WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.084
Volume 9, Issue 10, 414-424. Review Article ISSN 2277– 7105

DEVELOPMENT OF SOLID LIPID NANOPARTICLES METHODS AND ITS EVALUATION PARAMETER: A REVIEW

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Article Received on
11 July 2020,

Revised on 01 August 2020,
Accepted on 21 August 2020

DOI: 10.20959/wjpr20210-18510

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KEYWORDS: Solid lipid nanoparticles, Colloidal drug carriers, Homogenization.

INTRODUCTION

The application of nanotechnology in the dosage forms containing nanosized active ingredients revolutionized the field of pharmacy. National initiative on nanotechnology describes nanotechnology as the analysis of all particles with size ranging from 0.1 to 100 nm. The word nano is derived from the Greek word 'Nanos' meaning atom, or very small. The nanometer is one billionth of a meter in thicknes, or 10^{-9}m. The benefit of the small particle size is the ratio of surface atoms or molecules to the changes in the total number. This means that the surface area decreases and their surface function increases and changes in physical and biological properties.[1]

Nanoparticles

Nanoparticles are colloidal particles ranging from 1nm to 100 nm in size, active ingredients (drug or biologically active material) is dissolved or encapsulated in polymeric particle. Nanoparticles are mainly of two types as shown in fig.1.1

1. ***Nanocapsule:*** In this drug is encapsulated within central volume surrounded by continuous polymeric sheath.[2]
2. ***Nanosphere*:** It is a matrix type structure in which a drug is dispersed in polymer matrix.

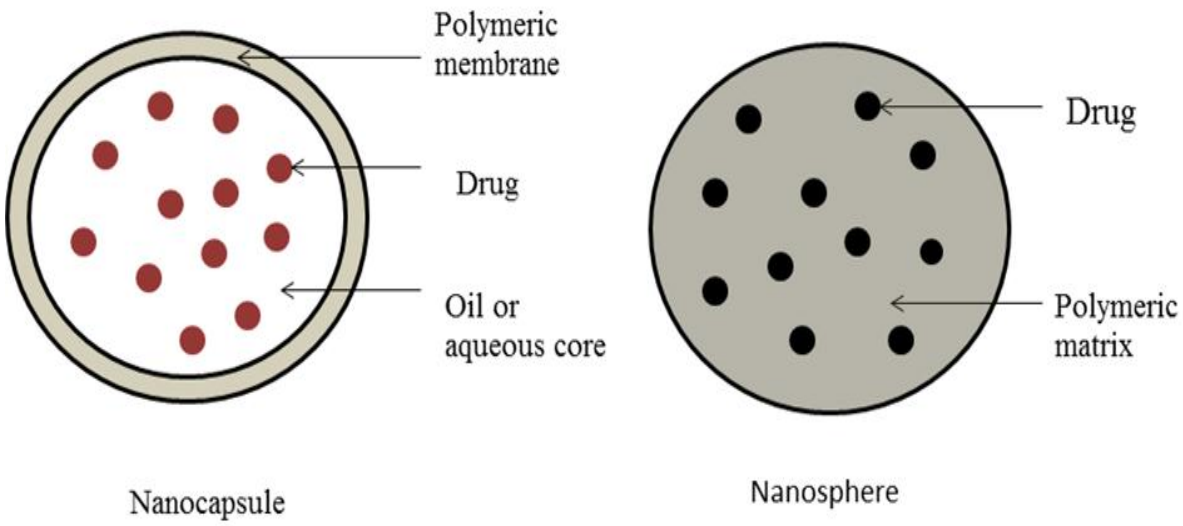

Fig. 1.1: Types of nanoparticle.

Solid lipid nanoparticles

"Solid lipid nanoparticle are colloidal drug carriers of submicron size consisting of physiological lipid, distributed in an aqueous surfactant solution." They consist of rigid hydrophobic center and phospholipid monolayer coating. The solid core consisting of a substance dissolved or dispersed in the high fat layer of the metal melting. Phospholipids hydrophobic chains are found within the fat matrix.

We have the ability to bring lipophilic or hydrophilic medicines.[3]

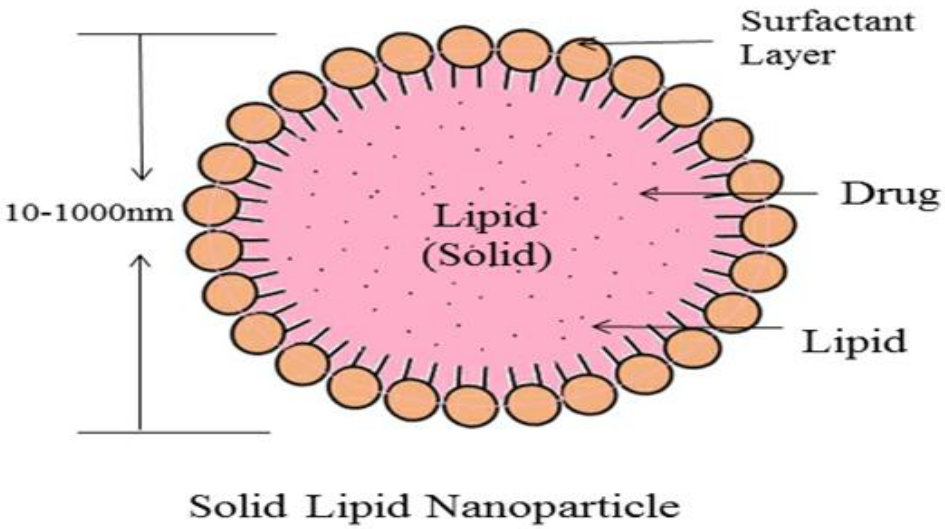

Fig. 1.2: Structure of solid lipid nanoparticle.[4]

Nanoparticles used can also be graded as metal nanoparticles, polymeric nanoparticles and solid lipid nanoparticles (SLN) throughout the drug delivery method. The key issue of the metal and polymeric nanoparticles is the adverse impact of metals and polymers used in the preparation of nanoparticles. The lipid used in the preparation of solid lipid nanoparticles are GRAS group (generally recognized as safe) substances. Certain SLN features include good tolerability, controlled drug release, stability (stabilized by surfactant), protection of degradation-sensitive drugs, and site specificity.[5]

Aims of solid lipid nanoparticles[6]

- Possibility of controlled drug release
- Increased drug stability
- High drug pay load
- No biotoxicity of the carrier
- Avoidance of organic solvents
- Incorporation of lipophilic and hydrophilic drugs.

Advantages of solid lipid nanoparticles[7]

1. Compared with liposome, SLNs have greater stability and ease of upgrade to production s ize.
2. In SLNs the lipid matrix is made of physiological lipid that reduces the risk of acute and c hronic toxicity.
3. Very high long term stability.
4. It is easy to manufacture than polymeric nanoparticles
5. Better control over release of encapsulated compound kinetics.
6. SLNs are enhancing the bioavailability of trapped bioactive.
7. Chemical defense of drugs introduced into the labile.
8. Raw materials used are same as that of emulsion.
9. Large scale production is possible
10. Lyophilization possible
11. High concentration of functional compounds can be achieved.

Disadvatages[8]

1. Poor drug loading capacity.
2. Drug expulsion after polymeric transition during storage

3. Relatively high water content of the dispersions (70-99.9%).
4. The poor ability due to partitioning effects to charge hydrophilic products.

Methods of preparation of solid lipid nanoparticles

1) High pressure homogenization

High pressure homogenization is a secure technique for preparing stable lipid nanoparticles. High pressure homogenizers force a high pressure liquid (100-2000 bar) in the range of only a few microns through a small gap. The fluid accelerates in a very short time to extremely high velocity (over 1000kph). The particles down to the submicron are affected by very high cavitation and shear stress. Lipid content is within the range of 5-10 % and is not a concern to the homogenizer. High pressure homogenization has two general approaches to methods of hot and cold homogenization, in both cases the preparatory phases include the integration of the drug into the bulk lipid by dissolving the drug into the melted lipid.[9]

a) Hot homogenization technique

Hot homogenization occurs at temperatures above the lipid melting point. A pre-emulsion is obtained by stirring in a high shear mixing system (e.g., ultraturrax) the drug charged lipid melt and the aqueous surfactant solution at the same temperature. The pre-emulsion consistency has an influence on the consistency of the final product. High pressure homogenization is done in a piston gap homogenizers at temperatures above the melting point of the lipid. High temperature results in lower particle size due to lower internal phase viscosity but high temperature can also increase carrier and drug degradation rate. High pressure homogenization raises the sample temperature for 500 bars at about 10^0 c. Homogenization step can be repeated many times but in most cases 3-5 homogenization cycles are appropriate at 500-1500 bar. The primary product is nanoemulsion that is produced by cooling to or below room temperature in hot homogenization solid lipid nanoparticles. Due to the small particle size, lipid crystallization is prevented, and the presence of emulsifier and sample can remain for several months as a super cooled melt.[10]

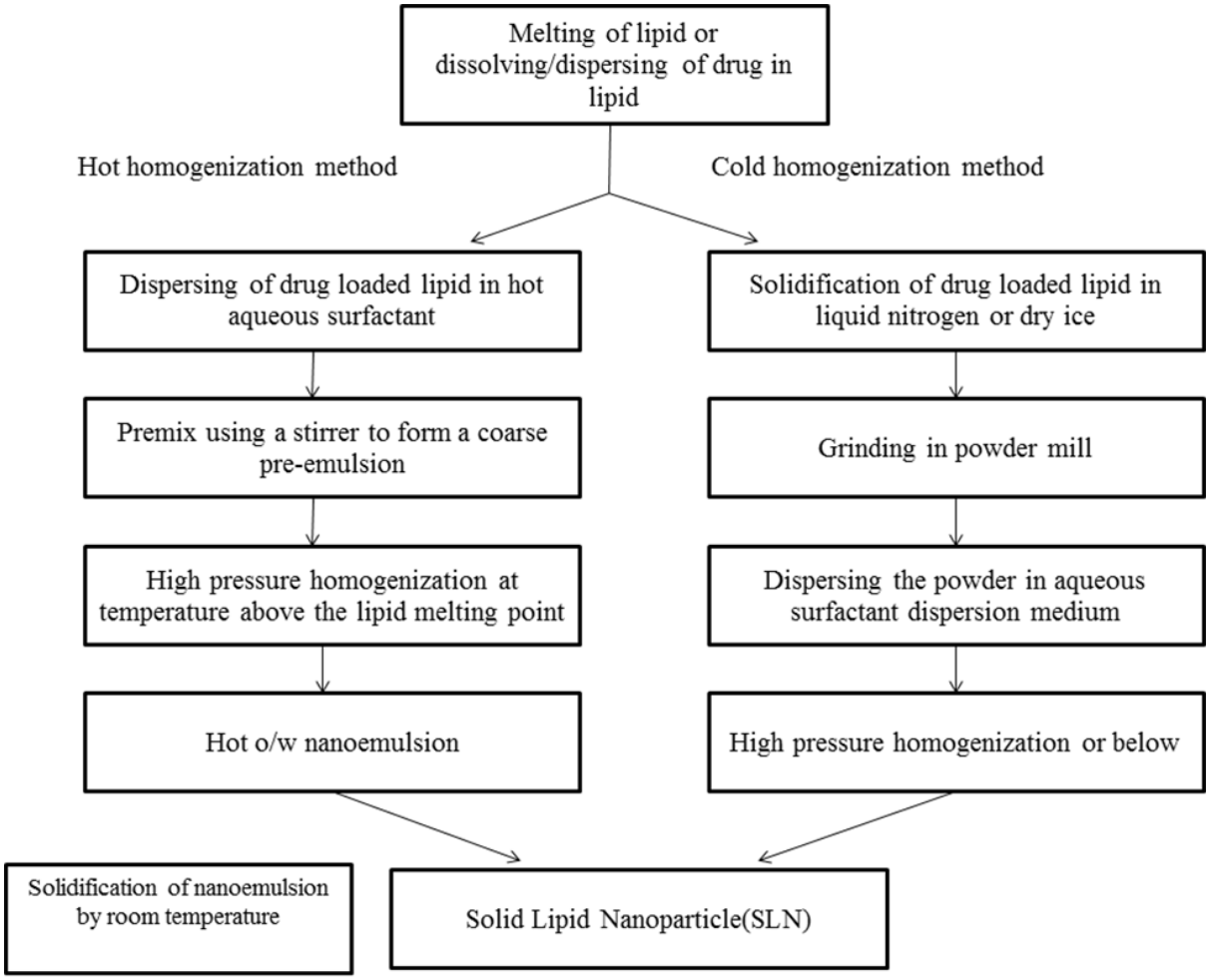

Figure 1.3: Schematic procedure of hot and cold homogenization techniques.

b) Cold homogenization technique

Cold homogenization is done with solid lipid and requires the stiffness of a suspension by high pressure. It requires highly efficient temperature control and regulation to ensure unmolten lipid state due to temperature rise during homogenization. Cold homogenization is designed to solve three problems related to hot homogenization:

1. Temperature induced drug degradation able equipment.
2. Drug distribution into the aqueous phase during homogenization.
3. Complexity of the crystallization step of the nanoemulsion leading to several modifications and/or super cooled melts.

The first step is the same as in hot homogenization that involves drug dissolution in molten lipid. The melting drug is quickly cooled which promotes the homogeneous distribution of the drug in the solid matrix. Low temperatures increase the fragility of communion between lipids and particles. Microparticles of dense lipids are spread in a chilled emulsifier solution.

The presuspension undergoes homogenization at or below room temperature by high pressure. For cold homogenized samples, larger particle sizes and broader size distribution are usually observed compared to hot homogenization.[11]

2) Ultrasonication or high speed homogenization technique

Solid lipid nanoparticles have been successfully prepared using high-speed homogenization or ultrasonic method to improve the oral bioavailability of poorly water-soluble drugs. Absorption is greatly improved by using this method's reared SLN formulation. SLNs can also be reared by stirring or sonication at high speed. It is very simple and effective compared to other approaches such as the process of hot and cold homogenization, since the equipment used in this procedure is easily available in every laboratory. The disadvantage of this approach is that the distribution of particle size is broad in the micrometer range and results in physical instability such as particle growth after storage and ultrasonic contamination of the metal.[12]

3) Microemulsion technique

This is a new technique for solid lipid nanoparticles, based on microemulsion dilution. They are prepared by stirring at 65-700 an optical transparent mixture usually consisting of a low melting fatty acid, an emulsifier, coemulsifiers, and water. Under stirring, the hot microemulsion is distributed into cold water (2-30). Typical volume ratios between the hot microemulsion and the cold water vary from 1:25 to 1:50 The microemulsion composition is critically determined by the dilution process. Droplet structure is already in the micron scale, therefore no energy is required to achieve particles of a submicron size.[13]

4) Solvent emulsification –Evaporation technique

In solvent emulsification-evaporation method, the lipophillic material and hydrophobic drug were dissolved in a water immiscible organic solvent (eg. Cyclohexane, dichloromethane, chloroform, toluene) and then that is emulsified in an aqueous phase using high speed homogenizer. The coarse emulsion was immediately passed through the microfluidizer to increase the performance of fine emulsification. The organic solvent was then evaporated at room temperature by mechanical stirring and reduced pressure (e.g. rotary evaporator) leaving nanoparticles precipitated by lipid.[14]

5) Solvent emulsification –diffusion technique

In the technique of diffusion of solvent emulsification, the solvent used (e.g. benzyl alcohol, butyl lactate, ethyl acetate, isopropyl acetate, methyl acetate) must be partly miscible with water and this technique can be applied in aqueous phase or in oil. At the outset solvent and water were mutually saturated to ensure the initial thermodynamic equilibrium of both liquids. The saturation step at that temperature was accomplished when heating is needed to solubilize the lipid. The lipid and drug were then dissolved in water-saturated solvent and this organic phase (internal phase) was emulsified using mechanical stirrer with solvent-saturated aqueous containing stabilizer (dispersed phase). After the formation of o/w emulsion, water (dilution medium), in typical ratio ranges from 1:5 to 1:10, were added to the system in order to allow solvent diffusion into the continuous phase, thus forming aggregation of the lipid in the nanoparticles.[15]

Characterization of solid lipid nanoparticles[16]

1. Particle size and zeta potential
2. Dynamic light scattering
3. Static light scattering/ diffraction
4. Electron microscopy
5. Atomic force microscopy (AFM)
6. Acoustic methods
7. Nuclear Magnetic Resonance
8. Differential Scanning Calorimetry
9. Powder X-ray Diffractometry (PXRD)
10. Storage Stability of SLN
11. *In vitro* and *ex vivo* methods for the assessment of drug release from SLN

Applications of solid lipid nanoparticles

Oral delivery

Oral administration of SLNs is possible as aqueous dispersion or after transformation into dosage form, i.e. in sachets, tablets, pellets, capsules or powder. In the granulation process the aqueous SLN dispersion can be used for the processing of the tablets instead of a granulation fluid. Alternatively SLN may be converted to a powder (e.g. spray drying) and added to the mixture of tablet powder. SLN powder can be used to fill hard gelatin capsules; or the SLN can be manufactured directly in PEG 600 liquid and filled in to soft gelatin

capsules. Because of the acidity and high ionic activity the stomach microclimate favors particle aggregation. For oral administration, antitubercular drugs such as rifampicin, isoniazide, pyrazinamide-loaded SLN systems were recorded which were able to reduce the dose amount and improve compliance with the patient.[17,18]

Parenteral delivery

Because of their small scale, SLNs may be delivered intravenously, intramuscularly, subcutaneously or into the target organ. The particles are stripped of the liver and spleen from circulation. SLN formulations with a reduced risk of blood clotting and accumulation may be used for systemic body distribution. The SLN formulations also have a continuous release depot of the drug when subcutaneously or intramuscularly administered. As far as body distribution is concerned, SLNs have been shown to induce higher concentrations of drugs in the heart, spleen and brain, while the solution has contributed to further liver and kidney distribution.[19]

Topical delivery

Topical applications of lipid nanoparticles were used for either therapeutic or cosmetic purposes, with promising results. SLNs have shown some protective behavior on the skin surface, such as a potential for UV blockage. SLNs can be formulated in creams, sprays, and gels. For SLN dispersions with low lipid content (up to 5%), smallest particle sizes are observed. In most cases it is important to integrate the SLN dispersion into an ointment or gel in order to obtain a consistency that can be applied to the skin. The integration step means that the lipid content will be further reduced. An improvement in the SLN dispersion's solid lipid content results in semisolid, gel-like systems that may be suitable for direct skin application.[20]

SLNs as gene vector carrier

SLN can be used in the formulation of the vector gene. In one study, a diametric HIV-1 HAT peptide (TAT 2) was inserted into the SLN gene vector to improve the gene transference. The lipid nucleic acid nanoparticles were prepared from a liquid nanophase containing water and a water miscible organic solvent where both lipid and DNA were separately dissolved by extracting the organic solvent, stable and homogeneously formed lipid-nucleic acid nanoparticles (70-100 nm). It is known as genospheres. It is targeted specific by insertion of an antibody-lipo polymer conjugated in the particle.

SLNs as Cosmeceuticals

The SLNs were used in sunscreen preparation and as an active carrier agent for molecular sunscreens and UV blockers. The in vivo study showed that after 4 weeks, skin hydration would increase by 31 per cent by adding 4 per cent SLN to a conventional cream. Compared to conventional formulations, better localization was achieved for vitamin A in upper layers of skin with glyceryl behenate SLNs.

SLNs as a targeted carrier for anticancer drug to solid tumors

It has been documented that SLNs are useful as drug carriers for treating neoplasms. Tamoxifen, an anticancer medication that has been integrated in SLN to extend medication release after i.v. Administration and enhancement of the permeability and retention effect of breast cancer. SLNs filled with drugs such as methotrexate and camptothecin have accomplished tumor targeting.[21]

SLNs in breast cancer and lymph node metastases

Local injections of Mitoxantrone charged SLN were designed to reduce toxicity and improve drug safety and bioavailability. It has been stated that the efficacy of doxorubicin (Dox) is enhanced by incorporation in SLN. In the technique the Dox was complexed with soybean-oil-based anionic polymer and dispersed together with a lipid in water to form Dox-loaded stable lipid nanoparticles. The program is increased its effectiveness and reduced breast cancer cells.

Stealth nanoparticles

This provides a novel and special method of drug delivery that the immune system evades rapid clearance. Those nanoparticles can potentially target different cells. Studies with stealth lipobodies labelled with an antibody have shown improved transmission to target tissue in accessible sites. Stealth SLNs with marker molecules and drugs have been successfully tested in animal models.[22]

CONCLUSION

Solid lipid nanoparticles do not, as proposed, ‘‘combine the advantages of other colloidal drug carriers and avoid the disadvantages of them’’. The results cannot simply be regarded as nanoemulsion with a solid core. Clear advantages of SLN include the composition (physiological compounds), the rapid and effective production process including the possibility of large scale production, the avoidance of organic solvents and the possibility to

produce carriers with higher encapsulation efficiency. Disadvantages include low drug-loading capacities, the presence of alternative colloidal structures (micelles, liposomes, mixed micelles, drug nanocrystals), the complexity of the physical state of the lipid (transformation between different modifications) and the possibility of super cooled melts which cause stability problems during storage or administration (gelation, particle size increase, drug expulsion). In summary, SLN are very complex systems with clear advantages and disadvantages to other colloidal carriers. Further work needs to be done to understand the structure and dynamics of SLN on molecular level in vitro and in vivo studies.

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