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Lipid nanoparticles: A challenging approach for oral delivery of BCS Class-II drugs

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ABSTRACT

In today's drug development world, combinatorial chemistry, high-throughput screening, and genomics have provided a technologic platform that produces a large number of new chemical entities with therapeutic potential each year. Its outcome the new chemical entities shifted towards higher molecular weight and increasing lipophilicity that results in poor water solubility which primarily affects the bioavailability of orally administered drugs. Hence, the poor aqueous solubility not only limits the drug's biological application but also challenges its pharmaceutical development. This review highlights the significant solubility problem and BCS/BDDCS formulation choices, and importance of lipid nanoparticles (LNPs). Also, this review summarizes the fate of lipid and lipid formulations in the human body, Lymphatic transport of drugs in the human body, Challenges of lipid-based delivery, the role of lipids in the enhancement of bioavailability, Mechanism of Lipid nanoparticles and BCS class II drugs as an ideal candidate for the LNPs formulation with their significant finding in research outcomes reported by the different researchers. Based on the available data, the lipid nanoparticles makes this drug delivery systems as one of the promising delivery systems and will be a solution to the formulation scientist. Also, it complies the key objectives of Green chemistry and sustainable chemistry.

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1. Introduction

In today's drug development world, combinatorial chemistry, high-throughput screening, and genomics have provided a technologic platform that produces a large number of new chemical entities (NCE) with therapeutic potential each year [1,2]. The pharmaceutical drug delivery market is also expected to grow from $1048.1 billion in 2015 to $1504.7 billion by 2020, with a compound annual growth rate of 7.5% [3]. Despite a vast number of novel drug molecules developed, only a few of them are successfully launched in the market. Because discovering and developing a drug is a time consuming and costly process with a recent estimation of about 13 years and US$900 million, respectively [4,5]. As well, the lack of efficacy (accounting for ~30% of failures), safety (toxicology and safety accounting for ~30%) [5], low bioavailability and adverse pharmacokinetics profile (accounting for ~40%) were the prime reason for attrition in the clinic. Hence, more drug candidate molecules are withdrawn before reaching clinical evaluation [4,6].

Also, the newly discovered drugs from the discovery and development processes are not suitable for oral delivery [7]. Because the properties of new chemical entities shifted towards higher molecular weight and increasing lipophilicity [8–11]. Consequently, the poor aqueous solubility of the lipophilic compounds has become an enduring problem in drug discovery as well as the early and late −stage pharmaceutical development process. Also, it was reported that ~40% of currently marketed drugs and up to 70% of compounds currently under development had been suggested to be poorly water-soluble [12–14]. As a result, an insufficient amount of drug reaches the systemic circulation followed by the site of action with a lack of pharmacological action and produce poor bioavailability. Which is a subject of major concern to formulation scientists [7]. Therefore, poor water solubility continues to be a challenge to successful drug development, design, and optimization [12]. Hence, there is a need of an essential alternative way to enhance the solubility in pharmaceutical

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development programs. Because, the solubility of the drug is one of its most important physicochemical properties in drug release and absorption, hence, playing an integral role in its bioavailability especially for an orally administered drug [1,15]. Moreover, for significant bioavailability, the orally administered drug not only depends on its solubility in the GIT but also its permeability across the cell membranes [16]. Hence, the drug molecules are required to be present in a dissolved form, for them to be transported across biological membranes [1,17]. Also, an essential prerequisite for the absorption of a drug by all mechanisms except endocytosis is that it must be present in aqueous solution. This fact, in turn, depends on the drug's aqueous solubility (Absolute or intrinsic solubility) and its dissolution rate [18].

In spite of poor solubility circumventing bioavailability problem, a drug in solution form is essential for the pharmaceutical product development stage such as for conducting toxicological, pharmacological, and pharmacokinetic studies [19,20]. Thus, poor aqueous solubility not only limits a drug's biological application but also challenges its pharmaceutical product development [20,21]. Besides, from the pharmaceutical point of view, during drug discovery and development stage, a critical question is probably whether a drug will be bioavailable after its oral administration. Because, orally administered solid dosage forms undergo disintegration, dissolution, and absorption to enter the blood stream and reach the site of action [22]. Except in the case of controlled-release formulations, the immediate-release dosage form undergoes disintegration and deaggregation rapidly. However, the two critical slower rate-determining steps (RDS) such as the rate of dissolution and the rate of drug penetration across the bio membrane limits the oral absorption of drugs [23,24].

Dissolution is the rate determining steps for hydrophobic, poorly aqueous soluble drugs like griseofulvin and spironolactone; absorption of such drug is often said to be dissolution-rate limited. Similarly, permeation across the membrane is the rate determining steps for hydrophilic, highly aqueous soluble drugs like cromolyn sodium or neomycin; absorption of such drug is often said to be permeation or transmembrane rate limited [25]. However, it is very difficult to state that when the solubility limitation begins to impact the absorption. For example, the required amount of a dose, i.e., drug potency. Due to poor bioavailability, a high dose is recommended to reach the systemic circulation and to maintain the minimum therapeutic level. As a result, the high dose causes the side effect, toxicity, wastage of the drug in the case of expensive drugs [26]. Thus, the knowledge about the intrinsic solubility, permeability characteristics, and determination of the rate of dissolution of drugs can provide information about their absorption [22,27].

2. Solubility

Solubility is closely related to dissolution which is a kinetic process that involves the detachment of drug molecules from the solid surface and subsequent diffusion across the diffusion layer surrounding the solid surface [28,29]. The Nernst- Brunner/Noyes-Whitney Equation (1) clearly stated the relationship between the solubility and dissolution rate [29,30]:

$$dc/dt = DAK_{w/o}(C_s - C_b)/Vh \quad (1)$$

Where, D is the diffusion coefficient (diffusivity) of the drug; A is the surface area of the dissolving solid, $K_{w/o}$ is the water/oil partition coefficient of the drug which is also called as the intrinsic dissolution rate constant. It is a characteristic of drugs, V is the volume of dissolution medium, h is the thickness of the stagnant layer, (C_s-C_b) is the concentration gradient for diffusion of the drug.

From the Nernst-Brunner/Noyes-Whitney equation, it is evident that compounds characterized by low solubility (C_s) will only establish a small concentration gradient (C_s-C_b), resulting in low dissolution rates [29]. Briefly, despite, e.g., gut permeability and fast uptake of the drug from the gut lumen the blood levels will be low because the drug does not dissolve sufficiently fast. At the same time, drug elimination from the blood takes place leading to this low drug levels. Also, the low concentration gradient between lumen and blood leads to relatively slow drug diffusion from the gut to the blood [31]. This fact, in turn, causes many problems in-vivo when poorly soluble drugs are administered via various routes of administration [29]. However, the modified Noyes–Whitney equation [32] provides some hints to improve the dissolution rate of even very poorly soluble drugs and to minimize the limitations on oral viability (Table 1). The main possibilities for improving dissolution according to this analysis are to increase the effective surface area by particle size reduction [33], to improve the wetting characteristics by adding wetting agent, to decrease the boundary layer thickness to ensure sink conditions for dissolution, and, to improve the apparent solubility of the drug under physiologically relevant conditions [34,35].

According to this concept, in the case of the poorly soluble drug, the particle size reduction may lead to super saturation insolubility. Because intrinsic solubility remains almost unaffected, the most profound effect of particle size reduction is observed on the increase in the dissolution rate through enhancement of the particle surface area (Fick's first law, Noyes-Whitey equation) [4,36]. Also, it was experimentally found that the thickness of the diffusion layer decreased as the particle size decreased, leading to faster transport of solvated molecules to bulk solution and, hence, faster dissolution [37]. There is a very simple traditional approach increasing the dissolution velocity by enlarging the surface, i.e., micronization. Micronization produces a reduced particle size in the range of 2–5 μm [38]. Numerous new drugs developed recently exhibited such a low solubility that micronization did not guarantee sufficient bioavailability. Hence, the particle size reduction process has moved to the next level of nanosization with a particle size below 1 μm and a typical size distribution between 200 and 500 nm [39]. Nanosized particles showed significant enhancement in the dissolution rate and bioavailability as compared with micronized particles resulting from enormous enhancement of the surface area [4]. The further information is detailed in the section of lipid nanoparticles.

Table 1
Influence of some parameters on dissolution rate of drug.

Parameters	Symbol	Influence on drug dissolution
Diffusion coefficient	D	Greater the value, faster the dissolution of the drug. Diffusion decreases as the viscosity of dissolution medium increase.
Surface area of the solid	A	Greater the surface area, faster the drug dissolution; can be micro/nanonisation of drug
Water/oil partition coefficient	$K_{w/o}$	Higher the value, more the coefficient of drug and its hydrophilicity and faster the dissolution in aqueous fluids.
Concentration gradient	(C_s-C_b)	Greater the concentration gradient, faster the diffusion and drug dissolution; can be increased by increasing drug solubility and the volume of dissolution medium
Thickness of the stagnant layer	H	More the thickness, lesser the diffusion layer, and drug dissolution; can be decreased by increasing agitation.

3. Biopharmaceutical classification system

A better understanding of the biopharmaceutical and physicochemical properties of drugs would be of great help for developing pharmaceutical products. Biopharmaceutics classification system (BCS) is a useful tool for decision-making in formulation development from a bio-pharmaceutical point of view [17,40,41]. Based on the two key physicochemical parameters, such as intestinal permeability and solubility Amidon et al. developed Biopharmaceutical Classification System (BCS) for the drugs [17]. Because the absorption of orally administered most of the drugs are either limited by their solubility in GIT or permeation across the intestinal membrane. It is evidenced by the following Equation (2) [42].

$$M = A.\ t_{res}.\ P_{eff}.\ C_{app} \quad (2)$$

M is the amount of drug absorbed; A is the surface area available for absorption, t_{res} is the residence time during which the drug remains within the site(s) of absorption, P_{eff} is the effective membrane permeability, and C_{app} is the apparent luminal drug concentration (Capp). According to this system, drug substances can be classified into four groups as shown in Table 2. Table 3 also shows the approaches employed to overcome formulation challenges in each class of drugs [1,23,40,43].

4. Biopharmaceutical drug disposition classification system

A major drawback of the BCS is that it does not provide a thorough understanding of how drug transport and drug metabolism may impact the pharmacokinetic performance of drug products. In accordance with, there are several extensions of BCS-like six-class BCS, quantitative BCS, pulmonary BCS, and Biopharmaceutical Drug Disposition Classification System (BDDCS). Out of these BDDCS (Table 4), the most popular extension of BCS was given by Chi-Yuan Wu and Leslie Z. Bennet in their seminal paper published in 2005 [44]. After reviewing 130 drugs listed in the WHO Essential Medicines List regarding their pharmacokinetic parameters, solubility, and permeability, they found a common theme linked the BCS to drug metabolism [1]. This guideline provides useful information regarding the overall disposition, including an importance of food effects, and transporter effect on post-absorption systemic drug concentration, the efflux, and absorptive transporters on oral absorption of the drug and routes of drug elimination following oral and intravenous dosing [1,34]. They suggested that those drugs are eliminated primarily via metabolism, then the drug should be classified as high permeability and those drugs are eliminated unchanged primarily via urine and bile, then the drug should be classified as low permeability [45]. According to BDDCS, the BCS class I and class II drugs are eliminated primarily via metabolism, and BCS class III and IV are eliminated primarily via urine and bile [1,34,46].

Also, he [44] suggested that efflux transporters are likely to predominate in the case of Class II drugs while both efflux and absorptive may influence Class IV compounds [44]. Due to high solubility and high permeability of Class I drugs, it significantly saturates the both absorptive and efflux transporter and thereby

Table 2
Biopharmaceutics classification system for drugs [1,17,23,41].

Class I: High Solubility high permeability	**Class II: Low Solubility high permeability**
Absorption Pattern: Well absorbed ***Rate-Limiting step in Absorption***: Gastric Emptying ***Examples***: Diltiazem, Propranolol, Metoprolol ***Challenges in Drug Delivery***: No major challenges for immediate release forms but major challenges need for CR forms to control the dissolution or drug release.	***Absorption Pattern***: Variable ***Rate-Limiting step in Absorption***: Dissolution ***Examples***: Nifedipine, Carbamazepine, Naproxen ***Challenges in Drug Delivery***: Formulations are designed to overcome solubility or dissolution problem by various means • Particle size reduction, • Solid dispersion, • Lipid-based formulations
Class III: High Solubility low permeability	**Class IV: Low Solubility low permeability**
Absorption Pattern: Variable ***Rate-Limiting step in Absorption***: Permeability ***Examples***: Insulin, Metformin, Cimetidine ***Challenges in Drug Delivery***: Approaches are employed to enhance permeability • Prodrugs, • Permeation enhancer	***Absorption Pattern***: Poorly absorbed ***Rate-Limiting step in Absorption***: Case by case ***Examples***: Taxol, Chlorthiazide, Furosemide ***Challenges in Drug Delivery***: Combination of strategies used for Class II and Class III drugs are employed to improve both dissolution and permeability.
Other absorption barriers: chemically or metabolically unstable compounds	
Class V drugs: High Solubility, High permeability and easily susceptible to luminal degradation, pre-systemic elimination or are effluxed by p-glycoproteins. Class V drugs are not comes under the BCS classification system. • Approaches to avoid luminal degradation: ◦ Enteric coating (for labile acid compounds) ◦ Lipid vesicles (micelles or emulsions/microemulsions) ◦ Prodrugs • Approaches to minimize pre-systemic metabolism: ◦ Coadministration of a drug with an enzyme inhibitor ◦ Lymphatic delivery (to avoid the first-pass metabolism), e.g., lipid prodrugs ◦ Explore effect of excipients on enzymatic inhibition • Approaches to minimize efflux mechanism: ◦ Coadministration with a P-gp efflux pump inhibitor ◦ Provide enough luminal concentration to saturate the efflux transporter ◦ Design prodrugs to evade efflux transporter ◦ Use of excipients that may inhibit efflux mechanism • Approaches to utilize carrier-mediated transport: ◦ Design prodrugs that are substrates for transporters	

Table 3
Conventional and Novel techniques for the bioavailability enhancement of BCS drugs.

Techniques used to enhance Bioavailability of BCS drugs [1,23,40,43].	
➢ ***Enhancement of drug solubility or dissolution rate***: This approach applies to Class II drugs according to BCS. ❖ Micronization ❖ Nanonisation ❖ Supercritical Fluid Recrystallization ❖ Spray Freezing into Liquid (SFL) ❖ Evaporative Precipitation into Aqueous Solution (EPAS) ❖ Use of Surfactants ❖ Use of salt forms ❖ Use of Precipitation inhibitors ❖ Alteration of pH of the Drug Microenvironment ❖ Use of Anhydrates, Solvates, Metastable Polymorphs, and Amorphs ❖ Solvent Deposition ❖ Precipitation ❖ Selective Adsorption on Insoluble Carriers ❖ Solid Solutions ❖ Eutectic Mixtures ❖ Solid Dispersions ❖ Molecular Encapsulation with Cyclodextrins	➢ ***Enhancement of drug permeability***: This approach applies to Class III drugs according to BCS. ❖ Lipid Technologies • Lipid solutions and suspensions • Coarse emulsion, microemulsion, SEDDS, and SMEDDS • Solid lipid nanoparticle • Nanostructured lipid carriers (NLC) • Lipid drug conjugates (LDG) nanoparticles • Liposomes ❖ Ion pairing ❖ Penetration Enhancers
➢ ***Enhancement of drug stability***: This approach applies to Class V drugs according to BCS. ❖ Enteric coating ❖ Complexation ❖ Use of Metabolism Inhibitors	➢ ***Enhancement of gastrointestinal retention***: This approach applies to Class II, III or V drugs according to BCS. ❖ Mucoadhesive Systems ❖ Swelling Systems ❖ Floating Systems ❖ High-Density Systems ❖ Microporous compartment system ❖ Magnetic Systems ❖ Super porous hydrogel systems ❖ Expandable, unfoldable and swellable systems ❖ Effervescent (gas generating) systems ❖ Microballoons/Hollow microspheres

Table 4
Biopharmaceutical Drug Disposition Classification System (BDDCS) and transporter effects following oral dosing [41,47].

Class I	**Class II**
• High solubility • Extensive metabolism • Transporter effect minimum	• Low solubility • Extensive metabolism • Efflux transporter effects predominate in the gut while absorptive and efflux transporter effects occur in the liver
Class III	**Class IV**
• High solubility • Poor metabolism • Absorptive transporters effects predominate (but may be modulated by efflux transporters)	• Low solubility • Poor metabolism • Absorptive and efflux transporters effects could be important

the oral bioavailability is not affected by these transporters, and the phenomena are vice-versa for Class IV drugs. In the case of Class II drugs, due to its high permeability and low solubility the drug saturates only the absorptive transporters, not the efflux transporter and the phenomena is vice-versa for Class III drugs [1]. Knowledge about the transporter effect and intestinal cytochrome P450 enzymes metabolism effect in the disposition of a specific drug will help direct lipid-based excipient selection and to prepare the lipid-based formulations with improved absorption [47].

5. Challenges of lipid-based drug delivery

The trends in drug discovery toward lipophilic molecules have increased the requirements to develop alternative drug-carrier systems for poorly-water soluble drug molecules. Therefore, drug-carrier systems utilizing lipid as the excipient are a promising tool, because lipids are known to enhance oral drug absorption and can be prepared with a low particle size [48]. A guidance document entitled “Food-Effect Bioavailability and Fed Bioequivalence” was issued by FDA in December 2002 [49]. The US FDA recommended high-fat meals for food-effect studies because such fatty meals (800–1000°cal, 25%–30% carbohydrates, 50%–65% fat, and 15%–20% protein) affect GI physiology and maximizing drug transfer into the systemic circulation [49].

From the various research study, it was reported that the bioavailability of some of the drugs is increased when co-administered with food [49]. For example, griseofulvin [50], halofantrine [51], danazol [52], troglitazone and atovaquone [49,53]. However, many drug molecules have negligible interaction with food. For example, BCS class I drugs. But the class II drugs have an altered absorption when co-administered with food. The reason for such enhanced bioavailability might be attributed to increased solubility, permeability, GIT residence time, biliary and pancreatic secretions, decrease metabolism and efflux activity, and transport via lymphatic system [49,54] in the presence of food [49,55]. Particularly, it is the lipid component of the food that plays a vital role in the absorption of lipophilic drugs, leading to enhanced oral bioavailability [56,57]. The high-fat meal elevates the TG-rich lipoproteins which react with the drug molecules [49,58] and increases the intestinal lymphatic transport, and also alter the drug disposition followed by the kinetics of poorly water-soluble drugs [49,59]. Besides, the presence of long chain fatty acids and

triglycerides in the food promotes the GIT residence time in the body [56,57]. This food effect on drug absorption leads to a grave concern for the sub-therapeutic plasma drug concentration when co-administered without food, and also may produce serious problematic effects for the drugs with a narrow therapeutic index, which generally have increased bioavailability. Therefore, monitoring or/and control of food intake is vital when treating such drugs [49,60].

However, food-dependent bioavailability can be significantly reduced by formulating the drug as a lipid-based formulation (LBF). Because, the LBF enhances the oral bioavailability through its lipid excipients, which is mainly comprise of mono, di, and triglycerides, oils constituting various combinations of glycerides, phospholipids, and sphingolipids [61]. These lipid excipients promote the molecular solubilization potential, permeability and lymphatic transport of the lipophilic drugs [49,62,63] thereby it reduces the dose of the drug [49] and also has the biocompatibility, manufacturing scalability, industrial adaptability property. So which eliminates various physiological barriers such as pre-systemic metabolism, gastrointestinal degradation, P-gp efflux and permeability related issues, etc. [61,64]. Besides, the lipid formulations can be modified in various ways to meet a wide range of product requirements as per the route of administration, disease condition, and also cost product stability, toxicity, and efficacy [65].

Furthermore, the lipid-based carriers have been evidenced to be attractive candidates for the preparation of pharmaceuticals, as well as diagnostics, vaccines, and nutraceuticals [65,66]. This fact, in turn, makes the lipid as a potential carrier for drug delivery. Besides, the inherent challenging property of lipid preventing the barriers associated with the delivery of the poorly-water soluble drug via oral route by formulating as a lipid-based drug delivery system (LBDDS). Also, the BCS and BDDCS system strongly suggested the lipid-based formulation for the lipophilic drugs. The reason is the usual problem associated with most of the drugs (Class II, III & IV drugs) includes either low aqueous solubility or poor intestinal permeability, both of which can adequately be taken care by LBDDS (eg. Liposomes, Niosomes, Self-emulsifying drug delivery system, solid lipid nanoparticles (SLNs), nanostructured lipid carrier (NLCs) etc.) [61] (Fig. 1).

6. In vivo fate of lipid in human body

The digestive phase initiates with the physical breakdown of lipid formulation by retropulsion, antral contraction, and gastric emptying into a coarse emulsion (aqueous gastric fluid and lipid digestion product) comprised of lipid droplet size ~0.5 μm with high surface area [67,68]. This is accompanied with enzymatic hydrolysis of triglycerides by the secretion of gastric lipase from the chief cells lining the gastric mucosa in the stomach, which results in the partial digestion of triglyceride to diglyceride and fatty acid [69]. Then the crudely emulsified lipid digestion products empty into the small intestine leads to the secretion of bile salts and biliary lipids from the gallbladder that stabilize the surface of the lipid emulsion and reduce its particle size, presenting a larger lipid surface area to the pancreatic lipase/co-lipase digestive enzymes, where quantitative digestion of triglyceride is completed by pancreatic lipase at the oil-water interface (Fig. 2) [69].

With sufficient bile salt concentrations, the product of lipid digestion is finally incorporated into bile salt micelles to form an intestinal mixed micellar phase. The intestinal mixed micellar phase co-exists with a number of physical species in the small intestine, including multilamellar and unilamellar lipid vesicles, simple lipid solutions, and fatty acid soaps [70–72]. Concisely, during the digestive process, bilamellar vesicles are generated

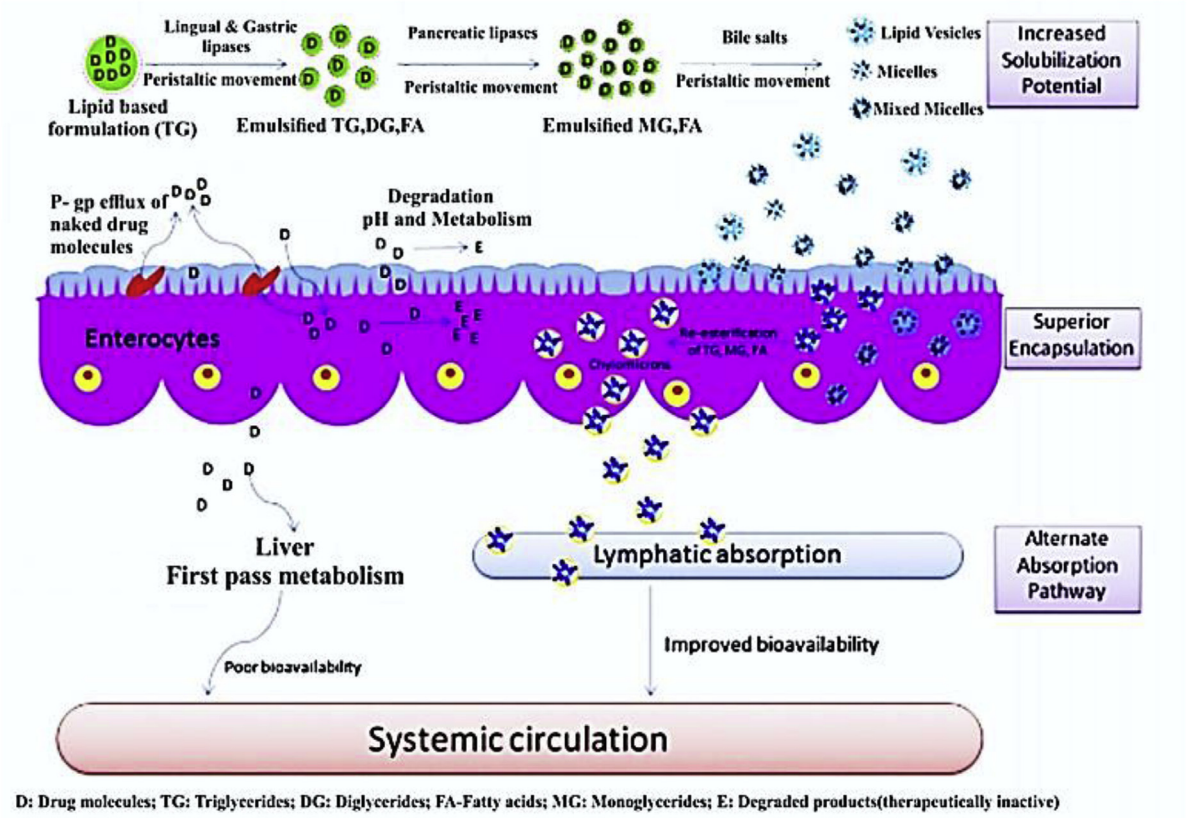

Fig. 1. Advantages associated with lipid-based drug delivery system. (D: Drug molecules; TG: Triglycerides; DG: Diglycerides; FA: Fatty acids; MG: Monoglycerides; E: Degraded products (therapeutically inactive)). Adapted and modified from Ref. [64] with permission.

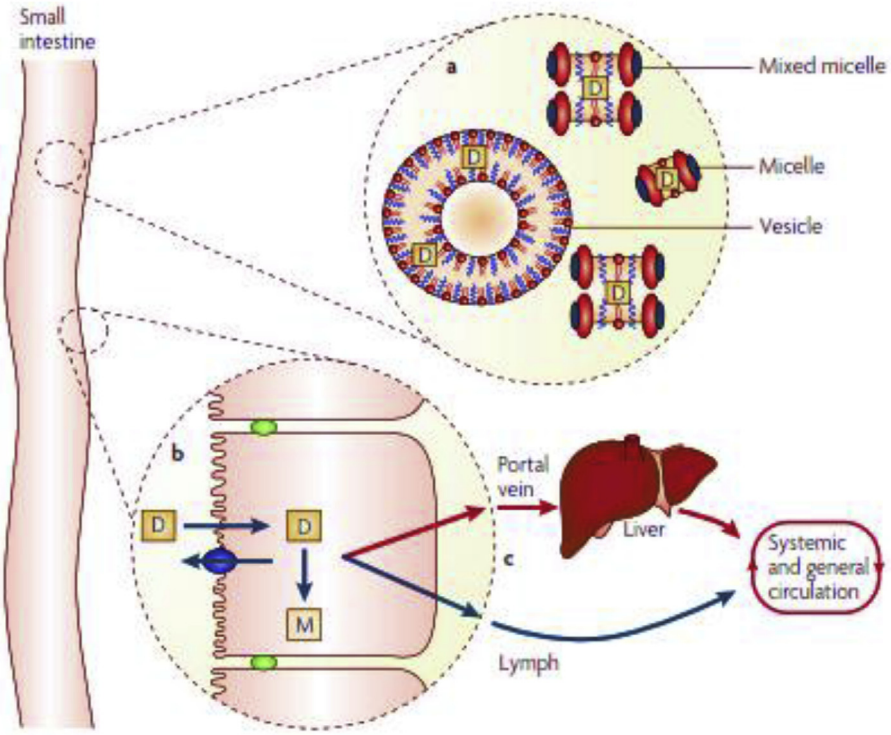

Fig. 2. The potential effect of lipids and lipidic excipients on drug absorption. Adapted from Ref. [69] with permission.

which usually transform into unilamellar vesicles. These spontaneously dissolve into micellar and mixed micellar phases with an increase in the surfactant (bile salt)-to-lipid ratio [71,73,74]. The phase transition produces the thermodynamic condition which is most favorable for effective absorption of lipid from the upper small intestine, whereas in the later part of the small intestine the lipolytic products dispersed as unilamellar and multilamellar vesicles which is more responsible for fat absorption in bile salt deficiency states [71] (Fig. 3).

Despite a lipid-based formulation undergoes similar mechanism

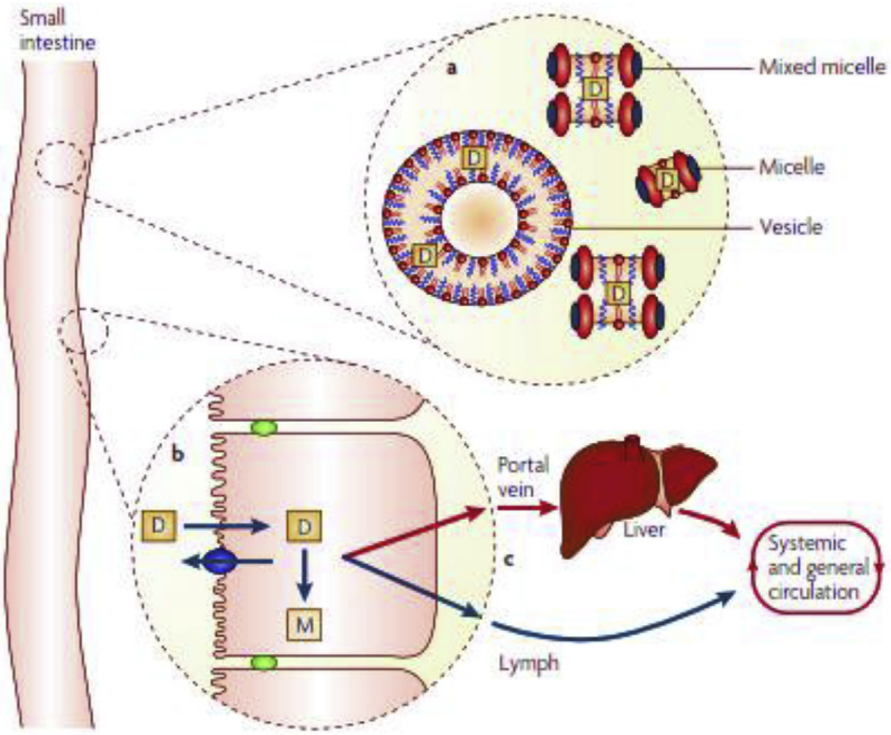

Fig. 3. Lipid digestion and drug solubilization in the small intestine. Adapted from Ref. [69] with permission.

of food-ingested lipids, the lipid-based nanoparticles can potentially generate off-target and immunogenic effects, which is mainly due to the absence of complement control proteins i. e self-discriminating molecules (such as) on the surface of the membrane, which protects "self " cells from attack by the complement system [75,76]. As well, the opsonins (serum proteins that bind to substrates leading to their being taken up by the RES) which generally prefer to adsorb on hydrophobic rather than hydrophilic surfaces [34]. So, the addition of PEG on the surface of nanoparticles render the hydrophilic property, thereby which prevent the opsonins adsorption on the surface of the nanoparticle and avoids the RES uptake [77,78].

Moreover, PEGylation also decreases transendothelial electrical resistance (TEER) values of cells and facilitates the paracellular transport of nanoparticles [79]. Recently, Fang et al. reported the prolonged-plasma concentration (24 h) in the docetaxel-loaded PEGylated NLCs then compare to drug solution (12 h). Also, he reported that it was due to PEGylation which prevented the opsonin binding to intact NLCs in systemic circulation thus avoiding their macrophage uptake [7,80]. Furthermore, the polysaccharide is used as an alternative choice for hydrophilic surface coating and also characterized by low immunogenicity, biocompatibility, stability, low toxicity, low cost and cryoprotection [81].

But in the case of NLCs, the interesting finding was reported that the incorporation of endogenous lipids (both synthetic and natural lipids), preventing the NLCs from triggering an immunological response as a result of their uptake by macrophages [82]. For example, the addition of high-density lipoprotein to NLCs prevented apolipoprotein A-I (apoA-1) from binding to NLCs carrying tanshinone IIA (a lipophilic cardiovascular drug), significantly reducing phagocytosis of high-density lipoprotein–NLCs [83]. Hence, the co-administration of lipophilic drugs with lipids, therefore, has the potential to recruit a number of endogenous lipid processing pathways to support drug absorption.

In addition to lipids, LBF also often contain other excipients (e.g., surfactants and co-solvents) that may further assist in drug solubilization, those that facilitate absorption and permeability across the enterocyte, and those that stimulate intestinal lymphatic transport [12]. Furthermore, the excipients of LBF (lipid, surfactants, and cosolvents) have an important role in the physiology of the body, such as energy storage (lipids), a part of biomembranes (phospholipids), and have an essential function in metabolism (bile acids). Hence, it considered as harmless and usually scheduled in the recognized as a safe category which is US FDA-approved. Moreover, they are degraded by lipases present in the GIT and lungs, where the rate of decomposition depends on the type of lipid used for synthesis [48,84]. Apart from this, there is a plenty of fatty alcohol dehydrogenase enzyme, a hepatic enzyme that helps in the degradation of fatty alcohols [85], for example, stearyl alcohol. Generally, the rate of breakdown of triglycerides with longer fatty acid chains is slower than those with shorter chains, and waxes degrade faster than glycerides [86]. Dong and Mumper [85] reported that the in vitro incubation of fatty alcohol-based SLNs with alcohol dehydrogenases demonstrated 80–90% decomposition after 15–24 h, which suggested similar degradation mechanism of SLNs in vivo [85]. Enzymatic decomposition causes increased the release of drug and break down of SLNs [48].

7. Lymphatic transport of drugs in human body

The lymphatic system is a complex network of specialized vessels distributed throughout the vascular regions of the body [87]. The lymphatic system does not form a circulatory system like blood vascular system and has a unidirectional flow of lymph, collecting lymph from peripheral tissue and emptying into the vascular system [88]. In blood vascular system, the direct uptake of TGs and phospholipids into the bloodstream is difficult due to its small in pore size, though the blood flow is ~500-fold higher than that of the intestinal lymph. The lymphatic capillaries consist of a single layer of thin-walled, non-fenestrated lymphatic endothelial cells. Due to the endothelial architecture of the lymphatic vessels, the thin wall permits the tissue fluid (interstitial fluid) from the interstitial space to enter the lymphatic capillary and facilitates the size-selective transport of high molecular weight substances like chylomicrons [89]. The lymph fluid is then emptied (average 3 L per day) via thoracic duct into the subclavian vein [90], and by-pass the drug with hepatic first-pass metabolism. The drug being transported in the circulatory system, in the form of either micelles or mixed micelles, may then be available in its free form. Since upon dilution with a large volume of the lymph/blood, surfactant concentration it may reduce below its CMC value and micelle may dissociate into monomers [91]. The drug transported as lipid vesicles may remain intact for extended periods and, thereby, can result in prolonged the release of the encapsulated drug [92].

Khoo et al., 2001 and Trevaskis et al., 2008 reported that the addition of triglyceride-rich lipoprotein (TRL) assembly with certain highly lipophilic drugs transports the formulation to the systemic circulation via the lymph rather than via the blood. Also, they reported that where the lipid absorption and lipoprotein synthesis are high especially after postprandial administration, the lymphatic transport may be the dominant means of drug transport and by-pass the first-pass hepatic metabolism [93,94]. Hence, together with dietary lipids, formulation-derived lipids also stimulate TRL assembly and lymphatic drug transport [12].

Moreover, it is no longer sufficient to consider only the traditional roles, such as solubilization capacity in the case of a surfactant, but the increasing evidence of the bioactive nature of many excipients must also be evaluated [95,96]. Excipients such as Tween 80, an oleic acid ester, promotes the production of chylomicron maybe via digestion of the tween to liberate oleic acid, a long chain unsaturated fatty acid, capable of increasing chylomicron production [95]. In contrast, the excipients such as pluronic block copolymers and cremophor EL decreases the chylomicron production in tandem with a decrease in P-gp efflux indicating a possible link between the two biochemical processes [96,97]. From these studies, it was evident that the Tween 80 as an ideal lymphotrophic excipient due to the property of solubilization of lipophilic drugs, inhibition of P-gp and stimulation of chylomicron production [47,95]. From the invivo fate of lipids and lymphatic transport of drugs in the human body, it can be deduced that the lipid has many advantages in LBDD. However, the enzymatic degradation and chylomicron production are main mechanisms for the termination of the effect of LNP [47,48]. Hence, it is very important to select appropriate excipient in the formulation design.

8. Lipid nanoparticle

Rapid advances in the ability to produce nanoparticles of uniform size, shape, and composition have started a revolution in science [98,99]. Recently, various nanonization (i.e., reduction of size at the Nano scale) strategies have emerged to increase the dissolution rates and bioavailability of numerous drugs that are poorly soluble in water [34,100]. Depending upon the material of delivery vehicle used for the nanoparticles, these are divided into the following three groups [34].

- Polymer-based nanoparticles
- Lipid-based nanoparticles
- Lipid–polymer hybrid nanoparticles

The use of polymer-aided nanoparticles in the market is limited by some of the characteristic features, viz., toxicity of the polymers, presence of solvent residues in the compound during production and purification, high cost, degradability, lack of suitable large-scale production units, requirement of high quality, and purity in the case of biodegradable polymer [101,102]. But, owing to lipid biocompatibility, protection against chemical and enzymatic degradation, gradual release of drug molecules from the lipid matrix, decreased adverse side effects and chronic toxicity of the drug-delivery systems [103] and versatility, lipid nanoparticles (LNPs) showed many advantages over polymeric nanoparticles, and have been widely used for drug delivery [104,105]. Also, these systems combine the attributes of both nanosized particles and lipid carriers to improve the bioavailability of active pharmaceutical ingredients (APIs).

Moreover, Lipid nanoparticles (e.g., solid lipid nanoparticles, SLNs) are at the forefront of the rapidly developing field of nanotechnology with several potential applications in drug delivery, clinical medicine, and research, as well as in other varied sciences [99]. Due to their small in size properties, the lipid nanoparticles can be developed to target the new therapeutics in the second and third level of drug targeting [99]. Hence, lipid nanoparticles hold great promise for reaching the goal of controlled and site-specific drug delivery and have attracted the wide attention of researchers [106]. Moreover, it possesses several advantages such as lack of organic solvent usage during the production processes using the high-pressure homogenization (HPH) method with extant machinery [107,108] and ease of large-scale manufacturing (Teeranachaideekul et al., 2007). Hence, these systems demand suitable conditions for drug delivery [107] and potentially attractive and marketable choices due to their natural components [109] and are easily scaled-up synthesis processes.

9. Mechanism of lipid nanoparticles

Concerning the typical lipid nanoparticles triglyceride-based composition, it is expected that after oral administration, they undergo similar mechanisms of food-ingested lipids [110]. Although the fundamental mechanism of improved oral bioavailability has not yet been explained, some aspects are accepted for a basic understanding of the absorption enhancement. Primarily, specific surface characteristics, morphology, and the comparatively smaller particle size are credited to the better oral uptake. It has been proved that increase in surface area associated with a reduction in particle size leads to adequate and consistent absorption in the GIT [111–113]. Also, the enhanced surface area, exposure of lipid moieties with epithelial membranes and bioadhesion of lipid nanoparticle (SLNs) to the GI wall seems to prolong the residence time of SLNs in the GIT, which probably results in improved oral absorption [48,111,112]. Elgart et al. clearly stated that there are three primary mechanisms after oral administration of lipid, lipophilic excipients and lipid-based formulation for increased absorption. They are

i. Pre-enterocyte level (solubilization of drug),
ii. Intra-enterocyte level (chylomicron formation),
iii. Post-enterocyte level (lymphatic drug transport).

Briefly, it was reported that the lipid nanoparticles have adhesive properties, thereby which adhere to the gut wall (enterocytes surface) and immediately release the drugs for direct absorption within the enterocytes. In parallel, the presence of lipid nanoparticles in the duodenum enhances the secretion of lipase/colipase and bile salt which hydrolyses the triglycerides into monoglycerides and fatty acids forming micelles, which re-solubilise the drug meanwhile it is released during the degradation of the nanoparticles. Furthermore, the bile salts interact with micelles and form mixed micelles which facilitate the absorption of these colloidal species by the enterocytes carrying the drug inside the cells. Overall, these mechanisms have been called the “Trojan horse” effect (Fig. 4) [114–116]. After absorption of formed micelles and mixed micelles in the enterocyte, where it gets converted to the chylomicrons upon re-esterification via monoacyl glycerol or phosphatidic acid pathway and subsequent stabilization by phospholipids. However, the penetration of unstirred water layer and mucin in the gastrointestinal tract is rate limiting factor. The formed chylomicrons are then subjected to lymphatic transport system via mesenteric lymph and ultimately enter the systemic circulation by lymphatic drainage at thoracic duct [61,117,118].

As well, a number of mechanisms of delivering the drug through the lymphatic areas after the oral administration are reported. These encompass M cells of Peyer's patches for vaccine delivery [119], the transcellular mechanism [93] and paracellular mechanism [120], of therapeutic agents and nanocarriers. For the uptake of lipid-based carriers, the transcellular pathway is the most relevant mechanism [121]. Besides, lipid-based carriers can encourage the formation of lipoproteins and intestinal lymphatic lipid flux, which is further affected by the physicochemical nature of lipids [120], and the presence of stabilizers [48,122]. The other transcellular routes by which lipid-based drug delivery systems get transported across enterocytes include macro-pinocytosis, clathrin-mediated, caveolae-mediated, and clathrin- and caveolae-independent endocytosis (principally lipid rafts comprising of sphingolipids-and cholesterol-rich microdomains) [123]. Fig. 5 depicts various absorption mechanisms by which lipid nanocarriers improve the oral bioavailability of drug substances [64].

Moreover, other than increased drug solubilization, increased intestinal lymphatic transport, Griffin, and O'Driscoll reported the following mechanisms by which the lipid-based formulations enhance the oral absorption of lipophilic drugs specifically for peptide and protein-like drugs. These encompass reduced enzymatic degradation, increased intestinal membrane permeability, fluidization of intestinal membranes, modulation of TJs, lipid-protein complex formation and modulating the enterocyte-based efflux and/or metabolic processes [124].

In addition to all, lipid-based formulation promotes the delayed gastric emptying, which increases the gastric residence time in the stomach thereby enhances the solubilization of drug molecules at the absorptive site and promotes the absorption of the drug [125,126]. Hence, the lipid nanoparticle increases the oral bioavailability of lipophilic drug through bio-adhesion mechanism along with various endogenous lipid absorption pathways such as solubilization, permeability across the enterocyte, absorption via the M cells of Peyer's patches, increased transcellular and paracellular transport, controlled drug release, delayed gastric emptying time, stimulation of lymphatic transport, and avoidance of intestinal first pass metabolism etc.

However there is a different mechanism to enhance the bioavailability of lipid nanoparticles after oral ingestion, it is very important to know the certain criteria and barriers which influence the enhancement of bioavailability of lipophilic drug molecules or lipid nanoparticles in the body or in the formulation along with its strategies (Table 5).

From the review it was clear that due to the unique property of lipid nanoparticle and its lipid constituent (wide variety of lipid constituents such as endogenous solubilizing components, permeability enhancer, P-gp inhibitor etc.), different choice of mechanism for absorption and permeation, no toxicity and its formulation opportunity such as avoidance of organic solvents during the production process makes this system as a one of the

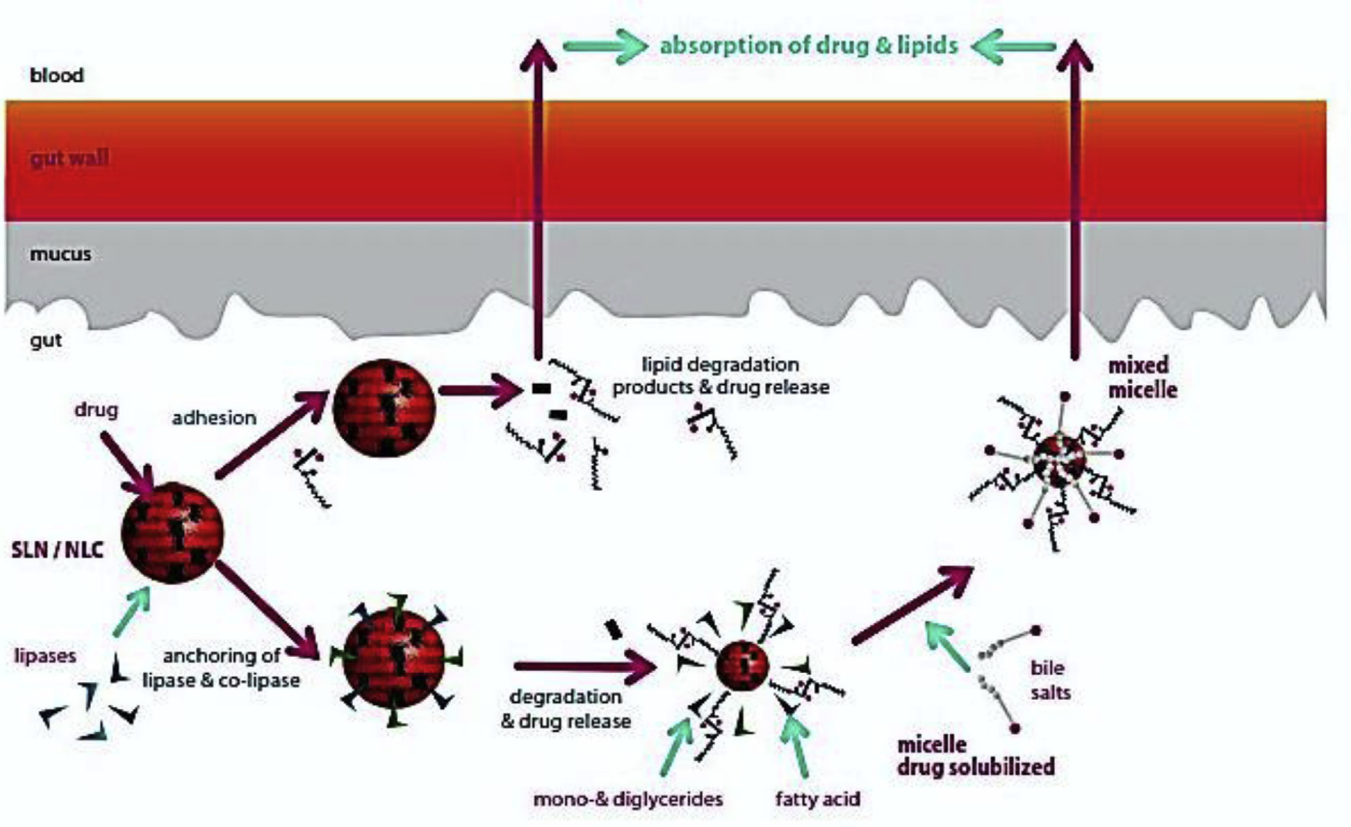

Fig. 4. Schematic representation of the mechanisms of intestinal absorption of drugs from lipid nanoparticles. Adapted and modified from Ref. [31], with permission.

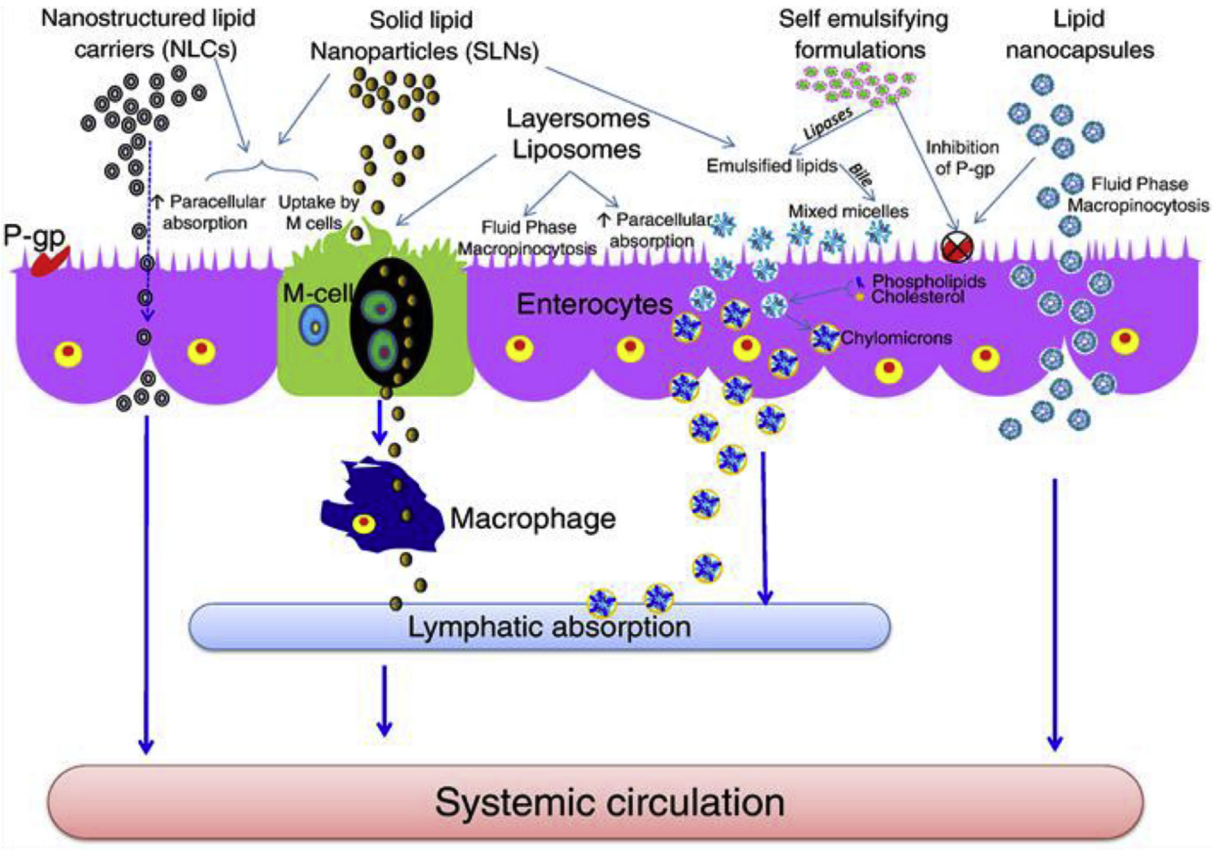

Fig. 5. Absorption mechanisms implemented by lipid- Nano carriers for improving the oral bioavailability of drug substances. Adapted from Ref. [64] with permission.

Table 5
Certain criteria and barriers which influence the enhancement of bioavailability of lipophilic drug molecules or lipid nanoparticles in the body or in the formulation along with its strategies.

Barriers	Strategies
The molecular solubilization of a drug: A lipophilic drug molecules in solution form is essential in GIT after oral administration to cross the enterocyte for absorption. Hence, the rate of dissolution and its extent acts as a rate-limiting steps for absorption.	The lipid-based carrier enhances the molecular solubilization of lipophilic drugs by micelles formation, similar to food ingested lipids [127].
The unstirred water layer (UWL): The UWL act as a diffusional barrier between the intestinal lumen into enterocytes for lipids and lipophilic molecules [128].	Due to the solubilization mechanism, the formed micelles and mixed micelles containing lipophilic drugs promotes the mass transport of lipophilic drug molecules across the UWL and enhancing the absorption through either by chylomicron formation, diffusion mechanism or carrier-mediated transport mechanism [126].
The enterocyte cell membrane: Next to UWL, the enterocyte cell membrane act as a barrier to reach the systemic circulation.	The penetration enhancing characteristics of lipid-carrier or non-ionic surfactants containing formulation promotes the permeability of cell membrane across the enterocyte and helps to reach the systemic circulation [126,129].
The multidrug efflux pumps and Phase I metabolism: It is the next main barrier for the lipophilic compounds specifically for BCS class II compounds [126,130].	The LBDDS with P-gp efflux pump inhibitor or enzyme inhibitor overcomes such barrier and promotes the absorption of BCS Class II drugs [131].
The cytochrome P450 enzymes in cellular microsomes of the enterocytes:	The LBDDS with CYP450 enzyme inhibitors, lipid prodrug approach are promoted the lipophilic drug absorption [132,133].

challenging formulation technique for the oral delivery of poorly water-soluble drugs. However, variation in the lipid constituents may alter the bioavailability of drug or bioactive including vaccines [134], and due to its lipophilicity, the chances of drug (lipid nano formulation) removal after oral ingestion is also possible which alter the bioavailability of drug molecules/lipid nanoparticles. But treating the surface of lipid nanoparticle with the surface modifying agent such as PEG helps to increase the residential time in the systemic circulation and avoiding the phagocytosis uptake.

10. BCS class II drugs: an ideal candidate for the LNPs formulation

Based on the BCS classification formulation selection guidelines, the LNPs are more efficient carrier system for BCS-II and BCS- IV drugs. Although the LBDD are more efficient carrier system for BCS IV drugs in order to increase the solubility and permeability, the extensively metabolized Class II drugs are ideal candidate for LNPs formulation to decrease the side effect, first pass metabolism, efflux transporters effect, CYP enzymes metabolism and to increase the enhancement of solubility, chylomicron production and lymphatic transport. Because of the 33% of marketed drugs and 70% of newly discovered drugs are BCS class II drugs [135]. Briefly, the disadvantage associated with the extensively metabolized class II drugs are (i) enterohepatic recycling, (ii) increased access to the metabolizing enzyme (CYP3A and phase II gut enzymes (e.g., glucuronosyltransferases, sulfotransferases) [135]) due to its high permeable nature, (iii) most likely affected by metabolic, efflux transporter, uptake transporter and transporter-enzyme interplay drug interactions in the liver as well as in the intestine. Moreover, the more lipophilic highly metabolized drugs tend to be more active toward wanted and off-targets because of a higher capability of nonspecific interactions and produces the high risk of toxicity. Therefore, it is more likely that drugs that are less lipophilic and less metabolized (Class IV drugs) are given at a higher dose since they are probably less potent and since there is less risk of toxicity [135]. But the high dose administration may cause the various dose-related toxicity, drug tolerance, and side effects. However, the physiological lipid made nanoparticle is the best choice for class II drugs. Because which prevent the extensive metabolism and enhance the absorption by increasing solubilization capacity, preventing drug precipitation on intestinal dilution, enhancing membrane permeability, inhibiting efflux transporters, reducing CYP enzymes, enhancing chylomicron production and lymphatic transport [47,69,136] along with portal blood circulation into systemic circulation with minimum dose. The BCS class II drugs used for the production of lipid nanoparticles (SLNs/NLCs) are lavishly discussed and tabulated along with its research findings in Table 6.

11. Conclusion

From the literature review, it was evident that the development of lipid nanoparticle formulations extensively suitable for oral delivery of poorly water-soluble drug with good therapeutic applications, bio-acceptability, and biodegradability. Because of their less toxicity, still, it is considered as a strongest and challengeable approach for the encapsulation of potent lipophilic drug in the pharmaceutical market specifically for BCS class-II drug. Moreover, it combines the advantages of other types of lipid-based formulations and colloidal drug delivery systems. Since they are composed of physiological lipid their invivo fate primarily resembles our biological fate of lipid thereby, it reduces the toxicity with concomitant improvement in stability under a hostile environment of GIT, and also its nano-size facilitates to improve the bioavailability by their increased surface area. Also, it increases the concentration of drug in the systemic circulation through by systemic and lymphatic transport. Hence, it is considered as a safe and promising carrier for the delivery of poor water soluble drug.

12. Expert opinion

Nowadays most of the drugs coming out of the drug discovery and development process are belongs to either BCS Class II or Class IV drugs with high molecular weight. The poor solubility with an increase in molecular weight drug faces many problems starting from the drug development (during formulation, pharmacological, toxicological and pharmacokinetic studies) to its biological application (solubility of the drug in the GIT and its permeability across cell membranes). Hence there is a need to increase the solubility of the drug (BCS Class II Drugs). Because it is not suitable for oral delivery of drugs. When compare to BCS Class IV drugs, the Class II drugs are the most suitable choice to formulate into a novel drug delivery system. Because in the case of Class II drugs the only barrier and way to alter the problem is solubility only whereas in Class IV drugs, both solubility and permeability act as barriers. Hence it is the best choice to select the Class II drugs to formulate into a novel drug delivery system.

Table 6
Various research findings of SLNs/NLCs formulations reported by different researches.

Type	Drug	Excipients	Method	Size (nm)	Research findings	Ref.
NLC	Acitretin	Precirol ATO 5, Labrasol	Solvent diffusion technique	223 ± 8.92	Greater efficacy in the treatment of Psoriasis along with a reduction in side effects.	[137]
SLN	Buspirone HCl	Cetyl Alcohol/Spermaceti, Tween 20 or Poloxamer	Emulsification-evaporation followed by ultrasonification	86 to123	Improvement of oral bioavailability	[138]
NLC	Calcipotriol	Myverol™ 18-04K, Precirol® ATO 5, Squalene, Pluronic® F68	Solvent evaporation method	267.3 ± 12.3	Enhanced skin permeation, negligible skin irritation, and the compatibility of the two drugs.	[139]
SLN	Carvedilol	Stearic Acid, Poloxamer 188, Sodium Taurocholate	Microemulsion	120–200, 600–800	Enhancement of oral bioavailability, Lymphatic uptake and bypass the hepatic first-pass metabolism	[122]
SLN	Clozapine	Dynasan 114, Dynasan 116, Dynasan 118, Epikuron 200, Poloxamer 188	Homogenization ultracentrifugation	96.7 ± 163.3	Increased BA, high distribution to brain and reticuloendothelial cells	[140]
SLN	Clozapine	Trimyristin, tripalmitin, tristearin	Hot homogenization, ultrasonication method	96.7 ± 3.8–163.3 ± 0.7	Improvement of bioavailability	[141]
SLN	Clozapine	Trimyristin, Tripalmitin, Tristearin	Microemulsion method	87.2 ± 46.9	Improvement of bioavailability	[142]
SLN	Clozapine	Trimyristin, Tripalmitin, Tristearin, Soylecithin 95%, Poloxamer 188, Stearylamine	Hot homogenization followed by ultrasonication	96.7 ± 3.8 - 163.3 ± 0.7	Improvement of oral bioavailability and tissue distribution	[141]
NLC	Cyproterone acetate	Precirol, Oleic acid, Miglyol, poloxamer 188.	HPH	200–250	Improvement of bioavailability	[143]
NLC	Docetaxel	GMS, Soyabean lecithin, Stearic acid, Oleic acid, Pluronic F68	Ultrasonification dispersion	193.47 ± 5.69	Improvement of bioavailability	[144]
NLC	Domperidone	Dynasan 114, Cetyl Resinoleate, Soy Phosphatidylcholine, Tween 80	HPH	32.23	Fairly spherical shaped, a stable particle with controlled release.	[145]
SLN	Fenofibrate	Vitamin E TPGS, Vitamin E 6100	Hot HPH	58	Improved oral bioavailability	[113]
NLC	Flurbiprofen (FB)	Compritol 888 ATO, SA, Miglyol1 812, Castor Oil,	HPH	179.7 ± 3.102	highly effective, a non-irritant carrier for topical administration of FB and improved drug permeation	[146]
NLC	Flurbiprofen	Compritol ATO 888, Miglyol 812, Gelucire 44/14, Solutol HS Tween 80 Glycerol	Probe ultrasonicator	55.4	Longer retention time due to mucoadhesive nature and improved penetration rate.	[144]
NLC	Fluticasone	Precirol ATO 5/labrasol	Modified microemulsion Method	380–408	Improved the stability and loading capacity of the drug.	[147]
NLC	Fluticasone propionate	Precirol ATO5, Labrasol, Tween80, Soyabean lecithin	Microemulsion technique	316–408	Particle size less than 1 μm maintained over 60 days, and high EE was achieved.	[147]
SLN	Ibuprofen	Stearic Acid, Triluarin, Tripalmitin	Solvent-free high-pressure homogenization (HPH)	175–189	Stable formulation and negligible cell cytotoxicity	[148]
NLC	Indomethacine	Compritol®888ATO5, Miglyol®ATO5, Lutrol®F68, Xanthum gum, Carbopol®934P	Ultrasonication	44.7–191.8	High encapsulation efficiency and delayed and sustained release properties of the drug	[149]
NLC	Itraconazole	GMS, Precirol/Oleic Acid, Miglyol	Hot high-pressure homogenization	177	Stable NLCs were prepared which retained their properties during nebulisation for pulmonary delivery.	[150]
NLC	Ketoprofen	Compritol®888 ATO, Labrafac lipophile, Lutrol® F68, Xanthum gum	Ultrasonication	494 ± 47	Improvement in the dissolution and skin permeation properties.	[151]
SLN	Ketoprofen	Mixture of beeswax and carnauba wax	Microemulsion technique	75 ± 4 - 250 ± 9.38	Faster drug release	[152]
NLC	Ketoprofen	Compritol 888 ATO/Labrafac Lipophile	Nanoemulsification and ultrasonication	300–500	Improvement in both the dissolution and the skin permeation properties of drug	[151]
SLN	Lopinavir	Compritol 888 ATO, Pluronic F 127	Hot homogenization-ultrasonication	230	Avoid first-pass metabolism	[153]
SLN	Lovastatin	Triglyceride, Phosphatidylcholine 95%, poloxamer 188	Hot homogenization-ultrasonication	60–119	Avoid first-pass metabolism and improved bioavailability	[154]
NLC	Lovastatin	Squalene, Pluronic F68, Precirol, ATO5, Myverol 18-04k, Soyabean phosphatidyl choline.	Probe sonicator	180–290	Controlled release of drug	[101]
NLC	Nevirapine	Steric Acid (SA), Oleic Acid (OA), Compritol 888 ATO Tween 80	Microemulsion	159.6	Uniform distribution of the particles and accelerated the release of effective formulations in the delivery of drug for viral therapy.	[155]
SLN	Nimesulide	Palmitostearate, Glyceryl Tristearate	Hot homogenization process	230.4 ± 5.6	Sustained drug release	[153]
SLN	Nitrendipine	Triglyceride, Phosphatidylcholine 95%, Poloxamer 188	Hot homogenization- ultrasonication method	102–123	Improved bioavailability	[97]
SLN	Nitrendipine		Hot homogenization–ultrasonication			[156]

(*continued on next page*)

Table 6 (*continued*)

Type	Drug	Excipients	Method	Size (nm)	Research findings	Ref.
		Tripalmitin, Glyceryl Monostearate, Cetyl Palmitate		110.6–115.4, 116.4–122.3, 132.6–137.4	Improvement of oral bioavailability and reduction of first-pass metabolism	
SLN	Praziquantel	Hydrogenated castor oil, Poly vinyl alcohol,	Hot homogenization and ultrasonication	344.0 ± 15.1,	Improvement of bioavailability and prolonged systemic circulation	[157]
NLC	Progesterone	Monostearin, Stearic Acid, Oleic Acid	Melt-emulsification technique	321.7–485.5	Potential drug delivery system for oral administration	[158]
SLN	Repaglinide	Glycerol Monostearate, Tristearin	Modified solvent injection method	175–350	Well tolerated toxicity level	[159]
SLN	Rifampicin,	Stearic Acid, Polyvinyl Alcohol	Emulsion-solvent diffusion	70–100	Improved bioavailability, stability and reducing dosing frequency	[160]
NLC	Tacrolimus	GMS/Oleic Acid	Hot sonication and homogenization method	123.4 ± 0.3	Penetration rate is 1.64 times increased than the commercial tacrolimus ointment, Protopic®	[161]

But it is very difficult to change the inherent solubility property of new chemical entities. Instead, to change the solubility of the drug, it is easy to increases the dissolution rate of the lipophilic drug by various formulation technique. Among the different techniques, the size reduction is a simplest traditional technique. The size reduction from macro to nano size increases the surface area and overcome the solubility problem associated with the lipophilic drug. Due to the unique properties of nanoparticles, it plays an important role in drug delivery. Among the different nanoparticle, the lipid nanoparticle represents a new technological platform in the pharmaceutical industry. Because, lipid nanoparticles combine advantages of other colloidal carriers, e.g., polymeric nanoparticles, liposomes, and conventional oil-in-water (o/w) emulsions.

Besides, LNPs are safe, versatile vehicles for drug and active delivery, suitable for different administration routes, ease of large-scale production, and avoidance of organic solvents. Also, it significantly prolongs the half-life of the drug in the circulation, minimizes the systemic toxicity, increases the wide therapeutic window and improves the bioavailability of drugs by 2- to 25-fold. Moreover, the clearance of lipid and lipid nanoparticle by phagocytosis is also overcome by surface modification with hydrophilic substances such as PEG. Due to its biodegradation and biocompatible nature, it secures the title of “Nano safe carrier”. But the presence of other excipients such as surfactants in the lipid nanoparticles may produce lower cytotoxicity than synthetic polymeric nanoparticles. From the review, it was clear that the formulation of lipid nanoparticle is more suitable for Class II drugs. Also, the thorough knowledge of the determination of pharmacokinetic data, physicochemical characteristics of formulation components, biological barriers, in-vitro/in-vivo stability prediction of lipid nanoparticles and pharmacological challenges of the individual formulated drugs makes this drug delivery as a one of the promising delivery for the solubility and permeability problem associated with the drugs to assure its good bioavailability.

Conflicts of interest

The author declares no conflict of interest.

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