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REVIEW

Solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs): recent advances in drug delivery

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Abstract Solid lipid-based nanoparticles (SLBNs) were developed as potential alternatives to other conventional drug delivery systems such as polymeric nanoparticles, liposomes, and emulsions. In general, SLBNs are divided into two types: solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs). SLNs are distinguishable from NLCs by the composition of solid particle matrix. SLBNs can be prepared by several methods including high pressure homogenization, solvent emulsification (or diffusion)-evaporation, and microemulsion technologies. Then, SLBNs can be characterized in terms of particle size distribution, surface charge, morphology, and crystallinity. SLBNs are well-tolerated and efficient carrier systems for parenteral, oral, inhalational, ocular, and dermal applications. This review provides an overview of the preparation and characterization technologies for SLBNs and focuses on recent advances in drug delivery using SLBNs.

Keywords: Solid lipid-based nanoparticles (SLBNs) · Solid lipid nanoparticles (SLNs) · Nanostructured lipid carriers (NLCs) · Drug delivery

Introduction

Drug-loaded nanoparticles have served as a new prototype in drug delivery for various therapeutic goals (Battaglia and Gallarate 2012). Among numerous types of nanoparticles, solid lipid-based nanoparticles (SLBNs) showed many advantages such as biocompatibility, production scalability, organic solvent-free preparation process, and wide application spectrum (Muller et al. 2000). Moreover, one fundamental advantage of SLBNs over other lipid-based colloidal drug delivery systems such as liposomes and nanoemulsions is their rigid morphology (Muller et al. 2011; Anton et al. 2008). Therefore, SLBNs have been intensively explored for drug delivery in the last decade.

SLBNs provide a lipophilic matrix in which drugs can be incorporated. Their particle sizes are mainly between 150 and 300 nm, and smaller sizes less than 100 nm or larger sizes up to 1,000 nm can be obtained as well. Two generations of SLBNs are distinguished: the first generation is solid lipid nanoparticles (SLNs); the second generation is nanostructured lipid carriers (NLCs). SLNs are prepared from lipids which are solid at room temperature as well as at body temperature. There are several advantages of SLNs formulations such as the protection of photosensitive, moisture sensitive and chemically labile drugs, biocompatibility and versatility of lipids used in SLNs, and cost-effective scale-up process (Shidhaye et al. 2008). However, SLNs prepared from one highly purified lipid can crystallize in a perfect crystalline lattice that allows smaller space for the incorporation of drugs (Fig. 1a), which may lead to a limited drug-loading capacity and stability problems including drug expulsion, particle growth and gelation (Muller et al. 2002a). To overcome these limitations of SLNs, NLCs have been developed. In case of NLCs, spatially different lipid molecules are mixed to create a lipid particle matrix as imperfect as possible (Fig. 1b) (Das and Chaudhury 2011; Muller et al. 2011). Generally, solid and liquid (oil) lipids are mixed to produce NLCs that are still solid at room

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temperature as well as at body temperature (Das and Chaudhury 2011; Chen et al. 2010). Due to many imperfections in NLCs, drug-loading capacity is enhanced and drug expulsion during storage is minimized.

Here, we review the preparation and characterization technologies for SLBNs (SLNs and NLCs) and their applications for drug delivery. Parenteral, oral, inhalational, ocular, and dermal drug delivery using SLBNs were outlined and discussed with recent examples.

Preparation

High pressure homogenization (HPH) has been well established for the large-scale production of SLBNs (Battaglia and Gallarate 2012). However, high temperatures and pressures (cavitation force) used in this method may cause significant thermodynamic and mechanic stress for the incorporated drug. Therefore, suitable alternative and easy handling production methods for SLBNs preparation have been widely investigated. SLBNs can be produced starting from microemulsion templates (Puri et al. 2009). Lipids are heated above their melting point, and then an aqueous phase containing surfactants and co-surfactants is added under stirring at the same temperature to form a clear O/W microemulsion. Multiple W/O/W emulsion can also be used to prepare SLBNs (Garcia-Fuentes et al. 2004). The microemulsion is then diluted in cool water (2–10 °C) to precipitate the SLBNs with reduced mean particle size and narrow size distribution. Solvent-based methods have been proposed to incorporate drugs with stability problems, despite toxicological issues of organic solvents used. One of the main advantages of solvent-based methods is the mild operating temperature suitable for thermo-sensitive drugs. Among them, solvent injection (or solvent displacement) method is based on dissolving the lipid in a water miscible organic solvent (e.g., ethanol, acetone, and isopropanol) and injecting this solution through a syringe needle in water under stirring, and then the lipid precipitates into nanoparticles upon contact with water (Schubert and Muller-Goymann 2003; Hu et al. 2002). As alternative solvent-based methods, O/W or W/O/W emulsions can be prepared using either a volatile or a partially water miscible organic solvent. Nanoparticles are formed when the solvent is removed either by evaporation (solvent evaporation method) (Griffin and O'Driscoll 2011) or by water dilution (solvent diffusion method) (Trotta et al. 2003). Another method using a membrane contactor has been developed for producing SLBNs (Charcosset et al. 2005). The lipid phase is heated in a pressurized vessel above its melting point, conveyed through a tube and pressed through the membrane pores, allowing the formation of small droplets. SLBNs are formed after cooling of the obtained water dispersion. In addition, phase inversion method has been developed based on spontaneous inversion between O/W and W/O transitional emulsion with three temperature cycles (85–60–85 °C) (Anton et al. 2008). The advantages and limitations of preparation methods for SLBNs are summarized in Table 1 (Iqbal et al. 2012; Das and Chaudhury 2011), and the schematic descriptions of preparation methods for SLBNs are shown in Figs. 2 and 3.

Typical SLNs formulations include 0.1–30 % solid lipid content, 0.5–30 % surfactant stabilizers, and 5 % of the

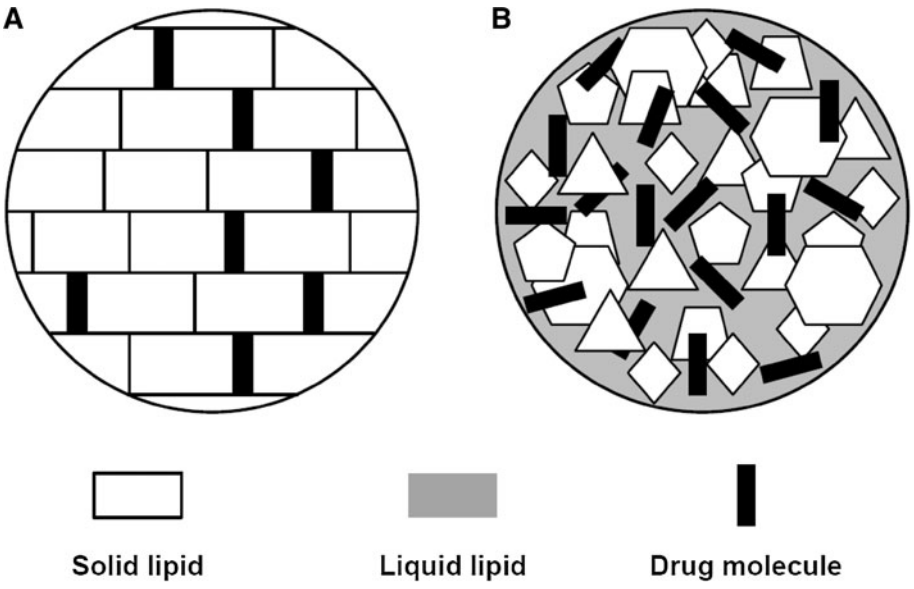

Fig. 1 Schematic description of SLNs (**a**) and NLCs (**b**). This figure was modified from Das and Chaudhury (2011) and Muller et al. (2011)

Table 1 Advantages and limitations of preparation methods for LNPs

Method	Advantage	Limitation	Reference
High pressure homogenization (HPH)	• Low cost • Good stability • Large-scale production	• Energy intensive process • High polydispersity • High temperature	Battaglia and Gallarate (2012)
Ultrasonification	• High shear mixing • Small particle size	• Metallic contamination • Energy intensive process	Das and Chaudhury (2011)
Microemulsion technique	• Low energy input • Avoidance of heating	• Low yield • Excessive use of surfactants	Puri et al. (2009)
Solvent emulsification (or diffusion)-evaporation	• Low energy input • Avoidance of heating • Small particle size	• Instability of emulsion • Residual organic solvent	Muller et al. (2008)
Solvent injection	• Fast production • Low energy input • Avoidance of heating	• Residual organic solvent	Schubert and Muller-Goymann (2003)
Membrane contractor	• Low energy input • Large-scale production • Control of particle size	• Clogging of membrane	Charcosset et al. (2005)
Phase inversion	• Low energy input • Organic solvent free	• Instability of emulsion	Anton et al. (2008)

This table was modified from Iqbal et al. (2012) and Das and Chaudhury (2011)

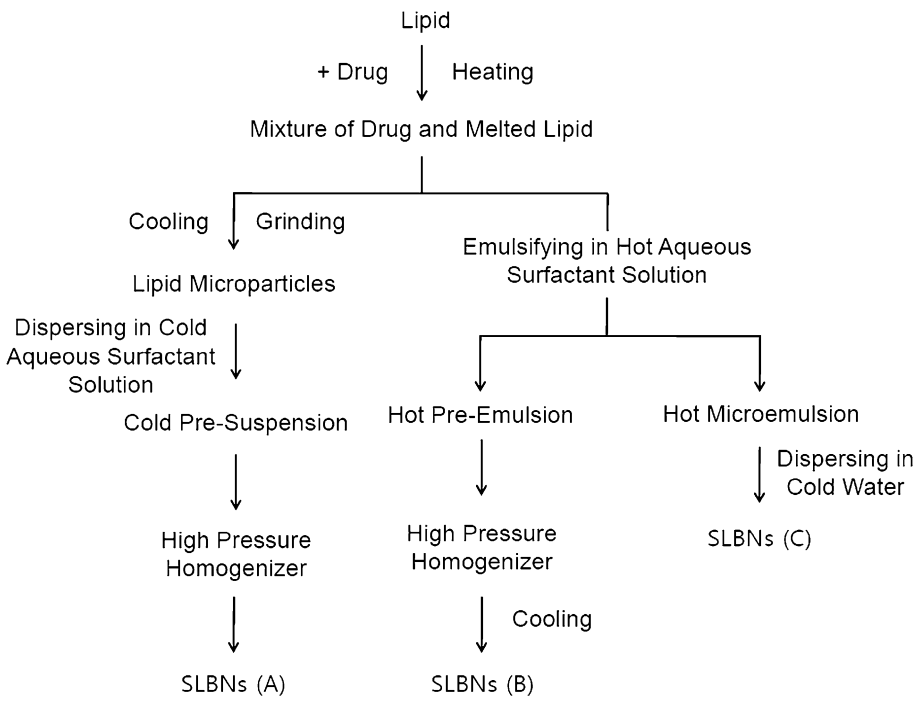

Fig. 2 Schematic description of preparation methods for SLBNs (*A* cold HPH; *B* hot HPH; *C* microemulsion technique)

incorporated drug (Puri et al. 2009). Solid-phase lipids used in SLNs include trimyristin, tristearin, trilaurin, stearic acid, cetyl palmitate wax, cetyl alcohol, imwitor 900, Compritol® 888 ATO, and Precirol® ATO 5 (Puri et al. 2009). Curdlan and PEG have been used for the prolonged retention of SLNs in systemic circulation. The drug loading sites in SLNs depend on the physicochemical properties of drug molecules. Lipophilic drugs disperse well in the lipid matrix, whereas hydrophilic drugs are thermodynamically immiscible and separate to the outside of the lipid matrix (Puri et al. 2009). For successful drug loading into SLNs, the drug needs to adequately partition into the lipid phase.

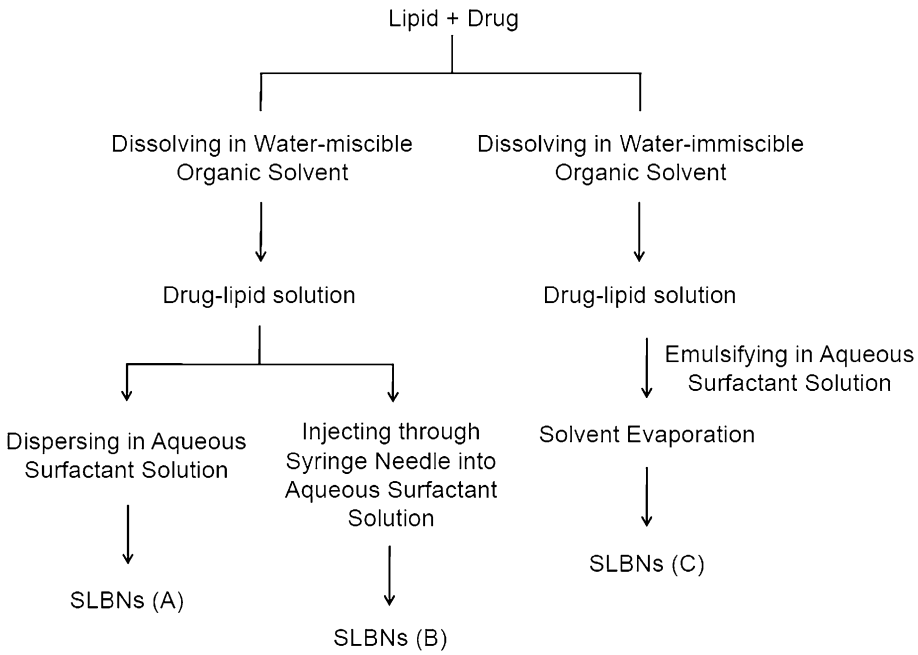

Fig. 3 Schematic description of preparation methods for SLBNs (*A* solvent diffusion; *B* solvent injection; *C* solvent emulsification-evaporation)

In the formation process of SLNs, rapid cooling step creates an unstable and disordered α-crystalline structure, which allows the drug to be stored into the amorphous area of SLNs (Puri et al. 2009). During the storage period, this α-crystalline state can be converted to a thermodynamically stable β-crystalline state (Puri et al. 2009). The partitioning of the drug in SLNs depends on the recrystallization rate of the lipid matrix and the resulting crystalline structure. Because drug molecules incorporate in the fatty acid chains, lipid layers and imperfect crystalline structures, a highly ordered and organized crystalline structure is not desirable for higher drug-loading capacities (Puri et al. 2009). It is important to note that the structural transformation from α-crystalline to β-crystalline can result in a burst release upon administration into the body, a significant drawback for SLNs in clinical settings (Battaglia and Gallarate 2012; Puri et al. 2009).

A mixture of solid- and liquid-phase lipids are used to prepare NLCs. Usually, about 5 % of drug (by weight) is incorporated in the lipid mixture upon initial NLCs production, and approximately 3–4 % drug loading is achieved (with typical encapsulation efficiencies of approximately 70 %) (Puri et al. 2009; Zhang et al. 2008). Liquid-phase lipids used in NLCs include oleic acid, capmul, and caprylic/capric triglycerides (Puri et al. 2009). Lipid selection is crucial for preparing stable drug-loaded NLCs. The chemical stability of the drug is dependent on the type of solid lipids incorporated into NLCs (Puri et al. 2009). Similarly, drug incorporation into lattice defects of NLCs may affect particle stability (Puri et al. 2009). The content of liquid-phase lipid incorporated can influence the size and surface morphology of particles. In a previous study, as the content of liquid-phase lipid (oleic acid) increased up to about 30 %, particle size decreased, and particle morphology became more spherical, smooth, and regular. Moreover, the initial drug release from NLCs was affected by the oleic acid content (Hu et al. 2006).

Characterization

Appropriate characterization of SLBNs is crucial for the management of product quality, stability, and drug release (Das and Chaudhury 2011; Mehnert and Mader 2001). There are several important characterization parameters such as particle size, particle size distribution, zeta potential (ZP), morphology, and crystallinity.

Particle size, polydispersity index, ZP, and morphology

Photon correlation spectroscopy (PCS) and laser diffraction (LD) are the most powerful and widely used techniques for routine measurement of particle size (Iqbal et al. 2012; Kakkar et al. 2011). PCS measures the fluctuation of the intensity of the scattered light caused by particle movement (Iqbal et al. 2012; Teeranachaideekul et al. 2007). This method covers size ranges from a few nm to 3 μm, which is sufficient to characterize SLBNs. However, LD can measure larger particle sizes of more than 3 μm (Iqbal et al. 2012; Muller et al. 2006; 2008). This method is based on the dependence of the diffraction angle on the particle radius (Fraunhofer spectra). Although PCS is relatively accurate and sensitive, it is generally recommended to use

both PCS and LD particularly for non-spherical particles (Iqbal et al. 2012; Das and Chaudhury 2011).

Because SLBNs are polydisperse in nature, measurement of polydispersity index (PDI) is crucial for the evaluation of particle size distribution. The PDI can also be measured by PCS (Xie et al. 2010). PDI values ranging from 0 to 0.5 are considered to be monodisperse and homogenous, but those of more than 0.5 indicate nonhomogenity and polydispersity. PDI values less than 0.3 are generally accepted as homogenous SLBNs (Zhang et al. 2009; Anton et al. 2008). The ZP means the overall charge of a particle in a specific medium, which can also be determined by PCS (Das and Chaudhury 2011; Pardeike et al. 2009). Stability of SLBNs during storage can be predicted from the ZP value. Generally, the ZP value of −30 mV is considered to be sufficient for stabilization of SLBNs (Mukherjee et al. 2008).

Scanning electron microscopy (SEM), transmission electron microscopy (TEM), and atomic force microscopy (AFM) can be used to determine the shape and morphology of SLBNs (Tsai et al. 2011). SEM utilizes electron transmission from the sample surface, whereas TEM utilizes electron transmission through the sample. Several SEM and TEM studies showed spherical shape of SLBNs (Kakkar et al. 2011; Varshosaz et al. 2010a, b; Sanjula et al. 2009). Although SEM may not be sensitive to the nano-size range, field emission SEM (FESEM) can be used to detect nano-size particles (Sahana et al. 2010). However, sample preparation process (e.g., solvent removal) may affect the particle's shape. Cryogenic FESEM may be helpful in this case, where liquid dispersion is frozen by liquid nitrogen and micrographs are taken at the frozen condition. Also, AFM technique is widely used for nanoparticle characterization. AFM provides a three-dimensional surface profile unlike electron microscopy providing two-dimensional image (Shahgaldian et al. 2003). AFM can provide structural, mechanical, functional, and topographical information about surfaces with nanometer- to angstrom-scale resolution (Patel et al. 2013).

Crystallinity and lipid modification

Crystallinity and lipid modification is also crucial for the characterization of SLBNs, because these parameters are strongly correlated with drug incorporation and release profiles (Souto et al. 2006). Thermodynamic stability and lipid packing density increase, and drug encapsulation efficiencies decrease in the following order: supercooled melt < α-modification < β-modification < β′-modification (Muller et al. 2000). However, lipid crystallization and modification may be retarded due to small particle sizes and emulsifiers. Differential scanning calorimetry (DSC) and X-ray diffractometry (XRD) are widely used techniques to determine the crystallinity and polymorphic behavior of the components of SLBNs (Sanjula et al. 2009; Radomska-Soukharev 2007). DSC is based on the fact that different lipid modifications possess different melting points and melting enthalpies. DSC provides information on the melting and crystallization behavior of all solid and liquid constituents of SLBNs. XRD can identify specific crystalline compounds based on their crystal structure (Estella-Hermoso de Mendoza et al. 2009). The patterns of XRD profiles can assess the length of the long and short spacing of the lipid lattice (Bunjes and Koch 2005). Infrared and Raman spectroscopy can also be used to investigate structural properties of lipids (Muller et al. 2000). However, they have not been frequently used to characterize SLBNs (Battaglia and Gallarate 2012).

Additional colloidal structures

The magnetic resonance techniques like nuclear magnetic resonance (NMR) and electron spin resonance (ESR) are useful for investigating dynamic phenomena and characteristics of SLBNs. Detection of supercooled melts due to the low line widths of the lipid protons is possible by ^{1}H NMR spectroscopy (Zimmermann et al. 2005). This technique is based on the different proton relaxation times in the liquid and semisolid/solid state. NMR also can characterize liquid nanocompartments in SLBNs. ESR requires a paramagnetic spin probes to assess SLBNs. Direct, repeatable, and noninvasive characterization of the distribution of the spin probe between the aqueous and lipid phase can be performed by ESR (Kuchler et al. 2010; Braem et al. 2007). However, NMR and ESR have been rarely applied to characterize SLBNs.

Applications

Parenteral drug delivery and targeting

Parenteral administration of lipidic material came to success, when nanoemulsion-based products such as Diazemuls (Diazepam, Actavis, Zug, Switzerland) and Diprivan (Propofol, AstraZenica, London, UK) were commercialized. However, upon injecting drug-loaded nanoemulsions into systemic circulation, the drug partitions rapidly from the oil phase to the water phase of the blood in milliseconds or seconds (Muller et al. 2011). Liposomes also represent the first generation of the novel lipidic carriers. The commercialization of various injectable liposomal products such as AmBisome® (Amphotericin B, Gilead Sciences, Foster city, US), Doxil® (Doxorubicin, Centocorortho biotech, Philadelphia, US) and DaunoXome® (Daunorubicin, Gilead sciences, Foster city US) clearly indicates the

potential advantages of liposomes as novel lipid carriers (Gill et al. 1995). However, major problems of liposomal formulation are associated with limited physical stability and high cost. Therefore, the potential of SLBNs have been explored for parenteral drug delivery, but little information is currently available regarding direct comparison between lipid emulsion/liposome and SLBNs in terms of physical stability and cost, which requires further investigation.

The administration of SLBNs via the parenteral route may improve systemic exposure profile and targeting. Docetaxel-loaded NLCs were developed to reduce toxicity and improve therapeutic efficacy for parenteral delivery (Liu et al. 2011). Dexamethasone-loaded SLNs for lung-targeted delivery showed a 17.8-fold larger area under the plasma concentration–time profiles (AUC) compared with drug solution (Xiang et al. 2007). Actarit (anti-rheumatic drug)-loaded SLNs were developed for enhanced passive drug targeting, improved therapeutic efficacy and reduced side-effects. Those SLNs showed an enhanced targeting efficiency to the spleen from 6.31 to 16.29 %, while significantly lowering the renal distribution after intravenous administration to mice compared with drug solution (Ye et al. 2008). Docetaxel-loaded SLNs were developed for cancer therapy, and those SLNs showed enhanced cellular uptake and targeting efficiency to cancers (Mosallaei et al. 2013). It was also reported that SLNs enhanced blood–brain barrier (BBB) permeation and/or brain targeting efficiency for several drugs such as paclitaxel (Koziara et al. 2004), clozapine (Manjunath and Venkateswarlu 2005), etoposide (Harivardhan Reddy et al. 2005), cisplatin (Doijad et al. 2008), and tobramycin (Bargoni et al. 2001).

Oral drug delivery

Oral administration is the most preferred dosing mode due to greater convenience, less pain, improved patient compliance, reduced risk of cross-infection and needle stick injuries (Kim et al. 2013; Yoon et al. 2011). Major portion of drug delivery market is occupied by oral drug delivery systems. However, oral drug delivery is often limited by several factors such as poor solubility, limited gastrointestinal absorption, extensive first-pass effects, and food effects (Han et al. 2012; Yoon et al. 2012). Colloidal drug carriers such as micelles, nanoemulsions, nanosuspensions, polymeric nanoparticles, and liposomes may overcome many of the solubility-related problems (Das and Chaudhury 2011). However, these drug delivery systems are associated with several drawbacks such as limited physical stability, aggregation, drug leakage on storage, lack of a cost-effective and quality-controlled large-scale production method, presence of organic solvent residues in the final product, and cytotoxicity (Muller et al. 2002a). Therefore, the potential of SLBNs have been explored for oral drug delivery, but little information is currently available regarding direct comparison between lipid emulsion/liposome and SLBNs in terms of physical stability, cost, production scalability, and toxicity, which requires further investigation. Examples of SLBNs for oral drug delivery are summarized in Table 2 (Das and Chaudhury 2011; Harde et al. 2011).

Lipids are known to enhance oral drug absorption (Holm et al. 2002; Charman 2000). A simple example from daily life is the oral absorption of lipophilic vitamins enhanced by oils. Orally administered lipid is dispersed in the gut to fine droplets of a few micrometers in size by bile salts and mechanical movement. Therefore, to be most effective, the drug should be closely associated with the lipid. The incorporation of drugs within SLBNs can facilitate the absorption enhancing effects of lipids. Orally administered SLBNs may adhere to the gut wall, and then the drug is released in the vicinity of absorption site (Aungst 2000). Moreover, SLBNs may be degraded by lipase/co-lipase complex being anchored onto their surface. Triglycerides of SLBNs are degraded into surface-active monoglycerides, forming micelles. Drugs present in the degrading lipids may be entrapped in the micelles. The micelles can also interact with bile salts present in the gut, leading to the formation of mixed micelles. Then, the lipids are absorbed via chylomicron formation primarily into lymphatic system, and simultaneously the drug "goes with the lipid", which is called as Trojan horse effect (Muller et al. 2002b). In addition, it has been well known that nanoparticulate systems including SLBNs may enhance oral drug absorption via intracellular uptake by M-cells of Peyer's patches in the gut (Harde et al. 2011). Therefore, SLBNs may serve as an efficient oral drug delivery system based on the above-mentioned mechanisms.

Inhalational and ocular drug delivery

Inhalational drug delivery has several advantages over conventional (parenteral and oral) dosage forms such as non-invasiveness, negligible first-pass effects, and reduced systemic toxicity. Inhaled drugs may reach directly to the lung epithelium, enhancing local drug concentrations. Particles smaller than 500 nm may enhance pulmonary deposition due to an increased diffusional mobility (Jaques and Kim 2000), and particles smaller than 260 nm can escape macrophagal clearance (Lauweryns and Baert 1977). Moreover, bioadhesive and lipophilic properties of SLBNs may prolong their residence in the lung, and sustained drug release from SLBNs can prolong the therapeutic effect as well as the inhalation interval (Patlolla et al. 2010; Pandey and Khuller 2005b). Surfactants and co-solvents are often used in SLBNs formulations to avoid lung inflammation caused by lipophilic drugs (Pardeike

Table 2 Implications and preparation methods of LNPs for oral drug delivery

Drug	Implication	Preparation method	Reference
Apomorphine	BA (↑)	Ultrasonification (SLNs)	Tsai et al. (2011)
Buspirone	BA (↑)	Solvent emulsification-evaporation (SLNs)	Varshosaz et al. (2010b)
Carvedilol	BA (↑)	Microemulsion (SLNs)	Sanjula et al. (2009)
	Lymphatic uptake		
Cyclosporin A	BA (↑)	HPH (SLNs)	Muller et al. (2006)
	Low variable BA		
Digoxin	GI absorption (↑)	Ultrasonification and HPH (SLNs)	Hu et al. (2010)
	BA (↑)		
Insulin	Stability (↑)	Solvent emulsification-evaporation (SLNs)	Yang et al. (2011)
	BA (↑)		
	Hypoglycemic effect (↑)		
Lovastatin	Stability (↑)	HPH (NLCs)	Chen et al. (2010)
	BA (↑)		
Methotrexate	BA (↑)	Solvent diffusion (SLNs)	Paliwal et al. (2009)
	Lymphatic uptake		
Pentoxifylline	BA (↑)	Ultrasonification and HPH (SLNs)	Varshosaz et al. (2010a)
	First-pass effects (↓)		
Praziquantel	BA (↑)	Ultrasonification and HPH (SLNs)	Xie et al. (2010)
Quercetin	GI absorption (↑)	Emulsification-sonification (SLNs)	Li et al. (2009a)
	BA (↑)		
Vinpocetin	GI absorption (↑)	HPH (NLCs)	Zhuang et al. (2010)
	BA (↑)		

This table was modified from Das and Chaudhury (2011) and Harde et al. (2011)

BA bioavailability

et al. 2011). Therefore, SLBNs have been explored in inhalational drug delivery for the treatment of pulmonary disorders. Celecoxib-loaded NLCs were deposited in the alveolar region with prolonged residence time after inhalational administration in Balb/c mice (Patlolla et al. 2010). The inhalation of anti-tubercular drugs-loaded SLNs achieved the undetectable level of bacilli in the lung of tuberculosis infected guinea pigs (Pandey and Khuller 2005a). Fluorescent-labelled insulin-loaded SLNs showed uniform distribution in the lung alveoli and improved both the in vitro and in vivo drug stability, together with enhanced bioavailability and prolonged hypoglycemic effects (Liu et al. 2008).

There are several barriers to ocular drug delivery, such as pre-corneal loss, transient residence time in the cul-de-sac, and limited permeability of the corneal epithelial membrane, leading to poor ocular bioavailability (Li et al. 2009a, b). Therefore, there is a clear need for more effective ocular formulations capable of promoting drug penetration and maintaining therapeutic levels. Recently, studies on novel ocular drug delivery systems such as microemulsion, microspheres, liposomes, and SLBNs have been reported (Chan et al. 2007; Gavini et al. 2004; Cavalli et al. 2002). Among them, SLBNs possess many useful features for ocular drug delivery such as controlled drug release, penetration-enhancing effects, prolonged retention, and biotolerability (Muller et al. 2002b). Flurbiprofen-loaded NLCs have been approved as the first line ophthalmic medication for the inhibition of miosis induced during cataract surgery process (Gonzalez-Mira et al. 2010). Moreover, SLNs enhanced the ocular retention time and bioavailability for tobramycin (Cavalli et al. 2002), cyclosporine A (Gokce et al. 2009), and timolol (Attama et al. 2009).

Dermal drug delivery

SLBNs are attractive colloidal lipidic nanocarriers for dermal drug delivery (Schafer-Korting et al. 2007; Uner and Yener 2007). Their various desirable effects on the skin include the ability to protect chemically labile ingredients, film formation, controlled occlusion, skin hydration, bioavailability enhancement, physical stability, and the possibility to modulate drug release (Muller et al. 2007). Upon dermal application, SLBNs adhere to the lipid film of the stratum corneum via hydrophobic interactions. The adsorbed SLBNs may repair bare patches in the lipid film of the skin and reinforces a thin film. This restoration of the

protective lipid film enhances skin hydration and normalizes the living conditions for cells underneath. The film has also occlusive properties, promoting the penetration of drugs into the skin. Thus, SLBNs can be regarded as an "invisible and penetration-enhancing occlusive plastic foil" (Muller et al. 2011). Moreover, they are well suited for use on damaged or inflamed skin, because they are based on non-irritant and non-toxic lipids (Muller et al. 2002b). SLNs enhanced skin penetration and pharmacological effects for glucocorticoids (Maia et al. 2000), cyproterone (Stecova et al. 2007), and sphingosin-1-phosphate (Muller et al. 2011), together with reduced side effects. NLCs were also applied to enhance skin penetration and/or pharmacological effects for ketoprofen (Cirri et al. 2012), celecoxib (Joshi and Patravale 2008), coenzyme Q10 (Obeidat et al. 2010), cyproterone (Stecova et al. 2007), and calcipotriol (Lin et al. 2010).

Conclusions

We have comprehensively reviewed the preparation and characterization technologies for SLBNs (SLNs and NLCs) and their applications for drug delivery. SLBNs formulations have shown many advantages over other conventional drug delivery systems such as polymeric nanoparticles, liposomes, and nanoemulsions. Therefore, vast researches on SLBNs have conducted for parenteral, oral, inhalational, ocular, and dermal drug delivery, and clearly showed the feasibility of SLBNs as a safe and efficient drug delivery system. However, despite such investigations on SLBNs, there are few pharmaceutical SLBNs products approved up to now. Further pre-clinical and clinical studies should be performed in near future to establish SLBNs formulations in the market.

Conflict of interest The authors report no conflict of interest.

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