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Solid Lipid Nanoparticles (SLN): Formulation and Fabrication

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ABSTRACT

Solid lipid nanoparticles (SLN) have emerged as a novel drug delivery system and have been utilized for delivering various kinds of drugs since the 1990s. These particles may consist of multiple solid lipids, including glycerides, waxes, and fatty acids, and can be stabilized by a wide range of surfactants. SLN have garnered significant attention from researchers due to its innovative and versatile nature. Moreover, such delivery system has numerous advantages over traditional colloidal carriers, such as liposomes, polymeric nanoparticles, and emulsions. Several research groups have been developing SLN formulations and fabrication techniques based on their intended purpose, and this research number is still increasing globally. Given the vast potential for the development of SLN in the future, coupled with the wide variety of materials and techniques to be considered during the manufacturing process, this paper provides an extensive overview of the general introduction of SLN, their benefits and drawbacks, and the numerous excipients which can be associated with the SLN formulation. Various aspects related to the models of drug incorporation and fabrication methods are also systematically discussed in this review. In addition, an analysis of the factors that impact the stability of the SLN will also be documented to provide further insight for future advancements in SLN research.

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INTRODUCTION

The optimal absorption of drugs necessitates the presence of two key factors: the high solubility of the drug and its ability to permeate the membrane. Over the past few decades, there has been a growing demand for enhanced water solubility and membrane permeability in various newly developed and marketed pharmaceutical products. This has presented a notable obstacle to developing and implementing drug delivery systems (Shah et al., 2014). Numerous challenges, including the toxicity of constituents and limited solubility, which diminishes the effectiveness and bioavailability of drugs, often impede the entry of fully developed drugs into the market (Mishra et al., 2018). Numerous drug delivery systems have been devised to tackle these concerns, with nanoscale delivery emerging as a leading advancement (Duan et al., 2020; Ganesan & Narayanasamy, 2017). The development of colloidal drug carriers, such as liposomes, nanoemulsions, and polymeric particles, has successfully resolved previous challenges (Duong et al., 2020; Plaza-Oliver et al., 2021; Shah et al., 2014). Despite the constraints imposed by individual systems, opportunities exist for enhancing these systems (Shirodkar et al., 2019).

SLN refer to colloidal systems that consist of solid lipids stabilized by hydrophilic surfactants and cosurfactants (Khallaf et al., 2016; Kuo & Hsu, 2017; Mu & Holm, 2018; Pignatello et al., 2018). SLN have attracted significant attention as a replacement for conventional nanocarriers, such as liposomes, emulsions, and polymeric nanoparticles (Hassan et al., 2020; Shirodkar et al., 2019; Wang et al., 2016). Compared to alternative colloidal drugs, SLN are able to achieve controlled drug release while simultaneously improving the physicochemical stability of lipophilic and hydrophilic molecules loaded with drugs. In addition, it is possible to address the obstacles associated with scaling up the production capacity and ensuring the sterility of liposomes and nanopolymer carriers. SLN comprise biocompatible lipids such as triglycerides, cetyl palmitic, alkanoic acid, and various synthetic or natural lipophilic compounds (Pignatello et al., 2018). Thus, SLN have exhibited significant potential as pharmaceutical carriers and are widely considered as prospective contenders for augmenting the absorption and oral bioavailability of specific biocompatible and biodegradable drugs (Hassan et al., 2020; Malvajerd et al., 2019; Maretti et al., 2014; Montoto et al., 2018; Mu & Holm, 2018; Plaza-Oliver et al., 2021; Shah et al., 2014; Tapeinos et al., 2017;

Weber et al., 2014; Yaghmur & Mu, 2021). SLN are now applicable for oral, topical, ophthalmic, and parenteral drug delivery (Khezri et al., 2020; Shah et al., 2014).

The categorization of SLN can be classified based on the type of system and the production method (Kathe et al., 2014). The primary constituent of SLN is a solid lipid that exhibits a solid state at ambient temperature. Variations in lipid content significantly impact the drug loading capacity and release profile of SLN. Apart from the production method and the molecular attributes of the active constituents, lipids can also affect the morphological and dimensional characteristics of SLN. The utilization of the SLN system presents a promising approach for enhancing drug compatibility with the lipid matrix through the conjugation of active therapeutic agents with lipid excipients (Kuo & Hsu, 2017; Mu & Holm, 2018).

This article provides an overview of the characteristics of SLN, with particular emphasis on the different excipients used in the formulation, the various manufacturing methods employed, and the potential impact of fabrication techniques on drug incorporation models within SLN. This review may be beneficial for the forthcoming design and development of SLN intended for particular applications associated with the medication's intended use.

SLN Overview

The initial iteration of SLN was formulated during the 1990s. SLN are potentially advantageous colloidal system that consist of lipids that are physiologically tolerated and have a melting point typically exceeding 40°C (to ensure solidification at body temperature). These lipids form a solid core enveloped by non-toxic surfactants and, in certain circumstances, cosurfactants (Figure 1), which stabilize the nanoparticles in dispersions (Bayón-Cordero et al., 2019; Rai & Alves Dos Santos, 2017). SLN have a size range that spans from 50 to 1000 nm. The objective behind the development of SLN was to establish a biocompatible platform that could effectively incorporate multiple pharmaceutical agents with varying chemical properties while simultaneously reducing drug degradation during the delivery process and serving as a controlled drug release mechanism (Kathe et al., 2014; Mirchandani et al., 2021; Shirodkar et al., 2019).

SLN have been widely used to enhance the solubility and bioavailability of various drugs (Mirchandani et al., 2021; Salah et al., 2020). Such delivery systems exhibit enhanced permeability due to their small size, in the range of 50-1000 nm, allowing them to overcome physiological barriers effectively. In terms of oral administration, the reduction in particle size is associated with a marked rise in the surface area of insoluble drug particles. This, in turn, leads to improved absorption through the monolayer cells of the gastrointestinal tract. In addition to their ability to be more readily absorbed by cells, SLN have been shown to enhance lymphatic delivery via microfold cells (M cells). Improved lymphatic transportation leads to a reduction in initial drug metabolism, thereby resulting in an improvement in drug bioavailability. The primary obstacle in the dermal system for topical administration is the impermeability of the *stratum corneum* to numerous drugs in adequate quantities. The diminutive size of particles also enables SLN to augment the bioavailability of drugs that permeate through viable skin. Due to their proximity to the *stratum corneum*, the quantity of the enclosed drug that reaches the intended site of action is amplified (Kumar & Randhawa, 2013).

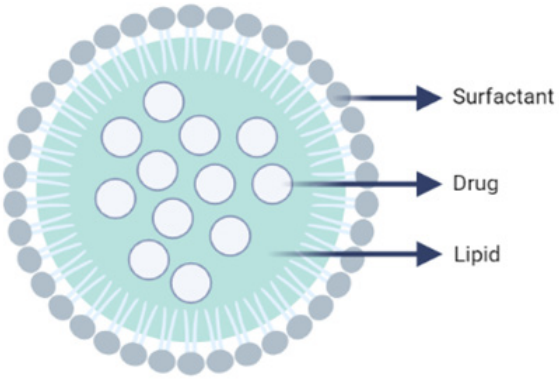

Figure 1. The structure of solid lipid nanoparticles (SLN) illustrates the presence of a surfactant, drug molecules, and a solid lipid matrix

The drug is dissolved in the lipid phase through a lipid core employed by SLN. The surface area of nanoparticles facilitates the release of drugs from the system upon exposure to an aqueous medium. With the utilization of SLN to improve tissue and cellular permeation, the targeted delivery of drug molecules and their therapeutic effectiveness can be augmented (Shirodkar et al., 2019).

The Purpose of Developing SLN

Nanoscale drug delivery techniques have been developed to tackle the concerns listed below (Bagul, 2018):

- The administration of drugs through oral delivery is associated with limited absorption, rapid metabolism, and excretion, ultimately leading to low or fluctuating drug concentrations.
- The inadequate solubility of drugs, which encompasses administering aqueous drug solutions through intravenous injections, poses a challenge.
- The considerable level of toxicity exhibited by certain pharmaceutical drugs. The conversion of drugs into SLN can enhance their targeted delivery and mitigate the potential for toxicity or adverse effects.

The assertion has been made that SLN possess the advantages of various colloidal carriers while circumventing their disadvantages. The purported benefits and disadvantages encompassed are (Bagul, 2018; Bayón-Cordero et al., 2019; Garud et al., 2012; Ghasemiyeh & Mohammadi-Samani, 2018; Mirchandani et al., 2021; Patidar et al., 2010; Peres et al., 2016; Salah et al., 2020; Yadav et al., 2013):

Advantages of SLN

- It shows the potency of drug targeting and controlled drug release.
- It is feasible to improve drug stability.
- The drug loading capacity of this carrier is superior to that of other carriers.
- It has the ability to transport both hydrophilic and lipophilic drug molecules.
- It exhibits exceptional biocompatibility and biodegradability.
- It is possible to increase the scale of production.
- It can increase the bioavailability of adsorbed active substances.
- It is possible to sterilize or lyophilize the system.
- The production cost is relatively lower than the other nanoparticles production.
- The production process does not yield any waste that poses a threat to human health or the environment.

Table 1. Lipids frequently used in SLN formulations (Geszke-Moritz & Moritz, 2016; Kumar et al., 2018)

Class	Example
Glycerol esters	Glyceryl trimyristate
	Glyceryl tristearate
	Glyceryl tripalmitate
	Glyceryl trioleate
	Glyceryl tricaprate
	Glyceryl monostearate
	Glyceryl distearate
	Glyceryl behenate
	Glyceryl palmitostearate
	Soybean oil
	Peanut oil
Waxes	Cetyl palmitate
	Beeswax
	Carnauba wax
Fatty acids	Myristic acid
	Stearic acid
	Palmitic acid
	Tetradecanoic acid
	Arachidic acid

Table 2. Some of the most frequently used surfactants according to their ionic characteristics (Duan et al., 2020; Geszke-Moritz & Moritz, 2016; Gordillo-Galeano & Mora-Huertas, 2018; Kathe et al., 2014)

Class	Example
No ionics	Polyoxyethylene (20) sorbitan monolaurate (Polysorbate 20, Tween® 20) Polyoxyethylene (20) sorbitan monostearate (Polysorbate 60, Tween® 60) Polyoxyethylene (80) sorbitan monooleate (Polysorbate 80, Tween® 80) Poloxamer® 188 Poloxamer® 407 Poloxamer® 182 Sorbitan monooleate
Anionics	Sodium lauryl sulfate Sodium glycolate
Cationics	1,2-dioleoyl-3-trimethylammonium-propane (DOTAP) Cetrimonium bromide
Amphoterics	Soybean lecithin (Lipoid® S75, Lipoid® S100) Egg lecithin (Lipoid® E) Phosphatidylcholine (Epikuron® 170, Epikuron® 200)
Co-surfactants	Propionic acid Butyric acid Polyvinyl alcohol (PVA) 1-Butanol Propylene glycol Polyethylene glycol Sodium taurocholate Glycerol

Disadvantages of SLN

- The particle size may increase during storage.
- The polymeric transition during storage is feasible to result in drug repulsion.
- It has a low loading capacity for hydrophilic drugs.

SLN Formulation

SLN formulation basically consists of following components, those are solid lipids, surfactants, water, and active ingredients. The used materials are generally recognized as safe (GRAS) starting materials (Gordillo-Galeano & Mora-Huertas, 2018).

Lipid

Lipids constitute the main component of the matrix that plays a crucial role in determining the nature of the colloidal system that utilizes them. The majority of commonly used lipids, about 70%, come from the categories of free fatty acids, fatty alcohols, and glycerol esters. Examples of such lipids include stearic acid, glyceryl behenate, tripalmitin, cetyl palmitate, tristearin, and glyceryl monostearate (Gordillo-Galeano & Mora-Huertas, 2018). The lipids that are listed in Table 1 are commonly employed in the manufacture of SLN.

Surfactant

Surfactants in SLN formulations (as presented in Table 2) are commonly used to reduce the interfacial energy between the aqueous and lipid phases during particle preparation. Surfactants have a tendency to make aggregation at the interface and establish a coating around the particles, thereby preserving the physical stability of the dispersion system during storage (Gordillo-Galeano & Mora-Huertas, 2018). The provision of charge stabilization to nanoparticles and preventing their aggregation can be attributed to the presence of charged surfactants. One study investigated by Kathe et al. (2014) reported the efficacy of surfactants in reducing aggregation caused by the addition of electrolytes. Their research demonstrated that stearic repulsion constitutes an effective mechanism for stabilizing SLN in suspension. A combination of surfactants generally exhibits enhanced stability (Kathe et al., 2014).

It is crucial to bear in mind the toxicity of the surfactant. It is not feasible to employ all surfactants for every type of SLN. The formulation of SLN typically involves the utilization of anionic and nonionic surfactants, with occasional employment of cationic surfactants. It is imperative to take into account of concerning the surfactants employed in drug formulations intended for oral, parenteral, and ocular administration. It is recommended to employ nonionic surfactants, such as poloxamer 188 and lecithin, for the aforementioned delivery routes (Kathe et al., 2014; Kumar & Randhawa, 2013; Talegaonkar & Bhattacharyya, 2019). The steric stabilization effect of nonionic surfactants has been used to prevent the aggregation of nanoparticles. The surfactants of ionic nature (e.g., sodium deoxycholate) increase the nanoparticles' surface charge, causing electrostatic repulsion and, thus, improving the physical stability (Souto et al., 2020). Cationic lipid nanoparticle preparations have utilized quaternary ammonium surfactants, whereas in most studies, soy or egg lecithin have been the preferred amphoteric stabilizing agents. Moreover, polyvinyl alcohol (PVA) is commonly chosen as a substitute stabilizing agent (Gordillo-Galeano & Mora-Huertas, 2018).

Additional components

Cryoprotectants like glucose, fructose, and sorbitol are employed in lyophilized SLN formulations. Moreover, chitosan serves as a coating agent, while parabens are utilized as preservative agents (Gordillo-Galeano & Mora-Huertas, 2018; Mishra et al., 2018).

Active molecules embedded in SLN

Lipid systems have been utilized to incorporate multiple active molecules, either independently or as a component of a codelivery approach. Several drugs are potential candidates for nanoparticle integration since their hydrophobic characteristics and poor water solubility. Those drugs respectively categorized as anesthetics, antipyretics, antibiotics, antiparasitics, analgesics, antiretrovirals, anticancer, and antihypertensive agents. Additionally, there have been reports on investigations regarding integrating nucleic acids and peptides into lipid particles (Gordillo-Galeano & Mora-Huertas, 2018).

Type of SLN and Models of Drug Incorporation Into SLN

The structural configuration of drugs incorporation into SLN depends on the chemical composition of the formula, the methodology employed in the manufacturing process, and the temperature at which the manufacturing process is carried out (Shirodkar et al., 2019). There are three types of drug incorporation into SLN, as presented in Figure 2:

SLN Type 1: Homogenous matrix model

SLN type 1, a model of solid solutions, is categorized as a homogeneous matrix model due to the molecular dispersion of the active ingredient within the lipid core or its existence as amorphous groups. The model, as mentioned earlier, is derived through the utilization of high-pressure homogenization (HPH) or cold homogenization methodologies conducted at temperatures surpassing the melting point of lipids (Ganesan & Narayanasamy, 2017; Shirodkar et al., 2019). The pharmaceutical agent is planned to be distributed at a molecular level, devoid of surfactants or solubility-enhancing agents, through a cold

Figure 2. Illustration of drug incorporation model of SLN: homogenous matrix of solid solution (left); drug-enriched shell (middle); and drug-enriched core (right).

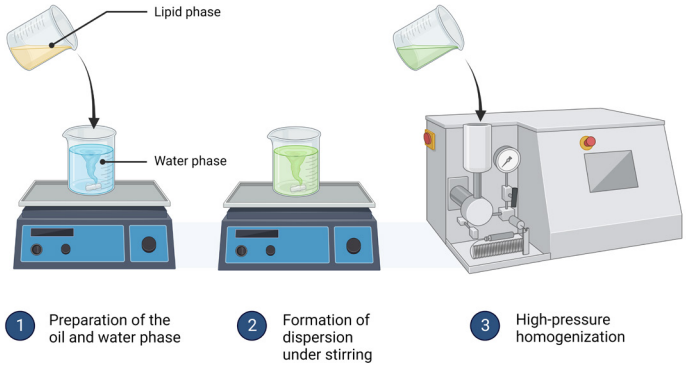

Figure 3. Preparation of SLN using high-pressure homogenization techniques

homogenization methodology (Dolatabadi et al., 2015). The pharmaceutical compound interacts significantly with the lipid component (Üner & Yener, 2007).

SLN Type 2: Drug-enriched shell model

The SLN type 2 is synthesized through a homogenization process that involves heat induction. This model asserts that the attainment of the lipid's recrystallization temperature results in forming a solid lipid core. Upon the reduction of the dispersion temperature, the o/w nanoemulsion experiences lipid precipitation, resulting in an elevation of drug concentration within the liquid lipid. The drug tends to concentrate within the outer shell of the solid lipid nanoparticle that remains in a liquid state. As a result, solidifying the outer shell will result in a significant amount of the drug being contained within it (Üner & Yener, 2007). The previous development tend to induce burst drug release causing dose dumping (Shirodkar et al., 2019). It was commonly acquired under low lipid concentrations in liquids, rendering them inadequate for sustained drug release (Ganesan & Narayanasamy, 2017).

SLN Type 3: Drug-enriched core model

In SLN type 3, drug precipitation takes place prior to the re-solidification of lipids. This phenomenon occurred when the drug concentration in the lipids approaching the point of solubility saturation, then a high drug concentration incorporated into the lipid. Upon cooling, the liquid lipid in the nanoemulsion reaches a state of supersaturation concerning the drug. Therefore, lipid solidification takes place after precipitation. The subsequent drop in temperature causes the lipid to recrystallize near the core, which has been enriched with drug molecules and now resembles a membrane structure (Shirodkar et al., 2019). This particular model is generally appropriate for drugs that require an extended-release profile within a specific time frame (Ganesan & Narayanasamy, 2017).

Preparation Method for Fabrication SLN

High-Pressure Homogenization (HPH)

The primary technique employed for producing SLN is high-pressure homogenization (Ganesan & Narayanasamy, 2017). The advantages of this technique are brevity, scalability, solvent-free nature, and compatibility with multiple high-pressure homogenization equipment manufacturers at a reasonable expense (Beloqui et al., 2016; Naseri et al., 2015). Nevertheless, this methodology necessitates a substantial energy input and can potentially elevate the specimen's temperature, rendering it inappropriate for substances that are susceptible to heat (Ganesan & Narayanasamy, 2017). High-pressure homogenization

can be conducted under varying temperature conditions, including high and low temperatures, commonly referred to as hot and cold homogenization (Figure 3). Both techniques require the dissolution or dispersion condition at temperatures roughly 5°C higher than its melting point (Souto et al., 2020).

Microemulsion technique

This technique involves liquefying the lipid and raising its temperature to match the aqueous phase containing the surfactant. Microemulsions can be generated through the addition of an aqueous solution to the lipid phase under a gentle stirring (Figure 4). The production of SLN can be achieved by dispersing the microemulsion in cold water (2-10°C) under stirring conditions. Subsequently, the system undergoes a rinsing process utilizing distilled water and filtration to eliminate any sizable particles. Additionally, the system may undergo lyophilization to eliminate any surplus water. Nonetheless, this approach exhibits certain drawbacks, such as the necessity for surfactants in relatively elevated concentrations, the potential for dilution upon the introduction of the microemulsion into the water, and a reduced concentration of particles that are suspended (del Pozo-Rodríguez et al., 2013; Souto et al., 2020).

Emulsification solvent-diffusion

This method commonly utilizes organic solvents that exhibit partial miscibility with water, including butyl lactate, methyl acetate, ethyl acetate, isopropyl acetate, and benzyl alcohol. The initial thermodynamic equilibrium of the two phases is achieved by co-saturating the organic solvent and water. An o/w emulsion can be generated through the dissolution of the lipid and drug in a saturated aqueous solvent, followed by emulsification into the phase with agitation (Figure 5). The emulsion is diluted with water at a ratio ranging from 1:5 to 1:10 to facilitate the diffusion of the solvent into the external phase. Upon the evaporation of the solvent, spontaneous formation of SLN occurs through lipid deposition. Subsequently, the solvent is eliminated through lyophilization or vacuum distillation. The present method applies to both hydrophilic and lipophilic pharmaceutical compounds and does not necessitate elevated temperatures (Duong et al., 2020).

Emulsification solvent-evaporation

The present technique involves the dissolution of the lipid matrix in an organic solvent immiscible with water, followed by its emulsification through the aqueous phase. The solvent was evaporated at reduced pressure,

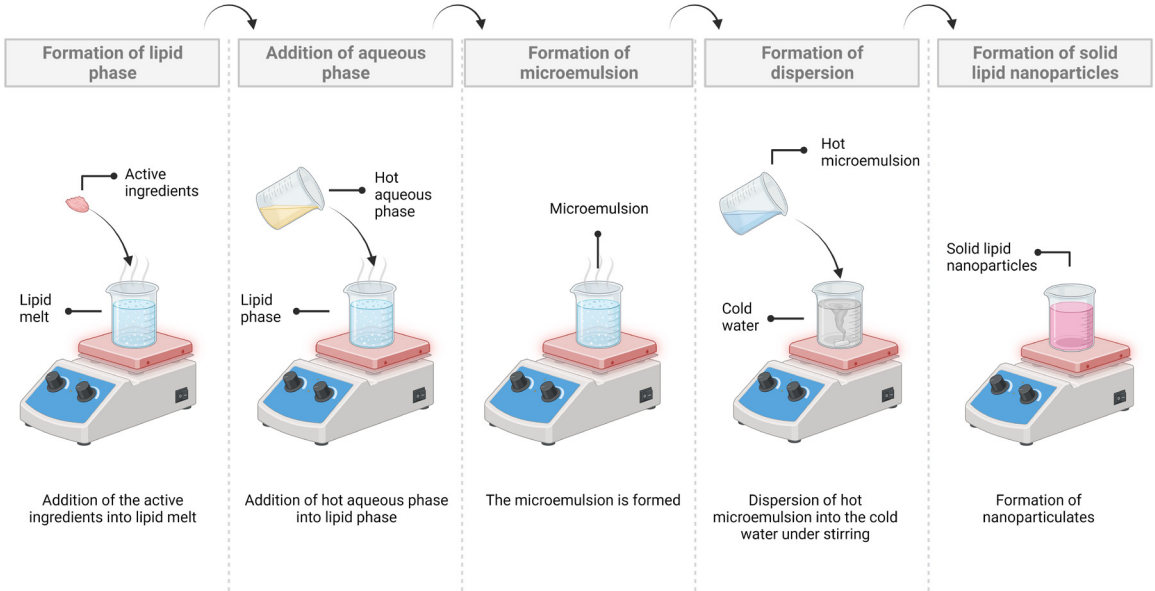

Figure 4. Microemulsion technique for preparation of SLN

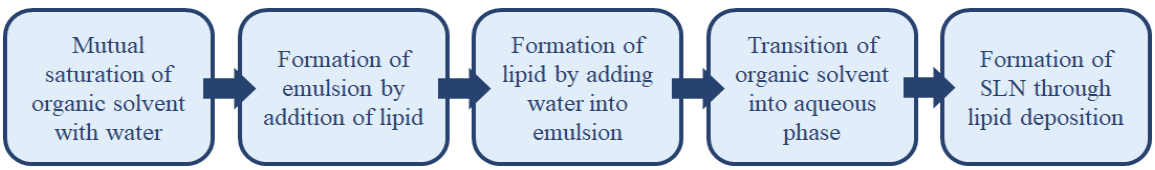

Figure 5. Emulsification solvent-diffusion technique for the manufacturing of SLN

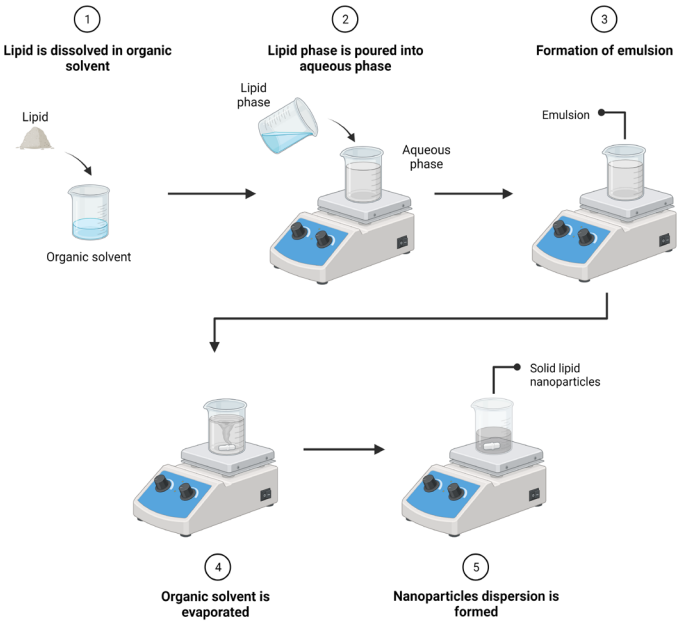

Figure 6. Emulsification solvent-evaporation technique for the fabrication of SLN

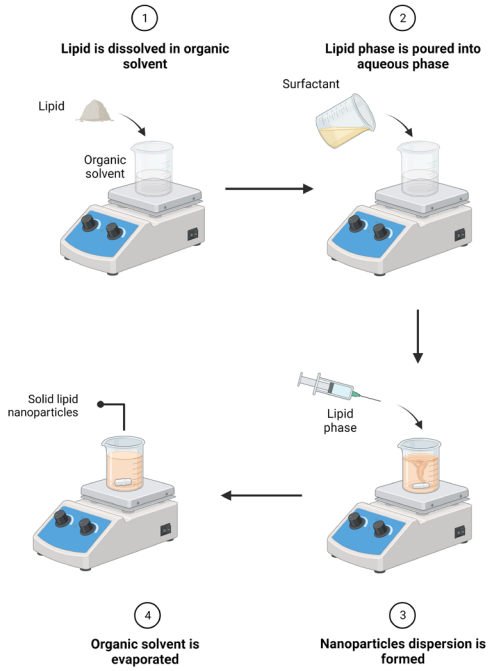

Figure 7. Solvent injection method for the preparation of SLN

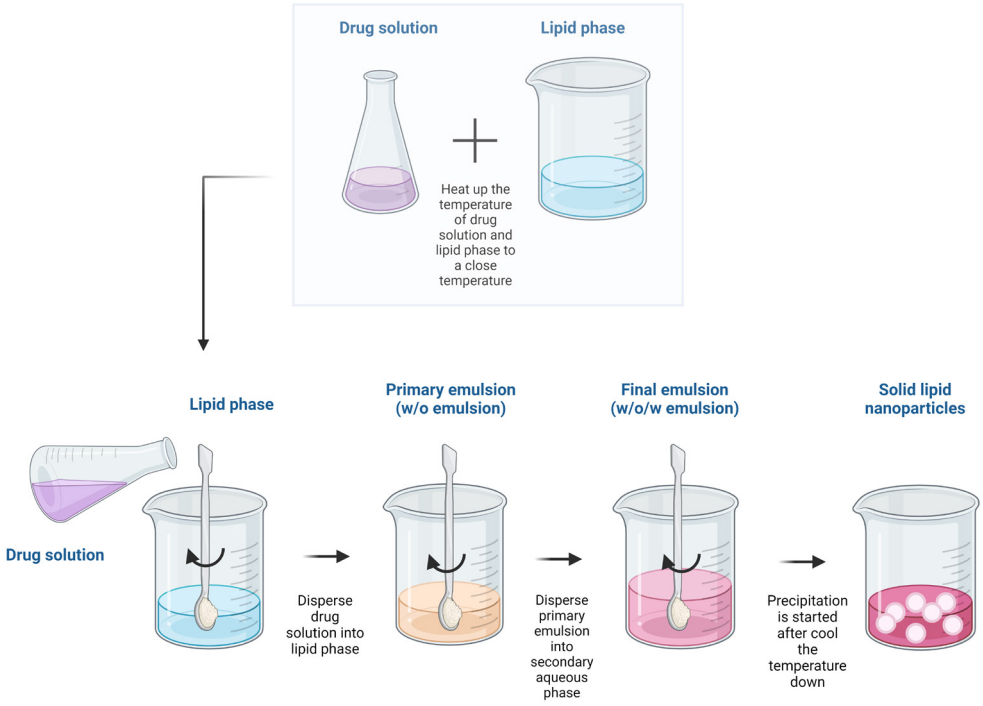

Figure 8. Schematic presentation of the w/o/w double emulsion technique for the fabrication of SLN

precipitating lipids in the aqueous medium and, consequently, the formation of nanoparticle dispersions (Figure 6). The method yields nanoparticles with a size range of 100 nm or less, contingent upon the constituents employed. However, the main drawback of this approach is the use of organic solvents, which can lead to harmful residues in the sample (Souto et al., 2020).

Solvent injection

The technique entails the dissolution of the lipid matrix in an organic solvent, followed by prompt injection of the resultant solution into an aqueous phase that comprises surfactants (Figure 7). The technique for acquiring sentinel lymph nodes is uncomplicated, adaptable, and productive. Nevertheless, utilizing organic solvents may lead to losses (Souto et al., 2020).

Water/oil/water double emulsion

The present methodology involves the preparation of SLN that incorporates hydrophilic pharmaceutical agents and diverse biomolecules such as peptides and insulin. As presented in Figure 8, the production of SLN was carried out by utilizing the solvent-in-water emulsion-diffusion method from a w/o/w double emulsion. The outcome of this phenomenon is the dispersion of organic solvents into the aqueous medium and the subsequent formation of SLN through precipitation. The efficacy of this approach is contingent upon the characteristics of the solvent and the interplay between the hydrophilic drug and both the solvent and excipients (Duan et al., 2020).

Stability of SLN

The stability SLN is influenced by various factors, such as the lipid matrix materials, surfactants, and storage conditions. It is essential to consider the optimal concentrations of surfactants, temperature, and light to ensure solid lipid nanoparticles' long-term stability (SLN). These factors should also be considered during the storage and processing of SLN (Kumar & Randhawa, 2013).

During storage, lipids undergo a polymorphic transition from a less stable to a more stable crystal state. The polymorphic modification of lipids is contingent upon the chemical composition of mentioned lipids. Triglycerides exhibit the presence of crystal modifications, such as α (alpha), β′ (beta prime), and β (beta). The lipids undergo a phase transition from the relatively unstable α modification to the more stable β modification upon storage after rapid cooling during the production of solid lipid nanoparticles (SLN) (Kumar & Randhawa, 2013). The kinetics of polymorphic transitions in triglycerides are significantly influenced by their chain length, with longer-chain triglycerides exhibiting a slower crystallization process than their shorter-chain

counterparts. SLN may exhibit gelation, with their propensity to gel being significantly influenced by β′ alteration resulting from factors such as light exposure, temperature, and shear stress. Moreover, the dimensions of the particles may fluctuate due to light exposure (Duan et al., 2020).

An additional significant instability mechanism is phase separation, which arises from the clustering of particles that may manifest in either a reversible form (flocculation) or an irreversible form (coalescence, sedimentation). Additionally, the occurrence of gelling phenomenon may transpire during the period of storage. To address these issues, appropriate surfactants may be employed. These surfactants can enhance the stability of SLN suspension through electrostatic repulsion, thereby augmenting the zeta potential (via anionic or cationic surfactants), or they can serve as steric stabilizers (*via* nonionic surfactants). It is noteworthy that surface stabilization, specifically the electrostatic stabilization and zeta potential, are highly susceptible to pH variations and electrolytes in the external phase. These factors can lead to the destabilization of the suspension (Battaglia & Gallarate, 2012).

The incorporation of electrolytes into SLN dispersion results in gel formation and augmentation in particle dimensions. Different sodium, calcium, and aluminum chloride concentrations were introduced to a compritol® formulation, destabilizing it. An evident trend of destabilization was noted as the concentration of electrolyte and the valence of cation increased, with Al^{3+} demonstrating the highest destabilizing effect, followed by Ca^{2+} and Na^{+}. An increased surfactant concentration can result in a more compact coverage at the interface, potentially affecting the crystal structure and stability of solid lipid nanoparticles (SLN) through surface-mediated crystal growth (Kumar & Randhawa, 2013).

CONCLUSION

SLN systems are designed to address various pharmaceutical aspects, such as enhancing bioavailability, controlling drug release, and optimizing stability. The properties of active and supplementary ingredients play a critical role in the formulation process determining the type of SLN. Despite their limitations, using SLN remains a viable option in nanotechnology to modify hydrophobic and hydrophilic drugs since SLN can be manufactured through a straightforward and purposeful process using materials that are known to be safe. Thus, those advantages indicate that SLN is a promising approach for drug delivery.

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CONFLICT OF INTEREST

The authors do not have any conflicts of interest to disclose.

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