Solid Lipid Nanoparticles

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Definition: Solid lipid nanoparticles (SLNs) are produced from physiologically biocompatible lipids. They have been proven to improve solubility, cellular uptake, and stability, reduce enzyme degradation, and prolong the circulation time of various drugs. SLNs have been applied in the oral, parenteral, transdermal, intranasal, ocular, and pulmonary drug delivery of different drugs, with enhanced safety, bioavailability, and overall therapeutic effects. In this entry, the authors summarize the primary features of SLNs, methods to prepare SLNs, and recent applications of SLNs in drug delivery. Owing to their advantages, SLNs are potential drug delivery systems to improve the management of various diseases and will, soon, be available for clinical use.

Keywords: solid lipid nanoparticles; nanostructured lipid carriers; drug delivery; oral; parenteral; transdermal; intranasal; ocular; pulmonary

1. Introduction

Nanotechnology-based drug delivery systems have increasingly been developed in the last decades and have significantly impacted the pharmaceutical sciences [1–3]. They play a critical role in delivering hydrophobic drugs, which comprise more than 40% of approved drugs [4]. The poor water solubility of these hydrophobic drugs is one of the major limiting steps that considerably affect drug release and bioavailability, which can be resolved using nanotechnology-based drug delivery systems. In addition, the incorporation of drugs in nanoparticles (NPs) increases drug stability, reduces enzyme degradation, prolongs circulation time, and improves the uptake of target cells, which, thereby, enhances the overall effectiveness and safety [5–7].

According to their chemical compositions and structure, nanotechnology-based drug delivery systems can be classified as inorganic NPs, polymeric NPs, and lipid-based NPs. Inorganic NPs are made up of inorganic materials, such as gold, silver, iron, and silica. Owing to some of the unique properties of the materials, these inorganic NPs may have distinct electrical, physical, optical, or magnetic features, such as the photothermal effects of gold NPs [8] or superparamagnetic properties of iron oxide NPs [9]. Inorganic NPs have good stability and are potential drug delivery systems in photothermal therapies, imaging, and diagnostics. However, as a result of their low water solubility and toxicity issues, they are not widely used in clinical applications [10,11]. Polymeric NPs are produced from a wide variety of natural or synthetic polymers. They include dendrimers, polymeric micelles, nanospheres, and polymersomes. Polymeric NPs can incorporate hydrophobic and hydrophilic drugs with different molecular weights, including small molecules, biological macromolecules, and proteins [12]. The advantages of polymeric NPs include biodegradability, biocompatibility, and co-delivery of different drugs. In addition, they can deliver drugs to targeted tissues with suitable surface modifications [13–15]. However, polymeric NPs have the disadvantages of toxicity and particle aggregation [5]. Lipid-based NPs have been widely investigated in the last decades. They have various advantages, such as biocompatibility, high bioavailability, high drug payloads, formulation simplicity, and self-assembly [5]. Lipid-based NPs include emulsions, liposomes, lipid NPs, and solid lipid

nanoparticles (SLNs). They can be fabricated from biodegradable and non-toxic materials, making them ideal systems for clinical applications [16,17]. The second generation of SLNs is sometimes termed nanostructured lipid carriers (NLCs). However, SLNs can be used to mention both SLNs and NLCs.

SLNs were developed in the mid-1990s [18] and have been considered alternative systems to liposomes, emulsions, micelles, and polymeric NPs, due to various advantages. They are produced from physiologically biocompatible and biodegradable lipids as well as other materials that are generally recognized as safe (GRAS), and, therefore, they are safe nanotechnology-based drug delivery systems [19,20]. The solid matrices can protect the drugs incorporated in SLNs, and, thereby, the drug stability is efficiently improved [21]. Both hydrophilic and hydrophobic drugs can be encapsulated in SLNs with higher entrapment efficiencies than liposomes [22]. The drug release from SLNs can be controlled by altering the lipid components [23,24]. The surface of SLNs can be modified to target specific tissues and enhance stability [25]. SLNs can be produced using non-solvent techniques, such as high-pressure homogenization and high-speed stirring [26]. These advantages enable the wide applications of SLNs in oral, parenteral, transdermal, intranasal, ocular, and pulmonary drug delivery [27,28].

Considering the increasing interest in SLNs, in this entry, we provide an overview of SLNs. This entry is structured as follows: the primary features of SLNs, methods to prepare SLNs, recent applications of SLNs in drug delivery, and conclusions.

2. Features of SLNs

2.1. Structural Features and General Components of SLNs

SLNs are spherical particles with a solid lipid matrix containing drug molecules and a surfactant layer to stabilize the SLNs in an aqueous phase (Figure 1). SLNs and NLCs are different regarding their lipid components. SLNs are produced from solid lipids, while the lipid component of NLCs is a mixture of solid and liquid lipids [29,30]. Matrices of SLNs are in α and β' forms (high energy modifications) after preparation. These matrices consist of similar lipid molecules, which tend to rearrange to β form, a more perfect modification. Therefore, during storage, drugs incorporated in SLNs may be expelled. The matrices of similar lipid molecules, also, have limited space for drug accommodation [31,32]. In contrast, the matrices of NLCs consist of different lipid molecules, which are imperfect or amorphous structures [33,34]. Among these lipid molecules, more space is available to accommodate drugs [35]. Therefore, compared with SLNs, NLCs may increase drug loading and reduce the drug expelled during storage.
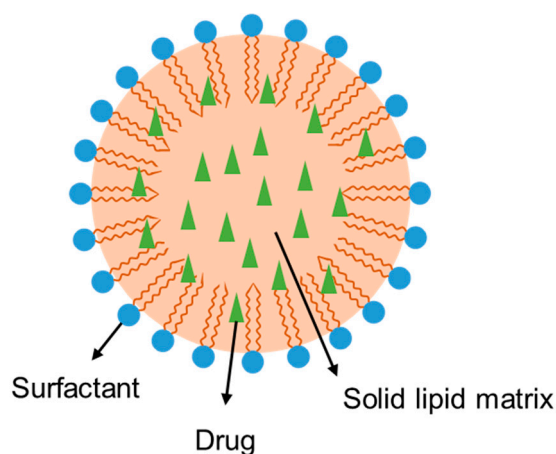
Figure 1. Structure of solid lipid nanoparticles (SLNs).

General ingredients to produce SLNs include solid lipids, liquid lipids (oils), and emulsifiers. Typical ingredients are listed in Table 1. The solid and liquid lipids commonly used in the preparation of SLNs are, usually, approved by American and European reg-

ulatory authorities for clinical applications [18]. Solubility of drugs in different lipids is sometimes determined, by which the lipids that can solubilize more drugs are selected for the preparation of SLNs [36]. Emulsifiers are crucial to stabilize the NPs. In SLNs, most of the emulsifiers are hydrophilic, such as polysorbate 80 (Tween 80), lecithin, poloxamer 407 (Pluronic F127), poloxamer 188 (Pluronic F68), phosphatidylcholine, PEG-40 castor oil (Cremophor®® RH40), sodium deoxycholate, and sodium dodecyl sulfate [18]. Emulsifiers can be screened to determine the optimum concentration. Typically, they are used in a range of 0.1–5% (*w/v*).

Table 1. Ingredients used for SLN preparation.

Ingredient	Examples	References
Solid lipid	Glyceryl palmitostearate (Precirol®® ATO 5)	[37–39]
	Glyceryl behenate (Compritol®® 888 ATO)	[37,40]
	Stearic acid	[41]
	Palmitic acid	[42]
	Tristearin	[39,43,44]
	Tripalmitin (Dynasan®® 116)	[45]
	Trimyristin (Dynasan®® 114)	[20]
	Cetyl palmitate	[46]
	Cholesterol	[47]
	Triolein	[44]
	Tricaprylin	[44]
Liquid lipid	MCT (Miglyol®® 812)	[37,48]
	Propylene glycol dicaprylocaprate (Labrafac®®)	[40]
	Caprylocaproyl Polyoxyl-8 glycerides (Labrasol®®)	[38]
	Propylene glycol monocaprylate (Capryl™ 90)	[39]
	Isopropyl myristate	[39]
	Oleic acid	[42–44]
	Squalene	[49,50]
	α-tocopherol	[51]
Emulsifier	Poloxamer 188	[37,40,47,50]
	Poloxamer 407	[39]
	Soybean lecithin, phosphatidylcholine	[20,43]
	Polysorbate 80	[20,42,43]
	Polysorbate 60	[44]
	PEG-40 castor oil (Cremophor®® RH40)	[38]
	Sodium deoxycholate	[51]
	Sodium dodecyl sulfate	[41]

2.2. Physicochemical Characterization

2.2.1. Particle Size and Polydispersity Index

The particle size is an essential parameter in the process control and quality assurance of the production of SLNs. The particle size affects the total surface area of the nanodispersion system and its physical stability. Particle size can be determined by dynamic light scattering (DLS) (also known as photon correlation spectroscopy) and laser diffraction [52]. DLS measures the particle size, based on the fluctuation of the scattered light intensity caused by the particles' movement. It is relatively sensitive and accurate, and its size ranges from a few nanometers to 3 μm [53]. Laser diffraction is based on the diffraction angle that relates to the particle radius in the nanodispersion. It can measure larger particle sizes than DLS [53,54]. Therefore, DLS is usually used to determine the particle size of SLNs. Light-weight microscopy is an alternative choice for samples that contain many size ranges [55].

The polydispersity index (PI) reflects the size distribution of a nanodispersion. A lower PI value indicates a more monodispersed nanodispersion [52]. Usually, a nanodispersion with a PI value < 0.5 is monodispersed and homogenous. A PI value > 0.5 indicates the

non-homogeneity and polydispersity of a nanodispersion [55,56]. However, most studies suggest a PI value < 0.3 as an indication of a good size distribution [56,57]. PI can be measured using DLS [58].

2.2.2. Zeta Potential

Zeta potential is the electric potential of NPs that comes from the adsorption of ions or the ionization of surface groups of the NPs. It depends on the surface chemistry of the NPs and the media surrounding them. The zeta potential of a nanodispersion is, usually, determined using DLS [58,59]. Zeta potential is used to predict the physical stability of a nanodispersion. A high zeta potential indicates a strong repulsion between the NPs, which can prevent particle aggregation. On the other hand, in a nanodispersion with a low zeta potential, the repulsion between the particles is exceeded by the attraction, resulting in the flocculation or coagulation of the nanodispersion [52]. Generally, an absolute zeta potential value higher than 30 mV is considered appropriate for the stabilization of a nanodispersion.

2.2.3. Entrapment Efficiency

Entrapment efficiency (EE) is the ratio of the drug entrapped into NPs and the total amount of drug used for production [60,61].

$$EE\% = \frac{\text{Amount of entrapped drug}}{\text{Amount of total drug}} \times 100 \qquad (1)$$

During the preparation of SLNs, different parameters of the process and formulation are usually varied to increase EE as high as possible [62]. The amount of the entrapped drug can be determined after separating the unentrapped drug from the SLN dispersions. Several methods are currently used, such as gel filtration chromatography [63], dialysis [64], ultracentrifugation [65,66], and filter membrane (MWCO 10–20 kDa) [67]. Entrapped-drug SLNs can be extracted and quantified. The unentrapped drug can, also, be quantified, and the amount of the entrapped drug is, then, indirectly determined [68].

2.2.4. Differential Scanning Calorimetry (DSC) and X-ray Diffraction (XRD)

DSC and XRD are widely used to investigate the crystallinity and polymorphic behavior of the components of SLNs [58]. It is essential, since the lipid matrix and the entrapped drug may undergo a polymorphic transition, which can result in an undesirable drug expulsion during storage [51]. Following the order super-cooled melt < α-modification < β′-modification < β-modification, the lipid-packing density and the thermodynamic stability increase, while the drug-incorporation rates decrease [23]. DSC is a technique that measures the heat loss or gain of a sample, as a function of the temperature. It reflects the physical and chemical changes of the samples, due to temperature changes. DSC is used to determine the crystallinity degree of an SLN sample, by comparing the melting enthalpy/g of the samples with that of the bulk material [52]. For example, the DSC thermograms exhibited a slight shift to a lower temperature of the Compritol 888 ATO endothermic peak in SLNs, due to the decreased crystalline structure. In addition, a reduction in the enthalpy of SLNs was evidence of the formation of a less-ordered state in the SLNs [35].

XRD can identify specific crystalline compounds, based on their crystal structure. It is based on the diffracted angles of the X-ray beam, which depends on the distance between the crystals' planes and the arrangement of the atoms [52]. Each type of crystalline material has a unique XRD pattern, including the position and the intensity of the diffractions. XRD can be used to predict the phase behavior and the arrangement manner of lipid molecules as well as characterize the structure of lipid and drug molecules [69]. Generally, DSC and XRD analyses are simultaneously performed, to evaluate the crystallinity and polymorphic behavior of SLNs.

2.2.5. Scanning Electron Microscopy (SEM), Transmission Electron Microscopy (TEM), and Atomic Force Microscopy (AFM)

SEM, TEM, and AFM are, generally, used to investigate the shape and morphology of SLNs, as well as determine particle size and size distribution [55]. SEM and TEM provide two-dimensional images of samples, whereas AFM enables the visualization of the three-dimensional surface. For SEM, an aqueous SLN dispersion is spread on a thin carbon film (sample holder). The sample is, then, placed inside of the vacuum column of the electron microscope. An electron beam at high energy hits the sample surface, and the secondary electrons are emitted. A detector counts the secondary electrons and transforms them into signals [52]. In the case of TEM, the electron beam is transmitted through the samples. SEM is not sensitive to the nano-size range; however, the use of field-emission SEM (FESEM) can solve this problem. Cryogenic FESEM may be useful to take the micrographs in the frozen condition, to prevent changes in the particle shape and morphology during the sample preparation process [55]. In AFM, the forces between a probing tip and a sample are measured and used to form a three-dimensional shape of the sample surface. It shows mechanical, functional, structural, and topographical information about surfaces, at a resolution from nanometer to angstrom [70,71]. Compared with SEM and TEM, AFM requires a simple sample preparation without the need of a vacuum.

Table 2 summarizes the physicochemical characterization of SLNs.

Table 2. Physicochemical characterization of SLNs.

Parameters	Characterization	References
Particle size	Dynamic light scattering and laser diffraction	[52]
Polydispersit index	Dynamic light scattering and laser diffraction	[52]
Zeta potential	Dynamic light scattering	[58,59]
Entrapment efficiency	Gel filtration chromatography	[63]
	Dialysis	[64]
	Ultracentrifugation	[65,66]
	Filter membrane	[67]
Crystallinity	Differential scanning calorimetry (DSC) and X-ray diffraction (XRD)	[35]
Shape and morphology	Scanning electron microscopy (SEM), transmission electron microscopy (TEM), and atomic force microscopy (AFM)	[52,55,70,71]

2.3. Drug Incorporation Models and Drug Release

There are three different models of drug incorporation in the lipid matrix of SLNs, including a homogenous matrix, drug-enriched shell, and drug-enriched core [24,52]. In the homogenous matrix model, the drug and lipid are homogeneously dispersed. This type of drug incorporation can be obtained for SLNs of highly lipophilic drugs, prepared by the hot homogenization method. In addition, the cold homogenization method can also lead to the homogenous matrix model. In this model, the release of the drug is due to its diffusion from the solid lipid matrix and the degradation of the lipid. This model was assumed valid for the lipid NPs loaded with prednisolone [72].

The drug-enriched shell model can be obtained, if the lipids precipitate faster than the drug during the cooling process. In this case, a lipid core is formed first, followed by the precipitation of a lipid–drug mixture, which forms the outer shell of the particles. Thus, most drug molecules are localized in the particle shell, whereas the lipid core of SLNs contains less or, even, none of a drug. SLNs with the drug-enriched shell usually show a burst release of the drug, as observed in the case of tetracaine [72].

In contrast, the drug-enriched core model is due to the faster precipitation of the drug compared with the lipids. This occurs when the drug concentration in the lipid is beyond its saturation solubility at production temperature. As a result, the lipid core contains more drug than the outer shell. The drug in the lipid core is, usually, associated with a prolonged release phase of the entrapped drug. It was reported that a low concentration of oxybenzone resulted in drug-enriched shell SLNs, with a fast release of the drug from

the SLNs. When the concentration of oxybenzone was increased, drug-enriched core SLNs were formed, and a sustained drug-release profile was observed [73].

During the preparation SLNs, several alternative drug incorporation types may exist, such as liposome, micelle, mixed micelle, and drug nanosuspension, due to liquid lipids [67,74]. These incorporation types are usually neglected. Besides the three major drug incorporation models discussed above, some mixed types can be formed. Thus, the structure of SLNs depends on the chemical nature of the drugs and lipids, their interactions, and the production conditions [68].

In vitro drug-release studies of SLNs can be carried out, using the dialysis bag and Franz diffusion cell method. The drug release profile is often biphasic, with an initial burst release phase, followed by a sustained release phase. The burst release phase is due to the release of drug molecules located on the surface or in the outer shell of the NPs. The sustained release phase results from the gradual release of the drug molecules entrapped in the lipid core [75]. Many factors may affect the drug release from SLNs, including the production temperature, lipid matrix, drug properties, surfactant, and drug concentration in the lipid matrix [62]. For example, a high temperature in the hot homogenization method and a high surfactant concentration induced burst release [76].

2.4. Stability and Safety

The lipids in SLNs are, generally, present in a mixture of α and β' polymorphs. By kinetic energy (e.g., light and temperature), they can be transformed to β polymorph accompanied by gel formation. The physical stability of SLN dispersions can be evaluated by changes in particle size, PI, and zeta potential. Increases in particle size and PI as well as a decrease in zeta potential are indicators of instability. Light and temperature can induce particle growth and reduce zeta potential. The physical stability of SLN dispersions is considerably improved by storing them at a low temperature and protecting them from light [77]. For example, three-month storage under light resulted in the gelation of an SLN dispersion and a decrease in zeta potential (from -24.7 to -18 mV). At elevated temperatures, the particle size of the SLNs increased, and zeta potential decreased to -15 mV. However, in cold conditions, the particle size of the SLNs was unchanged after three months [77]. Several studies indicated that SLN dispersions were physically stable for more than one year [78,79].

The transformation of SLN aqueous dispersions into dried states can prevent hydrolytic reactions and the Oswald ripening, by which the stability of SLN dispersions is improved. Lyophilization and spray-drying are promising methods to improve the chemical and physical stability of SLNs over an extended period. Lyophilization (also known as freeze-drying) is a low-temperature dehydration process, in which samples are frozen before the sublimation of ice under low pressure [80]. The low temperature allows the dried SLNs to maintain their original shape. Some cryoprotectant agents, such as glucose, sucrose, maltose, mannose, trehalose, and sorbitol, are used to prevent particle aggregation during lyophilization and improve the properties of SLNs after reconstitution [52]. Spray-drying is an alternative method to lyophilization to preserve SLNs [81]. In spray-drying, a feeding fluid is sprayed into a hot gas, by which the sprayed droplets are quickly dried [82,83]. However, the spray-drying of SLNs is not widely used, since the drying temperature and shear force might, potentially, cause lipid melting and particle aggregation. Therefore, the drying temperature should be lower than the melting point of the solid lipid used in SLNs. The ethanol–water mixtures can be used to disperse SLNs before spray-drying, to minimize lipid melting [18,24].

SLNs are usually produced from GRAS excipients. Therefore, they are well tolerated by animals and humans. These excipients should be used in acceptable concentrations. If a higher concentration is used, a toxicity study should be carried out to prove the safety of the excipients [52]. The oral, transdermal, intramuscular, and subcutaneous administration of SLNs is generally safe. The particle size is not a critical issue for these administration routes; a small proportion of microparticles might reduce the performance of the SLNs, but

will not result in toxic events [18]. However, the size distribution is crucial in intravenous injection, since the large particles may cause capillary blockage. The fine capillaries in humans have a diameter of about 9 μm; therefore, the particle size of SLNs should be in the submicron range [18]. Following intravenous injection, SLNs can bind to erythrocytes, affect blood clotting [24], and interact with albumin, to form a capping layer of albumin onto the surface of the NPs [84]. Many studies have reported that intravenous injection of SLNs was nontoxic in animals [85,86] and less toxic than polymeric NPs [87].

3. Methods for SLNs Preparation

SLNs have been produced using numerous methods. They can be classified into solvent-based, non-solvent, and other methods (Figure 2).
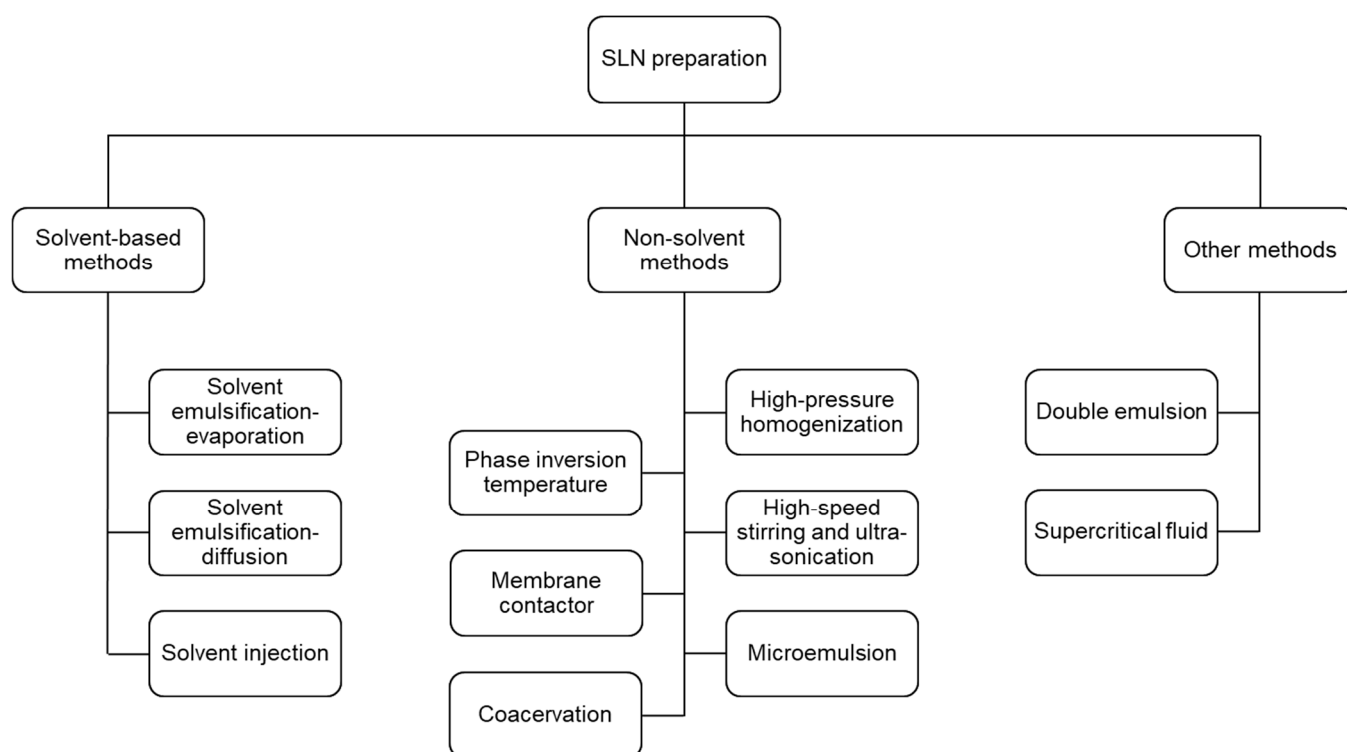
Figure 2. Classification of SLN preparation methods.

3.1. Solvent-Based Methods

3.1.1. Solvent Emulsification-Evaporation Method

The solvent emulsification-evaporation method includes two steps: (i) preparation of oil/water nanoemulsions and (ii) solvent evaporation. In this method, lipids and a drug are dissolved in a solvent or a solvent mixture to form the oil phase, which is, subsequently, emulsified in an aqueous phase. The solvents are water-immiscible organic solvents, such as dichloromethane, chloroform, cyclohexane, and toluene [88,89]. After oil-in-water nanoemulsions are formed, the organic solvent is evaporated. The solvent evaporation is, usually, carried out using a rotary evaporator or mechanical stirring. During solvent evaporation, the concentration of lipids in droplets increases gradually, resulting in lipid precipitation and the formation of SLNs [90].

This method is involved in the use of toxic organic solvents; therefore, it requires additional steps to remove the solvents and evaluate the toxicity of the formulations in vitro and in vivo. The resulting SLNs are, usually, in a high amount of water and should be concentrated by ultrafiltration or evaporation. On the other hand, the solvent emulsification-evaporation method is suitable for highly thermo-labile drugs, since it does not require high temperatures and physical stress, such as high-pressure homogenization

and high-speed stirring. The prepared SLNs, generally, exhibit a narrow size distribution, with a mean particle size of approximately 100 nm [3]. This method has been used to prepare SLNs loaded with some drugs, such as lupinifolin [91], cinnarizine [92], naloxone [93], progesterone [94], eplerenone [95], and perphenazine [96].

3.1.2. Solvent Emulsification-Diffusion Method

The solvent emulsification-diffusion method includes four steps: (i) mutual saturation of water and an organic solvent with each other, (ii) preparation of oil/water nanoemulsions, (iii) dilution with water, and (iv) solvent elimination. The first step produces water-saturated solvent and solvent-saturated water, to obtain an initial thermodynamic equilibrium of the water and organic phases. Therefore, in this method, organic solvents, such as benzyl alcohol, butyl lactate, methyl acetate, ethyl acetate, and isopropyl acetate are used, due to their partial miscibility with water. In the second step, drugs and lipids are dissolved in the solvent, followed by the emulsification of both phases to form an oil/water emulsion. In the third step, the emulsion is diluted with water by 5–10-fold. Upon dilution with water, the solvent diffuses into water, leading to the precipitation of lipids. As a result, SLNs are formed. The fourth step is to eliminate the solvent, usually by vacuum drying or lyophilization [97,98].

An obvious disadvantage of this method is the use of organic solvents, which results in a purification step to remove them [99]. The resulting dispersion contains a high amount of water and a low concentration of SLNs, due to the substantial dilution with water in the third step [52,97]. On the other hand, the solvent emulsification-diffusion method is feasible to scale up [100]. Similar to the solvent emulsification-evaporation method, this method can prevent drug exposure to high temperatures and physical stress. It enables the encapsulation of both hydrophilic and hydrophobic drugs, such as sesamol [99], lorazepam [101], tenofovir [102], sumatriptan [103], and uspirone [104].

3.1.3. Solvent Injection Method

The solvent injection method was first used to prepare SLNs in 2003 [105]. It includes three steps: (i) preparation of the water phase and oil phase, (ii) solvent injection, and (iii) solvent removal. In this method, the oil phase is prepared by dissolving lipids and drugs in a water-miscible solvent, such as ethanol, methanol, isopropanol, acetone, or a water-miscible solvent mixture. The aqueous phase is a water solution of an emulsifier or an emulsifier mixture. In the second step, the organic phase is loaded into a syringe with a needle and quickly injected into the aqueous phase, under continuous mechanical stirring. Oil droplets are, immediately, formed at the injection site. Under solvent diffusion, lipid concentration within these droplets increases, leading to the formation of SLNs stabilized by the emulsifier [67,105]. The third step is the removal of the solvent. Some modifications of the solvent injection method include a micro-channel with a cross-shaped junction [106] and a co-flowing micro-channel system [107]. Some drugs have been loaded into SLNs using the solvent injection method, such as pueraria flavones [108], ondansetron [67], nalbuphine [109], and resveratrol [110].

3.2. Non-Solvent Methods

3.2.1. High-Pressure Homogenization Method

The high-pressure homogenization (HPH) method is used to reduce the size of droplets and solid particles under extreme pressure conditions [111–114]. The HPH method has the advantages of organic solvent-free operation, short production time, and scale-up feasibility [18,115,116]. This method can be classified into hot and cold homogenization. The hot HPH method includes three steps: (i) preparation of a coarse emulsion, (ii) homogenization under high pressure, and (iii) cooling. In the first step, drugs and lipids are melted at a temperature typically 5–10 °C higher than the melting point of solid lipids. An aqueous phase containing emulsifiers is preheated to the same temperature as the lipid melt [117]. Two phases are mixed to produce a hot coarse emulsion. In the second step, the emulsion

is homogenized at the same temperature, using a homogenizer at 500–1500 bars for 3–5 cycles [118]. Under high pressure, the liquid mixtures are pushed through a narrow gap (few microns) of the homogenizer, at a high velocity (~1000 km/h), which results in high shear stresses and cavitational forces, to reduce the size of the droplets [119]. The third step is to cool down the nanoemulsions to form SLNs. This method has been used to prepare SLNs loaded with various drugs, such as celecoxib [120], atorvastatin [121], ketoconazole [122], fluoxetine [123], and ropinirole-dextran sulphate [124]. The hot HPH method is unsuitable for preparing SLNs loaded with heat-sensitive or hydrophilic drugs [52].

The cold HPH includes two steps: (i) preparation of lipid microparticles and (ii) homogenization under high pressure. In the first step, drugs and lipids are mixed at a high temperature, to prepare a homogeneous dispersion of drugs in lipid matrices [18]. The mixture is rapidly cooled down by dry ice or liquid nitrogen and, then, pulverized by a ball mill or a mortar to produce lipid microparticles (with size of ~50–100 μm). In the second step, the lipid microparticles are suspended in a cold aqueous solution containing surfactants. This suspension is, then, homogenized at a cold condition (0–4 °C) over 5–10 cycles at 500 bars [125]. This method is suitable for water-soluble drugs, to prevent drug loss during homogenization [18]. Some methods have been used to minimize drug loss, such as adjustment of the pH of the aqueous phase, in the cases of drugs with pH-dependent solubility [126,127] or preparation of dug-lipid conjugates [128]. The disadvantages of the cold HPH method include large particles and laborious processes [18]. This method has been used successfully to prepare SLNs loaded with toad venom extract [129], calf-thymus DNA and TRPsiRNA [130], and ondansetron [126].

3.2.2. High-Speed Stirring and Ultra-Sonication Methods

High-speed stirring (high-shear homogenization) is a straightforward and cost-effective method to prepare SLNs [52]. This method includes three steps: (i) preparation of water and lipid phases, (ii) homogenization, and (iii) cooling. In the first step, lipids and a drug are dispersed homogeneously at a high temperature (5–10 °C higher than the melting point of solid lipids), whereas an aqueous phase containing surfactants is prepared at the same temperature. In the second step, the two phases are mixed and homogeneously dispersed by a high-shear mixer, to form a hot oil/water emulsion. The third step is to cool down this emulsion to form SLNs [131–133]. This method is, usually, combined with ultra-sonication at the end of the second step, to reduce the size of the emulsion [134,135].

The high-speed stirring and ultra-sonication methods have the advantages of organic solvent-free operation and ease of implementation [136]. However, these methods are involved in high surfactant amounts [24], the exposal of drugs to high temperatures [137], and the contamination of metals originating from sonicator probes [18]. These methods have been successfully used to incorporate various drugs into SLNs, such as linagliptin [138], quercetin and resveratrol [139], amphotericin B [140], buspirone [141], clozapine [142], piribedil [143], primaquine [35], and astaxanthin [144].

3.2.3. Microemulsion Method

The microemulsion method includes two steps: (i) preparation of a microemulsion and (ii) dilution. In the first step, drug and lipids are mixed at a temperature above the lipids' melting point. An aqueous phase containing surfactant is preheated to the same temperature and, then, added to the lipid phase under mild stirring, to form a microemulsion [145,146]. In the second step, the microemulsion is poured into a cold aqueous solution, under mechanical stirring. This process results in the formation of SLNs, due to lipid precipitation [147]. This method is straightforward, reproducible, solvent-free, and feasible to scale up. However, it uses a large amount of surfactant and water, and, thus, a water-removal step is required [148]. The microemulsion method has been used to prepare SLNs loaded with curcumin [147], isotretinoin and α-tocopherol acetate [149], carbamazepine [150], artemether and lumefantrine [151], and cannabidiol [152].

3.2.4. Phase Inversion Temperature (PIT) Method

The PIT method is based on the use of non-ionic polyoxyethylated surfactants that have temperature-dependent properties. The ethoxy groups are highly hydrated at low temperatures, and, thus, the surfactants have a high hydrophilic-lipophilic-balance (HLB) value. At high temperatures, the ethoxy groups are dehydrated, which decreases the HLB value of the surfactants and increases their lipophilicity [153]. PIT is the temperature at which the surfactants have an equal affinity for aqueous and lipid phases [154,155]. The PIT method includes three steps: (i) heating, (ii) cooling, and (iii) the precipitation of lipids. In the first step, drugs, lipids, water, and surfactant are heated to a temperature > PIT, to form a water/oil emulsion. In the second step, the water/oil emulsion is rapidly cooled, to induce the formation of an oil/water nanoemulsion. The heating and cooling process can be carried out for several cycles (e.g., three cycles between 60 and 90 °C) [156,157]. The third step is to cool the oil/water nanoemulsion, to precipitate lipids and form SLNs. The PIT method is solvent-free and requires little energy input. However, the nanoemulsion has low stability. This method was used to prepare SLNs loaded with idebenone [158], metronidazole [159], and loratadine [160].

3.2.5. Membrane Contactor Method

The membrane contactor method requires the use of a specific membrane contactor. This method includes two steps: (i) preparation of a hot nanoemulsion by a membrane contactor and (ii) cooling. In the first step, drugs and lipids are mixed at a temperature above the solid lipids' melting point. The lipid phase is, then, pressed through the pores of a membrane under the same temperature, to produce small lipid droplets. On the other side of the membrane, an aqueous phase containing surfactants flows tangentially to the membrane surface and sweeps the lipid droplets away, to form a hot nanoemulsion. The second step is to cool down the nanoemulsion, to form SLNs [161]. The membrane contactor method has the advantages of scale-up feasibility and particle-size controllability [162,163]. However, its disadvantages include the requirement of a sophisticated system and the high clogging risk of the membrane. This method has been used to prepare SLNs loaded with vitamin E [164].

3.2.6. Coacervation Method

The coacervation method includes three steps: (i) preparation of a micellar solution, (ii) addition of a coacervating solution, and (iii) cooling. This method uses alkaline salts of fatty acids (e.g., sodium behenate and sodium stearate) as lipids. In the first step, lipids and drugs are dispersed in an aqueous solution of a polymeric stabilizer and heated, to form a clear micellar solution of the lipid alkaline salts [165,166]. In the second step, a coacervating solution is added dropwise, to precipitate the lipids. The third step is to cool down the suspension, for complete lipid precipitation [167]. The coacervation method is straightforward and solvent-free. However, it is not suitable for pH-sensitive drugs and only applicable to alkaline-salt lipids [167]. Some drugs have been loaded into SLNs using this method, such as temozolomide [168] and insulin [169].

3.3. Other Methods
3.3.1. Double Emulsion Method

The double emulsion method can be carried out with or without organic solvents. This method includes three steps: (i) preparation of a water/oil emulsion, (ii) preparation of a water/oi/water double emulsion, and (iii) precipitation of lipids. In the first step, an aqueous solution containing drugs and stabilizers is emulsified in a water-immiscible organic phase containing lipids [170,171] or in solvent-free molten lipids [172,173], to form a water/oil emulsion. In the second step, this emulsion is dispersed in an aqueous phase, to form a water/oil/water double emulsion. In the third step, the double emulsion is cooled down, to form SLNs [173]. If an organic solvent is used, it is evaporated to produce SLNs [174]. The double emulsion can be used to incorporate hydrophilic drugs

and biomolecules into SLNs [175,176]. However, it has the disadvantages of high drug loss and large particle size [52,137]. This method has been used to prepare SLNs loaded with some drugs, such as insulin [177], sulforhodamine 101 [173], raloxifene [178], and diethyldithiocarbamate [172].

3.3.2. Supercritical-Fluid-Based Methods

Supercritical fluid (e.g., supercritical CO2) can be used to aid the preparation of SLNs. In the supercritical-assisted-injection method, supercritical CO2 is added in an organic phase, before solvent injection into an aqueous phase. Upon injection, lipids rapidly precipitate to form SLNs [179]. Instead of solvent injection, the organic phase–supercritical CO2 mixture can be expanded through a nozzle, to form SLNs [180]. In the supercritical fluid extraction of emulsion method, an oil/water emulsion and supercritical CO2 are added to an extraction column, in a counter-current manner from the top and bottom, respectively. The supercritical CO2, quickly and entirely, extracts solvents in the oil phase of the emulsion, to form SLNs [181,182]. These supercritical-fluid-based methods can provide uniform-particle-size distributions and high solvent-extraction efficiencies [181,183]. However, these methods require organic solvents and expensive supercritical fluids [182]. Some drugs have been loaded into SLNs by supercritical-fluid-based methods, such as camptothecin [180] and praziquantel [183].

Table 3 summarizes the primary features of each preparation method.

Table 3. Physicochemical characterization of SLNs.

Method	Features	References
Solvent emulsification-evaporation	Suitable for highly thermo-labile drugs, no high temperatures and physical stress Toxic organic solvent removal	[91–95]
Solvent emulsification-diffusion	Suitable for highly thermo-labile drugs, does not require high temperatures and physical stress Toxic organic solvent removal, high water amount, and low SLN concentration	[101–104]
Solvent injection	Simple, fast production, no complicated instruments Toxic organic solvent removal	[67,108–110]
Hot high-pressure homogenization	Organic-solvent-free operation, short production time, and scale-up feasibility Unsuitable for heat-sensitive or hydrophilic drugs	[120–124]
Cold high-pressure homogenization	Suitable for water-soluble drugs to prevent drug loss Large particles and laborious processes	[126,129,130]
High-speed stirring and ultra-sonication	Organic-solvent-free operation and ease of implementation High surfactant amounts, exposal of drugs to high temperatures, and metal contamination	[138–143]
Microemulsion	Simple, reproducible, solvent-free, and feasible to scale up Large amount of surfactant and water	[149–152]
Phase inversion temperature	Based on non-ionic polyoxyethylated surfactants Solvent-free, little energy input Low stability of the nanoemulsion	[158–160]
Membrane contactor	Use of a specific membrane contactor Scale-up feasibility and particle-size controllability Sophisticated system and clogging risk of the membrane	[164]
Coacervation	Use of alkaline salts of fatty acids Straightforward and solvent-free Unsuitable for pH-sensitive drugs, only applicable to alkaline salt lipids	[168,169]
Double emulsion	Preparation of a water/oi/water double emulsion Suitable for hydrophilic drugs High drug loss and large particle size	[172,173,177,178]
Supercritical fluid	Uniform-particle-size distributions and high solvent-extraction efficiencies Use of organic solvents and expensive supercritical fluids	[180,183]

4. Recent Applications of SLNs in Drug Delivery

4.1. Oral Delivery

Following oral administration, drug-loaded SLNs can enter the bloodstream by various mechanisms, including lymphatic absorption [184,185], M cell uptake [140], paracellular transport [186], and receptor-mediated endocytosis and transcytosis [187,188]. Some lipid and surfactant components of SLNs may act as P-glycoprotein inhibitors, to increase drug permeation [189]. SLNs can be coated by some polymers (e.g., by chitosan), to

increase mucoadhesion and, thereby, enhance drug permeation [140]. Various studies have demonstrated that SLNs effectively increase drug solubility, absorption, and oral bioavailability. Musika et al. showed that the encapsulation of lupinifolin into SLNs increased its absorption significantly [91]. Primaquine-loaded SLNs showed a sustained release of drug in vitro and decreased erythrocyte hemolysis ~four–five-fold, compared with the free drug solution [35]. Eplerenone-loaded SLNs increased drug permeation through the rabbit intestine two-fold, compared with the aqueous drug suspension [95]. However, in vivo pharmacokinetics have not been reported in these studies.

Various studies demonstrated that SLNs improved the bioavailability of the drug loaded in animals. In a previous study, non-coated and chitosan-coated amphotericin B-loaded SLNs were developed, which exhibited a 1.92- and 2.36-fold increase in oral bioavailability of amphotericin B, respectively, compared to the marketed Amphotret® in rats. The positive-charge chitosan-coating layer increased penetration of SLNs into the negatively charged mucosal layer, to improve drug absorption [140]. Linagliptin-loaded SLNs increased drug permeability and oral bioavailability by ~three-fold, compared with linagliptin solution in rats [138]. Glargine insulin-loaded SLNs enhanced drug uptake ex vivo and, effectively, reduced blood glucose levels in healthy rats [169]. Pentazocine-loaded SLNs showed higher cellular permeation and a 1.8-fold increase in rat oral bioavailability, compared with a marketed tablet. The SLNs, also, reduced oxidative stress in rats with carrageenan-induced inflammatory pain [170]. Perphenazine-loaded SLNs exhibited 2- and 16-fold higher bioavailability in plasma and the brain, respectively, than the pure drug suspension. This formulation can be an effective system for brain-targeted delivery of perphenazine, to treat schizophrenia [96].

4.2. Parenteral Delivery

Following injection, SLNs may prolong the plasma circulation of drugs and thereby increase drug bioavailability. For example, SLNs loaded with 5-fluorouracil increased bioavailability and half-life ~3.6- and three-fold, respectively, compared with free 5-fluorouracil upon intraperitoneal injection [190]. The SLNs showed better tumor-growth inhibition in a subcutaneous xenograft than free 5-fluorouracil. SLNs loaded with ondansetron exhibited the sustained-release characteristic in rats, following subcutaneous administration [67,126]. The mean residence time and systemic exposure of the SLNs were higher than those of a drug solution. In another study, resveratrol-loaded SLNs increased the cellular uptake of resveratrol, induced mitochondrial dysfunction and apoptosis, and, thereby, showed better efficacy in treating breast cancer in xenograft tumor models than the free resveratrol [110].

4.3. Transdermal Delivery

SLNs are effective in transdermal delivery of both hydrophilic and hydrophobic drugs. SLNs are physiologically safe and able to hydrate the skin [191]. Some studies reported in vitro, ex vivo, or in vivo evaluation of SLNs or SLN gels. For example, tacrolimus-loaded SLNs showed 25–40% skin permeation, while SLN gel reduced skin permeation. However, SLN gels improved skin drug retention, which was suitable for the treatment of atopic dermatitis [192]. In a previous study, quercetin and resveratrol were co-loaded into SLN gel, to improve the drug disposition in the epidermal layers [139]. The permeation of these drugs from the SLN gel demonstrated was higher than that from the conventional gel, with an enhancer index of 1.95 and 1.50, respectively. The SLN gel, also, showed higher maximal drug concentration in the skin and area under the curve (AUC), for both quercetin and resveratrol, in the epidermal and dermal layers, suggesting the potential of SLN gel in treating skin cancer. In another study, SLNs loaded with isotretinoin and α-tocopherol acetate showed sustained drug release for 24 h and potent anti-acne action, without skin irritation [149]. In another study, tacrolimus-loaded thermosensitive SLN gel showed the penetration of SLNs into a deeper layer of skin, compared with a reference product in both ex vivo and in vivo studies [193].

4.4. Intranasal Delivery

SLNs are able to directly deliver drugs to the brain, to enhance the brain bioavailability of drugs [194]. It is attributed to the improvement in drug solubility, drug permeation, stability, and drug retention [143,195]. Levofloxacin and doxycycline co-loaded SLN gel showed effective brain targeting, compared to the drug solution, as indicated by the drug targeting efficiency (DTE%) > 100% and drug transport percentage (DTP%) > 0 [133]. In another study, piribedil-loaded SLN gel and piribedil-loaded SLN suspension exhibited higher brain AUC (four- and 3.1-fold, respectively) than a piribedil suspension [143]. SLNs loaded with sesamol showed DTE% of 764 and DTP% of 86.1, indicating effective brain targeting [99]. Ziprasidone-loaded SLNs were prepared to treat schizophrenia via nose-to-brain delivery [196]. The brain–blood concentration ratios for SLNs were higher than those for ziprasidone solution, at all time points. The SLNs, also, exhibited faster onset and increased brain targeting (DTE% = 476.8).

4.5. Ocular Delivery

SLNs are potential drug delivery systems to treat various ocular diseases. SLNs are compatible with biological membranes and have high mucoadhesiveness. They can improve the drug retention and uptake, reduce clearance by the eye's protective mechanisms, and, thereby, increase drug efficacy [197]. Previously, myriocin-loaded SLNs exhibited effective myriocin levels, in the back of the eye, in rabbits and mice [198]. The SLN ophthalmic formulation demonstrated potential for the treatment of retinitis pigmentosa. In another study, atorvastatin-loaded SLNs showed higher bioavailability in aqueous and vitreous humor than free atorvastatin [121]. The SLNs could be a potential self-administrable eye drop formulation, to treat age-related macular degeneration. In a previous study, epalrestat-loaded-SLNs-laden contact lenses were developed, which showed a high epalrestat accumulation in different ocular tissues, including the retina, in rabbits. Thus, the SLNs-laden contact lenses demonstrated the potential to deliver epalrestat to the posterior side of the eye for the treatment of some diabetic eye diseases, such as cataracts or diabetic retinopathy [199]. Recently, Nair et al. developed clarithromycin-loaded SLNs to improve the treatment of endophthalmitis [200]. The SLNs showed higher ex vivo permeation (~3-fold) and AUC (2.8-fold) in rabbits, compared with a drug solution.

4.6. Pulmonary Delivery

SLNs are used to deliver some drugs by inhalation, which can be employed to treat some lung diseases. For example, in a previous study, a prodrug of isoniazid (isonicotinic acid octylidene-hydrazide) was loaded into SLNs to treat Mycobacterium tuberculosis by inhalation [201]. The SLNs showed increases in intracellular antibiotic efficacy and macrophage uptake. The SLNs, also, exhibited better in vivo antibiotic effects in the lungs of rats. In another study, rapamycin-loaded SLNs were developed to treat extrapulmonary lymphangioleiomyomatosis [202]. The inhaled negatively charged rapamycin-loaded SLNs could, quickly, enter the lymphatic endothelium and, effectively, inhibit lymphangiogenesis. Inhalable SLNs can be employed for systemic or local delivery, to treat non-lung diseases. For example, dimethyl fumarate-loaded SLNs were, recently, prepared for pulmonary delivery, to improve the treatment of multiple sclerosis [203]. Mice with experimental autoimmune encephalomyelitis were treated with the SLNs by inhalation, which showed decreased brain and spinal cord injury as well as inflammation after 21 days of treatment.

4.7. Clinical Application State

Some lipid-based NP formulations have been approved by the United States Food and Drug Administration, including Doxil, DaunoXome, AmBisome, Visudyne, Marqibo, Onivyde, Vyxeos, and Onpattro [5]. They are liposomes and lipid NPs. Besides, lipid-based NPs have been successfully used to deliver mRNA. Two effective mRNA-based vaccines (BioNTech/Pfizer's COMIRNATY (New York, NY, USA) and Moderna's Spikevax (Cambridge, MA, USA)) to fight against the coronavirus disease of 2019 (COVID-19) are

based on lipid NPs [204,205]. Despite the rapid development, they are safe and highly effective. This success demonstrates the potential of lipid-based NPs in the delivery of drugs and biomolecules. To the best of our knowledge, only one SLN formulation (oxiconazole nitrate SLN-loaded gel) entered clinical trials (NCT03823040). Thus, more effort is required to make SLN formulations available for clinical use.

5. Conclusions and Prospects

SLNs have emerged as potential drug delivery systems to enhance the safety, bioavailability, and therapeutic effects of various drugs, during the last two decades. They have been widely investigated for oral, parenteral, transdermal, intranasal, ocular, and pulmonary drug delivery. SLNs will soon be available for clinical use, to improve the management of various diseases with different administration routes.

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