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SOLID LIPID NANOPARTICLES (SLN): PREPARATION, CHARACTERIZATION AND APPLICATIONS

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ABSTRACT

Muller and Gasco around 1990s were firstly developed and nominated solid lipid nanoparticles (SLN) for the sake of avoiding organic solvents involved in preparation of polymeric nanoparticles. It is an alternative carrier system to traditional colloidal carriers, such as emulsions, liposomes and polymeric micro and nanoparticles. SLN increases the bioavailability of poorly soluble drugs and it facilitates the drug absorbtion through lymphatic system, so it helps to prevent the hepatic first pass metabolism of drugs. This paper review the present state of production techiniques for solid lipid nanoparticles, advantages, disadvantages, characterization and application of solid lipid nanoparticles.

KEYWORDS: Novel carrier system, Nanoparticles Solid lipid nanoparticles, Bioavailability, Colloidal carrier.

INTRODUCTION[1]

A Lipid nanoparticle is typically spherical with an average diameter between 10 and 1000 nanometers. Solid lipid nanoparticle possess a solid lipid core matrix that can solubilize lipophilic molecules. The lipid core is stabilized by surfactant. The emulsifier used depends on the administration routes and is more limited for paraenteral administrations. The term lipid is used here in a broader sense and includes triglycerides, diglycerides, monoglycerides, fatty acids, steroids and waxes. All classes of emulsifiers have been used to stabilize the lipid dispersion. It has been found that the combination of emulsifiers might prevent particle agglomeration more efficiently.

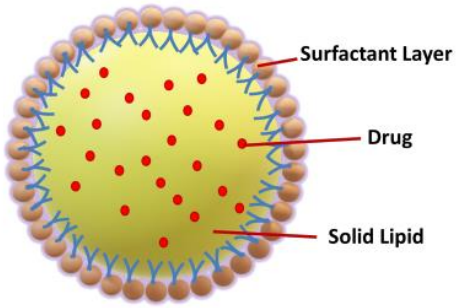

Figure 1: Solid lipid nanoparticle.

In vivo behavior of SLNs

The portal circulation facilitates accessibility of the administered drug into the systemic circulation. To understand the lipid digestion and absorption processes associated with the delivery of lipophilic drugs which play a crucial role in the transport of drugs to the lymphatic system we should understand the physiology of lipid digestion and absorption. Lipid digestion starts in the oral cavity by the action of lingual lipases. Digestion continues in the stomach by the action of both lingual and gastric enzymes. Initially formed lipid emulsion of lipid enters in duodenum in the form of fine droplets and undergoes various chemical and physical changes by the actions of bile and pancreatic juices. Bile and pancreatic juices provide pancreatic lipase, bile salts, and co lipase for the effective digestion and absorption of lipids. In the duodenum micellization along with emulsification and hydrolysis continues to promote absorption through the intestinal wall.

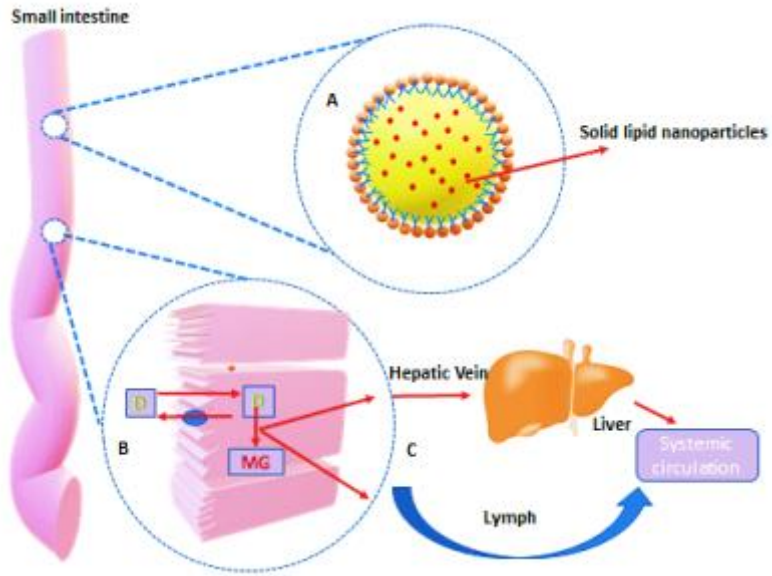

Figure 2: Digestion and absorption of triacylglycerides (TAGs).

TAGs are primarily digested by the pancreatic lipase in the upper part of the jejunum. Pancreatic lipase acts on the surface of emulsion particles and converts TAGs into 2-monoacylglycerol (2-MAG) and free fatty acids (FFAs). 2-MAG is the major form in which MAG is absorbed from the small intestine. FFAs are absorbed from the intestinal lumen into the enterocytes. Here it is used to biosynthesize the neutral fats. A number of proteins are involved in the uptake and transport of FFAs.

Biosynthesis of TAGs

Once inside the enterocytes, specific binding proteins carry fatty acids and MAG to the intracellular site, for the biosynthesis of TAG. In the case of SLNs, drug absorption through the lymphatic system is assisted by the lipid core of SLNs, which stimulates the formation of lipoprotein (chylomicrons) and absorbs free drugs associated with the lipoprotein. The lipoprotein (like chylomicrons) associated with hydrophobic drugs with a size <1µm in diameter facilitates selective lymph transport in the intestines. The compound was also exposed during the absorption process to Cytochrome P450 3A4 (CYP 3A4) enzymes found in enterocytes at higher concentrations and studies proved the role of these enzymes to improve drug bioavailability in the use of lipids. lymphatic transport of extreme lipophilic drugs (log P > 5, solubility in triglycerides (TG) > 50 mg/mL) was strongly correlated with the TG content of the lymph. Drugs with limited solubility (BCS II & IV) are suitable candidates for SLNs. Due to the presence of lipids, SLNs showed increased bioavailability because lipids are consumed by intestinal lymph (dietary or lipid dependent formula) and in combination with long-chain TGs transported (Lipid core formed into enterocytes of the intestinal lipoprotein after FA and MG re-esterification). Co-administration of lipid with drug promotes the synthesis of lipoprotein and therefore it enhances the lymphatic drug transport of drug. Lymphatic fluid (average 3 L a day) is pumped into the subclavian vein through a thoracic duct to shield this medicament from first-pass hepatic metabolism. Dispersed structures such as micelles or mixed micelles may be available in a circulatory system in their free form. When combined with significant quantities of blood/ lymph, the concentration of the surfactant will decrease below its critical micelles concentration and micelles may dissociate into monomers through it helps the drug transported as lipid vesicles in intact form over an extended period, and it leads to prolonging the release of the entrapped drug.

Advantages[2]

The benefit of various colloidal system including liposomes, nanoemulsion, and polymeric nanoparticles are all combined in SLNs. The following describes the main benefits of SLNs.

1. SLNs have no biotoxicity because the lipid utilized are biocompatable and biodegradable material.
2. It is possible to make SLNs without employing organic solvents.
3. The physical stability of SLNs is high.
4. SLNs can be used to achieve both drug targeting and controlled drug release.
5. Incorporation active compounds into SLNs can boost their stability.
6. Lipophilic and hydrophilic medication may be encapsulated in SLNs.
7. It is simple to produce SLN on a big scale.
8. SLNs are sterilizable.

Limitation

The flawless crystalline structure of SLN has several drawbacks as well, including a low drug loading efficiency and the potential for drug expulsion due to crystallization during storage.

1. Lipid dispersions have high water content.
2. Limited transdermal medication delivery.
3. Hydrophilic drug loading capacity is constrained.
4. Polymorphic change.
5. Increase in particle size while being storage.
6. Lipid dispersion gelation.
7. The toxicity of lipid Nanoparticle on retinol cells has not yet been thoroughly investigated.

METHOD OF PREPARATION OF SLN[3-15]

SLNs are made up of solid lipid, emulsifier andwater/solvent. The lipids used may be triglycerides (tri-stearin), partial glycerides (Imwitor), fatty acids (stearic acid, palmitic acid), and steroids (cholesterol) and waxes (cetyl palmitate). Various emulsifiers and their combination (Pluronic F 68, F 127) have been used to stabilize the lipid dispersion. The combination of emulsifiers might prevent particle agglomeration more efficiently. A clear advantage of SLN is the fact that the lipid matrix is made from physiological lipids which decreases the danger of acute and chronic toxicity. The choice of the emulsifier depends on

the administration route with a suitable number of emulsifier suitable for parenteral administration. Solid lipid nanoparticle can be prepared by different methods. They are

1. High shear homogenization.

a). Hot homogenization.

b). Cold homogenization

2. Ultrasonication \high speed homogenization

a). Probe sonication

b). Bath sonication

3. Solvent emulsification \ evaporation.
4. Microemulsion
5. Supercritical fluid technique.
6. Spray drying method.
7. Double emulsion method.

1. High shear homogenization

High shear homogenization technique were initially used for the production of solid lipid nanodispersions. 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 et al. 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 temp. 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.

a). 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, 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 10ºC at 500 bar). 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.

b). 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 micropaticles by ball/mortar milling. Typical particle sizes attained are in the range 50-100 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 state.

2. Ultrasonication or high speed homogenization

SLN were also developed by high speed stirring or sonication. A most advantages are that, equipments that are 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. 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. 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 at 65-700 which is typically composed of a low melting fatty acid (stearic acid), an emulsifier (polysorbate 20, 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. 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.

3. 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.

4. 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. Freitas and 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).

5. 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 emulsions.

CHARACTERIZATION OF SLN QUALITY AND STRUCTURE[16, 17]

Adequate and proper characterization of the SLNs is necessary for its quality control. However, 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. The important parameters which need to be evaluated for the SLNs are, particle size, size distribution kinetics (zeta potential), degree of crystallinity and lipid modification (polymorphism), coexistence of additional colloidal structures (micelles, liposome, super cooled, melts, drug nanoparticles), time scale of distribution processes, drug content, in vitro drug release and surface morphology. The particle size/size-distribution may be studied using 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).

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(s). 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 submicrometer particles.

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 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. 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.

5. Electron Microscopy

SEM and TEM provide a way to directly observe nanoparticles, physical characterization of nanoparticles with the former method being better for morphological examination. 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.

6. Atomic force microscopy (AFM)

In this technique, a probe tip with atomic scale sharpness is rastered across a sample to produce a topological map based on the forces at play between the tip and the surface. The probe can be dragged across the sample (contact mode), or allowed to hover just above (noncontact mode), with the exact nature of the particular force employed serving to distinguish among the subtechniques. 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.

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

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

8. Sterilization of SLNs

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.

ORAL LIPID BASED FORMULATIONS[18-22]

Among the benefits which oral lipid-based formulations can provide are included: Improvement and reduction in the variability of GI absorption of poorly water-soluble, lipophilic drugs. Possible reduction in, or elimination of, a number of development and processing steps (salt selection or identification of a stable crystalline form of the drug, coating, tastemasking, and reduced need for containment and clean-up requirements during manufacture of highly-potent or cytotoxic drug products). Reduction or elimination of positive food effect. Relative ease of manufacture using readily available equipment.

Different types of oral lipid based formulation are like, single-component lipid solutions, self-emulsifying formulations, selfemulsifying solid dispersion formulations and melt pelletization. It has been revealed that the most frequently chosen excipients for preparing oral lipidbased formulations were dietary oils composed of medium (coconut or palm seed oil) or long-chain triglycerides (corn, olive, peanut, rapeseed, sesame, or soybean oils, including hydrogenated soybean or vegetable oils), lipid soluble solvents (polyethylene glycol 400, ethanol, propylene glycol, glycerin), and various pharmaceutically- acceptable surfactants (Cremophor® EL, RH40 or RH60; polysorbate 20 or 80; D-α-tocopherol polyethylene glycol 1000 succinate (TPGS®); Span 20; various Labrafils®, Labrasol®, and Gelucires®). These formulations, which took the form of either bulk oral solutions or liquid-filled hard or soft gelatin capsules, were applied in instances where conventional approaches (solid wet or dry granulation, or water-miscible solution in a capsule) did not provide sufficient bioavailability, or in instances in which the drug substance itself was an oil (dronabinol, ethyl icosapentate, indometacin farnesil, teprenone, and tocopherol nicotinate). The total daily drug dose administered in these formulations, which range in complexity from simple solutions of the drug in a dietary oil up to multi-excipient, self-emulsifying drug delivery systems (SEDDS), range from less than 0.25 μg to greater than 2000 mg. The amount of drug contained in a unit-dose capsule product ranges from 0.25 μg to 500 mg and for oral solution products, from 1 μg/ml to 100 mg/ml. The total amount of lipid excipient administered in a single dose of a capsule formulation ranges from 0.5 to 5 g, but can range from as low as 0.1 ml to as high as 20 ml for oral solution products. Some of these products tolerate room temperature storage for only brief periods of time and require long-term storage at 2-8° due to chemical and/or physical stability issues.

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 in vivo fate of the carrier. Probably the most important enzymes of SLN 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 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.

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, 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 reticulo endothelial cells containing organs. The highest AUC ratio of SLN to drug solution among the tested organs was found in the brain.

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 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, gellike systems, which might be acceptable for direct application on the skin.

APPLICATIONS[23-37]

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. 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 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.

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. 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 flurbiprofenloaded SLN gel for topical application affer 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 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.

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 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 breast cancer and to enhance the permeability and retention effect. Tumour targeting has been achieved with SLNs 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 is enhanced its 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 in accessible sites. Stealth SLNs have been successfully tested in animal models with marker molecules and drugs.

CONCLUSION

Solid lipid nanoparticles are potential drug delivery system than the conventional delivery system. The major advantage is biocompatable, environmental friendly constituents preparation methods and that drug reaches the right site in the body, at the right time, at right concentration. Lipid nanoparticle are suitable carriers for both hydrophilic and lipophilic drugs. They can be administered by different routes such as topical, oral, parenteral, ocular, pulmonary, brain drug delivery system. Lipid nanoparticle are promising drug delivery systems for delivery of various pharmaceutically important active ingredients in future.

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