Section: Research Paper

Methods for Producing a Lipidic Drug Delivery System with Maximal Bioavailability Improving the Absorption of a Poorly Water-Soluble Anti-Hypertensive Drugs

Sobitha Rani* (Corresponding Author)[1]

[1] Associate Professor , Department of Pharmaceutics, Bhaskar Pharmacy College, Yenkapally, Moinabad, Hyderabad. Telangana, India-500075,

Email sobhitarani@gmail.com

V Lokeswara Babu[2]

[2]Associate Professor & HOD , Department of Pharmaceutics, Bhaskar Pharmacy College, Yenkapally, Moinabad, Hyderabad. Telangana, India-500075,

Satyabrata Jena.[3]

[3]Associate Professor, Department of Pharmaceutics, Bhaskar Pharmacy College, Yenkapally, Moinabad, Hyderabad. Telangana, India-500075

G Susmitha.[4]

[4]Assistant Professor, Department of Pharmacy Practice, Bhaskar Pharmacy College, Yenkapally, Moinabad, Hyderabad. Telangana, India-500075

Surisetty Sridevi.[5]

[5] Assistant Professor, Department of Pharmaceutics, Mallareddy College of Pharmacy, Maisammaguda, Dhulapally, Secunderabad, Hyderabad, Telangana, India-500014

N. Rajitha[6]

[6] Assistant Professor, Department of Pharmaceutics, Bhaskar Pharmacy College, Yenkapally, Moinabad, Hyderabad. Telangana, India-500075

Mannam Mounika[7]

[7] Assistant Professor, Department of Pharmaceutics, Bhaskar Pharmacy College, Yenkapally, Moinabad, Hyderabad. Telangana, India-500075

Sanjay Kumar Gupta[8]

[8] Associate Professor and HOD, Department of Pharmaceutics, Global College of Pharmacy, Moinabad, Hyderabad. Telangana, India-501504

Abstract— A standard delivery technique is utilised to provide the majority of pharmaceuticals used to treat various illnesses, which are often taken orally. Due to its weak water solubility, chemical stability, and pre-systemic metabolism, oral dosage has a low bioavailability. Pharmaceuticals with low solubility and bioavailability in water pose a challenge to formulation experts. One of the new technologies created to solve these issues is lipid-based medicine delivery systems (LBDDS). Increased bioavailability can be achieved by encapsulating or solubilizing the drug in lipid excipients, which can also aid in solubilization

and absorption. In this study, we seek to better understand the novel delivery methods that have been created for enhancing the oral bioavailability of pharmaceuticals with limited water solubility, as well as the role that solid lipid nanoparticles play in the pharmacokinetics of such compounds. Solid lipid nanoparticles may provide novel possibilities for the treatment of hypertension with enhanced oral delivery if thoroughly investigated.

Keywords— *Drug, Oral, Delivery, Solubility, Lipid, Bioavailability.*

INTRODUCTION

The majority of clinical applications continue to favour oral drug administration as the preferred method. Others have the perfect qualities for effective absorption throughout the gastrointestinal tract, whereas certain drugs are difficult. The biopharmaceutical classification system, which groups drugs based on their intestinal permeability and solubility, was developed by the Food and Drug Administration (FDA) in 1995 [1]. (rate of dissolution). Class I compounds should be well absorbed when administered orally because of their excellent solubility and permeability. Due to their low solubility, permeability, or both, all other compounds (Class II–IV) will present a challenge for the development of oral bioavailabilities. Classes II through IV contain an increasing number of unique chemical entities, many of which exhibit variable absorption in different parts of the human GI tract [2]. On the other hand, the low bioavailability of oral dose forms poses a significant design challenge. Aqueous solubility, drug permeability, dissolving rate, first-pass metabolism, presystemic metabolism, and sensitivity to efflux mechanisms are a few of the factors that influence oral bioavailability. Poor solubility and permeability are the most common causes of problems with oral bioavailability. One of the most important elements in achieving the correct medication concentration in systemic circulation and the necessary pharmacological response is solubility. When given orally, poorly water-soluble medications typically need high dosages to achieve therapeutic plasma concentrations [3]. For formulations for the creation of both new chemical entities and generic drugs, poor water solubility is a major issue. Aqueous solutions must be used for any medication that needs to be absorbed at the absorption site. For pharmaceutical formulations that are liquid in nature, water is the ideal solvent. The bulk of drugs have little water solubility and are either mildly basic or acidic [4]. One of the most difficult aspects in the drug development process is increasing drug solubility and, as a result, oral bioavailability, especially for oral drug delivery systems.

THE PROBLEM OF HYPERTENSION

Hypertension, a heart ailment, is the primary cause of high blood pressure. According to the Geneva-based World Health Organization, hypertension was to blame for 45 percent of ischemic heart disease deaths and 51 percent of stroke deaths in 2008. By 2008, there were 1 billion cases of hypertension, up from 600 million in 1980, providing a significant treatment challenge. Several studies have revealed an increase in the prevalence of hypertension in India. In their study, Kearney et al. [5] forecast that by 2025, there would be 213.5 million hypertensives in India, up from 118 million in 2000. African Americans have a 93 percent chance of developing hypertension in their lifetimes, compared to 92 percent for Hispanics, 86 percent for whites, and 84 percent for Chinese adults. Hypertension was the leading cause of death and disability-adjusted life years worldwide in 2010, and it was more likely to predict outcomes in women and African Americans than in white people. It is commonly forgotten that from SBP values of 180 mm Hg to DBP

values of 105 mm Hg, the risk of CVD increases log-directly. Both a 20 mm Hg increase in SBP and a 10 mm Hg increase in DBP are linked to an increased risk of dying from a stroke, coronary disease, or another vascular disease. Higher SBP and DBP are linked to a higher risk of CVD, angina, myocardial dead tissue (MI), heart failure (HF), stroke, peripheral vascular disease, and gastric aortic aneurysm in those under the age of 30. SBP has consistently been linked to an increase in CVD [6]. Despite the availability of a number of conventional antihypertensive dosage forms, the majority of them do not successfully treat hypertension due to their low absorption and limited water solubility (BA). Because they are P-gp substrates, several antihypertensive drugs undergo considerable first-pass metabolism, which lowers their bioavailability. Antihypertensive medications have some drawbacks, such as a short half-life and a high dose frequency. One option to deal with the issues caused by dosage frequency is to develop an extended-release formulation. In this way, nanomedicine or nano-treatments have made it possible to deliver medications to diseased areas and allow them to stay there for longer periods of time. Moreover, P-gp-mediated efflux, target selectivity, and hepatic first-pass metabolism are avoided by nanomedicine, allowing drugs to circulate for extended periods of time. Innovative drug delivery techniques, such as buccal [7], gastro retentive [8], osmotic controlled, solid dispersion, and liquid solid compacts [9], were developed in the early 2000s.

DRUG ABSORPTION PROCESS IN A LIPIDIC FORMULATION

Excipients such pure triglyceride oils, mixed glycerides, lipophilic surfactants, hydrophilic surfactants, and water-soluble co-solvents can be combined to create lipid formulations. These systems also increase gastrointestinal absorption by accelerating the dissolution process and encouraging the development of solubilized phases by reducing particle size to the molecular level, resulting in a solid-state solution inside the carrier. This is in addition to increasing drug transport to the systemic circulation via the intestinal lymphatic system, altering enterocyte-based transport, and enhancing drug uptake, efflux, and disposition.

Lymphatic System I Due to its large drainage system throughout the body, the lymphatic system is essential in the transportation of drugs to the systemic circulation. Targeting specific diseases known to spread via lymphatics, such as HIV and some lymphomas, and avoiding first-pass metabolism are two additional benefits of lymphatic medication delivery [11]. Figure 1 summarises how lipids affect medication absorption, bioavailability, and disposal following oral administration. Promising mechanisms include: I, increased intracellular concentration and residence time by surfactants caused by inhibition of P-gp and/or CYP450; II, lipid stimulation of lipoprotein/chylomicron production caused by increased membrane fluidity; III, increased intracellular concentration and residence time by surfactants d; and IV, increased intracellular concentration and residence time by surfactants d.

(ii) Solubilization and Digestion – The rate and amount of absorption are influenced by the drug's ability to dissolve in the aqueous environment of the gastrointestinal lumen and cross the lipophilic membrane of enterocytes [13]. When lipid-based formulations are taken orally, gastric lipase starts to break down both the formulation's TG and exogenous dietary triglycerides (TG). The mechanical mixing operations of the stomach produce a crude emulsion consisting of aqueous gastric fluid and waste products of fat digestion (propulsion, grinding, and retropulsion). In the small intestine, pancreatic lipase and its cofactor colipase203 convert TG into diglyceride, monoglyceride, and fatty acids. Colipase203 primarily converts TG to 2-monoglyceride and free fatty acid at the sn-1 and sn-3 positions.

Pancreatic phospholipase A2 hydrolyzes phospholipids (PL) from formulations or biliary origin at the sn-2 position to generate lysophosphatidylcholine and fatty acids [14].

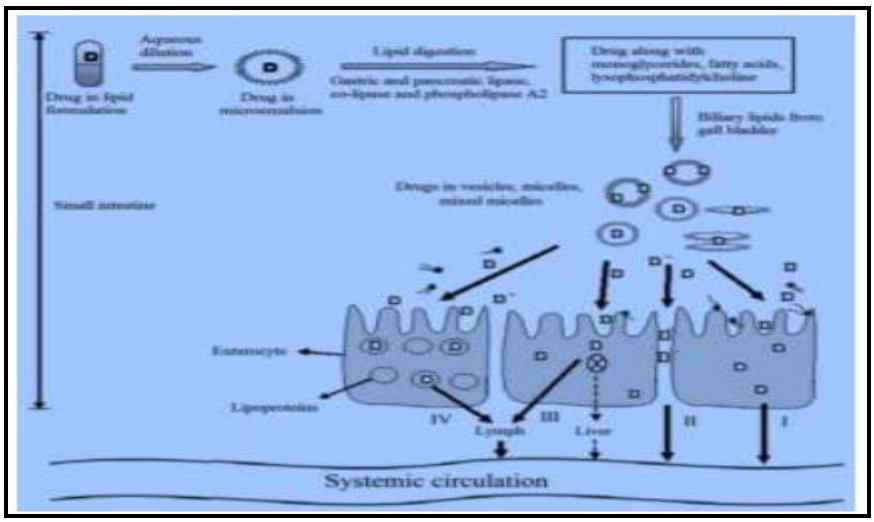

Figure 1- Displays a schematic of lipid-based formulation intestinal medication delivery.

As exogenous lipids enter the small intestine, the gall bladder secretes endogenous biliary lipids like BS, PL, and cholesterol. Bile salts can incorporate monoglycerides, fatty acids, and lysophospholipid (lipid digestion products) into micelles, unilamellar, and multilamellar vesicles. These lipid metabolites enhance the small intestine's solubilization and absorption of lipid digestion products and medicines (D). In Fig. 2, the oil droplet in the intestine is coloured to indicate undigested TG in the core (orange) and digested products including fatty acids (blue) and monoglycerides (green) on its surface.

THE ROLE OF LIPIDS IN IMPROVING BIOAVAILABILITY

When taken with food, several medicines have an increased bioavailability. Contrarily, several pharmaceuticals interact with food insignificantly or not at all. BCS class I drugs are not affected by food when taken, however class II pharmaceuticals are less absorbed when taken concurrently with food. When there is bioavailability, solubility, permeability, and the inhibition of efflux transporters may all contribute to an increase in bioavailability. Several drugs, such as grifofulvin, halofantrine, danazol, troglitazone, and atovaquone, have improved absorption when taken with food. The FDA released a handbook titled "Food-Effect Bioavailability and Feed Bioequivalence" in December 2002. Since they modify GI physiology and maximise medicine transfer into the systemic circulation, high-fat meals (800–1000 calories, 50–65 percent fat, 25–30 percent carbs, and 15-20 percent proteins) were recommended by the US FDA for food-effect research [15]. The oral bioavailability of lipophilic drugs is increased by the fatty content of food, which is particularly important for their absorption. This is explained by the abilities of a high-fat meal to increase intestinal wall permeability, promote pancreatic and biliary secretions, inhibit metabolism and efflux activity, prolong lymphatic transport, and decrease metabolism. Triglycerides and long-chain fatty acids have a critical function in extending GIT residence time. A high-fat meal also increases levels of TG-rich lipoproteins, which interact with drug molecules. Drug disposition, intestinal lymphatic transport, and ultimately the pharmacological effect kinetics of poorly soluble medications are all impacted by interactions between lipoproteins and drug molecules. When drugs are co-administered without food, this meal effect on

drug absorption raises serious questions about subtherapeutic plasma drug concentrations. Increased bioavailability in drugs with a low therapeutic index can have major negative effects, making this dietary effect a serious problem. So, when distributing such medications, it is vital to control or keep an eye on food consumption. However, by manufacturing the drug as a lipid-based formulation, which can improve the solubility and dissolution of lipophilic medications and facilitate the production of solubilized species from which absorption occurs, food-dependent bioavailability can be significantly reduced. Lipid-based formulations are a helpful tool since they minimise therapeutic dosage while increasing oral bioavailability.

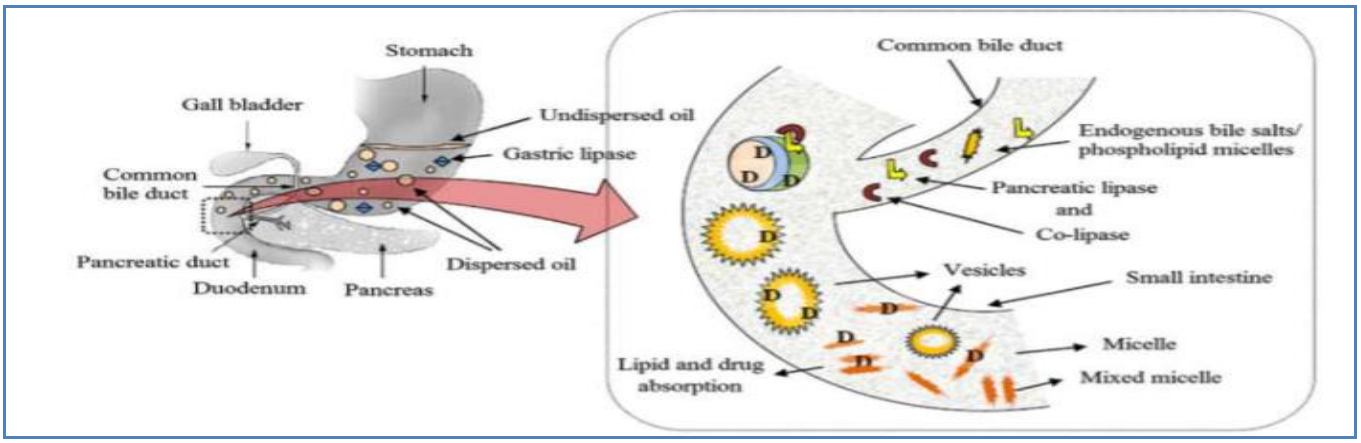

Figure 2- Small intestine lipid digestion and medication Solubilization

LIPID BASED DRUG DELIVERY SYSTEMS (LBDDS)

The development of suitable drug-carrier systems is becoming more and more important in order to effectively control, localise, and transport pharmaceuticals. LBDDS might minimise the inherent restriction of delayed and incomplete breakdown of poorly soluble medications, from which absorption may be achievable, by facilitating the creation of solubilized structures in the gastrointestinal tract (GIT) following digestion. An LBDDS, which generally consists of lipids, surfactants, and other components, may have a hydrophilic co-solvent. The lipid formulation classification system (LFCS), developed by Pouton, divides these systems into four classes (I-IV) based on their composition and the probable effects of dilution and digestion on their ability to prevent drug precipitation. It is easy to discern between the various systems that are marketed as "lipid-based delivery systems" using this classification approach, and it also offers a better way to compare and comprehend the provided data. The components, traits, advantages, and disadvantages of each set of LFCS's systems are listed in Table 1. Class I systems include straightforward oil solutions without surfactants and only mono-, di-, and/or tri-glycerides.

	Classes	I	II	IIIa	IIIb	IV
Composition (%)	Glycerides (mono-, di-, tri-glycerides)	100	40–80	40–80	< 20	0
	Lipophilic surfactants (HLB < 12)	0	20–60	20–40	0	0–20
	Hydrophilic surfactants (HLB > 12)	0	0	0	20–50	20–80
	Co-solvents	0	0	0–40	20–50	0–80
Characteristic features		Simple oil solution	Self-emulsifying ability	Self-emulsifying ability	Self-microemulsifying ability	Spontaneous formation of micellar dispersion

Table 1- Lipid formulation classification system by Pouton: structure, characteristics

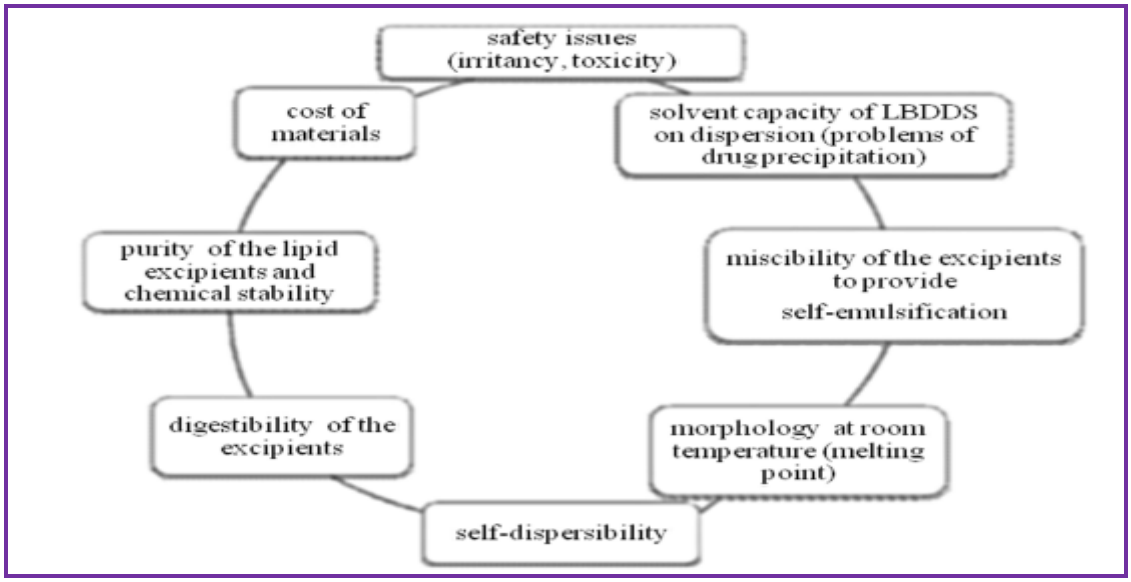

Figure 3- General selection criteria for excipients in LBDDS

In addition to the oil phase, Class II systems also contain lipophilic surfactants to improve the stability of the resulting emulsion and to increase the systems' capacity to bind medications. These LBDDS go by the moniker SEDDS. When hydrophilic substances (surfactants and/or co-solvents) are added to the oil phase, SMEDDS—Class III systems—are created. The most hydrophilic group, Class IV, includes systems that only comprise hydrophilic surfactants and hydrophilic co-solvents, which upon dilution with aqueous media produce a colloidal micellar dispersion.

SOLID LIPID NANOPARTICLES BLOOD PRESSURE REDUCING DRUG

How oral BA of poorly soluble medications were impacted by SLNs was studied by Harde et al. [16]. We want to discuss current advancements in the oral BA of poorly soluble antihypertensive drugs in this paper. Using a design of experiments approach, Narendar and Kishan [17] produced nisoldipine-loaded SLLNs for improved oral bioavailability. Nisoldipine, a calcium channel blocker, is used to treat high blood pressure. Because to weak water solubility and first-pass metabolism, it has a low oral BA of 5%. SLNs are therefore thought to increase oral BA by 2.45 times more than suspension formulation. As comparison to the control formulation, the half-life and MRT of SLNs were both doubled. This is demonstrated by the extended release of nisoldipine from the SLNs. Studies comparing SLNs and nanostructured lipid carriers for nisoldipine have also been published. In this study, the low water solubility drug nisoldipine's BA was improved by both nano carrier approaches. Angiotensin receptor 1 antagonist candesartan cilexetil is also permitted to treat hypertension. Since candesartan cilexetil is poorly soluble and undergoes pre-systemic metabolism, its bioavailability is less than 20%. As a result, an effort was made to enhance bioavailability utilising the SLN delivery system. Glycerides were used as the solid lipid matrix while making CC SLNs. The BA of CC loaded SLNs in albino Wistar rats was raised by more than 2.85 times at a dose of 10 mg/kg as compared to coarse CC suspension formulation. Zhang et al. showed that candesartan's oral bioavailability rose by a factor of 12 after being included in solid lipid nanoparticles in 2012[19]. Due to first-pass metabolism, feminodipine has a minimal bioavailability when taken orally. Several delivery

strategies, like solid lipid nanoparticles, are being researched to improve BA. To create felodipine-loaded solid lipid nanoparticles (SLNs), triglycerides were employed as the lipid matrix. These SLNs were subsequently created using a hot homogenization and sonication process. Male Wistar rats' pharmacokinetics of felodipineSLNs following oral administration were investigated. The BA of SLNs containing felodipine was 1.75 times higher than that of a coarse suspension of felodipine. Sandeep et al. demonstrated that lacidipine (LD)-coated solid lipid nanoparticles (LD-SLNs) improved oral bioavailability [20]. The LDSLNs were created in two steps. Initially, heat homogenization using monoglycerides, surfactants, and triglycerides (tripalmitin and tristearin) was carried out. The next step was ultrasonication (Poloxamer 188 and egg lecithin E80). Dynasan-116 (F3) LD-SLNs had an optimised size of 141.86 nm, a PDI of 0.293, a P of - 22.3 m, and an EE of 94.75 percent. They were stable for 60 days. Wistar rats were used in pharmacokinetic investigations as well. In comparison to LD suspension, the relative bioavailability of LD in SLNs was 2.03 times higher. According to the research, SLNs are a useful lipid-based carrier technology for increasing the oral bioavailability of LD. The hypertension medication nimodipine has a log P value of greater than 3 and an oral bioavailability of 13%. (NMD). A lipid administration device has been developed to boost oral BA. To enhance oral BA, nimodipine-loaded solid lipid nanoparticles (NMDSLNs) were created utilising a factorial approach. When given orally to male Albino Wistar rats, the pharmacokinetic investigation of optimised nimodipine-loaded SLNs revealed a 2.08-fold increase in relative bioavailability compared to NMD solution. Mild to moderate congestive heart failure is treated with carvingilol, a nonselective beta blocker (CHF). Water cannot dissolve it at all (0.01 mg/ml). Because to its limited solubility and substantial first-pass metabolism, carvingilol is swiftly absorbed after oral administration, with an absolute bioavailability of 18–25%. As a result, the creation of solid lipid nanoparticles increases the bioavailability of carvedilol. Carvedilol intranasally had a bioavailability that was more than five times higher than that of a typical drug suspension. Surface modified SLNs were developed by Veinshetty et al. [21] and coated with N-carboxymethyl chitosan (MCC) to inhibit intraduodenal transport and increase carvedilol oral BA. MCC coated SLNs showed a 2-fold increase in oral BA compared to C-SLNs. The findings imply that the SLN, coated with MCC, can be used orally to increase the bioavailability of drugs like carvedilol.

CONCLUSION

Low pharmaceutical bioavailability hinders efficient medication delivery via the oral route. There is now a lot of research being done to improve the oral bioavailability of drugs that are not well absorbed, especially when using innovative delivery systems and nano carriers. When formulating distribution options, it's essential to understand why the bioavailability is so poor. New antihypertensive drugs, novel subatomic targets, and nanotechnology-based delivery frameworks are currently through the crucial preclinical and clinical testing phases, with positive results. The viability of numerous novel antihypertensive molecular targets is now being assessed in contrast to hypertension drugs that are already on the market that have been approved by the FDA.

REFERENCES

[1] Food and Drug Administration. (2000). Guidance for industry: waiver of in vivo bioavailability and bioequivalence studies for immediate-release solid oral dosage forms based on a biopharmaceutics classification system. Food and Drug Administration, Rockville, MD.

[2]Broccatelli, F., Cruciani, G., Benet, L. Z., &Oprea, T. I. BDDCS class prediction for new molecular entities. Molecular pharmaceutics, 2012; 9(3):570-580.

[3]Dudhipala N. Influence of Solid Lipid Nanoparticles on Pharmaco-dynamic Activity of Poorly Oral Bioavailable Drugs. International Journal of Pharmaceutical Sciences and Nanotechnology. 2020 Jul 11; 13(4):4979-83.

[4]Yum SI, Schoenhard G, Tipton AJ, Gibson JW, Middleton JC, inventors; Durect Corp, assignee. Oral drug delivery system. United States patent US 8,133,507. 2012 Mar 13.

[5]Kearney, P. M., Whelton, M., Reynolds, K., Muntner, P., Whelton, P. K., & He, J. (2005). Global burden of hypertension: analysis of worldwide data. The lancet, 365(9455), 217-223.

[6]Whelton, P. K., Carey, R. M., Aronow, W. S., Casey, D. E., Collins, K. J., Himmelfarb, C. D., ... & MacLaughlin, E. J. (2018). 2017

[7]ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Journal of the American College of Cardiology, 71(19), e127-e248.

[8] Palem, C. R., Gannu, R., Doodipala, N., Yamsani, V. V., &Yamsani, M. R. (2011). Transmucosal delivery of domperidone from bilayered buccal patches: in vitro, ex vivo and in vivo characterization. Archives of pharmacal research, 34(10), 1701-1710.

[9]Narendar, D., Arjun, N., Someshwar, K., & Rao, Y. M. (2016). Quality by design approach for development and optimization of Quetiapine Fumarate effervescent floating matrix tablets for improved oral bioavailability. Journal of Pharmaceutical Investigation, 46(3), 253-263.

[10] Dudhipala, N. (2015). Enhancement of Solubility and Dissolution Rate of Trandolapril Sustained Release Matrix Tablets by Liquisolid Compact Approach. Asian Journal of Pharmaceutics (AJP): Free full text articles from Asian J Pharm, 9(4).

[11] Porter CJH, Trevaskis NL, Charman WN. Lipids and lipid-based formulations: optimizing the oral delivery of lipophilic drugs. Nat Rev Drug Discov2007;6:231–48.

[12] Nekkanti V, Sandeep K. (2012) "Development of novel lipid based drug delivery system for raloxifene hydrochloride". Int Res J Pharm; 3:166–73.
Driscoll CMO. (2002) Lipid based formulations for intestinal lymphatic delivery. Eur J Pharm Sci;15:405–15.

[13] van den Bosch H, Postema NM, de Haas GH, van Deenen L. On the positional specificity of phospholipase A from pancreas. BiochimBiophys Acta 1965; 98:657–9.

[14] Erlanson-Albertsson C. Pancreatic colipase. Structural and physiological aspects. BiochimBiophys Acta 1992;1125:1–7.

[15] Benet LZ, Cummins CL, Wu CY. Unmasking the dynamic interplay between efflux transporters and metabolic enzymes. Int J Pharm 2004;277:3–9

[16] Harde, H., Das, M., & Jain, S. (2011). Solid lipid nanoparticles: an oral bioavailability enhancer vehicle. Expert opinion on drug delivery, 8(11), 1407-1424.

[17] Narendar, D., & Kishan, V. (2017). Candesartan cilexetil nanoparticles for improved oral bioavailability. Ther deli, 8(2), 79-88.

[18] Dudhipala, N., Janga, K. Y., &Gorre, T. (2018). Comparative study of nisoldipine-loaded nanostructured lipid carriers and solid lipid nanoparticles for oral delivery: preparation, characterization, permeation and pharmacokinetic evaluation. Artificial cells, nanomedicine, and biotechnology, 1-10.

[19] Zhang, Z., Gao, F., Bu, H., Xiao, J., & Li, Y. (2012). Solid lipid nanoparticles loading candesartan cilexetil enhance oral bioavailability: in vitro characteristics and absorption mechanism in rats. Nanomedicine: Nanotechnology, Biology and Medicine, 8(5), 740-747.

[20] Sandeep, V., Narendar, D., Arjun, N., &Kishan, V. Lacidipine Loaded Solid Lipid Nanoparticles for Oral Delivery: Preparation, Characterization and In vivo Evaluation.

[21] Venishetty, V. K., Chede, R., Komuravelli, R., Adepu, L., Sistla, R., & Diwan, P. V. (2012). Design and evaluation of polymer coated carvedilol loaded solid lipid nanoparticles to improve the oral bioavailability: a novel strategy to avoid intraduodenal administration. Colloids and Surfaces B: Biointerfaces, 95, 1-9.