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Comprehensive Review on Solid Lipid Nanoparticles

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Abstract

Nowadays researchers have been focused on solid lipid carriers as colloidal drug carrier systems, which combine the advantages of other smart nanocarriers. Solid Lipid Nanoparticles (SLN), it remains solid at room temperature, developed a novel pharmaceutical delivery carrier system. This review article focused on various approaches in industrial scale-up techniques of solid lipid nanoparticles with its advantages and disadvantages. It may help the researcher to select an appropriate method for the development of SLN according to their choice of drug delivery.

Introduction

The SLN is submicron colloidal carriers with the particle size range from 50 nm to 1000 nm which are comprised of physiological lipids, dispersed in water or an aqueous surfactant solution. They are made up of solid hydrophobic core having a monolayer of phospholipid coating. The solid core encloses the drug dissolved or dispersed in the solid high melting fat matrix as shown in Figure 1. They are capable to carry both lipophilic and hydrophilic drugs [1-3].

Advantages of SLN

The solid lipid matrix, in the SLN, leads to the protection of drug-loaded in carriers from various chemical degradation; therefore, it can offer more drug stability. It can be prolonged drug release by reducing the fluctuation in the therapeutic region there for so it can have a control drug release profile with low toxicity [4]. It has the potential to simple and large scale production with low toxicity. SLN is produced by high-pressure homogenization, therefore basically scaling-up to medium scale level, and industrial production level should be possible [5,6]. The use of biocompatible compounds for preparing SLN allows the avoidance of the toxicity problems, which are often associated with the administration of polymeric nanoparticles. Polymeric nanoparticles may contain toxic monomer residues or solvents and may form toxic degradation products [7]. SLN can be incorporate both lipophilic as well as hydrophilic drugs as compared to other conventional colloidal carriers [8-13]. Production of lipid particles avoids the use of potentially toxic additives such as organic solvents or toxic monomers. Rigid solid particles prepared are stable against coalescence, and the lipid matrix prevents drug leakage from the carrier [14].

Disadvantages of SLN

However, leakage of drug content, high concentration of water content and insufficient drug loading may lead to the conversion of solid lipid nanoparticles to nanostructured lipid carriers [15-17]. It was reported that during storage there is a chance of polymeric transition of solid lipid due to the drug expulsion i.e. transition of lipid molecule from polymeric form to crystalline without changing the internal structure [18,19]. There are several reports on physical instability of SLN; upon prolonged storage [15,17-20].

Method of Preparation of SLN

Solid Lipid Nanoparticles (SLN) are dispersed systems extensively used in literature for drug delivery. Several methods are described in various literature to produce SLN, such as High-Pressure Homogenization (HPH) such as cold and hot homogenization, high-speed homogenization/ ultra-sonication, spray drying, double emulsion method, coacervation technique, cold dilution of microemulsion, emulsification solvent evaporation method solvent injection method film-ultrasound dispersion supercritical fluids, and membrane contactor technique. The current review also focuses on the various advantages and disadvantages of each of the said techniques.

High-pressure homogenization (HPH)

The most popular production technique is considered to be the High-Pressure Homogenization (HPH) which can be operating at low or high temperatures [21,22]. It has been reported that HPH

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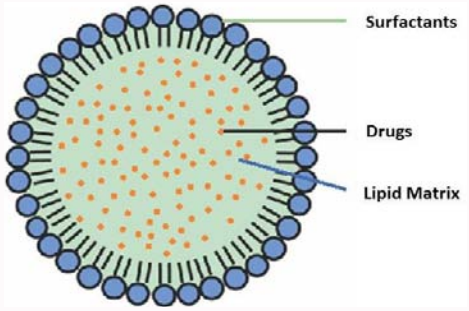

Figure 1: Structure of Solid lipid nanoparticle.

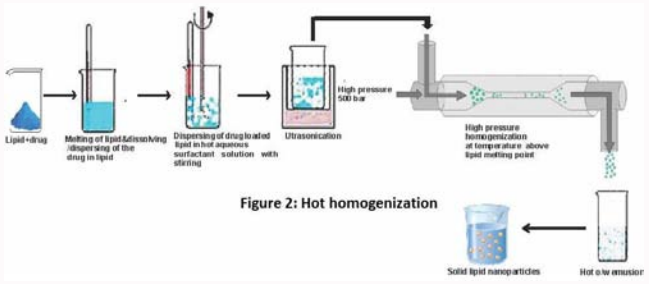

Figure 2: Hot homogenization.

is the technique used for more than fifty years for the production of parenteral nutrition, such as Intralipid® and Lipofundin® [23].

Hot homogenization: The first step in this process is the melting of the lipid and dissolving or dispersing of the drug in the lipid melt. Then dispersing this drug-loaded lipid melt in a hot surfactant solution. Premixing is carried out with the help of an ultrasonicator. Then this emulsion is passed through the high-pressure homogenizer, where the temperature should be kept above the lipid melting point. Finally, hot O/W nanoemulsion is cooled down to room temperature where the lipid recrystallizes and leads to the formation of nanoparticles [24] (Figure 2).

Cold homogenization: The first step of this technique is the same as that of hot homogenization which includes dispersion or dissolving or solubilization of the drug in the melted lipid. Then the drug lipid mixture is rapidly solidified either with the help of liquid nitrogen or dry ice. The drug-loaded solid lipid is milled by using a roller mill or ball mill to a micron size range of 50-micron to 100 micron and further microparticles are dispersed in chilled emulsifier solution to obtain a pre-suspension (Figure 3). Then this pre-suspension is subjected to high-pressure homogenization at room or below room temperature, where the cavitation force is strong enough to break the microparticles to SLN [25].

Advantages: Hot homogenization method is most suitable for hydrophobic or lipid derivate, direct incorporation of such drugs are easy in this method. This method is suitable for large scale-up.it was reported that this technique can be used to produce small particle diameter with a low poly dispensability index usually below 0.2 [22-25]. HPH technique doesn't require any usage of toxic organic solvent.

Disadvantages: When hot homogenization compares with cold homogenization, SLN developed by cold homogenization particle size and poly dispensability index is more. By using cold homogenization, we can only minimize the thermal contact of the

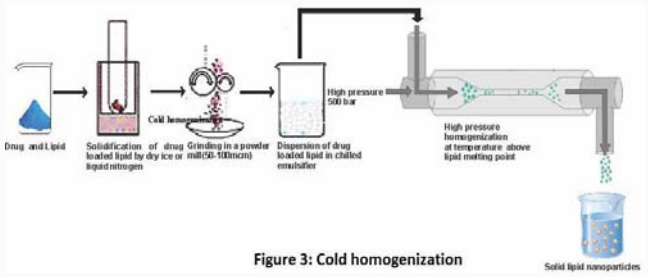

Figure 3: Cold homogenization.

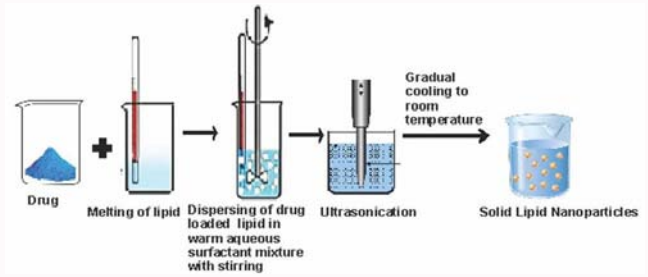

Figure 4: High- speed homogenization.

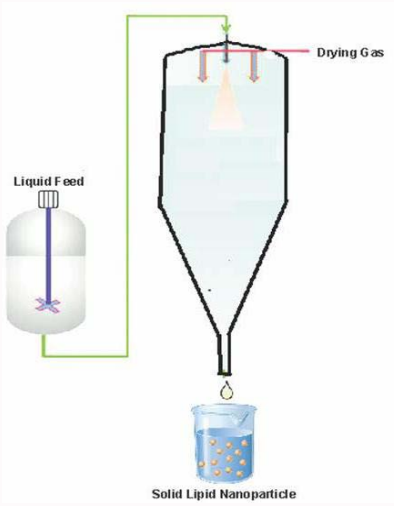

Figure 5: Spray drying.

drug, but it does not completely avoid it because it also required the melting of the lipid/drug mixture in the first step of preparation. During High-pressure homogenization temperature of the sample will be increased gradually. Generally, 3-5 homogenization cycles at 500-1500 bars are required to prepare SLN. While increasing the number of homogenization cycle or the homogenization pressure it may lead to an increase of particle size because of particle coalescence which caused by the high kinetic energy of particles.

High-speed homogenization and/or ultrasonication

This method is used to obtain concentrated lipid nanoparticle dispersion [26]; the first step in this method is the addition of drug into melted lipid. This methodology is built on dispersing the melted lipid in the warm aqueous phase (about 5°C to 10°C above its melting point to prevent recrystallization during the process,) containing surfactants by high shear homogenization to form an emulsion. The obtained pre-emulsion was ultrasonicated using probe sonicator on a laboratory scale with a water bath (at 0°C) (Figure 4). The obtained

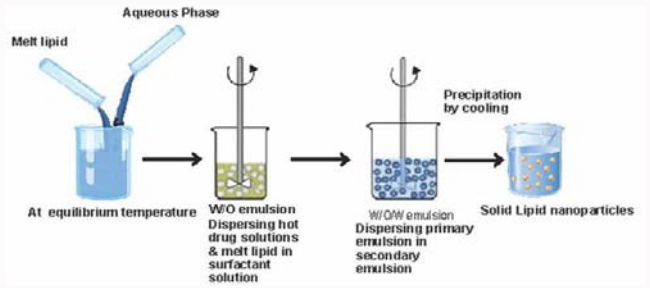

Figure 6: Double emulsion method.

nanoemulsion (o/w) was filtered through a 0.45 µm membrane in order to remove impurities carried in during ultrasonication. Then they obtained SLN is stored at 4°C [27].

Advantages: It was reported that curcuminoids SLNs were fabricated using the hot nanoemulsion procedure employed high-speed homogenizer and ultrasonic probe on laboratory and curcuminoids SLN showed physical and chemical stability for up to 6-month storage because of both small particle size and being in a dry powder [27,28].

Disadvantages: The preparation of LNP with these methods involves several critical process parameters like high temperatures, high pressures, high emulsifier concentrations, etc. For example, heat and cavitation cause significant thermo dynamical and mechanical stress for the resulting product and also products get contaminated with impurities during ultra-sonication.

Spray drying

It is considered to be an alternative method to the lyophilization process. This recommends the use of lipid with a melting point more than 70°C. It was reported that there are different approaches to produce drug-loaded SLN-based formulations by Spray Drying (SD). In the first approach is that the drug-loaded SLN nanosuspension can be converted into a powder (Figure 5) in the second approach a suspension of drug-loaded SLN in a polymer solution yields SLN/polymer composites, which can later dissolve to give free SLN; the third one is a solution of lipid, drug, and polymer can be converted into SLN-loaded polymer particles in the SD step, and again the latter can be dissolved in an aqueous medium to free the SLN, and finally, a lipid/drug/polymer solution can be processed into a molecular dispersion composite, which then self-assembles into drug-loaded SLN when water is added.

Advantages: It was reported that Spray drying has extensively explored to generate formulations of active pharmaceutical ingredients with systems containing etravirine, ivacaftor, tacrolimus, itraconazole, and everolimus [29,30]. Spray drying can be commonly used in the bottom-up self-assembly of nanoscale objects [31]. Completely dried SLN is obtained by this method and which is cost-effective than the lyophilization process.

Double emulsion method

In the double emulsion method, the hydrophilic drug is dissolved in aqueous solution and then was emulsified in melted lipid. This primary emulsion was stabilized by adding suitable stabilizers such as gelatin, poloxamer-407. Then this stabilized primary emulsion was dispersed in an aqueous phase containing hydrophilic emulsifier like PVA. Further, the double emulsion was stirred and was isolated by filtration [32] (Figure 6).

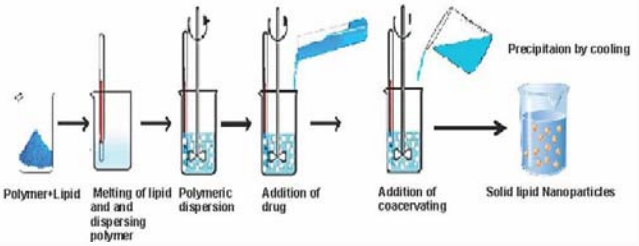

Figure 7: Coacervation Technique.

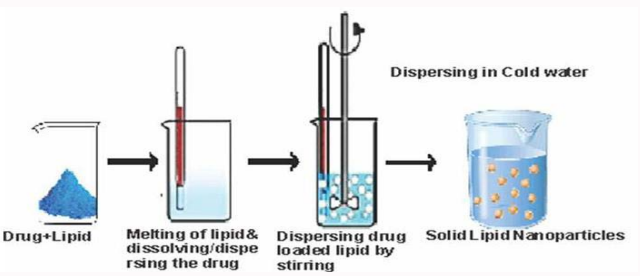

Figure 8: Cold dilution method.

Advantages: This technique was selected because it makes the encapsulation of peptides feasible. Additionally, the surface of the particles could be modified through the incorporation of Poloxamer 188 or the lipid derivative PEG 2000-stearate into the formulation.

Disadvantages: The preparation of SLN with these methods involves several critical process parameters like high emulsifier concentrations [32].

Coacervation Technique

This is a solvent-free technique for SLN production new, solvent-free SLN and it was defined as coacervation: briefly, when the pH of a micellar solution of fatty acid alkaline salt is lowered by acidification, fatty acid precipitates owing to proton exchange between the acid solution and the soap. This technique is based on the acidic precipitation of soap micellar solutions [33-36]. The first step in this method is preparation of aqueous polymeric stabilizer stock solution. Dispersion of the sodium salt of the fatty acid in the prepared polymeric stabilizer stock solution, and this mixture is heated above the Krafft point of the sodium salt of the fatty acid with constant stirring to obtain a clear solution. Then add the dug solubilizes in ethanol to the clear solution, with constant stirring, until a single phase is obtained. Finally, add the coacervating solution i.e. acidifying the solution. By the drop by the addition of this solution yields a nanosuspension. Further cooling of the suspension in a water bath, under constant agitation, yields drug-loaded nanoparticles (Figure 7).

Advantages: SLN can encapsulate dug with high efficiency in its monomeric form Coacervation technique, a solvent-free, and easy to scaleup, feasible and versatile method, based on a phase transformation from soap micellar solution into fatty acid solid particles by acid addition.

Cold dilution of microemulsion

This work is a novel technique for the preparation of SLNs called cold dilution of the microemulsion is used [37]. It was reported that cold dilution of microemulsion as a modified method of solvent diffusion method [38]. In this method the first step is the preparation

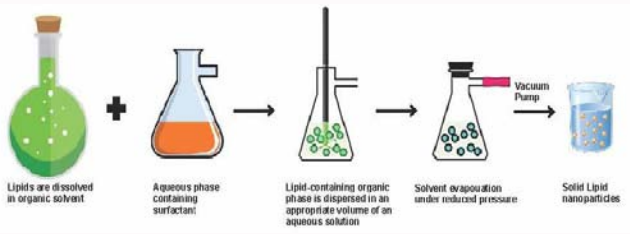

Figure 9: Emulsification solvent evaporation method.

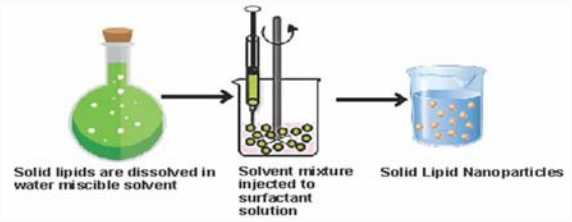

Figure 10: Solvent injection technique.

of O/W emulsion at room temperature; here solid lipid dissolved in a partially water-soluble organic solvent is the hydrophobic phase and drugs are dissolved in a water-miscible solvent and then those hydrophilic and lipophilic phases are kept at equilibrium condition, finally both phases are kept under continuous stirring at room temperature to form O/W emulsion. This o/w nanoemulsion is further cooled at room temperature or 4°C to precipitate SLN from it (Figure 8).

Advantages: All the ingredients used are biocompatible; no organic solvents are used in the preparation this technique does not require low or high temperature. No need for pH modification, ultrasonication, homogenization, or pressure variations. Also, toxic organic solvents are not required, which is beneficial for scale-up.

Emulsification solvent evaporation method

In this method, the first step is lipids are dissolved in an organic solvent (e.g. cyclohexane). The lipid phase is then emulsified in an aqueous phase which containing drug at high-pressure homogenization. The organic solvent was removed from the emulsion by evaporation under reduced pressure (40 mbar to 60 mbar). Evaporation of solvent leads to precipitation of the lipid in the aqueous medium yields drug-loaded nanoparticles [33] (Figure 9).

Advantages: This method is easily scalable and a continuous process.

Disadvantage: It is an extremely cost-effective process and in which poly dispersed distributions may occur. Toxicological problems arising from solvent residues [38].

Solvent injection technique

The lipids are dissolved in water-miscible solvent (e.g. acetone, isopropanol, and methanol) and this mixture (1 mg/ml to 100 mg/ml) is introduced into an injection needle aqueous media contains surfactant with constant stirring (330 rev/min) and filter the nanosuspension formed to remove the excess of lipid [39-41] (Figure 10).

Advantages: This technique does not require low or high temperatures. No need for pH modification, ultrasonication, homogenization, or pressure variations.

Film-ultrasound dispersion

In this method the lipid, as well as the drug, were dissolved into suitable organic solutions, then aqueous phase containing surfactant solution is introduced to the lipid phase with continuous stirring and upon evaporation of the organic solutions, a lipid film is formed. Further, continue the stirring using the ultrasound with the probe solicitor finally, the SLN with tiny and poly dispersed particle size is formed [42] (Figure 11).

Supercritical fluids

It has been reported by numerous researchers that Supercritical Fluids (SCFs) based techniques have been effectively utilized in several fields such as the micronization extraction of natural matter, impregnation of metals or drugs in aerogels, membranes and scaffolds production [43-48]. Supercritical Assisted Injection in a Liquid Antisolvent (SAILA) is an effective method, which includes injection of a solution that contains solid solute dissolved in an organic solvent containing controlled quantities of SC-CO_2, in an antisolvent (e.g.: water) solution. To obtain particle precipitation, the solute should be such a way that it has to be soluble in the solvent, but not in the antisolvent simultaneously, the solvent and the antisolvent have to be completely miscible. SC-CO_2 dissolved in the solution solvent-solute, decrease the mixture viscosity and surface tension that will favor the atomization in the antisolvent. A saturator that contains high surface packing's and ensures long residence times are used and a near-equilibrium solution between solute, solvent, and CO_2 is formed. Then, this expanded liquid solution is sent to a thin wall injector and sprayed into the precipitation vessel containing the antisolvent mixing of the two fluids produces a rapid supersaturation and particle precipitation, consequently (Figure 12) [48].

Advantages: This process offers several advantages no thermal degradation, use of nontoxic solvents, directly producing a stabilized water suspension and it provides good control on particle size distribution [46-49].

Membrane contactor technique

It is a novel technique to prepare the SLN. In this technique at a temperature above the melting point of the lipid, it was pressed through the membrane pores to form small droplets. At the same time, the aqueous phase was circulated tangentially inside the membrane module with constant stirring and also bows the droplets being formed at the pore outlets. When it cools at room temperature, SLN is formed. In which both the phases were placed in the thermo stated bath to maintain sufficient temperature and pressure at the liquid phase was created by nitrogen gas [42,50] (Figure13).

Advantages: SLN preparation using a membrane contactor is shown to be its facility of use, the control of the SLN size by an appropriate choice of process parameters and it's scaling up ability.

Disadvantages: The main drawbacks of this method are potential metal contaminations, physical instability like particle growth upon storage.

Conclusion

SLN have been developed to overcome the drawback associated with conventional colloidal drug carrier and also it can promise combines the advantage of polymeric nanoparticles, fat emulsions, and liposomes such as the feasibility of incorporation of both lipophilic and hydrophilic drugs, improved physical stability, ease of scale-up, and manufacturing. In this review article author made an

attempted to explore the various approaches in method of preparation of SLNs including novel and modified method with its advantages and feasibility. It is concluded that various techniques used in the method of preparation of SLN was found to be as simple as compared to other conventional drug carriers.

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