, and masking the bitter taste.

1 INTRODUCTION

The mouth dissolving films consist of a very thin oral strip that is simply applied to the patient's tongue or any oral mucosal tissue. After being immediately soaked by saliva, the film quickly hydrates and adheres to the application site. After that, it breaks down and dissolves quickly to release the medication for oral mucosal absorption, or, if the formula is changed, it will keep the quick-dissolving properties, allowing for gastrointestinal absorption when swallowed. Without the need for water or measuring instruments, MDFs provide quick, precise dosing in a safe, effective, and portable format. For the rapid release of one or more APIs, MDFs, which are typically the size of a postage stamp, disintegrate on a patient's tongue in a matter of seconds.

Patients who have difficulty taking traditional oral dosage forms and those who want the convenience of any-time dosage when water is unavailable both require fast-dissolving dosage technologies.

Fear of choking prevents many pediatric and geriatric patients from taking solid medications. Tablet size was the most common complaint, followed by taste and a larger surface area. More patient-friendly dosage

forms have been used more frequently over the past two decades3.

As an alternative to fast-dissolving tablets, fast dissolving film is made with hydrophilic polymers and quickly dissolves or disintegrates in the mouth without the need for water within a few seconds. The fast dissolving film is basically a postage stamp-sized ultrathin strip containing an active pharmaceutical ingredient and other excipients. The majority of films that dissolve quickly contain taste-masked active ingredients. Patients swallow the soluble and insoluble excipients as well as these disguised active ingredients.

The active agents are released from these films, which typically dissolve in a matter of seconds. However, depending on the thickness of the film and the polymer matrix that is chosen, the drug can be released more slowly. A water-based dosage form can be described as a film or strip. Polymer that dissolves quickly, allowing the dosage form to hydrate, adhere, and dissolve when placed on the tongue or in the oral cavity for quick local or systemic drug delivery. This new delivery method, a medicated oral strip with a proprietary bilayer structure, was developed by Zengen Inc. These films typically contain hydrocolloids that dissolve in water, such as HPMC, pullulan, pectin, carboxymethy cellulose, an effective dose of the active agent, and additional additives like flavoring agents, plasticizers, and preservatives. The thickness and combination of hydrocolloids in a thin film determine its disintegration and dissolution characteristics.

The sensations of sweetness and sourness can be found on the sides and tip of the tongue, respectively, while bitterness can be found at the back of the tongue and salty sensations can be found on the sides and tip of the tongue. These four tastes are represented by different receptors on the tongue. A fundamental flavor known as umami was recently discovered. Monosodium glutamate (MSG), which is primarily found in seaweed, and disodium inosinate (IMP), which is found in meat and fish, produce umami, the fifth distinct flavor. The 7th, 9th, and 10th cranial nerves carry electrical impulses to these taste-perceiving brain regions from the above taste receptors, which bind to molecules in saliva.

1.1 Ideal Characteristics of a Suitable Drug Candidate

- The drug ought to taste good.
- The dosage ought to be as low as possible.
- Drugs with a lower molecular weight and a moderate molecular mass are preferred.
- Excellent stability in saliva and water
- At the pH of the oral cavity, it should be partially unionized.
- It ought to be able to penetrate the tissue of the oral mucosa.

1.2 Benefits of Oral Thin Films

- In the oral cavity, a larger surface area encourages rapid disintegration and dissolution. When compared to ODTs, oral films are less fragile because they are flexible.
- Customer care and storage
- Dysphagic patients have been more receptive to the treatment

because it is simple to swallow and does not require water.

- The dosage form can be consumed whenever and wherever the individual chooses.
- Due to the oral or buccal mucosa's high vascularization, drugs can enter the systemic circulation directly and bypass first-pass hepatic metabolism.
- Upgraded oral bioavailability of particles that go through first pass impact. For the rapid release of one or more APIs, OTFs are typically the size of a postage stamp and disintegrate on a patient's tongue in a matter of seconds.

2 COMPOSITION OF THE SYSTEM

1) Drugs: Several classes of drugs, such as omeprazole, salbutamol sulphate, antitussives, expectorants, antihistamines (cetrigine), nonsteroidal anti-inflammatory drugs (NSAIDs), chlorpheniramine maleate (antiallergic), and zolmitriptan, can be made into films that dissolve in the mouth. The OS18 can typically contain between 5% and 30% of active pharmaceutical ingredients.

2) Water-Soluble Polymers Film formers are made of water-soluble polymers. In the fields of medicine and nutrition, the use of film-forming polymers in dissolvable films has received a lot of attention. The films' mechanical properties and rapid disintegration are achieved by the water-soluble polymers. By increasing the molecular weight of the polymer film bases, the disintegration rate of the polymers is slowed down. Pullulan, carboxmethylcellulose cekol 30, Polyvinylpyrollidone PVP K-90, Pectin, Gelatine, Sodium Alginate, Hdroxypropylcellulose, Polyvinyl alcohol, Maltodextrin, and eudragit-RD are among the water-soluble polymers utilized as film formers. A novel film-forming polymer is polymerized rosin.

The formulation of plasticizers (plasticizer, etc.) have been identified as significant influences on films' mechanical properties. The addition of plasticizers has also resulted in improvements to the films' mechanical properties, such as 1) tensile strength and 2) elongation used in 1 to 20 percent of the dry polymer weight as w/w. These properties may be affected by their concentration. Glycerol, dimethyl, diethyl, and dibutylpthalate, citrate derivatives like tributyl and triethyl citrate, polyethylene glycol, and castor oil, among others, are common plasticizers.

- A number of studies on the effects of various plasticizers on gelatin strips found that malic acid was a superior plasticizer over citric, oleic, and tartaric acids because it did not crystallize when the film was dried.
- Polyethylene glycol with a low molecular weight was found to be a superior plasticizer to polyethylene glycol with a high M.W.
- When glycerine and propylene glycol are used as plasticizers in the concentration range of 16–20%w/w, maltodextrin can also be plasticized and turned into an oral dissolving film. This process has been found to be more advantageous than when

propylene glycol is used because it has miscibility issues with maltodextrin.

3) Saliva Stimulating Agents

The salivary stimulants are used to increase the production of saliva that would help the formulations of the rapid dissolving films dissolve more quickly. Among the salivary stimulants, citric acid is the most commonly used, followed by malic acid, ascorbic acid, and tartaric acid. Between 2 and 6% w/w of the strip's weight, these agents are used together. Additionally, sweeteners stimulate salivary flow.

4) Surfactants

Surfactants are used as solubilising or wetting or dispersing agent so that the film is getting dissolved within seconds and release active agent immediately. Some of the commonly used are:

- Sodium lauryl sulphate, benzalkonium chloride, bezthonium chloride, tweens etc. Most important surfactant is polaxamer407 that is used as solubilizing, wetting and dispersing agent.

3 EVALUATION OF ORAL THIN STRIP

3.1 Appearance

All prepared films were checked for their appearances either they are transparent or opaque.

3.2 Weight Variation

All batches were evaluated for its weight variation and thickness. Weight variation is evaluated by using electronic balance and Avg. weigh is calculated.

3.3 Thickness

Thickness of the prepared film was measured by micrometer screw gauge at different strategic locations. This is essential to ascertain uniformity in the thickness of the film as this is directly related to the accuracy of dose in the strip.

3.4 Mechanical Properties

Mechanical properties like Tensile Strength, % Elongation, and Folding Endurance were evaluated:

3.5 Tensile Strength

It was measured using Tensiometer. The films of size 2×2 cm^2 and free of physical imperfections were placed between two clamps held 10 mm apart. The films were to be pulled by clamp at a rate of 5mm/min.

Tensile strength =Load at failure × 100/ Strip thickness × Strip width

3.6 Percentage Elongation

It was calculated by measuring the increase in length of the film after tensile measurement by using the following formulae.

Percent Elongation = [L-L0] X 100 / L0

Where L was the Final length and L0 was initial length.

3.7 Folding Endurance

It was measured by folding the film at the same place repeatedly until a visible crack is observed. This gives an indication of brittleness of the film.

3.8 Surface pH

The films were allowed to swell in closed petridish at room temperature for 30 minutes in 1 mL of distilled water. Solution was placed under

digital pH meter to determine the surface pH.

3.9 Disintegration Time

Disintegration time provides an indication about the disintegration characteristics and dissolution characteristics of the film. The require size of film (2×2 cm2) was placed in a stainless steel wire mesh containing 25 mL of pH 6.8 simulated salivary fluid. Time taken by film to break and dissolve was measured as in-vitro disintegration time and invitro dissolution time.

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REVOLUTIONIZING BRAIN DRUG DELIVERY: THE POTENTIAL OF INTRANASAL LIPOSOMES

Sunitha Chintala
Asst. Professor, Department of Pharmacognosy, Princeton College of Pharmacy, Hyderabad, Telangana, India
Dr. Kokkula Satyanarayana
Professor, Department of Pharmacognosy, Princeton College of Pharmacy, Hyderabad, Telangana, India

Abstract - One of the most difficult areas of pharmaceutical science research is targeting drug molecules to the brain. The BBB must be cleared before drugs that treat CNS diseases can enter the brain through the blood compartment. The blood-cerebrum obstruction (BBB) addresses an unrealistic impediment for countless medications, including anti-microbials, hostile to neoplastic specialists, and an assortment of focal sensory system (CNS)- dynamic medications. As a result, a variety of methods, such as liposomes, colloidal drug carriers, micelles, chimeric peptide technology, the intranasal and olfactory route of administration, and nanotechnology, have been proposed to enhance drug delivery to this tissue. The self-forming enclosed lipid bilayer that formed upon hydration led to the discovery of a liposome, also known as a lipid vesicle; Liposomes have been studied as carriers of a variety of pharmacologically active agents, including antineoplastic, antimicrobial, chelating, steroids, vaccines, and genetic materials, and their role in the formulation of potent drugs to improve therapeutics has been significant. Due to their ability to alter the entrapped drugs' pharmacokinetics and pharmacodynamics, liposomes are an effective drug delivery system. Liposomes have been extensively utilized for in vivo brain delivery. The nasal route for systemic drug delivery has recently attracted a lot of attention. In comparison to other methods of drug administration, it has a number of advantages, including rapid absorption, the avoidance of intestinal and hepatic presystemic disposition, and a high potential for drug transfer to the CSF. Additionally, the nasal route is a potential alternative for drugs that are only available intravenously for systemic administration, such as vaccines and drugs made of peptides and proteins too, intranasal course has additionally been effectively taken advantage of for bypassing the blood mind boundary [BBB] and in this way conveying drug particles to focal sensory system [CNS].

Keywords: Liposomes, blood-brain barrier, olfactory region, and the nasal route.

1 INTRODUCTION

The brain is a delicate organ that has been very well protected by nature. The cerebrum is protected against possibly poisonous substances by the presence of two hindrance frameworks: the blood-brain-blood-spinal-fluid (BCSFB) and blood-brain-brain barrier Depending on the tasks they perform, these barriers have distinct morphological and physiological characteristics. Brain endothelia have the most intimate cell-to-cell connections of any tissue: "Tight junctions" or zonula occludens

are CNS-specific structures formed by endothelial cells adhering strongly to one another. Endothelial cell movement and cell migration are prevented by these tight junctions. This permeability barrier, which includes the brain capillary endothelium, is referred to as the BBB. Tight epithelium that is similar in nature to this barrier can also be found in other organs (the skin, bladder, colon, and lung). It is believed to be the most significant obstacle in the process of developing CNS drugs because of its stringent permeability, which restricts the amount of promising drugs that can reach the target brain tissues.

2 BLOOD BRAIN BARRIER

The brain is unique as a drug delivery organ: while it positions among organs with the best blood supply. The blood–brain barrier (BBB) severely restricts tissue access to the brain, which receives approximately 20% of human cardiac output. It is now well known that the BBB is a one-of-a-kind membrane barrier that tightly separates the brain from the blood that is circulating.

Because of the BBB, the transport of potentially neuroactive drugs from the blood into the brain is rarely limited by blood flow (as is the case with highly diffusible drugs like diazepam), but it is frequently limited by extraction. As a result, the main issue with drug delivery or targeting the brain is permeability. The BBB's structure is broken down into two parts: the ependymal barrier and the endothelial or capillary barrier. Blood capillaries in the central nervous system (CNS) are structurally distinct from those in other tissues; A permeability barrier separates the extracellular fluid in brain tissue from the blood in brain capillaries as a result of these structural differences. The tiny pores that enable the rapid movement of solutes from the circulation into other organs are missing from the capillaries of the brain and spinal cord of vertebrates; A layer of special endothelial cells without fenestrations and sealed by tight junctions line these capillaries. Because its surface area is approximately 5000 times greater than that of the BCSFB, it is generally accepted that the BBB is the primary pathway through which serum ligands are taken up.

3 INTRANASAL DRUG DELIVERY

Nasal drug delivery has been around since the early days of topical applications of drugs intended for local effects8. The nasal route was introduced at the beginning of the 1980s as a promising systemic delivery alternative to other traditional drug delivery methods. There are numerous advantages to intravenous drug administration over other methods.

In particular for drugs that have biological effects on the central nervous system (CNS) and limited blood–brain permeability (BBB), recent advancements in nasal drug delivery have suggested that intranasal administration is a safe and acceptable route for brain targeting.

There are currently a lot of products for the nose on the market that are meant to treat local diseases like allergic rhinitis, pain, and centrally acting drugs because the direct pathway from the nose to the

brain may provide a faster and more specific therapeutic effect.

4ANATOMY AND PHYSIOLOGY

The adult human nasal cavity has a total volume of approximately 15 ml11 and a surface area of approximately 150cm^2. The nasal septum divides the nasal cavity along its center into two halves. The two cavities open to the facial side through the foremost nasal gaps and to the rhinopharynx by means of the back nasal openings and every one of two nasal depressions can be partitioned into various locales: nasal vestibule, inferior, middle, and superior turbinates, as well as the olfactory region, frontal, sphenoidal, and cribriform ethmoid bone plates. The nasal associated lymphoid tissue (NALT), which is mostly in the nasopharynx, is also found in the nasal cavity. The respiratory area contains three nasal turbinates: superior, middle, and inferior, which extend from the lateral wall of the nasal cavity in each half. It is thought that the primary location for drug absorption into systemic circulation is the respiratory region.

The olfactory district in men covers an area of around 10cm^2 and is situated on prevalent turbinate on inverse septum, and assumes a fundamental part in transportation of medications to the mind and the CSF. The olfactory receptor cells are bipolar neurons with a single dendritic that extends from the cell body to the free apical surface.

5 DEMERITS OF INTRANASAL DRUG DELIVERY

- Delivery is expected to decrease with increasing molecular weight of drug.
- Some therapeutic agents may be susceptible to partial degradation in the nasal mucosa or may cause irritation to the mucosa.
- Nasal congestion due to cold or allergies may interfere with this method of delivery.
- Frequent use of this route may result in mucosal damage.

6 LIPOSOMES

The majority of the time, the goal of using colloidal carriers is to improve the bioavailability of drugs by increasing their diffusion through biological membranes, increase their specificity toward cells or tissues, or shield them from enzyme inactivation.

Due to their simplicity and ease of scaling up, colloidal drug carriers, such as micelles, emulsions, liposomes, and nanoparticles (nanospheres and nanocapsules), have been extensively utilized for brain drug delivery.

Liposomes are self-assembling colloidal structures made up of lipid bilayers that surround an aqueous compartment. These compartments can contain a wide range of hydrophilic drugs. Liposomes are spherical vesicle structures with an inner monolamellar lipid bilayer that covers internal aqueous compartments and an outer lipophilic phospholipid bilayer that is relatively impermeable.

Compared to unencapsulated agents, liposomes have been shown to provide stable encapsulation for a variety of drugs; As a result, liposomes have been proposed for use in a variety of research, industrial, and medical contexts, particularly as carriers of therapeutic and diagnostic compounds.

Due to their poor water soluble nature, lipophilic drugs are typically entrapped almost entirely within the lipid bilayers of liposomes. As a result, issues such as the loss of an entrapped drug during storage are uncommon. Drugs that are hydrophilic can either be found in the external water phase or entangled in the aqueous cores of liposomes. It is important to note that the percentage of hydrophilic drugs that liposomes encapsulate depends on the composition of the bilayer and how the liposomes were prepared.

7 INTRANASAL DRUG DELIVERY FOR BRAIN TARGETING

With a porous endothelial membrane and a highly vascularized epithelium that provides a rapid absorption of compound into the systemic circulation, avoiding the hepatic first pass elimination, the strategy of delivering drug through the intranasal route may be effective in the delivery of therapeutic proteins such as brain delivered neurotropic factor (BDNF) to the olfactory bulb as a treatment for Alzheimer's disease. Additionally, intranasal drug delivery enables lower doses, quicker onset of pharmacological activity, quicker attainment of therapeutic blood levels, and fewer adverse effects. The pharmacokinetic profiles of lipophilic drugs, which are typically identical to those obtained from intravenous injections and have a bioavailability close to 100 percent, were reported to be generally well absorbed from the nasal cavity. The high likelihood of drug transfer to the cerebrospinal fluid via the olfactory region in the nasal cavity is a distinctive feature of intranasal drug delivery. Late improvements in nasal medication conveyance have proposed intranasal organization as a protected and satisfactory course for cerebrum focusing on, particularly for drugs with natural impacts on the focal nerves framework (CNS) and restricted blood-mind porousness (BBB).

The mucociliary clearance, which shortens the residence time of nasally applied dosage forms, and the poor nasal permeability of many drugs are the primary issues with nasal delivery. In order to get around these limitations, a number of different approaches have been tried. Vesicular drug delivery systems offer promising alternatives that outperform conventional systems in many ways. In order to improve the effectiveness of their final formulation, a number of pharmaceutical methods can be used. In nasal drug delivery, liposomes are preferred to other vesicular systems. Due to their surface viscosity, liposomes can hinder mucociliary clearance when administered through the nose and are known to maintain the drug's release.

8 CONSIDERATIONS FOR BRAIN TARGETING OF INTRANASAL LIPOSOMES

In liposome research, the main issue is poor liposomal stability. Physical stability issues, such as the loss of drug entrapped in the liposome and a change in size upon storage, as well as chemical degradation of the liposome components, contribute to the instability issue. Loss of captured material can be limited by expanding the unbending nature of the bilayer film or lessening the water content of

liposome plans creating the alleged proliposomes.

Axonal transport rates range from 20–400 mm/day to a slower 0.1–4 mm/day depending on the drug that is taken. When designing intranasal delivery for brain targeting, very important physicochemical factors such as lipophilicity, molecular size, degree of dissociation, and administration route must be taken into account. When developing brain-targeted nasal drug delivery systems, formulation factors must also be taken into account. The most common preparations for intranasal drug delivery are liquid formulations, liquid sprays, and drops. The nasal shower stores anteriorly in the nasal chamber give more prominent home time, while the drops are scattered all through the length of the nasal cavity. Nasal sprays are more likely to deliver to the brain because they deposit more anteriorly. The posterior nasal passage typically has a higher permeability than the anterior passage.

9 CONCLUSION

The discussion revealed that liposomes are promising carriers for delivering drugs beyond the BBB for central nervous system examination. The vast majority of the possibly accessible medications for CNS treatments are huge hydrophilic particles, e.g., peptides, proteins and oligonucleotides that don't cross the BBB. The development of a suitable liposomal carrier to encapsulate neuroactive compounds is one of the most promising applications of liposomal technology. In the treatment of neurodegenerative diseases, these hydrophilic preparations and other medications that are normally administered parenterally will probably have a lot of potential for development via the nasal route.

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