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Preparation, Characterization, and Applications of Solid Lipid Nanoparticles: A Theoretical Review

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Abstract

Scientists have shown significant interest in solid lipid nanoparticles (SLNP) as carriers for drug delivery in recent years. This interest stems from their unique characteristics, including biocompatibility, biodegradability, cost-effectiveness, and appropriate production processes. The SLNP is an emulsion of lipids in water, emphasizing the lipid being in a solid state at room and body temperature. The formula for preparing the SLNP is primarily composed of solid lipids and surfactants. We can get three models depending on the site and the behaviors of drug distribution in the solid particles. The distribution of drugs can occur within the lipid matrix, in the core of lipid particles, or on the particle shells. This review provided a basic introduction to SLNP. Additionally, this paper focused on the main preparation, characterization methods, and different applications of SLNP. This paper covers various preparation methods such as microemulsion, double emulsion, high-pressure homogenization, solvent emulsification evaporation, solvent emulsification diffusion, supercritical fluid extraction, and solvent injection. The characterization methods are carried out by dynamic light scattering, scanning electron microscopy, differential scanning calorimetry, Fourier transform infrared spectroscopy and powder X-ray diffraction. The applications of SLNP are generally topical, parenteral, pulmonary, oral, and ocular routes of administration.

Keywords: Nanotechnology, SLNP, Solubility, Nanoparticles, Nanoemulsion

1 Solid Lipid Nanoparticles

Scientists have shown significant interest in solid lipid nanoparticles (SLNP) as carriers for drug delivery in recent years. This interest stems from their unique characteristics, including biocompatibility, biodegradability, and cost-effectiveness as well as their appropriate production processes[1]. The SLNP was first defined as an alternative carrier system in the 1990s to overcome the limitations of the other lipid-basic nanocarrier systems. The SLNP is an emulsion of lipids in water, with emphasis on the lipid being in a solid state at room and body temperature [2]. The researchers at Novel Drug Delivery Systems (NDDS) have considered that the probability of controlling drug release is higher when dealing with a solid lipid matrix in comparison to liquid lipid [3]. The composition of the formula for the preparation of the SLNP contains solid lipids like cholesterol, glycerol monostearate, triglycerides, and steroids. The formula also includes surfactants such as polysorbates and phospholipids, along with various types of poloxamers [4], [5], [6], [7]. These main excipients will give the SLNP structure as shown in Fig. 1. Selecting the correct surfactant is critical because it heavily relies on other formulas, maintains stability, and influences the differentiation drug's behavior when the lipid matrix changes. Mostly, the particle size will decrease with the increase in emulsifier concentration, while the particle size will increase with the increase in lipid quantity in the formula [8], [9].

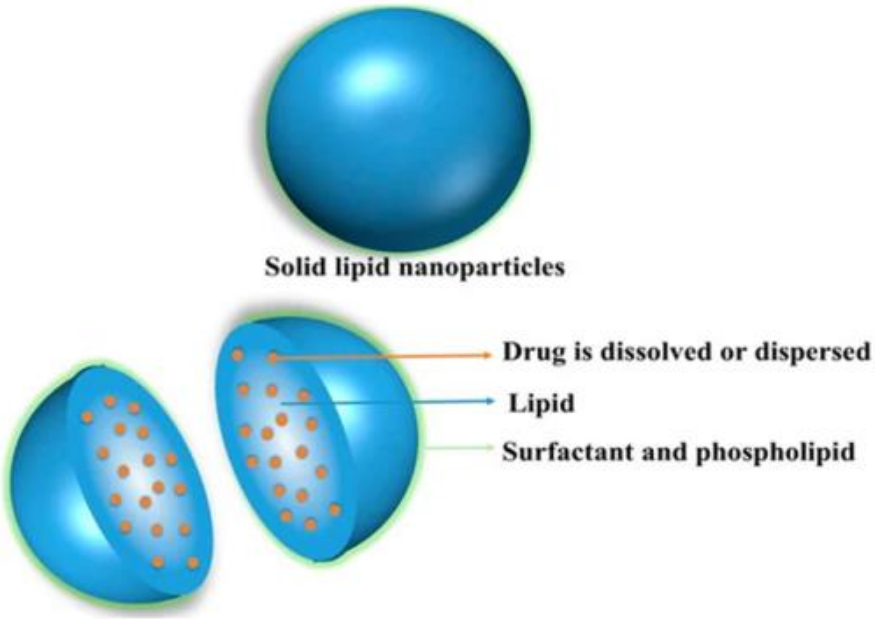


Figure 1: Basic structure of SLNP [10]

Depending on the site and the behaviors of drug distribution in the solid particle, we can get three models as shown in Fig. 2. The distribution of drugs can occur within the lipid matrix [11], in the core of lipid particles [12], or on the particle shells[13],[14].

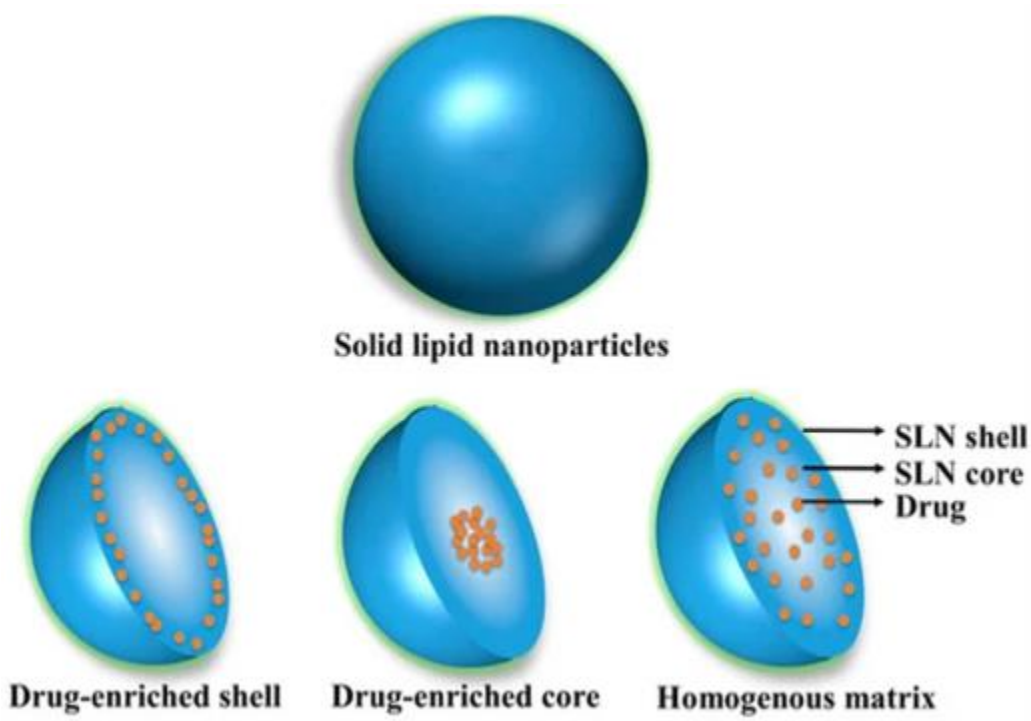


Figure 2: Different drug distribution models within the SLNP [10]

1.1Advantages of The Solid Lipid Nanoparticles

SLNPs offer numerous advantages. Their ability to encapsulate both hydrophilic and lipophilic drugs is one key benefit.

Solubility and dissolution enhancements with SLNP ultimately lead to improved bioavailability. Moreover, the reduction of frequent doses with sustained therapeutic effects and targeting based on SLNPs' ability to reach facilities effectively controlled the release of drugs. Because of the lipid's compatibility with the human body, self-biodegradability, and avoidance of waste product accumulation, SLNPs have a lower risk of toxicity and adverse reactions. Additionally, SLNPs can enhance drug stability by protecting them from degradation, oxidation, and enzymatic degradation. On the other hand, preparation methods are considered to be cost-effective for large-scale productions.[3].

1.2 Preparation of Solid Lipid Nanoparticles

1.2.1 Microemulsion Method

The SLNP will be prepared in two phases. The first phase will be prepared by dissolving the drug in the melted lipid, which is heated first to above the melting point of the lipid. The second phase will be prepared by dissolving the surfactant in the aqueous medium and

heating it to the lipid melting point. Then the aqueous phase will add to the oil phase to form a stable microemulsion. This microemulsion then will disperse on cold water (2–10 °C). This step will lead to the solidification of nano lipids. That will disperse in the cooled water to form solid lipid nanoparticles. This method has several advantages, including suitability for large-scale production, solvent-free nature, and being considered an easy method. The disadvantages of this method include the high-water usage and the high surfactant concentration required. Freeze-drying can remove the water [15].

1.2.2 Double Emulsion Method

This method is suitable for loading hydrophilic drugs into the SLNs. By dissolving the drug in the aqueous phase in one container and then adding this phase to the melting oil (the oil phase), we produce a water/oil emulsion. The emulsion will then break up in the secondary aqueous phase with the help of the surfactant, making a water/oil/water double emulsion. The SLNP will then settle out by cooling and precipitating [16]. Figure 3 describes the steps for this method.

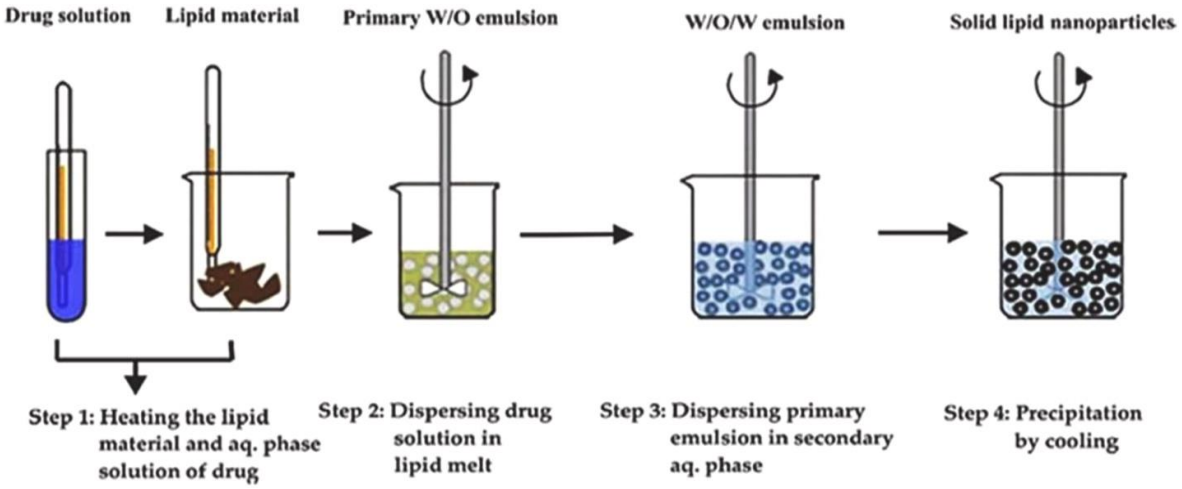


Figure 3: Double emulsion method for SLNP preparation[17].

1.2.3 High-Pressure Homogenization

By heating the lipid and drug above the lipid melting point by 5–10 °C, the first step will be considered. Depending on the second step in this method, we can get two sub-methods [18][19]:

a. The hot method involves dispersion of the lipid phase (the result of the first step) at the melting point temperature of the lipid in the aqueous phase with stirring (shacking at high speed), then by high pressure (100–1000 bar) homogenous colloidal emulsion will be produced. In this step, the particle size reduction will depend on the desired particle size. By cooling the colloidal emulsion, the SLNs will be produced[20].

b. The cool method entails rapidly cooling the lipid phase (the result of the first step) with dry ice or nitrogen in a liquid state, followed by milling the product into fine powder (microparticles). In the next step, this fine powder will disperse into the aqueous phase in

the presence of the surfactant. The SLNP will form by homogenizing this dispersion at high pressure (500 bar), making this method suitable for heat-sensitive drugs[21].

1.2.4 Solvent Emulsification Evaporation Method

This method used a water-miscible solvent to prepare the SLNP-like chloroform. The formula will be prepared by dissolving the lipid and the drug in the solvent and then dispersing them into the aqueous phase to form dispersed nanoparticles. After the organic solvent evaporates, the SLNP precipitate will result [22], [23].

1.2.5 Solvent Emulsification Diffusion Method

This method used a solvent that was partially miscible with water, like ethyl acetate. The first step in preparation involves saturating the two phases together to achieve thermodynamic equilibrium for both phases. The drug and lipid will dissolve in the water-saturated solvent phase, and the resulting solution will disperse in the solvent-saturated water phase, which also contains the emulsifier, creating an oil/water emulsion. Next, a dilution process will add distal water to the emulsion, allowing the solvent to diffuse into the aqueous phase. You can discard the solvent by freeze-drying or vacuum distillation [24], [25].

1.2.6 Supercritical Fluid Extraction

The process begins with the lipid phase preparation, which involves melting the lipid and adding the drug. Next, the lipid phase will add to the aqueous phase at the lipid melting point to form an emulsion, which we then homogenize to form the colloidal emulsion. The next step involves extracting the colloidal emulsion through supercritical fluid extraction, which uses carbon dioxide as an example to extract SLNs. This method is characterized by high particle size homogeneity [26], [27].

1.2.7 Solvent Injection Method

To form the organic phase, the lipid and drug dissolve in a water-miscible solvent or a mixture of solvents. The aqueous phase is prepared by dissolving the emulsifier in water. The needle will then quietly inject the organic phase into the aqueous phase. As the organic solvent permeates the aqueous phase, it leaves behind nanoparticles [28], [29].

Table 1 provides examples of various methods used in SLNP perorations for many drugs.

Table 1 : Examples of various methods used in SLNP preparation for many drugs.

Drugs example	Method of preparation	Reference
Cefixime	Microemulsion technique	[30]
Meropenem	Hot homogenization and ultrasonication method	[31]

Lutein	ultrasonic assisted emulsion evaporation-low temperature method	[32]
Ceftriaxone	Double emulsion method	[33]
Cefepime	Microemulsion-ultrasonication method	[34]
Curcumin	High-pressure homogenization	[35]
Amphotericin B	High-pressure homogenization	[36]

1.3 Main excipients of Solid lipid Nanoparticles

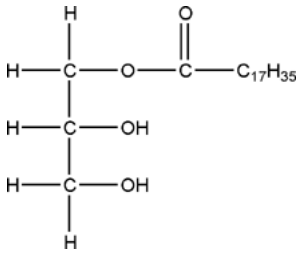
1.3.1 Lipids

Lipids are the primary components of lipid nanoparticles and, as a result, make up the main part of the structure, and play a significant role in determining the characteristics of these colloidal systems. Typically, free fatty acids, fatty alcohols, glycerol esters, and waxes are used. Additionally, it includes phospholipids, glycolipids, and sphingolipids. Furthermore, some lipids, such as glyceryl monostearate, already have surfactant properties that promote the production of particles[37].

Glycerol Monostearate is an example of lipids

Table 2: Glycerol monostearate physicochemical properties [38].

Chemical name	Octadecanoic acid monoester with 1,2,3, -propanetriol
CAS registry number	31566-31-1
Molecular weight	358.6
Empirical formula	$C_{12}H_{24}O_4$
Specific gravity	0.92

solubility	Soluble in hot ethanol, chloroform, fixed oil, ether, hot acetone, and mineral oils. Insoluble in water but can disperse in aqueous phase
Melting point	Equal or more than 55 C
Chemical structure	

1.3.2 Surfactants

Surfactant agents serve as key components in the preparation of SLNP. During the particle preparation process, these agents can lower the surface tension energy between the aqueous and lipid phases by accumulating at the binding interface and forming a protective layer around the SLNP particles. This will improve the dispersion's physical stability. Polysorbate 80 (Tween 80) is an example of a widely used surfactant in SLNP preparations[37].

1.3.2.1 Tween 80 as an example of surfactants

Tweens (polysorbates) are non-ionic surfactants used in different applications of pharmaceutical formulations, like surfactants for increasing poor drug solubility and stability enhancement as stabilizers. The chemical structure of tween is formed by a sorbitan ring that is attached to four different chains of ethylene oxide. One of these chains, or maybe more than one, is esterified with different chain lengths at different degrees of saturation of fatty acid [39] . The United States Food and Drug Administration (FDA) has approved Tween 80 for use in formulations for various routes of administration, including parenteral, oral, and topical. For that, and due to its biocompatibility, Tween 80 attracted high attention from researchers in last year’s [40].

1.4 Characterization of SLNP

1.4.1 Dynamic Light Scattering (DLS)

DLS is a suitable method for detecting particles in the nanometric range. The particle size distribution of SLNPs can be detected and represented as the polydispersity index (PDI). Monodisperse distributions exhibit PDI equal to or close to zero. On the other hand, a high polydispersity index "closed to one" indicated a polydisperse distribution of particles within the sample[41]. Generally, the particle size average in SLNP preparation is preferred to be less than 400 nm. Particle sizes less than 250 nm are more associated with polydispersity indexes smaller than 0.3[42].

A zeta sizer instrument uses dynamic light scattering (DLS) to detect the particle hydrodynamic diameter, polydispersity, particle size distribution (PSD), and zeta potential[43]. The zeta sizer uses a triple reading of the diluted sample to give the result as the mean and standard deviation[42].

1.4.2 Scanning Electron Microscope (SEM)

Scanning electron microscopy (SEM) is a morphology analysis technique that focuses on the surface of a particle and produces a three-dimensional image of that particle[44]. This technique's image-creating principle is based on the emission of an electron beam on the sample's surface. SEM uses a focused beam of high-energy electrons to scan the surface of the sample. This electron beam's interactions with the sample surface will generate secondary electrons. The detector will collect these secondary electrons as signals and use them for imaging[45]. The SEM will reveal the particle size, shape, presence of aggregation, polydispersity, and crystal-to-amorphous habit [46].

1.4.3 Differential Scanning Calorimetry (DSC)

DSC's thermal analysis provides information on the physical state and structure of the SLNP particles, as well as the interactions between formula components. Similarly, it is possible to identify the various phase transitions that occur in the sample. Normally, DSC and Powder X-ray Diffraction (PXRD) measurements provide a deep analysis of the crystal structure parameters.[47], [48]. DSC makes it possible to quantify how energetically and conformationally changes and phase transitions rely on temperature. In recent years, technological developments have been adding more development, such as high-sensitivity equipment, which in turn has made DSC a very valuable technique for analyzing the thermodynamic properties of many pharmaceutical products like lipid carriers [49], [50].

1.4.4 Fourier Transform Infrared Spectroscopy (FTIR)

The Fourier transform infrared (FTIR) is among the most important analytical techniques available today for analyzing a wide range of substrates. FTIR spectra provide a piece of information about the main functional groups that are presented in substrate structure. FTIR spectra provide a piece of information about the main functional groups that are presented in the substrate structure. Therefore, FTIR provides information about the foundational chemical interaction between the drug and excipients within the SLNP formula. One of the biggest advantages of this technology was that it could analyze any sample in any state [51]. By carefully choosing the sampling procedure, one may analyze, among other things, liquids, solutions, pastes, powders, films, fibers, gases, and surfaces. The FTIR spectrum's disappearance or introduction of new bands can provide information on the evolution of matter and its interactions with other substances [52]. FTIR is an easy, quick, suitable, non-invasive, and cost-effective method. Some variation in absorbance of magnitude 10^{-3} can aid in the understanding of the synthesis of NPs due to the high sensitivity of FTIR [53].

1.4.5 Powder X-ray Diffraction (PXRD)

PXRD is a potent, nondestructive method for crystalline compound characterization. Besides all the advantages of PXRD, which include the average grain size, crystallinity, strain, and crystal defects, it also offers details on phases, structures, and preferred crystal orientations[54]. PXRD peaks arise from the constructive interference of a monochromatic X-ray beam, dispersed at specific angles from each set of lattice planes in a sample. The distribution of atoms inside the lattice determines the peak intensities. As a result, the PXRD pattern represents the unique fingerprint of the material's periodic atomic groupings[44]. In the drug design, discovery, development, and formulation processes, X-ray powder diffraction can help set up a formulation because it gives unique polymorph identification and helps figure out the mixture's composition and the amount of each. It does this by revealing the morphology and crystallinity percentage. Nonambient analysis using PXRD can also be used to examine the impact of moisture on the physical characteristics of medications [55].

1.5 Applications of SLNP

1.5.1 Topical Route of Administration

The anatomy of the skin, particularly the stratum corneum, makes drug penetration into the skin so challenging that it serves as a significant barrier in the treatment of skin-related diseases. The SLNPs developed a high level of characterization of skin layer penetration and permeation, which is one of the important techniques for overcoming this limitation. In addition to the basic benefits of SLNP, moisturizing the skin will make it easier for the drug to penetrate deeper into the skin. The strong contact and good skin adhesion of SLNP also make it better for topical use [56], [57], [58], [59], [60].

1.5.2 Parenteral Administration

The controlled release behaviour and SLNP colloidal dimensions of this nanoparticulate carrier highlight its flexibility, enabling both parenteral and non-parenteral drug delivery and protection. Publications have documented the use of SLNP via parenteral routes, including biodistribution and pharmacokinetic investigations following intravenous and intraperitoneal injections[61],[61]. The SLNP preparation will lead to changes in physicochemical properties, particle size, and drug release. The different roles of drug release, such as burst, sustained, or controlled release, have an important focus on the parenteral route. The SLNP can serve as a targeting technology in oncology, delivering the drug into the tumor tissue, thereby enhancing its efficacy[62].

1.5.3 Pulmonary Route of Administration

This administration route has garnered significant attention as a novel approach, primarily due to its high surface area, low side effects resulting from the local avoidance of first-pass metabolism, and its ability to reduce both dose and strength, thereby minimizing adverse effects. Compared to other systems, using SLNP in this route has positive results, such as increasing bioavailability. That is the result of SLNP's various advantages, such as

biocompatibility, biodegradability, controlling release, minimum toxicity, and stability profile. The high concentration at the site of administration with a low systemic, minimizing adverse effect gives the SLNP a safe and low toxic profile. Also, the SLNP can have high systemic bioavailability for systemic delivery purposes by pulmonary route of administration [63], [64], [65], [66].

1.5.4 Oral Route of Administration

The predominant route of administration is the oral route of administration due to the patient's compliance with it and easy administration. However, this route of administration has difficult limitations with poorly soluble drugs that decrease bioavailability, hepatic first-pass metabolism, and enzymatic degradation. The SLNP technology can provide solutions for these limitations due to release control, sustained release, an increase in solubility at the nano level due to the surface area increasing or the effect of the lipid carrier on particle behavior, an increase in dissolution rate, protection from enzymatic activity, and covering until reaching the absorption site[67]

1.5.5 Ocular Route of Administration

The eye is considered a relatively complex organ due to its intricate structure, which has led to challenges in therapeutic diversity. Delivering medication through the eye is an interesting endeavor for researchers due to the distinctive eye structure and unique anatomy that are obstacles to drug permeation and reaching the desired outcome [68]. Because of the simplified production and ease of use by patients, the high percentage of eye formulas prepared as eye drops is nearly 90%. The main precorneal loss of drug that decreases the real reach amount of the active pharmaceutical ingredient to the site of absorption is the tear fluid (as dilution and rapid turnover), low connecting time of formula with eye surface, and lacrimal drainage system that will be led to make rapid contact time for the formula with the permeation surface. Due to precorneal elimination, the real drug that reaches the cornea and sclera is 1–5% of the total quantity. So, the formula's increasing duration is an important criterion for the development of topical eye formulas [69]. Therefore, topical administration is appropriate for the anterior segment and has a correlation with disease. Solid lipid nanoparticles as a novel drug delivery system have many properties to overcome this barrier in treatment, like the crossing of the blood-ocular barrier, increasing contact time, sustained release of a drug, protection from drainage, and enzyme activity of lacrimal fluid. In cases of posterior segment-related disease, drug delivery is a more difficult issue, so different processes are used to deliver the drug to this site of action. The ocular-related disease is not suitable for treatment with topical preparation; there are some different routes, like subretinal injection, subconjunctival injection, intravitreal injection, and retrobulbar injection. New drug delivery systems, such as lipid nanoparticles, can serve as a suitable alternative to conventional invasive methods that may be uncomfortable or painful (the methods mentioned above)[70], [71], [72], [73], [74].

1.6 Stability of Solid Lipid Nanoparticles

The presence of water in high proportions may lead to phase separation of the SLNP formula when storing it in liquid form for a long time. Therefore, reducing the water content will prevent hydrolytic reactions and phase separation. Freeze drying is a suitable method for solidifying the nanoparticles[75]. The storage temperature can significantly impact the stability of drug formulations in the form of SLNPs. Drug-loaded solid lipid nanoparticles (SLNPs) exhibit enhanced stability when stored at temperatures higher than freezing. This is because storing at higher or extremely low temperatures can cause physical instabilities, leading to particle aggregation and an increase in particle size and PDI. It can also modify the lipid crystalline structure, resulting in drug expulsion. The aggregation of nanoparticles during storage at relatively high temperatures can be attributed to the heightened kinetic energy of the particles, which promotes their collision. In addition, elevated temperatures can cause deformation of the structural integrity offered by the surfactant film, resulting in the clustering of particles.
Additionally, it is crucial to be aware of the melting points of lipids when storing SLNPs, to ensure that the matrix remains in a solid state, which guarantees the retention of the drug[76].

Conclusion

In conclusion, SLNP appears to be a good delivery strategy for hydrophilic and lipophilic drugs, and chemical instability drugs. This paper includes many methods for SLNP preparation that are suitable for hydrophilic, lipophilic, and heat-sensitive drugs. When the microemulsion method is suitable for lipophilic drugs, the double-emulsion method is suitable for hydrophilic drugs. On the other hand, methods like cold homogenization, solvent emulsification, evaporation, solvent injection, and supercritical fluid methods are particularly advantageous for preparing SLNP with heat-sensitive drugs due to their ability to maintain low processing temperatures. Characterizing SLNP is crucial to understanding their physicochemical properties, stability, and performance. Dynamic light scattering measures the size and polydispersity index. Scanning electron microscopy offers surface morphology and particle shape visualization. Powder x-ray diffraction and differential scanning calorimetry are methods that determine the crystallinity and polymorphism of a substance. On the other hand, Fourier transform infrared spectroscopy will identify the functional groups and the interactions between drugs and other excipients. The applications of SLNP based on the route of administration can include enhancement of bioavailability, sustained drug release, and drug protection for the oral route. While delivering the active ingredient and improving skin penetration for topical administration. Targeting and improving systemic distribution are important features for parenteral administration. On the other hand, SLNP's main advantages for ocular administration are improved drug retention and reduced irritation.

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Author Contribution
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