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DEVELOPMENT OF LIPIDIC DRUG DELIVERY SYSTEM FOR BIOAVAILABILITY IMPROVEMENT OF THE POORLY WATER-SOLUBLE ANTIHYPERTENSIVE DRUG

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ABSTRACT

The majority of drugs used to treat various ailments are taken orally and delivered via a traditional delivery. Because of its weak water solubility, chemical stability, and pre-systemic metabolism, oral administration has a low bioavailability. In terms of solubility and bioavailability, poorly water-soluble drugs pose a challenge to formulation experts. One of the new technologies meant to solve such issues is lipid-based drug delivery systems (LBDDS). Higher solubilization and absorption can be achieved by encapsulating or solubilizing the medicine in lipid excipients, resulting in increased bioavailability. We attempt to explore the different innovative delivery strategies created for the increase of oral bioavailability of poorly water-soluble medicines in this review, as well as the significance of solid lipid nanoparticles in the pharmacokinetics of poorly soluble antihypertensive drugs. Solid lipid nanoparticles may provide new possibilities in the treatment of hypertension with enhanced oral delivery if properly investigated.

KEYWORDS: *Bioavailability, Oral, Drug, Delivery, Solubility, Lipid.*

I. INTRODUCTION

For the majority of clinical applications, oral drug administration is still the preferred method. Some drugs have the ideal properties for good absorption throughout the gastrointestinal tract, while others cause problems. The Food and Drug Administration (FDA) introduced the biopharmaceutical classification system in 1995 [**1**], which classifies drugs according to their solubility (dissolution rate) and intestinal permeability. Class I compounds have high permeability and solubility and are expected to be well absorbed when administered orally. All other compounds (Class II-IV) have low solubility, permeability, or both, which will make developing oral bioavailabilities difficult. In Classes II-IV, there are an increasing number of new chemical entities, many of which have variable absorption in different parts of the human GI tract [**2**].

The poor bioavailability of oral dosage forms, on the other hand, is a significant challenge in their design. Aqueous solubility, drug permeability, dissolution rate, first-pass metabolism, presystemic metabolism, and susceptibility to efflux mechanisms are just a few of the factors that influence oral bioavailability. Poor solubility and permeability are the most common causes of oral bioavailability problems. One of the

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most important parameters for achieving the desired drug concentration in systemic circulation and achieving the required pharmacological response is solubility. To achieve therapeutic plasma concentrations after oral administration, poorly water-soluble drugs frequently require high doses [**3].** Low aqueous solubility is a major issue in both new chemical entity and generic development formulations. At the absorption site, any drug that needs to be absorbed must be in the form of an aqueous solution. For liquid pharmaceutical formulations, water is the solvent of choice. The majority of drugs have low aqueous solubility and are either weakly acidic or basic [**4**].

One of the most difficult aspects of the drug development process, particularly for oral-drug delivery systems, is increasing drug solubility and thus oral bioavailability. There are several methods for improving the solubility of poorly water-soluble drugs that have been reported in the literature. The techniques are chosen based on a variety of factors, including the properties of the drug in question, the nature of the excipients to be chosen, and the nature of the intended dosage form.

II. PROBLEM OF HYPERTENSION

Hypertension is a cardiovascular disease that causes high blood pressure. According to the World Health Organization in Geneva, hypertension was responsible for 45 percent of deaths due to ischemic heart disease and 51 percent of deaths due to stroke in 2008. In 1980, 600 million people had hypertension, but by 2008, the number had risen to 1 billion, posing a significant treatment challenge. Several studies have revealed an increase in the prevalence of hypertension in India in the past. In their research, Kearney et al. [**5**] anticipated that India's hypertension burden would quadruple from 118 million in 2000 to 213.5 million by 2025.

African Americans have a 93 percent probability of developing hypertension in 40 years, Hispanics have a 92 percent chance, whites have an 86 percent chance, and Chinese adults have an 84 percent chance. In 2010, hypertension was the leading cause of mortality and disability-adjusted life-years worldwide, and it was a more prominent supporter of events in women and African Americans than in whites. The risk of CVD increases in a log-direct way from SBP levels of 180 mm Hg to DBP values of 105 mm Hg, which is often overlooked. A 20 mm Hg increase in SBP and a 10 mm Hg increase in DBP are both linked to an increase in the risk of death from stroke, coronary sickness, or other vascular disease. Higher SBP and DBP are linked to an increased risk of CVD, angina, myocardial dead tissue (MI), heart failure (HF), stroke, peripheral blood vessel disease, and gastric aortic aneurysm in those under 30 years old. SBP has been reliably linked to increased CVD [**6**].

Despite the fact that there are numerous conventional antihypertensive dosages forms available, the majority of them fail to treat hypertension due to their low aqueous solubility, resulting in low bioavailability (BA). Some antihypertensive drugs are P-gp substrates and undergo considerable first-pass metabolism, resulting in decreased bioavailability. Antihypertensive medication also has other drawbacks, such as a short half-life and a high dose frequency. Designing an extended-release formulation is one technique to tackle the issues associated with dosage frequency. In this regard, nanomedicine or nano-treatments open up a new method for delivering therapeutics to diseased locations and allowing them to stay there for longer periods of time. Nanomedicine also avoids hepatic first-pass metabolism, P-gp-mediated efflux, and target specificity, allowing treatments to circulate for longer periods of time. Various innovative drug delivery techniques, such as buccal [**7**], gastro retentive [**8**], osmotic controlled, solid dispersion, and liquid solid compacts, were developed in the early 2000s[**9**].

III. DRUG ABSORPTION PROCESS IN LIPID FORMULATION

Excipients such as pure triglyceride oils, mixed glycerides, lipophilic surfactants, hydrophilic surfactants, and water-soluble co-solvents can be blended to create lipid formulations in practise. These systems improve gastrointestinal absorption by speeding up the dissolution process and encouraging the development of solubilized phases by reducing particle size to the molecular level, resulting in a solid-state solution within the carrier, enhancing drug transport to the systemic circulation via the intestinal lymphatic system, and changing drug uptake, efflux, and disposition by altering enterocyte-based transport and enhancing drug transport to the systemic circulation via intestinal lymphatic system [**10**]

Lymphatic System

Given its enormous drainage network throughout the body, the lymphatic system plays an essential role in the transfer of drugs to the systemic circulation. Avoidance of first-pass metabolism and targeting of specific diseases known to spread via lymphatics, such as certain lymphomas and HIV, are some of the benefits of lymphatic drug transport [**11**]. Figure 1 summarises the ways through which lipids alter medication absorption, bioavailability, and disposition following oral delivery. The following mechanisms are promising: I, increased intracellular concentration and residence time by surfactants due to inhibition of P-gp and/or CYP450; II, lipid

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stimulation of lipoprotein/chylomicron production due to increased membrane fluidity; III, increased intracellular concentration and residence time by surfactants due to inhibition of P-gp and/or CYP450; IV, increased intracellular concentration and residence time by surfactants due to inhibition of P-gp and/or CYP450 [**12**]

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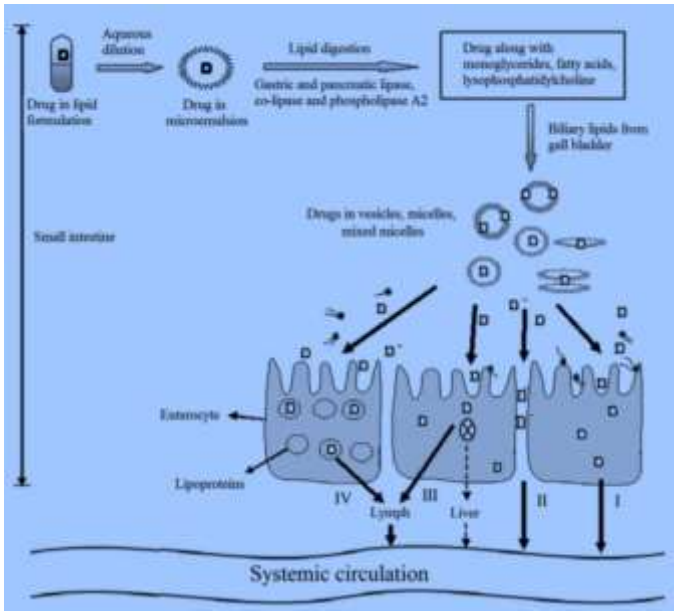

Figure 1 Schematic diagram of mechanisms of intestinal drug transport from lipid-based formulations

Solubilization and Digestion

The rate and amount of absorption are determined by the balance between a drug's solubility in the aqueous environment of the gastrointestinal lumen and its penetration over the lipophilic membrane of enterocytes [**13**]. Gastric lipase starts the digestion of exogenous dietary triglyceride (TG) and formulation TG after oral administration of lipid-based formulations. Simultaneously, the stomach's mechanical mixing (propulsion, grinding, and retropulsion) helps form a crude emulsion (comprised of aqueous gastric fluid and lipid digestion products). TG is broken down into diglyceride, monoglyceride, and fatty acids in the small intestine by pancreatic lipase and its cofactor colipase203, which acts primarily at the sn-1 and sn-3 positions of TG to produce 2-monoglyceride and free fatty acid.

By hydrolyzing at the sn-2 position of phospholipids (PL), pancreatic phospholipase A2 digests formulation-derived or biliary-derived phospholipids (PL) to yield lysophosphatidylcholine and fatty acid [**14**]. The presence of exogenous lipids in the small intestine stimulates the secretion of endogenous biliary lipids, such as bile salt (BS), PL, and cholesterol, from the gall bladder. In the presence of bile salts, previously generated monoglycerides, fatty acids, and lysophospholipid (lipid digestion products) are integrated into a range of colloidal structures, including micelles and unilamellar and multilamellar vesicles. Because of these produced lipid metabolites, the small intestine's solubilization and absorption capacity for lipid digestion products and drugs (D) is greatly increased.

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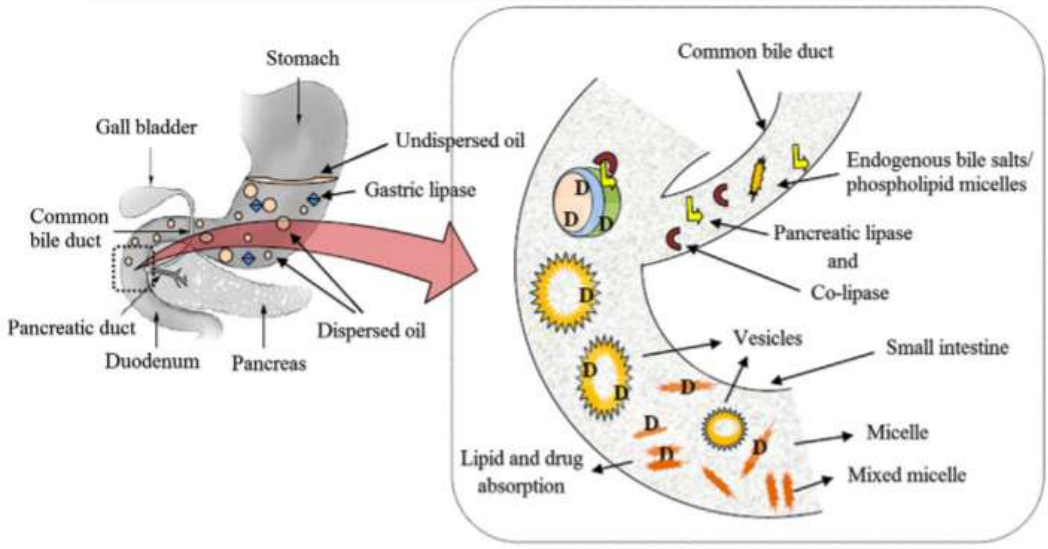

Figure 2: Lipid digestion and drug solubilization process in the small intestine.

The oil droplet in the intestine is depicted in various hues in Fig. 2 to illustrate undigested TG in the core (orange) and digested products such as fatty acid (blue) and monoglyceride (green) on the droplet's surface.

IV. THE IMPORTANCE OF LIPIDS IN IMPROVING BIOAVAILABILITY

When some drugs are taken with food, their bioavailability is increased. Many pharmacological compounds, on the other hand, have little to no interaction with food. Food has no effect on the absorption of BCS class I drugs, but it does impair the absorption of class II drugs when they are co-administered with food. Solubility, permeability, and inhibition of efflux transporters in the presence of bioavailability may all play a role in increased bioavailability. Grifofulvin, halofantrine6, danazol5, troglitazone, and atovaquone are some of the drugs that have improved bioavailability when given with food. FDA issued a guidance document in December 2002 titled "Food-Effect Bioavailability and Fed Bioequivalence." Because high fat meals (800–1000 calories, 50–65 percent fat, 25–30 percent carbohydrates, and 15–20 percent proteins) affect GI physiology and maximise drug transfer into the systemic circulation, the US FDA recommended them for food-effect studies [**15**].

The lipid component of food, in particular, plays a critical role in the absorption of lipophilic drugs, resulting in increased oral bioavailability. This is explained by a high fat meal's ability to stimulate biliary and pancreatic secretions, decrease metabolism and efflux activity, increase intestinal wall permeability, and prolong gastrointestinal tract (GIT) residence time and lymphatic transport. Triglycerides and long-chain fatty acids are important in extending GIT residence time. A high-fat meal also increases the levels of TG-rich lipoproteins, which interact with drug molecules. This interaction of lipoproteins with drug molecules improves intestinal lymphatic transport, changes drug disposition, and, ultimately, changes the pharmacological action kinetics of poorly soluble drugs. When co-administered without food, this food effect on drug absorption raises serious concerns about subtherapeutic plasma drug concentrations. Increased bioavailability can cause major side effects in drugs with a restricted therapeutic index;therefore, this dietary effect is a serious problem. As a result, when administering such drugs, food consumption must be controlled or monitored.

However, by formulating the drug as a lipid-based formulation, which can increase the solubility and dissolution of lipophilic drugs and facilitate the formation of solubilized species from which absorption occurs, food-dependent bioavailability can be significantly reduced. As a result, lipid-based formulations can be used to lower drug dosage while increasing oral bioavailability.

V. ANTIHYPERTENSIVE DRUGS IN SOLID LIPID NNAOPARTICLES

The effect of SLNs on oral BA of poorly soluble drugs was studied by Harde et al. [**16**]. We attempt to discuss updates in the oral BA of poorly soluble antihypertensive drugs in this review.

Using a design of experiments approach, Narendar and Kishan [**17**] developed nisoldipine-loaded SLLNs for improved oral bioavailability. Nisoldipine is a calcium channel blocker that is used to treat high blood pressure. Due to poor aqueous solubility and first-pass metabolism, it has a low oral BA of 5%. As

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a result, when compared to suspension formulation, SLNs are said to increase oral BA by 2.45 times. In comparison to the control formulation, the half-life and MRT of SLNs were also doubled. The sustained release of nisoldipine from the SLNs demonstrates this.

Comparative investigations of nanostructured lipid carriers and SLNs for nisoldipine have also been published. Both nano carrier systems improved the BA of a poorly water-soluble drug like nisoldipine in this study [**18**]. Angiotensin receptor 1 antagonist candesartan cilexetil is also indicated for the treatment of hypertension. Because of its poor solubility and pre-systemic metabolism, candesartan cilexetil had a bioavailability of less than 20%. As a result, an attempt was made to improve bioavailability utilising the SLN delivery system. Triglycerides were used as solid lipid matrix in the manufacture of CC SLNs. At a dose of 10 mg/kg, the BA of CC loaded SLNs was raised by more than 2.85 times compared to coarse CC suspension formulation in albino Wistar rats. Zhang et al., 2012**[19]** observed a 12-fold increase in candesartan oral bioavailability following integration into solid lipid nanoparticles.

Because of first-pass metabolism, felodipine has a low oral bioavailability. Alternative delivery systems, such as solid lipid nanoparticles, are being studied as a way to improve BA. As a result, felodipine-loaded solid lipid nanoparticles (SLNs) were created employing triglycerides as lipid matrix and manufactured using a hot homogenization and sonication process. The pharmacokinetics of felodipineSLNs in male Wistar rats following oral treatment were investigated. When compared to a felodipine coarse suspension, the BA of felodipine loaded SLNs was 1.75 times higher. Sandeep et al., [**20**], demonstrated lacidipine (LD) loaded solid lipid nanoparticles (LD-SLNs) for enhancing oral bioavailability. The LDSLNs were made in two stages. Using triglycerides (tripalmitin and tristearin), monoglycerides, and surfactants, the first stage was heated homogenization, followed by ultrasonication (Poloxamer 188 and egg lecithin E80). Dynasan-116 (F3) LD-SLNs with a size of 141.86nm, a PDI of 0.293, a P of - 22.3m, and an EE of 94.75 percent were optimised and stable for 60 days. In addition, Wistar rats were used in pharmacokinetic investigations. When compared to the LD suspension, the relative bioavailability of LD in SLNs was 2.03 times higher. The findings point to SLNs as a viable lipid-based carrier technology for increasing LD oral bioavailability.

Nimodipine (NMD) is an antihypertensive medication with a log P value of more than 3 and a 13 percent oral bioavailability. As a result, a lipid delivery system has been developed to boost oral BA. By adopting a factorial design, nimodipine loaded solid lipid nanoparticles (NMDSLNs) were created to boost the oral BA. When delivered orally to male Albino Wistar rats, the pharmacokinetic investigation of optimised nimodipine loaded SLNs demonstrated a 2.08-fold increase in relative bioavailability compared to NMD solution. These NMD-SLNs are regarded potential vehicles for oral delivery due of their increased bioavailability.

Carvedilol is a nonselective beta blocker that's used to treat mild to moderate congestive heart failure (CHF). It is almost water insoluble (0.01 mg/ml). Because of its low solubility and extensive first-pass metabolism, Carvedilol is rapidly absorbed after oral administration, with an absolute bioavailability of 18-25 percent. As a result, solid lipid nanoparticle formulation improves carvedilol bioavailability. Intranasally, carvedilol's bioavailability was increased by more than 5 times compared to plain drug suspension. Surface modified SLNs coated with N-carboxymethyl chitosan (MCC) were developed by Veinshetty et al., [**21**] to avoid intraduodenal administration and increase carvedilol oral BA. In comparison to C-SLNs, MCC coated SLNs showed a 2-fold increase in oral BA. As a result, the findings imply that the SLN can be taken orally after being coated with MCC to increase the bioavailability of drugs like carvedilol.

VI. CONCLUSION

Poor medication bioavailability is a key stumbling block to effective drug delivery via the oral route. A lot of research is being on right now, notably with innovative delivery techniques and nano carriers, to improve the oral bioavailability of poorly absorbed drugs. Before sketching out delivery systems, it's also crucial to understand why the bioavailability is so low. New antihypertensive drugs, novel subatomic targets, and nanotechnology-based delivery frameworks are currently in the crucial stages of preclinical and clinical testing, with promising results. Numerous novel antihypertensive molecular targets are in the exploration stage, and their feasibility is being assessed against established officially existent antihypertensive treatments.

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*

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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 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.*
7. *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.*
8. *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.*
9. *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).*
10. *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.*
11. *Nekkanti V, Sandeep K. (2012) "Development of novel lipid based drug delivery system for raloxifene hydrochloride". Int Res J Pharm; 3:166–73.*
12. *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.*