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Solid Lipid Nanoparticles- A Breakthrough In Novel Drug Delivery System

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ABSTRACT

Solid lipid nanoparticles (SLNs) are the superseding drug delivery system in the nanotechnology sphere. SLNs has been developed at the beginning of 1990s with potential applications in the field of pharmaceuticals, cosmeceuticals, clinical medicine along with research as a substitute to the traditional colloidal carrier systems such as emulsions, liposomes since they exclude those downsides of the traditional system. SLN s offers a great way for controlled drug delivery and site targeting drug delivery as well. This article gives general information about the solid lipid nanoparticles, their production procedures and characterization. In addition to that, the recent advancements of drug delivery systems using SLNs were reviewed.

Keywords: Solid lipid nanoparticles, colloidal carriers, drug delivery.

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INTRODUCTION

In recent years, significant effort has been committed to develop nanotechnology for drug delivery, since it offers an appropriate means of delivering small molecular weight drugs and macromolecules such as proteins, peptides or genes to cells and tissues moreover, prevents them against enzymatic degradation. Solid lipid nanoparticles (SLNs) which are introduced in 1991 were an innovative approach to the traditional colloidal carriers such as emulsions, liposomes and polymeric micro particles. SLNs are sub-micron colloidal carriers that are made up of a physiological lipid ranging from 50-100 nm that are dispersed in water or in aqueous surfactant solution (Figure 1). SLN merges the benefit of diverse colloidal carriers as well as avoids some of their disadvantages. (Figure 2) [1-3].

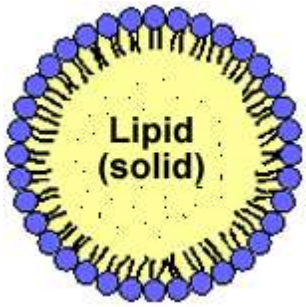

Figure 1: Structure of Solid Lipid Nanoparticle (SLN)

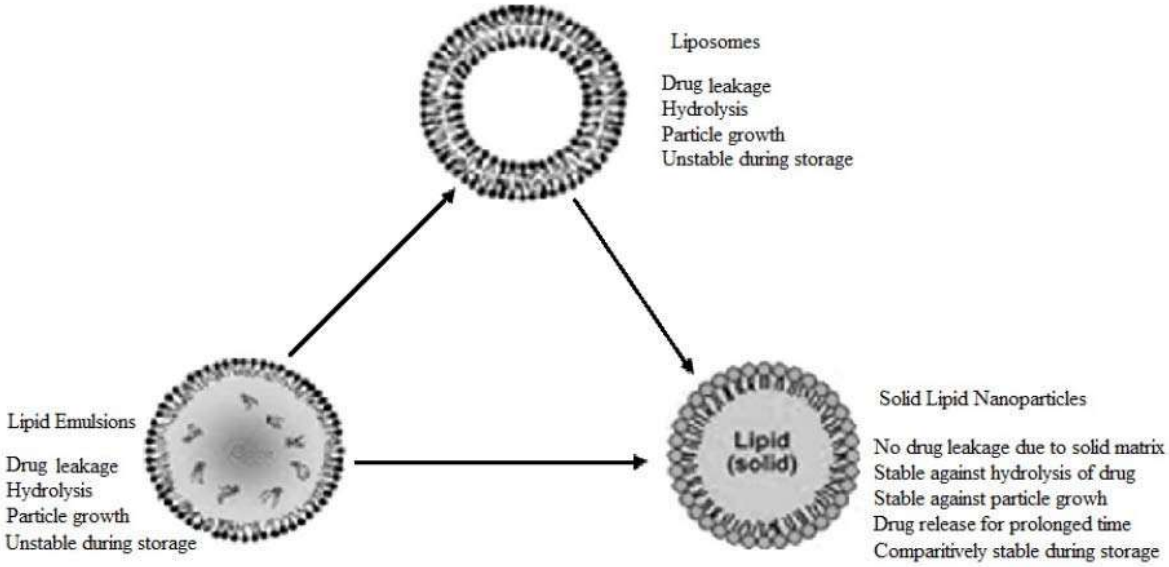

Figure 2: A diagrammatic representation on SLN over emulsions and liposomes

SLNs as measured up to other colloidal carriers liquid lipid is substituted by solid lipid. The use of solid lipid instead of liquid lipid is advantageous as it has been shown to increase control over the release kinetics of encapsulated compounds and to improve the stability of incorporated chemically-sensitive lipophilic ingredients. SLN can be used to improve the bioavailability of

drugs and owing to their solid particle matrix they can protect incorporated ingredients against chemical degradation and allow modification of release of the active compounds as well [4,5].

Advantages of SLN

SLNs provide a wide range of advantages over the traditional colloidal carrier systems and they are chosen as they give the possibility of controlled drug release and drug targeting. SLNs have the ability to increase drug stability and provide high drug payload. It can incorporate lipophilic as well as hydrophilic drugs. SLNs avoid the use of organic solvents and they do not possess any bio toxicity of the carrier. Diminishes the danger of acute and chronic toxicity by the making use of biodegradable physiological lipids moreover, avoid the use of organic solvents in production method via dermal application they achieve site specific delivery of drugs and increased drug penetration into the skin. Option of scaling up is another advantage of SLNs. It protects chemically labile agents from degradation in the gut and sensitive molecules from external environment. SLNs show improved stability in contrast to liposomes. It helps to improve the bioavailability of entrapped bioactive and chemical production of labile incorporated compound. High concentration of functional compound can be achieved. Lyophilisation is possible with solid lipid nanoparticles [5].

METHODS FOR PREPARATION OF SOLID LIPID NANOPARTICLES

High pressure homogenization

1. Hot homogenization
2. Cold homogenization

Ultrasonication/high speed homogenization

1. Probe ultrasonication
.2. Bath ultrasonication

Micro emulsion based method

Supercritical fluid method

Solvent emulsification-diffusion/evaporation method

Double emulsion method

Spray drying method

Precipitation technique

Film-ultrasound dispersion

HIGH PRESSURE HOMOGENIZATION

This method is a potent technique which was initially applied for the preparation of SLNs. In this method the liquid is impelled at a high pressure (100-2000 bar) through a narrow gap of few

microns. The fluid gets accelerated to a short distance with very high velocity of over 1000km/h. The particles get disrupted if the shear stress and cavitation force will be higher. Two methods to achieve HPH are hot homogenization and cold homogenization [6, 7].

1. Hot homogenization

This process functions at higher temperature than the melting point of the lipid which is similar to homogenization of emulsion. It could be carried out by the use of high pressure homogenizers and high intensity ultrasound [4]. A pre-emulsion of the drug integrated lipids melted and the aqueous emulsifier phase is achieved by high-shear mixing device at the same temperature. The quality of the final product to a great extent has been affected by that of the pre-emulsion and it is desirable to obtain droplets in the size range of a few micrometers. Lower particle sizes are gained because of lower viscosity of the lipid phase at higher processing temperatures which results in drug and carrier degradation acceleration [5]. A good product is achieved due to several passes through the high-pressure homogenizer; typically 3-5 passes [6]. Due to increase in the homogenization period, it results in particle size enlarging due to particle coalescence which occurs because of the high kinetic energy of the particles. Degradation of active compound and metal contamination due to high intensity ultrasound is a drawback of this method [7, 8].

2. Cold homogenization

Cold homogenization method has been carried out to avoid the problems related to hot homogenization technique like temperature mediated drug, carrier degradation acceleration and consequently release of drug into the aqueous phase during homogenization. First stage in cold homogenization is same as hot homogenization method where the rest of the process differs from it. The drug loaded lipid melt is cooled quickly by ice or liquid nitrogen for the distribution of drug in lipid matrix. The obtained particle sizes are in the range 50-100 microns. Demerits of cold homogenized samples are larger particle sizes and the broader size distribution. However, cold homogenization lowers the thermal exposure of the sample [9, 10].

ULTRASONICATION OR HIGH SPEED HOMOGENIZATION

For the production of SLNs, sonication or high speed stirring method can be used. A simple method using the common equipment for the technique. Disadvantages of this method include large particle size and metal contamination due to ultrasonication [11].

MICROEMULSION BASED SLN PREPARATIONS

This is based on the dilution of micro emulsions where SLNs are produced by stirring an optically transparent mixture at 65-70° which is normally 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. Then, by stirring the hot micro emulsion is dispersed in cold water. The volume ratio of the hot micro emulsion to cold water usually ranges from 1:25 to 1:50. The dilution process is verified by the composition of the micro emulsion. As reported previously, the droplet structure is already contained in the micro emulsion and as a result, no energy is needed to get submicron particle sizes [12, 13].

SUPERCRITICAL FLUID TECHNIQUE

This novel technique has the advantage of solvent-less processing for SLN preparation. SLN preparation is based on the fast expansion of supercritical carbon dioxide solutions (RESS) method. Carbon dioxide (99.99%) was the fine candidate as a solvent for this method [14, 15].

SOLVENT EMULSIFICATION/EVAPORATION METHOD

This technique is based on SLN dispersions by precipitation in oil/water emulsions. The lipophilic compound is dissolved in water immiscible organic solvent such as cyclohexane, which is emulsified in an aqueous phase [16]. SLN dispersion is formed by precipitation of the lipid in the aqueous medium after evaporation of the solvent. The mean diameter of 25 nm with cholesterol acetate as model drug and lecithin/sodium glycocholate mixture as emulsifier has been reported for the prepared SLN. The reproducibility of the result was verified by Siekmann and Westesen, who produced the cholesterol acetate SLN with mean size of 29 nm [17].

DOUBLE EMULSION METHOD

This procedure is based on solvent emulsification evaporation for incorporating hydrophilic drug into SLNs. In order to avoid drug partitioning to outer water phase during solvent evaporation in the external water phase of w/o/w double emulsion, the drug is encapsulated with a stabilizer. After evaporation of organic solvent by rotary, SLNs were recovered by centrifugation at 12000 ×g for 30 min at 4°C [18].

Characterization of SLNs

SLNs are being evaluated to control the quality and to know if they are suitable for the intended type of administration or not. The main factors to be taken into account are particle size and the (solid) state of the particle matrix. The leading techniques which have been used for particle size measurement are photon correlation spectroscopy and laser diffraction [19].

The zeta potential, a measurement of surface charge which could be measured by a zetameter is an important factor in preventing aggregation and allows predicting the storage stability of the colloidal dispersions.

For the morphological studies such as sphericity and aggregation of SLNs, Scanning Electron Microscopy (SEM), Transmission Electron Microscopy (TEM) and Atomic Force Microscopy (AFM) are the methods to examine nanoparticles.

The polymorphic behaviour and crystallinity of lipids strongly affects drug encapsulation and release rate. Differential scanning calorimetry and X-Ray diffractometry are the basic techniques that are used to investigate the behaviour of lipids [20, 21].

Applications of SLNs

Diverse applications of SLNs are shown in Figure. 3 and are discussed below.

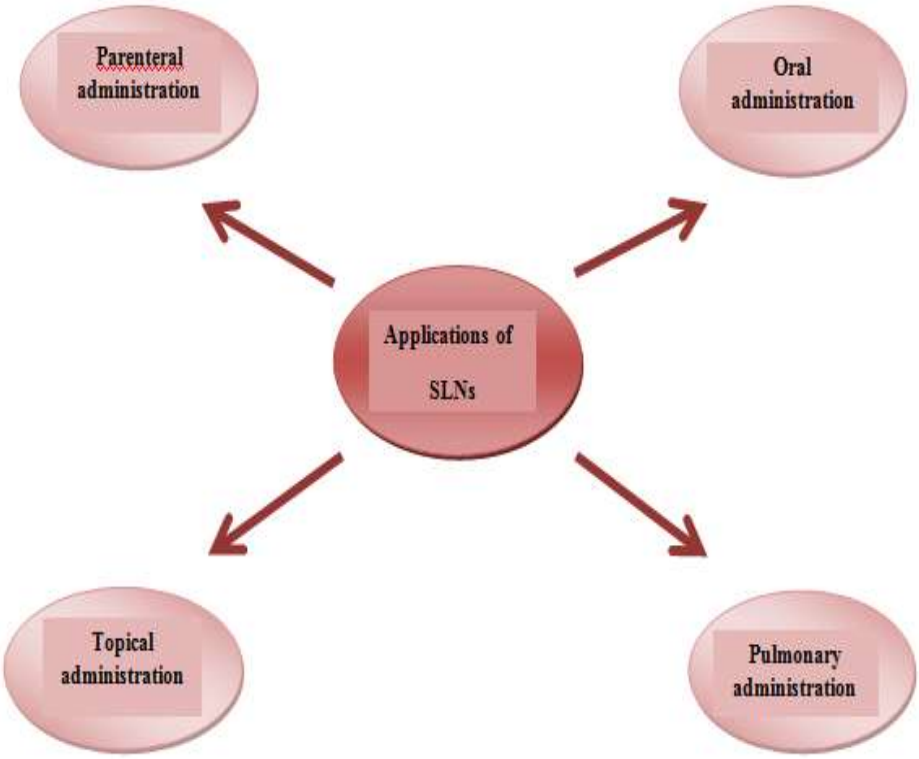

Figure 3: **Applications of SLNs**

Drug delivery using SLNs

SLNs have been reported to be useful as drug carriers to treat various diseases as well as cancer. They offer a distinctive drug delivery system to prevent rapid clearance by the immune system[22]. Stealth SLNs can be utilized to target specific tissues in accessible cells. Fluorescent markers together with drugs (Fluorescent SLNs) have been successfully evaluated in animal models. Methotrexate, paclitaxel and camptothecin- loaded SLNs have been reported for tumour targeting. Longer circulation times have been achieved by paclitaxel [23, 24].

SLNs can penetrate the blood–brain barrier (BBB) owing to adsorption of blood proteins such as apolipoproteins on their surface which can facilitate the adherence to endothelial cells. This effect was studied for the drugs like tobramycin, doxorubicin and idarubicin.

Various administration routes such as oral, topical, parenteral and pulmonary have been reported for drug delivery using SLNs (Table.1) [25, 26].

Table 1: Various methods used for the preparation of SLN

Drug	Type of disease	Preparation method
Docetaxel	Cancer	Hot homogenization method
Indomethacin	Ocular inflammation	Hot homogenization method
Repaglinide	Diabetes mellitus	Modified solvent diffusion method
Safranal	Sunburn	High-shear homogenization
Sesamol	Hepatic dysfunction	Micro emulsification method
Risperidone	Schizophrenia	High pressure homogenization
Rifampicin	Bacterial infection	Microemulsion
Insulin	Diabetes mellitus	Double emulsion method
Doxorubicin	Cancer	Hot homogenization
Alendronate	sodium Bone disease	Hot homogenization
Aceclofenac	Inflammation	Ultrasonication
Stavudine, delavirdine	HIV infections	Microemulsion
Gemcitabine	Tumours	Solvent emulsification

Oral administration of SLNs

Oral administration of SLNs is practical as aqueous dispersion or after transforming into dosage form i.e. tablets, pellets, capsules or powder in sachets. Anti-tubercular drugs like rifampicin, isoniazide, pyrazinamide-loaded SLN systems have been reported for oral administration, which were able to reduce the dose amount and enhances patient compliance. In addition, various anticancer drugs loaded SLNs such as camptothecin and tamoxifen were reported for this administration route as well [27, 28].

Parenteral administration of SLNs

Because of the small size of SLNs, they can be administered intravenously, intramuscularly, subcutaneously or to the target organ. It has been reported that SLN drug delivery system can enhance the transport of standard anticancer drugs like paclitaxel and doxorubicin into cancer cells and improve the cytotoxicity effect against sensitive cancer cells and their multi-drug resistant variant cells, compared to free drug solutions [29, 30]. In addition, the pharmacokinetic studies of doxorubicin loaded SLNs showed higher blood levels compared to a commercial drug solution after intravenous injection in rats. On the subject of body distribution, SLNs showed elevated drug concentrations in lung, spleen and brain, whilst the solution causes a distribution more into liver

and kidneys. The distribution of camptothecin incorporated SLNs showed increased uptake in some organ especially in brain following intravenous administration [31-33].

Topical administration of SLNS

Topical applications of SLNs have been reported with promising results for therapeutic purposes. It has a potential advantage of direct drug delivery to the site of action, which will generate higher tissue concentrations. A variety of drug such as anticancer, vitamin-A, isotretinoin, flurbiprofen has been incorporated in SLNs for topical applications as well [34, 35].

Pulmonary administration of SLNS

Pulmonary route of administration has some exclusive characteristics such as large surface area, avoidance of the first-pass effect, high capability for solute exchange, excellent vascularisation, and ultra fineness of the alveolar epithelium that can facilitate systemic delivery. In addition to that, degradation of drugs in the lung is slow because of low extracellular and intracellular enzyme activity [36]. Thus, even the compounds with low absorption rates can be absorbed to a relative high amount after pulmonary administration [37]. For the local treatment of airway diseases, the pulmonary application stands out by direct reaching the lung epithelium and thus the site of action which indicates that there is a fast onset of action and the necessary dose is reduced compared with traditional administration routes like the oral route. Furthermore, following local delivery of feebly absorbed drugs, high-dose exposures to the systemic circulation and therefore systemic adverse effects are minimized or avoided [38-40].

Gene delivery using SLNs

Booming gene therapy is defined as expression of the therapeutic gene in the target organ or tissue [41, 42]. Viral gene delivery/viral vector and non-viral gene delivery/non-viral vector are the two sorts of gene therapy method. In the first method, the genes are transferred by a virus into the cells because of virus ability in penetrating cells [43, 44]. Although a high level of gene expression has been reported with viral gene delivery, it can have oncogenic and immunogenic effects and induce inflammation that delivers transgene expression transient. Non-viral vectors can surmount some of these concerns and compared to viral vectors they have significant manufacturing and safety advantages [45, 46].

Cationic SLNs usually have been used for gene delivery as a result of possible electrostatic interaction between the negative charges of the DNA and the positive charges of the lipid which allows the formation of a complex called lipoplex. These lipoplexes can develop a structure that shields the DNA and direct it towards the target cells [47, 48].

In future, gene expression studies will definitely pave a way for the achievement of rational design approaches in the development of cationic SLNs as their remarkable capability to penetrate into cells and to achieve spatially- and temporally- controlled release for targeted gene silencing [49].

CONCLUSION

SLNs are a novel and biocompatible colloidal drug that merges the advantages of both liposomes and polymeric nanoparticles and concurrently avoid some of their drawbacks. They have already proven to be good formulations in pharmaceuticals and cosmeceuticals and gives significant opportunities for improving medical therapeutics.

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