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Enhancing Oral Bioavailability of Poorly Water Soluble Drugs through Solid Lipid Nanoparticles: Recent Advancements

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Abstract

To date, the oral route is considered as a proffered route for drug delivery having high patient compliance. However, the therapeutic efficacy of the drug given through the oral route is hampered by its low solubility, low bioavailability, and stability issues in the harsh gastric environment. Solid lipid nanoparticles (SLNs) have emerged as a potential system that can overcome the oral bioavailability issues associated with poorly water-soluble drugs. The SLNs have both properties of lipid emulsion and polymeric nanoparticles and thus offer various benefits, such as high biocompatibility, biodegradability, protect the drug from degradation, improved drug stability in gastrointestinal tract, controlled drug release, avoid organic solvents, and ease of manufacturing. This review discussed the recent advancements in SLNs with regards to the oral bioavailability of poorly water-soluble drugs. The key components and methods of preparation of SLNs were also discussed. To conclude, studies performed to date have shown promising results with SLNs in enhancing the oral bioavailability of poorly water-soluble drugs with a high degree of biocompatibility.

Keywords: Bioavailability, Drug delivery, Nanoparticle, Oral delivery, Solid-lipid nanoparticle, Solubility, Sustained release

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Introduction

To date, the oral route is considered the most convenient and safest route for drug delivery with high patient compliance and low cost. However, this route is also associated with some limitations due to the physicochemical properties of the drug and physiological barriers. The poor water solubility and poor permeability of the drug through biological membrane result in poor bioavailability following oral administration.[1,2] In addition, hepatic first-pass metabolism of the orally administered drug also results in poor bioavailability.[3] Other challenges associated with oral routes are chemical and enzymatic degradation of the drug and P-glycoprotein mediated efflux.[4] Various factors affecting the oral bioavailability of the drug was illustrated in Figure 1.

The poor drug solubility does not only affect bioavailability, but it presents a great challenge for formulation development. The poor water solubility could also result in the slow onset of action, unproportional dose distribution, and steady-state plasma concentration is difficult to achieve. As a result, frequent dosing is required, which has been associated with various side effects.[5] Therefore, there is a need for a drug delivery system that can overcome these challenges and enhance the therapeutic outcome of poorly water-soluble drugs.

To date, nanoparticulate (NPs) systems have emerged as potential drug delivery carriers that can overcome the challenges associated with the oral route. To date, different types of NPs based on natural and synthetic polymers, lipids, and oils have been investigated for the improvement of oral bioavailability.[6,7] Among these NPs developed to date, solid-lipid NPs (SLNs) are of great interest in having advantages of lipid and polymers. The present review covers various aspects of SLNs, such as advantages and limitations, structural framework, mechanism of absorption, method of preparations, and recent advancements.

SLNs

In the last few decades, lipid nanocarriers have been emerged as potential carriers for overcoming the existing limitations. The SLNs are nano-sized colloidal carriers mainly composed of physiologically accepted biocompatible lipids dispersed in surfactant solution prepared in water.[8] The SLNs have combined advantages of lipid and polymer nanocarriers. The lipid part enhances their biocompatibility, biodegradability, drug stability in the gastrointestinal tract (GIT) environment, and membrane permeation. While the solid matrix protects the loaded drug and releases them in a sustained manner.[9,10] These combined dual properties make SLNs an ideal candidate for oral drug delivery to achieve a better therapeutic outcome.

To date, SLNs have been investigated for oral, parenteral, transdermal, and ocular applications. It has been seen that following oral administration, SLNs enhance the drug solubility, their membrane permeation, and oral bioavailability.[11,12] A site-specific drug targeting of poor water-soluble using site directing legend can be possible through intravenous administration of SLNs.[13] Moreover, the studies have reported improved skin permeation and therapeutic outcomes using SLNs in the form of cream or gel.[14] Compared to other nanocarriers, SLNs offers various benefits, as mentioned in Figure 2.

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Despite various advantages, SLNs are also associated with some limitations, such as physical instability in terms of particle growth, aggregation, and burst release. These shortcomings are more risk full in parenteral administration.[15] The lipid melt, lipid-drug interaction, miscibility of the drug with lipid, and extent to which the drug can dissolve in the lipid effects the encapsulation efficiency of the SLNs. However, an overall benefit compared to other nanocarriers makes them a system of choice for oral administration and to overcome associated challenges.

Composition of SLNs

The structural framework of SLNs is composed of lipid and surfactant or stabilizers. In addition, preservatives, co-surfactant/co-stabilizer and charge modifier were also used in the fabrication of SLNs. The surfactants help in stabilizing the SLN formulations by reducing the interfacial tension between the hydrophobic lipid surface and the aqueous surface.[16] The lipids used for SLNs include Beeswax, Stearic acid, Cholesterol, Caprylic/capric triglyceride, Cetyl palmitate, Glyceryl stearate (-mono, and -tri), Glyceryl trilaurate, Glyceryl trimyristate, Glyceryl behenate (Compritol), Glyceryl tripalmitate, Monostearate monocitrate, Solid paraffin, and Behenic acid. The surfactants used for the SLNs preparations are Phosphatidylcholine, Soy and Egg lecithin, Poloxamer, Poloxamine, and Polysorbate 80. The co-surfactants used are Sodium dodecyl sulfate, Tyloxopol, Sodium oleate, Taurocholate sodium salt, and Sodium glycocholate, Butanol. The cryoprotectant used is gelatin, glucose, mannose, maltose, lactose, sorbitol, mannitol, glycine, polyvinyl alcohol, and polyvinyl pyrrolidone. In addition, charge modifiers used to develop SLNs of desired properties includes dipalmitoyl phosphatidylcholine, stearylamine, dicetyl phosphate, and dimyristoyl phosphatidylglycerol.[17]

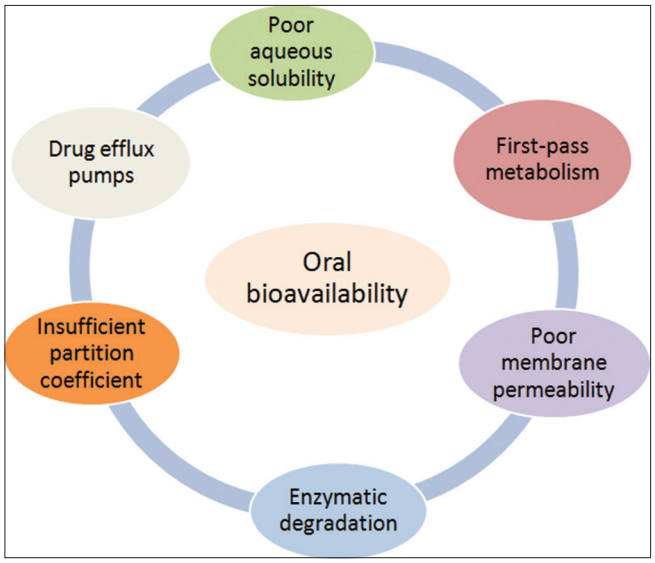

Figure 1: Factors affecting oral bioavailability of the poor water-soluble drugs

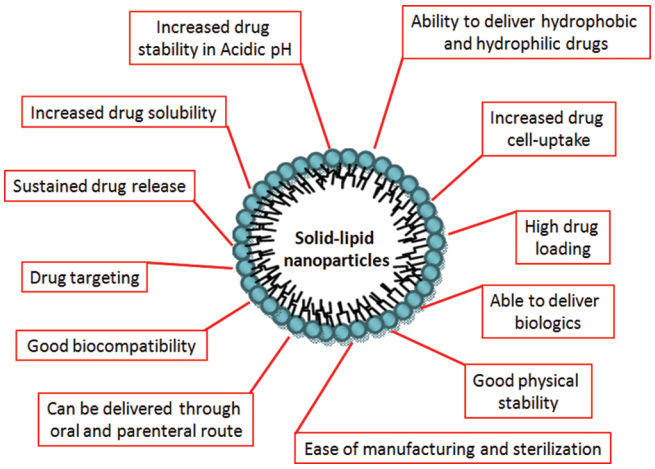

Figure 2: Advantages of solid lipid nanoparticles compared to other nanocarriers systems

Absorption Mechanism of SLNs

There is more than one transport mechanism involved in the absorption of the drug from the GIT following its oral administration [Figure 3].[18] Studies have shown that the NPs uptake could be mediated through two mechanisms, such as intracellular uptake through the M-cells in the gut and intercellular or paracellular uptake.[19] In addition, lipase-mediated chylomicron formation further increases the SLNs absorption.[20] The M-cell uptake is size-dependent where the drug is significantly transported to the systemic circulation through the intestinal lymphatic system. The uptake increases with a decrease in SLNs size.[20] Lymphatic absorption of SLNs or poor water-soluble drugs avoids the hepatic first-pass effect and increases the drug plasma concentration.[21]

The previous study showed a different proposition of drug-loaded SLNs from all segments of GIT. Results showed that only 6% of SLNs were absorbed from the stomach while 82% were absorbed from the intestine and colon region. The large surface area and the presence of M-cells at the intestinal and colon region enhance the SLNs uptake.[22] The SLNs size and surface properties are the critical parameters that have a significant impact on their absorption.[23] Compared to large particles, smaller particles have greater absorption. However, studies showed that the larger

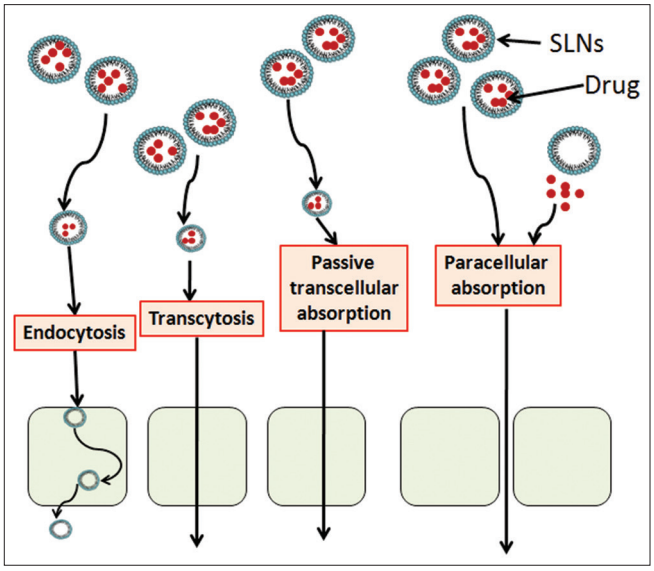

Figure 3: Various mechanisms of solid lipid nanoparticles absorption through the intestine after peroral administrations

particles remain in the M-cell of the Peyer's patches which can also facilitate their absorption into the lymphatic systems[21] Figure 3.

The surface charge and hydrophobicity of the SLNs affect their bioadhesion and absorption. The SLNs with high hydrophobicity value can retain in the M-cells of Peyer's patches for a longer duration.[24] Studies have shown that the SLNs with negative or neutral charges have higher uptake through M-cells compared to the positively charge SLNs.[25] Moreover, surface modification with legend can enhance the SLNs uptake.[26] In addition, the overall protein binding and protein absorption also affect the SLNs uptake, increases the phagocytosis and hepatic first-pass metabolism.[27]

Method of Preparations

To date, different techniques have been used for the development of SLNs, such as high shear homogenization, ultrasonication or high-speed homogenization, cold homogenization, hot homogenization, microemulsion based method, supercritical fluid-based method, solvent emulsification/evaporation method, double emulsion method, and spray drying method.[28,29]

High Shear Homogenization

In this method, the lipid nanodispersion was prepared through processing the fluid or particles between two solid surfaces under high shear. The advantages of this method are its scalability and low cost. However, the method is not suitable with high lipid content and could result in high polydispersibility and damage to the biomolecules.[30]

Ultrasonication or High-speed Homogenization

This process involves the formation, growth, and collapse of bubbles in the aqueous system. This method of preparation is simple and gives a small particle size (30–180 nm). However, the method is also associated with different limitations, such as less entrapment efficiency, possible metal contamination, and physical instability on storage of the formulations.[31,32]

Hot Homogenization

Hot homogenization involves melting of the lipid phase above its melting point. At the same time, the aqueous surfactant phase is also heaved to the same temperature as the lipid phase. The surfactant phase is added to the lipid phase and homogenized at elevated temperature. This method is scalable and could result in small size SLNs at higher processing temperature. The limitations of this method are possible thermal degradation of the drug and particle aggregation can occur at a very high speed result in large particle size SLNs.[33]

Cold Homogenization

The solid lipid suspension was homogenized at elevated pressure with critical control over the temperature. The cold homogenization technique overcomes the temperature-mediated drug degradation and possible polymorphic changes during hot homogenization. The initial step is similar to the hot homogenization technique, i.e., melting the lipid and addition of the drug into it. However, in this case, the lipid melt is rapidly cooled down to ensure homogeneous drug distribution in the lipid melt. The drug mixed lipid is preceded with the help of mortar milling to result in micron size particles. After that, the micron size dispersion is added to the surfactant solution and homogenized at high speed controlling the temperature change. Compare to the hot homogenization technique, the cold method give a larger particle size and wide particle size distribution.[34]

Microemulsion Based Methods

The SLNs are developed through stirring low melting lipid, an emulsifier, co-emulsifier, and water. This hot microemulsion is dispersed in cold water with continuous stirring. The ratio of hot microemulsion and the cold water is also crucial. With low energy input, the method gives low NP yield.[35,36]

Supercritical Fluid-based Method

This is a new technique involved in the solvent-free processing of SLNs. The rapid expansion of the supercritical carbon dioxide solutions is used for the fabrications of SLNs.[37,38]

Solvent Emulsification/Evaporation Method

This method consists of three-step for the development of SLNs, which are:

1. Step-1 involves the addition of the lipid to the organic solvent to form a clear homogeneous solution
2. In step-2, the prepared lipid solution was added to an aqueous solution to form emulsion using a high-speed homogenizer
3. In step-3, after the formation of nanoemulsion through high-speed homogenization, the resulting nanoemulsion kept overnight on continuous stirring to remove the organic solvent.

Finally, the NPs are collected through filtration followed by lyophilization. This method gives SLNs with small size and high entrapment efficiency.[39,40]

Double Emulsion Method

This method is also known as multiple emulsion method generally used for the development of SLNs loaded with hydrophilic drug using surface-active agents. This method involves three steps; (1) preparation of o/w or w/o emulsion, (2) addition of prepared w/o emulsion into the solution of polymer or surfactant with continuous stirring to form w/o/w emulsion, and (3) formation of SLNs through solvent 5 evaporation. This method gives quite a large particle suitable for surface modification.[8]

Spray Drying Method

This method is an economical method used to transform the lipid nanodispersion directly into the final product form, i.e. dried SLNs. However, the method is also associated with limitations, such as particle aggregation and partial meting due to high shear force and increase in temperature. Lipid having a melting point above 70°C is suitable for use by this technique.[41]

Recent Advancements

The SLNs are known to improve oral bioavailability of the poorly water-soluble drug by their ability to avoid first-pass metabolism

resulting in high plasma concentration. Some of the previous studies performed to enhance the oral bioavailability of drug-using SLNs are listed in Table 1.[42-56]

In a recent study, SLNs were prepared through acoustic cavitation assisted hot melt mixing technique for controlled release and enhanced the oral bioavailability of fenofibrate, ibuprofen, ketoprofen, and nabumetone. The prepared tristearin based SLNs were of less than 350 nm particle size having high entrapment efficiency (>80%). The SLNs showed excellent biocompatibility against Raw 264.7 cells and released the loaded drug *in-vitro* in 3 days.[57] In another recent study, Praziquantel-loaded SLNs were prepared using hot high shear homogenization. High hydrophobic character and its low water solubility are the main limitations with praziquantel for its oral delivery. The developed NPs have the mean particle size of 300 nm with a polydispersibility index (PDI) of about 0.20 and entrapment efficiency of about 92.31%. The developed SLNs showed biocompatibility with fibroblast cell lines (L929). The praziquantel-loaded SLNs were found more effective against *Schistosoma mansoni* death than praziquantel alone.[58]

In another recent study, rosuvastatin calcium-loaded SLNs were developed to enhance oral bioavailability of poorly water-soluble drug rosuvastatin. The developed SLNs have a size range of ~134 and 351 nm with PDI of ~ 0.130–0.33 and zeta potential of ~−17 mV–−41 mV. The pharmacokinetic studies showed a significant improvement in Cmax (1.4 fold) and AUClast (8.5 fold) by rosuvastatin-loaded SLNs in comparison with the pure drug.[59] In another study, Zedoary turmeric oil (ZTO) which has a strong antitumor activity, was loaded into SLNs to improve its solubility and oral bioavailability. Moreover, the developed ZTO–loaded SLNs were also coated with chitosan. The size of the developed ZTO-SLNs and chitosan-coated ZTO-SLNs was found as 134.3 ± 3.42 nm and 210.7 ± 4.59 nm. Due to the chitosan coating, the surface charge of the SLNs was changed from −8.93 ± 1.92 mV to +9.12 ± 2.03 mV. In-vivo studies in rat showed higher accumulation of chitosan-coated ZTO-SLNs than ZTO-SLNs with enhanced bioavailability.[60]

Cilnidipine (CND)-loaded SLNs were developed using emulsification-solvent evaporation method for solubility and oral bioavailability enhancement. Box–Behnken design was used for the optimization of CND-loaded SLNs. The particle size, PDI, zeta potential and LE% of optimized formulations were 207.1 ± 2.9 nm, 0.27 ± 0.1, −22.2 ± 1.9 mV and 15.9 ± 1.3%. Pharmacokinetic studies showed a higher Fabs of CND-SLNs (0.66) compare to free CND (0.27). The Cmax and AUC0–∞ was significantly higher in CND-SLNs (572.4 ± 25.3 ng/mL and 5588.6 ± 229.5 ng/mL × h) as compared to free CND (363.6 ± 23.5 ng/mL and 2316.1 ± 163.6 ng/mL × h). Moreover, the MRT of CND-SLNs (9.8 ± 0.9 h) was significantly higher compared to free CND (5.7 ± 0.5 h).[61] To enhance the oral bioavailability of curcumin, SLNs were developed using tristearin and polyethylene glycol (PEGylated) emulsifiers. *In-vitro* mucus-covered gut epithelium permeation studies showed that the curcumin loaded in long-PEGylated SLNs rapidly permeated the epithelium due to the neutral surface charge of the micelles, resulting in a >12.0–fold increase in bioavailability compared to curcumin solution in a rat model.[62]

In another recent study, the oral bioavailability of poor water-soluble [6]-Shogaol, an alkylphenol compound was enhanced through SLNs. The shogaol-loaded SLNs were developed through high-pressure homogenization and has a mean particle size and zeta potential of 73.56 ± 5.62 nm and −15.2 ± 1.3 mV. An *in-vivo* study using hyperuricemia/gouty arthritis rat model showed a lowering of uric acid level and reduced production of interleukin-1β and tumor necrosis factor-α.[63] In another recent study, SLNs were developed to improving the oral bioavailability and the therapeutic effectiveness of glibenclamide. The SLNs were developed through emulsion solvent evaporation technique. The *in-vivo* studies using PEGylated SLNs showed better hypoglycemic effect compared to the plain drug.[64]

In a recent study, glyceryl monostearate-based SLNs were developed to improve the oral bioavailability of olmesartan medoxomil using a hot homogenization method. The developed SLNs release the drug *in-vitro* in a controlled manner for a minimum of 24 h. The *in-vivo* pharmacokinetic study showed a significant increase in Cmax of 1610 ng/mL, higher AUC of 15492.50 ng/mL, and enhanced relative bioavailability by almost 2.3 folds compared to the marketed formulation.[65] In another

Table 1: Various studies performed using SLNs to improve oral bioavailability of drugs

Drug	Method	Lipid	Emulsifier	Ref
Camptothecin	Hot homogenization	Stearic acid	Soya lecithin, Poloxamer 188	[44]
Clozapine	Homogenization ultracentrifugation	Dynasan 114, 116, 118	Epikuron 200 Poloxamer 188	[45]
Cyclosporine A	Hot homogenization	Imwitor 900	Tagat S Sodium cholate	[46]
Cryptotanshinone	Ultrasonic and high pressure homogenization	Glyceryl monostearate Compritol 888 ATO	Soya lecithin Tween80 Sodium dehydrocholate	[47]
Fenofibrate	Hot homogenization	Vitamin E TPGS, Vitamin E 6100	-	[48]
Idarubicin	Microemulsion	Stearic acid	Epikuron 200 Sodium taurocholate	[49]
Insulin	Ultrasonication	Stearic acid	Poloxamer 188 Soya lecithin	[50]
Lovastatin	Hot homogenization ultrasonication	Triglyceride	Poloxamer 188	[51]
Lopinavir	Hot homogenization ultrasonication	Compritol 888 ATO	Pluronic F 127	[52]
Methotrexate	Solvent evaporation	Stearic acid tristearin Compritol 888 ATO	Soya lecithin	[53]
Nitrendipine	Hot homogenization ultrasonication method	Triglyceride	Poloxamer 188	[54]
Puerarin	Solvent injection method	Monostearin	Soya lecithin, Poloxamer 188	[55]
Tobramycin	Microemulsion	Stearic acid	Epikuron 200 Sodium taurocholate	[56]
Rifampicin	Emulsion-solvent diffusion	Stearic acid	Polyvinyl alcohol	[57]
Vinpocetine	Ultrasonic-solvent emulsification	Glyceryl monostearate	Soya lecithin tween-80	[58]

SLNs: Solid lipid nanoparticles

study, glyceryl monostearate SLNs were developed using high shear homogenization technique to improve the solubility and oral bioavailability of glyburide. The antidiabetic activity was evaluated in rat skeletal muscle cells (L6 myocytes) and in streptozotocin and high-fat diet-induced diabetic rats. *In vivo* results showed that the glyburide-loaded SLNs normalize the blood glucose levels and serum biochemical parameters compared to that of streptozotocin controls.[66]

In another study, ezetimibe-loaded SLNs were developed using a high-pressure homogenizer to improve solubility and oral bioavailability of ezetimibe. The particle size, PDI, zeta potential, and %EE of ezetimibe-loaded SLNs were 156.9 nm, 0.125 and −20.5 mV, and 90.7% EE. Enhanced bioavailability was found during *in-vivo* in rats compared to marketed formulations.[67] In another recent study, ritonavir-loaded SLNs were developed by solvent evaporation followed by ultrasonication using Compritol 888 and sodium lauryl sulfate. The SLNs were optimized using Box Behnken design. The particle size (300 nm), PDI (0.361), and zeta potential (−32.4 mV) were also found to be in acceptable ranges. The encapsulation efficiency ranged from 53.20 ± 4.13 to 73.04 ± 2.85%. The results of pharmacokinetic studies showed that the extent of absorption of SLNs was much higher in the spleen and thymus compared to that in the plasma. This indicated that the developed SLNs could enhance the bioavailability and intestinal lymphatic target specificity.[68]

Conclusion

The past decades have witnessed significant development in the field of nanotechnology and its therapeutic applications. Among various nanocarriers, SLNs emerge as a potential system that can overcome various limitations associated with conventional oral drug delivery systems. They have combined properties of lipid emulsion and polymeric NPs which help in protecting the drug in a harsh GIT environment and enhance the biocompatibility of the overall system. The SLNs offers various benefits which make them an ideal candidate for enhancing the solubility and oral bioavailability, such as the ability to enclose both hydrophilic and hydrophobic molecules, avoid the use of organic solvent, enhance biocompatibility due to lipid system, sustained drug release, improved stability, and ease of manufacturing and scalability. All the studies conducted so far have shown significant promising results of SLNs in enhancing solubility and oral bioavailability of poorly water-soluble drugs.

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