



# AMERICAN JOURNAL OF PHARMTECH RESEARCH

Journal home page: <http://www.ajptr.com/>

## Solid Lipid Nanoparticles: A Promising Approach In Drug Delivery System

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### ABSTRACT

Solid lipid nanoparticles (SLN) introduced in 1991 represent an alternative carrier system to traditional colloidal carriers, such as emulsions, liposomes and polymeric micro- and nanoparticles. SLN are aqueous colloidal dispersions, the matrix of which comprises of solid biodegradable lipids. These lipid nanoparticles modify drug release, body distribution and kinetics of associated drugs. Solid lipid nanoparticles hold great promise for reaching the goal of controlled and site specific drug delivery and hence have attracted wide attention of researchers. This review presents a broad treatment of solid lipid nanoparticles discussing their advantages, limitations, production techniques, drug incorporation, loading capacity and drug release, characterization and applications. The potential of SLN to be exploited for the different administration routes is highlighted also.

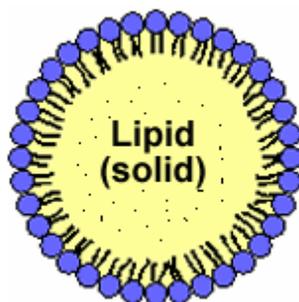
**Key words:** Solid lipid nanoparticles , colloidal drug carriers, homogenization, Drug Targeting.

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Received 30 August 2012, Accepted 10 September 2012

## INTRODUCTION

Colloidal particles ranging in size between 10 and 1000 nm are known as nanoparticles. They are manufactured from synthetic/natural polymers and suited to optimize drug delivery and reduce toxicity. Over the years, they serve as a variable substitute to liposomes as drug carriers. The successful implementation of nanoparticles for drug delivery depends on their ability to penetrate through several anatomical barriers, sustained release of their contents and their stability in the nanometer size. However, the scarcity of safe polymers with regulatory approval and their high cost have limited the wide spread application of nanoparticles to clinical medicine<sup>1</sup>. To overcome these limitations of polymeric nanoparticles, lipids have been put forward as an alternative carrier, particularly for lipophilic pharmaceuticals. These lipid nanoparticles are known as solid lipid nanoparticles (SLNs), which are attracting wide attention of formulators world-wide<sup>2</sup>. Solid lipid nanoparticles introduced in 1991 represent an alternative carrier system to tradition colloidal carriers such as - emulsions, liposomes and polymeric micro – and nanoparticles. Nanoparticles made from solid lipids are attracting major attention as novel colloidal drug carrier for intravenous applications as they have been proposed as an alternative particulate carrier system. SLN are sub-micron colloidal carriers ranging from 50 to 1000 nm, which are composed of physiological lipid, dispersed in water or in aqueous surfactant solution. SLN offer unique properties such as small size, large surface area, high drug loading and the interaction of phases at the interface and are attractive for their potential to improve performance of pharmaceuticals<sup>3</sup>. They are considered as alternative materials to polymers which is identical to oil in water emulsion for parenteral nutrition, but the liquid lipid of the emulsion has been replaced by a solid lipid shown on Figure. 1



**Figure. 1: Structure of solid lipid nanoparticle (SLN)**

In order to overcome the disadvantages associated with the liquid state of the oil droplets, the liquid lipid was replaced by a solid lipid, which eventually transformed into solid lipid nanoparticles. The reasons for the increasing interest in lipid based system are many – fold and include

- Lipids enhance oral bioavailability and reduce plasma profile variability.
- Better characterization of lipoid excipients.
- An improved ability to address the key issues of technology transfer and manufacture scale-up<sup>4</sup>.

**Advantages of SLN:** <sup>5-8</sup>

- ❖ Excellent biocompatibility.
- ❖ Improve stability of pharmaceuticals.
- ❖ High and enhanced drug content.
- ❖ Control and / or target drug release.
- ❖ Easy to scale up and sterilize.
- ❖ Better control over release kinetics of encapsulated compounds.
- ❖ Chemical protection of labile incorporated compounds.
- ❖ Much easier to manufacture than biopolymeric nanoparticles.
- ❖ No special solvent required.
- ❖ Conventional emulsion manufacturing methods applicable.
- ❖ Raw materials essential the same as in emulsions.
- ❖ Very high long-term stability.
- ❖ Application versatility.
- ❖ Can be subjected to commercial sterilization procedures.
- ❖ Enhanced bioavailability of entrapped bioactive compounds.

**Disadvantages of SLN:** <sup>6, 9-10</sup>

- ❖ Particle growth.
- ❖ Unpredictable gelation tendency.
- ❖ Unexpected dynamics of polymeric transitions.
- ❖ Poor drug loading capacity
- ❖ Relatively high water content of dispersion

**Aims of solid lipid nanoparticles:** <sup>7,9,11</sup>

- ❖ Increased drug stability.
- ❖ High drug pay load.
- ❖ Avoidance of organic solvents.
- ❖ Incorporation of lipophilic and hydrophilic drugs.
- ❖ Possibility of controlled drug release.

- ❖ No bio-toxicity of the carrier.

#### METHODS OF SLN PREPARATION:

Various methods have been developed for the preparation of aqueous dispersion of lipid nanoparticles. The different production methods use biocompatible lipids or lipid molecules with a history of safe use in medicine. The essential excipients of SLN are solid lipids as matrix material and amphipathic lipids as surface stabilizers. Solid lipids such as saturated monoacid triglycerides (tristearin, tripalmitin, trilaurin etc), hard fat, cetyl palmitate, fatty acids (stearic acid, behenic acid etc) and cholesteryl acetate are recommended to be used as matrix for solid lipid nanoparticles. Compatible emulsifiers such as phospholipids, bile salts and Poloxamers are preferred as stabilizers<sup>12</sup>. The various methods for preparation of SLN are as follows:

1. High pressure homogenization
  - a. Hot homogenization technique
  - b. Cold Homogenization technique
2. Ultrasonication or high speed homogenization
3. Micro emulsion based SLN preparation
4. Double emulsion method
5. Solvent emulsification/evaporation
6. Spray drying method
7. SLN preparation by using supercritical fluid
8. Precipitation technique
9. Film-ultrasound dispersion

#### **1. High pressure homogenization (HPH):**

##### **A. Hot homogenization:**

Hot homogenization is carried out at temperatures above the melting point of the lipid and can therefore be regarded as the homogenization of an emulsion. A pre-emulsion of the drug loaded lipid melt and the aqueous emulsifier phase (same temperature) is obtained by high-shear mixing device. HPH of the pre-emulsion is carried out at temperatures above the melting point of the lipid. In general, higher temperatures result in lower particle sizes due to the decreased viscosity of the inner phase. However, high temperatures increase the degradation rate of the drug and the carrier. Increasing the homogenization pressure or the number of cycles often results in an increase of the particle size due to high kinetic energy of the particles<sup>13</sup>. Kovacevic A et al., were prepared solid lipid nanoparticle by using hot homogenization technique. They used two polyhydroxy surfactants Plurol®Stearique WL1009 – (PS) and Plantacare® 810 – (PL).The

particle size of solid lipid nanoparticle was found 200 nm by both of surfactant and All dispersions with both surfactants were physically stable for 3 months at room temperature<sup>14</sup>. Silva AC et al., were encapsulated risperidone in solid lipid nanoparticles<sup>15</sup>. Alex MR et al. had prepared solid lipid nanoparticle of poor orally available lopinavir with glyceryl behenate by this technique<sup>16</sup>.

### **B. Cold homogenization :**

Cold homogenization has been developed to overcome various problems associated with hot homogenization such as: Temperature-induced drug degradation, drug distribution into the aqueous phase during homogenization, Complexity of the crystallization step of the nanoemulsion leading to several modifications and/or super cooled melts. In this technique the drug containing lipid melt is cooled, the solid lipid ground to lipid microparticles and these lipid microparticles are dispersed in a cold surfactant solution yielding a pre-suspension. Then this pre-suspension is homogenized at or below room temperature, the gravitation force is strong enough to break the lipid microparticles directly to solid lipid nanoparticles<sup>17, 18</sup>.

### **2. Ultrasonication or high speed homogenization:**

SLN were also developed by high speed stirring or sonication. A most advantages is that, equipment whatever use here are very common in every lab. The problem of this method is broader particle size distribution ranging into micrometer range. This lead physical instabilities 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<sup>19,20</sup>. Castelli F et al., were prepared Solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC) of indomethacin by ultrasonication method<sup>21</sup>.

### **3. Micro emulsion based SLN preparation:**

This method is based on the dilution of microemulsions. As micro-emulsions are two-phase systems composed of an inner and outer phase (e.g. o/w microemulsions). They are made by stirring an optically transparent mixture at 65-70°C, which typically composed of a low melting fatty acid (e.g. stearic acid), an emulsifier (e.g. polysorbate 20), co-emulsifiers (e.g. butanol) and water. The hot microemulsion is dispersed in cold water (2-3°C) under stirring. SLN dispersion can be used as granulation fluid for transferring in to solid product (tablets, pellets) by granulation process, but in case of low particle content too much of water needs to be removed. High-temperature gradients facilitate rapid lipid crystallization and prevent aggregation. Due to the dilution step; achievable lipid contents are considerably lower compared with the HPH based

formulations<sup>22-24</sup>.

#### **4. 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<sup>25</sup>.

#### **5. Solvent emulsification/evaporation:**

In this technique the solid lipid is dissolved in a water-immiscible organic solvent (e.g. cyclohexane, or chloroform) 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<sup>26</sup>. Westesen prepared nanoparticles of tripalmitate by dissolving the triglyceride in chloroform. This solution was emulsified into an aqueous phase by high pressure homogenization. The organic solvent was removed from the emulsion by evaporation under reduced pressure. The mean particle size ranges from approximately 30 to 100 nm<sup>27</sup>.

#### **6. Spray drying method:**

It is an alternative technique to the lyophilization process. This indicates the use of lipid with melting point more than 70°C. The optimum results were obtained with SLN concentration of 1% in a solution of trehalose in water or 20% trehalose in ethanol-water mixture<sup>28</sup>.

#### **7. SLN preparation by using supercritical fluid:**

This is a relatively new technique for SLN production and has the advantage of solvent-less processing. 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<sup>29,30</sup>.

#### **8. Precipitation technique:**

Solid lipid nanoparticles can also be produced by a precipitation method which is characterized by the need for solvents. The glycerides will be 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<sup>31</sup>.

#### **9. 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<sup>32</sup>.

**DRUG INCORPORATION AND LOADING CAPACITY OF SLN:**

Many different drugs have been incorporated in SLN such as Timolol, Deoxycorticosterone, Doxorubicin, Pilocarpine, Thymopentin etc. A very important point to judge the suitability of a drug carrier system is its loading capacity. The loading capacity is generally expressed in percent related to the lipid phase (matrix lipid plus drug). Westesen et al. studied the incorporation of drugs using loading capacities of typically  $1\pm 5\%$ , for Ubidecarenone loading capacities of up to 50% were reported<sup>33</sup>. For Tetracaine and etomidate capacities of  $10\pm 20\%$  are reported<sup>34</sup>, for retinol up to 5%<sup>35-36</sup>, for coenzyme Q10 20%<sup>37</sup> and for cyclosporin  $20\pm 25\%$ <sup>38, 39</sup>. Factors determining the loading capacity of drug in the lipid are, for example:

1. solubility of drug in melted lipid;
2. miscibility of drug melt and lipid melt;
3. chemical and physical structure of solid lipid matrix;
4. polymorphic state of lipid material.

Crystalline structure is of course related to the chemical nature of the lipid which is a key factor to decide in determining whether a drug will be expelled or firmly incorporated in the long-term. Therefore, for a controlled optimization of drug incorporation and drug loading, intensive characterization of the physical state of the lipid particles by NMR, X-ray and other new techniques in this area such as ESR is highly essential. The solubility should be higher than required because it decreases when cooling down the melt and might even be lower in the solid lipid. To enhance the solubility in the lipid melt one can add solubilizers. An optimal SLN carrier can be produced in a controlled way when a certain fraction of  $\alpha$ -form can be created and preserved during the storage time. By doing this the normal SLN carrier transforms to an intelligent drug delivery system by having a built-in trigger mechanism to initiate transformation from  $\alpha$ - to  $\beta$ -forms and consequently controlled drug release<sup>40, 41</sup>.

**Drug release from SLN:**

There is an inverse relationship between drug release and the partition co-efficient of the drug and it is found that higher surface area due to smaller particle size in the nanometer size range gives higher drug release. Slow drug release can be achieved when drug is homogeneously dispersed in the lipid matrix. Drug release also depends on the type and the drug entrapment model of SLN. Crystallinity behaviour of the lipid and high mobility of the drug lead to fast drug release. There is an inverse relationship between crystallization degree and mobility of drug. Factors contributing to a fast release are the large surface area, a high diffusion co-efficient due to small molecular size, low viscosity in the matrix and a short diffusion distance  $\delta$  for the drug.

The increase in the velocity with decreasing particle size was reported. A major problem during the work with lipid nanopellets was the burst release observed with these systems. A similar burst release was obtained when incorporating tetracaine and etomidate into SLN independent on the production method. Prolonged drug release was first obtained when studying the incorporation of prednisolone. This demonstrated the principle suitability of the SLN system for prolonged drug release. Even more important it was possible to modify the release profiles as a function of lipid matrix, surfactant concentration and production parameters (e.g. temperature). In vitro drug release could be achieved for up to 5 to 7 weeks<sup>42, 43</sup>.

## **INFLUENCE OF LIPIDS AND SURFACTANTS USED IN SLN PRODUCTION:**

### **Influence of the lipid:**

Using the hot homogenization, it has been found that the average particle size of SLN dispersions is increasing with higher melting lipids. These results are in agreement to the general theory of HPH and can be explained by the higher viscosity of the dispersed phase. However, other critical parameters for nanoparticle formation will be different for different lipids. Examples include the velocity of lipid crystallization, the lipid hydrophilicity (influence on self-emulsifying properties) and the shape of the lipid crystals (and therefore the surface area). It is also noteworthy, that most of the lipids used represent a mixture of several chemical compounds. The composition might therefore vary from different suppliers and might even vary for different batches from the same supplier. However, small differences in the lipid composition (e.g. impurities) might have considerable impact on the quality of SLN dispersion (e.g. by changing the zeta potential, retarding crystallization processes etc.). For example, lipid nanodispersions made with cetyl palmitate from different suppliers had different particle sizes and storage stabilities. The influence of lipid composition on particle size was also confirmed on SLN produced via high-shear homogenization.

### **Influence of the emulsifier:**

The choice of the emulsifiers and their concentration is of great impact on the quality of the SLN dispersion. High concentrations of the emulsifier reduce the surface tension and facilitate the particle partition during homogenization. The decrease in particle size is connected with a tremendous increase in surface area. The increase of the surface area during HPH occurs very rapidly. The process of a primary coverage of the new surfaces competes with the agglomeration of uncovered lipid surfaces. The primary dispersion must contain excessive emulsifier molecules, which should rapidly cover the new surfaces. The excessive emulsifier molecules might be present in different forms e.g. molecular solubilized (emulsifier monomers), in form of

micelles or liposomes. The time scale of the redistribution processes of emulsifier molecules between particle surfaces, water-solubilized monomers and micelles or liposomes is different. In general, micelle-forming low molecular weight surfactants will rapidly achieve the new equilibrium. Redistribution processes will take a longer time for high molecular weight surfactants. Indeed, it has been reported that SLN stabilized with surfactant mixtures (Lipoid S 75/ poloxamer 188 or tyloxapol /lecithin) have lower particle sizes and higher storage stability compared to formulations with only one surfactant. The addition of sodium glycocholate to the aqueous phase as co-emulsifying agent decreases the particle size, too. Different emulsifier compositions might require different homogenization parameters. For example, the maximal degree of dispersing was obtained with 500 bar and three cycles for poloxamer 188 stabilized systems. Homogenization with pressures of 1000 or 1500 bar did not result in further reduction of the particle size. In contrast, pressures of 1500 bar proved to be the best for lecithin (Lipoid S 75) stabilized systems. The importance of the emulsifier for the quality of the lipid nanodispersion was also demonstrated on micro emulsion based SLN dispersions. The particle size of the SLN dispersion produced with the ionic surfactants was considerably smaller compared to the nonionic formulation<sup>12,44</sup>.

#### CHARACTERIZATION OF SLN:

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 as follows:

##### **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. PCS (also known as dynamic light scattering) measures the fluctuation of the intensity of the scattered light which is caused by particle movement. This method covers a size range from a few nanometers to about 3 microns. PCS is a good tool to characterize nanoparticles, but it is not able to detect larger micro particles. Electron Microscopy provides, in contrast to PCS and LD, direct information on the particle shape. ZP measurements allow predictions about the storage stability of colloidal dispersion<sup>45,46</sup>.

##### **2. Dynamic light scattering (DLS):**

DLS, also known as PCS or quasi-elastic light scattering (QELS). It 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<sup>47</sup>.

### **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:**

It measures the attenuation of the scattered sound waves as a means of determining size through the fitting of physically relevant equations<sup>32</sup>.

### **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 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<sup>47</sup>.

### **7.Atomic force microscopy (AFM) :**

A probe tip with atomic scale sharpness is rastered across a sample to produce a topological map based on forces at play between the tip and the surface.

### **8.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<sup>32</sup>.

### **Sterilization of SLN:**

For intravenous and ocular administration, SLN must be sterile. The temperature reach during

sterilization by autoclaving presumably causes a hot o/w micro emulsion to form in the autoclave, and probably alters the size of the hot nanoparticles. On subsequent slow cooling, the SLN reformed, but some nano-droplets may coalesce, producing larger SLN than the initial ones. SLN are washed before sterilization, amounts of surfactants and co surfactants present the hot systems are smaller, so that the nano-droplets may be not sufficiently stabilized<sup>48</sup>.

#### **In-vitro drug release studies:**

In-vitro drug release studies are mainly useful for quality control as well as for the prediction of in-vivo kinetics. Release profile of drug can be conducted in dialysis tubing or without tubing. In dialysis, the SLNs dispersion is introduced into prewashed dialysis tubing, which is then hermetically sealed and then dialyzed against dissolution medium at constant temperature with constant stirring. Samples were taken at different times, centrifuged and assayed for drug content. Levy and Benita (1990) have reported a new technique which avoids the enclosure of the colloidal drug carrier in a dialysis sac and is based on reverse dialysis. This method is not sensitive enough to characterize rapid release rate of drug from colloidal carrier<sup>49</sup>.

#### **Storage stability:**

The physical stability of the SLNs during prolonged storage can be determined by monitoring changes in particle size, drug content, appearance and viscosity. This can also be done by thin layer chromatography. 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.

4°C - Most favourable storage temperature.

20°C - Long term storage did not result in drug loaded SLN aggregation or loss of drug.

50°C - A rapid growth of particle size was observed<sup>50,51</sup>.

#### **ROUTES OF ADMINISTRATION AND THEIR BIODISTRIBUTION:**

Interactions of the SLN with the biological surroundings including: distribution processes and enzymatic processes. Various administration routes are:

##### **1. 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. Basically SLN can be used for all parenteral applications suitable for polymeric nanoparticles. This ranges from intra articular to intravenous administration. Studies using

intravenously administered SLN have been performed by various groups<sup>52</sup>. Gasco et al. produced stealth and non-stealth solid lipid nanoparticles and studied them in cultures of macrophages<sup>16,17</sup> and also after loading them with Paclitaxel *in vivo*. The *i.v.* administered SLN led to higher and prolonged plasma levels of Paclitaxel. Interestingly both non-stealth and stealth SLN showed a similar low uptake by the liver and the spleen macrophages<sup>53,54</sup>.

## **2. Oral administration:**

Controlled release behaviour of SLNs is reported to enable the bypass of gastric and intestinal degradation of the encapsulated drug, and their possible uptake and transport through the intestinal mucosa. However, the assessment of the stability of colloidal carriers in GI fluids is essential in order to predict their suitability for oral administration. For the production of tablets the aqueous SLN dispersion can be used instead of a granulation fluid in the granulation process. Alternatively SLN can be transferred to a powder (e.g. by spray-drying) and added to the tableting powder mixture<sup>55</sup>.

## **3. Topical application:**

Regarding the regularity aspect, topical application is relatively unproblematic. The major advantages for topical products are the protective properties of SLN for chemically labile drugs against degradation and the occlusion effect due to film formation on the skin<sup>56</sup>. Stability enhancement was reported for coenzyme Q10 and also for the very sensitive retinol<sup>57</sup>. A major step forward was the development of the 'intelligent' SLN (ISLN) which can be exploited for topical but also for all other delivery routes. Intelligent SLN means that the SLN releases in a controlled way the incorporated drug/ active ingredient after it receives a triggering impulse. Such triggering impulses are the increase in temperature or the loss of water from an SLN dispersion or an SLN-containing cream<sup>58</sup>.

## **4. Pulmonary Administration:**

SLNs have been proved to possess a high tolerability that may lead drug targeting to lung macrophages. Particles in the lungs are easily accessed by lung macrophages that suggest the use of the SLNs system for treating infections of the mononuclear phagocytic system (MPS). It is difficult to reach to particular parasites such as mycobacterium with a normal course treatment. Within the MPS macrophages, liver and spleen macrophages are more accessible than the parasites in the lung macrophages. Videira et al. 2002 developed SLNs (200 nm) as a carrier of drugs to the lungs, through alveolar airways to the lymphatic system thus minimizing MPS uptake and increasing the concentration at the tumour site. SLNs were prepared by using Compritol 888ATO as lipid, tween-80 as emulsifier by hot melt homogenization. Particle

deposition and further particle clearance were evaluated after inhalation lipid particles using gamma scintigraphy imaging analysis<sup>59</sup>.

#### APPLICATIONS:

##### **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<sup>60,61</sup>.

##### **Brain targeting through SLNs:**

SLNs can improve the ability of the drug to penetrate through the blood-brain barrier and is a promising drug targeting system for the treatment of central nervous system disorders. In a study to overcome the limited access of the drug 5-fluoro-2'-deoxyuridine (FUdR) to the brain, 3',5'-dioctanoyl-5-fluoro-2'-deoxyuridine (DO-FUdR) was synthesized and incorporated into solid lipid nanoparticles (DO-FUdR-SLN). The concentrations of FUdR in various organs were determined by reversed-phase high-performance liquid chromatography (RP-HPLC) after intravenous administration of DO-FUdR-SLN, DO-FUdR or FUdR<sup>62</sup>. Kreuter et al. showed significant transport of various drugs (e.g. dalargin, tubocurarine and doxorubicin) into the brain using polysorbate-coated polybutylcyanoacrylate (PBCA) nanoparticles<sup>63-65</sup>. It is interesting that the nanoparticles mediated drug transport to the brain depends on the coating of particles with polysorbates. Other surfactants such as poloxamer 407, poloxamine 908 or cremophor RH 40 led to no effects. Another study is done to investigate the specific drug targeting of anti carcinogenic drugs such as camptothecin (CA) after intravenous (i.v) injection by solid lipid nanoparticles<sup>66-67</sup>.

##### **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<sup>68-70</sup>. 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.

**SLNs for topical use:**

SLNs 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 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<sup>71-74</sup>.

**Application of SLNs in cancer chemotherapy:**

Due to drawback of the liposomes, microparticles, supramolecular bio-vectors, polymeric conjugates, such as physical instability, difficulties in scale-up, lack of specific tumor targeting and cytotoxicity of the polymers; research groups have focused on nanoparticles prepared using lipid matrices<sup>75</sup>. There are many reports describing potentials of lipid nanoparticles for parenteral delivery particularly for the treatment of cancer. tamoxifen citrate and tamoxifen citrate loaded nanoparticles were administered by intravenous injection in rats and the pharmacokinetic parameters were determined. The  $t_{1/2}$  and mean residence time of TC-loaded SLNs in plasma was about 3.5-folds ( $p < 0.001$ ) and 3-fold ( $p < 0.001$ ) higher, respectively than free tamoxifen, this indicates the potential of TC-loaded SLNs as a long circulating system in blood.43 SLNs have been reported to be useful as drug carriers to treat neoplasms<sup>76</sup>. Tumour targeting has been achieved with SLNs loaded with drugs like methotrexate<sup>77</sup> and camptothecin<sup>78,79</sup>.

**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<sup>80</sup>.

**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<sup>81,82</sup>.

#### **SLN for potential agriculture application :**

Essential oil extracted from *Artemesia arboreseens L* when incorporated into SLN, were able to reduce the rapid evaporation compared with emulsions and the systems have been used in agriculture as suitable carrier of safe pesticides<sup>83</sup>.

#### **Liver targeting through SLNs :**

SLNs are an attractive carrier system to polymeric nanoparticles, increasing attention from different groups. The surface properties of SLNs can also be modified to alter the pharmacokinetic behaviour of the incorporated drug. This can be done by using the amphiphilic solvation enhancer PE-PEG. Both SLN and SLN-PE-PEG incorporation of 3'-Azido-3'-deoxythymidine palpitae (AZT-P) significantly decreased the urinary excretion of (AZT-P) but increased the localization of (AZT-P) in liver. Higher levels were obtained after i.v. injection of (AZT-P). Similarly 5-FU has poor liposoluble properties and it dissolves readily in aqueous media. Synthesis of a more lipophilic prodrug is an effective method for lipophobic drugs to form stable SLNs<sup>84, 85</sup>.

#### **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<sup>86, 87</sup>.

#### **CONCLUSIONS:**

SLN are very complex systems with clear advantages and disadvantages to other colloidal carriers. A lot of research on SLN as carrier system has rationalized the approach that SLN are the non trivial systems with complex lipid compositional matrix and internal particle microstructure which could be a potential colloidal drug carrier system to administer active compounds or pharmacologically difficult molecules such as proteins, peptides, hormones, genes, DNA, RNA or viral vectors for targeting to exert their related benefits. Still various new dimensions and implications are being pooled by the scientific community to utilize these system

as industrially viable and we can expect many patented dosage forms in the form of SLNs in the future.

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