Garud et al., International Current Pharmaceutical Journal 2012, 1(11): 384-393
http://www.icpjonline.com/documents/Vol1Issue11/08.pdf

International Current Pharmaceutical Journal

REVIEW ARTICLE OPEN ACCESS

Solid Lipid Nanoparticles (SLN): Method, Characterization and Applications

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ABSTRACT

Solid lipid nanoparticles (SLN) have emerged as a next-generation drug delivery system with potential applications in pharmaceutical field, cosmetics, research, clinical medicine and other allied sciences. Recently, increasing attention has been focused on these SLN as colloidal drug carriers for incorporating hydrophilic or lipophilic drugs. Proteins and antigens intended for therapeutic purposes may be incorporated or adsorbed onto SLN, and further administered by parenteral routes or be alternative routes such as oral, nasal and pulmonary. The obstacles associated with conventional chemotherapy may be partially overcome by encapsulating them as SLN. The present review focuses on the utility of SLN in terms of their advantages, production methodology, characterization and applications. If properly investigated, SLNs may open new vistas in therapy of complex diseases.

***Key Words*:** Solid lipid nanoparticles, drug delivery, drug incorporation.

INTRODUCTION

Targeted delivery of a drug molecule to specific organ sites is one of the most challenging research areas in pharmaceutical sciences. By developing colloidal delivery systems such as liposomes, micelles and nanoparticles, new frontiers have opened for improving drug delivery. Nanoparticles with their special characteristics small particle size, large surface area and the capability of changing their surface properties have numerous advantages compared with other delivery systems (Kreuter, 1997). Nanoparticles are solid colloidal particles ranging from 10 to 1000 nm (1.0 μm), in which the active principles (drug or biologically active material) are dissolved, entrapped, and/or to which the active principle is adsorbed or attached (Chowdary *et al.*, 1997). In recent years, significant effort has been devoted to develop nanotechnology for drug delivery, since it offers a suitable means of delivering small molecular weight drugs, as well as macromolecules such as proteins, peptides or genes to cells and tissues and prevents them against enzymatic degradation (Rao *et al.*, 2004). The advantages of nanoparticles as drug delivery systems are that they are biodegradable, non-toxic, and capable of being stored for longer periods as they are more stable (Chowdary *et al.*, 1997).

Since a decade, trials are being made to utilize solid lipid nanoparticles (SLN) as alternative drug delivery system to colloidal drug delivery systems such as lipid emulsions, liposomes and polymeric nanoparticles. SLN combines the advantages of different colloidal carriers and also avoids some of their disadvantages. SLN can be used to improve the bioavailability of drugs, e.g. cyclosporine A (Muller *et al.*, 2008), and to obtain sustained release of lipophilic drugs like camptothecin (Yang *et al.*, 1999).

Solid lipid nanoparticles (SLN) are aqueous colloidal dispersions, the matrix of which comprises of solid biodegradable lipids (Swathi *et al.*, 2010). SLNs combine the advantages and avoid the drawbacks of several colloidal carriers of its class such as physical stability, protection of incorporated labile drugs from degradation, controlled release, excellent tolerability (Sarathchandiran, 2012). SLN formulations for various application routes (parenteral, oral,

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dermal, ocular, pulmonar, rectal) have been developed and thoroughly characterized in vitro and in vivo (Mulla *et al.*, 2010).

Advantages of SLN

- Use of biodegradable physiological lipids which decreases the danger of acute and chronic toxicity and avoidance of organic solvents in production methods (Rupenagunta *et al.*, 2011)
- Improved bioavailability of poorly water soluble molecules (Fahr and Liu, 2007)
- 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 of SLN

- Poor drug loading capacity,
- Drug expulsion after polymeric transition during storage
- Relatively high water content of the dispersions (70-99.9%) (Schwarz *et al.*, 1994).

METHODS OF PREPARATION

High shear homogenization (HSH)

Initially used for the production of solid lipid nanoemulsions, this method is reliable. It involves high pressure homogenization which pushes the liquid with high pressure (100-2000 bar) through a narrow gap ranging a few microns. The fluid accelerates to a very short distance at very high viscosity of over 1000 km/h. Very high shear stress and cavitation forces disrupt the particles down to submicron range. As low as 5% to as high as of 40% lipid content has been investigated. Two general approaches to achieve HSH are hot homogenization and cold homogenization.

Hot homogenization is generally carried out at temperatures above the melting point of the lipid. A pre-emulsion of the drug loaded lipid melt and the aqueous emulsifier phase (same temperature) is obtained by high shear mixing device. The resultant product is hot o/w emulsion and the cooling of this emulsion leads to crystallization of the lipid and the formation of SLNs. Smaller particle sizes are obtained at higher processing temperatures because of lowered viscosity of the lipid phase. However, high temperature leads to the degradation rate of the drug and the carrier. Increasing the homogenization temperature or the number of cycles often results in an increase of the particle size due to high kinetic energy of the particles. Generally, 3-5 homogenization cycles at a pressure of 500-1500 bar are used (Mehnert and Mader, 2001; Jenning *et al.*, 2002).

Cold homogenization has been developed to overcome the temperature related degradation problems, loss of drug into the aqueous phase and partitioning associated with hot homogenization method. Unpredictable polymeric transitions of the lipid due to complexity of the crystallization step of the nanoemulsion resulting in several modifications and/or super cooled melts. Here, drug is incorporated into melted lipid and the lipid melt is cooled rapidly using dry ice or liquid nitrogen. The solid material is ground by a mortar mill. The prepared lipid microparticles are then dispersed in a cold emulsifier solution at or below room temperature. The temperature should be regulated effectively to ensure the solid state of the lipid during homogenization. However, compared to hot homogenization, larger particle sizes and a broader size distribution are typical of cold homogenization samples (Ekambaram *et al.*, 2012).

Ultrasonication

Ultrasonication or high speed homogenization is another method for the production of SLNs. The advantage of this method is that the equipment used is commonly available at lab scale. However, this method suffers from problems such as broader size distribution ranging into micrometer range. Potential metal contaminations, physical instability like particle growth upon storage are other drawbacks associated with this technique (Elldem *et al.*, 1991).

Table 1: A list of drugs and polymers used for the preparation of SLNs using different methods.

Drug	Polymer	Method of preparation	Reference
Olanzapine	Hydrogenated soyaphosphatidylcholine	Modified high pressure homogenization	Vivek *et al.* (2007)
Rizatriptan	Tristearin,Phospholipon80	Modified solvent injection method	Nair *et al.* (2011)
Alendronate NP	PLGA,Ethyl acetate, PF68	Double emulsion solvent diffusion	Cohen-Sela *et al.* (2009)
Clozapine	Dynasan114,116,	Hot homogenization	Venkateswarlu *et al.* (2004)
Tetracaine,	Tristearin,Dynasan112,		Zur Muhlen *et al.*(1998)
Etomidate,	Campritol 888ATO,		Schwarz *et al.* (1994)
Prednisolone	Lipoid S75		
Vitamin A	Compritol 888ATO, Miglyol 812,	Hot homogenization	Muller *et al.* (1999)
Retinol	Dynasan 116		Jenning *et al.* (2000)
Gatifloxacin	Chitosan-Na aliginate	Modified Coacervation	Motwani *et al.* (2008)
Insulin	PEG'Glycolgrafted chitosan	Ionic gelation	Zhang *et al.* (2008)
Paclitaxel	Tripalmitin, phosphatidylcholine	Microemulsion	Cavalli *et al.* (2000)
Insulin	Hydrophobized cholesterol bearing pullulan	Ultra sonication	Akiyoshi *et al.* (1998)
Mitoxantrone	Glyceryl behenate, Campritol 888ATO, lecithin		Lu *et al.* (2006)
Vinpocetine	Glyceryl monostearate,DCM, soyalecithin	Ultrasonic solvent emulsification	Luo *et al.* (2006)
Insulin	Cetyl palmitate	Solvent emulsification evaporation	Sarmento *et al.* (2007)
5-Fluorouracil	Dynasan 114,118, triglyceride, soyalecithin	Double emulsion Solvent evaporation	Yassin *et al.* (2010)
Methotrexate	Cetyl alcohol, Campritol 888 ATO,Tween 80	Microemulsion congealing technique	Misra *et al.* (2002)
Gatifloxacin	Sodium alginate, Chitosan	Modified coacervation	Motwani *et al.* (2008)

Microemulsion based SLN preparation

Gasco and coworkers (1997) developed SLNs based on the dilution of microemulsions. These are made stirring an optically transparent mixture at 65-70°C which is typically composed of a low melting fatty acid like stearic acid, an emulsifier (e.g. polysorbate 20, polysorbate 60, soyaphosphatydylcholine and taurodeoxycholic acid sodium salt), co-emulsifiers (e.g. butanol, sodium monooctylphosphate) and water. The hot microemulsion is dispersed in cold water (2-3°C) under stirring (Waghmare *et al.*, 2012). 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. The SLN dispersion can be used as granulation fluid for transferring in to solid product like tablets and pellets by granulation process, but in case of low particle content too much of water need to be removed. The 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 (De Labouret *et al.*, 1995).

Supercritical Fluid technology

This is a novel technique recently applied for the production of SLNs (Cavalli *et al.*, 1996). A fluid is termed supercritical when its pressure and temperature exceed their respective critical value. The ability of the fluid to dissolve compounds increases. This technology comprises of several processes for nanoparticle production such as rapid expansion of supercritical solution (RESS), particles

from gas saturated solution (PGSS), aerosol solvent extraction solvent (ASES), supercritical fluid extraction of emulsions (SFEE). The advantages of this technique includes avoidance of the use of solvents, particles obtained as a dry powder, instead of suspensions, requires mild pressure and temperature conditions. Carbon dioxide solution is the good choice as a solvent for this method (Chen *et al.*, 2006).

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 (Sjostrom *et al.*, 1992). 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 (1996), who produced the cholesterol acetate nanoparticles of mean size 29 nm.

Solvent emulsification-diffusion

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. Here, the lipid matrix is dissolved in water-immiscible organic solvent followed by emulsification in an aqueous phase. The solvent is evaporated under reduced pressure resulting in nanoparticles dispersion formed by precipitation of the lipid in aqueous medium (Muller *et al.*, 2000 and Trotta et al, 2003).

Double Emulsion

In this method, 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. Li *et al.* (2010) prepared solid lipid nanoparticles loaded with bovine serum albumin (BSA) using double emulsion method.

Spray Drying

It is an alternative technique to lyophilization in order to transform an aqueous SLN dispersion into a drug product. This is a cost-effective method than lyophilization and recommends the use of lipid with melting point >70°C. This method causes particle aggregation due to high temperature shear forces and partial melting of the particle. According to Freitas and Mullera (1998) best results were obtained with SLN concentration of 1% in a solution of trehalose in water or 20% trehalose in ethanol-water mixtures (10/90 v/v).

Solvent injection technique

Here, the solid lipid is dissolved in water miscible solvent. The lipid solvent mixture is injected into stirred aqueous phase with or without surfactant. Finally, the dispersion filtered to remove excess lipid. Emulsion within the aqueous phase helps to produce lipid droplets at the site of injection and stabilize SLNs until solvent diffusion gets completed (Schubert *et al.*, 2003). Mishra *et al.* (2010) prepared and evaluated SLNs using Solvent injection method for delivery of Hepatitis B surface antigen for vaccination using subcutaneous route.

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 nanoparticles, but is capable for the detection of larger microparticles (Pandey *et al.*, 2005). 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.

Zeta potential measurement can be carried out using zeta potential analyzer or zetameter. Before measurement, SLN dispersions are diluted 50-fold with the original dispersion preparation medium for size determination and zeta potential measurement (Luo *et al.*, 2006). 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.

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 (Meyer and Heinzelmann, 1992).

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 (Mukherjee *et al.*, 2009).

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.

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.

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 (Siekmann and Westesen, 1994).

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.

APPLICATIONS OF SLN

SLN for Parenteral Application

Wissing *et al.* (2004) intensively reviewed parenteral use of SLN. 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. 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 (Olbrich et al 2001; Tabatt *et al.*, 2004; Pedersen et al 2006).

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 (Kreuter 2001; Wang *et al.*, 2002). Fundaro et al, 2000, 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.

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 (Lee *et al.*, 1994). 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 (Muller and Keck 2004; Prego *et al.*, 2005). In a recent report, coating polymeric nanoparticles with PEG gave promising results as vaccine carriers (Vila *et al.*, 2004). The role of PEG coating of polylactic acid nanoparticles in improving the trans mucosal transport of the encapsulated bioactive molecule reported to be successful by Tobio et al, 1998. This concept can be useful for solid lipid nanoparticles.

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 (Agu *et al.*, 2001; Banga 2003). 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 (Videira *et al.*, 2002). 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 (Pandey *et al.*, 2005a and 2005b). 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.

SLN for Ocular Application

Ocular drug administration via SLN has been reported several times (Friedrich et al 2005). Biocompatibility 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. Cavalli *et al.*, (2002) evaluated SLN as carriers for ocular delivery of tobramycin in rabbit eyes. As a result SLN significantly enhanced the drug bioavailability in the aqueous humor. Cavalli *et al.*, (1995) also 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.

SLN for Rectal Application

A few reports are available on the rectal drug administration via SLN in the literature (Sznitowska *et al.*, 2000). Sznitowska *et al.*, 2001 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.

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 (Wissing and Muller 2003). 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 (Dingler *et al.*, 1999), tocopherol acetate (Wissing and Muller 2001), retinol (Jenning *et al.*, 2000), ascorbyl palmitate (Uner *et al.*, 2005a and 2005b), clotrimazole (Souto *et al.*, 2004), triptolide (Mei *et al.*, 2003), phodphyllotoxin (Chen *et al.*, 2006) and a nonsteroidal antiandrogen RU 58841 (Munster *et al.*, 2005) for topical application. A completely new, recently discovered area of application is the use of SLN in sun-protective creams (Waghmare *et al.*, 2012).

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 (Murthy, 2005). 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 (Wong *et al.*, 2006).

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 (Pandey *et al.*, 2005).

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 of ecologically safe pesticide (Lai *et al.*, 2006).

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