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A REVIEW: SOLID LIPID NANOPARTICLES

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ABSTRACT

Solid lipid nanoparticles (SLN) are one of the most rapidly evolving nanotechnology formulations, with numerous applications in fields such as drug delivery, clinical medicine, research, and a variety of other sciences. SLN are nanometer-sized spherical particles that are dissolved in water or aqueous surfactant solution and treated with lipophilic or hydrophilic drugs. Also improving the solubility and bioavailability of poorly soluble drugs can be done with biodegradable and bio acceptable polymers that can also resolve the harmful effects of traditional drug carriers. The different development strategies and their assessment were the subject of this review report. The major applications of SLNs, primarily targeted drug delivery, are discussed, as are the analytical methods used in SLN evaluations.

Keywords: solid lipid nanoparticles, methods of preparation, evaluation, applications.

INTRODUCTION

One of the most difficult research fields of pharmaceutical sciences is targeted drug delivery systems. New challenges for improving drug delivery have emerged as a result of the development of colloidal delivery systems such as liposomes, micelles, and nanoparticles. Lipids are regarded as a more physiological choice than many other materials used as drug carriers, especially polymers, and are expected to have a high biocompatibility. Solid lipid nanoparticles are at the forefront of the rapidly emerging field of nanotechnology, with numerous potential applications in drug delivery, clinical medicine, research, and a variety of other fields. Solid lipid nanoparticles (SLN), which were first introduced in 1991, are an alternative to traditional colloidal carriers. The structure is made up of nanometer-sized spherical solid lipid particles that are dispersed in water or an aqueous surfactant solution. It's the same as an oil-in-water emulsion for parentral nutrition, but the emulsion's liquid lipid (oil) has been substituted by a solid lipid, resulting in Solid Lipid Nanoparticles. Different production methods for solid lipid nanoparticles that are suitable for large-scale production and applications are described. As an alternative particulate carrier system, nanoparticles made from solid lipids are gaining a lot of attention as a new colloidal drug carrier for intravenous use. A solid lipid core is surrounded by a monolayer phospholipid shell in SLNs. Chemically labile drugs are protected and drug release is prolonged by the solid state of nanoparticulate matrix. The drug is dissolved or dispersed in the solid high melting fat matrix in the solid centre. Phospholipid hydrophobic chains are found in the fat matrix. They may transport lipophilic or hydrophilic drugs.

Advantages of SLN

- Use of biodegradable physiological lipids which decreases the danger of acute and chronic toxicity and avoidance of organic solvents in production methods.
- Improved bioavailability of poorly water soluble molecules.
- Site specific delivery of drugs, enhanced drug penetration into the skin via dermal application and possibility of scaling up.
- Protection of chemically labile agents from degradation in the gut and sensitive molecules from outer environment.
- SLNs have better stability compared to liposomes.
- Enhance the bioavailability of entrapped bioactive and chemical production of labile incorporated compound.
- High concentration of functional compound achieved.

- Lyophilization is possible.

Disadvantages of SLN

- Poor drug loading capacity.
- Drug expulsion after polymeric transition during storage.
- Relatively high water content of the dispersions (70-99.9%).
- The low capacity to load water soluble drugs due to partitioning effects during the production process.
- Unforeseen motion of polymeric transition.

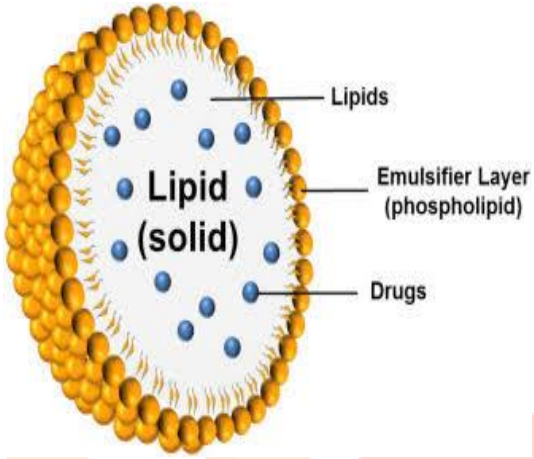

Fig. 1 Structure of Solid Lipid Nanoparticle

Methods of preparation of solid lipid nanoparticles

` 1. High pressure homogenization

A. Hot homogenization

B. Cold homogenization

2. Ultrasonication /high speed homogenization

A. Probe ultrasonication

B. Bath ultrasonication

3. Solvent evaporation Method

4. Solvent emulsification-diffusion method

5. Supercritical fluid method

6. Microemulsion based method

7. Double emulsion method

8. Precipitation technique

9. Film-ultrasound dispersion

10. Solvent Injection Technique

11. Using Membrane Contractor

1. High pressure homogenization (HPH)

It is a dependable and efficient technique that is being used for the first time to make SLNs. High-pressure homogenizers force a liquid through a narrow gap at a high pressure (100–2000 bar) (in the range of a few microns). The fluid accelerates from a very low velocity to a very high velocity (over 1000 km/h) over a very short time. The particles are disrupted down to the submicron scale by extremely high shear stress and cavitation forces. Generally, a lipid content of 5-10% is used, but up to 40% lipid content has been investigated. Hot homogenization and cold homogenization are the two forms of HPH. In both cases, a preparatory step involves dissolving or dispersing the drug in the lipid melt to incorporate it into the bulk lipid.

A] Hot Homogenization

It's done at temperatures above the lipid's melting point, so it's called emulsion homogenization. A high-shear mixing system is used to create a pre-emulsion of the drug-loaded lipid melt and the aqueous emulsifier phase (at the same temperature). The composition of the pre-emulsion has a significant impact on the final product, and droplets in the micrometre range are ideal. Higher temperatures cause the inner phase viscosity to decrease, resulting in smaller particle sizes. High temperatures, on the other hand, accelerate the degradation of the drug and the carrier. The homogenization process can be replicated as required. It's important to remember that high-pressure homogenization raises the sample's temperature (approximately 10°C for 500 bar). 3–5 homogenization cycles at 500–1500 bar are usually acceptable. Due to particle coalescence, which occurs as a result of the particles' high kinetic energy, raising the homogenization pressure or the number of cycles often leads to an increase in particle size. Since the lipid is in a liquid state, the primary product is a nanoemulsion, which solidifies when cooled to room temperature. Lipid crystallisation can be greatly slowed due to the small particle size and the presence of emulsifiers, and the sample may remain as a super cooled melt for several months.

B] Cold Homogenization

Cold homogenization, on the other hand, is done with solid lipids and thus represents a high-pressure milling of a suspension. Due to the rise in temperature during homogenization, effective temperature control and regulation is needed to ensure that the lipid remains unmolten. Cold homogenization was formulated to overcome the hot homogenization technique's three major flaws.

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 pressure.

The first step is the same as in hot homogenization, and it involves solubilizing or dispersing the drug in the bulk lipid melt. The drug-containing melt is quickly cooled, ensuring that the drug is distributed uniformly in the solid matrix. Low temperatures make the lipid more fragile, resulting in particle comminution. In a chilled emulsifier solution, solid lipid microparticles are dispersed. At or below room temperature, the pre-suspension is homogenized under high pressure. Cold homogenized samples, on average, have larger particle sizes and a wider size range than hot homogenized samples.

2. Ultra sonication and high speed homogenisation

Ultrasonication or high-speed homogenization methods are often used to make SLNs. Smaller particle sizes require a combination of ultrasonication and high-speed homogenization. It reduces shear stress, but it has some drawbacks, including the possibility of metal contamination and physical instability, such as particle growth during storage. A probe sonicator or a bath sonicator is used in this procedure.

3. Solvent evaporation method

The lipophilic material is dissolved in a water-insoluble organic solvent (for example, cyclohexane) and emulsified in an aqueous phase. Nanoparticles dispersion is produced by precipitation of the lipid in the aqueous medium following the evaporation of the solvent, yielding nanoparticles with a mean size of 25 nm. High pressure homogenization was used to emulsify the solution in an aqueous phase. Evaporation under reduced pressure (40–60 mbar) was used to extract the organic solvent from the emulsion.

4. Solvent emulsification diffusion method

This technique can produce particles with average diameters of 30-100 nm. The most significant benefit of this method is the absence of heat during the preparation. Lipids are dissolved in the organic phase in a water bath at 50 °C, and an acidic aqueous phase is used to change the zeta potential to form SLN coacervation, followed by simple separation by centrifugation. The SLN suspension was made easily. After centrifugation, the entire dispersed device can be re-suspended in distilled water.

5. Supercritical fluid method

This is a relatively new method for producing SLN that has the benefit of not requiring the use of solvents. This platform technology for powder and nanoparticle preparation comes in a number of new variations. SLN can be prepared by the rapid expansion of supercritical carbon dioxide solutions (RESS) method. Carbon dioxide (99.99%) was the good choice as a solvent for this method.

6. Micro-emulsion based method

Microemulsion is used to make SLNs; Gasco first proposed the microemulsion technique in 1993, and Mumper and Jay patented the process in 2006. In the year 2000, Char- cosset C explained the altered microemulsion process. The production of SLNs is dependent on the dilution of microemulsions, and they are produced by stirring an optically transparent mixture at 65-70oC. It is used to make o/w microemulsions and is usually composed of a low melting fatty acid, emulsifier, co-emulsifiers, and water. However, emulsifying wax is melted at 37–55 °C and the addition of water which is heated at a similar temperature with minimal stirring in order to shape homogenous milky slurry, after the addition of surfactant in water, a steady and clear o/w microemulsion in the form of a liquid matrix is produced. At that point, it is cooled at room temperature or at 4 °C in order to precipitate SLNs from it.

7. Double emulsion method

This process is used to make SLNs and relies on solvent emulsification and an evaporation method filled with hydrophilic drugs, which has recently been introduced to the scientific community. The hydrophilic compound is encapsulated in the internal water phase of a w/o/w two fold emulsion, along with a stabiliser to avoid drug partitioning to the external water phase during solvent evaporation. It's used in the manufacture of sodium cromoglycate-containing SLNs.

8. Precipitation method

Which is used to make SLNs particles, but solvents are needed for characterization. Glyceride is dissolved in an organic solvent in the first step, and then emulsified in an aqueous process in the second. The lipid precipitates nanoparticles framed after the solvent evaporates. The use of organic solvents has a distinct disadvantage.

9. Film ultrasound dispersion

The lipid and the drug were placed in suitable organic solutions, and a lipid film was created after decompression, rotation, and evaporation of the organic solutions. The aqueous solution containing the emulsions was then added. Finally, the SLN with the small and uniform particle size is developed using ultrasound with the probe to diffuser.

10. Solvent injection technique

It is a novel method for producing SLN that has many advantages over other methods, including the use of a pharmacologically suitable organic solvent, ease of handling, and a fast production process that does not require technologically sophisticated equipment. It works by precipitating lipids from a dissolved lipid solution. The solid lipid was dissolved in a water miscible solvent (such as ethanol, acetone, or isopropanol) or a water miscible solvent mixture in this process. The lipid solvent mixture was then injected into a stirred aqueous phase with or without surfactant using an injection needle. The resulting dispersion was then filtered to eliminate any excess lipid using filter paper. By lowering the surface tension between water and solvent, the presence of an emulsifier in the aqueous process helps to create lipid droplets at the injection site and stabilise SLN before solvent diffusion is complete.

11. Membrane contractor method

The lipid phase is forced through the membrane pores at a temperature above the lipid's melting point, resulting in the formation of small droplets. Inside the membrane module, the aqueous phase circulates and sweeps away the droplets that form at the pore outlets. Following the cooling of the preparation to room temperature, SLN are formed.

Principle of Drug Release from SLN:

The general standards of medication discharge from lipid nanoparticles are as per the following:

1. Higher drug discharge is achieved by a larger surface area due to the small molecule size measured in nanometers.

2. Slow drug release is possible when the medication is evenly distributed across the lipid system. It is determined by the SLN sort and drug entanglement model.

3. The lipid carrier's crystallinization behaviour and the drug's high portability result in rapid medication discharge.

4. In the drug-enriched shell model, quick initial drug release occurs in the first 5 minutes due to the outer layer of particle's greater surface area of drug depositon on the particle surface.

5. When the particles were sufficiently large, i.e. lipid macromolecules, the burst release was reduced with increasing particle size, and a prolonged release was possible.

6. Since a low surfactant concentration contributes to a minimal burst and prolonged drug release, the form of surfactant and its concentration, which will interact with the outer shell and influence its structure, should be noted as an essential outer factor.

7. The effect of particle size on drug release rate is dependent on a number of factors, including the SLN formulation's composition (such as surfactant, lipid structural properties, and drug), as well as the manufacturing method and conditions (such as production time, equipment, sterilisation and lyophilization).

There are three drug incorporation models which describe drug release from SLN

A) Homogenous matrix model

B) Drug enriched shell with lipid core

C) Drug enriched core with lipid shell

A] Solid solution model

This model was created using the cold homogenization technique. No drug-solubilizing surfactant is used. In a lipid matrix, the drug is distributed. The lipid and the drug have a good relationship.

B] Core-shell model (drug-enriched shell)

This model was created using the hot homogenization technique. Lipid core formation at lipid recrystallization temperature. The drug is repartitioned to the lipid process after cooling the obtained dispersion. Drug concentration in the membrane's immediate vicinity

C] Core-shell model enriched core)

the dispersion Cooling causes the substance, which is dissolved in the lipid, to become super saturated. Drug precipitation in melted lipid. Finally, further cooling caused the lipid to recrystallize. Creating a drug-rich core.

Evaluation of SLN

In vitro drug release

Dialysis tubing: Dialysis tubing may be used to achieve in vitro drug release. The pre-washed dialysis tubing can be hermetically sealed with the solid lipid nanoparticle dispersion. The dialysis sac is then dialyzed at room temperature against a suitable dissolution medium, with samples withdrawn from the dissolution medium at appropriate intervals, centrifuged, and drug content determined using a suitable analytical process.

Reverse Dialysis: A number of small dialysis sacs containing 1 ml of dissolution medium are put in SLN dispersion in this technique. After that, the SLNs are displaced into the medium.

Franz diffusion cell: The SLN dispersion is put in the Franz diffusion cell's donor chamber, which is lined with a cellophane membrane. The dispersion is then compared to a suitable dissolution medium; samples are taken from the dissolution medium at appropriate intervals and tested for drug content using appropriate methods such as spectroscopy and HPLC.

Characterization of SLN's

1.Particle Size and Shape

SLNs are submicron sized, particle size and shape is determined by:

a) **Photon Correlation Spectroscopy (PCS)** It's an established method based on dynamic scattering of laser light caused by Brownian motion of particles in solution or suspension. This method can be used to calculate particles in the size range of 3 nm to 3 mm. The PCS unit consists of a laser source, a temperature-controlled sample cell, and a detector. To detect scattered light, a photomultiplier is used as a detector. The rate of light scattering from the particles determines the PCS diameter.
b) **Electron Microscopy** - Physical characterization of lipid nanoparticles such as overall form and morphology are measured using electron microscopy methods such as scanning electron microscopy (SEM) and transmission electron microscopy (TEM). It allows particle sizes and distributions to be determined. The electrons in a SEM are transmitted from the sample's surface, whereas electrons in a TEM are transmitted through the sample. The detection limit for TEM is lower.

2. Zeta potential

A zeta potential analyzer or a zetameter may be used to calculate zeta potential. The magnitude of electrostatic repulsion or attraction between particles in the aqueous suspension of SLN is determined by the zeta potential. The zeta potential can be a useful parameter in predicting the formulations' long-term stability. The colloidal suspension can be stabilised by electric repulsion at high zeta potentials (e.g., more than +30mV or less than -30mV). Electric repulsion usually results in less interaction between the particles and less aggregation. Colloidal systems containing steric stabilisers, for example, can exhibit good long-term stability even when the zeta potential is as low as 0mV.

3. Nuclear magnetic resonance (NMR)

Nanoparticles' size and qualitative nature can also be determined using NMR. Chemical shift's selectivity complements molecular mobility's sensitivity to provide knowledge on the physicochemical status of components within the nanoparticle.

In vitro drug release

Dialysis tubing

Dialysis tubing could be used to obtain in vitro drug release. The solid lipid nanoparticle dispersion is put in pre-washed, hermetically sealed dialysis tubing. The dialysis sac is then dialyzed at room temperature against a suitable dissolution medium; samples are then withdrawn from the dissolution medium at appropriate intervals, centrifuged, and analysed for drug content using a suitable analytical process.

Reverse dialysis

A number of small dialysis sacs containing 1 mL of dissolution medium are put in SLN dispersion in this technique. After that, the SLNs are displaced into the medium.

Ex vivo model for determining permeability across the gut

The movement of enalaprilat SLNs through the rat jejunum was demonstrated by Ahlin et al. After sacrificing the animal for the analysis, the rat jejunum (20–30 cm distal from the pyloric sphincter) was excised from the rats. Qing Zhi Lu et al. excised 10 cm long duodenal segments (1 cm distal to pyloric sphincter); jejunum (15 cm to pyloric sphincter), ileum (20 cm proximal to cecum), and colon (2 cm distal to cecum) segments were immediately cannulated and ligated on both sides for their permeability studies.

Applications of SLN

1] Parenteral administration

Animals were given SLN via intravenous injection. After i.v. injection in rats, pharmacokinetic trials of doxorubicin integrated into SLN revealed higher blood levels than a commercial drug solution. In terms of body distribution, SLN was observed to cause higher drug concentrations in the lungs, spleen, and brain, while the solution caused a distribution that was more concentrated in the liver and kidneys. The area of parenteral application for SLN is very wide . Subcutaneous injection of drug-loaded SLN, such as erythropoietin (EPO) or interferon-β, can be used for commercial purposes. Intraperitoneal and intraarticular routes are two other options. Because of the application region, drug-loaded SLN administered intraperitoneally can prolong the release. Furthermore, when compared to injecting drug micro particles, incorporating the drug into SLN can reduce irritancy.

2] Transdermal application

SLN dispersions with low lipid content have the smallest particle sizes (up to 5 percent). The low concentration of dispersed lipid as well as the low viscosity make dermal administration difficult. In most cases, the SLN dispersion must be incorporated into an ointment or gel in order to produce a solution that can be applied to the skin. The lipid content is further reduced during the incorporation process. As the solid lipid content of the SLN dispersion is increased, semisolid, gel-like systems emerge, which may be suitable for direct skin application.

3] Topical application

Topical application is relatively unproblematic from the standpoint of regularity. The defensive properties of SLN for chemically labile drugs against degradation, as well as the occlusion effect due to film forming on the skin, are the two most important advantages for topical products. Many compounds, such as retinol or vitamin C, cannot be incorporated because of their chemical instability, particularly in the cosmetics industry. Retinol can only be incorporated when certain safety measures (such as noble gasing) and special packaging materials are used during processing (e.g. aluminium).

4] Pulmonary administration

The pulmonary administration of SLN tends to be a rather interesting application. The particle size of SLN powders is too small to be applied to the lungs, and they will be exhaled. Aerosolization of aqueous SLN dispersions is a very simple process. The crucial thing to remember is that the SLN does not clump together during the aerosolization process. The aerosol droplets were obtained by colliding with the beaker's glass wall. This essentially proves that SLN are appropriate for lung delivery. The drug can be released in a controlled manner from the lipid particles after localization into the bronchial tube and alveoli.

5] Ophthalmic administration

Many studies have been carried out to see whether nanoparticles can be used to deliver medicines to the eye over a longer period of time. The primary challenge in ophthalmologic formulation is rapid removal from the eye, which necessitates nasal clearance of the applied drug. It could be shown that nanoparticles have improved adhesiveness, resulting in higher drug levels at the target site of action. However, the fundamental issue was that nanoparticles had a low level of toxicological acceptance. Gasco demonstrated that SLN have a longer retention period in the eye. Radiolabile formulations and γ-scintigraphy were used to validate this. The lipids in SLN are easily metabolised, opening up new ways for ophthalmological drug delivery that do not affect vision.

6] SLN in Cancer chemotherapy

Several chemotherapeutic agents have been encapsulated in SLN and their in vitro and in vivo effectiveness has been studied over the last two decades. Tamoxifen, an anticancer medication, has been integrated into SLN to extend the drug's release after i.v. administration in breast cancer patients (Murthy, 2005). SLN filled with drugs including methotrexate and camptothecin has been used to target tumours. Metoxantrone SLN local injections were developed to minimise toxicity while also improving the drug's safety and effectiveness in the treatment of breast cancer and lymph node metastases.

CONCLUSION

Although solid lipid nanoparticle drug delivery technology has significant potential for improving medical therapies, its full potential has yet to be achieved. The focus of the review was on the many elements of SLNs and their use in the encapsulation of various medications. This review article covers different methods of preparation their advantages and evaluation, characterization parameters along with their applications in different fields. Because of the SLN potential for facilitating controlled drug delivery to a target tissue

and its biocompatibility, there will be much investigation in improvement of quality, efficacy, and safety profile of drugs using them in the future.

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