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Research Article

EXPLORING INNOVATIVE APPROACHES FOR THE PREPARATION OF SOLID LIPID NANOPARTICLES: ADVANCEMENTS IN DRUG DELIVERY FOR MODERN MEDICINE

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Abstract

Solid lipid nanoparticles represent an advanced pharmaceutical technology designed to address challenges related to drug bioavailability and drug delivery targeting. This detailed overview delves into various methodologies used to create SLNs, providing insights into the formulation strategies, manufacturing processes, and characterization methods used throughout their development. Important topics discussed are the choice of lipid matrix, emulsification techniques, and how process variables affect the physical characteristics of solid lipid nanoparticles. Furthermore, the review explores the latest advancements in SLN preparation, including novel approaches such as Nano-emulsion techniques, microfluidics, and alternative lipid sources. By providing rather than giving a complete overview of SLN production methods, this review aims to enhance knowledge of their potential for use in drug delivery applications and pharmaceutical research.

Keywords: Solid lipid nanoparticles (SLNs), Drug delivery, Nano-emulsion techniques, Lipid matrix, Formulation strategies.

1. INTRODUCTION

Lipid-based Nanosystems have been identified as promising nanocarriers for encapsulating various active chemicals in recent years. Solid lipid nanoparticles offer excellent physical and colloidal stability and great biocompatibility. By carefully selecting the components and adhering to the preparation procedures, we may create carrier structures with the required physicochemical attributes and biological qualities [1]. In the early 1990s, Solid lipid nanoparticles were proposed as a viable substitute for the lipid based carriers currently used in nanomedicine. They bear a resemblance to emulsions of oil in water. But, In contrast to emulsions, SLNs use a *solid lipid* in place of the liquid lipid at room temperature, this allows SLNs to incorporate both hydrophobic and Hydrophilic drugs. The active pharmaceutical ingredients (API's) in solid lipid nanoparticles are encapsulated in lipids. They are also called colloidal particles, *10-1000 nm* in diameter. SLNs are composed of organic matter and carbon [2,3]. As shown in Figure1. Recent years have underscored the imperative understanding that the mere advancement of novel drugs is insufficient to guarantee progress in drug therapy. [3] The creation of suitable Drug delivery Techniques becomes a strategic imperative as SLNs address issues with significant plasma level changes and limited solubility in water, while also combining the benefits of traditional systems with some of their main drawbacks, such as poor absorption, rapid metabolism, and elimination. When compared to alternative distribution methods, nanoparticles have several benefits due to their special qualities such as nanoparticle *size*, huge *surface area*, and the ability to modify surface characteristics. [4] Nanotechnology is a rapidly growing field, and Solid lipid nanoparticles are the *core components* of this exciting new field of pharmaceutical research [5]. This technique presents a promising option for the advancement of treatments since it has several potential uses in drug delivery and pharmaceutical research [6].

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Solid lipid nanoparticles, stabilized by *surfactants*, offer a compelling profile, seamlessly integrating advantages from conventional carriers. SLN features a robust matrix, safeguarding chemically volatile API, and allowing precise modulation of drug release. [7] Solid Lipid nano-particles are nanoparticles of an active substance that are dispersed in a water medium with the help of a surfactant. Moreover, SLN exhibits the potential to their enhance the *physical stability* of the formulation owing to its diminutive size.[8] Nevertheless, there are several disadvantages to SLNs as well, such as Drug loading being limited for water-soluble drugs, low solubility in lipid melts, and the potential for drug release and particle agglomeration while being stored.[4] One of the most significant drawbacks of SLNs is that unintentional and uncontrolled strengthening of the crystal structure during their formation and preservation may result in the release of the enclosed medication [9]. The utilization of ecologically safe, biodegradable components and production methods may be their main benefit. The majority of the nanoparticles in this category are classified as *class I*in the nanotoxicological categorization system due to their small size and biodegradable nature. [10] A key benefit of SLNs is that the lipid core is composed of *biological lipids*, thereby mitigating the potential for toxicity.

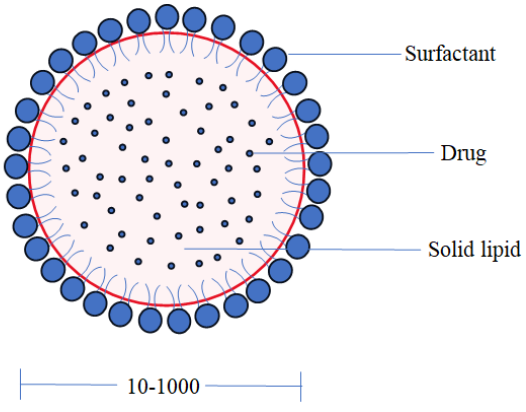

Figure 1. Figure of solid lipid Nanoparticle

1.2. Lipids utilized in SLN

Table 1.1. Varieties of lipids utilized in SLN

Sr. no.	Lipids	Examples	References
1.	Fatty acids	Lauric acid, Dodecanoic acid, Tetradecanoic acid, Palmitic acid, oleic acid, (octadecanoic acid) Stearic acid, behenic acid, , Octadecadienoic acid (linoleic acid)	[4,2,12,13,14]
2.	Triglycerides	Tripalmitin, Trilaurin, trimyristin, Tricaprin, Hydrogenated coco glycerides, triolein, Tripalmitin Dynasan® 116, tri caprylate, Tristearin Dynasan®118, medium-chain triglycerides (MCT), Trimyristin Dynasan®114, Glyceryl behenate	
3.	Diglycerides	Glyceryl Distearate	
4.	Monoglycerides	Glyceryl hydroxyl stearate, Glyceryl behenate, Glyceryl monostearate.	
5.	Mixed Glycerides	Glyceryl palmitostearate	
6.	Hydrogenated glycerides	Hydrogenated coconut oil glycerides, hydrogenated palm kernel oil glycerides	
7.	Cyclic complexes	Para-acyl calixarenes, Cyclodextrin	
8.	Waxes	Cetyl palmitate, Beeswax, Carnauba wax	
9.	Hard fat	Hydrogenated coco-glycerides, Hydrogenated vegetable oil, Polyethylene glycol glycerides	
10.	Cationic lipids	Cetrimide, stearyl amine (SADioleoyltrimethylammonium propane (DOTAP), benzalkonium chloride, (CPC) cetylpyridinium chloride, dimethyl dioctadecyl ammonium bromide	
11.	Others	Anhydrous milk fat, cocoa butter, soybean oil, Castor oil, Hydrogenated ricinus oil, Arachis oil, cocoa butter, hydrogenated palm oil, goat fat fully hydrogenated soybean oil	

1.3. Advantages and Disadvantages of Solid Lipid Nanoparticles:

Table 2. Advantages and Disadvantages of Solid Lipid Nanoparticles. [11]

Advantages	Disadvantages
SLNs offer enhanced Stability and Scalability.	Inadequate Drug Loading Capacity
Reduced Toxicity Risk	Drug Expulsion Post Polymeric Transition
Long-Term Stability	Elevated Water Content in Dispersions
Ease of Manufacturing	Limited Hydrophilic Drug Loading Capacity
Controlled Release Kinetics	
Enhances Bioavailability of poorly water-soluble compounds.	
Chemical Protection for Labile Compounds	
Same Raw Material as Emulsion	
SLNs enable the achievement of high concentrations of functional compounds.	

2. PREPARATION METHODS

2.1. High-energy methods

1. High Pressure Homogenization:

This method's benefit is that it produces SLNs with tiny particle sizes and an excellent ability to entrap. High-pressure homogenization involves pumping a molten lipid quickly and at a pressure of *500–5000* bar through a small opening. Typically, a lipid content of *5–10%* is employed, however, studies have looked at up to 40%. Hot homogenization and cold homogenization are two techniques for HPH.[15]

a) SLN preparation Using Hot homogenization:

The possibility of scaling up, low manufacturing time, and lack of organic solvents Unfit for medications that are hydrophilic or heat-sensitive

1. Combine lipid and drug above melting point
2. Add surfactant in water at the same temperature
3. Emulsify using a shear device to form pre-emulsion
4. Cool to room temperature for recrystallization
5. Perform 3–5 homogenization cycles at 500–1500 bar
6. Optimize parameters for smaller particle sizes *(<500 nm)*
7. Avoid over-homogenization to prevent particle size increase
8. Characterize final SLNs for desired properties

b) Cold homogenization:

Ideal for medications that dissolve in *water* to avoid medication loss big particles and time-consuming procedures

1. Cool lipid melt with a drug to solidify
2. Grind solid lipids into microparticles
3. Disperse lipid microparticles in cold surfactant solution
4. Homogenize the mixture at RT or below
5. Use gravity to break lipid microparticles into SLNs
6. Achieve particle sizes ranging from 50–1000 nm

[13,16]

2. Ultrasonic/high-speed homogenization:

Easy installation and operation without the need for organic solvents high levels of surfactant, medication exposure to high temperatures, and metal pollution

1. Melt solid lipids, and add medication.
2. Combine with the warmed aqueous phase, with surfactant.
3. Maintain a temperature 5°C above the lipid melting point.
4. Homogenize with high-speed stirring.
5. Further, refine with ultra-sonication.
6. Filter Nano emulsion to remove foreign particles.
7. Cool to form SLNs/NLCs.
8. Consider bath sonication for particle size control.
9. Monitor surfactant and lipid concentrations.
10. Store SLNs between 5°C and 4°C for stability.

11. *Freeze-dry SLNs with 5% mannitol* as a cryoprotectant for enhanced stability.
12. Minimize exposure to high temperatures and metal contamination (2), (17).

3. Supercritical Fluid Method:

Uniform distributions of particle sizes and high extraction efficiency of solvents Use of costly supercritical fluids and organic solvents

1. Dissolve lipids and drugs in chloroform.
2. With a surfactant, transfer an organic solution into a water phase.
3. Run the mixture through a homogenizer with *high pressure*.
4. Introduce the emulsion to the ascend, top of the extraction column.
5. Simultaneously introduce *supercritical CO2* into the extraction column from the bottom.
6. Supercritical CO2 rapidly extracts the organic solvent from the emulsion.
7. Collect the resulting SLNs or NLCs from the bottom of the extraction column. [2, 16,18]

2.2. Low energy methods

1. Microemulsion based method:

1. Dissolve the drug in molten lipids over the point at which they melt.
2. As the lipids melt, prepare an aqueous phase (water and surfactant) preheated to room temperature.
3. To create a clear, stable microemulsion, gently mix the aqueous phase into the lipid phase.
4. Transfer the microemulsion into a cold aqueous solution (between 2 and 10°C) and mix it gently with a machine.
5. Ascertain that the volume of the heated emulsion is 25–50 times less than that of the cold aqueous phase.
6. After dilution, Nanoemulsion forms, and lipids crystallize into solid lipid nano-particles or nanostructured lipid carriers.
7. The method has been successfully utilized to create SLNs with small particle sizes *(<200 nm)* and low polydispersity indexes *(<0.2)*.
8. The SLNs prepared using this method have shown enhanced efficacy compared to free drug molecules in various studies.
9. Large-scale production can be achieved by preparing microemulsion in a tank with temperature control and then pumping it into a cold-water tank for lipid precipitation.
10. The method for diluting microemulsions is simple and reproducible, but it requires a significant amount of water and high surfactant usage.
11. *Lyophilization or ultra-filtration* can remove excess water from SLN and NLC dispersions, thereby concentrating the product.[10,16]

2. Hot microemulsion technique/microemulsion dilution technique

Method 1 (Direct Method):

1. Accurately weigh each non-aqueous microemulsion component chosen from phase diagrams and placed into glass vials.
2. The vials should be filled with the necessary amount of water.
3. Vials should be placed in the jacket and stirred for *10 minutes at 1500 rpm* at 65°C (PATO5) or 80°C. for C888 at 65°C or 80°C respectively.
4. The formulations should be allowed to reach room temperature while being stirred magnetically.

Method 2 (Stepwise Method):

1. Measure and fill glass vials with non-aqueous components.
2. At the appropriate temperature, stir the mixture until the solid lipid melts and a homogeneous forms, which should take about 3-4 minutes.
3. Add the hot water phase in *200 µl* increments.
4. The mixture should be stirred for an additional 5 minutes.
5. The mixture should be allowed to reach room temperature while being stirred magnetically at *1500 rpm* [19,20].

3. Microemulsion cooling technique

1. Melt emulsifying wax at 37-55°C.
2. To create a uniform slurry, add water at the same temperature while swirling very little.
3. Add a suitable polymeric surfactant to the water phase in predetermined proportions.
4. Cool the undiluted microemulsion to RT or 4°C.
5. SLNs precipitate from the cooled microemulsion.
6. Select matrix material from excipients like waxes or polymeric surfactants.
7. Operate at mild temperatures for rapid, reproducible, and cost-effective production.
8. Ensure all ingredients are potentially biocompatible.
9. Reach high entrapment efficiency, particularly for water-insoluble medications.
10. Easily incorporate cell-specific ligands for targeted delivery on the SLN surface.[10]

4. Dual/Double emulsion method:

Creating a double emulsion of water, oil, and water Ideal for *hydrophilic medications* large particle size and high drug loss

1. Dissolve the drug (typically hydrophilic) in an aqueous solvent to create the inner aqueous phase.
2. Disperse the inner aqueous phase into a lipid-containing emulsifier (oil phase) to form the primary emulsion (w/o).
3. Add an aqueous solution (e.g., hydrophilic emulsifier such as poloxamer) to the primary emulsion to create the double emulsion (w/o/w).
4. Stir the mixture thoroughly.
5. Isolate the double emulsion by filtration.

This technique enables the production of lipid nanoparticles without the need to melt the lipid, allowing for potential surface modification for stability. However, the final particles tend to be polydisperse, limiting precise control and application in certain fields [12,17].

5. Phase inversion method by temperature (PIT):

Based on surfactants made of non-ionic polyoxyethylene devoid of solvents and requiring minimal energy Low level of Nanoemulsion stability

1. Select solid lipids, non-ionic surfactants, and aqueous phase components.
2. Heat the oil phase and aqueous phase separately to about 90°C (above the phase transition temperature).
3. To create a water-in-oil (W/O) emulsion, add the aqueous phase to the oil phase dropwise while stirring continuously.
4. Let the emulsion cool while stirring constantly at room temperature.
5. Observe for turbidity clearance at the PIT.
6. Below the phase inversion temperature, an oil-in-water (O/W) Nanoemulsion is formed.
7. Characterize SLNs and store them appropriately.[9,10,22]

6. Membrane contactor method:

Use of a particular membrane contactor Scale-up viability and controllability of particle size Complex system and membrane blockage potential

1. Use a *pressure vessel* to raise the lipid phase's melting point.
2. Pass the heated lipid phase through a module containing a *Kerasep clay film*.
3. Permit the *membrane pores* to allow the lipid phase to migrate dilatorily to the layer surface.
4. Simultaneously, isolate the water phase within the module.
5. To enable the formation of smaller particles, push the lipid phase via the membrane's openings.
6. SLNs are formed in the water phase after cooling.
7. Adjusting process parameters like lipid content, lipid phase pressure, and aqueous cross-flow velocity helps control particle size.
8. Maintain the temperature of the aqueous phase below the melting point of the lipid to cause the lipidic phase to rapidly solidify in the aqueous phase and reduce the SLNs.
9. Utilize membrane contactors for SLN formulation, offering feasibility, particle size control, and easy scalability.[10, 23]

7. Coacervation technique:

Usage of fatty acid and alkaline salts Simple and solvent-free Not suited for medications that are sensitive to pH; only works with alkaline salt lipids.

1. Make an alkaline salt micellar solution using soap, a fatty acid. By dissolving the chosen salt (e.g., sodium stearate, sodium palmitate) in water at a temperature above its Krafft point.
2. Optionally, To improve micellization, either dissolve the medication straight into the micellar solution or first pre-dissolve it with a tiny amount of ethanol.
3. Select a stabilizing agent such as (dextran, hydroxypropyl methylcellulose, polyvinyl acetate/polyvinyl alcohol, or polyoxyethylene/polyoxypropylene polymers) among the non-ionic surface-active polymers.
4. Prepare an acid solution (coacervating solution) and heat it to a temperature that is above the fatty acid sodium salt's Krafft point, between 40 and 50 °C. Higher temperatures may be required for salts like sodium arachidate and behenate.
5. Mix the micellar solution and the acid solution, leading to Fatty acid nanoparticle precipitation due to proton exchange.
6. Rapidly cool the obtained suspension to 15 °C to stabilize the SLNs.
7. Modify the reaction conditions to regulate the size of SLNs, such as lipid concentration in both the micellar solution and the kind/quality of polymer stabilizer that was employed.

Enhance the interaction between the coacervating solution and the fatty acid salt to get a homogenous and stable nanoparticle suspension. [10, 24, 25]

8. Organic solvent-free melt dispersion technique

1. Heat the lipid phase (e.g., stearic acid) above its melting point.
2. To create the initial emulsion (W1/O), disperse the heated lipid phase in water using a low HLB surfactant.
3. To create the second emulsion (W1/O/W2), combine a warm, aqueous solution of a surfactant with a high HLB (like Tween 80). into the first emulsion and homogenize.
4. The double emulsion should be added to cooled water while shaking to encourage the synthesis of solid lipid nanoparticles.
5. Optionally, incorporate desired substances like dyes into the internal aqueous phase or lipid phase before forming the emulsions.[26, 27]

2.3. Organic solvent approaches

1. Solvent evaporation emulsion method: (Solvent based method)

Ideal for medications that are extremely thermolabile, with no extreme heat, or physical strain Removal of toxic organic solvents

1. Dissolve drugs and lipids in water-immiscible organic solvents (such as cyclohexane and chloroform).
2. Emulsify the solvent-drug-lipid solution in a phase of water to create nano-dispersions.
3. Evaporate the organic solvent in a rotary evaporator or with mechanical stirring.
4. Lipid precipitation after solvent evaporation results in the formation of solid lipid nanoparticles and nanostructured lipid carriers.
5. maximize the amount of lipids in the organic phase to control particle sizes of SLNs and NLCs.
6. Ensure avoidance of high temperatures to protect thermo-labile drugs during encapsulation.
7. Perform additional purification steps such as further evaporation or ultra-filtration to concentrate the suspension.[7,14]

2. Solvent emulsion and diffusion method: (Solvent-based method)

Ideal for medications that are extremely thermolabile, and don't require extreme heat or physical strain Removal of toxic chemical solvents, a large volume of water, and a low concentration of SLN

1. Achieve initial thermodynamic equilibrium by reciprocal saturation between water and an organic solvent.
2. Dissolve Medications and lipids in the water-soluble organic solvent.

3. Emulsify the solvent-saturated lipid-drug solution in the water phase containing a stabilizer under stirring, forming an (o/w) emulsion.
4. Dilute the emulsion with water (1:5 to 1:10) to let the solvent diffuse into the continuous watery phase.
5. Spontaneously form SLNs as lipid precipitation occurs.
6. Remove the organic solvent by either lyophilization or vacuum distillation.
7. Optimize formulation parameters such as lipid type and solvent choice to achieve desired particle sizes and polydispersity indexes.
8. Explore various drugs and lipid combinations to encapsulate both hydrophilic and hydrophobic drugs.
9. Minimize exposure of drugs to extreme conditions by avoiding high temperatures and physical stress.
10. Scale up the method for industrial production.
11. Purify the SLN and NLC dispersions by removing residual organic solvent, similar to the microemulsion method.

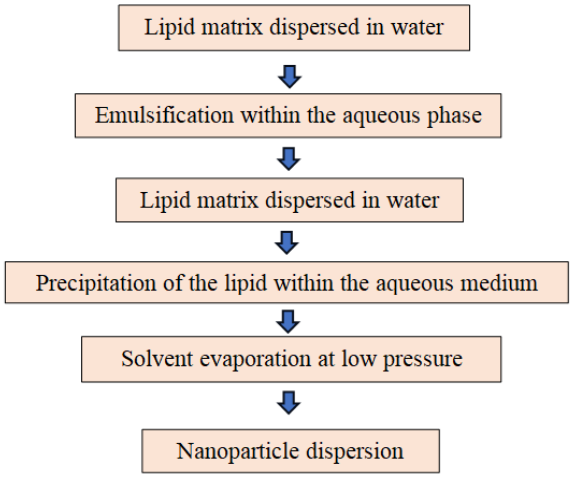

Figure 2. Emulsification diffusion Technique. [16]

3. Solvent injection Method (or solvent displacement): (Solvent-based method)

Easy to use, quick manufacturing, and no complex equipment Removal of toxic organic solvents

1. Dissolve lipid and active ingredients in a water-miscible or organic solvent.
2. Use a syringe needle to inject the organic solvent solution into a vigorously stirred water phase (distilled water).
3. As the solution contacts water, the lipid precipitates, forming nanoparticles.
4. SLNs are created when the organic solvent rapidly dissolves inwater.
5. The lipid molecules self-assemble into nanoparticles due to the hydrophobic interactions.
6. Collect the SLN dispersion.

Optionally, filter the dispersion to remove any large particles or aggregates.[28]

4. Preparation of SLN using the Membrane Contactor Method

A specialized membrane contactor module is employed. The module includes a ceramic membrane (pore diameters often falling between 0.1 and 0.45 μm) that separates the water phase from the lipid phase.

1. The lipid phase (containing the solid lipid) is heated.
2. The heated lipid phase is allowed to flow parallel across the ceramic membrane surface.
3. Simultaneously, the water phase circulates on the other side of the membrane.
4. As the lipid phase contacts the membrane, it forms small droplets due to the temperature difference.
5. These droplets solidify into solid lipid nanoparticles (SLNs). [10,29]

2.4. Other scale-up methods

1. Hot Melt Extrusion Coupled with HPH

Combining hot melt extrusion with HPH enhances the scalability of SLN preparation

1. Pump raw materials into extruder barrels at elevated temperatures exceeding lipid melting point.
2. Connect the high-pressure homogenizer at the end of the extruder barrel with an insulated connector.
3. To reduce size, maximize process variables like lipid content, screw design, and residence duration.
4. Produce SLNs below 200 nm by varying parameters such as screw speed, barrel temperature zone, and liquid addition zone.
5. Ensure complete melting of materials and liquification of drug particles before exposure to emulsifier.
6. Control barrel temperature and screw speed to facilitate emulsion formation between melted medication and surfactant owing to the extruder space's shear generation. [7]

2. Liquid Flow-Focusing and Gas Displacing Method in Microchannel

1. Dissolve lipids in a water-based surfactant and organic solvent to create a lipid solution.
2. Microchannels are configured with specific junctions for lipid and aqueous solutions, as well as gas insertion.
3. Simultaneously inject lipid and aqueous solution streams into the cross-junction of the microchannel to focus liquid flow.
4. To assist in the development of SLNs, By using the T-shaped connection, inject inert gas into the main flow upward to create a slug flow of gas-liquid combination.
5. Use hydrodynamic focusing to create SLNs with narrow size distributions and tiny diameters.
6. Continue gas sparging along with liquid flowfocusing on solids inside the microchannels.
7. Achieve supersaturation of lipids by synthesis of SLNs as a result of the organic solvent's diffusion into the aqueous phase.
8. Large gas bubbles split upper liquid streams, forming Taylor bubbles and suspending gas-liquid SLNs.
9. Prevent deposition of SLNs into microchannels by Taylor bubbles liquid slug flow motions, ensuring continuous SLN production.
10. Ensure SLNs flow freely and smoothly via microchannels to produce SLNs continuously.

3. Nanoprecipitation Using Static Mixers

1. Choose a suitable lipid and organic solvent for dissolving the lipid.

2. Dissolve the lipid in the selected organic solvent to prepare a homogeneous lipid solution.
3. Prepare the aqueous phase using deionized water or an aqueous buffer solution.
4. Install the static mixer in the system. Ensure proper connection and secure it in place.
5. Simultaneously inject the lipid solution and the water phase into the static mixer at controlled flow rates.
6. The static mixer facilitates efficient mixing of the lipid solution and water phase, promoting rapid and homogeneous mixing.
7. Collect the resulting SLN suspension at the outlet of the static mixer.
8. Characterize the obtained SLNs for particle size, size distribution, morphology, and stability.
9. Fine-tune process variables such as lipid concentration, mixing conditions, and flow rate for optimization.
10. Scale up the nanoprecipitation process using static mixers for large-scale production of SLNs while maintaining efficient mixing and particle size control.[7]

4. Dual Centrifugation

SLNs are usually made by HPH above the lipid's melting temperature. This method is resource-intensive and not suitable for processing multiple samples simultaneously. An alternative method, dual centrifugation, is introduced for SLN preparation.

1. Weigh ingredients into 2 mL vessels.
2. Place vessels in a heated centrifuge.
3. Apply additional rotation for intensive stressing.
4. Add grinding media to the vessels.
5. Initiate the emulsification process for 10 minutes.
6. Monitor sample temperatures, ensuring they stay below 90°C.
7. Adjust process variables as needed.
8. Analyse particle sizes to ensure they're below 200 nm with a narrow size distribution.
9. Document process parameters and results.[7,10,30]

5. Sray Drying

1. Prepare an ethanolic solution containing lipids and the desired drug.
2. Atomize the solution using centrifugal, ultrasonic, or electrostatic atomization methods.
3. Subject the spray to hot gas to induce rapid solvent evaporation, forming solid lipid nanoparticles (SLN).
4. Separate hot air from SLNs using a cyclone separator or electrostatic precipitator.
5. Control process parameters including temperature, humidity, feed composition, rate of drying, and gas flow rate.
6. Optimize SLN characteristics such as dimensions, dispersion, form, density, and morphology.
7. Ensure macroscopic powder qualities meet standards for bulk density, dispersibility, tap density, and flowability.[7,10]

3. CHARACTERIZATION

Table 3. Characterization Methods of Solid Lipid Nanoparticles [1,31]

Parameters	Characterization
Polydispersity index and Particle size	Dynamic light scattering/ Photon correlation spectroscopy (PCS) and laser diffraction
Shape, morphology, and imaging	Scanning electron microscopy (SEM), Atomic force microscopy and transmission electron microscopy (TEM), Atomic force microscopy (AFM)
Zeta potential	Photon correlation Spectroscopy /(DLC), (ELC) Electrophoretic Light Scattering,
Crystallinity	Differential thermal analysis/Differential scanning calorimetry and X-ray diffraction (XRD)
Encapsulation efficiency	Size exclusion/Gel filtration chromatography, Ultracentrifugation, Filter membrane, Dialysis, etc.
Structure and drug-lipid interaction	NMR spectroscopy,FTIR Fourier transform infrared spectroscopy, Raman spectroscopy

APPLICATIONS [32]

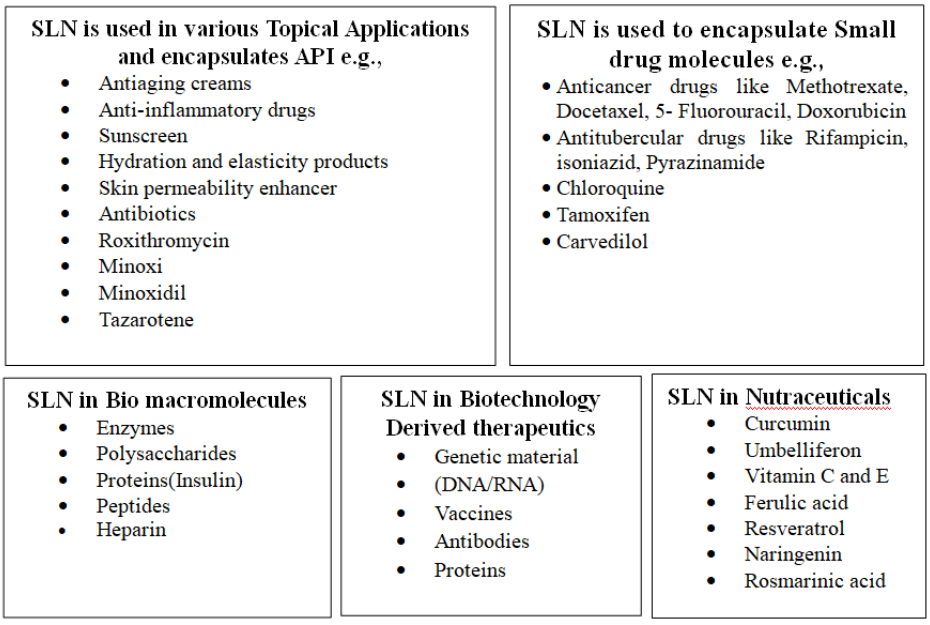

Figure 3. Applications of SLNs for different class of therapeutics

Examples of applications of solid lipid nanoparticles:

1. **Drug Delivery:** SLNs have been extensively explored as carriers for drug delivery systems.[33]
2. **Cosmetics:** SLNs are utilized in cosmetic formulations for delivering active ingredients such as vitamins, antioxidants, and UV filters. They provide improved stability and skin penetration, enhancing the efficacy of cosmetic products. [34]
3. **Food Industry:** SLNs have emerged as potential carriers for bioactive compounds in food products. They can encapsulate lipophilic substances, enhancing their solubility, bioavailability, and stability in food matrices [35].

4. FACTORS AFFECTING SOLID LIPID NANOPARTICLES

1. **Type of lipid:** The choice of lipid affects the particle size, stability, crystallinity, and drug-encapsulating capacity of SLNs. Different lipids have different melting points, solubility, and compatibility with drugs.
2. **Type of surfactant:** The types, concentration, and ratio of surfactant to lipid can influence the size, zeta potential, and drug release of SLNs
3. **Method of preparation:** There are various methods to prepare SLNs, such as high-pressure homogenization, microemulsion, solvent injection, and sonication. Every approach has benefits and drawbacks, and it might have an impact on the physicochemical characteristics and functionality of SLNs.
4. **Process parameters:** The process parameters, such as temperature, pressure, speed, time, and solvent type, can also affect the quality and characteristics of SLNs. The optimal process parameters depend on the type of lipid, surfactant, and method used [9].
5. **Drug-lipid compatibility:** The drug's compatibility with the lipid matrix affects drug encapsulation efficiency and release profile [36,37].
6. **Solvent choice:** The choice of solvent(s) used in the preparation process can influence SLN characteristics. Solvents should be carefully selected to ensure lipid solubility and compatibility with the drug and other formulation components [7,10,37,38].
7. **Antioxidants/stabilizers:** Incorporating antioxidants or stabilizers can enhance SLN stability by preventing lipid oxidation and particle aggregation during storage.[39,40]
8. **Particle size and distribution:** For SLN performance, size distribution and particle size control are essential. Particle size and distribution are affected by variables such as lipid content, surfactant-to-lipid ratio, and processing factors.[13,14]
9. **Sterilization and storage conditions:** Sterilization methods and storage conditions (e.g., temperature, and humidity) can affect SLN stability and shelf-life [13].
10. **Scale-up considerations:** Sterilization methods and storage conditions (e.g., temperature, and humidity) can affect SLN stability and shelf-life [7,37].

5. RECENT ADVANCES AND FUTURE DIRECTIONS

1. **SLNs for Theranostics:** Solid lipid nanoparticles, which are tiny vesicles made of lipids (fats), can also be used for Theranostics. They have the potential to deliver drugs and imaging agents simultaneously. They can deliver drugs and imaging agents non-invasively [9]
2. **Silence Therapeutics:** ST utilizes SLN technologies to create precise medicines targeting specific disease-related genes for unmet medical needs. The progress in SLN technologies also positions Silence Therapeutics for wider acceptance in the pharmaceutical sector, improving the effectiveness of RNA interference therapies.[42]
3. **Industrial Significance:** SLNs are gaining industrial attention due to their potential for large-scale manufacturing. Several SLN-based Formulations are currently in clinical trials, hinting at their increasing presence in the market.[7,43]
4. **Continuous Processing:** In the pharmaceutical industry, continuous processing aims to minimize batch-to-batch variations. Implementing continuous methods ensures consistent SLN production.[7]

6. FUTURE PERSPECTIVES

1. SLNs as Drug Delivery Systems

SLNs are effective for delivering drugs with low solubility in water, short half-life, and low chemical stability.[36]

2. Quality of Production:

By altering hardware aspects and formulation processing components, consistent and repeatable quality of SLN production can be achieved.[36, 45]

3. Production Challenges:

There are difficulties like phase separation, sterilization, and polymorphism. Supercritical fluid (SCF) and other temperature-controlled techniques can be used to address polymorphism. Phase separation can be managed with optimized lyophilization processes, enhancing stability and reducing microbial growth incidents. [7]

4. Sterilization:

Sterilization remains a challenge due to the sensitivity of lipids to gamma irradiation and thermolabile substances. Filtration methods offer a solution, although batch capacity and filter pore size are considerations.

5. Protein Corona Formation and Enzyme Degradation:

Translation is hindered by the development of protein corona and the breakdown of enzymes. Pre-clinical research to address these issues is made easier by developments in high throughput screening (HTS) and bio-corona characterization estimating techniques. [46, 47]

6. Scale-up Efforts:

Encouraging scale-up efforts is crucial for bringing SLNs to market. Like nanosuspensions, SLNs can go through phases of processing like spray drying and lyophilization.

Industrial Benchmark and Regulatory Guidelines:

Adherence to commercial standards, including clean rooms, Distinct production facilities, validated machines, safety protocols, and employee education, is essential. Clear

regulatory guidelines, similar to those for liposomes, provide a framework for SLN development and approval [7].

7. Clinical Studies and Market Adoption:

Ongoing clinical studies indicate a positive trajectory for SLN technologies in reaching the pharmaceutical market. With advancements in research and regulatory clarity, SLNs are poised for broader adoption in the pharmaceutical industry [7, 48].

7. CONCLUSION

This review comprehensively examines the innovative approaches in the formulation of solid lipid nanoparticles (SLNs) and their advancements in drug delivery for modern medicine. The abstract succinctly introduces the key topics covered, including types of lipids used in SLNs, various preparation methods, characterization techniques, factors influencing SLN preparation, applications of SLNs, recent advances, and future directions. Through a thorough analysis of these aspects, it is evident that SLNs hold significant promise as a drug delivery system, offering enhanced durability, Sustained release, and targeted delivery capabilities. Furthermore, the exploration of recent advances highlights the continuous evolution of SLN technology, paving the way for more efficient and effective pharmaceutical therapies. Looking ahead, future directions suggest further research into optimizing SLN formulations, exploring novel applications, and addressing challenges to facilitate their widespread adoption in modern medicine. Overall, this review underscores the importance of SLNs as anadaptable medication delivery platform, driving advancements in therapeutic strategies and ultimately improving patient outcomes.

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