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A REVIEW ON SOLID LIPID NANOPARTICLES

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ABSTRACT

Formulations using Solid lipid nanoparticles (SLN) are promising area of nanotechnology with significant applications in various fields like Novel drug delivery, clinical medicine and pharmaceutical research due to their unique size dependent properties in the development of drug therapy. These different substances have been entrapped into lipid Nano-particles, extending from lipophilic and hydrophilic molecules, including labile compounds, such as proteins and peptides. SLN are with a nanometer range can protect the drug in contradiction of *in-vitro* and *in-vivo* degradation and it release the drug in controlled way and also offers the possibility of drug targeting. The different production methods which are suitable for large scale production and applications of solid lipid nanoparticles are defined. The present review focuses on the utility of SLN in terms of their advantages, production methodology, characterization and applications.

KEYWORDS: Solid lipid nanoparticles, Advantages, Preparation and Characterization.

INTRODUCTION

Targeted delivery system is one of the most challenging research areas in pharmaceutical sciences. By developing colloidal delivery systems such as liposomes, micelles and nanoparticles, new challenge have opened for improving drug delivery. Compared to many other materials used as drug carriers, in particular to polymers, lipids are regarded as a more physiological option and a high biocompatibility is expected. From all the different types, Solid lipid nanoparticles are at the forefront of the rapidly developing field of nanotechnology with several potential applications in drug delivery, clinical medicine and research as well as in other varied sciences. Solid lipid nanoparticles (SLN) introduced in 1991 represent an alternative carrier system to tradition colloidal carriers.[1]

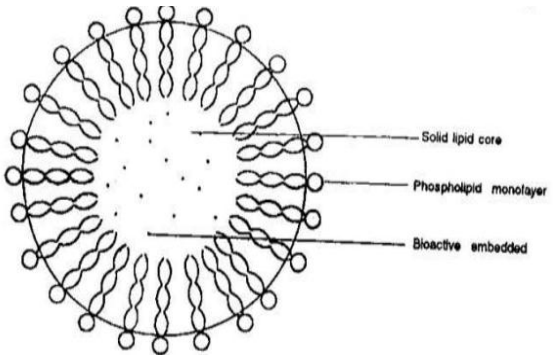

Fig 1: Proposed structure of SLN.

SLN combine the advantages of polymeric nanoparticles, fat emulsion and liposomes but simultaneously avoid some of their disadvantages. They have many advantages such as good biocompatibility, non-toxic, stable against coalescence, drug leakage, hydrolysis, biodegradable, physically stable and good carrier for lipophillic drugs. There are major difference between lipid emulsion and liposomes. The basic structure of a lipid emulsion is a neutral lipophilic oil core surrounded by monolayer of amphiphilic lipid. In contrast, liposomes contain an outer bilayer of amphiphilic molecule such as phospholipid with an aqueous compartment inside.[2]

ADVANTAGES OF SLN

1. The shelf-life stability of SLNs can be very good. Lipids can be chosen that do not hydrolyse in aqueous suspension.
2. Easy to manufacture than bipolymeric nanoparticles.
3. SLNs have better stability and ease of upgradability to production scale as compared to liposome.
4. Controlled release kinetics.
5. Most of the materials for preparing SLNs are low cost with ease of scale-up for industrial production.
6. SLNs can be enhancing the bioavailability of entrapped bioactive.
7. Chemical protection of labile incorporated compound.
8. Large scale production possible.
9. Lyophilization possible.
10. Site specific delivery of drugs, enhanced drug penetration into the skin via dermal application.

11. No toxic metabolites are produced.[3]

DISADVANTAGES OF SLN

1. Poor drug loading capacity.
2. Relatively high water content of the dispersions (70 - 99.9%).
3. Drug expulsion after polymeric transition during storage.
4. The low capacity to load hydrophilic drugs due to partitioning effects during the production process.
5. Need to remove too much water in tablet / pellet production.[4]

PRINCIPLES OF DRUG RELEASE FROM SLNS

Drug release is affected by particle size, where tiny particles have larger surface area, therefore, the majority of the drug associated would be at or close to the particle surface, leading to quick drug release. Whereas, larger particles have bulky cores which permit more drug to be encapsulated and gradually diffuse out. It is a challenge to formulate nanoparticles with the smallest size possible and with maximum stability. The common ideology of drug release from lipid nanoparticles is as follows. There is an opposite association between drug release and the partition co-efficient of the drug.

– Larger surface area due to smaller particle size in nanometric range gives high drug release.

– When the drug is homogenously dispersed in the lipid matrix, slower drug release can be achieved. It depends on type of drug entrapment model of SLN.[5]

COMPOSITIONAL PROFILE OF SLNS

Lipid and surfactant/stabilizer are the key components used to fabricate SLNs along with co-surfactant, preservatives, cryoprotectant, and charge modifiers (Table 1). By reducing the interfacial tension between the aqueous environment and the hydrophobic surface of the lipid core, surfactants help in stabilizing the SLN structure.

Table 1: Ingredients used in SLNs-based formulations.[6]

Ingredients	Examples
Lipid component	Beeswax, Stearic acid, Cholesterol, Caprylic/capric triglyceride, Cetylpalmitate, Glyceryl stearate (-mono, and -tri), Glyceryl trilaurate, Glyceryl trimyristate, Glyceryl behenate (Compritol), Glyceryl tripalmitate, Hardened fat (Witepsol E85, H5 and W35), Monostearate monocitrate, Solid paraffin, Behenic acid
Surfactant/Emulsifiers	Phosphatidyl choline, Soy and Egg lecithin, Poloxamer, Poloxamine, Polysorbate 80
Co-surfactant	Sodium dodecyl sulphate, Tyloxopol, Sodium oleate, Taurocholate sodium salt, Sodium glycocholate, Butanol
Preservative	Thiomersal
Cryoprotectant	Gelatin, Glucose, Mannose, Maltose, Lactose, Sorbitol, Mannitol, Glycine, Polyvinyl alcohol, Polyvinyl pyrrolidone
Charge modifiers	Dipalmitoyl phosphatidyl choline, Stearylamine, Dicetylphosphate, Dimyristoyl phophatidyl glycerol

PREPARATION OF SOLID LIPID NANOPARTICLES

1. High pressure homogenization technique

➢ **Hot homogenization technique**

Hot homogenization is carried out at temperatures above the melting point of the lipid and can therefore be regarded as the homogenization of an emulsion. A pre-emulsion of the drug loaded lipid melt and the aqueous emulsifier phase (same temperature) is obtained by high-shear mixing device (Ultra-Turrax). The quality of the final product is affected by the quality of pre-emulsion to a large extent and it is desirable to obtain droplets in the size range of a few micrometers. In general, higher temperatures result in lower particle sizes due to the decreased viscosity of the inner phase. However, high temperatures also accelerate the degradation rate of the drug and the carrier. The homogenization step can be repeated several times. It should always be kept in mind, that high pressure homogenization increases the temperature of the sample (approximately 10°C for 500 bar). In most cases, 3–5 homogenization cycles at 500–1500 bar are sufficient. Increasing the homogenization pressure or the number of cycles often results in an increase of the particle size due to particle coalescence which occurs as a result high kinetic energy of the particles. The primary product is a nanoemulsion due to the liquid state of the lipid which on cooling at room temperature leads to solid particles. Due to the small particle size and the presence of emulsifiers, lipid crystallization may be highly retarded and the sample may remain as a super cooled melt for several months.

➢ **Cold homogenization technique**

Cold homogenization method has been carried out to omit the following problems of the hot homogenization technique like temperature mediated drug and carrier degradation acceleration and consequently release of drug into the aqueous phase during homogenization. First stage in cold homogenization is the same with hot homogenization method but the next steps are different. The drug loaded lipid melt is cooled quickly by ice or liquid nitrogen for distribution of drug in the lipid matrix. The acquired particle sizes are in the range 50-100 microns for this method. Disadvantages of cold homogenized samples are larger particle sizes and a broader size distribution. However, this method reduces the thermal exposure of the sample.[7]

2. Solvent emulsification-diffusion technique

SLNs can also be produced by solvent emulsification-diffusion techniques. The mean particle size depends upon lipid concentration in the organic phase and the emulsifier used. Particles with average diameters of 30-100 nm can be obtained by this technique. Avoidance of heat during preparation is the most important advantage of this technique. In this method, the lipid matrix is dissolved in a water-immiscible organic solvent followed by emulsification in an aqueous phase. The solvent is evaporated under reduced pressure, resulting in a nanoparticulate dispersion formed by precipitation of the lipid in aqueous medium.[8]

3. Microemulsion based technique

This method is based on the dilution of microemulsions. As micro-emulsions are two-phase systems composed of an inner and outer phase (e.g. o/w microemulsions). They are made by stirring an optically transparent mixture at 65-70°C, which typically composed of a low melting fatty acid (e.g. stearic acid), an emulsifier (e.g. polysorbate 20), co-emulsifiers (e.g. butanol) and water. The hot microemulsion is dispersed in cold water (2-3°C) under stirring. SLN dispersion can be used as granulation fluid for transferring in to solid product (tablets, pellets) by granulation process, but in case of low particle content too much of water needs to be removed. High-temperature gradients facilitate rapid lipid crystallization and prevent aggregation. Due to the dilution step; achievable lipid contents are considerably lower compared with the High pressure homogenization based formulations.[9]

4. Precipitation technique

The lipid is dissolved in an organic solvent (e.g., chloroform) and the solution is emulsified into an aqueous phase. After evaporation of the organic solvent, the lipid is precipitated, forming nanoparticles.[10]

5. Supercritical fluid method

This is a relatively new technique for SLN production and has the advantage of solvent-less processing there are several variations in this platform technology for powder and nanoparticle preparation. 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. Spray drying method

Spray drying might be an alternative procedure to lyophyilization in order to transform an aqueous SLN dispersion into a dry product, but this method is scarcely used in SLN formulations although spray drying is cheaper than that of lyophylization. Spray drying might potentially cause aggregation due to high temperatures, shear forces and partial melting of the particles. Over all best result are obtained by using 1%solutions of 30% trehalose in water or 20%trehalose in ethanol-water mixtures.[11]

7. Membrane contractor method

The present study investigates a new process for the preparation of SLN using a membrane contactor, to allow large scale production. The lipid phase is pressed, at a temperature above the melting point of the lipid, through the membrane pores allowing the formation of small droplets. The aqueous phase circulates inside the membrane module, and sweeps away the droplets forming at the pore outlets. SLN are formed by the following cooling of the preparation to room temperature. The influence of process parameters (aqueous phase and lipid phase temperatures, aqueous phase cross-flow velocity and lipid phase pressure, membrane pore size) on the SLN size and on the lipid phase flux is investigated. Also, vitamin E loaded SLN are prepared, and their stability is demonstrated.[12]

8. Ultra sonication and high speed homogenisation

SLNs are also prepared by ultrasonication or high speed homogenization techniques. For smaller particle size combination of both ultrasonication and high speed homogenization is required. It reduces shear stress but has some disadvantages like potential metal contamination, physical instability like particle growth upon storage. In this probe sonicator or bath sonicator is used.

9. 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 second step, formed w/o microemulsion is added to a mixture of water, surfactant and co-surfactant 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.

10. Film ultrasound dispersion

The lipid and the drug were put into suitable organic solutions, after decompression, rotation and evaporation of the organic solutions, a lipid film is formed, then the aqueous solution which includes the emulsions was added. Using the ultrasound with the probe to diffuser at last, the SLN with the little and uniform particle size is formed.[13]

CHARACTERIZATION OF SOLID LIPID NANOPARTICLES

- **Particle size and Zeta potential**

The physical stability of SLNs depends on their particle size. Photon correlation spectroscopy (PCS) and laser diffraction (LD) are the most powerful techniques for determination of particle size. PCS (also known as dynamic light scattering) measures the fluctuation of the intensity of the scattered light, which is caused by particle movement. The particle size determination by photon correlation spectroscopy (PCS) detects size range of 3nm to 3µm and by laser diffraction in size range of 100 nm to 180 µm. Although PCS is a good tool to characterize nano-particles, but is capable for the detection of larger micro particles. Zeta potential is an important product characteristic of SLNs since its high value is expected to lead to deaggregation of particles in the absence of other complicating factors such as steric stabilizers or hydrophilic surface appendages. It is usually measured by zetameter. Before measurement, SLN dispersions are diluted 50-fold with the original dispersion preparation medium for size determination and zeta potential measurement.

- **Nuclear magnetic resonance (NMR)**

The size and the qualitative nature of nanoparticle can be determine by NMR. The selectivity afforded by chemical shift complements the sensitivity to molecular mobility to provide information on the physicochemical status of components within the nanoparticle.[14]

- **X-ray diffraction (powder X-ray diffraction) and differential scanning calorimetry (DSC)**

The geometric scattering of radiation from crystal planes within a solid allow the presence or absence of the former to be determined thus permitting the degree of crystallinity to be assessed. Another method that is a little different from its implementation with bulk materials, DSC can be used to determine the nature and speciation of crystallinity within nanoparticles through the measurement of glass and melting point temperatures and their associated enthalpies.[15]

- **Acoustic methods**

Another ensemble approach, acoustic spectroscopy, measures the attenuation of sound waves as a means of determining size through the fitting of physically relevant equations. In addition, the oscillating electric field generated by the movement of charged particles under the influence of acoustic energy can be detected to provide information on surface charge.

- **Atomic force microscopy (AFM)**

In this technique, a probe tip with atomic scale sharpness is rastered across a sample to produce a topological map based on the forces at play between the tip and the surface. The probe can be dragged across the sample (contact mode), or allowed to hover just above (non contact mode), with the exact nature of the particular force employed serving to distinguish among the sub techniques. That ultra-high resolution is obtainable with this approach, which along with the ability to map a sample according to properties in addition to size.[16]

- **Electron Microscopy**

Scanning electron microscopy (SEM) and transmission electron microscopy (TEM) provide way to directly observe nanoparticles. SEM is however better for morphological examination. TEM has a small size limit of detection.

- **Static Light Scattering (SLS)/Fraunhofer Diffraction**

This method studies the pattern of light scattered from a solution of particles is collected and fit to fundamental electromagnetic equations in which size is the primary variable. It is fast and rugged method, but requires more cleanliness than DLS, and advance knowledge of the particles' optical qualities.[17]

APPLICATIONS OF SOLID LIPID NANOPARTICLES

- **Topical use**

SLNs used for topical application for various drug such as anticancer, vitamin-A, isotretinoin, flurbiprofen. Using glyceryl behenate, vitamin A-loaded nanoparticles can be prepared. This method is useful for the improvement of penetration with sustained release. The isotretinoin-loaded lipid nanoparticles were formulated for topical delivery of drug. Production of the flurbiprofen-loaded SLN gel for topical application offer a potential advantage of delivering the drug directly to the site of action, which will produce higher tissue concentrations. Dermal delivery of Doxorubicin would be an ideal way in maximising drug efficiency against skin cancer accompanying with minimising side effects.

- **SLNS as Cosmeceuticals**

Cosmeceuticals is rising as the major application target of these carriers. Carrier systems like SLNs and NLC were formulated with a point of view to meet manufacturing needs like scale up, qualification and validation, simple technology, low cost etc. The SLNs have been applied in the preparation of sunscreens and as an active carrier agent for molecular sunscreens and UV blockers. SLN and NLCs have proved to be controlled release innovative occlusive topicals. Better localization has been achieved for vitamin A in upper layers of skin with glyceryl behenate SLNs compared to conventional formulations. The first two cosmetic products containing lipid nanoparticles were introduced to the market in 2005.

- **SLNs in Breast Cancer and Lymph Node Metastases**

Mitoxantrone-loaded SLN local injections were formulated to reduce the toxicity and improve the safety and bioavailability of drug efficacy of doxorubicin (Dox) has been reported to be enhanced by incorporation in SLNs. In the methodology the Dox was complexed with

soybean -oil-based anionic polymer and dispersed together with a lipid in water to form Dox-loaded solid lipid nanoparticles. The system has enhanced its efficacy and reduced breast cancer cells.

- **SLNs as a Targeted Carrier for Anticancer Drug to Solid Tumors**

SLNs have been reported to be useful as drug carriers to treat neoplasm's. Tumour targeting has been achieved with SLNs loaded with drugs like methotrexate and Camptothecin. Tamoxifen an anticancer drug is incorporated in SLN to prolong release of drug after iv.

- **Oral SLN in Antitubercular Chemotherapy**

Antitubercular drugs such as Rifampacin, Isoniazide, Pyrazinamide-loaded SLN systems were able to reduce the dosing frequency and improve patient compliance. Antitubercular drugs loaded SLNs were prepared using solvent diffusion technique.[18]

MARKETED PRODUCTS OF SLN

Lipid based drug delivery system have been used to improve the bioavailability of BCS class 2 drugs. Market survey data show that about 4% of commercial products of oral lipid based formulations are available in the US, UK and Japan market. Marketed products of SLNs are listed in Table no.2.

Table 2: List of Marketed Products.

Product Name	Main Active Ingredient	Producer/Distributors
Nano Lipid Restore	Coenzyme Q-10 and Omega unsaturated fatty acids.	Chemisches Laboratorium Dr. Kurt Richter, CLR Berlin
Intensive Serum Nanorepair Q-10	Q-10, Polypeptide, Mafane Extract (Antiwrinkle effect)	Dr. Rimpler Gmbh
NLC Deep Effect	Coconut oil, tamanu tree extract	Beate Johnen

CONCLUSION AND FUTURE PERSPECTIVE

SLN constitute an attractive colloidal drug carrier system due to successful incorporation of active compounds and their related benefits. The present review has focused on increasing awareness about nano technological field in drug delivery with the emergence of several promising approaches like solid lipid nanoparticles, nano structured lipid carriers, lipid drug conjugates etc. for improving medical therapeutics.. SLNs have already been proven as good formulations in cosmeceuticals and other allied fields, they must occupy a considerable place in the pharmaceutical market. To exploit the broad applications of lipid based nanoparticulate formulations, it is essential that the pharmaceutical industries specialized in the development of new drug delivery systems should engage in novel formulation technology to promote their scale up and bring them onto the pharmacist's shelves. SLN offer an economical and patient-friendly device for administration of drugs by various routes to maximize effectiveness while avoiding adverse effects on non-target tissues.

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