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SOLID LIPID NANOPARTICLES: A NOVEL POTENTIAL CARRIER APPROACH

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ABSTRACT

Solid lipid nanoparticles (SLNs) are the effective lipid based colloidal carriers which were introduced as an alternative to the conventional carriers such as micro emulsions, liposomes, micro particles and nanoparticles based on synthetic polymers or natural macromolecules. Typically they enhance the oral bioavailability of the low aqueous soluble drugs due to their potential to enhance gastrointestinal solubilization and absorption via selective lymphatic uptake. These properties can be harvested to improve the therapeutic efficacy of the drugs with low bioavailability, as well as to reduce their effective dose requirement. This paper presents an overview about the choice of the drug candidates, advantages, methods of preparation such as high pressure homogenization, ultrasonication/high speed homogenization, solvent evaporation/emulsification, supercritical fluid method, micro emulsion based method and spray drying method are discussed. Appropriate analytical techniques for characterization of solid lipid nanoparticles such as photon correlation spectroscopy, scanning electron microscopy, differential scanning calorimetry etc. are discussed. Applications with respect of routes of administration such as oral, parenteral, topical, pulmonary etc are elaborated in detail.

KEYWORDS

Solid Lipid Nanoparticles, Advantages, Methods, Characterization and Applications of SLNs.

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INTRODUCTION

The field of Novel Drug Delivery System is emerging at an exponential rate with the deep understanding gained in diversified fields of Biotechnology, Biomedical Engineering and Nanotechnology[1]. Many of the recent formulation approaches utilize Nanotechnology that is the preparation of Nanosized structures containing the API[2]. Nanotechnology, as defined by the National Nanotechnology Initiative (NNI), is the study and use of structures roughly in the size range of 1 to 100 nm. The overall goal of

nanotechnology is the same as that of medicine: to diagnose as accurately and early as possible and to treat as effectively as possible without any side effects using controlled and targeted drug delivery approach[3]. Some of the important Drug Delivery System developed using Nanotechnology principles are- Nanoparticles, Solid Lipid Nanoparticles, Nanosuspension, Nanoemulsion, Nanocrystals[4].

A solid lipid nanoparticle (SLN) (Figure No.1) is typically spherical with -an average diameter between 10 to 1000 nanometers. Solid lipid nanoparticles possess a solid lipid core matrix that can solubilize lipophilic molecules. The lipid core is stabilized by surfactants (emulsifiers). The term lipid is used here in a broader sense and includes triglycerides (e.g. tristearin), diglycerides (e.g. glycerol bahenate), monoglycerides (e.g. glycerol monostearate), fatty acids (e.g. stearic acid), steroids (e.g. cholesterol), and waxes (e.g. cetyl palmitate). All classes of emulsifiers (with respect to charge and molecular weight) have been used to stabilize the lipid dispersion. It has been found that the combination of emulsifiers might prevent particle agglomeration more efficiently[5].

Advantages of SLN[6,7]

- Use of biodegradable physiological lipids which decreases the danger of acute and chronic toxicity and avoidance of organic solvents in production methods.
- Improved bioavailability of poorly water soluble molecules.
- Site specific delivery of drugs, enhanced drug penetration into the skin via dermal application.
- Possibility of scaling up.
- Protection of chemically labile agents from degradation in the gut and sensitive molecules from outer environment.
- SLNs have better stability compared to liposomes.
- Enhance the bioavailability of entrapped bioactive and chemical production of labile incorporated compound.
- High concentration of functional compound achieved.
- Lyophilization possible.

Disadvantages[8]

- Poor drug loading capacity.
- Drug expulsion after polymeric transition during storage.
- Relatively high water content of the dispersions (70-99.9%)[8].
- The low capacity to load water soluble drugs due to partitioning effects during the production process.

METHODS OF PREPARATION FOR SLN

Homogenization Method

Lipid nanoparticles can be produced by either the hot or cold high pressure homogenization technique. Shows schematically the steps of these two methods. The active compound is dissolved or dispersed in melted solid lipid for SLN or in a mixture of liquid lipid (oil) and melted solid lipid for NLC. Hot homogenization technique applied to lipophilic and insoluble drugs & Cold homogenization technique is used for hydrophilic drugs[8].

Solvent evaporation method

SLN can also prepared by solvent evaporation method. The lipophilic material is dissolved in a water-immiscible organic solvent (e.g. cyclohexane) that is emulsified in an aqueous phase. Upon evaporation of the solvent, nanoparticles dispersion is formed by precipitation of the lipid in the aqueous medium by giving the nanoparticles of 25 nm mean size. The solution was emulsified in an aqueous phase by high pressure homogenization. The organic solvent was removed from the emulsion by evaporation under reduced pressure (40–60 mbar)[9].

Solvent emulsification-diffusion method

SLNs can also be produced by solvent emulsification-diffusion technique. The mean particle size depends upon lipid concentration in the organic phase and the emulsifier used. Particles with average diameters of 30-100 nm can be obtained by this technique. Avoidance of heat during the preparation is the most important advantage of this technique[10].

Micro emulsion based method

SLN's can be produced by micro emulsification method of molten lipids as the internal phase, and the subsequent dispersion of the micro emulsion in an aqueous medium under mechanical stirring. They are

made by stirring an optically transparent mixture at 65-70oc 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 mono octyl phosphate) and water. The hot micro emulsion is dispersed in cold water under stirring. Typical volume ratios of the hot micro emulsion to cold water are in the range of 1:25 to 1:50. 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 dilution process is critically determined by the composition of the micro emulsion[10].

Supercritical fluid method

This is an alternative method of preparing SLNs by particles from gas saturated solutions (PGSS). This technique has several advantages such as (i) avoid the use of solvents; (ii) Particles are obtained as a dry powder, instead of suspensions, (iii) mild pressure and temperature conditions. Carbon dioxide solution is the good choice as a solvent for this method[11].

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[12].

Double emulsion method

In double emulsion technique the drug (mainly hydrophilic drugs) was dissolved in aqueous solution, and then was emulsified in melted lipid. This primary emulsion was stabilized by adding stabilizer (e.g. gelatin, poloxamer-407). Then this stabilized primary emulsion was dispersed in aqueous phase containing hydrophilic emulsifier (e.g. PVA). Thereafter, the double emulsion was stirred and was isolated by filtration. Double emulsion technique avoids the necessity to melt the lipid for the preparation of peptide-loaded lipid nanoparticles and the surface of the nanoparticles could be modified in order to sterically stabilize them by means of the incorporation of a lipid/-PEG derivative. Sterical stabilization significantly improved the resistance of these colloidal systems in the gastrointestinal fluids[13].

Precipitation technique

The glycosides are dissolved in an organic solvent (e.g. chloroform) and the solution will be emulsified in an aqueous phase. After evaporation of the organic solvent the lipid will be precipitated forming nanoparticles[14].

Film-ultrasound dispersion

The lipid and the drug were put into suitable organic solutions, after decompression, rotation and evaporation of the organic solutions, a lipid film is formed, then the aqueous solution which includes the emulsions was added. Using the ultrasound with the probe to diffuser at last, the SLN with the little and uniform particle size is formed[14].

High-speed homogenization followed by ultrasonication method

SLNs are also prepared by ultrasonication or high speed homogenization techniques. To achieve smaller particle size, combination of both ultrasonication and high speed homogenization is required[15].

CHARACTERIZATION OF SLNS

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 evaluated for the SLNs include particle size, size distribution kinetics (zeta potential), degree of crystallintity and lipid modification (polymorphism), coexistence of additional colloidal structures (miscelles, liposome, super cooled melts, drug nanoparticles), time scale of distribution processes, drug content, *in-vitro* drug release and surface morphology.

Particle size and Zeta potential

The physical stability of SLNs depends on their particle size. Photon correlation spectroscopy (PCS) and laser diffraction (LD) are the most powerful techniques for determination of particle size. PCS (also known as dynamic light scattering) measures the fluctuation of the intensity of the scattered light, which is caused by particle movement. The particle size

determination by photon correlation spectroscopy (PCS) detects size range of 3nm to 3μm and by laser diffraction in size range of 100 nm to 180 μm. Although PCS is a good tool to characterize nano-particles, but is capable for the detection of larger micro particles. The LD method is based on the dependence of the diffraction angle on the particle size (Fraunhofer spectra). Smaller particles cause more intense scattering at high angles compared to the larger ones[16].

Zeta potential measurement can be carried out using zeta potential analyzer or zeta meter. Before measurement, SLN dispersions are diluted 50-fold with the original dispersion preparation medium for size determination and zeta potential measurement. Higher value of zeta potential may lead to deaggregation of particles in the absence of other complicating factors such as steric stabilizers or hydrophilic surface appendages. Zeta potential measurements allow predictions about the storage stability of colloidal dispersions[17].

Electron Microscopy

Scanning electron microscopy (SEM) and transmission electron microscopy (TEM) provide way to directly observe nanoparticles. SEM is however better for morphological examination. TEM has a small size limit of detection[18].

Atomic Force Microscopy (AFM)

In this technique, a probe tip with atomic scale sharpness is rastered across a sample to produce a topological map based on the forces at play between the tip and the surface. The probe can be dragged across the sample (contact mode), or allowed to hover just above (non-contact mode), with the exact nature of the particular force employed serving to distinguish among the sub techniques. That ultra-high resolution is obtainable with this approach, which along with the ability to map a sample according to properties in addition to size, e.g., colloidal attraction or resistance to deformation, makes AFM a valuable tool[19].

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. The advantages of the method are the speed of analysis, lack of required calibration and sensitivity to submicrometer particles[20,21].

Static Light Scattering (SLS)/Fraunhofer Diffraction

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

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[20].

Differential Scanning Calorimetry (DSC)

DSC and powder X-ray diffractometry (PXRD) is performed for the determination of the degree of crystallinity of the particle dispersion. The rate of crystallinity using DSC is estimated by comparison of the melting enthalpy/g of the bulk material with the melting enthalpy/g of the dispersion[22].

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 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[23,24].

Storage Stability of SLN

The physical properties of SLN's during prolonged storage can be determined by monitoring changes in zeta potential, particle size, drug content, appearance and viscosity as the function of time. External parameters such as temperature and light appear to be of primary importance for long - term stability. The zeta potential should be in general, remain higher than -60Mv for a dispersion to remain physically stable[8].

4^{o}C - Most favorable storage temperature.

20^{o}C - Long term storage did not result in drug loaded SLN aggregation or loss of drug.

50^{o}C - A rapid growth of particle size was observed.

***In vitro* and *ex vivo* methods for the assessment of drug release from SLN**

A large number of drugs including very hydrophilic molecules have been postulated to be incorporated into SLN. Various methods used to study[8].

The in vitro releases 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.

APPLICATIONS OF SLN

SLN for Parenteral Application

SLN are very suitable for systemic delivery because they consist of physiologically well-tolerated ingredients and they have good storage capabilities after lyophilization and/or sterilization. When injected intravenously, SLN are sufficiently small to circulate in the microvascular system and prevent macrophage uptake in case of hydrophilic coating. Therefore, SLN have been suggested for viral and non-viral gene delivery[25]. Cationic SLN has been demonstrated to bind genes directly via electrostatic interactions, and have potential benefits in targeted gene therapy in treatment of cancer. The charge of particles can also be modulated via the composition, thus allowing binding of oppositely charged molecules[26-28].

Treatment of central nervous system diseases such as brain tumors, AIDS, neurological and psychiatric disorders is often constrained by the inability of potent drugs to pass blood brain barrier (BBB). Hydrophilic coating of colloids improves the transport of these through BBB and tissue distribution[29,30]. Prepared doxorubicin loaded stealth and non-stealth SLN and observed that the stealth nanoparticles were present in blood at higher concentrations than non-stealth SLN after 24 h following intravenous administration[31].

SLN for Nasal Application

Nasal administration was a promising alternative noninvasive route of drug administration due to fast absorption and rapid onset of drug action, avoiding degradation of labile drugs (such as peptides and proteins) in the GI tract and insufficient transport across epithelial cell layers[32]. In order to improve drug absorption through the nasal mucosa, approaches such as formulation development and prodrug derivatization have been employed. SLN has been proposed as alternative transmucosal delivery systems of macromolecular therapeutic agents and diagnostics by various research groups[33,34]. In a recent report, coating polymeric nanoparticles with PEG gave promising results as vaccine carriers[35]. The role of PEG coating of polylactic acid nanoparticles in improving the transmucosal transport of the encapsulated bioactive molecule. This concept can be useful for solid lipid nanoparticles[36].

SLN for Respiratory Application

The lungs offer a high surface area for drug absorption by avoiding first-pass effects. Rapid drug absorption by aerosolization of drugs (in the 1-3 μm size range) occurs since the walls of alveoli in the deep lung are extremely thin[37,38]. Lymphatic drainage plays an important role in the uptake of particulates in the respiratory system. SLN can be proposed as carriers of anti-cancer drugs in lung cancer treatment or peptide drugs to improve their bioavailability. Assessment of inhaled radio-labeled SLN bio distribution has been described and the data showed an important and significant uptake of the radio-labeled SLN into the lymphatic after inhalation[39]. In a recent study, antitubercular drugs (rifampicin, isoniazid and pyrazinamide) were incorporated into various formulations of solid lipid particles ranged from 1.1-2.1 μm and formulations were nebulized to guinea pigs by mouth for direct pulmonary delivery. Nebulization of solid lipid particles carrying antitubercular drugs

was observed to be successful in improving drug bioavailability and reducing the dosing frequency for better management of pulmonary tuberculosis[16,40].

SLN for Ocular Application

Ocular drug administration via SLN has been reported several times[41]. Bio-compatibility and mucoadhesive properties of SLN improve their interaction with ocular mucosa and prolong corneal residence time of the drug, with the aim of ocular drug targeting. Evaluated SLN as carriers for ocular delivery of tobramycin in rabbit eyes[42]. As a result SLN significantly enhanced the drug bioavailability in the aqueous humor. Studied pilocarpine delivery via SLN, which is commonly used in glaucoma treatment, earlier. They reported very similar results in order to enhance the ocular bioavailability of drug[43].

SLN for Rectal Application

A few reports are available on the rectal drug administration via SLN in the literature, incorporated diazepam into SLN for rectal administration in order to provide a rapid action. They applied SLN dispersions on rabbits and performed bioavailability studies. They found that lipid matrix which is solid at body temperature is not an advantageous system for diazepam rectal delivery. They decided to employ lipids which melt around body temperature in their next experiments. This area seems very open to investigation, especially when the benefits of rectal route are taken into consideration. PEG coating seems to be a promising approach on rectal delivery and consequently, enhancement of bioavailability[44,45].

SLN for Topical application

SLN and NLC are very attractive colloidal carrier systems for skin applications due to their various desirable effects on skin besides the characteristics of a colloidal carrier system. They are well suited for use on damaged or inflamed skin because they are based on non-irritant and non-toxic lipids[46]. Researchers have reported intensively on the topical application of SLN. During the last few years, SLN and NLC have been studied with active compounds such as Vitamin E[47], Tocopherol acetate[48], Retinol[49], Ascorbyl palmitate[50,51], Clotrimazole[52], Triptolide[53], Phodphyllotoxin[54] and a nonsteroidal antiandrogen RU 58841[55] for topical application. A completely new, recently discovered area of application is the use of SLN in sun-protective creams[56].

SLN in Cancer chemotherapy

From the last two decades several chemotherapeutic agents have been encapsulated in SLN and their *in-vitro* and *in-vivo* efficacy have been evaluated. Tamoxifen, an anticancer drug have been incorporated in SLN to prolong the release of drug following i.v. administration in breast cancer[57]. Tumor targeting has been achieved with SLN loaded with drugs like methotrexate and camptothecin. Metoxantrone SLN local injections were formulated to reduce the toxicity and improve the safety and bioefficacy of the drug in treating breast cancer and lymph node metastases[58].

Oral SLN in antitubercular chemotherapy

Antitubercular drugs such as rifampsin, isoniazide, pyrazinamide-loaded SLN systems were able to reduce the dosing frequency and improve patient compliance. Antitubercular drugs loaded SLNs were prepared using solvent diffusion technique[16].

SLN for potential agriculture application

Essential oil extracted from Artemisia arborescens 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.

Solid lipid nanoparticles for delivering peptides and proteins

Solid lipid particulate systems such as solid lipid nanoparticles (SLN), lipid micro particles (LM) and lipospheres have been sought as alternative carriers for therapeutic peptides, proteins and antigens. The research work developed in the area confirms that under optimized conditions they can be produced to incorporate hydrophobic or hydrophilic proteins and seem to fulfill the requirements for an optimum particulate carrier system. Proteins and antigens intended for therapeutic purposes may be incorporated or adsorbed onto SLN, and further administered by parenteral routes or by alternative routes such as oral, nasal and pulmonary. Formulation in SLN confers improved protein stability, avoids proteolytic degradation, as well as sustained release of the incorporated molecules. Important peptides such as cyclosporine A, insulin, calcitonin and somatostatin

have been incorporated into solid lipid particles and are currently under investigation. Several local or systemic therapeutic applications may be foreseen, such as immunisation with protein antigens, infectious disease treatment, chronic diseases and cancer therapy.

SLN as potential new adjuvant for vaccines

Adjuvants are used in vaccination to enhance the immune response. The safer new subunit vaccines are less effective in immunization and therefore effective adjuvants are required. New developments in the adjuvant area are the emulsion systems. These are oil-in-water emulsions that degrade rapidly in the body. Being in the solid state, the lipid components of SLNs will be degraded more slowly providing a longer lasting exposure to the immune system.

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[63].

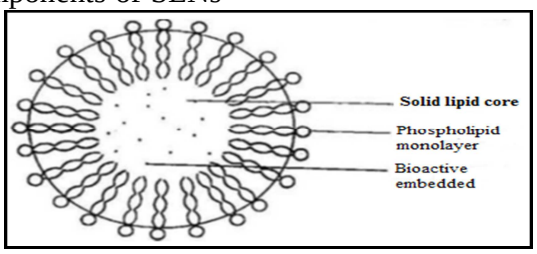

Figure No.1: Structure of Solid Lipid Nanoparticle

CONCLUSION

Solid lipid nanoparticle technology presents significant opportunities for improving medical therapeutics which combine the advantages of fat emulsions, liposomes; polymeric nanoparticles. SLNs delivery can be an innovative way to administer molecules into the target site in a controlled manner by possibly alleviating the solubility, permeability and toxicity problems associated with the respective drug molecules. High physical stability and drug loading are advantageous to SLNs.

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CONFLICT OF INTEREST

None declared.

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