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SOLID LIPID NANOPARTICLES: RECENT ADVANCES IN NOVEL DRUG CARRIER SYSTEMS

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ABSTRACT

Solid lipid nanoparticles (SLN) have emerged as a next-generation drug delivery system with potential applications in pharmaceutical field, cosmetics, research, clinical medicine and other allied sciences. The present review focuses on the utility of SLN in terms of their advantages, production methodology, characterization and applications. Solid lipid Nanoparticles were developed in early 1990s as an alternative to other traditional colloidal carriers like liposome's, polymeric Nanoparticles and emulsions as they have advantages like controlled drug release and targeted drug delivery with increased stability. SLNs are rapidly developing nanotechnology with several applications in drug delivery system, clinical medicine and other science. The ability of SLNs to incorporate drug into nanocarrier that offer new type in drug delivery system. Therefore SLNs is reaching the goal of controlled and site specific drug delivery system.

KEYWORDS: Solid lipid Nanoparticle drug delivery.

INTRODUCTION

Nanoparticles are colloidal particles ranging from 10 to 1000 nm (1.0 µm), in which the active principles (drug or biologically active material) are dissolved, entrapped, and/or to which the active principle is adsorbed or attached.[1] Recently, significant effort has been taken to develop nanotechnology for drug delivery, as it offers a suitable means of delivering low molecular weight drugs, as well as macromolecules such as peptides, proteins or genes to cells and tissue. Nanoparticles can be used to provide targeted delivery of many drugs, to sustain the drug effect in target tissue, to improve oral bioavailability and to enhance the stability of therapeutic agents against enzymatic degradation.[2] SLN are obtained from

GRAS (generally recognized as safe) lipids and surfactants, devoid of toxicity. SLN have a number of advantages over traditional colloidal systems, such as physical stability, protection of the active substance, controlled release of the active substance, biocompatibility, selective orientation, absence of organic solvents,[3,4] General ingredients include solid lipid(s), surfactant(s) and water. The term lipid is used here in a broad sense and includes triglycerides (e.g. tristearin), partial glycerides, fatty acids (e.g. stearic acid), steroids (e.g. cholesterol) and waxes (e.g. cetyl palmitate). All classes of surfac- tants (with respect to charge and molecular weight) have been used to stabilize the lipid dispersion.[5]

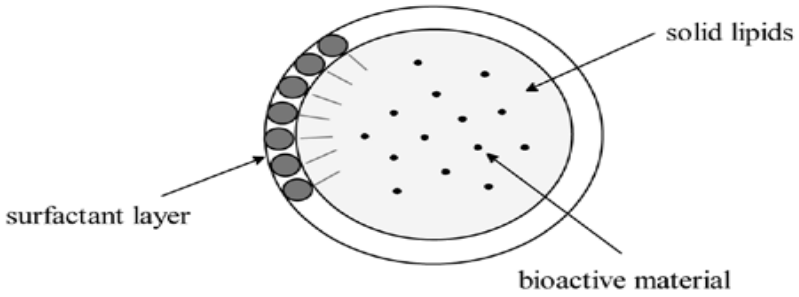

Figure 1: Structure of solid lipid nanoparticles stabilized by surfactant layer.

As previously mentioned SLN combine the advantages and are free of faults typical for other colloidal carriers with micro- and nanoparticles. The key advantages of SLN are:

• Controlled release and orientation of active substance.
• Increase of the active substance stability.
• The capability to include lipo- and hydrophilic substances.
• No biotoxicity.
• No necessity to use organic solvents.
• No problems related to large-scale production and sterilizing.
• High loading (drug loaded).

Advantages of SLN

- Use of biodegradable physiological lipids which decreases the danger of acute and chronic toxicity and avoidance of organic solvents in production me-thods.[6]
- Improved bioavailability of poorly water soluble molecules.[7]
- Site specific delivery of drugs, enhanced drug penetration into the skin via dermal application.
- Possibility of scaling up.

- Protection of chemically labile agents from degrada-tion 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 com-pound.
- High concentration of functional compound achieved.
- Lyophilization 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%).[8]

Routes of Administration

SLNs are given by following route of administration

1. Oral administration.
2. Parenteral administration.
3. Transdermal application

1. *Oral administration*

Forms of SLNs preparation which are given by oral route are aqueous dispersions. SLNs loaded dosage form such as tablets, pellets and capsule. The microclimate of the stomach favors particle aggregation due to the acidity and high ionic strength. It is to be expected that food will have a large impact on SLN performance.[9]

2. *Parenteral administration*

SLNs generally administered intravenously to animals. Distributions of SLN were found to have higher drug concentrations in lung, spleen and brain, while the solution led to more distribution into liver and kidneys.[10] SLN showed higher blood levels in comparison to a commercial drug solution after intravenous.

3. Transdermal application

The smallest particle sizes are observed for SLN dispersions with low lipid content (up to 5%). Disadvantages of dermal administration are low concentration of the dispersed lipid and

the low viscosity. The incorporation of the SLN dispersion in an ointment or gel is necessary in order to achieve a formulation which can be administered to the skin.[11]

Characterization of SLNs

Characterization of the SLNs is necessary for its quality control. Characterization of SLN is a serious challenge due to the colloidal size of the particles and the complexity and dynamic nature of the delivery system. Parameter which are to be evaluated: Particle size, zeta potential, drug release, surface morphology. Polymorphism, degree of crystalline, time scale of distribution processes.

1. Particle Size and Zeta Potential

There are so many techniques for the particle size and zeta potential (size distribution) like photon correlation spectroscopy (PCS), transmission electron microscopy (TEM), scanning electron microscopy (SEM), atomic force microscopy (AFM), scanning tunneling microscopy (STM) or freeze fracture electron microscopy (FFEM).[12]

2. Electron Microscopy

Scanning electron microscopy (SEM) and transmission electron microscopy (TEM) provide a way to directly observe Nanoparticles and physical characterization of Nanoparticles. TEM has a smaller size limit of detection, is a good validation for other methods and one must be cognizant of the statistically small sample size and the effect that vacuum can have on the particles.[12]

3. Nuclear Magnetic Resonance (Nmr)

NMR is used to determine both size and nature of nanoparticles. The selectivity afforded by chemical shift complements the sensitivity to molecular mobility to provide information on the physicochemical status of components within the nanoparticle.

Atomic Force Microscopy (AFM)

In this technique, a probe tip with atomic scale sharpness is kept 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 (noncontact mode), with the exact nature of the particular force employed serving to distinguish among the sub techniques.[12] That ultrahigh resolution is obtainable with this approach, which along with the ability to map a sample according to properties in addition to size.

Preparation Methods of SLNs

There are different methods of SLNs preparation like:

1. High shear homogenization

High shear homogenization technique were initially used for the production of solid lipid nanodispersions.[13,14] Both methods are widespread and easy to handle. However, dispersion quality is often compromised by the presence of micro particles. High-speed homogenization method is used to produce SLN by melt emulsification.[15,16]

2. Hot homogenization

Hot homogenization is carried out at temperatures above the melting point of the lipid and is similar to 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 (like silversion-type homogenizer). The quality of the pre-emulsion affects the quality of the final product to a great extent and it is desirable to obtain droplets in the size range of a few micrometers. High pressure homogenization of the pre-emulsion is done above the lipid melting point. Usually, lower particle sizes are obtained at higher processing temperatures because of lowered viscosity of the lipid phase.[16]

3. Cold homogenization

The cold homogenization process is carried out with the solid lipid and therefore is similar to milling of a suspension at elevated pressure. To ensure the solid state of the lipid during homogenization, effective temperature regulation is needed,[17] Cold homogenization has been developed to overcome the following problems of the hot homogenization technique such as: Temperature mediated accelerated degradation of the drug payload, Partitioning and hence loss of drug into the aqueous phase during homogenization, Uncertain polymorphic transitions of the lipid due to complexity of the crystallization step of the nanoemulsion leading to several modifications and/or super cooled melts.

4. Ultrasonication or high speed homogenization

SLN were also developed by high speed stirring or sonication.[18,19] A most inportant advantage is that, equipments whatever used here are very common in every lab. The problem of this method is broader particle size distribution ranging into micrometer range. This lead physical instability likes particle growth upon storage. Potential metal contamination due to ultrasonication is also a big problem in this method. So for making a

stable formulation, studies have been performed by various research groups that high speed stirring and ultrasonication are used combined and performed at high temperature.

5. SLN prepared by solvent emulsification/evaporation

For the production of nanoparticle dispersions by precipitation in o/w emulsions the lipophilic material is dissolved in water-immiscible organic solvent (cyclohexane) that is emulsified in an aqueous phase. Upon evaporation of the solvent nanoparticle dispersion is formed by precipitation of the lipid in the aqueous medium. The mean diameter of the obtained particles was 25 nm with cholesterol acetate as model drug and lecithin/sodium glycocholate blend as emulsifier. The reproducibility of the result was confirmed by Siekmann and Westesen, who produced the cholesterol acetate nanoparticles of mean size 29 nm.[20]

6. Double emulsion method

Novel method based on solvent emulsification evaporation has been used for preparation of hydrophilic loaded SLNs.[21] The drug is encapsulated with a stabilizer to prevent drug partitioning to external water phase during nsolvent evaporation in the external water phase of w/o/w double emulsion.

7. Spray drying method

It's a cheaper method than lyophilization. This method causes particle aggregation due to high temperature, shear forces and partial melting of the particle. The best result was obtained with mSLN concentration of 1% in a solution of trehalose in water or 20% trehalose in ethanolwater mixtures (10/90 v/v).[22]

Applications of SLN

1. Per oral administration

Per oral administration forms of SLN may include aqueous dispersions or SLN loaded traditional dos-age forms, e.g. tablets, pellets or capsules. The microclimate of the stomach favors particle aggregation due to the acidity and high ionic strength. It can be expected, that food will have a large impact on SLN performance. The plasma levels and body distribution were determined after administration of CA–SLN suspension versus a CA solution (CA-SOL). Two plasma peaks were observed after administration of CA–SLN. The first peak was attributed to the presence of free drug; the second peak can be attributed to controlled release or potential gut uptake of SLN. These two peaks were also found in the total CA

concentration–time profiles of all measured organs. It was also found that the incorporation into SLN protected CA from hydrolysis. The conclusion from this study was that SLN are a promising sustained release system for CA and other lipophilic drugs after oral administration. Increased bioavailability and prolonged plasma levels have been described after per oral administration of cyclosporine containing lipid nanodispersions to animals.[23]

2. Parenteral administration

SLN have been administered intravenously to animals. Pharmacokinetic studies of doxorubicin incorporated into SLN showed higher blood levels in comparison to a commercial drug solution after i.v. injection in rats. Concerning the body distribution, SLN were found to cause higher drug concentrations in lung, spleen and brain, while the solution led to a distribution more into liver and kidneys. Parenteral application is a very wide field for SLN. Subcutaneous injection of drug loaded SLN can be employed for commercial aspect, e.g., erythropoietin (EPO), interferon-β. Other routes are intraperitonial and also intra-articular. Intraperitoneal application of drug-loaded SLN will prolong the release because of the application area. In addition, incorporation of the drug into SLN might reduce irritancy compared to injecting drug micro particles.[23]

3. Transdermal application

The smallest particle sizes are observed for SLN dispersions with low lipid content (up to 5%). Both the low concentration of the dispersed lipid and the low viscosity are disadvantageous for dermal ad-ministration. In most cases, the incorporation of the SLN dispersion in an ointment or gel is necessary in order to achieve a formulation which can be administered to the skin. The incorporation step implies a further reduction of the lipid content. An increase of the solid lipid content of the SLN dispersion results in semisolid, gel-like systems, which might be acceptable for direct application on the skin.[24]

4. Topical application

Regarding the regularity aspect, topical application is relatively unproblematic. The major advantages for topical products are the protective properties of SLN for chemically labile drugs against degradation and the occlusion effect due to film formation on the skin. Especially in the area of cosmetics there are many compounds such as retinol or vitamin C which cannot be incorporated because of the lack of chemical stability. Incorporation of retinol is only possible when applying certain protective measures during production (e.g. noble gasing) and using special packing materials.[25]

5. Ophthalmic administration

Many investigations have been made to use nanoparticles for prolonged release of drugs to the eye. The basic problem of ophthalmologic formulation is the fast removal from the eye, which implies clearance of the applied drug through the nose. It could be shown for nanoparticles that an increased adhesiveness is available leading to higher drug levels at desired site of action. However, the basic problem was that the nanoparticles are of limited toxicological acceptance. It was shown by Gasco that SLN have a prolonged retention time at the eye. This was confirmed by using radiolabiled formulations and γ-scintigraphy. The lipids of SLN are easy to metabolize and open a new ways for ophthalmological drug delivery without impairing vision.

6. Pulmonary administration

A very interesting application appears to be the pulmonary administration of SLN. SLN powders cannot be administered to the lung because the particle size is too small and they will be exhaled. A very simple approach is the aerosolization of aqueous SLN dispersions. The important point is that the SLN should not aggregate during the aerosolization. The aerosol droplets were collected by collision of aerosol with a glass wall of a beaker. This basically demonstrates that SLN are suitable for lung delivery. After localization into the bronchial tube and in the alveoli, the drug can be released in a controlled way from the lipid particles.[27]

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