Review Article

A Review on Solid Lipid Nanoparticles

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ABSTRACT

SLN are introduced in 1991 as an alternative carrier system for traditional colloidal carriers, such as liposomes, emulsions and polymeric micro and nanoparticles. Lipid nanoparticles are unique in size and their ability to incorporate drugs into nanocarriers offers a new prototype in drug delivery that could be used for secondary and tertiary levels of drug targeting. Hence, solid lipid nanoparticles hold great promise for reaching the goal of controlled and site specific drug delivery and hence have attracted wide attention of researchers. SLNs are stabilized by surfactants and polymers. Solid matrix of nanoparticles are protecting incorporated active substances against chemical degradation and providing high flexibility to modify release profiles. This review presents a broad treatment of solid lipid nanoparticles discussing about controlled drug release, drug targeting, drug stability, production procedures, advantages, limitations and their possible remedies. Appropriate analytical techniques for the characterization of SLN like photon correlation spectroscopy, scanning electron microscopy, differential scanning calorimetry are highlighted. Aspects of SLN route of administration and the *in vivo* fate of the carriers are also discussed.

Keywords: Colloidal Drug Carriers, Solid lipid nanoparticles (SLN), Targeting, Stability, Sterilization, Bio-distribution.

INTRODUCTION

Nanoparticles are developed to overcome the following problems:

- I: poor absorption, rapid metabolism and elimination
- II: Poor drug solubility
- III: high toxicity (eg: cancer drugs)

Several systems, including micelles, liposomes, polymer nanoparticles, nanoemulsions, solid dispersion and nanocapsules have been developed. A promising strategy to overcome these problems involves the development of suitable drug carrier system like solid lipid nanoparticles. In the middle of the 1990s, the attention of different research groups focused on alternative nanoparticles made from solid lipids, the so called solid lipid nanoparticle (SLNs). 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 fields. Due to their unique size-dependent properties, lipid nanoparticles offer the possibility to develop new therapeutics. The ability to incorporate drugs into nanocarriers offers a new prototype in drug delivery that could be used for secondary and tertiary levels of drug targeting. Hence, solid lipid nanoparticles hold great promise for reaching the goal of controlled and site specific drug delivery and hence have attracted wide attention of researchers[1, 3].

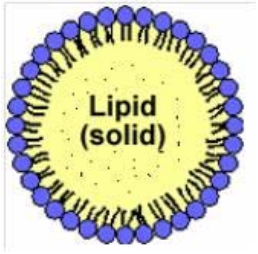

Figure 1: Structure of solid lipid nanoparticle (SLN)

Solid lipid nanoparticles (SLNs) are considered to be the most effective lipid based colloidal carriers, introduced in early nineties. This is the one of the most popular approaches to improve the oral bioavailability of the poorly water soluble drugs. SLNs are in the submicron size range of 50-1000 nm and are composed of physiologically tolerated lipid components which are in solid state at room temperature. The schematic representation of different particulate drug carriers such as emulsions and liposomes and their advantages are compared with SLNs in combine all the advantages of polymeric nanoparticles, fat emulsions and liposomes.

Aims of SLN's[1,2,3,6, 8]

Aims:
- Possibility of controlled drug release and drug targeting
- More affordable (less expensive than polymeric/surfactant based carriers).
- Incorporation of lipophilic and hydrophilic drugs feasible
- Avoidance of organic solvents.
- Problems with respect to large scale production and sterilization
- Increased drug stability.
- High drug payload.
- No biotoxicity of the carrier because, most lipids are biodegradable

Figure 2: Schematic representation of aims

Advantages Of SLN [1,2,3]

- Their small size and relatively narrow size distribution permits sire specific drug delivery.
- Controlled and sustained release of active drug can be achieved.
- Improved bioavailability, protection of sensitive drug molecules from the outer environment (water, light)
- Controlled release by incorporation of poorly water soluble drugs in the solid lipid matrix.
- Easy to scale up and sterilize.
- Better control over release kinetics of encapsulated compounds.
- Enhanced bioavailability of entrapped bioactive compounds.
- Chemical protection of labile incorporated compounds.
- Much easier to manufacture than biopolymeric nanoparticles.
- No special solvent required.
- Conventional emulsion manufacturing methods applicable.
- Raw materials essential are the same as in emulsions.
- Very high long-term stability.
- Application versatility.
- Can be subjected to commercial sterilization procedures.

Disadvantages of SLN[2, 4,6]

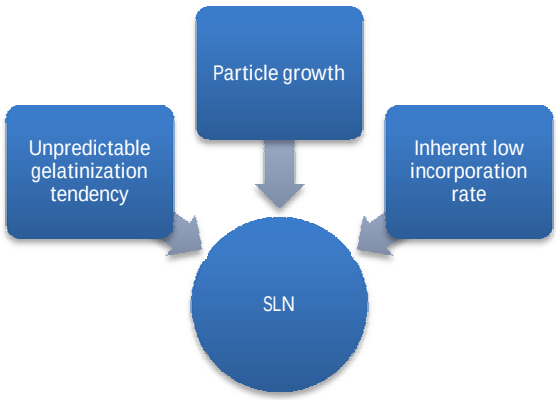

Figure 3: Schematic representation of SLN disadvantages

Nanostructured lipid carriers (NLC)[3,6]

SLNs have two major problems. To overcome these NLCs are introduced. The problems are drug loading and expulsion. The problems are visualised in three ways.

- The use of spatially different lipids leads to larger distances between the fatty acid chains of the glycerides and general imperfections in the crystal and thus provides more room for accommodation of guest molecules.
- The highest drug load could be achieved by mixing solid lipids with small amounts of liquid lipids (oils). Drugs showing higher solubility in oils than in solid lipids can be dissolved in the oil and yet be protected from degradation by the surrounding solid lipids.
- Since drug expulsion is caused by ongoing crystallization or transformation of the solid lipid, this can be prevented by the formation of a third type, the amorphous type NLC. Here the particles are solid but crystallization upon cooling is avoided by mixing special lipids like hydroxyl octacosanyl, hydroxyl stearate and isopropyl myristate. The NLCs have mainly been investigated in the topical and dermatological preparations in the delivery of clotrimazole, ketoconazole, other antifungal imidazoles and ascorbyl palmitate.

Lipid drug conjugates (LDC)

SLNs have a problem of low capacity of hydrophilic drug loading due to partitioning effects during the production process. Only highly potent low dose hydrophilic drugs may be suitably incorporated in the solid lipid matrix. In order to overcome this limitation, the so called LDC nanoparticles with drug loading capacities of up to 33% have been developed. An insoluble drug-lipid conjugate bulk is first prepared either by salt formation (e.g. with a fatty acid) or by covalent linking (e.g. to ester or ethers). The obtained LDC is then processed with an aqueous surfactant solution (such as Tweens) to a nanoparticle formulation using high pressure homogenization (HPH). Such matrices may have potential application in brain targeting of hydrophilic drugs in serious protozoal infections.

Table 1: Comparative properties of solid lipid nanoparticles, polymeric nanoparticles, Liposomes and lipid emulsion[2,5]

Property	SLN	Polymer Nanoparticles	Liposomes	Lipid Emulsion
Systemic Toxicity	Low	> to SLN	Low	Low
Large scale production	Yes	No	Yes	Yes
Cytotoxicity	Low	> to SLN	Low	Low
Residues from organic solvents	No	Yes	May or Maynot	No
Sterlized by autoclaving	No	No	No	Yes
Sustained release	Yes	No	< to SLN	No
Avoidance of RES	No	No	Yes	Yes

SLN preparation

Ingredients: SLNs are made up of solid lipid, emulsifier and water/solvent.

Lipids: Triglycerides (e.g. tri-stearin), Glycerol monostearate (Imwitor), Fatty acids (e.g. stearic acid, palmitic acid), Steroids (e.g. cholesterol), Waxes (e.g.

cetylpalmitate), Tripalmitin, Cacao butter, Monostearin, Lecithin, Tribehenate (Compritol 888 ATO), Trimyristin [Dynasan® 114]

Emulsifiers:Pluronics F 68, 127 the combination of emulsifiers might prevent particles agglomeration more efficiently.

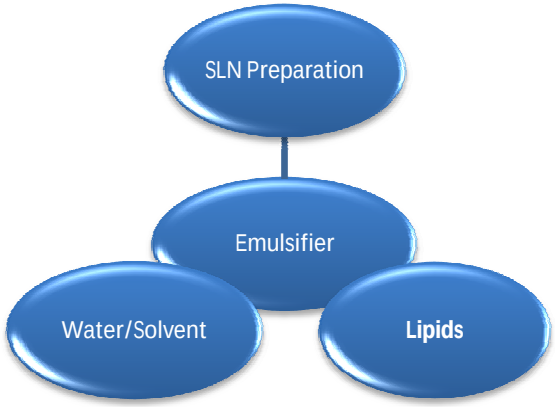

Figure 4: Schematic representation of SLN preparation

PREPARATION TECHNIQUES FOR SLNs[1,2,3,4,14,15,16]

There are different methods of SLNs preparation like

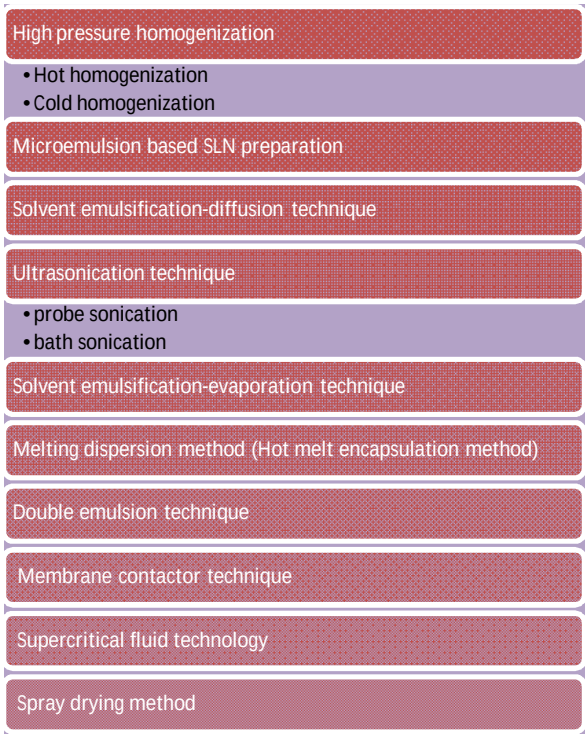

Figure 5: Schematic representation of SLN preparation techniques

1. High pressure homogenization (HPH)

High pressure homogenization is a powerful technique used for the production of SLNs with high pressure (100-200 bars) through a narrow gap. The fluid accelerates on a very short distance to very high velocity (over 1000 Km/h). Very high shear stress and cavitation forces disrupt the particles down to the submicron range. Generally 5-10% 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, work on the same concept of mixing the drug in bulk of lipid melt.

Hot homogenization: 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. HPH of the pre-emulsion is carried out at temperatures above the melting point of the lipid. In general, higher temperatures result in lower particle sizes due to the decreased viscosity of the inner phase. However, high temperatures increase the degradation rate of the drug and the carrier. Increasing the homogenization pressure or the number of cycles often results in an increase of the particle size due to high kinetic energy of the particles.

Cold homogenization[2,4,15]

Cold homogenization has been developed to overcome various problems associated with hot homogenization such as:

- Temperature-induced drug degradation,
- Drug distribution into the aqueous phase during homogenization,
- Complexity of the crystallization.

In this technique the drug containing lipid melt is cooled, the solid lipid is ground to lipid micro particles and these lipid micro particles are dispersed in a cold surfactant solution yielding a pre-suspension. When this pre-suspension is homogenized at or below room temperature, the gravitational force is strong enough to break the lipid micro particles directly to solid lipid nanoparticles.

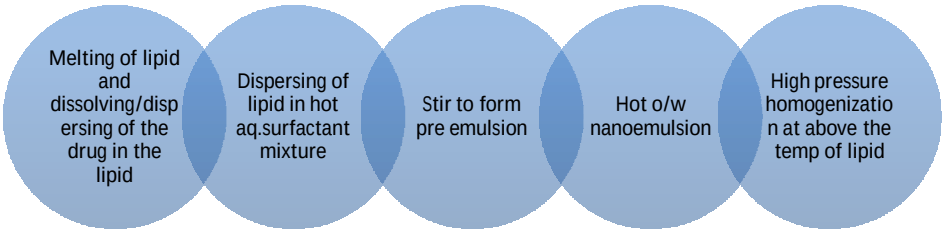

Figure 6: Schematic representation of hot homogenization technique

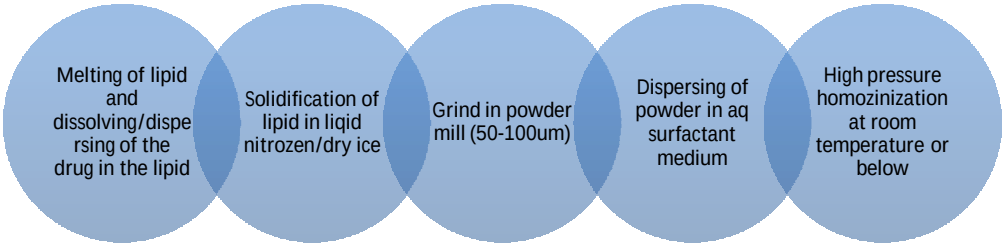

Figure 7: Schematic representation of cold homogenization technique

Advantages

- Low capital cost.
- Demonstrated at lab scale.

Disadvantages

- Energy intensive process.
- Polydisperse distributions.
- Unproven scalability.

2. Micro emulsion based SLN preparation [2,5,15]

Gas co and other scientists have developed and optimized a suitable method for the preparation of SLN via micro emulsion. Micro emulsion was an optically transparent mixture at 65-70°c or a slightly bluish solution which is typically composed of

- low melting lipid,
- emulsifier(s),
- Co-emulsifier and water.

A typical volume ratio of the hot micro emulsion to cold water is usually in the range of 1:25 to 1:50. The excess water is removed by ultra-filtration in order to increase the particle concentration and remove excess of emulsifier(s) residue. Considering micro emulsions, the temperature gradient and pH value fix the product quality in addition to the composition of the micro emulsion. High temperature gradients facilitate rapid lipid crystallization and prevent aggregation.

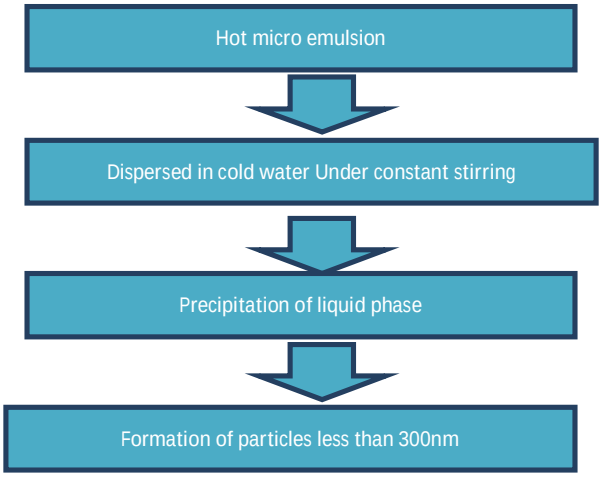

Figure 8: Schematic representation of microemulsion technique

Advantages

- Low mechanical energy input.
- Theoretical stability.

Disadvantages

- Extremely sensitive to change.
- Labor intensive formulation work.
- Low nanoparticles due to dilution of lipid concentrations.

Ultrasonication/high speed homogenization: [14,15]

SLNs are also be prepared by ultrasonication or high speed homogenization techniques. For smaller particle size combination of both ultrasonication and high speed homogenization is required.

Advantages

- Reduced shear stress.

Disadvantages

- Potential metal contamination.
- Physical instability like particle growth upon storage.

3. Solvent evaporation: [15,16]

SLNs can also prepared by solvent evaporation method. The solution is emulsified in an aqueous phase by high pressure homogenization. The organic solvent is removed from the emulsion by evaporation under reduced pressure (39–60 mbar).

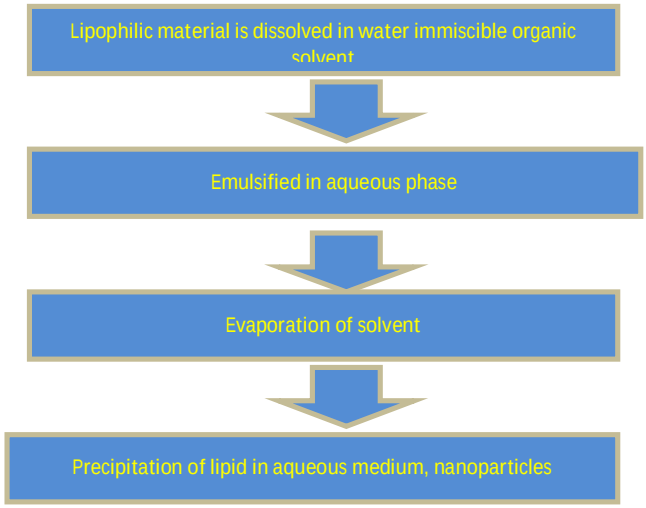

Figure 9: Schematic representation of solvent evaporation technique

Advantages

- Scalable.
- Mature technology.
- Continuous process.
- Commercially demonstrated.

Disadvantages

- Extremely energy intensive process.
- Polydisperse distributions.

4. Solvent emulsification-diffusion method: [15]

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.

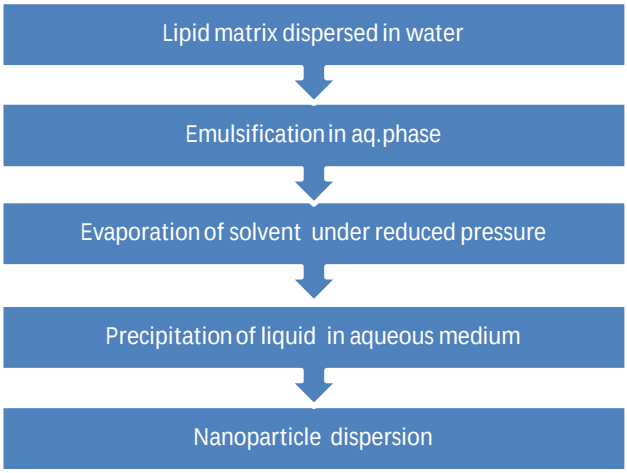

Figure 10: Schematic representation for emulsification-diffusion method

5. Supercritical fluid method: [16]

This is an alternative method of preparing SLNs by particles from gas saturated solutions (PGSS).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 good choice as a solvent for this method.

Advantages

- Solvent free method.
- Particles are obtained as a dry powder, instead of suspensions.
- Mild pressure and temperature conditions.
- Carbon dioxide solution is the good choice as a solvent for this method.

6. Spray drying method: [5,15,16]

It's an alternative technique to lyophilization in order to transform an aqueous SLN dispersion into a drug product. It's a cheaper method than lyophilization. This method causes particle aggregation due to high temperature, shear forces and partial melting of the particle. Frites and Muller recommended the use of lipid with melting point more than 70° C by using this method. The best result was obtained with SLN concentration of 1% in a solution of trehalose in water or 20% trehalose in ethanol-water mixtures (10/90 v/v).

Types Of SLNs:[1,5,6]

The types of SLNs depends on

- The chemical nature of the active ingredient and lipid,
- The solubility of actives in the melted lipid,
- Nature and concentration of surfactants,
- Type of production and the production temperature.

SLN, Type I or homogenous matrix model:

The SLN type I is derived from a solid solution of lipid and active ingredient. A solid solution can be obtained when SLNs are produced by the cold homogenation method. A lipid blend can be produced containing the active in a molecularly dispersed form. After solidification of this blend, it is ground to avoid or minimize the enrichment of active molecules in different parts of the lipid nanoparticles.

SLN, Type II or drug enriched shell model:

It is achieved when SLNs are produced by the hot technique and the active ingredient concentration in the melted lipid is low during the cooling process of the hot o/w nanoemulsions. The lipid will precipitate first, leading to a steadily increasing concentration of active molecules in the remaining melt, an outer shell will solidify containing both active and lipid. The enrichment of the outer area of the particles causes burst release. The percentage of active ingredient localized in the outer shell can be adjusted in a controlled shell model by the incorporation of coenzyme Q 10.

SLN, Type III or drug enriched core model:

Core model can take place when the active ingredient concentration in the lipid melt is high and relatively close to its saturation solubility. Cooling down of the hot oil droplets will in most cases reduce the solubility of the active in the melt. When the saturation solubility exceeds, active molecules precipitate leading to the formation of a drug enriched core [7].

Drug incorporation models of SLN[1, 2,6,17]

Factors affecting loading capacity of a drug in lipid are:

- Solubility of drug in lipid melt.
- Miscibility of drug melt and lipid melt.

- Chemical and physical structure of solid matrix lipid.
- Polymorphic state of lipid material.

Drug incorporation models are as follows:

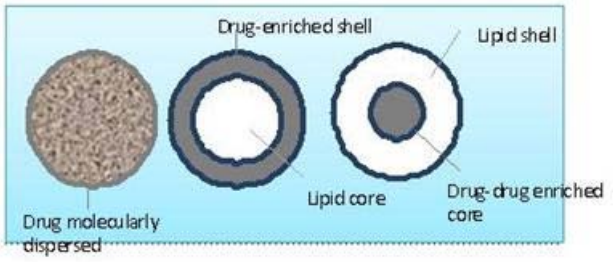

Figure 11: Schematic representation for drug incorporation models

- Drug is molecularly dispersed in lipid matrix when SLN is prepared by cold homogenization.
- In Drug-enriched shell model the solid lipid core forms upon recrystalization
- Drug-enriched core model: Cooling the nanoemulsion leads to a super saturation of the drug which is dissolved in the lipid melt leads to recrystalization of the lipid.

Drug incorporation and loading capacity[6,7]

The particle size, loading capacity and the size distribution of SLNs is found to vary with lipid (triglycerides, fatty acids, steroids, waxes etc), emulsifier (anionic, cationic, non - ionic) and the method of preparation.

Factors determining the loading capacity of the drug in the lipid are[4,6,7]

- Solubility of the melted lipid.
- Miscibility of the drug melt in the lipid melt.
- Chemical and physical structure of solid lipid matrix.
- Polymorphic state of lipid material.

The pre – requisite to obtain a sufficient loading capacity is a sufficiently high solubility of the drug in the lipid melt. Typically the solubility should be higher than required because, it decreases when cooling down the melt and might be even lower in the solid lipid. To enhance the solubility in the lipid melt one can add solubilizers. In addition, the presence of mono and diglycerides in the lipid used to promotes drug solubilization. The chemical nature of the lipid is also important because lipids which form highly crystalline particles with a perfect lattice lead drug expulsion.

Estimation of incorporated drug

Entrapment efficiency[1,6,14,28]

This is of great prime importance in SLN, since it influences the release characteristics of drug molecule. The amount of drug encapsulated per unit weight of nanoparticles is determined after separation of the entrapped drug from the SLN formulation. This separation can be carried out using the techniques such as ultracentrifugation, centrifugation filtration and or gel permeation chromatography.

$$\% \text{ Drug entrapment} = \frac{\text{Mass of drug in nanoparticles}}{\text{Mass of drug used in formulation}} \times 100$$

Centrifugation filtration[13]

Filters such as ultra free – mc or ultra sort – 10 are used along with classical centrifugation techniques. The degree of encapsulation can be assessed indirectly by determining the amount of drug remaining in supernatant after centrifugation filtration/ultra-centrifugation of SLN suspension oral tentatively by dissolution of the sediment in an appropriate solvent and subsequent analysis.

Principles of drug release[6,7]

The drug release from lipid nanoparticles is as follows:

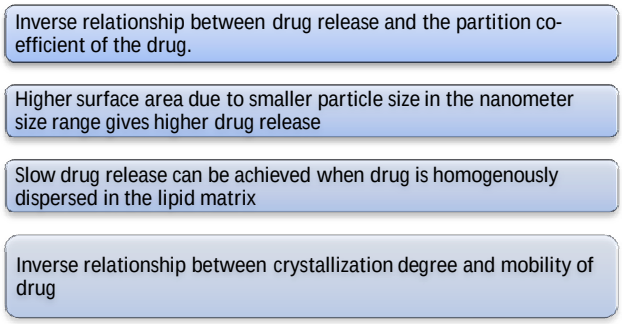

Figure 12: Schematic representation for drug release

Factors contributing to a fast release are the large surface area, a high diffusion co - efficient due to small molecular size, low viscosity in the matrix and a short diffusion distance δ for the drug. The increase in the velocity with decreasing particle size was reported.

Stability [24,29]

SLN and nanoemulsions have remarkable similarities with respect to their composition and production methods. However, SLN cannot simply be regarded as colloidal structures (micelles, mixed micelles, liposomes), it has additional features (super cooled melts, different modifications, and non-spherical shapes) which contribute to or determine the stability of the colloidal lipid suspension. Gelation phenomena, increase in particle sizes and drug expulsion from the lipid carrier are the major problems of storage stability. As described above, there is a close relation between the modifications of the lipid, gelation, particle aggregation and drug expulsion. A supercooled melt, which is the first product formed after hot homogenization, represents a nanoemulsion. It is characterised by spherical lipid droplets and a high incorporation rate for guest molecules (e.g. drugs). The transformation of the lipid melt to lipid crystals results in an increase of particle surfaces, a decrease of the loading capacity of the lipid and therefore, it leads to increased stability problems. Stability of the lipid dispersions decreases as stability of the lipid modification increases.

In vitro and *ex vivo* methods for the assessment of drug release from SLN[18,19,20, 25]

Various methods used to study the *in vitro* release of the drug are:

- Side by side diffusion cells with artificial or biological membrane
- Dialysis bag diffusion technique
- Reverse dialysis bag technique
- Agitation followed by ultracentrifugation or centrifugal ultra filtration

Figure 13: Schematic representation for *in vitro* release of the drug

In vitro drug release[10]

Dialysis tubing

In vitro drug release could be achieved using dialysis tubing. The solid lipid nanoparticle dispersion is placed in pre - washed dialysis tubing which can be hermetically sealed. The dialysis sac is then dialyzed against a suitable dissolution medium at room temperature, the samples are withdrawn from the dissolution medium at suitable intervals, centrifuged and analyzed for the drug content using a suitable analytical method.

Reverse dialysis

In this technique a number of small dialysis sacs containing 1 ml of dissolution medium are placed in SLN dispersion. The SLN's are then displaced into the medium.

Ex vivo model for determining permeability across the gut[13,18]

Ahlin et al., demonstrated the passage of enalaprilat SLNs across rat jejunum[13]. In short the rat jejunum (20 – 30 cm distal from the pyloric sphincter) was excised from the rats after sacrificing the animal used for the study. Qing Zhi Lu et al., excised 10 cm long segments of duodenum (1 cm distal to pyloricsphincter); jejunum (15 cm to pyloric sphincter), ileum (20 cm proximal to cecum) and colon (2 cm distal to cecum) which were immediately cannulated and ligated on both sides and used for their permeability studies[18].

Analytical characterization of SLN

An adequate characterization of the SLNs is necessary for the control of the quality of the product. Several parameters have to be considered which have direct impact on the stability and release kinetics:

- Particle size and zeta potential.
- Degree of crystallinity and lipid modification.
- Co – existence of additional structures and dynamic phenomena.

Measurement of particle size and zeta potential[22,25]

Photon correlation spectroscopy (PCS) and laser diffraction (LD) are the most powerful techniques for routine measurements 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. This method covers a size range from a few nanometers to about 3 microns. PCS is a good tool to characterize nanoparticles, but it is not able to detect larger micro particles. Electron Microscopy provides, in contrast to PCS and LD, direct information on the particle shape. The physical stability of optimized SLN dispersed is generally more than 12 months. ZP measurements allow predictions about the storage stability of colloidal dispersion.

Dynamic light scattering (DLS)[24,25]

DLS also known as PCS records the variation in the intensity of the scattered light on the Microsecond time scale.

Static light scattering (SLS)/Fraunhofer diffraction

SLS is an ensemble method in which the light scattered from a solution of particles is collected and fit into fundamental primary variable.

Acoustic methods

It measures the attenuation of the scattered sound waves as a means of determining size through the fitting of physically relevant equations.

Nuclear magnetic resonance (NMR)[28]

NMR can be used to determine both the size and qualitative nature of nanoparticles.

Electron microscopy[26,35]

Scanning electron microscopy (SEM) and Transmission electron microscopy (TEM) are the direct methods to measure nanoparticles, physical characterization of nanoparticles with the former method being used for morphological examination. TEM has a smaller size limit of detection.

Powder X - ray diffraction and differential scanning calorimetry (DSC)[25,29]

The geometric scattering of radiation from crystal planes within a solid allow the presence or absence of the former to be determined thus the degree of crystallinity to be assessed. DSC can be used to determine the nature and the speciation of crystallinity within nanoparticles through the measurement of glass and melting point temperature.

STERILIZATION OF SLNS

For intravenous and ocular administration SLNs must be sterile. The high temperature reach during sterilization by autoclaving presumably causes a hot o/w microemulsion to form in the

autoclave, and probably modifies the size of the hot nanodroplets. On subsequent slow cooling, the SLNs are reformed, but some nanodroplets may coalesce, producing larger SLN than the initial ones. Since SLN are washed before sterilization, amounts of surfactant and cosurfactant present in the hot system are smaller, so that the nano droplets may be not sufficiently stabilized.

For parenteral administration, SLN dispersions must be sterile. The mean particle diameter of SLNs is often more than 200 nm, so sterile filtration is not possible in these cases. Autoclaving the finished dispersion is not practical as the lipids melt at temperatures used to terminally heat-sterilize pharmaceutical products, and the molten lipid droplets coalesce as there is no applied shear to prevent this. Options are therefore limited to aseptic manufacturing processes following sterilization of the starting materials (gamma or e-beam irradiation of the final dispersion) or exposure to ethylene oxide gas (EO). Bacterial endotoxins in raw materials need to be monitored, especially when raw materials are of natural origin. It may be possible to lyophilize the SLN dispersion, and this lyophile can be irradiated or exposed to EO[8]

ROUTES OF ADMINISTRATION AND THEIR BIODISTRIBUTION[1,2,3,4,22,25]

The *in vivo* fate of the solid lipid nanoparticles will depend mainly on the administration route and distribution process (adsorption of biological material on the particle surface and desorption of SLN components into the biological surrounding). SLN are composed of physiological or physiologically related lipids or waxes. Therefore, pathways for transportation and metabolism are present in the body which may contribute to a large extent to the *in vivo* fate of the carrier. Probably the most important enzymes of SLNs degradation are lipases, which are present in various organs and tissues. Lipases split the ester linkage and form partial glycerides or glycerol and free fatty acids. Most lipases require activation by an oil/water interface, which opens the catalytic center (lid opening). *In vitro* experiment indicates that solid lipid nanoparticles show different degradation velocities by the lipolytic enzyme pancreatic lipase as a function of their composition (lipid matrix, stabilizing surfactant)

Per oral administration

Per oral administration forms of SLN may include aqueous dispersions or SLN-loaded traditional dosage forms such as 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, however no experimental data is published on this issue. The question concerning the influence of the gastric and pancreatic lipases on SLN degradation *in vivo* remains open, too. Unfortunately, only few *in vivo* studies have been performed yet.

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. Regarding distribution, SLN were found to have higher drug concentrations in lung, spleen and brain, while the solution led to more distribution into liver and kidneys.

Transdermal application

The smallest particle sizes are observed for SLNs dispersions with low lipid content (up to5%). Both the low concentration of the dispersed lipid and the low viscosity are disadvantageous for dermal administration. 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 of the SLN dispersion resulting in semisolid, gel-like systems, which might be acceptable for direct application on the skin.

Ocular administration

Biocompatibility and muco-adhesive properties of SLNs improve their interaction with ocular mucosa and prolong corneal residence time of the drug, with the aim of ocular drug targeting.

Nasal administration

Nasal route is preferred due to its fast absorption and rapid onset of drug action also avoiding degradation of labile drugs in the GIT and insufficient transport across epithelial cell layers.

Respiratory delivery

Nebulisation of solid lipid particles carrying anti-tubercular drugs, anti-asthmatic drugs and anti cancer was observed to be successful in improving drug bioavailability and reducing the dosing frequency for better management of pulmonary action.

APPLICATIONS

There are several potential applications of SLNs some of which are given below:

SLNs as gene vector carrier

SLN can be used in the gene vector formulation. In one work, the gene transfer was optimized by incorporation of a diametric HIV-1 HAT peptide (TAT 2) into SLN gene vector. There are several recent reports of SLN carrying genetic/peptide materials such as DNA, plasmid DNA and other nucleic acids. The lipid nuclic acid nanoparticles were prepared from a liquid nanophase containing water and a water miscible organic solvent where both lipid and DNA are separately dissolved by removing the organic solvent, stable and homogeneously sized lipid-nuclic acid nanoparticles (70-100 nm) called genospheres were formed. It is made target specific by insertion of an antibody-lipo polymer conjugated in the particle.

SLNs for topical use

SLNs and NLCs have been used for topical application for various drugs such as tropolide, imidazole antifungals, anticancers, vitamin A, isotretinoin, ketoconazole, DNA, flurbiprofen and glucocorticoids. The penetration of podophyllotoxin-SLN into stratum corneum along with skin surface lead to the epidermal targeting. By using glyceryl behenate, vitamine A-loaded nanoparticles can be prepared. The methods are useful for the improvement of penetration with sustained release. The isotretinoin-loaded lipid nanoparticles was formulated for topical delivery of drug. Soyabean lecithin and tween80 are used for the hot homogenization method for this. The methodology is useful because of the increase of accumulative uptake of isotretinoin in skin. Production of the flurbiprofen loaded SLN gel for topical application offer a potential advantages of delivering the drug directly to the site of action, which will produce higher tissue concentrations.

Polyacrylamide, glycerol and water were used for the preparation of this type of SLN gel.

SLNs as cosmeceuticals

The SLNs have been applied in the preparation of sunscreens and as an active carrier agent for molecular sunscreens and UV blockers. The *in vivo* study showed that skin hydration will be increased by 31% after 4 weeks by addition of 4% SLN to a conventional cream.SLN and NLCs have proved to provide controlled release innovative occlusive topical formulations. Better localization has been achieved for vitamin A in upper layers of skin with glyceryl behenate SLNs compared to conventional formulations.

SLNs for potential agriculture application

Essential oil extracted from *Artemisia arboreseens* L when incorporated in SLN, were able to reduce the rapid evaporation compared with emulsions and the systems have been used in agriculture as a suitable carrier of ecologically safe pesticides. The SLN were prepared here by using compritol 888 ATO as lipid and poloxamer 188 or Miranol Ultra C32 as surfactant.

SLNs as a targeted carrier for anticancer drug to solid tumor:

SLNs have been reported to be useful as drug carriers to treat neoplasms. Tamoxifen, anticancer drug incorporated in SLN to prolong release of drug after i.v. administration in breast cancer and to enhance the permeability and retention effect. Tumour targeting has been achieved with SLN loaded with drugs like methotrexate and camptothecin.

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 efficacy and reduced breast cancer cells.

Oral SLNs in antitubercular chemotherapy

Antitubercular drugs such as rifampicin, isonizide, pyrazinamide-loaded SLN systems, were able to decrease the dosing frequency and improve patient compliance. By using the emulsion solvent diffusion technique this antitubercular drug loaded solid lipid nanoparticles are prepared. The nebulization in animal by incorporating the above drug in SLN also reported for improving the bioavailability of the drug.

Stealth nanoparticles

These provide a novel and unique drug-delivery system they evade quick clearance by the immune system. Theoretically, such nanoparticles can target specific cells. Studies with antibody labelled stealth lipobodies have shown increased delivery to the target tissue inaccessible sites. Stealth SLNs have been successfully tested in animal models with marker molecules and drugs.

Methods to prolong brain retention of SLNs[25]

The body distribution of SLNs is strongly dependent on their surface characteristics like size, surface hydrophobicity, surface mobility etc. The SLNs have been proposed as suitable systems to deliver hydrophilic drugs like diminazine and also for other BCS class IV drugs like paclitaxel, vinblastine, camptothecin, etoposide, cyclosporine etc[2,24,27,39]. These carriers can gain access to the blood compartment easily (because of their small size and lipophilic nature) but the detection of these particles by the cells of the reticuloendothelial system(RES) i.e. the mononuclear phagocytic system; MPS cells of the liver (Kupffer) and that of spleen macrophages is a major limitation for their use. Uptake of nanoparticles by RES could result in therapeutic failure due to insufficient pharmacological drug concentration build up in the plasma and hence at the BBB. To overcome these limitations various researchers have tried to increase the plasma half-life of SLNs by the following methods.

Surface coating with hydrophilic polymers/surfactants[35]

The high rates of RES mediated detection and clearance of colloidal carriers by liver, significantly reduces the half-life of the drug. The interaction of the colloidal carriers with blood plasma proteins (opsonins) and thus with the membranes of macrophages (opsonization) is believed to be the major criteria for clearance of these systems from the blood stream. Hence to prevent this clearance and to increase their availability at the target site the RES removal of these particulate systems should be prevented. This RES recognition can be prevented by coating the particles with a hydrophilic or a flexible polymer and/or a surfactant.

Transfection agent[37]

Cationic SLNs for gene transfer are formulated using the same cationic lipid as for liposomal transfection agents. The differences and similarities in the structure and performance between SLN and liposomes were investigated. PCS showed that the prepared SLNs were smaller in diameter than the corresponding liposomes while AFM supported the expected structural differences. DNA binding differed only marginally. Cationic lipid composition governs the in vitro transfection performance than the colloidal structure it is arranged in. Hence, cationic SLN extends the range of highly potent non-viral transfection agents by one with favorable and distinct technological properties. Combination of cationic SLN with the nuclear localization signal TAT2 increased transfection efficiency hundredfold.

Targeted delivery of solid lipid nanoparticles for the treatment of lung diseases[4,38]

Targeted delivery of drug molecules to organs or special sites is one of the most challenging research areas in pharmaceutical sciences. By developing colloidal delivery systems such as liposomes, micelles and nanoparticles a new frontier was opened for improving drug delivery. Nanoparticles with their special characteristics such as small particle size, large surface area and the capability of changing their surface properties have numerous advantages compared with other delivery systems. Targeted nanoparticle delivery to the lungs is an emerging area of interest.

Solid lipid nanoparticles in tuberculosis disease[2,39]

SLNs have longer stability and better encapsulation efficiency than liposomes and, as opposed to polymeric nanoparticles, the production process involves minimal amounts of organic solvents. SLN have been used to encapsulate Anti Tubercular Drugs (ATD) and were proved to be successful in experimental tuberculosis. Antitubercular drugs such as rifampicin, isoniazid, and pyrazinamide SLN systems were able to decrease the dosing frequency and to improve patient compliance. ATD were co-incorporated into SLN to evaluate the potential of these carriers in tuberculosis chemotherapy via the oral route.

SLN applied to the treatment of malaria[1,39,]

The main drawbacks of conventional malaria chemotherapy are the development of multiple drug resistance and the nonspecific targeting to intracellular parasites, resulting in high dose requirements and subsequent intolerable toxicity. Nanosized carriers have been receiving special attention with the aim of minimizing the side effects of drug. Several nanosized delivery systems have already proved their effectiveness in animal models for the treatment and prophylaxis of malaria. A number of strategies to deliver antimalarials using nanocarriers and the mechanisms that facilitate their targeting to Plasmodium infected cells are discussed in this review. Taking into account the peculiarities of malaria parasites, the focus is placed particularly on lipid-based (e.g., liposomes, solid lipid nanoparticles and nano and microemulsions) and polymer-based nanocarriers (Nanocapsules and nanospheres)[39] .

CONCLUSION

The major advantages of SLNs include preparation by using lipids which simulates physiological lipids, large scale production and avoidance of organic solvents. SLNs are relatively young delivery systems and hold great promise for their systemic investigation and exploitation.

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