Expert Opinion

Solid lipid nanoparticles: an oral bioavailability enhancer vehicle

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Introduction: The therapeutic efficacy of perorally administered drugs is often obscured by their poor oral bioavailability (BA) and low metabolic stability in the gastrointestinal tract (GIT). Solid lipid nanoparticles (SLNs) have emerged as potential BA enhancer vehicles for various Class II, III and IV drug molecules.
Area covered: This review examines the recent advancements in SLN technology, with regards to oral drug delivery. The discussion critically examines the effect of various key constituents on SLN absorption and their applications in oral drug delivery. The relationship between the complexity of absorption (and various factors involved during absorption, including particle size), stability and the self-emulsifying ability of the lipids used has been explored.
Expert opinion: The protective effect of SLNs, coupled with their sustained/controlled release properties, prevents drugs/macromolecules from premature degradation and improves their stability in the GIT. An extensive literature survey reveals that direct peroral administration of SLNs improves the BA of drugs by 2- to 25-fold. Overall, the ease of large-scale production, avoidance of organic solvents and improvement of oral BA make SLNs a potential BA enhancer vehicle for various Class II, III and IV drugs.

Keywords: bioavailability enhancement, lipids, nanotechnology, oral absorption, oral drug delivery, solid lipid nanoparticles, stability

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1. Introduction

The oral route is considered as the most natural, convenient and safest route of drug administration involving higher patient compliance, lesser complications and lower cost as compared to parenteral drug delivery. Despite these expounding attributes, therapeutic efficacy of peroral delivery systems is pretentious and often obscured due to a number of factors associated with certain physicochemical properties of drugs as well as physiological constraints. Poor solubility and/or poor permeability of drugs are the main causes for their poor oral bioavailability (BA). Physicochemical and metabolic instability in both stomach and liver negatively influence the drug concentration in blood. Hepatic first-pass metabolism is another major cause of poor BA upon peroral administration. Poor solubility of the drugs not only affects oral BA but also encumbers the development of suitable delivery system. Nevertheless, oral formulations are being developed keeping in consideration the basic biological and pharmaceutical approaches of drug delivery via the oral route.

In order to overcome the challenges associated with oral drug delivery, nanoparticles (NPs) are considered as alternatives to various conventional drug delivery techniques and often used to improve the oral BA of drugs. A number of nanoparticulate systems based on biocompatible polymers, lipids and oils have come to the fore, which can be efficiently used to improve the oral BA of drugs either by increasing the drug permeability or by overcoming the first-pass effect

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Article highlights.

- SLNs can effectively overcome the challenges associated with oral delivery of drugs that have low solubility, poor permeability, instability in the GIT, P-gp efflux and presystemic drug metabolism.
- Peroral administration of drug-loaded SLNs are restricted due to their instability in the acidic-enzymatic milieu of the GIT. Therefore, various researchers have tried to administer SLNs via the intraduodenal route.
- The rate and extent of absorption of SLNs by oral administration is lesser as compared to intraduodenal administration, but still higher than free drug.
- A combination of triglycerides with non-ionic emulsifier has been observed to lower the clumping and also reduce lipase-mediated degradation of SLNs after oral administration.
- Moreover, filling of freeze-dried SLNs in enteric-coated hard gelatin capsule or SLNs coated with enteric polymer for oral administration improves patient compliance when compared with intraduodenal administration.

This box summarizes key points contained in the article.

and/or P-gp efflux. Apart from these, NPs can also improve the stability of drugs in the gastrointestinal tract (GIT) while modulating their physicochemical and biological properties. In this connection, solid lipid nanoparticles (SLNs) have roused particular interest. SLNs with combinational advantages from different carrier systems have emerged as propitious carriers in the armory of oral drug delivery systems. Nanopellets [1], lipospheres [2] and SLNs [3-5] are the analogous systems made of solid lipids introduced by different co-workers having a range of properties. The main reasons for development of SLNs are combinational advantages from different carrier systems such as liposomes and polymeric NPs. Similar to nanoemulsions and liposomes, they are composed of physiologically accepted biocompatible excipients (fatty acids and lipids). Identical to polymeric NPs, their solid matrix can effectively protect the incorporated active ingredients against chemical degradation under harsh biological milieu and provide the highest flexibilities in the modulation of the drug release profiles. Further, they can be produced at large industrial scale by high-pressure homogenization [6-9]. All these constructive attributes make SLNs excellent carriers for oral drug delivery.

SLNs can be administered by various routes such as oral, parenteral as well as transdermal/topical. Oral/intraduodenal administrations of SLNs are believed to enhance BA of drugs by improving transport through intestinal epithelial layer and by protecting them against the hostile environment of GIT. Intravenous administration of SLNs can be used for the delivery of poorly water-soluble drugs or site-specific drug targeting by anchoring suitable site directing ligand [10]. Topical administration of SLNs as cream or hydrogel has been reported to improve skin penetration, therapeutic efficacy, sun blocking activity and follicular targeting [11].

With their unique particulate nature, SLNs offer a range of advantages over other colloidal system as shown in **Table 1** [12]. Some of the advantages of SLNs are listed as follows:

- biocompatibility and non-toxicity of excipients, as compared to toxicologically less acceptable solubilizing excipients such as Cremophor EL
- high drug payload
- feasibility of incorporation of both lipophilic and hydrophilic drugs and other bioactives [13]
- possibility of controlled drug release and drug targeting [14]
- increased drug stability [14]
- avoidance of organic solvents during preparations [13]
- decreased drug toxicity with protective effect against serious toxicity, for example, triptolide-induced hepatotoxicity [15]
- lipids used for their production are relatively cheaper than synthetic polymer used in polymeric NPs, for example, PLGA
- Ease of large-scale production and sterilization [16].

Despite these perceived advantages, physical instability characterized by particle growth and burst release of drug has weighed down the practical applicability of parenteral SLNs. Particle aggregation and growth may lead to emboli formation, which results in potentially lethal complication [17]. Over the last few years, a number of reviews on various aspects of SLN technology, including their methods of preparation, characterization and applications in different fields, have been published [4,7,12]. However, till date, no review has appraised the recent leaps in SLN technology with respect to oral drug delivery. Muchow *et al.* has reviewed the mechanistic aspects of oral absorption of SLNs along with high-pressure homogenization-aided production and regulatory aspects of the oral SLNs [18] while Estella-Hermoso de Mendoza *et al.* discussed SLNs as oral carriers for chemotherapeutic agent delivery [19]. The current review, therefore, examines the recent advancements in SLN technology with regards to oral drug delivery. Starting with an overview of mechanisms and factors involved in the absorption of drug-loaded SLNs through various sites of GIT, our discussion extends its depth and breadth towards the effect of various key constituents on SLN absorption and their possible exploitation in the field of oral drug delivery. Selection of excipients and mechanism of SLN absorption have been critically analyzed to highlight the key issues concerned with improved oral BA of drugs with poor BA, reduced toxicity and improved stability of drugs entrapped in SLNs. The primary goal of the present contribution is to convey information about the state-of-the-art SLN, and to critically address the limitations as well as the need for further progress and clinical development.

Table 1. Advantages of SLNs over other nanoparticulate systems.

Parameter	SLNs	Liposomes	Polymeric nanoparticles	Nanoemulsions	Nano suspensions
Ability to deliver hydrophobic and hydrophilic drugs	Yes	Yes	Yes	Yes	Only hydrophobic drugs
Physical stability	Good	Poor	Good	Moderate	Good
Biological stability	Moderate	Poor	Good	Moderate	Moderate
Biocompatibility	Good	Good	Moderate	Good	Moderate
Drug targeting	Moderate	Moderate	Moderate	Poor	Poor
Drug loading	High	Low to moderate	Moderate	High	High
Ability to deliver biotechnological therapeutics	Moderate	Moderate	Moderate	Poor	No
Oral delivery	Possible	Not possible	Possible	Possible	Possible
Parenteral delivery	Possible	Possible	Possible	Possible	Possible

SLN: Solid lipid nanoparticles.

2. Methods of preparation of SLNs

Intially, Speiser and coworkers (1986) were the first to report the preparation of 'nanopellets' by formation of initial nanoemulsion by using high-shear homogenizer or ultrasonication followed by subsequent spray drying [1]. Later, Domb (1993) described an almost similar process for the preparation of 'lipospheres' [2]. However, both techniques yielded polydispersed populations that failed to produce population of submicron particles. Thereafter, Muller and coworker (1994) subsequently commenced research efforts to improve SLN formulations [3]. The preparation of SLNs mainly involves formation of a precursor oil-in-water 'nanoemulsion' followed by subsequent solidification of the dispersed lipid phase. To prepare SLNs with smaller particle size and narrow polydispersity index, nanoemulsion preparation is a very critical step. Thus, various mechanical and chemical methods have been proposed for the preparation of nanoemulsion. The mechanical methods include high-shear homogenization (HSH), high-pressure homogenization (HPH) and ultrasonication, which provide large mechanical forces [14,15,20-21]. However, the high energy input increases operating expenses and mechanical contamination risks and can inhibit the activity or increases instability of mechanically and thermally sensitive biological molecules. In an attempt to avoid the large mechanical energy inputs, some researchers pursued more chemically elegant approaches, namely, microemulsions and solvent emulsification/diffusion-evaporation techniques [22-26]. However, nevertheless, this system is also fraught with disadvantage because of the inherent instability of many emulsion systems; the process for solidifying the dispersed phase creates thermodynamically challenging phase transitions that may contribute to polydispersity and particle instability. Advantages and mechanism of various methods used for the preparation of different SLNs have been described in **Tables 2** and 4.

3. Absorption of drug-loaded SLNs

Absorption is a vital process bridging digestive system and life of human. This process takes place right from the mouth to the stomach, small intestine and finally colon. Like micro/macromolecules, drugs get absorbed through GIT membrane by one or more transport mechanism [27]. Absorption of nanoparticulate systems may be possible by one or more of the aforementioned mechanisms. Absorption of any NPs system is based on the different mechanistic approaches of absorption and also their properties, which ultimately affect absorption.

3.1 Mechanistic approach of SLN absorption

NPs are colloidal drug carriers that hold significant promise for peroral drug delivery. Generally non-engineered NPs of 50 – 1000 nm [28] and microspheres < 10 μm have shown the adequate particulate uptake into lymphatics. However, microparticles showed only 2 – 3% of absorption through Peyer's patches and were retained in the gut of rats and mice for protracted time periods [29-31]. In addition, NPs were taken up in particulate form by the intestine and transferred to various organs of lymphatic systems in the body. Two possible mechanism of NPs uptake (**Figure 1**) are: (1) intracellular uptake via the M-cells of Peyer's patches in the gut and (2) intercellular/paracellular uptake [31]. Additionally, in case of lipid based systems containing self-emulsifying excipients, apart from M cell and paracellular uptake, absorption through lipase mediated chylomicron formation into lymphatic system (similar to absorption of long chain fatty acids via facilitated chylomicron formation) further increases the absorption [32]. Through M cell uptake, drugs can be effectively transported to the systemic circulation through intestinal lymphatics via thoracic lymph duct. At the capillary level, the intercellular junctions between endothelial cells of lymphatic capillaries are more open as compared to blood capillaries that results in molecular sieving of NPs of large size directly into

Table 2. Different methods of preparation proposed for formulation of SLNs.

Method	Mechanism	Advantages	Disadvantages	Ref.
HSH	Particles or fluid undergoes shear between two solid adjacent area	Scalable Low cost	Not for high lipid contents High polydispersity damage to biomolecules	[21,62]
Ultrasonication	Formation and implosive collapse of bubbles due to cavitation, i.e., 'the formation, growth, and implosive collapse of bubbles in a liquid'	Low particle size: 30 – 180 nm Low shear stress	Metal shading leads to contamination Less entrapment efficiency Energy intensive process Unproven scalability	[15,63-64]
HPH	Shear due to intense turbulent eddies	Very effective dispersing technique	Extremely energy intensive process High polydispersity	[14,20,59]
Hot HPH	Intense cavitations because of the large pressure drop through the valve	Scalable commercially available	Temperature-induced drug degradation Drug distribution into the aqueous phase during homogenization Complexity of crystallization step of nanoemulsion leading to several modifications and supercooled melts	
Cold HPH		No temperature induced drug degradation or crystalline modification	Not reported	
Solvent emulsification (or diffusion) evaporation	Emulsification (or diffusion) of globules followed by evaporation leads to precipitation as particles	Small particle size ≤ 24 nm Avoidance of heat Low viscous system formed Low energy input	Instability of emulsion Low dispersing degree Insolubility of lipids in organic solvents Additional solvent removal procedure Toxicological issue (residual solvent)	[25,26,50]
Microemulsion based SLN preparations	Spontaneous interfacial tension reduction	Low energy input Theoretical stability	Low nanoparticle yield Labor intensive	[22-24]
Membrane contractor	Lipid phase is pressed through the membrane pores allowing the formation of small droplets	Large-scale production Facility of use Control of size	Clogging of membrane	[65,66]
PIT method	Spontaneous inversion of o/w to w/o transitional emulsion with increase in temperature	Less energy intensive Solvent free Good for heat liable molecules	Incorporation of additional molecules influence inversion phenomenon Instability of emulsion	[67,68]

HPH: High pressure homogenization; HSH: High shear homogenization; PIT: Phase-inversion temperature; SLN: Solid lipid nanoparticles.

lymphatics, avoiding direction to blood capillaries. The M cell uptake of NPs was found to be size-dependent (i.e., smaller the size, higher the uptake), but independent of the animal model [31]. Thus, nanoparticulate systems can effectively improve BA and mean residence time (MRT) with concomitant enhancement of therapeutic efficacy.

Improvement of oral BA after oral administration of NPs has secured many advantages. Lymphatic delivery is helpful not only for absorption of poorly soluble drugs but also for targeting drug carriers to the lymphatics. Moreover, lymphatic delivery of NPs evades the hepatic first-pass effect, and increases plasma concentration of drug.

Bargoni *et al.* (1998) studied the possible uptake pathways of SLNs after intraduodenal administration. They suggested that similar to polymeric NPs, SLNs are also uptaken via M cells of Peyer's patches as studied in Sprague Dawley rats. This transcellular process coupled with stimulation of chylomicron formation by enterocytes further enhanced the absorption process. Chylomicron formation aids in the dissolution and assimilation of lipophilic molecules into nonpolar core and thereby promotes the absorption of water-insoluble drugs. Since SLNs are composed of a lipid core, apart from M cell uptake, lipase mediated chylomicron formation is another mechanism of absorption that differs

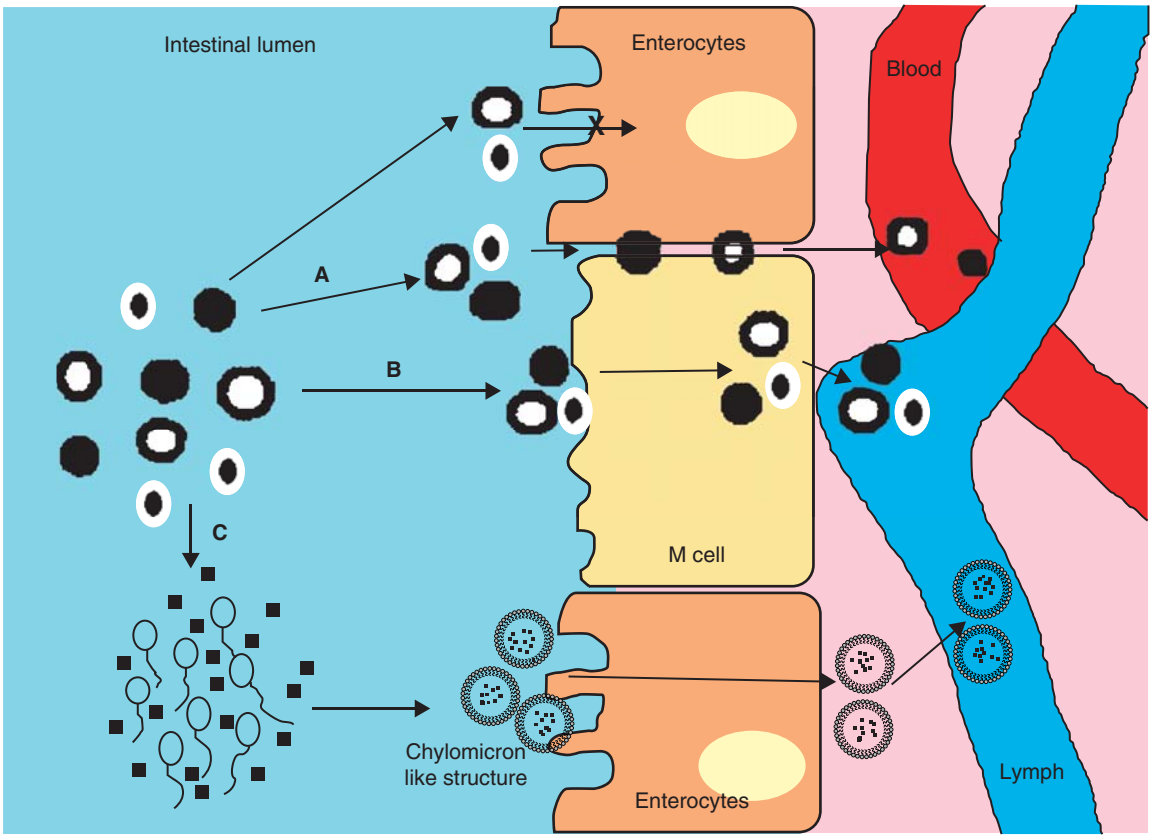

Figure 1. Absorption of SLNs through intestine after peroral administrations: A. paracellular absorption, **B.** M cell uptake via Peyer's patches, **C.** chylomicron-assisted enterocytes absorption. Different shapes of SLNs represent different drug incorporation models (solid solution model, core-shell models with drug-enriched shell and drug-enriched core).
SLN: Solid lipid nanoparticles.

from polymeric NPs [29]. By virtue of being transported via Peyer's patches and chylomicron formation, SLNs offer latent advantages of direct lymphatic transport and bypass the liver first-pass effect. In addition, they also offer the possibility of targeting drugs to lymph, which have potential application in the treatment of lymphatic cancers and relevant infections such as leishmaniasis, malaria and AIDS [29].

However, intestinal translocation of NPs can also be possible in certain circumstances. Little is known about reproducibility and controlled M cell uptake of NPs. Generally, the level of NP uptake is very low and there is little evidence that particles penetrate further into the mesenteric lymph nodes. Therefore, low and unpredictable uptake is likely to limit the potential of particulate carriers as drug delivery systems [33]. But due to high hydrophobicity SLNs might show less translocation as compared to other NPs with enhanced permeability.

Yuan *et al.* (2007) further validated the mechanism of transportation and absorption of SLNs via the oral route. For this study, the fluorescence marker, namely, octadecylamine-fluorescein-isothiocyanate (ODA-FITC)-loaded stearic acid SLNs, were perorally administered to male Sprague Dawley rats. The concentration-time profile of SLNs in plasma after oral administration showed improved BA along with dose dependent biphasic distribution response as shown in **Figure 2**. The first peak of SLNs in blood was attained within 1 – 2 h indicating that SLNs were transported quickly from the GIT into systematic circulation. Subsequently, concentration of SLNs started to decrease due to macrophage uptake and distribution of SLNs among different organs. The second peak appeared at ~ 6 – 8 h after the appearance of first peak; nevertheless, its concentration was appreciably lower than that of the first peak ($C_{max\ first\ peak} > C_{max\ second\ peak}$). It was due to release and distribution of SLNs from particular organs into systemic circulation. This biphasic distribution was further confirmed by intravenous administration [25]. In later course of study, Yuan *et al.* (2007) calculated that actual transportation efficiency of SLNs upon oral administration was only 30%, and it was proportionally increased with increasing concentration of SLNs and time. The SLNs showed linear and extensive absorption from GIT within certain range of concentrations. It was seen that ~ 77.9% of absorbed SLNs were transported into systematic circulation via lymph through M cell uptake, which is the major transport pathway. The rest of the absorbed

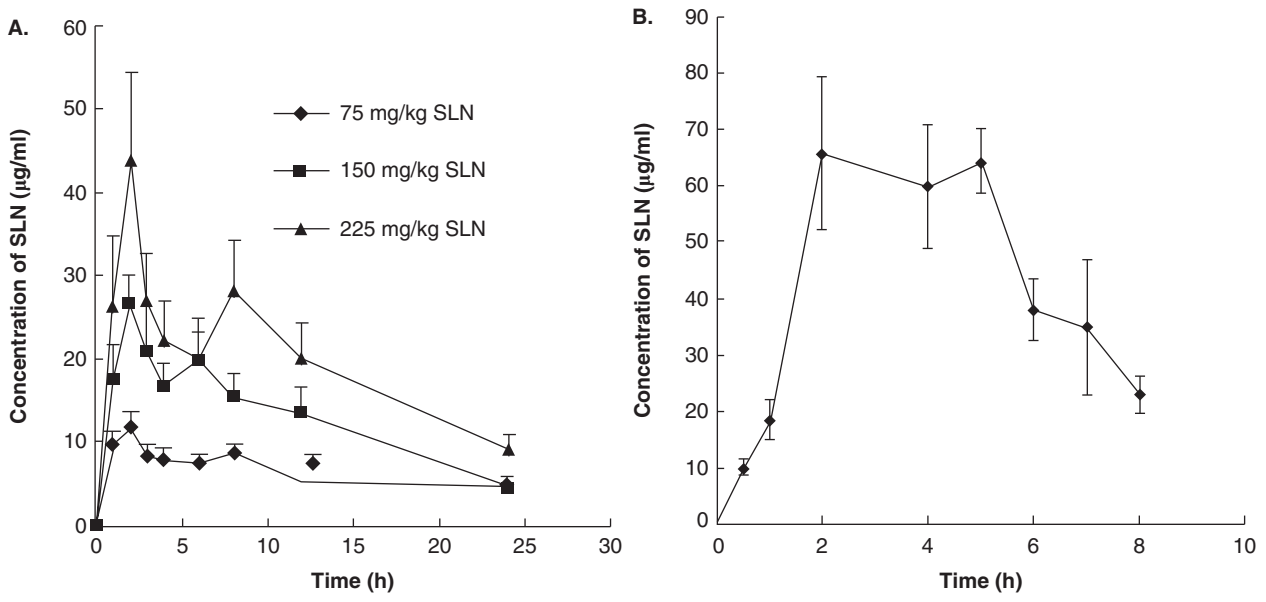

Figure 2. A. Biphasic response of ODA-FITC-loaded SLNs in plasma after oral administration; **B.** Biphasic response of ODA-FITC-loaded SLNs in lymph after oral administration.

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ODA-FITC: Octadecylamine fluorescein isothiocyanate; SLN: Solid lipid nanoparticles.

SLNs were transported directly into blood through capillary vessel or intestinal epithelial cells by exploiting the paracellular pathway [25].

Li *et al.* (2009) also showed enhanced oral absorption of drug-loaded SLNs through different segments of the GIT with different patterns and extents of absorption. To confirm this mechanistic absorption of SLNs, quarcetin-loaded SLNs (QT-SLNs) were administered by oral route in Sprague Dawley rats and their pattern of absorption observed in both stomach and intestine. The results indicated that QT-SLNs could be absorbed in all GIT segments with different percentage and pattern of absorption. The absorption of SLNs was only 6% from stomach while 82% from intestine and colon region. It was clearly shown that large surface area for adhesion, presence of M cells in Peyer's patches, were preferable mechanism for oral absorption of NPs in intestine and colon. Pharmacokinetic results further confirmed improved BA by more than fivefold using QT-SLNs as compared to quercetin suspension [34]. **Figure 3** shows possible absorption mechanism and extent of absorption from a different region of GIT.

3.2 Factors affecting absorptions of SLNs through GIT

Apart from mechanistic absorption of NPs, particle size and surface properties of NPs are also important parameters that further affect the absorption process [28]. An extensive literature survey elucidated that particle size is one of the critical parameter for any orally administered system at the submicron level. In fact, smaller particles have been reported to show greater absorption as compared to larger particles independent of animal model, while larger particles are retained for longer duration in the Peyer's patches as compared to smaller particles, which exhibit very high uptake and are easily released from Peyer's patches thereby facilitating their transport to the lymphatic system [29]. Desai *et al.* (1996) also showed biodegradable nanoparticles of 100 nm size had 15- to 250-fold higher uptake efficiency as compared to larger sized microparticles (> 500 nm) [35]. Further, particles > 500 nm have been reported to show erratic delivery through the abdominal cavity and targeting was restricted. Thus, like other nanoparticulate system, submicron SLNs absorb to significantly higher extent than larger particles.

Surface properties (hydrophobicity and surface charge) also influence the bio-adhesion and consequently the gastric transit time of NPs [15]. NPs with higher hydrophobicity exhibited relatively higher accumulation in the Peyer's patches and vice versa [29]. Surface charge of NPs also plays an important role in M cells uptake. For instance, negatively charged and neutral NPs showed higher M cell uptake than positive-charged NPs [36]. Similarly, surface modification of NPs using specific ligands, namely, lectin further increases their M cell uptake [37].

After the absorption of SLNs, adsorption of the plasma proteins on the NPs surface can take place. This adsorption phenomenon changes with the surface properties of SLNs and determines the ultimate fate of the SLNs in biological milieu. Adsorption of the plasma protein causes either phagocytosis or promotes prolonged circulation and also targeting to specific tissue. The adsorption of these plasma proteins

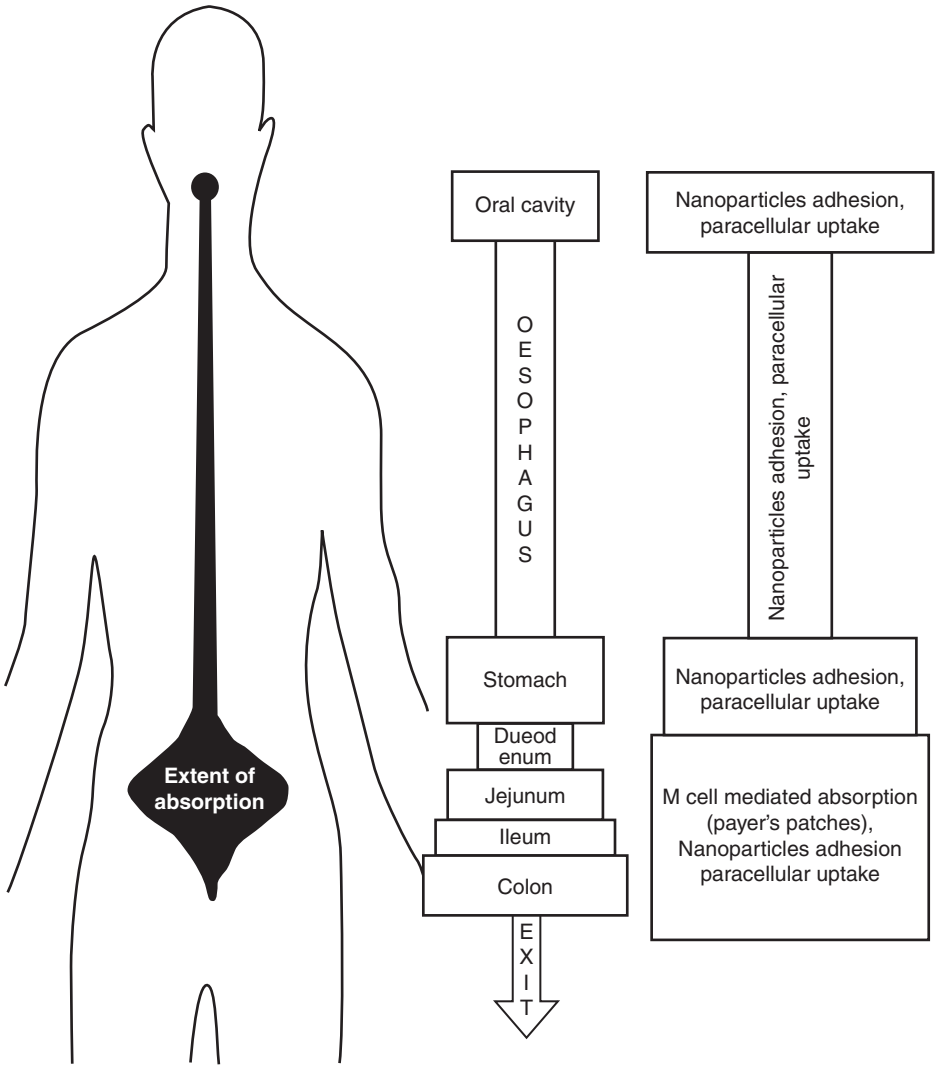

Figure 3. Absorption of NPs by oral route from a different segment of the GIT. Figure indicates possible absorption mechanisms and extent of NP absorption from different regions of GIT.
GIT: Gastrointestinal tract; NP: Nanoparticles.

depends on the concentration of the protein and their binding with the NP surface [38]. Thus, protein adsorption reduces MRT and $t_{1/2}$ of NPs by increasing the phagocytosis and first-pass metabolism.

4. Factors to be considered for the optimization of oral SLNs

Acceptable SLNs with optimum particle characteristics result in improved delivery of bioactives. Types of materials, their compositions and various process parameters should be optimized for acceptable and stable SLN formation for oral delivery purposes. The various parameters that influence the absorption and stability of SLNs *in vivo* are discussed as follows.

4.1 Lipids

Lipids are the main constituents of the SLNs. SLNs can be formulated using either wax or glyceride as bulk material. To date, most published data deal with glyceride SLNs. However, little is known on the wax-based carriers. These two types of SLNs differ with respect to drug encapsulation efficacy, particle size and size distribution after formulation, storage and crystal packing. For example, glyceride SLNs showed good drug encapsulation, but suffered from poor physical stability. On the contrary, wax SLNs possessed good physical stability but lacked in sufficient drug encapsulation in the solidified state. These differences were attributed to the different crystal packing of the formulations. Less ordered crystal lattices favored higher drug inclusion, as in the case of glyceryl monosterate and glyceryl behenate SLNs. The highly ordered crystal

packing of wax SLNs comprised of beeswax or cetyl palmitate led to drug expulsion, but resulted in superior physical stability [39]. In order to improve the oral stability of SLNs, a mixture of glycerides and wax could be the best choice.

Radomska-Soukharev (2007) demonstrated that the selection of lipid excipients was dependent on chemical stability of excipients itself and SLNs stability. They also assessed the effect of the various lipids excipients on stability of SLNs keeping the surfactant mixture and concentration constant. SLNs, which comprised relatively higher percentage of triglycerides, showed negligible decomposition during incubation at 25°C. Among these, Dynasan 118 (Tristearin) showed the highest chemical stability (loss by only 4%) even after 2 years of storage at room temperature, that is, 25°C. Generally, for most of the lipids, the lipid degradation was in the range of 2 – 5% and maximum upto 10% over 2 years of storage at 25°C [40].

Lipids also affect formation and stabilization of the SLNs. With the increase in melting point of the lipids, average particle size of the SLNs was increased, which was due to the higher viscosity of the lipid melt [12]. Various other properties of the lipids, such as velocity of lipid crystallization, the lipid hydrophilicity (influence on self-emulsifying properties), shape and surface area of the lipid crystals, and source of chemicals used (mixture of several chemical compounds), affect SLN formation. These factors have major influence on zeta potential, crystallization process and thus stability of SLNs. Also increasing the lipid contents over 5 – 10%, results in larger and broader particle size distributions. It was probably due to the reduction in homogenization efficiency due to the higher viscosity of dispersed phase, which can be overcome by using higher percentage of the emulsifier and co-emulsifier system [12]. Recrystallization index of lipids determine particle size of the system. Dispersions with a highly recrystallized lipid phase (high recrystallization index) showed an increased particle size growth [9], which is a major concern in case of oral delivery.

SLNs prepared from triglycerides (or solid lipids) should be solid at storage temperature and completely recrystallize during cooling step. If recrystallization of the particles is not enforced by cooling below a critical recrystallization temperature, the particles can remain in the metastable supercooled state for a long period of time and the formulation appears as emulsion and not suspension of particles [41]. SLNs in supercooled state may be unstable in the GIT environment, possess low entrapment efficiency and be prone to burst release. Thus for preparation of stable SLNs, the heating as well as cooling step should be carefully controlled.

Manjunath and Venkateswarlu (2006) studied the effect of lipid chain length on drug release profile of SLNs. As shown in **Figure 4**, higher chain length of the lipid resulted in higher plasma concentration of nitrendipine (NDP). They also reported that lipid matrix might undergo diffusion or degradation by lipase and, therefore, drug release phenomenon depends on nature of the lipid matrix. Triglycerides with long chain fatty acids showed slower degradation than short chain fatty acids, and thus resulted in slow drug release from the SLN matrix. Higher AUC and lower clearance from SLNs with longer chain length lipid is clearly shown in **Figure 4B** [42]. Enhanced BA was observed with longer chain lipids, which might be due to increased uptake via Peyer's patches and long circulation of SLNs.

It is not only the lipids but also charge modifiers that affect the absorption of SLNs through the GIT. Nitrendipine-loaded SLNs (NDP-SLNs) prepared from higher chain length lipids coupled with positively charged stearylamine showed higher serum AUC and MRT following intraduodenal administration. Positive charge NDP-SLNs enhanced their lymphatic uptake as compared to their negatively charged counterpart. Positively charged NDP-SLNs prepared using different triglycerides enhanced the BA of nitrendipine from 3.21- to 5.35-fold [42].

Selections of the lipids also affect the drug loading into SLNs. Therefore, solubility study of the drug in lipid melt plays a significant role. Screened lipids show higher entrapment efficiency and consequently lower the amount of lipid required. Therefore, the dose of SLNs can be reduced since the absorption process also depends on particle concentration, which is saturable [43]. Vivek *et al.* showed the effect of lipid matrix on entrapment of olanazepine. According to their report, entrapment efficiency followed this order: tristrearin-SLNs > Precirol-SLNs > Witepsol E85-SLNs > Glyceryl monostearate-SLNs. This order of entrapment efficiency was correlated with partitioning of olanazepine in a lipid-PBS system and was comparable to the solubility of the drug in different lipid melts [44]. This selection of proper lipids aids in the formation of stable SLNs with high therapeutic payload.

4.2 Emulsifiers

SLNs closely resemble an emulsion in the hot stage and emulsifiers play a significant role in the formation of stable SLNs. In the hot stage, the emulsifier distributes at o/w interface, while in the cooled state it helps to avoid conglomeration of SLNs. Crystallization of lipid is a major phenomenon during the emulsification process. However, use of emulsifier could slow down this process. Awad *et al.* (2008) showed that both the crystal structure and stability of SLNs was influenced by exposure of surfactant at interface via surface-mediated crystal growth. It was further demonstrated that at low concentrations of Tween 20, SLNs rapidly gelled during cooling step due to aggregation of particles. This aggregation was driven by hydrophobic attraction between crystalline lipid surfaces, which were insufficiently coated by emulsifier. Upon addition of 1 – 5% w/w of Tween 20, SLNs became increasingly stable. At low Tween 20 concentration, surfactant adsorption onto solid lipid surfaces was observed, while crystal structures of SLNs tend to become increasingly complex at higher Tween 20 concentrations, which was evidenced by the appearance of additional thermal

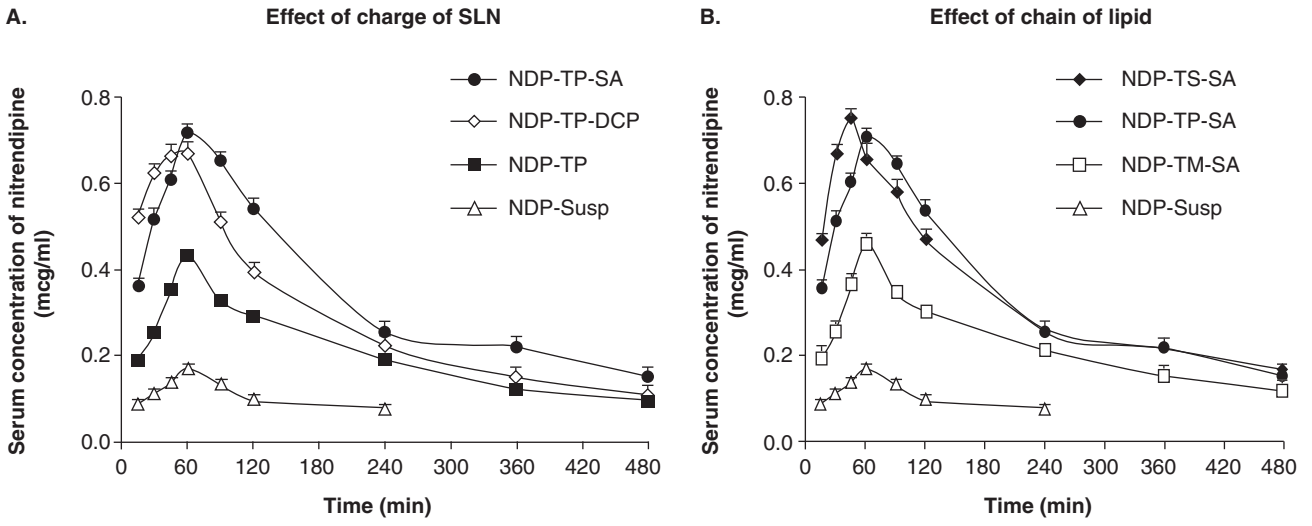

Figure 4. Mean serum concentration of NDP, time profiles after intraduodenal administration: **A**. effect of charge of SLNs of NDP-Susp, NDP-TP, NDP-TP-DCP and NDP-TP-SA; **B.** Effect of chain length of lipid of NDP-Susp, NDP-TM-SA, NDP-TP-SA and NDP-TS-SA to rats (10 mg/kg) (n = 6).
Reproduced with permission from [42].
NDP: Nitrendipine; SLN: Solid lipid nanoparticles.

transition peaks in the differential scanning calorimetry (DSC) thermogram [45]. By changing the nature and concentration of the stabilizing emulsifier, gelation after a certain period of storage time can be avoided [9].

Proper selection and concentration of emulsifier does not only stabilize but also increases the entrapment efficiency of drug in SLNs. For example, paclitaxel SLNs in Brij 78 and Poloxamer F68 showed difference in paclitaxel entrapment (47 and 75%, respectively). Brij 78 increased solubility of paclitaxel in water and, therefore, reduced the amount of drug partitioned in hot lipid droplet during solidification [46]. Similarly, Poloxamer 188 was used in different concentrations, and it was found that 5% of Poloxamer 188 was sufficient to cover and produce stable SLNs. An increase in the concentration of Poloxamer 188 resulted in increased particle size, aggregation and decrease in the hydrophobicity of drug-loaded SLNs, which in turn reduced lymphatic uptake and consequently the oral BA [32].

Adsorption of Poloxamer 188 and 407 on the surface of NPs inhibited their uptake from both small and large intestine, suggesting reduction in adhesion to gut-associated lymphoid tissue (GALT) and other epithelial tissues in the presence of the poloxamer coating [30]. Similarly, SLNs may show reduced uptake if higher concentration of the emulsifier is used. Moreover, charge developed on the surface of the SLNs by emulsifier may also affect the drug release and stability of SLNs [42].

4.3 Miscellaneous

Apart from the key factors as described earlier, there are a range of other factors that affect the particle size, stability and ultimately the oral absorption of SLNs. These include drug properties, methods of preparation, homogenization related parameters and solvents. To avoid the heterogeneous crystallization of the drug-loaded particles, a lipophilic drug with higher melting point than the lipid matrix should be selected [47]. Drug properties and lipid characteristics should be complementary for higher stability and entrapment efficiency.

Choice of preparative method plays an important role in synthesis of SLNs with optional particle characteristics and stability. Heating and cooling rate (or solidification rate) of o/w lipid nanoemulsion is another important factor that controls the particle size and polydispersity index (PDI). They cause uneven crystallization of the lipid matrix, which gives irregular release pattern. Generally, high cooling rate favors a homogenous distribution of the drug within the lipid matrix. Cyclosporin A (CycA) was not able to crystallize at a high cooling rate and remained in either liquid-like state (amorphous) or frozen thermotropic liquid-crystal state. Distortion of the crystal lattice of Imwitor 900 (Glyceryl monostearate) has been reported to increase with increasing CycA concentration leading to reduction of onset temperature and melting peak [20].

Various parameters related to homogenization such as homogenization speed and time, increase in temperature during homogenization as well as preparative method of SLNs should be considered and optimized during the formulation of drug-loaded SLNs. Radomska-Soukharev (2007) recommended that formulations produced by the hot homogenization technique didn't have any effect on the chemical stability of lipid excipient [40]. Therefore, the method of preparation critically affects the particle size, stability and

distribution of drug in lipid matrix and should be properly selected and controlled.

Particle size of SLNs has been found to be greatly influenced by the nature as well as polarity of the solvent used during preparation. Shastri *et al.* (2005) reported that size of SLNs decreases with the change in solvent property [48]. Higher the solvent polarity, higher is the diffusion rate leading to diminution in particle size, while lower solvent polarity results in slower lipid packing transitions, and thus larger particles. Similarly, Vitorino *et al.* (2011) suggested that solvent: lipid ratio is also one of the important factor affecting particle size of SLNs, that is, large amount of solvent produces less viscous inner phase for a longer time resulting in smaller sized particles irrespective of solvent and lipid type [49].

5. Stability of SLNs after peroral administration

Stability of SLNs mainly depends on stability of solid lipids in their nanoparticulate form, since they are more prone to degradation and coalescence.

SLNs do not always represent the suspension type of colloidal system. SLNs formed from solid lipids are metastable supercooled melts (e.g., trilaurin) at room and refrigerator temperature. Such systems can be considered as o/w emulsion or coalescence system but not as dispersion of SLNs [41]. To avoid generation of an unstable metastable form of SLNs, the cooling rate and stabilizer play important roles. Excessive supercooling or cooling at room temperature results in the formation of o/w metastable SLNs. Similarly, insufficient stabilizer concentration results in formation of gel-like system or particle growth, which hinders the recrystallization process. These metastable SLNs have poor shelf life and GIT stability [41].

It was found that the gelation process was accelerated with increasing temperature, light and external energy such as shear forces. Any input of energy through either mechanism seems to destabilize physically critical SLNs dispersion [9]. Similarly, being lipidic system, the stability of SLNs in GIT should be checked. Various external energy sources, namely, acidic stress, fluid mobility, temperature and so on along with a mixture of enzymes such as lipase or colipase present in entire GIT segment can cause the degradation of these natural lipidic systems.

Drug-loaded SLNs, when stored at refrigerated temperature were found to be more stable than room temperature storage. The net effect of pH on stability of methotrexate-loaded SLNs (MTX-SLNs) was studied and found to be remarkable. All MTX-SLNs were stable in SIF (pH 7.4) for 6 h; however, an increased particle size along with high drug release was observed upon incubation in SGF (pH 1.2) for 2 h. Moreover, methotrexate-loaded stearic acid SLNs (MTX-SA-SLNs) were observed to be highly unstable in SGF as evident by clump formation at 2 h [50].

The stability of SLNs in enzymatic solution of pancreatic lipase and colipase was studied by measuring the free fatty acid (FFA) content by turbidimetry. These SLNs were unstable in GI medium and exhibited degradation and aggregation phenomenon. Degradation velocity and thus stability was dependent on the nature of the lipid matrix. Shorter chain lipids (Dynasan 114) showed higher degradation while the longer chain lipids (Compritol 888 ATO) showed slower degradation rate. By using emulsifier (Poloxamer 188), degradation could be prevented and higher stability could be achieved. Therefore, selection of the emulsifier is important for the production of optimized stable SLNs. SLNs prepared using Dynasan (triglycerides) and sodium cholate (bile salt) demonstrated high physical stability with minimal particle aggregation in enzymatic solution. Bile salts in the concentration range of 0.2 – 1.5 mM inactivated lipase, but not colipase, and thus caused reduction in adsorption and degradation by lipase. By using bile salts, it was possible to increase the stability, but still it showed time-dependent aggregation. Also longer chain lipids (Compritol 888 ATO) with the nonionic emulsifier (Poloxamer) showed little degradation/aggregation due to steric stabilization. The decrease in adsorption of the active protein is described as the 'windscreen wiper effect' [51]. This phenomenon can be useful for the preparation of slow biodegradable SLNs for oral administration [10].

6. Applications of SLNs by oral route

As discussed earlier, the oral route is the most preferred route of administration of drugs. Use of SLNs can be an attractive option for oral drug delivery vehicles as they hold tremendous potential to improve the oral BA of drugs, concomitant reduction of drug toxicity and stability of drug in both GIT and plasma. Subsequent sections discuss some examples of application of SLNs in the context of oral drug delivery.

6.1 Improvement in oral BA of drugs using SLNs

SLNs, like other nanoparticulate systems, are transported into systemic circulation via lymph upon oral administration and this results in improved BA of drugs as shown in **Table 3**. Absorption mechanisms involve paracellular and intracellular transport through the GIT tract.

SLNs can improve oral BA of drugs by virtue of their unique capability to bypass presystemic hepatic metabolism resulting in enhanced plasma concentration. Manjunath and Venkateswarlu (2005) improved the oral BA of clozapine, an antipsychotic drug that undergoes extensive first-pass metabolism resulting in poor BA (< 27%). BA of clozapine-loaded SLNs was improved 2.45-fold as indicated by marked increase in AUC and subsequent decrease in clearance rate. Stearylamine modified clozapine-loaded SLNs showed further 4.51-fold increase in BA [52]. Similarly, Munjunath and Venkateswarlu (2006) improved oral BA and therapeutic efficacy of nitrendipine (NDP) by using charge modifier and triglycerides as NDP-loaded SLNs (NDP-SLNs). NDP is a highly lipophilic and poorly water soluble drug used in the treatment of hypertension. It has very poor absolute BA (10 – 20%)

Table 3. Example of drugs showing improved oral BA upon encapsulation in SLNs.

Drug	Absolute oral BA	Improved oral BA	Ref.
Otcadecylamine-fluorescein isothiocyanate (fluorescence marker)	Nil	30-fold	[25]
Clozapine	< 27%	2.45- to 4.51-fold	[62]
Quarcetine	1% (in human)	5-fold	[18]
Nitrendipine	10 – 20%	3.21- to 5.35-fold	[42]
Rifampicin, isoniazid and pyrazinamide	60 – 90% (low $t_{1/2}$)	10-, 29-, 13-fold, resp.	[26]
Vinpocetine	~ 50%	3.06- to 4.16-fold (different SLN formulations)	[56]
Fenfibrate	Variable (30 – 50% in fasting state, while 60 – 90% after meal)	2-fold	[58]
Idarubicin	20 – 30%	4-fold	[22]
Lovastatin	< 5%	1.73- (lovastatin) and 3.24- fold (lovastatin hydroxy acid)	[55]
Lopinavir	Unknown	2.13-fold (oral), 4.91-fold (intraduodenal)	[53]

BA: Bioavailability; SLN: Solid lipid nanoparticles.

because of its extensive first-pass effect; such behavior may be attributed to its high lipophilicity, which ultimately results in a wide degree of variability of PK parameters. Cationic charge and higher chain length lipids showed increased AUC and MRT after intraduodenal administration. Improved BA was due to the increased uptake and long circulation in plasma of NDP-SLNs [42].

Aji Alex *et al.* improved oral BA of lopinavir, a protease inhibitor used for the treatment of HIV infections. Lopinavir-based solid lipid nanoparticles (Lo-SLNs) showed significant improvement in BA (2.13-fold) upon oral administration, while after intraduodenal administration it was improved 4.91-fold within 6 h [53]. This study showed that SLNs can be administered by the oral as well as the intraduodenal route, albeit the fact that the latter showed greater BA than the former.

In our laboratory, we have successfully developed SLNs for oral delivery of amphotericin B and we have been able to improve its BA 9.4-fold after oral administration and 24.8-fold after intraduodenal administration (unpublished data). Based on these observations, we suggested filling of freeze-dried SLNs in enteric-coated capsules, which can be administered orally and will be able to avoid sarcastic SGF milieu and release the SLNs in intestine for further absorption. This delivery in capsule form has good patient compliance when compared to intraduodenal administration.

Puerarin is a cardioprotective agent used in cerebrovascular diseases, which is greatly restricted due to its poor solubility and short elimination $t_{1/2}$. Currently, no oral formulation of puerarin is available and frequent intravenous administration of high doses may lead to severe and acute side effects. However, puerarin-loaded solid lipid nanoparticles (Pue-SLNs) after single intragastric administration showed 3.1-fold increase in oral BA. Further, high tissue distribution in the heart may also be correlated with the improved efficacy and reduced side effects associated with free puerarin [54].

Lovastatin is a hypolipidemic drug that also exhibits poor BA (< 5%) due to extensive hepatic first-pass effect and metabolism in the gut. Intraduodenal administration of lovastatin-tripalmitin based SLNs (LOV-TP-SLNs) illustrated that both lovastatin and its metabolite (lovastatin hydroxyl acid) had 2 – 3 times higher average peak plasma concentrations and $AUC_{0-\infty}$ as compared to free lovastatin suspension. They also explained that the increase in relative BA was mainly due to enhanced M cell uptake and chylomicron formation of SLNs and not due to the amorphous form of lovastatin [55].

Vinpocetine, a mitotic inhibitor, is greatly restricted due to its poor solubility and extensive first-pass effect. Vinpocetine-loaded SLNs led to increase in surface area and saturation solubility, which resulted in increased release rate and thus dissolution rate of the drug. SLNs were absorbed through Peyer's patches showing higher transport in the lymphatic system and, therefore, reduced the first-pass metabolism of drug [56]. Similarly, SLNs of cryptotanshinone, a poorly water-soluble drug, showed twofold improved oral BA than free drug due to increased solubilization capacity and change in metabolism behavior [57].

Orally administered fenofibrate showed quite good absorption ranging from 30 to 90% depending on GIT condition (especially stomach), however, plasma level of fenofibric acid was considerably low due to its rapid excretion (low $t_{1/2}$) and/or little accumulation in fat tissue. Thus, Hanafy *et al.* (2007) prepared SLNs for sustained release of fenofibrate from lipid matrix, which subsequently reduced conversion of fenofibrate into fenofibric acid. Remarkably, fenofibrate-loaded SLNs showed steady oral absorption upto 8 h with a steady release profile of fenofibric acid from SLNs, resulting in approximately twofold increase in BA in terms of rate and extent compared to the reference formulations [58].

Prolonged release from lipid matrix and lipophilic nature of NPs maintained plasma concentration of idrarubicin (IDA) for 24 h and improved BA as compared to IDA solution alone. Significant changes in pharmacokinetic parameters (AUC, $t_{1/2}$, V_d and Cl) and biodistribution in different tissues suggested that it did not only reduce the cardiotoxicity but also increased the clinical efficacy of idarubicin due to its higher intracellular accumulation [22].

6.2 Enhancing stability of drug

Matrix encapsulation nature of SLNs can also protect drugs from adverse conditions encountered in the GIT. Metabolism of drugs especially by hydrolysis in GIT or in plasma can be controlled by encapsulating them in SLNs. SLNs control the release of drug from the solid lipid matrix and, therefore, prevent direct exposure of the drug to metabolizing enzymes.

Bioactive compounds, namely, carotenoids, omega-3 fatty acids or phytosterols, are necessary to improve long-term health. However, these bioactive compounds tightly bind to the food matrix and/or are highly lipophilic with very poor aqueous solubility resulting in poor absorption and limited BA. Crucially, these compounds being natural in origin are chemically unstable. To overcome this problem, Weiss *et al.* suggested the use of SLNs for delivery of such bioactives. SLNs have been effectively used to improve stability of such bioactives while enabling their sustained release from particulate matrix [13].

SLNs were prepared by cold homogenization technique for formulation of protein and peptides as high temperature and high homogenization speed was thought to denature the proteins during SLN preparation. Hence, protein-loaded SLNs were prepared by cold homogenization process with the critical control on different formulation parameters in order to minimize duration of exposure to elevated temperature and also reduce pressure during each homogenization cycles [59]. It was found that integrity and activity of the lysozyme could be preserved throughout the process, which suggested that SLNs have the ability to protect proteins/peptides from the harsh environment of the GIT and are also able to improve their permeability through M cell uptake.

Similarly, the matrix effect of the SLNs provided sustained release effect as well as improved protection against acid instability of drugs. Yang *et al.* (1999) studied body distribution of camptothecin-loaded SLNs showing improved lactone stability, which prevented toxic acid salt formation of drug and subsequent loss of *in vivo* anticancer activity [14].

A fixed dose combination (FDC) is a combination of two or more first-line anti-TB drugs in a single formulation at a fixed proportion. Rifampicin (RIF) and isoniazid are first line anti-TB drugs widely used for treatment of tuberculosis. But isoniazid accelerates hydrolytic degradation of rifampicin into a poorly absorbed derivative 3-formyl rifamycin SV (3-FRSV) in the acidic environment of the stomach. Further 3-FRSV reversibly reacts with isoniazid and leads to formation of isonicotinyl hydrazone. Therefore, a significantly less amount of RIF remains for absorption by the oral route. This ultimately resulted in poor oral BA of these anti-TB drugs. Anti-TB drug loaded SLNs improved the stability of drugs in GIT and also bypassed the first-pass metabolism. This in turn resulted in improved oral BA with decreased systemic side effects due to reduction in dosing frequency [26].

6.3 Reduction in toxicity and side effects of drug(s)

As described earlier, because of encapsulation and sustained release of drug in and from the lipid matrix, the direct exposure of the drug to body tissue is minimized and this aids in the reduction of drug-induced toxicity. Clinical use of triptolide (TP) is restricted due to its hepatotoxic effect and the drug also has poor oral BA due to poor aqueous solubility. Triptolide-loaded SLNs (TP-SLNs) prepared by emulsification-ultrasound method has been shown to alleviate the problems of solubility and toxicity associated with its usage [15].

7. Various oral SLN formulations

Over the last few years, research into the development of oral SLNs triggered phenomenal interest among the pharmaceutical community. **Table 4** furnishes a non-exhaustive list of representative SLN-based formulations studied by researchers for enhancement of oral BA of various drug/bioactives.

8. Summary

SLNs can be extensively used as carriers for oral delivery, particularly for drugs having poor BA. They can effectively overcome the various problems associated with oral delivery of drugs that suffers from low solubility and poor permeability, are unstable in the GIT and undergo extensive first-pass metabolism. SLN-mediated oral delivery not only enhances the BA of drugs entrapped into the protective solid lipid matrix but also reduces their toxicity with concomitant improvement in stability under hostile environment of GIT. Further, ease of large-scale production, avoidance of organic solvents during preparation and use of biocompatible excipients make drug-loaded SLNs highly amenable to commercialization. Considering the excellent attributes of SLNs as oral delivery vehicles, various functionalized SLNs such as quantum dots-encapsulated SLNs (for oral diagnostic purpose) [48], polymeric SLNs and mannosylated SLNs (for site-specific delivery of an anticancer drug) [60] are currently under way. The latter offer supplementary advantages over unmodified SLNs with regards to their prolonged sustained release and higher stability over normal SLNs [61].

9. Expert opinion

The exploitation of nanotechnology for oral application has roused phenomenal interest over the last two decades. Alteration in solubility and permeability of class II – IV drugs

Table 4. Various SLNs formulations studied by different researcher to improve the oral bioavailability of drugs.

Drug	Problem	Usefulness	Lipid	Emulsifier	Method used	Particle size (nm)	Ref.
Bioactive food (carotenoids, omega-3 fatty acids, phytosterols)	Highly lipophilic, limited solubility (poor BA), chemical instability, binding with food	Improve stability, BA, no binding with food	Triglycerides (suggested)	Mixture of nonionic and ionic surfactant (suggested)	–	–	[13]
Camptothecin	Poor solubility, acid liability	Improved stability and sustained release effect	Stearic acid	Soya lecithin, Poloxamer 188	Hot HPH	196.8 ± 21.3	[14]
Clozapine	Poor oral BA (27%) due to first-pass effect	Increased BA, high distribution to brain and reticuloendothelial cells	Dynasan 114, Dynasan 116, Dynasan 118	Epikuron 200, Poloxamer 188	Homogenization-ultracentrifugation	96.7 – 163.3	[52]
Cyclosporine A	Poor solubility and limited absorption window, first-pass metabolism, P-gp efflux	Improved BA, less variation in plasma conc.	Imwitor 900	Tagat S and sodium cholate	Hot HPH	157	[20,69]
Cryptotanshinone	Poorly water soluble	Increases the solubilization capacity, changes metabolism behavior, improved oral BA	Glyceryl monostearate (GMS), Compritol 888 ATO (CP)	Soya lecithin, Tween 80, Sodium dehydrocholate	Ultrasonic and high-pressure homogenization method	121.4 ± 6.3 (GMS) and 137.5 ± 7.1 (CP)	[57]
Fenofibrate	Poor soluble, low oral BA	Improved oral BA	Vitamin E TPGS, Vitamin E 6100	–	Hot HPH	58	[58]
Idarubicin	Poor BA	Improved BA, modifies the PK and tissue distribution	Stearic acid	Epikuron 200, sodium taurocholate	Microemulsion	80 ± 10	[22]
Insulin	GIT unstability, poor BA	Improved stability	Stearic acid, WGA-*N*-glut-PE	Poloxamer 188, Soya lecithin	Ultrasonication	58 – 60	[63]
Lovastatin	Hepatic first-pass metabolism (poor BA)	Avoid first-pass metabolism, improved BA	Triglyceride	Phosphatidylcholine 95%, poloxamer 188	Hot homogenization-ultrasonication	60 – 119	[55]
Lopinavir	Hepatic first-pass metabolism (CYP450 & P-gp efflux)	Avoid first-pass metabolism	Compritol 888 ATO	Pluronic F 127	Hot homogenization-ultrasonication	230	[53]
Lysozyme/peptides/vaccine	GIT unstability, poor permeability	Improved stability and permeability, retention of integrity and activity	Witepsol E85, Softisan 142, cetyl alcohol	Poloxamer 182	Cold homogenization	540 – 660	[59,70]
Methotrexate	Low oral BA	Improved oral BA	Stearic acid, Monostearin, Tristearin, Compritol 888 ATO	L-α-soya lecithin	Solvent diffusion method	120 – 167	[50]

BA: Bioavailability; GIT: Gastrointestinal tract; HPH: High pressure homogenization; SLN: Solid lipid nanoparticles.

Table 4. Various SLNs formulations studied by different researcher to improve the oral bioavailability of drugs (continued).

Drug	Problem	Usefulness	Lipid	Emulsifier	Method used	Particle size (nm)	Ref.
Nitrendipine	Poor BA, poorly solubility, high first-pass metabolism	Improved BA	Triglyceride	Phosphatidylcholine 95%, Poloxamer 188	Hot homogenization-ultrasonication method	102 – 123	[42]
Puerarin	Poor solubility, short half life	Improved BA	Monostearin	Soya lecithin, Poloxamer 188	Solvent injection method	160	[54]
Octadecylamine-fluorescein isothiocyanate (Fluorescence marker)	No BA	Improved BA (30 %)	Stearic acid	Polyethylene glycol monostearate	Solvent diffusion method	202.7 ± 4.25	[25]
Quercetin	Poor solubility and low hydrophilicity thus poor BA	Improved BA	Glyceryl monostearate	Soya lecithin, Tween-80 and PEG 400	Emulsification-solidification	155.3 ± 22.1	[34]
Rifampicin, Isoniazid and Pyrazinamide	Acid degradation, low BA	Improved BA and stability, Reducing dosing frequency	Stearic acid	Polyvinyl alcohol	Emulsion-solvent diffusion	–	[26]
Tobramycin	Poor oral BA, high side effects	Improved BA, sustained drug release, lymphatic Targeting	Stearic acid	Epikuron 200, Sodium taurocholate	Microemulsion	70 – 100	[23]
Triptolide	Drug-induced hepatotoxicity, problem in solubility	Increase bioavailability, controlled release, decrease toxicity with protective effect	Tristearin glyceride	Poloxamine 908, soybean lecithin	Probe soniation	116	[15]
Vinpocetine	Poor aqueous solubility and extensive first-pass metabolism	Improved oral BA by increased saturated solubility and reduced metabolism	Glyceryl monostearate	Soya lecithin, Tween 80, Polyoxyethylene hydrogenated castor oil	Ultrasonic-solvent emulsification	70 – 200	[56]

BA: Bioavailability; GIT: Gastrointestinal tract; HPH: High pressure homogenization; SLN: Solid lipid nanoparticles.

by using NPs have wide application in the field of oral drug delivery. However, commercialization of these nanoformulations and their subsequent implementation in the clinical regimen is yet to take place owing to the instability of these carrier systems in the GIT, nonacceptable excipients, residual solvents, difficulties in large-scale production and sterilization. In such a scientific panorama, SLNs with their protective matrix-type nature and physiologically acceptable composition stand as promising carrier for oral drug delivery.

SLNs as carriers improve therapeutic performance by either oral or parenteral or topical route. The hydrophobic nature of solid lipids offers the lateral advantage of high payload of lipophilic and amphoteric molecules, ranging from small molecules to large proteins. However, high temperature may cause denaturation of biomacromolecules. SLNs improve the inherent properties of drugs by recuperating both solubility and permeability. Targeting of drug-loaded SLNs to specific organs, coupled with their sustained release properties makes SLNs effective carriers for potent and toxic therapeutic agents (such as anticancer drugs). Further, avoidance of organic solvent during preparation and ease of industrial scale-up make these SLNs more amenable to commercialization in comparison to other nanoparticulate carriers. All these attractive attributes make SLNs a promising carrier for various therapeutic agents with poor physicochemical properties and intrinsic toxicity.

To recapitulate, lipids are the safest key constituents of the SLNs, which form a protective matrix-type system where the drug gets homogenously dispersed throughout. Lipids containing a mixture of glycerides and wax may improve both entrapment efficiency of drug and stability of SLNs than the isolated constituents due to appropriate amalgamation of different properties. Reports suggest that various properties of lipids such as lipid crystallization velocity, recrystallization index and self-emulsification affect particle size and stability, which are major concerns for the oral route. A longer chain lipid with charge modification improves absorption and stability of SLNs in GIT after peroral administration.

In our opinion, SLNs are equally viable as oral drug delivery systems and as parenteral system. By virtue of possessing nanoparticulate nature, SLNs improve the solubility of drugs, avoid first-pass metabolism and increase permeability, thereby enhancing the oral BA of drugs. Nanoparticulate nature of SLNs facilitates their absorption through M cells of Peyer's patches, which in turn enables the carrier system to bypass the effect of first-pass metabolism and P-gp efflux. Apart from M-cell-mediated uptake, chylomicron formation is the additional absorption mechanism that improves the permeation of SLNs in the GIT. Particle size < 500 nm is another critical parameter for the absorption of SLNs. However, peroral administration of drug-loaded SLNs are restricted due to their instability in the acidic-enzymatic milieu of the GIT. To bypass the effect of acidic pH in stomach, various researchers have tried SLN administration via the intraduodenal route. Although the rate and extent of absorption of SLNs by oral administration is lesser as compared to intraduodenal administration, it is still higher than free drug. Also, clumped SLNs can redisperse after the relocation from stomach to duodenum where the environment is slightly acidic (pH 6.8) (unpublished data from our laboratory). The problem can be also circumvented by using a combination of triglycerides with non-ionic emulsifier. Such a composition has been observed to reduce the clumping as well as lipase-mediated degradation of SLNs due to the presence of non-ionic emulsifier on their surface. Moreover, filling of freeze-dried SLNs in enteric-coated hard gelatin capsule or SLNs coated with enteric polymer for oral administration can improve patient compliance than intraduodenal administration. Further, protective effect of SLNs coupled with their sustained/controlled release properties prevents drugs/macromolecules from premature degradation and improves their stability in GIT. An extensive literature survey reveals that direct peroral administration of SLNs improve BA of drugs 2- to 25-fold, which is quite reasonable for practical applications. Overall, ease of large-scale production, avoidance of organic solvents and improvement of oral BA make SLNs a potential BA enhancer vehicle for various class II, III and IV drugs.

Declaration of interest

The authors state no conflict of interest and have received no payment in preparation of this manuscript.

Bibliography

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Speiser P. Lipid nano pellets as drug carriers for oral administration. EP0167825; 1986
2. Domb AJ. Lipospheres for controlled delivery of substances. USS0188837; 1993
3. Lucks JS, Muller RH. Medication vehicles made of solid lipid particles (solid lipid nanospheres - SLN). EP0605497; 1994
4. Schwarz C, Mehnert W, Lucks JS, et al. Solid lipid nanoparticles (SLN) for controlled drug delivery. I. Production, characterization and sterilization. J Control Release 1994;30:83-96
5. Muller RH, Mehnert W, Lucks JS, et al. Solid lipid nanoparticles (SLN): an alternative colloidal carrier system for controlled drug delivery. Eur J Pharm Biopharm 1995;41:62-9

• **First Article on the solid lipid nanoparticles.**

6. Kayser O, Lemke A, Hernandez-Trejo N. The impact of nanobiotechnology on the development of new drug delivery systems. Curr Pharm Biotechnol 2005;8:3-5
7. Muller RH, Mader K, Gohla S. Solid lipid nanoparticles (SLN) for controlled drug delivery - a review of the state of the art. Eur J Pharm Biopharm 2000;50:161-77
8. Muller RH, Maassen S, Schwarz C, et al. Solid lipid nanoparticles (SLN) as potential carrier for human use: interaction with human granulocytes. J Control Release 1997;47:261-9
9. Freitas C, Muller RH. Correlation between long-term stability of solid lipid nanoparticles (SLN™) and crystallinity of the lipid phase. Eur J Pharm Biopharm 1999;47:125-32
10. Muller RH, Maaben S, Weyhers H, et al. Phagocytic uptake and cytotoxicity of solid lipid nanoparticles (SLN) sterically stabilized with poloxamine 908 and poloxamer 407. J Drug Target 1996;4:161-70
11. Wissing SA, Muller RH. Cosmetic applications for solid lipid nanoparticles (SLN). Int J Pharm 2003;254:65-8
12. Mehnert W, Mader K. Solid lipid nanoparticles: Production, characterization and application. Adv Drug Deliv Rev 2001;47:165-96
13. Weiss J, Decker EA, McClements DJ, et al. Solid lipid nanoparticles as delivery systems for bioactive food components. Food Biophys 2008;3:146-54

•• **This article gives suggestion on application of SLNs in the delivery of bioactive foods.**

14. Yang S, Zhu J, Lu Y, et al. Body distribution of camptothecin solid lipid nanoparticles after oral administration. Pharm Res 1999;16:751-7
15. Mei Z, Li X, Wu Q, et al. The research on the anti-inflammatory activity and hepatotoxicity of triptolide-loaded solid lipid nanoparticle. Pharm Res 2005;51:345-51
16. Shegokar R, Singh KK, Muller RH. Production & stability of stavudine solid lipid nanoparticles-From lab to industrial scale. Int J Pharm 2010; doi:10.1016/j.ijpharm.2010.08.014
17. Wissing SA, Kayser O, Muller RH. Solid lipid nanoparticles for parenteral drug delivery. Adv Drug Deliv Rev 2004;56:1257-72
18. Muchow M, Maincent P, Muller RH. Lipid Nanoparticles with a solid matrix (SLN®, NLC®, LDC®) for oral drug delivery. Drug Dev Ind Pharm 2008;34:1394-405
19. Estella-Hermoso de Mendoza A, Campanero MA, Mollinedo F, et al. Lipid nanomedicines for anticancer drug therapy. J Biomed Nanotechnol 2009;5:323-43
20. Muller RH, Runge S, Ravelli V, et al. Oral bioavailability of cyclosporine: Solid lipid nanoparticles (SLN®) versus drug nanocrystals. Int J Pharm 2006;317:82-9
21. Xie S, Pan B, Wang M, et al. Formulation, characterization and pharmacokinetics of praziquantel-loaded hydrogenated castor oil solid lipid nanoparticles. Nanomedicine 2010;5:693-701
22. Zara GP, Bargoni A, Cavalli R, et al. Pharmacokinetics and tissue distribution of idarubicin-loaded solid lipid nanoparticles after duodenal administration to rats. J Pharm Sci 2002;91:1324-33
23. Cavalli R, Bargoni A, Podio V, et al. Duodenal administration of solid lipid nanoparticles loaded with different percentages of tobramycin. J Pharm Sci 2003;92:1085-95
24. Gasco MR. Methods for producing solid lipid microparticles having a narrow size distribution. USS0188837; 1993
25. Yuan H, Chen J, Du Y-Z, et al. Studies on oral absorption of stearic acid SLN by a novel fluorometric method. Colloids Surf B Biointerfaces 2007;58:157-64
26. Pandey R, Sharma S, Khuller GK. Oral solid lipid nanoparticle-based antitubercular chemotherapy. Tuberculosis 2005;85:415-20
27. Florence AT. Issues in oral nanoparticle drug carrier uptake and targeting. J Drug Target 2004;12:65-70
28. Florence AT. The oral absorption of micro-and nanoparticulates: neither exceptional nor unusual. Pharm Res 1997;14:259-66

•• **An important article to know the factors affecting absorption of NPs.**

29. Bargoni A, Cavalli R, Caputo O, et al. Solid lipid nanoparticles in lymph and plasma after duodenal administration to rats. Pharm Res 1998;15:745-50

•• **An essential article to understand various mechanism of absorption of NPs.**

30. Florence AT, Hillery AM, Hussain N, et al. Nanoparticles as carriers for oral peptide absorption: Studies on particle uptake and fate. J Control Release 1995;36:39-46
31. Kreuter J. Peroral administration of nanoparticles. Adv Drug Deliv Rev 1991;7:71-86
32. Sanjula B. Effect of poloxamer 188 on lymphatic uptake of carvedilol-loaded solid lipid nanoparticles for bioavailability enhancement. J Drug Target 2009;17:249-56
33. O'Hagan DT. Intestinal translocation of particulates-implications for drug and antigen delivery. Adv Drug Deliv Rev 1990;5:265-85
34. Li H, Zhao X, Ma Y, et al. Enhancement of gastrointestinal

absorption of quercetin by solid lipid nanoparticles. J Control Release 2009;133:238-44

•• **An excellent summary on absorption of SLNs from a different segment of the GIT.**

35. Desai MP, Labhasetwar V, Amidon GL, et al. Gastrointestinal uptake of biodegradable microparticles: effect of particle size. Pharm Res 1996;13:1838-45

36. Jepson MA, Clark MA, Foster N, et al. Targeting to intestinal M cells. J Anat 1996;189:507

37. Rieux Ad, Fievez V, Garinot M, et al. Nanoparticles as potential oral delivery systems of proteins and vaccines: a mechanistic approach. J Control Release 2006;116:1-27

38. Goppert TM, Muller RH. Adsorption kinetics of plasma proteins on solid lipid nanoparticles for drug targeting. Int J Pharm 2005;302:172-86

39. Jenning V, Gohla S. Comparison of wax and glyceride solid lipid nanoparticles (SLN®). Int J Pharm 2000;196:219-22

40. Radomska-Soukharev A. Stability of lipid excipients in solid lipid nanoparticles. Adv Drug Deliv Rev 2007;59:411-18

41. Westesen K, Bunjes H. Do nanoparticles prepared from lipids solid at room temperature always possess a solid lipid matrix? Int J Pharm 1995;115:129-31

42. Manjunath K, Venkateswarlu V. Pharmacokinetics, tissue distribution and bioavailability of nitrendipine solid lipid nanoparticles after intravenous and intraduodenal administration. J Drug Target 2006;14:632-45

43. Schubert MA, Muller-Goymann CC. Characterisation of surface-modified solid lipid nanoparticles (SLN): influence of lecithin and nonionic emulsifier. Eur J Pharm Biopharm 2005;61:77-86

44. Vivek K, Reddy H, Murthy RSR. Investigations of the effect of the lipid matrix on drug entrapment, in vitro release, and physical stability of olanzapine-loaded solid lipid nanoparticles. AAPS PharmSciTech 2007;8:16-24

45. Awad TS, Helgason T, Kristbergsson K, et al. Temperature scanning ultrasonic velocity study of complex thermal transformations in solid lipid nanoparticles. Langmuir 2008;24:12779-84

46. Chen D-B, Yang T-z, Lu W-L, et al. In vitro and in vivo study of two types of long circulating solid lipid nanoparticles containing Paclitaxel. Chem Pharm Bull (Tokyo) 2001;49:1444-7

47. Zur Muhlen A, Schwarz C, Mehnert W. Solid lipid nanoparticles (SLN) for controlled drug delivery–drug release and release mechanism. Eur J Pharm Biopharm 1998;45:149-55

48. Shastri VP, Sussman E, Jayagopal A. Functionalized solid lipid nanoparticles and methods of making and using same. USS0083781; 2006

49. Vitorino C, Carvalho FA, Almeida AJ, et al. The size of solid lipid nanoparticles: An interpretation from experimental design. Colloids Surf B Biointerfaces 2011;84:117-30

50. Paliwal R, Rai S, Vaidya B, et al. Effect of lipid core material on characteristics of solid lipid nanoparticles designed for oral lymphatic delivery. Nanomedicine: NBM 2009;5:184-91

51. Muller RH, Ruhl D, Runge SA. Biodegradation of solid lipid nanoparticles as a function of lipase incubation time. Int J Pharm 1996;144:115-21

52. Manjunath K, Venkateswarlu V. Pharmacokinetics, tissue distribution and bioavailability of clozapine solid lipid nanoparticles after intravenous and intraduodenal administration. J Control Release 2005;107:215-28

53. Aji Alex MR, Chacko AJ, Jose S, et al. Lopinavir loaded solid lipid nanoparticles (SLN) for intestinal lymphatic targeting. Eur J Pharm Sci 2011;42:11-18

•• **This article compared BA of SLNs after both oral and intraduodenal administration.**

54. Luo CF, Yuan M, Chen MS, et al. Pharmacokinetics, tissue distribution and relative bioavailability of puerarin solid lipid nanoparticles following oral administration. Int J Pharm 2011;410:138-44

55. Suresh G, Manjunath K, Venkateswarlu V, et al. Preparation, characterization, and in vitro and in vivo evaluation of lovastatin solid lipid nanoparticles. AAPS PharmSciTech 2007;8:162-70

56. Luo Y, Chen D, Ren L, et al. Solid lipid nanoparticles for enhancing vinpocetine's oral bioavailability. J Control Release 2006;114:53-9

57. Hu LD, Xing Q, Meng J, et al. Preparation and enhanced oral bioavailability of cryptotanshinone-loaded solid lipid nanoparticles. AAPS PharmSciTech 2010;11:1-6

58. Hanafy A, Spahn-Langguth H, Vergnault G, et al. Pharmacokinetic evaluation of oral fenofibrate nanosuspensions and SLN in comparison to conventional suspensions of micronized drug. Adv Drug Deliv Rev 2007;59:419-26

59. Almeida AJ, Runge S, Muller RH. Peptide-loaded solid lipid nanoparticles (SLN): influence of production parameters. Int J Pharm 1997;149:255-65

60. Jain A, Agarwal A, Majumder S, et al. Mannosylated solid lipid nanoparticles as vectors for site-specific delivery of an anti-cancer drug. J Control Release 2010;148:359-67

61. Hu L, Tang X, Cui F. Solid lipid nanoparticles (SLNs) to improve oral bioavailability of poorly soluble drugs. J Pharm Pharmacol 2004;56:1527-35

62. Manjunath K, Reddy JS, Venkateswarlu V. Solid lipid nanoparticles as drug delivery systems. Methods Find Exp Clin Pharmacol 2005;27:127

63. Zhang N, Ping Q, Huanga G, et al. Lectin-modified solid lipid nanoparticles as carriers for oral administration of insulin. Int J Pharm 2006;327:153-9

64. Xie S, Zhu L, Dong Z, et al. Preparation; characterization and pharmacokinetics of enrofloxacin-loaded solid lipid nanoparticles: influences of fatty acids. Colloids Surf B Biointerfaces 2011;83:382-7

65. Ahmed El-Harati A, Charcosset C, Fessi H. Influence of the formulation for solid lipid nanoparticles prepared with a membrane contactor. Pharm Dev Technol 2006;11:153-7

66. Charcosset C, El-Harati A, Fessi H. Preparation of solid lipid nanoparticles

using a membrane contactor. J Control Release 2005;108:112-20

67. Montenegro L, Campisi A, Sarpietro MG, et al. In vitro evaluation of idebenone-loaded solid lipid nanoparticles for drug delivery to the brain. Drug Dev Ind Pharm 2011;37:737-46

68. Anton N, Benoit JP, Saulnier P. Design and production of nanoparticles formulated from nano-emulsion templates–A review. J Control Release 2008;128:185-99

69. Muller RH, Runge SA, Ravelli V, et al. Cyclosporine-loaded solid lipid nanoparticles (SLN®): Drug–lipid physicochemical interactions and characterization of drug incorporation. Eur J Pharm Biopharm 2008;68:535-44

70. Rao KK. Polymerized solid lipid nanoparticles for oral or mucosal delivery of therapeutic proteins and peptides. PCTIB2007000896; 2007

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