International Journal of Pharmaceutical Development & Technology

e ISSN - 2248 - 910X

www.ijpdt.com

Print ISSN - 2248 - 9096

SOLID LIPID NANOPARTICLES: FOR ENHANCEMENT OF ORAL BIOAVAILABILITY

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ABSTRACT

Solid lipid nanoparticles are emerging as alternative carriers to colloidal systems for controlled and targeted drug delivery. SLNs combine the advantages of different colloidal carriers, like emulsions, liposome's, (physically acceptable) polymeric nanoparticles (controlled drug release from lipid matrix) etc. Additional advantages include, lack of coalescence after reaching to room temperature, better physical stability and lack of appreciable drug leakage from the particles. In recent years much work has been focused in the development of SLNs as delivery systems for anticancer drugs, peptides, genetic material, cosmetics etc. SLNs find applications in site specific drug delivery, local action, and enhancement of bioavailability.

Key words: Solid lipid nanoparticles, colloidal carriers, nanoparticles, bioavailability.

INTRODUCTION

The discovery and development of new chemical entities with desirable therapeutic properties alone is not sufficient to ensure progress in drug therapy for it seldom fulfils the medical expectations. Exciting experimental data obtained from in vitro studies are very often followed by disappointing results in vivo. Main reasons for the therapy failure include insufficient drug concentration due to poor absorption, rapid metabolism and elimination (e.g., Peptides and Proteins), drug distribution to other tissues combined with high drug toxicity (e.g., Anti cancer drugs), poor drug solubility which excludes i.v. injection of aqueous drug solution, high fluctuation of variable plasma levels due to unpredictable bioavailability after peritoneal administration, including the influence of food on plasma levels (e.g., Cyclosporine).

A promising strategy to overcome these problems involves the development of suitable carrier systems. Now the in vivo fate of the drug is no longer mainly determined by the properties of the drug, but by the carrier system, which should permit a controlled and localized release of the active drug according to the specific needs of the therapy [1].

Carrier systems find application both in the development of new drugs and enhancement of potential of old drugs. The therapeutic molecules are delivered at the site of action in a desired manner by the carrier system. The same existing, old drugs can find a new potential in its intelligently designed carrier system and said to be given a new lease of life. NDDS- novel drug delivery systems are gaining importance in drug delivery for its size and stability. The drug delivery approaches, in general, aim to develop a carrier system which can hold the molecule effectively and then navigate them towards the right destination without affecting the tissues en route and at the same modifying the drug release character as well as drug receptor interactions. Various such systems, which have gained an utmost importance, include Colloidal Carriers like vesicular systems, micro particulate systems and nanoparticles (Liposomes, Niosomes, Pharmacosomes, Polymeric and lipid nanoparticles etc). Cellular Carriers like released erythrocytes, antibiotics, platelets and leukocytes. Supramolecular Delivery Systems like micelles, polymeric micelles, aquasomes, and polymer based systems bioerodible mucoadhesive, polymers, and soluble synthetic polymeric carriers. Macromolecular Systems like antibody enzyme complex and biospecific antibiotics [2].

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Solid lipid Nanoparticles

Solid lipid nanoparticles have been reported as an alternative drug delivery device to traditional polymeric nanoparticles. SLNs are in submicron size range (50-1000nm) and are composed of physiologically tolerated lipid components. At room temperature the particles are in solid state. These are made of biocompatible and biodegradable materials capable of incorporating lipophilic and hydrophilic drugs.

Factors to be considered in the manufacturing of solid lipid nanoparticles:

SLNs are particles made from solid lipids (i.e., lipids solid at room temperature and also at body temperature) and stabilized by surfactant(s). Common ingredients used in the preparation of SLNs are lipids (Matrix materials), emulsifiers, co emulsifiers, and water.

Excipients used in the formulation of SLNs:

Lipid matrices: Bees wax, Behenic acid, Caprylic acid, cetylpalmitate, Cholesterol, Glycerylmonostearate, Glyceryltrilaurate, Glyceryltristearate, Glyceryltrimyristate, Glyceryltripalmitate, Glycerylbehenate, Hardened fat, Stearic acid, Solid paraffin, Softisan142.

Emulsifiers: Phosphatidyl choline 95%, Soyalecithin, Egg lecithin, Poloxamer188, Poloxamer 407, Polysorbate 80.

Coemulsifiers: Tyloxapol, Taurocholate sodium, Taurodeoxycholic acid sodium salt, Sodium dodecyl sulphate, Sodium glycholate, Sodium oleate, Cholesteryl hemisuccinate.

Cryoprotectants: Trehalose, Glucose, Mannose, Maltose, Lactose, Sorbitol, Mannitol, Glycine, Polyvinyl pyrrolidine, Gelatin.

Chargemodifiers: Stearylamine, Diacetyl phosphate dipalmitoyl phosphatidylcholine **(DPPC)**

Preservatives: Thiomersal

Selection of Lipids:

Lipid crystallinity, lipophilicity, loading capacity, melting point and purity of lipid are the important factors to be considered while selecting a lipid. SLNs are prepared using lipids of less ordered crystal lattices favour successful drug inclusion, compared to those prepared using highly ordered crystal packing lipids. Lipids that form highly crystalline particles with a perfect lattice cause drug expulsion. Lipids with less perfect crystals have many imperfections, which provide space to accommodate the drugs. Lipophilicity of the glycerides increase as the hydrocarbon chain length increases. Therefore, lipophilic drugs are better soluble in lipid melts of longer fatty acid chain lengths. Loading capacity of the drug in lipid melt, physical and chemical structure of the lipid matrix and polymorphic state of lipid materials. Melting point of the lipid has influence on average particle size of SLNs dispersions. Purity of the lipids is important to produce SLNs of good quality. Impurities may alter the zeta potential of formulation and there by stability can be affected. Lipid matrices used for the production of SLNs for I.V administration should be toxicologically accepted, biodegradable and suitable for sterilization by autoclaving [3].

Selection of emulsifier:

An emulsifier should be nontoxic, compatible with other excipients, capable of producing desired size, with minimum amount used, and also provide adequate stability to the SLNs. Another aspect to be considered in the selection of emulsifier is its in vivo fate. Type and amount of emulsifier influences the size of the particle and also their stability. The amount of emulsifier should be optimum to cover the surface of nanoparticles.

Selection of co-emulsifier:

Phospholipids used in SLNs are neither soluble in continuous phase nor form highly dunamic micelles. The excess phospholipids molecules form small unilamellar vesicles, which exhibit limited mobility. Therefore they are unable to immediately cover the newly created crystalline interfaces during re crystallization of solid lipids. Due to the low mobility of the phospholipid molecules, sudden lack of emulsifier on the surface of the particle leads to aggregation and increase in particle size of SLNs. To avoid this co emulsifiers like glycocholate (ionic) as well as tyloxapol (nonionic polymer) are employed [4].

Drug lipid solubility

Solubility of the drug in the lipid melt is more than in the solidified lipid and this is the important parameter that decides the entrapment efficiency and loading capacity. Medium chain glycerides posses the optimal characteristic of solubilisation of the drugs as well as formation of microemulsions. On the other hand, long chain glycerides with higher melting points are necessary for preparation of SLNs. The presence of mono and diglycerides in the lipid as matrix material promotes drug solubilization.

Preparation of solid lipid nanoparticles:

Different approaches exist for the production of finely dispersed lipid nanoparticles dispersions.

1. High shear homogenization:

High shear homogenization techniques were initially used for the production of solid lipid Nano dispersions. 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. Olbrich investigated the influence of different process parameters, including emulsification time, stirring rate and cooling condition on the particle size and zeta potential. Lipids used in this study included trimyristin, tripalmitin, a mixture of mono, di and triglycerides (Witepsol W35, Witepsol H35) with glycerol behenate and poloxamer 188 used as steric stabilizers (0.5% w/w). For Witepsol W35 dispersions the best SLN quality was obtained after stirring for 8 min at 20,000 rpm followed by cooling 10 min and stirring at 5000 rpm at a room temperature. In contrast, the best conditions for Dynasan116 dispersions were a 10-min emulsification at 25,000 rpm and 5 min of cooling at 5,000 rpm in cool water (≈160). Higher stirring rates did not significantly change the particle size, but slightly improved the polydispersity index.

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 Silverson -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, although this might also accelerate the drug and carrier degradation. Better products are obtained after several passes through the high-pressure homogenizer (HPH), typically 3-5 passes. High pressure processing always increases the temperature of the sample (approximately 10° at 500bar). In most cases, 3-5 homogenization cycles at 500-1500 bar are sufficient. Increasing the homogenization leads to an increase of the particle size due to particle coalescence, this occurs because of the high kinetic energy of the particles.

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. 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. The first preparatory step is the same as in the hot homogenization procedure and includes the solubilization or dispersion of the drug in the lipid melt. However, the subsequent steps differ. The drug containing melt is cooled rapidly (using dry ice or liquid nitrogen) to favor homogenous drug distribution in the lipid matrix. In effect, the drug containing solid lipid is pulverized to microns. Chilled processing further facilitated particle milling by increasing the lipid fragility. The SLNs are dispersed in a chilled emulsifier solution. The dispersion is subjected to high pressure homogenization at or below room temperature with appropriate temperature control keeping in view the usual rise in temperature during high pressure processing. However, compared to hot homogenization, larger particle sizes and a broader size distribution are typical of cold homogenized samples. The method of cold homogenization minimizes the thermal exposure of the sample, but it does not avoid it due to the melting of the lipid/drug mixture in the initial step.

4. Ultrasonication or high speed homogenization

SLN were also developed by high speed stirring or sonication. The problem of this method is broader particle size distribution ranging into micrometer range. This lead to physical instabilities
like 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.

6. Micro emulsion based SLN preparations:

Gasco and co-workers developed SLN preparation techniques which are based on the dilution of microemulsions. They are made by stirring an optically transparent mixture which is typically composed of a low melting fatty acid (stearic acid), an emulsifier (polysorbate20, polysorbate 60, soy phosphatidylcholine, and sodium taurodeoxycholate), co-emulsifiers(sodium monooctylphosphate) and water. The hot microemulsion is dispersed in cold water (2-30) under stirring. Typical volume ratios of the hot microemulsion to cold water are in the range of 1:25 to 1:50. The dilution process is critically determined by the composition of the microemulsion. According to the literature, the droplet structure is already contained in the microemulsion and therefore, no energy is required to achieve submicron particle sizes. With respect to the similarities of the production procedure of polymer nanoparticles described by French scientists, different mechanisms might be considered. Fessi produced polymer particles by dilution of polymer solutions in water. According to De Labouret, *et al.,* the particle size is critically determined by the velocity of the distribution processes. Nanoparticles were produced only with solvents which distribute very rapidly into the aqueous phase (acetone), while larger particle sizes were obtained with more lipophilic solvents. The hydrophilic co-solvents of the microemulsion might play a similar role in the formation of lipid nanoparticles as the acetone for the formation of polymer nanoparticles [5].

7. SLN preparation by using supercritical fluid:

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.

8. Spray drying method:

It's an alternative procedure to lyophilization in order to transform an aqueous SLN dispersion into a drug product. It's a cheaper method than lyophilization. This method cause particle aggregation due to high temperature, shear forces and partial melting of the particle. Freitasand Mullera recommends the use of lipid with melting point >700 for spray drying. 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).

9. Double emulsion method

For the preparation of hydrophilic loaded SLN, a novel method based on solvent emulsification-evaporation has been used. Here the drug is encapsulated with a stabilizer to prevent drug partitioning to external water phase during solvent evaporation in the external water phase of w/o/w double emulsion.

Types of solid lipid nanoparitlces:

The types of SLNs depend on the chemical nature of the active ingredient and lipid, the solubility of active ingredients in the melted lipid, nature and concentration of surfactants, type of production and the production temperature. Therefore three incorporation models have been proposed for study.

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 SLN 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 in its solid state 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 SLN 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 nanoemulsion 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.

SLN, Type III or drug enriched core model- Core model can take place when the active ingredient concentration in the lipid melt is high & relatively close to its saturation solubility. Cooling down of the hot oil droplets 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. Due to the different chemical shifts it is possible to attribute the NMR signals to particular molecules or their segments. Simple 1H spectroscopy permits an easy and rapid detection of super cooled melts. ESR requires the addition of paramagnetic spin probes to investigate SLN dispersions. The corresponding ESR spectra give information about the

micro viscosity and micro polarity. ESR permits the direct, repeatable and noninvasive characterization of the distribution of the spin probe between the aqueous and the lipid phase. Experimental results demonstrate that storage induced crystallization of SLN leads to an expulsion of the probe out of the lipid into the aqueous phase. ESR spectroscopy and imaging is expected to give new insights about the fate of SLN in vivo [6].

Characterization of Solid lipid nanoparticles

1. Measurement of particle size and zeta potential:

Photon correlation spectroscopy (PCS) and laser diffraction (LD) are the most powerful techniques for routine measurements of particle size. The Coulter method is rarely used to measure SLN particle size because of difficulties in the assessment of small nanoparticle and the need of electrolytes which may destabilize colloidal dispersions. PCS (also known dynamic light scattering) measures the fluctuation of the intensity of the scattered light which is caused by the particle movement. This method covers a size range from a few nanometers to about 3 microns. This means that PCS is a good tool to characterize nanoparticles, but it is not able to detect larger microparticles. They can be visualized by means of LD measurements. This method is based on the dependence of the diffraction angle on the particle radius (Fraunhofer spectra). Smaller particles cause more intense scattering at high angles compared to the larger ones. A clear advantage of LD is the coverage of a broad size range from the nanometer to the lower millimeter range. The development of polarization intensity differential scattering (PIDS) technology greatly enhanced the sensitivity of LD to smaller particles. However, despite this progress, it is highly recommended to use PCS and LD simultaneously. It should be kept in mind that both methods do not 'measure' particle size. Rather, they detect light scattering effects which are used to calculate particle size. For example, uncertainties may result from non–spherical particle shapes. Platelet structures commonly occur during lipid crystallization and have also been suggested in the SLN. Further, difficulties may arise both in PCS and LD measurements for samples which contain several populations of different size. Therefore, additional techniques might be useful. For example, light microscopy is recommended, although it is not sensitive to the nanometer size range. It gives a fast indication of the presence and character of microparticles (microparticles of unit form or microparticles consisting of aggregates of smaller particles). Electron microscopy provides, in contrast to PCS and LD, direct information on the particle shape. However, the investigator should pay special attention to possible artifacts which may be caused by the sample preparation. For example, solvent removal may cause modifications which will influence the particle shape. 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.

2. Dynamic light scattering (DLS):

DLS, also known as PCS or quasi-elastic light scattering (QELS) records the variation in the intensity of scattered light on the microsecond time scale. This variation results from interference of light scattered by individual particles under the influence of Brownian motion, and is quantified by compilation of an autocorrelation function. This function is fit to an exponential, or some combination or modification thereof, with the corresponding decay constant(s) being related to the diffusion coefficient. Using standard assumptions of spherical size, low concentration, and known viscosity of the suspending medium, particle size is calculated from this coefficient. The advantages of the method are the speed of analysis, lack of required calibration, and sensitivity to sub micrometer particles [7].

3. Static light scattering/Fraunhofer diffraction:

Static light scattering (SLS) is an ensemble method in which the pattern of light scattered from a solution of particles is collected and fit to fundamental electromagnetic equations in which size is the 12 primary variable. The method is fast and rugged, but requires more cleanliness than DLS, and advance knowledge of the particles' optical qualities.

4. 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.

5. Nuclear magnetic resonance (NMR):

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

6. Electron microscopy:

SEM and TEM provide a way to directly observe nanoparticles, physical characterization of nanoparticles. TEM has a smaller size limit of detection, is a good validation for other methods, and affords structural required, and one must be cognizant of the statistically small sample size and the effect that vacuum can have on the particles.

7. Atomic force microscopy (AFM):

n 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 (noncontact mode), with the exact nature of the particular force employed serving to distinguish among the sub techniques. That ultrahigh resolution is obtainable with this approach, which along with the ability to map a sample according to properties in addition to size, e.g., colloidal attraction or resistance to deformation, makes AFM a valuable tool [8].

8. 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 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.

9. Sterilization of SLN's

For intravenous and ocular administration SLN 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 SLN 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 nanodroplets may be not sufficiently stabilized.

10. Routes of administration and their biodistribution

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 i*n vivo* fate of the carrier. Probably the most important enzymes of SLN degradation are lipases, which are present invarious 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) [9].

a. 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 favours 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 have been publish on this issue to our knowledge. 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.

b. 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.Yang *et al*. reported on the pharmacokinetics and body distribution of camptothecin after i.v.injection in mice. In comparison to a drug solution SLN was found to give much higher AUC/dose and mean residence times (MRT) especially in brain, heart and reticuloendothelial cells containing organs. The highest AUC ratio of SLN to drug solution among the tested organs was found in the brain.

c. Transdermal application:

The smallest particle sizes are observed for SLN 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 [10].

11. *In vitro drug release*

Dialysis tubing- *In vitro* drug release could be achieved using dialysis tubing. The SLNs dispersions is placed in a prewashed dialysis tubing which can be hermetically sealed (Mullen A 1998). The dialysis sac is then dialyzed against a suitable dissolution medium at room temperature; the samples are withdrawn from the medium at suitable intervals, centrifuged and analyzed for drug content using a suitable method (U.V. spectroscopy, HPLC etc). The maintenance of sink condition is essential [11].

Reverse dialysis- In this technique a number of small dialysis as containing 1 ml of dissolution medium are placed in SLN dispersion. The SLNs are then displaced into the dissolution medium. The direct dilution of the SLNs is possible with this method; however the rapid release cannot be quantified using this method [12].

Franz diffusion cell- The SLNs dispersions is placed in the donor chamber of a Franz diffusion cell fitted with a cellophane membrane. The dispersion is then dialyzed against a suitable dissolution medium at room temperature; the samples are withdrawn from the dissolution medium at suitable intervals and analyzed for drug content using a suitable method (U.V. spectroscopy, HPLC etc). The maintenance of sink condition is essential [13].

***Ex vivo* model for determining permeability across the gut**-By taking the tissue from animal and rinsing it to remove other contents after washing with ice cold standard ringer solution, cut it into segments, and mount side by side diffusion chambers with an exposed tissue area of 1 cm^2.
SLNs loaded with drug placed on the mucosal side, dispersed in ringer containing the paracellular transporter sodium flourescein conferring for tissue integrity [14].

Applications

Solid lipid Nanoparticles possesses a better stability and ease of upgradability to production scale as compared to liposomes. This property may be very important for many modes of targeting. SLNs form the basis of colloidal drug delivery systems, which are biodegradable and capable of being stored for at least one year. They can deliver drugs to the liver *in vivo* and *in vitro* to cells which are actively phagocytic [15]. There are several potential applications of SLNs some of which are given below:

a. 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 acid. The lipid nucleic 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-nucleic acid nanoparticle (70-100 nm) were formed. It's called genospheres. It is targeted specific by insertion of an antibody-lipo polymer conjugated in the particle [16].

b. 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, flurbiprofenand 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 were formulated for topical delivery of drug. The soyabean lecithin and Tween 80 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 after a potential advantage 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 [17].

c. 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 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 [18].

d. 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.

e. SLNs as a targeted carrier for anticancer drug to solid tumors

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

f. 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 [19].

g. 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 anti tubercular 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.

h. 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 in accessible sites.
Stealth SLNs have been successfully tested in animal models with marker molecules and drugs [20].

CONCLUSION

Lipid nanoparticle drug delivery technology presents significant opportunities for improving medical therapeutics, but the technology's potential remains unrealized. Several technology challenges remain unsolved. Appropriate control of particle size and size distribution, short-term and long-term lipid crystallinity, drug loading profile, drug release kinetics, and greater control of biodistribution once. SLNs delivery can be an innovative way to administer molecules into the target site in a controlled manner by possibly overcoming or alleviating the solubility, permeability and toxicity problems associated with the respective drug molecules. High physical stability of these systems is another advantage. On the other hand the use of solid lipids as matrix material for drug delivery is well known from lipid pellets for oral drug delivery (Runge S et al., 1996). So SLNs is a new era technology which has been taken over by the pharmaceutical industry. The possibility of incorporating both the lipophillic and hydrophilic molecules and the possibility of the several administrations make the SLNs delivery system all the more promising. SLNs will open a new channel for an effective delivery of a vast variety of drug molecules including analgesics, antitubercular, anticancerous, antiaging, antianxiety, antibiotics, and antiviral agents to the target site.

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