

Basics of Solid Lipid Nanoparticles Formulation

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Article History:

Received: August 14, 2024

Revised: September 6, 2024

Accepted: September 15, 2024

ePublished: September 30, 2024

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Abstract

Lipid nanoparticles (LNPs) have captured significant attention in the past few years and are widely used. Nanostructured lipid carriers (NLCs) and solid lipid nanoparticles (SLNs) are two lipid-based NPs with potential applications in research, drug delivery, cosmetics, and other fields. By modifying the size range, they can be used through different routes. Physically stable and targeted SLNs with good release profiles have been designed to overcome the limitations of emulsions and liposomes. NLCs are modified SLNs that enhance loading capacity and stability. Regardless of the preparation method, an initial emulsion is essential. The quality of the initial emulsion can affect the desired size range. This study highlights the critical features required to prepare the initial emulsion wisely and rationally.

Keywords: Preparation method, SLNs, NLCs, Formulation, Size range

Introduction

In recent decades, different carrier systems have been developed for drug delivery to modify the release profiles and improve formation effectiveness for improved outcomes.¹ These novel drug delivery systems have not only facilitated the successful targeting of numerous new pharmaceuticals but have also allowed for the better delivery of existing drugs.² Most commonly used drugs exhibit poor biopharmaceutical properties, including rapid metabolism, low solubility, low permeability, rapid elimination, reduced safety, and poor tolerability, making drug delivery a long-term challenging obstacle.³ The development of a wide range of tailored drug delivery systems using nanoparticles (NPs) is altering the scientific landscape for disease treatment.^{4,5} The desired drug is adsorbed, dissolved, attached, encapsulated, or entrapped into or onto a nano-matrix.^{6,7} NPs, nanospheres, or nanocapsules can be constructed based on the method of preparation and the different release characteristics and properties to achieve better drug delivery or encapsulation. Colloidal particles known as NPs range in size from 10 to 1000 nm.⁸ To reduce toxicity and optimize drug delivery, synthetic or natural polymers are used in their preparation⁹. Recently, they have been considered a promising substitute for liposomes.¹⁰ The ability of NPs to permeate various anatomical barriers and maintain their stability within the target size range is crucial for their successful application in drug administration.⁴ However, the widespread clinical application of NPs faces limitations

due to the high cost of safe polymers.¹¹ Lipid nanoparticles (LNPs), due to the availability of biocompatible and non-toxic lipid ingredients, can solve these limitations. LNPs can be categorized into two groups: solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs).¹² These LNPs have a spherical morphology and an average size range of 40 to 1000 nm. They consist of a solid-phase lipid as the dispersion phase and a surfactant as the emulsifier.¹³ At room temperature and body temperature, SLNs' dispersed phase remains solid. Glyceride mixtures, extremely purified triglycerides, or even waxes may be utilized. The second generation of SLNs, known as NLCs, modifies the potential drawbacks of SLNs. NLCs enhance stability and capacity loading during storage.¹⁴ Unlike SLNs, the lipidic phase in NLCs comprises both liquid and solid lipids. SLNs and NLCs are advantageous for parenteral, gene transfer, and other medication administrations due to their extensive properties.¹⁵⁻¹⁷ These formulations were created to improve treatment effectiveness while reducing the adverse effects of the potent medications. Several techniques are frequently employed for the preparation of SLNs, including high-pressure homogenization (hot and cold homogenization), evaporation or diffusion, solvent emulsification, ultrasonication or high-speed homogenization, supercritical fluid extraction of emulsions (SFEE), and spray drying¹⁸⁻²¹. Regardless of the preparation method, an initial emulsion is needed. The better the initial emulsion, the more easily the desired size range could be achieved.

However, cumulative decades of research on NLP preparation methods have paved the way for researchers. In this review, we strived to analyze numerous articles to categorize the formulating approach.

Composition of Solid Lipid Nanoparticles and Nanostructured Lipid Carriers

The chemical and physical characteristics of nanomaterials can be altered by size reduction, distinguishing them from their bulk and molecular counterparts. LNP formulations consist of two phases: approximately 0.1–30 (% w/w) of lipids dispersed in an aqueous phase. To improve stability, a combination of surfactants at concentrations ranging from 0.5% to 5% is added.²² For SLNs, the lipid phase consists solely of solid lipids, while in NLCs, the lipid phase comprises both liquid and solid lipids.²³ “Lipid” is a general term that encompasses triglycerides, steroids, fatty acids, partial glycerides, and waxes.²⁴ Lipid compounds derived from animal or vegetable sources are biocompatible, safe, and biodegradable.²⁵

Different classes of emulsifiers, varying in molecular weight and charge, are used to stabilize lipid dispersions.²⁶ According to the literature, using multiple emulsifiers more efficiently prevents particle agglomeration.²⁷ Table 1 lists the lipids that are most frequently utilized. The selection of surfactant or surfactant mixtures at suitable concentrations, considering the route of administration, is crucial for parenteral administrations and helps to maintain SLN stability. Since surfactant changes the surface characteristics of SLN, it has a substantial impact on SLN's quality.^{28,29} Proper selection of lipids and surfactants will impact physicochemical properties, particle size, long-term stability during storage, release behavior, and drug loading.³⁰

Formulation Preparation Strategy

Emulsifiers reduce surface tension due to the amphiphilic structure created by the alignment of hydrophobic and hydrophilic groups.³¹ Concerning the chosen lipid, the emulsifiers are selected since they need to be quantitatively and qualitatively compatible.³² To form an emulsion, it is essential to determine the hydrophilic-lipophilic balance (HLB) of the components which relate to their solubility.³³ The required HLB (rHLB) of the desired dispersion can be estimated through calculations based on the HLB of the lipid and the emulsifier(s). The stability of the overall formulation depends on choosing the best chemical emulsifier and estimating the rHLB³⁴. The emulsifier mixture must be adjusted to the lipid chains' tail interface to produce oil droplets in an aqueous phase.³⁵ Emulsifiers can either be adsorbed on the surface directly or loaded into the lipoidal matrix itself.³⁶

Concerning the hydrophilic group and its nature (i.e., HLB), emulsifiers are selected.³⁷ As the name suggests, emulsifiers with a non-ionic nature lack an ionic charge. Polysorbates and Poloxamers dissolve in the aqueous phase of emulsions, and the long polyoxypropylene chains allow

Table 1. The Components Utilized to Make SLN

SLN Preparation Components	
Lipid	Emulsifiers/Co-emulsifiers
Triglycerides	
Tricaprin	Poloxamer 182, 188, 407, 908
Trilaurin	Tyloxapol
Tristearin	Polysorbate 20, 60, 80
Trimyristin	Soybean lecithin (Lipoid S75, Lipoid S100)
Tripalmitin	Egg lecithin (lipoid E80)
Hydrogenated coco-glycerides (Softisan 142)	Phosphatidylcholine (Epikuron 170, Epikuron 200)
Hard fat type	
Glyceryl monostearate (Imwitor 900)	Sodium cholate
Glycerol palmitostearate (Precirol ATO5)	Sodium glycocholate
Glyceryl Behenate (Compritrol 888 ATO)	Sodium taurodeoxycholate
Palmitic acid	Sodium taurocholate
Decanoic acid	Sodium mono octyl phosphate
Stearic acid	Sodium taurodeoxycholate
Behenic acid	Butyric acid
Acidan N12	Butanol
Witespol W35, H35, H42, E85	Sodium docusate

Note. SLN: Solid lipid nanoparticle.

aggregation and stabilization.³⁸⁻⁴⁰ Sorbitan fatty acid esters dissolve within melted lipids and are adsorbed onto the surface more effectively.⁴¹ To avoid particle aggregation, an electrostatic charge is needed to improve the zeta potential; as a result, the use of ionic emulsifiers is essential.^{42,43} The negative and positive ions in the molecules of the ionic emulsifiers enhance the absorption of particles in the gastrointestinal system.⁴⁴ Another subclass of emulsifiers frequently employed is phospholipids.⁴⁵⁻⁴⁷ The fatty chain makeup of phospholipids derived from soy or egg phosphatidylcholine varies. Due to its amphiphilic qualities, it can also be used to increase permeability for topical administration, reduce particle size, and enhance emulsion stability,⁴⁸ as illustrated in Table 2.

Solid Lipid Nanoparticle Preparation Methods

The method used to solubilize the lipid determines whether the production of SLN should use organic solvents or not.⁴⁹ The suitable method is chosen based on the drug's characteristics such as thermal stability, molecular weight, and solubility.^{50,51} SLN preparation methods are summarized in Box 1.

Among the techniques mentioned above, high-speed homogenization (HPH) is the most practical one (both cold and hot HPH). After melting lipids, the drug is solubilized or distributed.⁵² In hot HPH, the mixture of the lipid phase with an aqueous surfactant solution is

Table 2. Common Emulsifiers and Their Characteristics in the Formulation

Type of Emulsifier	System's Structure	Size Range	Class	Example
Ions and small molecules	Nature of dispersed and continuous phase: O/W, W/O	0.1–5 µm		Short-chain fatty acids (e.g., Sodium Oleate), Lecithin
Non-ionic surfactants	Micelles/ Lamellar structures	size range: 10-100 nm		Polyoxyethylene sorbitan fatty acid esters (Tween®) Sorbitan fatty acid esters (Span®) Polyoxyethylene sorbitol esters (Mirj®) Alkyl aryl polyether alcohols (Tyloxapol) Polyoxypropylene poloxamer, pluronic, or Lutrol® (forming a triblock copolymer) Sugar esters Esters of acids, including lauric, oleic, palmitic, and stearic
Surfactant mixtures	Micellar emulsions (microemulsions)	5–50 nm. They are thermodynamically stable.		Tween®/ Span® Blends, pluronic-based systems
Ionic surfactant	Macroemulsions	20–100 nm. Similar to macroemulsions, only having kinetic stability.	Cationic Anionic	Stearylamine, cationic lipids, Esterqua Bile salts, sodium cholate, sodium taurocholate
Other phospholipid	Liposomes/Bilayer structures			Soy or egg, phosphatidylcholine
Non-ionic polymer	Bilayer droplet	100-1000 nm		Polyethylene Glycol Polymers
Polyelectrolyte	Double and multiple emulsions	100-5000 nm		Alginate, Chitosan, Polyacrylic Acid
Mixed polymer and surfactant	Mixed emulsions	variable		Example: Tween® 80 with Polyvinylpyrrolidone
Liquid crystalline phase	Hexagonal/Cubic	10-200nm		Examples: Monoolein, Glyceride systems
Solid particle	Pickered Emulsions	50-500 nm		Examples: Silica, Titanium Oxide, Solid Lipid Nanoparticles (SLN)

Note. SLN: Solid lipid nanoparticle.

Box 1. Techniques Used in Solid Lipid Nanoparticle Preparation

Different Methods of SLN Preparation
High shear homogenization
• Cold homogenization
• Hot homogenization
Ultrasonication/high-speed homogenization
• Bath ultrasonication
• Probe ultrasonication
Solvent emulsification/evaporation
Micro emulsion
Supercritical fluid
Spray drying
Double emulsion

homogenized by high shear homogenization.⁵³ To obtain the desired particle size, HPH is used to process the pre-emulsion.⁵⁴ Then, the lipid in the obtained nanoemulsion is recrystallized following a temperature decrease, and the SLN is formed.⁵⁵

There are noticeable differences between the cold and hot HPH method⁵⁶. The first is that the mixture of the drug in the melted lipid (solubilized or dispersed) is primarily cooled⁵⁷. To produce a microparticle suspension, the solid lipid mixture is grounded by a mortar in a solution containing aqueous surfactant.⁵⁸ HPH is used at room temperature or below to deliver a homogeneous microparticle suspension, forming NPs.⁵⁹ In cases when the drug exhibits sensitivity to heat, cold HPH can be used.⁶⁰ Distributing drugs in the aqueous phase leads to the production of supercooled melt products during

homogenization, and hot HPH results in crystallization. To overcome these drawbacks, cold HPH was developed.⁶¹

Due to its simplicity in scaling up, hot HPH has become the most frequently used technique, while methods such as high shear homogenization or sonication are less commonly utilized.⁶² High shear homogenization or sonication is used to facilitate the emulsification of the aqueous and lipid phases, heated to the same temperature. However, the final dispersion contains microparticles and NPs, which presents a notable disadvantage. The phases are heated above the lipid melting point in the microemulsion technique⁶³ and subsequently diluted with cooled water to form a nanoemulsion that will be cooled to form the SLN. While stirring, the critical factor is a temperature control that maintains the lipid in its melted condition.⁶⁴

Another technique for SLN synthesis is the double emulsion technique. In this method, a primary water-in-oil (w/o) emulsion is prepared using a high-shear homogenizer by solubilizing the drug in an aqueous phase, which is then added to the lipid phase containing a suitable emulsifier. The resulting mixture is further dispersed in a continuous aqueous surfactant phase to form the final water-in-oil-in-water (w/o/w) emulsion.⁶⁵ As a result of the drug being charged in the internal aqueous phase, hydrophilic drugs, proteins, and peptides could avoid chemical and enzymatic degradation.⁶⁶ The solvent evaporation technique is used for insoluble lipid drugs. An o/w emulsion is formed from the dispersion of a not water-miscible but lipid-soluble organic solvent in a solution consisting of an aqueous surfactant.^{67,68} The

Table 3. Quality Tests for Solid Lipid Nanoparticle

Characteristics	Description	Equipment Used
Mean particle size, electrical charge, and distribution		DLS
Microscopy	Verifying the particle's surface morphology, size distribution, and potential alternative forms that may have developed simultaneously.	SEM, SFM, and TEM
Thermal analysis	Studying polymorphic variations of lipid materials, crystallization, and thermal behavior.	DSC, TGA, TMA, and DTA
Crystallinity and polymorphism	Evaluation of crystallinity	X-ray
Infra-red spectroscopy	Molecular characterization of SLN	FTIR

Note. SLN: Solid lipid nanoparticle; DLS: Dynamic light scattering; SEM: Scanning electron microscopy; SFM: Scanning force microscopy; TEM: Transmission electron microscopy; DSC: Differential scanning calorimetry; TGA: Thermogravimetric analysis; TMA: Thermomechanical analysis; DTA: Differential thermal analysis; FTIR: Fourier-transform infrared spectroscopy.

organic solvent is evaporated during stirring.

The solvent displacement method was originally used to obtain polymeric NPs.⁶⁹ Using this method, the lipid phase is dissolved in a water-miscible organic solvent and then added to the aqueous surfactant solution by injection.⁷⁰ After diffusion or distillation, the solvent is completely removed, leading to the formation of LNPs by precipitation.

In the emulsification-diffusion process, the lipid is initially dissolved in a semi-polar organic solvent before being mixed with an aqueous surfactant solution to produce a w/o emulsion.⁷¹ Adding an excessive amount of water to the emulsion results in solvent diffusing out from the droplets, leading to SLN formation.⁷²

In another method known as phase inversion, the first step is to melt all components and stir using a magnet, then cool down to lower temperatures.⁷³ Three temperature cycles are employed to achieve the inversion process specified by a temperature range. Then, cold water is added to create an irreversible shock, which leads to the development of stable NPs.⁷⁴ In recent years, a novel approach has been developed in which SLN is obtained by controlled coacervation, initiated from fatty acid alkaline salts.⁷⁵

Tests Used for Quality and Structure Characterization of Solid Lipid Nanoparticles

As a drug delivery system, the physicochemical characterization of SLNs is essential for assessing their safety and stability. The most crucial factors investigated in nearly every SLN production-based study include lipid matrix polymorphism behavior, crystallization, and the colloidal stability of SLNs (Table 3).⁶ The most commonly used methods are presented in Box 1.

Conclusion

SLNs are complex systems with distinct benefits and drawbacks compared to other colloidal carriers. The issues of drug expulsion and stability in SLNs necessitated the development of NLCs. SLNs and NLCs have exhibited different structural forms depending on their lipid composition and the incorporated drugs. The highly unordered lipid matrix of NLCs enhances drug encapsulation, stability, and release profile. These

structures and other lipid NPs can be synthesized both in laboratory settings and on a large scale. Further studies are needed to comprehend the dynamics of LNPs in both in vivo and in vitro phases. Physically and chemically, SLNs provide a safe solid lipid-based delivery system suitable for transporting proteins and medicines with low water solubility. Investigating these characteristics is important as they significantly affect the biopharmaceutical behavior of SLNs. Although knowledge in this field has advanced considerably, it is still crucial to evaluate drug interactions with SLNs to predict their in vitro pharmacological profile. Ultimately, for SLNs to be recognized as a new generation of drug carriers, comprehensive structural studies are required.

Authors' Contributions

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Competing Interests

The authors declare no conflict of interests.

Ethical Approval

Not applicable.

Funding

This study was self-funded by the authors and received no external financial support from any funding organization.

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