Solid Lipid-based Delivery System for Oral Delivery of Drugs: A Review

Ch. Niranjan Patra, Sudhansu Bhusan Routray

Department of Pharmaceutics, Roland Institute of Pharmaceutical Sciences, Berhampur, Biju Patnaik University of Technology, Rourkela, Odisha, India

Abstract

Solid lipid-based drug delivery systems such as lipospheres, solid lipid nanoparticles, and nanostructured lipid carriers have high stability, high carrier capacity, feasibility of incorporation of both hydrophilic and hydrophobic substances, and feasibility of variable routes of administration, including oral, topical, and parenteral and pulmonary routes. Highly lipophilic and poorly water-soluble compounds that also undergo extensive presystemic intestinal metabolism are the ultimate candidates for incorporation into solid lipid-based drug delivery systems to obtain increased and less variable bioavailability (BA). Increase in biliary and pancreatic secretions, stimulation of lymphatic transport, improvement of intestinal wall permeability, reduction of metabolism and efflux activity, and alteration in mesenteric and liver blood flow, which appreciably contribute to improved oral BA of the drug.

Key words: Lipospheres, nanostructured lipid carrier, oral bioavailability, solid lipid nanoparticles

INTRODUCTION

The oral route is considered to be the most suitable and safest route of drug administration with improved patient compliance. Poor solubility and poor permeability of active pharmaceutical ingredients are the foremost causes for low oral bioavailability (BA). Major share of the pharmaceutical market is occupied by oral drug delivery systems. However, oral drug delivery is continuously looking into newer avenues due to the factors such as poor aqueous solubility, poor gastrointestinal (GI) absorption, rapid metabolism, fluctuation in the drug plasma/serum level, and variability due to presence and nature of food. These factors may cause disappointing *in vivo* results leading to failure of the drug delivery systems.[1] To overcome these problems colloidal drug delivery system vis-à-vis micelles, nanoemulsions, nanosuspensions, polymeric nanoparticles (NPs), and liposomes were developed. However, these systems are coupled with many limitations, such as limited physical stability, aggregation, drug leakage on storage, lack of a suitable low cost large-scale production method yielding a product of a quality accepted by the regulatory authorities, presence of organic solvent residues in the final product, cytotoxicity,[2] and unsuitability for oral administration especially with liposomes. These problems have been effectively resolved by the use of lipid-based drug delivery systems such as lipospheres, solid lipid NPs (SLN), and nanostructured lipid carrier (NLC) generally, lipid-based drug delivery systems have high stability, high carrier capacity, feasibility of incorporation of both hydrophilic and hydrophobic substances, and feasibility of variable routes of administration, including oral, topical, and parenteral and pulmonary routes.[3]

Lipid-based formulations can alter the oral absorption of active ingredients through different mechanisms. They stimulate the lymphatic transport of active ingredients and interact with enterocyte based transport.[4] Lipid formulations increase the drug solubilization and absorption for water-insoluble drugs. Drug suspended in the lipid matrix has been shown to get absorbed better than the conventional solid dosage forms.[5] This could be due to the enhanced wetting of the hydrophobic drug particles in the presence of lipid matrix. The presence of surfactant in the formulation may improve the wetting further. Higher entrapment of drug in the micelles may be due to the embedment in the lipidic matrix. The primary role of ingested lipids and the lipolytic products

Address for correspondence:
Dr. Ch. Niranjan Patra, Department of Pharmaceutics,
Roland Institute of Pharmaceutical Sciences,
Berhampur - 760 010, Odisha, India.
Phone: +91-9437262308.
E-mail: drniranjanrips@gmail.com

is to impact the drug dissolution of poorly water-soluble drugs by forming different colloidal particles with bile components, which are able to maintain a larger quantity of hydrophobic drugs in solution through micellar solubilization.[6]

Liposheres, SLN and NLC are the analogous drug delivery systems made of solid lipids having a range of properties. The main reasons for the development of solid lipid-based DDS 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 modulation of the drug release profiles. Further, they can be manufactured at a large industrial scale. In the present review article, the authors have focused on solid lipid-based delivery system for oral delivery of drugs.

Liposheres

Liposheres are lipid-based water dispersible solid particles of size between 0.01 and 100 µm in diameter composed of a solid hydrophobic lipid core (triglycerides), stabilized by a layer of phospholipid molecules embedded in their surface. The liposheres are suitable for oral, parenteral, and topical drug delivery of active pharmaceutical ingredients and are designed to overcome the drawbacks associated with colloidal systems.[7] The internal core contains the active pharmaceutical ingredient dissolved or dispersed in the solid fat matrix.[8] Various liposheres have been used for the controlled delivery of various types of drugs including anti-inflammatory compounds, local anesthetics, antibiotics, and anticancer agents, as well as carriers of vaccines and adjuvants.[9] Advantages of the use of liposheres for oral administration include the possibility for drug protection from hydrolysis, as well as increased drug BA and prolonged plasma levels.[10] In addition, the matrix is composed of physiological components and/or excipients of accepted status (e.g., GRAS status), which reduces the risk for acute/chronic toxicity. Conversely, the disadvantages of such delivery systems are related mostly with their preparation techniques relating to high pressure and quick temperature changes and include high pressure induced drug degradation, lipid crystallization, gelation phenomena, and coexistence of several colloidal species.[11] These days, numerous techniques are employed to produce liposheres, such as high-pressure homogenization (HPH), hot and cold homogenization, and solvent emulsification evaporation.[10] An alternative method is *in situ* preparation of liposheres with a particle size below 100 nm. This method was developed using a dispersible preconcentrate system.[8] This pro-nanoliphere is based on a solution containing the drug, triglyceride, phospholipid, and other additives in a mixture of common surfactants, and an organic solvent that is miscible with all components. This solution spontaneously forms NPs when gently mixed in an aqueous media, such as the upper GI lumen content.

SLN

SLNs are prepared from lipids which remain solid at room temperature and body temperature with sizes typically in the range of 50–1000 nm. Different solid lipids are used to prepare SLNs, such as witepsol,[12] Tripalmitin/Dynasan® 116,[13] Cetyl Alcohol,[14] Cetyl palmitate,[15] Compritol® 888 ATO,[16] Glyceryl monostearate,[17] Precirol® ATO5,[18] Trimyristin/Dynasan® 114[19] Tristearin/Dynasan® 118,[13] stearic acid,[14] and Imwitor® 900.[20] SLN formulations offer several advantages vis-à-vis protection of drug from light, moisture and chemicals, improvement in BA of lipophilic drugs, scaling up of the preparation technique to industrial scale, and use of organic solvents can be avoided to produce SLNs. SLN are also associated with several limitations such as presence of high amount of water, lower drug-loading capacity due to crystalline structure of solid lipid and expulsion of encapsulated drug. Storage may lead to change in drug release profile, polymorphic transitions, particle growth and gelation of the dispersion.

NLC

NLCs have been developed by mixing different lipid molecules to create a lipid particle matrix as imperfect as possible. In general, solid and liquid (oil) lipids are mixed to produce NLCs that are still solid at room temperature as well as at body temperature.[18] Due to many imperfections in NLCs, drug-loading capacity is enhanced, and drug expulsion during storage is minimized. NLCs offer several advantages[2] such as drug-loading capacity are better than SLNs, drug release profile can be easily modulated, drug leakage during storage is lower than SLNs, and production of final dosage forms (e.g., tablets, capsules) is feasible.

Mechanisms of oral absorption of solid lipid-based drug delivery systems

High solubility and permeability are considered prerequisites for GI absorption of drugs. Many drugs have exhibited poor and uneven BA due to their poor aqueous solubility.[21] Coadministration of high-fat meals may enhance the BA of such drugs. Ingestion of a high-fat meal leads to prolongation of residence time of GI tract, increase in biliary and pancreatic secretions, stimulation of lymphatic transport, improvement of intestinal wall permeability, reduction of metabolism and efflux activity, and alteration in mesenteric and liver blood flow, which appreciably contribute to improved oral BA of the drug.[22] Therefore, the design of lipid-based formulations may reduce the inherent limitations of slow and incomplete dissolution of poorly soluble drugs and facilitate the formation of solubilized phases from which absorption may occur. Drug is absorbed through GI tract together with fat (lipid). The lipids are degraded by enzymes in the gut leading to the formation of surface active mono- and diglycerides on the surface of the lipid droplets or solid lipid particles. These molecules detach

and form micelles. Drug dissolved in the lipid is taken up to the micelle (solubilized) during the detachment and micelle-forming process. These micelles then interact with surface-active bile salts and form mixed micelles. Subsequently, the drug is absorbed together with the micelles. Materials absorbed across the small intestine epithelial cells can enter either lymphatic or blood capillaries. The majority of orally administered drugs reach to the systemic circulation by absorption into the portal blood. However, some extremely lipophilic compounds (log P >5) reach to the systemic circulation through lymphatic route. Hence, lipid can augment lymphatic uptake of several drugs, especially lipophilic drugs or large molecular weight macromolecules.[23] Furthermore, lymphatic capillaries are significantly more permeable to NPs than the blood capillaries. Drugs that are absorbed through the intestinal lymphatic system are protected from hepatic first-pass metabolism due to the unique anatomy and physiology. The oral BA of the drugs, which undergo high hepatic first-pass metabolism, can, therefore, be significantly enhanced by transport through the lymphatic system.[24] However, lymphatic absorption depends on the length of the fatty acid chains. Khoo *et al*.[25] found that long-chain triglycerides are more effective in promoting absorption in comparison to medium-chain triglycerides. Researchers have shown that fatty acids with C-14 chains to C-18 chains promote lymphatic absorption.

Preparation of solid lipid-based drug delivery systems

Various formulation techniques exist for the production of lipospheres, SLNs, and NLCs. Among them, HPH and microemulsion techniques have demonstrated strong potential for scaling up to industrial production scale. The following sections describe different existing approaches for lipospheres, SLN, and NLC formulations. However, in some instances combination of different methods has been utilized to prepare the NPs.

HPH

HPH is a reliable and suitable technique for the preparation of lipid NPs. There are two types of HPH, hot HPH, and cold HPH.

Hot HPH

In this technique, initially, the lipids are melted at 5–10°C above their melting points and the drug is dissolved or homogeneously dispersed in the molten lipids. Simultaneously, a hot aqueous surfactant solution (preheated at the same temperature) is added to the drug-lipid molten mixture and homogeneously dispersed (pre-emulsion) by a high shear mixing device. Subsequently, this hot pre-emulsion is passed through high-pressure homogenizer at the same temperature. This homogenization process is repeated until

the nanoemulsion of desired particle size is obtained. The obtained emulsion is then cooled down to room temperature. During this cooling down, lipid droplets of the emulsion re-crystallize and form lipid particles with solid matrix.[26]

Cold HPH

In this method, the lipids are melted at 5–10°C above their melting points and the drug is dissolved or homogeneously dispersed in the molten lipids. Then, the molten mixture of drug-lipid is rapidly cooled down by means of liquid nitrogen or dry ice and subsequently milled to microparticles by means of a ball mill or mortar. These microparticles are suspended in a cold aqueous surfactant solution and then homogenized at or below room temperature forming lipid NPs. This cold HPH technique is suitable for hydrophilic or thermo-labile drugs as this method are expected to avoid temperature-induced drug degradation and drug distribution into the aqueous phase during homogenization.[26]

Emulsification sonication

The first part of this method is similar to HPH. The coarse hot oil-in-water emulsion obtained is ultrasonicated using probe sonicator till the desired sized nanoemulsion is formed. Finally, lipid NPs are obtained by allowing hot nanoemulsion to cool to room temperature.[27] However, metallic contamination of the product may happen during sonication by probe sonicator.

Microemulsion

In this method, first the solid lipids are melted, and the drug is dissolved/dispersed in the molten lipids. After that, aqueous surfactant–cosurfactant solution (pre-heated above the melting temperature of solid lipid) is added to the lipid melt with mild agitation to obtain transparent microemulsion. Subsequently, the microemulsion is dispersed in cold water (2–10°C) with mild agitation, where the microemulsion breaks into ultrafine nanoemulsion droplets which immediately crystallize to form SLNs.[28]

Solvent emulsification evaporation

In this technique, first, the lipids are dissolved in a water-immiscible organic solvent (e.g., cyclohexane, chloroform, acetone, and dichloromethane) and then emulsified in an aqueous phase containing surfactants under continuous stirring. The organic solvent evaporates during emulsification, which results in lipid precipitation. As the whole formulation procedure can be conducted at room temperature, this technique is highly suitable for thermo-labile drugs.[29] However, the major concern is the production of very dilute dispersion that needs to be concentrated by means of ultra-filtration or evaporation. Another concern is the use of organic

solvent, some of which may remain in the final preparation.

Solvent diffusion

In contrary to solvent emulsification evaporation technique, partially water-miscible organic solvents (e.g., benzyl alcohol and ethyl formate) are used in the solvent-diffusion technique.[30] In this case, organic solvents are mutually saturated with water to ensure the initial thermodynamic equilibrium of both liquids. The transient oil-in-water emulsion is passed into water under continuous stirring, which leads to solidification of dispersed phase forming lipid NPs due to diffusion of the organic solvent. However, similar to the microemulsion technique, dilute nanoparticle dispersion is produced, which needs to be concentrated by ultrafiltration or lyophilization. Usage of the organic solvent is also a concern as some of it may remain in the final preparation.

Solvent injection

In this method, lipids are dissolved in a water-miscible solvent (e.g., acetone, isopropanol, and methanol) or water-miscible solvent mixture and quickly injected into an aqueous solution of surfactants through an injection needle.[31] The advantages of this method are the easy handling and fast production process without technically sophisticated equipment (e.g., high-pressure homogenizer). However, the main disadvantage is the use of organic solvents.

Double emulsion

The double emulsion (w/o/w) method is based on solvent emulsification evaporation method.[32] This method is mainly for the production of lipid NPs loaded with hydrophilic drugs. In this case, the drug and stabilizer are encapsulated in the inner aqueous phase of the w/o/w double emulsion. A stabilizer is necessary to prevent drug partitioning to the outer aqueous phase during solvent evaporation. This type of formulations is usually named as "lipospheres" due to their comparatively larger particle size than SLNs.

Melt dispersion ultrasonication method

The lipids and phosphatidylcholine were blended and melted at a 10°C above the melting point of lipid along with the drug to form a uniform and clear oil phase. Meanwhile, the aqueous phase consisting of dispersing surfactant was maintained at the same temperature. The oil phase was added to the aqueous phase, and both phases were mixed by the aid of agitation at the same temperature to form a microemulsion. This warm microemulsion was diluted in cold water (2–3°C) under mechanical stirring to form NLC dispersion.[33]

Characterization of solid lipid-based drug delivery system

There are several important characterization techniques as follows.

Particle size

Particle size plays a critical role in the GI absorption and their clearance by the reticuloendothelial system.[34] Hence, the precise determination of the particle size is very important. Particle size <300 nm is advisable for the intestinal transport.

Photon correlation spectroscopy (PCS)

PCS and laser diffraction (LD) are the most widely used techniques for the particle size measurement of lipid NPs.[35] PCS is also known as dynamic light scattering. The fluctuation of the intensity of the scattered light, caused by particles movement, is measured by this technique.

Polydispersibility index (PDI)

As lipospheres, SLNs, and NLCs are usually polydisperse in nature, measurement of PDI is important to know the size distribution of the NPs.[35] Lower PDI value is indicative for the monodispersed nanoparticle. Most of the researchers accept PDI value <0.3 as an optimum value.

Zeta potential (ZP)

The ZP indicates the overall charge a particle acquires in a specific medium.[35] Stability of the nanodispersion during storage can be predicted form the ZP value. The ZP indicates the degree of repulsion between close and similarly charged particles in the dispersion. High ZP indicates highly charged particles. In general, high ZP (negative or positive) prevents aggregation of the particles due to electric repulsion and electrically stabilizes the nanoparticle dispersion. On the other hand, in the case of low ZP, attraction exceeds repulsion, and the dispersion coagulates or flocculates. However, this assumption is not applicable for all colloidal dispersion, especially the dispersion which contains steric stabilizers. The ZP value of −30 mV is enough for good stabilization of nanodispersion. The ZP of the nanodispersions can be determined by PCS.

Shape and morphology

Scanning electron microscopy (SEM), transmission electronmicroscopy (TEM), and atomic force microscopy are very useful techniques to determine the shape and morphology of lipid NPs.[36] These techniques can also determine the particle size and size distribution. SEM utilizes electron transmission from the sample surface, whereas TEM utilizes electron transmission through the sample.

Crystallinity and polymorphism

Determination of the crystallinity of the components of liposheres, SLN and NLC formulations are crucial as the lipid matrix, as well as the incorporated drug, may undergo a polymorphic transition leading to a possible undesirable drug expulsion during storage.[36] Lipid crystallinity is also strongly correlated with drug incorporation and release rates. Thermodynamic stability and lipid packing density increase, whereas drug incorporation rates decrease in the following order: Supercooled melt, α-modification, β′-modification, and β-modification. However, lipid crystallization and modification changes might be highly retarded due to the small size of the particles and the presence of emulsifiers.

Differential scanning calorimetry (DSC) and X-ray diffraction (XRD)

DSC and XRD are two widely used techniques to determine the crystallinity and polymorphic behavior of the components of the SLNs/NLCs.[36] DSC provides information on the melting and crystallization behavior of all solid and liquid constituents of the particles, whereas XRD can identify specific crystalline compounds based on their crystal structure.

Regulatory aspects

One of the key pre-requisites for introducing new technology and new products to the market is meeting regulatory requirements, not only with regard to excipients but also qualification and validation of production lines.[37] In general, for the production of lipid NPs, only excipients accepted by the regulatory authorities are used, which means excipients with a GRAS status (FDA). In the latter case, these excipients need to be used in their accepted concentrations. If distinctly higher concentrations are used, a limited toxicity study might be necessary to prove the safety of the excipient in this concentration. All lipids, surfactants, and stabilizers used in the production of capsules, pellets, and tablets can be fully exploited for the production of oral lipid suspensions. There is definitely no lack of accepted excipients.

Oral administration

Several drugs have been formulated as liposheres, SLN, and nano lipid carriers (NLC). The following sections discuss about the studies performed on different drugs for oral administration through liposheres, SLNs, and NLCs. Summarized literature on oral drug delivery of liposheres [Table 1], SLN [Table 2] and NLC [Table 3] are presented in tabular form.

Liposheres

Carbamazepine: In a study, liposheres of carbamazepine were prepared by melt dispersion technique using Precifac

ATO 5 in the various drug-lipid ratios.[38] The effect of drug-lipid ratio, the surfactant added, emulsion stabilizer, and stirring speed also was identified as the key variables affecting the formation of discrete spherical liposheres and drug release rate. The preparation conditions were optimized using 0.4% w/v span 20 (hydrophilic-lipophilic balance, HLB = 8.6) as a surfactant and 1% w/v gelatin solution as a stabilizer in the presence of a high level of water. Increasing the lipid: Drug ratio produced more spherical, smooth, and round liposheres. All the prepared liposheres exhibited slow release profiles dictating the Higuchi mode of release. We saw that the higher the sphere size and the ratio of Precifac ATO 5, the slower is *in vitro* drug release.

Rifampicin (RMP): In another study novel cospray dried RMP phospholipid liposheres (SDRPL) to influence on RMP solubility and oral BA.[39] Solid-state techniques were employed to characterize the liposhere formulation. SDRPL solubility was determined in distilled water. The oral BA of the liposheres was evaluated in Sprague Dawley rats. Liposheres exhibited amorphous, smooth spherical morphology with a significant increase ($P < 0.001$) insolubility of SDRPL (2:1), 350.9 ± 23 versus 105.1 ± 12 µg/ml and SDRPL (1:1) 306.4 ± 20 versus 105.1 ± 12 µg/ml in comparison to RMP. SDRPL exhibited enhanced activity against *Mycobacterium* tuberculosis, H37Rv strain, with over two-folds less minimum inhibitory concentration than the free drug. Liposheres exhibited higher peak plasma concentration, faster Tmax and enhanced area under the curve (AUC) in comparison to pure RMP. Thus, SDRPL represents a promising carrier system exhibiting enhanced antimycobacterial activity and oral BA of RMP.

Bovine serum albumin in another study, the challenge in the oral delivery of protein drugs is to enhance their oral BA.[40] Herein, we report the uniform-sized liposhere prepared by premix membrane emulsification combined with W1/O/W double-emulsion method as a potential oral carrier for proteins. The protein-loaded liposhere was composed of a hydrophobic poly (d, L-lactide-co-glycolide) (PLGA) core and the lipid molecules self-assembled at the interface of W1/O and O/W2. During the preparation, the protein structure was effectively maintained. Compared with PLGA microsphere, the liposhere achieved a higher loading capacity (LC, 20.18%), entrapment efficiency (EE, 90.82%), and a lower initial burst (24.73%). Importantly, the liposheres also showed high transcytotic efficiency with human microfold cell (M cell) model, leading to a potential enhancement of intestinal absorption. This result, together with the above studies supported that the PLGA-lipid liposhere could be a promising platform for enhancing the proteins oral BA.

SLN

Lopinavir, in a study, was successfully encapsulated in glyceryl behenate based Lo-SLN for its ultimate use to target

Name of the drug	Lipids	Method	Results	References
Table 1: Literature review on lipospheres				
BSA	PLGA	Premix membrane emulsification combined with W/O/W double-emulsion method	Enhancing the proteins oral bioavailability	[40]
Placebo	Compritol 888 ATO Precirol ATO 5 Witepsol H15 Miglyol 812	Emulsification followed by system cooling	Durability and consistency of the lipid microspheres were better with Compritol 888 ATO	[47]
Lercanidipine hydrochloride	CSA	Modified melt dispersion technique	Buoyant lipospheres with sustain release	[48]
Glimepiride	Compritol 888 ATO	Melt dispersion technique	Sustain release	[49]
Indomethacin	CSA, SA and CA	Modified fusion method	Drug release was sustained for 8 h	[50]
Diclofenac potassium	Phospholipon 98H Softisan154	Fusion method	Formulations exhibited good analgesic effect compared with the reference	[51]
Retinyl acetate and progesterone	Glyceryl tristearate (tristearin), glyceryl tribehenate (tribehenin) and glyceryl tripalmitate (tripalmitin)	Melt dispersion technique, solvent evaporation or w/o/w double emulsion method	All drugs were released in a control manner	[52]
Lithium carbonate	Beeswax, CSA, Spermaceti CA	Meltable emulsified dispersion cooling induced solidification technique	Results demonstrate the potential use of waxes/fat for the fabrication of controlled release devices	[53]
Rifampicin	Lipoid S-75	Spray drying	Lipospheres can be produced by an industrially viable, easily scalable technology with capability for modulating the size and functions	[39]
Ibuprofen	Beeswax Phospholipon 90H	Hot emulsification	Improved analgesic and anti-inflammatory activity for the prolonged period of time	[54]
Ofloxacin	CA	Melt dispersion technique	Liposphere system enhance the bioavailability of ofloxacin by 2.45 fold after oral administration	[55]
Pioglitazone hydrochloride	Compritol 888 ATO	Melt dispersion (homogenization) technique	High drug entrapment and sustain release	[56]

BSA: Bovine serum albumin, CSA: Cetostearyl alcohol, SA: Stearyl alcohol, CA: Cetyl alcohol

intestinal lymphatic vessels.[41] SLNs, with a mean particle size of 230 nm (PDI <0.27) and surface electrical charge of approximately -27 mV, were produced by hot homogenization process followed by ultrasonication. *In vitro* release studies at pH 6.8 phosphate buffer and pH 1.2 HCl 0.1 N showed a slow release in both media. From the intestinal lymphatic transport study, it became evident that SLN increased the cumulative percentage dose of lopinavir secreted into the lymph, which was 4.91-fold higher when compared with a conventional drug solution in methylcellulose 0.5% (w/v)

as a suspending agent (Lo-MC). The percentage BA was significantly enhanced. The AUC for the Lo-SLN was 2.13-fold higher than that obtained for the Lo-MC of similar concentration. The shelf life of optimized formulation was assessed based on the remained drug content in the stabilized formulation and was shown to be 21.46 months.

Zaleplon (ZL), in another study, a hypnotic drug was formulated as SLN to improve oral BA (~30%).[42] The SLNs of ZL were developed by using Box–Behnken design (BBD).

Table 2: Literature review on solid-lipid nanoparticles

Name of the drug	Lipids	Method	Results	References
Zaleplon	Compritol 888 ATO	Film formation method following hot homogenization and ultrasonication	Controlled release with 2.66 times improvement in oral bioavailability	[42]
Simvastatin	Compritol 888 ATO	Solvent injection method	SLN of simvastatin showed 220% bioavailability and substantiating the protective action of SLNs against liver metabolism	[43]
Houttuynia cordata extract	Poloxamer 188 poloxamer 407	Hot homogenization and ultrasonication method followed by freeze drying	Sustained release of quercitrin from *Houttuynia cordata* extracts	[57]
Hydrochlorothiazide	Precirol ATO5	Hot high-shear homogenization followed by ultrasonication method	Increased diuretic effect and a sustained drug release and, consequently, enhanced HCT oral bioavailability	[58]
Olmesartan medoxomil	Glyceryl monostearate	Solvent emulsion-evaporation method	2.32-fold enhancement in relative bioavailability	[59]
Alendronate Sodium	Glyceryl monostearate, stearic acid, Compritol 888 ATO, and Precirol ATO5	Solvent injection technique	Nanoparticles are a promising formula for the delivery of alendronate sodium, eliminating its esophageal side effects and enhancing its bioavailability	[60]
Efavirenz	Compritol ATO 888, glyceryl monostearate, Precirol, stearic acid	Rotary evaporation and homogenization	Good stability and 10.98-fold increase in AUC in comparison to ES	[61]
Glibenclamide	Precirol Compritol	Emulsion of solvent evaporation technique	Significantly stronger hypoglycemic effect with respect to the drug alone, in terms of both shorter onset time and longer duration of the effect	[62]

ES: Efavirenz suspension

A design space with three formulation variables at three levels was evaluated in BBD. Amount of lipid (A1), amount of surfactant (A2), and concentration of co-surfactant (%) (A3) were selected as independent variables, whereas, particle size (B1), entrapment efficiency (B2), and ZP (ZP, B3) as responses. ZL-SLNs were prepared by hot homogenization with ultrasonication method and evaluated for responses to obtain optimized formulation. *In vivo* studies were performed in Wistar rats. The optimized formulation with 132.89 mg of lipid, 106.7 mg of surfactant and 0.2% w/v of cosurfactant ensued in the NPs with 219.9 ± 3.7 nm of size, −25.66 ± 2.83 mV surface charge, and 86.83 ± 2.65% of entrapment efficiency. SEM studies confirmed the spherical shape of SLN formulations. The DSC and XRD studies revealed the transformation of the crystalline drug to amorphous form in SLN formulation. *In vivo* studies in male Wistar rats demonstrated an improvement in the oral BA of ZL from SLN over control ZL suspension. The enhancement in the oral BA of ZL from SLNs, developed with the aid of BBD, explicated the potential of lipid-based NPs as a potential carrier in improving the oral delivery of this poorly soluble drug.

Simvastatin in another study, SLNs of simvastatin were developed to enhance oral BA by minimizing its first-pass metabolism.[43] SLNs were prepared by solvent injection technique and optimized by 23 full factorials experimental design using Design Expert software. The SLN formulations were optimized for the amount of compritol, the concentration of poloxamer, and volume of acetone to achieve desired responses of particle size, entrapment efficiency (EE), and cumulative drug release (CDR). Response surface plots were constructed to study the influence of each variable on each response, and the interactions between any two variables were also analyzed. Formulation F10 with a particle size of 271.18 nm, % EE of 68.16% and % CDR of 76.23%, and

Table 3: Literature review on nanostructured lipid carriers				
Name of the drug	Lipids	Method	Results	References
Atorvastatin	2% Gelucire® 43/01	Emulsification using high-speed homogenization followed by ultrasonication	Increase in bioavailability as compared to atorvastatin suspension and commercial product	[44]
Raloxifene hydrochloride	Glyceryl monostearate and Capmul MCM C8	Solvent diffusion method	3.75-fold enhancements in bioavailability with optimized NLCs formulation than plain drug suspension.	[45]
Curcumin	N-acetyl-L-cysteine	Solvent evaporation followed by ultrasonication	This approach could be a promising drug delivery system for improving the oral performance of BCS class IV drugs	[63]
Sirolimus	Precirol ATO 5 oleic acid	High-pressure homogenization	1.81-folds increase in oral bioavailability	[64]
Fenofibrate	Compritol 888 ATO, Labrafil M 1944CS	Hot homogenization followed by an ultrasonication method	A potential delivery system for improvement of loading capacity and control of drug release	[65]
Rosuvastatin	Stearic acid Compritol ATO 888 oleic acid	High shear homogenization followed by Ultrasonication	Enhanced bioavailability with two-folds as compared to the marketed conventional tablet	[66]
Tacrolimus	Capmul MCMC8 solution HS15 Compritol 888ATO	Modified SEPS and modified HPH	NLCs seem to be tremendously beneficial nanocarriers for enhancing in vivo, lymphatic and thereby therapeutic prospect of TL	[67]
Carvedilol	Stearic acid and oleic acid	Microemulsion followed the probe sonication technique	Remarkably improved the oral bioavailability	[68]

SEPS: Solvent emulsification evaporation-probe sonication, HPH: High-pressure homogenization

highest desirability value of 0.645 was selected as optimized formulation. The optimized formulation was evaluated for biodistribution and pharmacokinetics by technetium-99m (Tc-99m) radiolabeling technique in mice. The relative BA of simvastatin from optimized SLNs was found to be 220%, substantiating the protective action of SLNs against liver metabolism. Simvastatin continuously entered in liver to exert its therapeutic action that was evidenced by biodistribution study even though the drug initially bypassed the liver metabolism.

NLC

Atorvastatin (AT) in a study, AT-NLCs were prepared by emulsification using high-speed homogenization followed by ultrasonication to improve its solubility and bypass hepatic effect.[44] The prepared NLCs showed particle size between 162.5 ± 12 and 865.55 ± 28 nm while ZP values varied between -34 ± 0.29 and -23 ± 0.36 mV. They also showed high encapsulation efficiency (>87%) and the amorphous state of the drug in a lipid matrix. Pharmacokinetic parameters of optimized formulation (NLC-1; composed of 2% Gelucire® 43/01, 8% capryol® PGMC, 2% Pluronic® F68,

and 0.5% lecithin) revealed 3.6- and 2.1-fold increase in BA as compared to AT suspension and a commercial product (Lipitor®), respectively. These investigations demonstrated the superiority of NLCs for improvement of oral BA and *in vivo* performance of AT.

NLC formulation of Raloxifene (RLX) hydrochloride in another study showed improvement in oral BA.[45] RLX loaded NLCs were prepared by a solvent diffusion method using glyceryl monostearate and Capmul MCM C8 as solid lipid and liquid lipid, respectively. A full 3^2 factorial design was utilized to study the effect of two independent parameters, namely solid lipid to liquid lipid ratio and concentration of stabilizer on the entrapment efficiency of prepared NLCs. Solid-state characterization studies (DSC and XRD) in optimized formulation NLC-8 revealed the transformation of RLX from crystalline to amorphous form. Optimized formulation showed 32.50 ± 5.12 nm average particle size and -12.8 ± 3.2 mV ZP that impart good stability of NLCs dispersion. *In vitro* release study showed burst release for initial 8 h followed by sustained release up to 36 h. *In vivo* pharmacokinetic study was carried out that showed 3.75-fold enhancements in BA with optimized NLCs formulation than

plain drug suspension. These results showed the potential of NLCs for significant improvement in oral BA of poorly soluble RLX.

Baicalin in another study a novel baicalin-loaded NLC (BA-NLC) system for oral delivery to enhance the BA.[46] BA-NLC was prepared by emulsion evaporation and low temperature solidification technique and optimized by a five-factor four-level uniform design. The results showed that the optimized BA-NLC was nearly spherical in shape with a mean diameter of 244.7 nm. The entrapment efficiency and drug loading were $59.51 \pm 0.57\%$ and $3.54 \pm 0.11\%$, respectively. *In vitro* drug release revealed a pattern with burst release initially and sustained release afterward for BA-NLC. Moreover, BA-NLC exhibited prolonged MRT and increased AUC compared to pure BA. All the detailed evidence indicated that BA-NLC could be a potential delivery system for the oral administration of BA.

CONCLUSION

The present intense interest in solid lipid-based drug delivery system in oral delivery is resulting in large amounts of research funding into the use of solid lipids as potential drug delivery systems such as lipospheres, SLN, and nanostructured lipid carriers. In the present review article, we have critically reviewed lipid-based drug delivery systems such as lipospheres, SLN, and NLC as potential oral drug delivery systems for various drugs to improve oral BA, sustain/control release, and to improve stability. Highly lipophilic and poorly water-soluble compounds that also undergo extensive presystemic intestinal metabolism are the ultimate candidates for incorporation into solid lipid-based drug delivery systems to obtain increased and less variable BA. Increase in biliary and pancreatic secretions, stimulation of lymphatic transport, improvement of intestinal wall permeability, reduction of metabolism and efflux activity, and alteration in mesenteric and liver blood flow, which appreciably contribute to improved oral BA of the drug.

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