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# Solid Lipid Nanoparticles: Formulation, Preparation, and Characterization: A Review

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## Abstract

The nano drug delivery system has emerged as a novel therapeutic approach for improved efficacy of the existing drug molecules. Polymeric nanoparticles, lipid based nanoparticles such as solid lipid nanoparticles (SLNs), nanostructured lipid carriers, lipid drug conjugates, ethosomes, liposomes, and self-emulsifying drug delivery systems are a few of the nano carriers used for drug delivery. Among the lipid based nanoparticles, SLNs are promising in terms of a biocompatible carrier for enhancing the bioavailability, controlled release, and targeted drug action. This review explains the formulation components of SLN, various methods of preparation of SLNs, and the characterization parameters of SLNs. The current successful research on SLN formulation also enlightens. The capability of various drugs for increasing therapeutic efficacy can be achieved through SLN and in the future, new directions in further improvement are expected.

**Keywords:** Biodegradable, Homogenization, Nanoparticle, Nanostructured lipid carrier, Solid lipid nanoparticle

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## Introduction

Nanoparticles are colloidal particles with nano size. The diameters of these nanoparticles are ranging from 1 to 1000 nanometers. The unique size-dependent characteristics of nanoparticles make them quickly emerging nano drug delivery carriers. At present, various nanoparticles are used as carriers for drug delivery, which is explained in Table 1.[1] The biocompatibility of the lipid matrix is the major advantage for lipid nanoparticles (LNPs) for major application drug delivery. The LNPs are of various types, this is depicted in Figure 1.[2,3] They can be categorized as solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), lipid-drug conjugates (LDCs), and lipid nanocapsules.[4] The size of SLNs and NLCs is in the range of 10–1000 nm.

## SLNs

SLNs are a better alternative to the other nano drug delivery carriers such as emulsion, polymeric nanoparticles, and liposomes [Table 2].[5] Biocompatibility, stability during storage, and preventing the degradation of a drug are the major advantages of SLNs which emerged in 1991. SLNs are colloidal drug carriers of submicron size made up of solid lipid and having 50–1000 nm.[6] SLNs are composed of solid lipid, surfactants, and, somewhere co-surfactants [Figure 2].[7] SLNs which are used orally have many advantages over the formulations used conventionally. Enhanced solubility, stability, increased bioavailability, and enhanced membrane permeability are the few advantages over conventional formulations. The SLNs also have a prolonged half-life and lesser side effects due to tissue targeting.[8]

## LDCs

The lipids are conjugated to drug molecules called LDCs. The lipophilicity of the drug increases with the LDCs. Other properties of drugs can also be changed with LDC. Enhanced oral bioavailability, lymphatic system targeting, tumor targeting, and less toxicity are a few of the advantages of LDCs.[9]

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## NLCs

NLCs are the colloidal drug carriers like the SLNs. The solid lipid of SLN is partly replaced with a liquid lipid or a mixture of liquid lipids. The major disadvantage of SLN is the drug expulsion from the lipid matrix. The lipid solidification and subsequent crystallization in the SLN lead to the expulsion of the drug from the SLN. To solve this instability, the solid lipid is partly replaced with liquid lipid. The liquid lipid may be a mixture of liquid lipid or singly a lipid liquid. The lipid phase in NLC is a solid state at room temperature and also in physiological body temperature. The better loading capacity and increased stability are the advantages of the NLC over the SLN. A large quantity of drugs is accommodated in the imperfections of NLC, which is formed due to solid and liquid lipid arrangement within the NLC. The recrystallization of solid lipids does not happen in the NLC, which allows more stability.[10] SLNs are completely prepared from solid lipids, whereas NLCs are prepared from solid lipids and liquid lipids.

## Advantages[11,12]

- Biocompatibility of the lipids and biodegradable nature of the lipids, that remain solid at physiological body temperature and controlled drug release, making SLNs an efficient nano drug delivery system.[7]

**Table 1:** Classification of nanoparticle drug delivery systems[1]

| *Biodegradable Nanoparticle* | *Biodegradable/ non-biodegradable* | *Biodegradable/ non-biodegradable* |
|---|---|---|
| Solid lipid nanoparticle | Polymerosomes | Carbon nanotube |
| Nanostructured lipid carrier | Polymeric nanoparticles | Magnetic nanoparticle |
| Niosome | | Silica nanoparticle |
| Nanoemulsion | | |
| Nano crystals | | |
| Liposome | | |

**Table 2:** Comparison with other lipid-based formulations[11]

| *Solid Lipid Nanoparticle* | *Liposome* | *Lipid Emulsion* |
|---|---|---|
| No drug leakage due to solid matrix | Drug leakage | Drug leakage |
| Stable against hydrolysis of drug | Hydrolysis | Hydrolysis |
| Stable against particle growth | Particle growth | Particle growth |
| Prolonged drug release | - | - |
| Comparatively stable during storage | Unstable during storage | Unstable during storage |


**Figure 1:** Lipid-based nano drug delivery system[2,3]

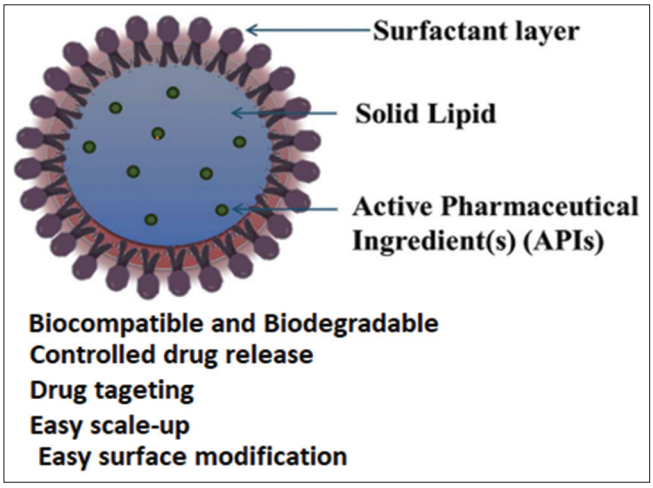


**Figure 2:** Solid lipid nanoparticle

- Controlled, sustained, and targeted drug release.
- The nonsolvent method of manufacturing SLNs can be adopted such as high-pressure homogenization or high-speed stirring methods, which do not use toxic organic solvents.
- Solid lipid matrices, showing high stability, are typical of SLN and NLCs.
- Drug delivery systems such as SLNs and NLCs can be employed for hydrophilic and hydrophobic drugs and with high entrapment efficiency.
- Targeted and site specific drug delivery can be achieved with SLNs coated with ligands.[13]
- The absorption and bioavailability of the drug can be improved with SLNs.
- Drug stability is improved with the SLNs.
- Can cause prolonged drug release.[14]
- SLN can be formulated with both lipophilic and hydrophilic drugs.
- The scalability is less costly and easier.
- SLN could be readily lyophilized and sterilized.
- Chemical degradation of the drug is reduced with SLNs.

Prolonged systemic circulation and effective transcellular transport at the delivery site are the features of nanosized SLNs.[5]

The advantages of SLN are depicted in Figure 3.

## Disadvantages[5,15]

- Particle size growth may be possible with SLNs.
- *In vitro* dissolution studies show changes in drug release profile.
- Lipid/aqueous partitioning is a formulation Challenge to face in loading of hydrophilic drugs in SLNs.
- Preparation techniques such as high-pressure homogenizers, ultrasonics, for SLNs are expensive and skill dependent.
- High-pressure-induced drug degradation is a major drawback in the manufacturing of SLNs.
- SLNs have a poor drug loading capacity, which is a drawback.
- The polymorphic transition during storage leads to drug expulsion from SLNs. low entrapment efficiency is also a drawback.[16]
- Water soluble drug loading in SLNs with low capacity and the high water content of SLN dispersions (70–99.9%) is a drawback of SLNs.[16]

## Types of SLNs

Models for drug incorporation in SLN include homogenous matrix, drug enriched shell, and drug enriched core model.[17] The various drug incorporation models are shown in the Figure 4

### Homogeneous Matrix Model

The drug is uniformly distributed in the solid lipid, in the uniform matrix model, or homogenous matrix model. SLN preparation by a cold homogenization technique, without using surfactants results in the preparation of the solid solution. When the lipid mixture is solidified, it is crushed to reduce the drug accumulation in different parts of SLNs.[17]

### Drug Enriched Shell Model

This model forms in the case of the hot homogenization technique to prepare SLNs. When the melted lipid contains the

API in minimal concentration, the drug enriched shell models are formed. In a hot O/W nanoemulsion, the lipid first precipitates when it is cooled. Therefore, in the melt, a higher concentration of drug molecules is formed. There is the formation of lipid core at the recrystallization temperature of the lipid. Repartitioning of the drug to the lipid phase happens during the cooling of the obtained dispersion. The concentration of drug achieved in the surrounding membrane in the Core-shell model. The dissolved drug in the lipid leads to supersaturation due to the cooling of the dispersion. There is the formation of drug enriched core, during the precipitation of drug in the lipid melt and then further cooling of the lipid melt causes the recrystallization of the lipid. The outer shell is finally solidified, containing both the lipid and drug.[18]

**Table 3:** Lipids used in solid lipid nanoparticle preparation

| *Triglycerides* | *Hard fat types* | *Monoglycerides* | *Fatty acids* |
|---|---|---|---|
| Tricaprin | Witespol W35 (a mixture of triglycerides 65–80%, diglycerides 10–35%, and monoglycerides 1–5%) | Glyceryl monostearate (Imwitor 900) | Stearic acid |
| Trilaurin | Witespol H35 triglycerides with portions of diglycerides (max. 15%) and max. monoglycerides 1%) | Glyceryl Behenate (Compritol 888 ATO) | Palmitic acid |
| Trimyristin (Dynasan 114) | Witespol H42 | Glyceryl palmitostearate (Precirol ATO 5) | Decanoic acid |
| Tripalmitin (Dynasan 116) | Witespol E85 | Cetyl palmitate (Crodamol CP) | Behenic acid |
| Tristearin (Dynasan 118) | | | |
| Hydrogenated coco-glycerides (Softisan 142) | | | |

## Drug Enriched Core Model

During the supersaturation process of dispersion cooling the crystallized drug forms a drug enriched center. The crystallized drug forms a membrane around the drug enriched core, already formed. The dissolved drug in the lipid leads to supersaturation during the dispersion cooling, which results in drug recrystallization before lipid recrystallization.[18]

## Drug Release from SLN

The weakly bound drug on the surface of SLN exhibits a bust effect, an initial rapid release of a drug. Following this quick process, the medication is released in a regulated and slow manner due to either drug diffusion through the SLN's lipid matrix and erosion or degradation of the matrix.[5]

# Ingredients for SLN

The Formulation ingredients should be Generally Recognized as Safe-GRAS. The formulation of SLNs includes a solid lipid core [Table 3], a surfactant [Table 4], and water with active drug and a liquid lipid if it is NLC[10] Surfactants or emulsifiers added to stabilize the lipid core.[19] Other ingredients added to SLN are also listed in Table 5.

# Production Methods

The SLN is prepared by various methods; these methods are classified as follows. The advantage and disadvantages of each method are summarized in Table 6. The various formulations of SLN currently published are given in Table 7.

- High pressure homogenization (HPH)
  - Hot homogenization
  - Cold homogenization
- Micro emulsion based method
- Ultra-sonication or high-speed homogenization
- Spray drying
- Supercritical fluid technology
- Solvent evaporation method
- Solvent-injection method
- Solvent emulsification-diffusion method
- Double emulsification method

**Table 4:** Emulsifiers used in solid lipid nanoparticle preparation

| *Phospholipid* | *Ethylene oxide/propylene oxide copolymers* | *Sorbitan ethylene oxide/propylene oxide copolymers* | *Bile salts* |
|---|---|---|---|
| soybean lecithin (Lipoid S 75, Lipoid S 100) (Amphoteric) | Polaxamers 182 (nonionic) | Polysorbate 20, 60, 80 | Sodium cholate (anionic) |
| Egg lecithin (Lipoid E 80) (Amphoteric) | Polaxamer 188 (PLURONIC F-68) (nonionic) | Polyoxyethylene sorbitan monolaurate (Polysorbate 20) Tween 20 (nonionic) | Sodium glycocholate (anionic) |
| Phosphatidylcholine (Epikuron 170, Epikuron 200 (Amphoteric) | Polaxamer 407 (PLURONIC F-127) (nonionic) | Polyoxyethylene sorbitan monostearate (Polysorbate 60) Tween 60 (nonionic) | Taurocholic acid sodium salt |
| | Poloxamine 908 | Polyoxyethylene sorbitan monooleate (Polysorbate 80) Tween 80 (nonionic) | Taurodeoxycholic acid sodium salt |
| Other Emusifiers<br>Butanol<br>Butyric acid<br>Dioctyl sodium sulfosuccinate<br>Monooctyl phosphoric acid sodium | | | |

- Membrane contractor method
- Microwave-assisted microemulsion-based technique

## Secondary Production Methods

- Freeze-drying
- Sterilization

### HPH

SLNs are primarily prepared by the HPH method. Two types of HPH techniques are used for SLN preparation, are hot homogenization and cold homogenization. In both of the homogenization processes, the drug is dissolved or dispersed into the lipid melt. The various advantages of this HPH method as compared to other methods are using a technology that is water based, obtaining the product with a narrow particle size distribution, Homogenization equipment are having regulatory acceptance, and the industrial production lines can be designed with HPH technique.[20] This technique involves HPH, in which the lipid and drug melt are introduced through a narrow micro size gap with high pressure (100–2000 bar).[21]

**Table 5:** Other ingredients used in solid lipid nanoparticle preparation

| | |
|---|---|
| Co-surfactant | Sodium dodecyl sulfate, Tyloxopol, Sodium oleate, Butanol, Taurocholate sodium salt, sodium glycocholate |
| Charge modifier | Phophatidyl glycerol, Stearylamine, Dicetylphosphate, Dimyristoyl phosphatidyl glycerol, Dipalmitoyl phosphatidyl choline |
| Cryoprotectant | Glucose, Mannose, Maltose, Lactose, Sorbitol, Mannitol, Glycine, Polyvinyl alcohol, Polyvinyl pyrrolidone, Gelatin, |
| Preservative | Thiomersal |

*Hot homogenization*

Preparation of SLNs is accomplished using the hot homogenization technique. This procedure is performed at a certain temperature above the melting point of the lipid. Into melted lipid, the drug is dissolved or dispersed. The aqueous emulsifier is dissolved in the aqueous phase and by taking both the phases a pre-emulsion is prepared by high shear mixing device. o/w emulsion is finally formed. In the next step, cooling this emulsion the lipid crystallization takes place and finally, the SLN is formed. The viscosity of the lipid phase is lowered due to higher processing temperature and as a result, smaller particle sizes of SLN are obtained.[6] High process temperature may increase the drug degradation rate and also the carrier degradation which is a disadvantage. During the homogenization process, the drug may enter into the aqueous phase, which may be another disadvantage. In general, 3–5 homogenization cycles with a pressure of 500–1000 bars are applied for SLNs preparation.[20] SLN were prepared using the high-pressure homogenizer withfive homogenization cycles to get the SLNs.[22] The complete procedure flow chart of hot homogenization has depicted in Figure 5

*Cold homogenization*

In the cold homogenization process drug is dissolved into lipid melt. Dry ice or liquid nitrogen is used to cool the lipid melt. The solid mass formed is ground by a mortar mill. This Milling produces nanoparticles of 50–100 nm size range. Then the cold emulsifier solution is taken and these nanoparticles are dispersed into it. Further HPH is subjected to this nanoparticle dispersion at or below room temperature.[17] Vinorelbine-loaded SLNs were obtained by the cold homogenization technique.[23] The complete procedure flow chart of cold homogenization has depicted in Figure 6.

**Table 6:** Methods of preparation and their advantages and disadvantages

| *Methods of preparation of solid lipid nanoparticle* | *Advantage* | *Disadvantage* |
|---|---|---|
| Hot high pressure homogenization | Low capital cost.<br>Speed, Scalability, avoidance of organic solvent.<br>Lab scale demonstration is possible. | Polydisperse particle distributions.<br>Unproven scale up.<br>Drug degradation at high temperature. |
| Cold high pressure homogenization | Prevention of drug degradation | Large particles, Broad size distribution. |
| Micro-emulsion | Less mechanical energy input<br>Stability is high. | Extremely sensitive to change. |
| Ultrasonication | shear stress is low | Metal contamination is possible<br>Physical instability like particle aggregation on storage |
| Spray drying | | |
| Supercritical fluid method | Solvents not used.<br>Particles are obtained in a dry powder form.<br>Temperature and pressure condition is mild.<br>Carbon dioxide is preferred as a solvent for this method. | Use of organic solvent, high expense |
| Solvent evaporation | Commercially Scalable technique.<br>Continuous process. | The process is highly energy intensive.<br>Polydisperse distributions. |
| Solvent injection | No special equipment is needed, simple | The additional solvent removal procedure |
| Solvent emulsification-diffusion method | Application for both hydrophilic and hydrophobic drugs, no heat required. | The additional solvent removal procedure |
| Double emulsification method | Applicable to hydrophilic drugs | Low EE and DL |
| Membrane contractor method | Scalability, Control of size | Clogging of the membrane |
| Microwave-assisted micro- emulsion-based technique | | |

**Table 7:** PDI values

| *PDI value* | *Remark* |
|---|---|
| 0-0.5 | Monodisperse and homogenous |
| More than 0.5 | Non homogeneity and polydispersity |
| Less than 0.3 | Homogenous |

PDI: Polydispersisity index

## Microemulsion Based Method

Microemulsions have two phases lipid phase and the aqueous phase. The aqueous phase consists of the surfactant or co-surfactant phase. To prepare the SLN, the lipid phase is melted which consists of fatty acids and glycerides. The aqueous surfactant and co-surfactant mixture are taken and are heated to an equal temperature as of the lipid melt. The aqueous phase is added under slow stirring to the lipid phase. After this microemulsion is formed, it is mechanically dispersed in a cold aqueous medium (38°C±2).[24] Finally, the SLN is produced. The principle is that when the microemulsion is added into water, it leads to lipid phase precipitation from the emulsion. In the end, fine particles of SLN are formed.[25] The complete procedure flow chart of micro emulsion based method has depicted in Figure 7.


**Figure 3:** Advantages of solid lipid nanoparticles

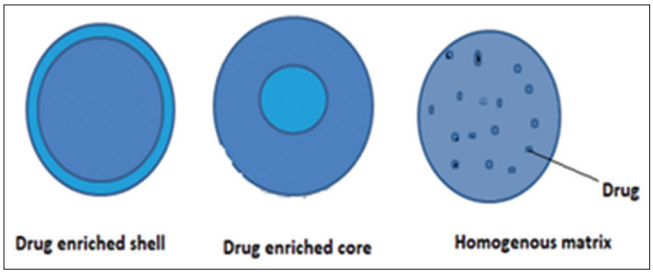


**Figure 4:** Drug incorporation models[6]

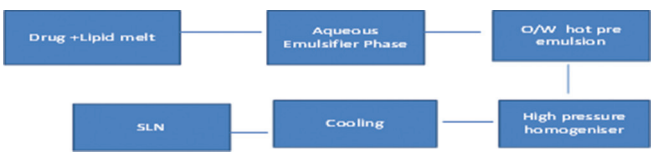


**Figure 5:** Hot homogenization process

## Ultra-sonication or High-speed Homogenization

The method involves the process of heating a solid lipid above its melting point at a temperature of 5–10°C. Surfactant solution in the aqueous phase is also heated up to the equal temperature of the melted lipid phase. Then the lipid melt is dispersed into the aqueous phase with high-speed homogenization conditions which is then subjected to ultrasonication process by a probe sonicator. Then the emulsion is formed and is cooled at room temperature, to produce the SLNs. This technique uses simple instruments. Organic solvents are not used in these methods. The product may contain metal contaminants and microparticles, which is a major drawback of this method.[26] The aqueous phase containing the surfactant in large amounts is a disadvantage, and this method cannot produce a narrow particle size of SLNs which is the cause of instability while storage.[27] The complete procedure flow chart of ultrasonication or high speed homogenization has depicted in Figure 8.

## Spray Drying

In the spray drying technique, high melting (≥70°C) lipids are used. This method is an alternative to the lyophilization method. The nanospray drying technique was used to prepare ultrafine powders of polysaccharide-coated SLN carriers by Wang *et al.*[28]

## Supercritical Fluid Technology

For SLN production this is a new method. When A fluid exceeds its critical value of temperature and pressure it is termed a supercritical fluid. This supercritical fluid has enough capacity to dissolve compounds. This technology involves many processes for

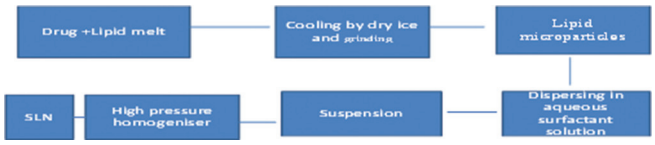


**Figure 6:** Cold homogenization process


**Figure 7:** Microemulsion based method


**Figure 8:** Ultrasonication or high speed homogenization

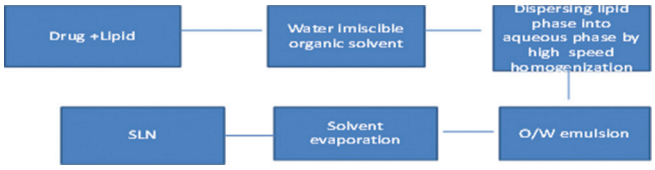


**Figure 9:** Solvent emulsification/evaporation

**Table 8:** Various solid lipid nanoparticle formulations

| *Name of the drug* | *Lipids* | *Emulsifier* | *Method of preparation* | *Reference* |
|---|---|---|---|---|
| Bortezomib | Trimyristin (Dynasan-114), tripalmitin (Dynasan116) and tristearin (Dynasan-118) | Egg Lecithin Poloxamer-188 | Hot homogenization followed by the ultrasonication | [43] |
| Brigatinib | Stearic acid | Soya lecithin | Solvent emulsification/evaporation technique using probe-sonication | [29] |
| Sorafenib | Glyceryl behenate | Soybean lecithin, poloxamer 188 | High-speed shearing and ultrasonic treatment. | [44] |
| Erlotinib | Glyceryl behenate, (Compritol 888 ATO) | Poloxamer 407(PLURONIC F 127), tween 80 | Hot homogenization method | [45] |
| Ceritinib | Glyceryl monostearate, glyceryl tripalmitate, glyceryl behenate (Compritol 888 ATO) glyceryl tristearate, glyceryl palmitostearate | Soy lecithin, Poloxamer-188 | Single emulsification and solvent evaporation method | [42] |
| Cisplatin | Stearic acid | Tween 80, Solutol HS 15 | Microwave-assisted technology | [36] |
| Indirubin | Cetyl palmitate | polysorbate 80 | HPH | [22] |
| Vinorelbine | GMS | Poloxamer 188 (F68) | Cold homogenization technique. | [23] |
| doxorubicin | Glyceryl caprate (Capmul MCM C10) | Polyethylene glycol 660 hydroxystearate (Solutol HS15) | Solvent emulsification-diffusion method | [33] |

HPH: High-pressure homogenization, GMS: Glyceryl monostearate

nanoparticle preparation such as the aerosol solvent extraction solvent, the rapid expansion of supercritical solution, particles from gas saturated solution, and supercritical fluid extraction of emulsions. The advantages of this technique are solvents are not used, final particles are in dry powder form.[20] The various processes of supercritical fluid technology and the benefits of this in the production of SLN are novel techniques in the present era.[16]

## Solvent Emulsification/Evaporation

In this method, water-immiscible organic solvents are used to dissolve the lipids. Water-immiscible organic solvents are cyclohexane, dichloromethane, toluene, and chloroform.[12] Then the surfactant is dissolved in the aqueous phase. The organic phase is added to the aqueous phase and finally, o/w emulsion is formed. Then the emulsion is evaporated under reduced pressure and the organic solvent phase is removed. After evaporation of the organic phase the lipids precipitate in the aqueous phase and the dispersion of nanoparticles takes place in the aqueous phase. The main disadvantage is the use of organic solvent in the process. The variation in particle size can be produced, depending on the type of solid lipid and surfactant used in the process.[18,29] [18,29] The complete procedure of solvent emulsification or evaporation has depicted in Figure 9

## Solvent Injection Method

In this method, water miscible solvent or solvent mixture is taken, for example, methanol, ethanol, isopropanol, or acetone. The drug is dissolved into the solvent or solvent mixture. The emulsifier is added to water and the aqueous phase is prepared.[30] Then with continuous mechanical stirring Injection of organic phase into the aqueous phase carried out by a needle. Slowly the SLN is formed. Modified solvent injection technique is used to prepare andrographolide (AD) SLNs. The lipid used is cetyl alcohol (10 mg) and the drug AD (1 mg). Both the lipid and the drug are dissolved in ethanol (1 ml), which forms the organic phase. Surfactant (0.2% tween 80) and stabilizer (0.2% polyvinyl alcohol) are dissolved in 10 ml water which forms the aqueous phase. The organic phase was rapidly injected into the aqueous phase by an injection needle under stirring. The dispersion was continuously stirred for 30 min. After stirring, the dispersion was kept for 12 h for the solvent evaporation completely. The excess lipid is removed by filtering with filter paper.[31] The advantage of the solvent injection method is, it requires simple instruments and a rapid production process.[30] To prepare Curcumin SLNs, the solvent injection method is used which is simple, effective, and versatile and finally, the curcumin SLNs are obtained.[32] The complete procedure flow chart of solvent injection has depicted in Figure 10.

## Solvent Emulsification Diffusion

In this technique, the solvent used are benzyl alcohol, butyl lactate, ethyl acetate, isopropyl acetate, methyl acetate, which are partially miscible with water. Initially, the partial water miscible solvent is made saturated with water. Then to this water saturated solvent, lipid, and drug added and dissolved a solvent saturated aqueous solution with a stabilizer is prepared. The organic phase was emulsified with an aqueous phase using a mechanical stirrer to form o/w emulsion. Finally, water is added to the emulsion as a dilution medium in the ratio from 1:5 to 1:10. The solvent diffuses into the continuous phase. In the end, the nanoparticles are formed.[1,12]

This method is used to prepare Methotrexate SLNs. 10-ml of acetone and ethanol (1:1 v/v) mixture is taken. 100 mg of lipid (stearic acid, monostearin, tristearin, and Compritol 888 ATO) is taken and dissolved in the acetone and ethanol mixture. Both are heated in a water bath at a temperature of 45°C. The acidic aqueous phase of the drug MTX (10% w/v) is prepared and it also contains 1% w/v soya lecithin. The total amount prepared is 200 ml. Then the lipid phase is added to the aqueous phase under mechanical stirring continuously. The instrument's operation specifications are 4000 rpm at room temperature (25–28°C) for 5 min. Finally, the SLNs suspension was prepared. Centrifuged at 4000 rpm for 20 min, the SLN dispersion was resuspended in distilled water. Soya lecithin

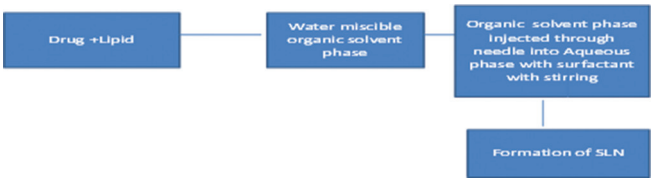


**Figure 10:** Solvent injection method

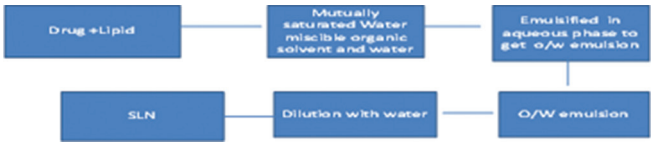


**Figure 11:** Solvent emulsification and diffusion method

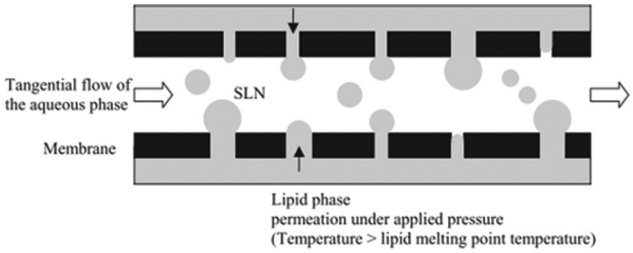


**Figure 12:** Membrane contractor method

of different concentrations was used to prepare SLNs. Solvent emulsification-diffusion method is also used to prepare SLNs loaded with doxorubicin.[33] The complete procedure flow chart of solvent emulsification and diffusion has depicted in Figure 11.

## SLN Produced by Double Emulsion Method

For the production of SLN loaded with a hydrophilic drug, aqueous based solutions are used to dissolve the hydrophilic drug. Then it is emulsified in the melted lipid. For the stabilization of the primary emulsion, the emulsifier is added. The prepared primary emulsion is now dispersed in the aqueous phase and a hydrophilic emulsifier is added to this aqueous phase. Finally, the double emulsion is formed. This emulsion is blended and then separated by filtration. This double emulsion method is used for the preparation of SLN loaded with hydrophilic drugs, which is based on solvent emulsification and evaporation. For the emulsification process for the primary w/o emulsion, hydrophilic drugs (peptides) are encapsulated by this technique.[12,21]

## Membrane Contractor Method

This method includes the pressing of the lipid phase with a temperature higher than the melting temperature of the lipid. So that it forms small droplets of melted lipid. The aqueous phase flows in the membrane module and the flow is tangential. During this flow of the aqueous phase, it carries away the lipid droplets forming at the pore. After cooling the preparation below the lipid melting point, at room temperature, the SLN is formed.[34] In large scale SLN production, the membrane contractor technique is a new method.[35] The complete procedure flow chart of membrane contractor tecnique has depicted in Figure 12

## SLN Preparation using the Microwave-assisted Microemulsion-based Technique

This technique is used to prepare SLNs. This process involves heating inside a microwave reactor tube. A mixture of all the formulation components such as stearic acid, Tween 20, and water are heated in a microwave reactor tube at a temperature of 80°C with constant stirring for 10 min. A microemulsion of o/w type is formed. Miconazole nitrate or econazole nitrate was added in the formulation ingredient. This is heated in the reactor tube to get the SLNs. o/w microemulsion was dispersed in cold water with continuous magnetic stirring to produce the SLN dispersion.[26] Cisplatin-loaded SLNs are produced by using the microwave assisted technique.[36]

The secondary production methods are Freeze drying and sterilization in the production of SLNs.

## Freeze-drying

Lyophilization or freeze drying increases the chemical and physical stability of hydrolyzable drugs for oral administration over extended periods. The hydrolytic reaction is prevented due to freezing drying. During freeze drying of the product, the removal of water may cause aggregation of the nanoparticles, which can be avoided by adding cryoprotectants.[24] The cryoprotectant effect is observed by adding trehalose, mannitol, sucrose, and fructose at the concentration of 5% and 10% w/v and these are added to the SLN before freeze drying.[33]

## Sterilization

SLN must be sterile for the formulations meant for intravenous and ocular administration. To achieve sterilization, the various methods are employed are filtration, autoclaving, aseptic production, and gamma irradiation. The sterilization with autoclave causes hot o/w microemulsion formation and size modification of nanodroplets. To avoid this problem, sterilization of the starting materials or exposure to ethylene oxide gas (EO) can be adopted for an aseptic manufacturing process for the SLNs. The lyophilized SLN dispersion can be sterilized by exposing it to EO. Freitas observed that particle destabilization may happen due to chemical reactions. To give a protective effect to the formulation purging with nitrogen can be a process. To prevent the increase in particle size of the SLN, the lipid content is lowered (to 2%) and surface modification of the glass vials is also implemented.[17,24]

# Characterization and Evaluation of SLNs

The SLNs are characterized with their different parameters to assess the quality of the final SLN formulation. The various parameters which are generally studied for the SLNs are, particle size and size distribution, zeta potential, the coexistence of additional colloidal structures which may be micelles, liposome, supercooled melts, drug nanoparticles, degree of crystallinity, and lipid modification (polymorphism), drug content, surface morphology, and *in vitro* drug release.[24]

The various parameters for characterization and evaluation of SLNs are

- Particle size and polydispersity index (PDI)
- Surface morphology

- Zeta potential
- Degree of crystallinity
- Co-existence of additional colloidal structures
- Encapsulation parameters
- *In vitro* drug release

## Particle Size and PDI

The particle size/size distribution is studied using various techniques such as photon correlation spectroscopy (PCS), transmission electron microscopy (TEM), laser diffraction (LD), scanning electron microscopy (SEM), scanning tunneling microscopy, atomic force microscopy, or freeze fracture electron microscopy.[24] Particle size distribution of SLNs can be measured by PDI. The PDI can also be measured by PCS and the values of PDI are given in Table 8.[37]

## Surface Morphology

Electron microscopy technology like SEM is used for 3D images of the particles and surface morphology. The size and shape of nanoparticles and internal structure are depicted by TEM.[6]

## Zeta Potential

Zeta potential is a formulation characteristic of SLNs shows information about colloidal stability. Zeta meter is used to measure the zeta potential. Storage stability of colloidal dispersion is described by zeta potential. Particles generally do not aggregate due to repulsion created by electric charges due to high zeta potential. For the colloidal dispersion to be stabilized, the zeta potential value should be >±30 mV. Electrostatic repulsion plays an important factor in the stability of colloidal dispersion. Particles under storage conditions may also be stabilized with zeta potential near zero. Steric stabilization is another aspect to avoid aggregation of particles, by creating a physical barrier around the nanoparticles. Hydrophilic polymers (e.g. PEG) are used to coat the SLN for steric stabilization.[6] The ZP value of −30 mV is essential for the stabilization of SLNs.[37]

## Degree of Crystallinity

Powder X-ray diffractometry is the technique used to study the crystal structure of the SLN. If there is any lipid modification then the crystal changes lead to a change in the thermodynamic stability of the crystal, lipid packing density, and change in the drug incorporation into the dosage form. X-ray powder diffraction technique measures the geometric scattering of radiation from the various crystal planes of the solid and the degree of crystallinity is studied.[26]

The nature of crystals and degree of crystallinity of lipid within nanoparticles influence the drug incorporation and the drug release rate. The degree of crystallinity can be determined using a thermo-analytical technique such as differential scanning calorimetry (DSC). The DSC makes use of the principle that different melting points and melting enthalpies are different for various lipid modifications. DSC also depicts the interaction of drugs with LNPs. The inclusion of drug molecules in the crystal lattice can change the melting point, if there is no change in melting point it shows that there is no interaction between drug and lipid.[26]

## Co-existence of Additional Colloidal Structures

For the SLN dispersions, there may be the coexistence of other colloidal structures such as micelles, liposomes, mixed micelles, supercooled melts, and drug nanoparticles in addition to the SLNs. The various analytical techniques, such as NMR and ESR, are the tools to predict the dynamic phenomena of colloidal structures and the characteristics of various nanoparticles in colloidal lipid dispersions.[38]

## Encapsulation Parameters

The amount of drugs entrapped or loaded in the SLN has to be determined. It is a very essential parameter for the SLN characterization.[39] The amount of drug which is encapsulated in the nanoparticle per unit weight has to be determined for the final characterization of SLNs. First, the free drug and the solid lipid are separated from the aqueous medium. The various parameters such as Entrapment efficiency (EE) and drug loading capacity (LC) are determined. The drug content is determined by spectrophotometry.[40]

$$EE\ (\%) = \frac{Amount\,(mg)\,of\ loaded\ drug\ determined\ experimentaly}{Theoretical\ amount\ of\ drug\,(mg)\,in\ formulation} \times 100$$

$$LC\ (\%) = \frac{Amount\,(mg)\,of\ loaded\ drug\ determined\ experimentaly}{Theoretical\ amount\ of\ lipid\,(mg)\,in\ formulation} \times 100$$

## *In vitro* Drug Release

*In vitro* drug release from SLN can be achieved by the dialysis method and the static or dynamic Franz diffusion method.[39] The drug which is entrapped in the SLN is homogenously dissolved in the solid lipid matrix, sometimes the drug is localized in different regions of the drug matrix.[41] The *in vitro* drug release is studied by using the dialysis membrane method. In this method, the dialysis membrane with molecular weight 12000–14000 was soaked in water using 0.01 M HCL dissolution media. The dialysis membrane has both donor and acceptor compartment. A 150 mg of SLN formulation is filled in the donor compartment and 100 ml of release medium is filled with the receptor compartment. The temperature maintained is 37 ± 0.5°C. About 3 ml sample is withdrawn from receiver compartment at intervals of 15, 30, 45, 60, 90, 120, 240, and 360 min followed by dilution with dissolution medium. The samples are analyzed for UV absorbance at $\lambda$ max 319.6 nm. The complete procedure is followed for the dissolution study.[42]

# Conclusion

The SLNs form an excellent drug delivery system for various types of drugs with limited bioavailability. Anticancer drugs with efficient drug delivery with improved therapeutics have possible due to SLNs. The various methods of preparation of SLNs and modifications in the method of preparations are continuously

developing to improve the quality of SLN in the manufacturing process. Characterization process of SLN with improved techniques benefits for producing quality SLNs.

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