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Solid Lipid Nanoparticles For Oral Drug Delivery- Advancements, Challenges And Future Perspectives - A Review

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ABSTRACT: Solid lipid nanoparticles (SLN) have a number of possible uses in research and in drug delivery. They are at the forefront of the quickly evolving field of nanotechnology. Solid-Lipid nanoparticles present a chance to create novel therapeutics because of their special size-dependent characteristics. Drug targeting is made possible by the ability to incorporate drugs into nanocarriers, which provides a new drug delivery prototype. Thus, solid lipid nanoparticles are generating a lot of interest from researchers due to their great potential for achieving the aim of controlled and site-specific drug delivery. This review covers introduction,advantages,disadvantages,aim,methods of preparation, characterization, evaluation and applicationThe analytical methods for characterizing SLN, are Measurement of particle size and zeta ,electron microscopy, and photon correlation spectroscopy, Atomic Force Microscopy are emphasized. Aspects of SLN route of administration and the in vivo fate of the carriers are also discussed.

Key words: solid lipid nanoparticles, oral drug delivery, drug targeting, applications.

INTRODUCTION:

Solid lipid nanoparticles (SLNs) were discovered by Gasco and Muller in 1991. In the up-and-coming scientific world nanotechnology is nowanovel technology for upcoming generations. SLNs are sub-micron colloidal carriers ranging from 50 to 1000 nm, which are composed of physiological lipid, dispersed in water or in aqueous surfactant solution. SLN offer unique properties such assmall size,large surface area, high drug loading and the interaction of phases at the interface and are attractive for their potential to improve performance of pharmaceuticals(1,2,3).SLNs are spherical in shape anddiameter ranging from 10 to 1000nm.

In order to overcome the disadvantages associated with the liquid state of the oil droplets, the liquid lipid was replaced by a solid lipid, which eventually transformed into solid lipid nanoparticles.

The reasons for the increasing interest in lipid based system are many fold which includes.

1. Lipids enhance oral bioavailability and reduce plasma profile variability.
2. Better characterization of lipid excipients.
3. An improved ability to address the key issues of technology transfer and manufacture scale-up.

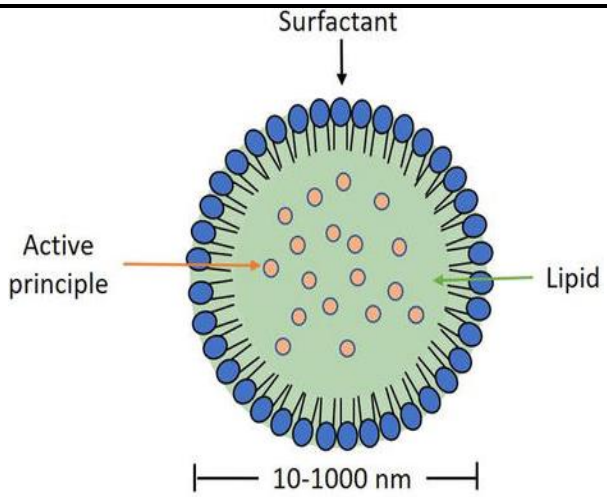

Figure 1: structure of SLNs

ADVANTAGES:

SLN**s** provide biocompatibility, long term stability along with control release which are easy to manufacture using conventional emulsion methods which do not require use of special solvents which helps in large scale production. It offers enhanced bioavailability and chemical protection of labile compounds. (1, 3)

DISADVANTAGES:

The medication stacking limit is poor and increased particle growth causes instability with relatively high water content of the dispersion. There is unpredictable gelation tendency and unexpected dynamics of polymeric transitions. Difficulty in physical handling along with limited drug loading and burstloading capacity.

Aims of solid lipid nanoparticles: (3, 4)

- Possibility of controlled drug release.
- Increased drug stability.
- High drug pay load.
- No bio-toxicity of the carrier.
- Avoidance of organic solvents
- Bioavailability of entrapped bioactive compounds
- Possibility of controlled drug release and drug targeting.
- Incorporation of lipophilic and hydrophilic drugs
- No biotoxicity of the carrier
- Avoidance of organic solvents
- No problems with respect to large scale production and
- Increased drug stability

METHODS OF PREPARATION OF SLNs: (2,3)

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. Micro emulsion-based method
7. Spray drying method
8. Double emulsion method
9. Membrane contactor technique
10. Melting dispersion method

1. High pressure homogenization (HPH):

It is a reliable and powerful technique, which is used for the production of SLNs. High pressure homogenizers push a liquid with high pressure (100–2000 bar) through a narrow gap (in the range of a few microns). The fluid accelerates on a very short distance to very high velocity (>1000 Km/h). Very high shear stress and cavitation forces disrupt the particles down to the submicron range. Generally 5 to10% lipid content is used but up to 40% lipid content has also been investigated. Two general approaches of HPH are hot homogenization and cold homogenization, both works on the same concept of mixing the drug in bulk of lipid melt.

A. **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 drug-loaded lipid melt is dispersed in a hot surfactant solution. With the help of an ultrasonicator premixing is carried out. This emulsion is then passed through the high-pressure homogenizer, where the temperature should be kept above the lipid melting point. Then finally, at room temperature hot O/W nanoemulsion is cooled down where the lipid recrystallizes and leads to the formation of nanoparticles [5] (Figure 2).

B. Cold homogenization:

In this method the first step is the same as that of hot homogenization technique which includes dissolving or dispersion or solubilization of the drug in the melted lipidwith the help of liquid nitrogen or dry ice. The drug lipid mixture is rapidly solidified as ice. The drug loaded solid lipid was milled by using a roller mill or ball mill to a micron size range of 50 to 100 micron, further microparticles are dispersed in chilled emulsifier solution to obtain a pre-emulsion (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 [6].

2. ULTRASONICATION/HIGH SPEED HOMOGENIZATION:

SLNs can also be made using high-speed homogenization or ultrasonication methods. It is necessary to combine Ultrasonication and high speed homogenization for getting lowersize of particles.

3. **SOLVENT EMULSIFICATION EVAPORATION METHOD:**

The hydrophobic drugis dissolved in an organic solvent such as cyclohexane, chloroform and toluene .Then emulsified in an aqueous phase using high pressure homogenizer. The dispersion is sonicated for 5mins to produce uniform sized SLNs.Then the solution was homogenized under high pressure and emulsified in an aqueous phase. Then the emulsionis transferred to the flask and placed on rotary evaporator. The solution is then evaporated under reduced pressure. Then the emulsion is centrifuged to separate the nanoparticles from remaining liquid. The nanoparticles are then washed several times to remove solvent and nanoparticles are then dried and stored.

4. **SOLVENT EMULSIFICATION DIFFUSION METHOD:**The particles with average diameters of 30-100 nm can be obtained by this technique. Voidance of heat during the preparation is the most important advantage of this technique. In this technique lipid is, generally dissolved in the organic phase in water bath at50 °C and used an acidic aqueous phase in order to adjust the zeta potential to form coacervation of SLN, then they are easy separation by centrifugation. The entire dispersed system can then be centrifuged and re-suspended in distilled water [7,8, 9,10].

5. **SUPER CRITICAL FLUID METHOD:** This is relatively new method of production of SLNs. The main advantage of these technique is that it can be used at low temperature and does not use organic solvents to make SLNs. A suitable option for this procedure is to rapidly expand supercritical carbon dioxide (99.99%) solutions to produce SLNs. (11)

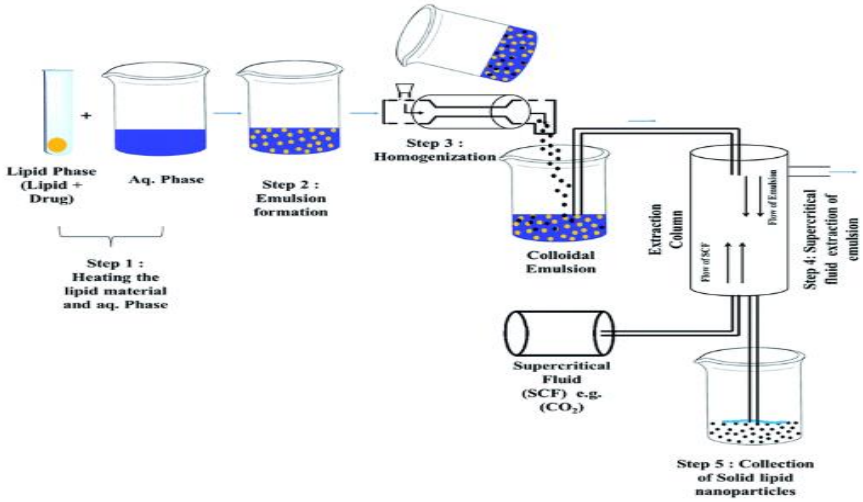

Figure 2: Illustrates the super critical fluid method for preparation of SLNs

6. MICROEMULSION BASED METHOD:

NGasco and co-workers developed SLN preparation techniques.The lipid used for the preparation of SLNs is selected based on its melting point, solubility, and stability. Examples of lipids that can be used for SLN preparation include glyceryl behenate, stearic acid, and cetyl palmitate. For the formation of the microemulsion a mixture of oil, surfactant, co-surfactant and aqueous phase is prepared to form a clear, isotropic solution. The oil phase and aqueous phase are mixed together and the surfactant and co-surfactant are added to this mixture. The mixture is then stirred vigorously until a clear, transparent solution is obtained. Then the lipid is melted and added to the microemulsion while stirring continuously. The mixture is then stirred further until it forms a white, milky emulsion. The emulsion is then cooled to room temperature and the SLNs start to solidify. The solidification process can be accelerated by refrigeration or freeze-drying.[12,13,14].

7. **Spray drying method:**

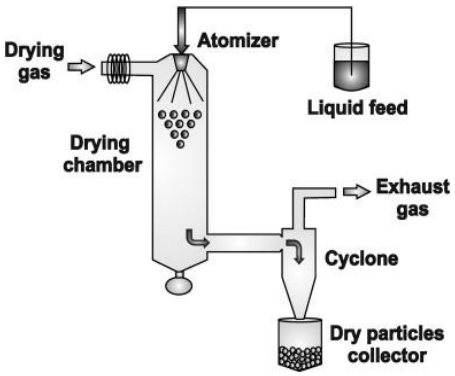

Figure 3: Illustrates the spray drying method of SLNs preparation

It is an alternative technique to the lyophilization process. This recommends the use of lipid with melting point more than 70° C. The best results were obtained with SLN concentration of 1% in a solution of trehalose in water or 20% trehalose in ethanol-water mixture.

8. Double emulsion based method:

Warm w/o/w double microemulsions can be prepared in two steps. Firstly, w/o microemulsion is prepared by adding an aqueous solution containing drug to a mixture of melted lipid, surfactant and co-surfactant at a temperature slightly above the melting point of lipid to obtain a clear system. In the secondstep, formed w/o microemulsion is added to a mixture of water, surfactant and cosurfactant to obtain a clear w/o/w system. SLNs can be obtained by dispersing the warm micro double emulsions in cold then washed with dispersion medium by ultra filtration system. Multiple emulsions have inherent instabilities due to coalescence of the internal aqueous droplets within the oil phase, coalescence of the oil droplets, and rupture of the layer on the surface of the internal droplets. In case of SLNs production, they have to be stable for few minutes, the time between the preparations of the clear double microemulsions and its quenching in cold aqueous medium, which is possible to achieve[15,16].

9. Membrane contractor method: Through the membrane pores the lipid phase is forced 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.

CHARACTERIZATION:

Measurement of particle size and zeta potential:

Many methods can be used to measure particle size. However, photon correlation spectroscopy (PCS) and laser diffraction (LD) are th e most widely used methods. PCS is also known as dynamic light scattering. PCS is used to measure fluctuations in the intensity of sc attered light affected by particle motion. This method can measure particles ranging from nanometer to micrometer. PCS is a better m ethod for characterizing nanoparticles, but it is not an efficient method for measuring particle size and shape. Unlike PCS and LD, ele ctron microscopy is a better method to determine the shape of nanoparticles. The physical stability of SLN lasted more than 12 month s. ZP helps predict storage stability of colloidal dispersions.[17,18]

Photon Correlation Spectroscopy (PCS):

The method is based on how laser light is scattered due to Brownian motion of particles in solution/suspension. This method measures particle sizes between 3 nanometers and 3 millimeters. The PCS configuration consists of a laser source, a sample cell (temperature regulated) and a detector. A photomultiplier tube is used as a detector to detect scattered light. The PCS diameter is based on the light scattering intensity of the particle.(19)

Electron Microscopy:

The morphological aspects of SLNs and their particle shapes can be assessed using several microscopic techniques such as scanning electron microscopy (SEM) and transmission electron microscopy (TEM). These methods have also been used to assess the distribution of drug particles in sentinel lymph nodes. SEM is based on the surface of the sample including the electron transport while TEM only considers the sample through which the electron transport passes.(20)

Atomic Force Microscopy (AFM):

Surface properties of the sentinel lymph node can be measured using an advanced microscopic technique called atomic force microscopy.Applied as a new tool. AFM allows visualizing images of SLNs where the original unmodified shape can be clearly distinguished from other particles. With this method, different forces acting between the probe and the sample can be measured. By placing the sample and probe in close proximity, images of the particle surface can be acquired and viewed at 0.01 nm resolution.

Determination of Incorporated Drug:

The amount of drug present in the SLN plays an important role in determining the properties of the SLN, which should be assessed. The amount of drug present per unit weight of SLN can be determined by centrifugation or gel permeation chromatography. These methods determine the amount of drug by separating lipid and free drug present in the aqueous medium. HPLC, fluorescene spectrophotometry are some of the methods used to perform drug testing. (21)

EVALUATION STUDIES:

Entrapment efficiency:

The entrapment efficiency of SLN dispersion is determined by centrifugation method. [23] SLN dispersion containing an equivalent to 5 mg of drug was centrifuged at 20000 rpm for one hour in a refrigerated centrifuge to collect the supernatant liquid. The collected liquid was filtered to measure the free drug concentration after suitable dilution with a fresh phosphate buffer saline pH 7.4. The absorbance was measured at 207 nm in a UV spectrophotometerto calculate the entrapment efficiency using the following formula:

$$\text{Entrapment efficiency} = \frac{(\text{Weight of initial drug} - \text{Weight of free drug})}{\text{Weight of initial drug}} \times 100$$

In vitro drug release:

The in vitro release from different SLN dispersions was determined using the dialysis bag diffusion technique. [24] An accurately weighed amount of drug-loaded SLN dispersions containing the drug equivalent to 2.5 mg was transferred to a dialysis bag and sealed. The sealed bag was then suspended in a beaker containing 250 ml of phosphate buffer saline pH 7.4 and stirred at a constant speed of 50 rpm at 37°C ± 0.5°C. Aliquots were withdrawn at predetermined intervals from the receptor compartment up to 12 hours and the same was replaced with fresh buffer. Then the drug content was determined spectrophotometrically by measuring the absorbance at 207 nm.

Particle size analysis/scanning electron microscopy:

The mean diameter of the SLNs in the dispersion was determined by photon correlation spectroscopy (PCS) at a fixed angle of 90°, at 25°C.[25] Before the measurement, one drop of sample was taken from each selected formulated nanosuspension and diluted in 10 ml of the dispersion medium (distilled water). The surface morphology of SLN was characterized by scanning electron microscopy.[26]

Stability studies:

Stability studies were carried out for the formulations having high entrapment efficiency by storing the formulations at two different temperatures, 4°C and 25 ± 2°C[27] and the drug content was estimated every 15 days, to find any change in the entrapment efficiency of the SLN.

Applications of SLNs:

- Cancer chemotherapy:

Over the past two decades, many anticancer drugs have been formulated in the SLN system, resulting in improved efficacy and signifi cantly reduced side effects. This chemotherapeutic drug, when encapsulated in the SLN system, exhibites increased stability and phar macokinetics with reduced toxicity, demonstrating that SLN is a suitable vehicle for delivery of such drugs. Not only anticancer small molecules, but also macromolecules such as antisense oligonucleotides are delivered to liver cancer cells by lipid-coated particles. (28)

- Brain drug delivery:

Ultrafine SLN particles with a diameter of less than 50 nm are advantageous agents for targeting drug to brain .this could be attributed to increased drug penetration
across the bloodbrain barrier, particularly SLNs coated with polysorbate surfactants showed increased drug transport.

- Parasitic diseases:

SLNs and nanostructured lipid transporters (NLCs) are granular in nature and their inherent structure shows good potential in the treat ment of parasitic infections. (29) With respect to encapsulation capabilities and targeting capabilities, extensive studies of these syste ms are needed to find multifunctional, efficient, and cost effective ways to deliver antiparasitic drugs.

- Ultrasonic drug and gene delivery:

Ultrasonic drug and gene delivery by nanocarriers has tremendous potential because of the wide variety of drugs and genes could be delivered to targeted tissues by fairly noninvasive means.(30) Liquid emulsions and solid nanoparticles are used with ultrasound to deliver genes in vitro and in vivo.

- Pulmonary disorders:

Nanoparticles with their special characteristics have numerous merits in targeted drug delivery compared with other systems. Targeted nanoparticles delivery to the lungs is an emerging area of interest.(31)SLN powders can be used in dry powder inhaler form by spray-drying with lactose as an excipient.

- Topical applications:

In future, it is expected that SLN replace other carriers for tropical formulations, SLN are usually prepared from well tolerated excipients and possess adhesive properties which helps in the formation of film on the skin due to their small particle size which may assist the drug penetration through stratum corneum. SLN and NLC have been used for topical applications for various drugs such as triploid and glucocorticoids (32,33). Hydrophilic and hydrophobic drugs including corticosteroids and anticancer agents like doxorubicin and paclitaxel have been delivered through SLN. (34)

- Cosmeceuticals:

SLN have been applied in the preparation of sunscreens.

- Oral administration:

SLN can also be administered by oral route in an aqueous dispersion form rather than its traditional solid forms.

CONCLUSION:

Solid-lipid nanoparticles show great promise as a drug delivery system for oral administration. While there are still challenges to overcome, continued research and development in this field could lead to significant advancements in drug delivery technology.SLNs are novel delivery systems and hold great promise for their systemic exploration and development.It is quite evident from the literature that SLNs-based formulations have been developed and patented for diversified applications includingstability of molecules, oral bioavailability, and deeper penetration of the bioactive across skin, cosmetic applications, targeted drug delivery using ligand anchoring over surface.

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