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SOLID LIPID NANOPARTICLES: AN ADVANCED DRUG DELIVERY SYSTEM

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ABSTRACT

Solid lipid nanoparticles are at the forefront of the rapidly developing field of nanotechnology with several potential applications in drug delivery, research and clinical medicine, as well as in other varied sciences. Solid lipid nanoparticle (SLN) dispersions have been proposed as a new type of colloidal drug carrier system suitable for intravenous administration. Solid lipid nanoparticles (SLNs) technology represents a promising new approach to lipophilic drug delivery. Solid lipid nanoparticles are spherical lipid particles ranging in size from 1 to 1000 nm and are dispersed in water or in aqueous surfactant solution. It is identical to an oil-in-water emulsion, but the liquid lipid (oil) of the emulsion has been replaced by a solid lipid, i.e., yielding Solid Lipid Nanoparticles. SLN are particles made from solid lipid or lipid blends produced by high pressure homogenization. The biodegradable and bioacceptable nature of SLNs makes them less toxic as compared to polymeric nanoparticles. SLNs can also be used to improve the bioavailability of drugs. In this present review this new approach is discussed in terms of their advantages, disadvantages, methods, characterization, pharmacokinetic studies, in-vivo studies, in-vitro studies, and special features

INTRODUCTION: A high potential for drug delivery has been attributed to particulate drug carriers, especially small particles such as micro particles and colloidal system in nanometer range [1]. Nano particulate drug delivery system may offer plenty of advantages over conventional dosage forms which include improved, reduced toxicity, enhanced bio distribution and improved patient compliance [2].

Colloidal particles ranging in size between 10 and 1000 nm are known as nanoparticles. They are manufactured from synthetic/natural polymers and ideally suited to optimize drug delivery and reduce toxicity. Over the years, they have emerged 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 [3].

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 [4]. SLNs are colloidal carriers developed in the last decade as an alternative system to the existing traditional carriers (emulsions, liposomes and poly Solid lipid nanoparticle (SLN) dispersions have been proposed as a new type of

colloidal drug carrier system suitable for intravenous administration. The system consists of spherical solid lipid particles in the nanometer ranges, which are dispersed in water or in aqueous surfactant solution. Generally, they are made of solid hydrophobic core having a monolayer of phospholipids coating. The solid core contains the drug dissolved or dispersed in the solid high melting fat matrix.

The hydrophobic chains of phospholipids are embedded in the fat matrix. They have potential to carry lipophilic or hydrophilic drugs or diagnostics[5]. They are a new generation of submicron-sized lipid emulsions where the liquid lipid (oil) has been substituted by a solid lipid.

SLN offer unique properties such as small size, large surface area, high drug loading and the interaction of phases at the interfaces, and are attractive for their potential to improve performance of pharmaceuticals, neutraceuticals and other materials [6].

Nanotechnology: Nanotechnology is the science of matter and material that deal with the particle size in nanometers. These are small colloidal particles that are made of non biodegradable & biodegradable polymers and their diameter is around 200nm [7].

- **Nanoparticles:** Nanoparticles are solid polymeric, submicronic colloidal system range between 5-300nm consisting of macromolecular substances that vary in size 10nm to 100nm.The drug of interest is dissolved, entrapped, adsorbed, attached or encapsulated into the nanoparticle matrix [8]. 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 tissue. Nanoparticles hold promise for per oral drug delivery, which represents so far the most common and convenient route of administration. The advantages of using nano particles loaded with drugs is because of their small size which can penetrate through small capillaries are taken up by cells and allow the drug release at right rate and dose at specific sites in the body for a certain time to release the accurate delivery, which enhances the therapeutic effect and reduces the toxicity and side effects. The use of biodegradable materials for nanoparticles preparation allows sustained release within the target site over a period of days or even weeks. The advantages of nanoparticles as drug delivery system are that they are biodegradable, non-toxic, and capable of being stored for longer periods. In addition, their potential uptake as well as their stability in the GIT indicates that nanoparticles are expected to be the promising carriers for the transport of drugs. These attributes make nanoparticles more suitable for the purpose of sustained release and improvement of bioavailability [9].

Definition of SLNs: It is identical to an oil-in-water emulsion for parenteral nutrition (e.g., Intralipid, Lipofundin), but the liquid lipid (oil) of the emulsion has been replaced by a solid lipid, i.e., yielding solid lipid nano particles. SLN are particles made from solid lipid or lipid blends produced by high pressure homogenization. The mean photon correlation spectroscopy (PCS) diameter is typically between approximately 80nm to 1000nm. Particles below 80nm are more difficult to produce because very often they do not recrystallized [10]. The SLN are dispersed in an aqueous outer phase and stabilized by surfactants, e.g., Tween80, sodium dodecyl sulfate (SDS), lecithin. Alternatively, they can be produced surfactant free using steric stabilizers (e.g.poloxamer180) or an outer of increased viscosity (e.g. ethyl cellulose solution).SLN can also be produced in nonaqueous media, e.g., PEG-600 or oils like Miglyol 812.

Solid Lipid Nanoparticles: Solid lipid nanoparticles (SLNs) are considered to be the most effective lipid based colloidal carriers (**fig. 1**), introduced in early nineties. This is the one of the most popular approaches to improve the oral bioavailability of the poorly soluble drugs. SLNs are in the range of submicron size (50-1000 nm) and are composed of physiologically tolerated lipid components which are in solid state at room temperature [11, 12]. They have many advantages such as good biocompatibility, low toxicity and lipophillic drugs are better delivered by solid lipid nanoparticles and the system is physically stable [13]. Solid lipid nanoparticles may be a promising sustained release and drug targeting system for lipophilic CNS antitumor drugs [14].

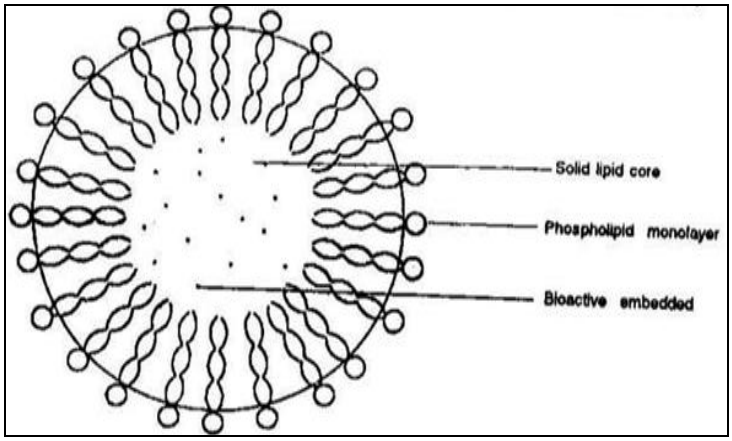

FIGURE 1: STRUCTURE OF SOLID LIPID NANOPARTICLE

ADVANTAGES: SLNs combine the advantages of polymeric nanoparticles, fat emulsions and liposomes.

1. Controlled release of the incorporated drugs can be achieved for several weeks. Further, by coating with or attaching ligands to SLNs, there is an increased scope of drug targeting.

2. The nanoparticles and SLNs particularly those in the range of 120-200 nm are not taken up readily by the cells of the RES (Reticuloendothelial System) and bypass thus liver and spleen filtration [15].

3. Very high long-term stability.

4. High drug pay load.

5. Excellent reproducibility with cost effective high pressure homogenization method as the preparation Procedure [16].

6. The feasibility of incorporating both hydrophilic and hydrophobic drugs.

7. Can be subjected to commercial sterilization procedures.

8. Can be freeze dried to form powdered formulation.

Disadvantages of SLNs: Potential disadvantages of SLNs are such as:

1. Poor drug loading capacity.

2. Drug expulsion after polymeric transition during storage.

Uptake by SLNs: The majority of orally administered drugs gain access to the systemic circulation by absorption into the portal blood. However, some extremely lipophilic drugs (log P > 5, solubility in TG > 50 mg/ml) gain access to the systemic circulation via lymphatic route, which avoids hepatic first pass metabolism. Therefore, highly metabolized lipophilic drugs may be potential candidates for solid lipid nanoparticles, a lipid based delivery. Compounds showing increased bioavailability in the presence of lipids (dietary or lipid-based formulation) are absorbed via the intestinal lymph as they are generally transported in association with the long- chain TGs lipid core of intestinal lipoproteins formed in the enterocyte after re-esterification of free FAs and MGs. Short- chain TGs are primarily absorbed directly in the portal blood. Hence it is likely that the drug transport via the lymphatic requires co administration of lipid to stimulate lipoprotein formation [17].

The lymph fluid is emptied (average 3 L per day) via thoracic duct into the subclavian vein, thus protecting the drug from hepatic first-pass metabolism. The drug being transported in the circulatory system, in the form of either micelles or mixed micelles, may then be available in its free form, since upon dilution with a large volume of the lymph/blood, surfactant concentration may reduce below its cmc value and micelle may dissociate into monomers. The drug transported as lipid vesicles may remain intact for extended periods and, thereby, can result in prolonged release of the encapsulated drug. Fig. 2 represents is the diagrammatic presentation of the various mechanisms by which solid lipid nanoparticles enhance the bioavailability of drugs [18, 19, 20].

Mechanism of Oral Absorption Enhancement:

A. **Dissolution/solubilisation**: SLNs entering into the GI tract, stimulates the gallbladder contractions and biliary and pancreatic secretions, including bile salts (BS), phospholipids (PL) and cholesterol, due to the lipids present in the formulation [21]. These products, along with the gastric shear movement, form a crude emulsion which promotes the solubilisation of the co administered lipophilic drug [22]. Further, the surface active agents present in the SLNs may further stimulate the solubilization of the lipophilic compound.

B. **Affecting intestinal permeability:** A variety of lipids have been shown to change the physical barrier function of the gut wall and hence, enhance the permeability [23].

C. **Prevent first pass metabolism:** Solid lipid nanoparticles have been reported to enhance oral bioavailability of certain highly lipophilic drugs by accessing to systemic circulation via lymphatic route hence preventing their first pass metabolism.

D. **Gastric residence time:** Lipids in the GI tract provoke delay in gastric emptying which results in increased residence time of the co administered lipophilic drug in the small intestine. This enables better dissolution of the drug at the absorptive site.

LIST OF EXCEPIENTS USED FOR SOLID LIPID NANOPARTICLES [24]:

Lipids	Hard fats	Emulsifiers or co emulsifiers
Non digestible lipids	Witepsol W 35	Soy Lecithin
Mineral oils	Witepsol S 35	Egg lecithin
Sucrose poly esters	Witepsol H 42	Phosphatidyl choline
Digestble lipids	Witepsol E 85	Poloxamer 188
Triglycerides	Glycerylmonostearate(Imwitor 900)	Poloxamer 182
Tricaprin	Glycerylbehanate(compritol 888 ATO)	Poloxamine 407
Trilaurin	Glycerylpalmityl stearate(precirol ATO 50)	Poloxamine 908
Trimyristin	Cetyl palmitate	Tyloxapol
Tripalmitin	Stearic acid	Polysorbate 20
Tristearin	Palmitic acid	Polysorbate 60
Hydrogenated cocoglycerides	Decanoic acid	Polysorbate 80
Diglycerides	Behanic acid	Sodium cholate
Fatty acids	Acidan N 12	Sodium glycocholate

Status of excepients used for Solid Liquid Nanoparticles [25]: Depending on route of administration, SLN must be differentiated in terms of status of excipients.

The three major routes are:

1) **External administration (e.g. topical).**
2) **Oral administration.**
3) **Parenteral administration**.

For external administration the complete range of excipients used for cosmetics and pharmaceutical ointments / creams can be used. This provides a vast variety, especially with regard to the cosmetic excipients. There is no need to use any excipient which has not yet been accepted. For oral administration of SLN, all excipients can be employed that are frequently used in traditional oral dosage forms such as tablets, pellets, and capsules. Even surfactants with cell membrane-damaging potential, e.g. SDS, can be used. SDS is contained in many oral products and accepted as an excipient by the regulatory authorities. In general, all GRAS substances and materials of approved GRAS status can be employed. In addition, SLN can be made from food lipids and using surfactants contained in food (e.g. surfactants from ice cream, such as e.g. Sugar esters of course it needs to be considered that an excipient used in the food industry is not automatically accepted in pharmaceutical products; however the required documentation process is relatively unproblematic. The situation is different for parenteral administration. The basic point is that SLN are a novel system; solid lipids have not yet been administered parenterally before-in contrast to liquid lipids (o/w emulsions for intravenous administration, prolonged release oil-based injectables for intramuscular administration).

However, the glycerides used for SLN production are composed of compounds (glycerol, fatty acids) which are also present in emulsions for parenteral nutrition. This means that, apart from drug delivery, the SLN are an additional nutritive. The only difference to emulsions for parenteral nutrition is that the composition of the glycerides is different. The oils contain glycerides of mixed composition of medium and long chain triglycerides (MCTs, LCTs). The glycerides used for SLN production need to be solid, i.e. are composed of longer chain fatty acids. In addition, many lipids are monoacid triglycerides, i.e. composed of just one fatty acid.

Examples are Dynasan114 with myristic acid, Dynasan116 with palmitic acid, and Dynasan118 with stearic acid. In some cases the lipids used are mixtures of mono, di and triglycerides. Some of them are more or less just one glyceride type or contain preferentially one glyceride, e.g. triglyceride of behanic acid in the commercial lipid Compritol [with smaller fractions of mono (12-18%) and diglycerides].

Preparation of Solid Liquid Nanoparticles: SLNs are prepared from lipid, emulsifier and water/solvent by using different methods (Table2) and are discussed below:

1. **High Pressure Homogenization (HPH):** High shear homogenization techniques were initially used for the production of solid lipid nanodispersions. It is a reliable and powerful technique. High pressure homogenizer's pushes liquid with high pressure (100–2000 bar) through a narrow gap (in the range of a few microns). The fluid accelerates on a very short distance to very high velocity (over 1000 km/h). Very high shear stress and cavitation forces disrupt the particles down to the submicron range. Generally 5-10% lipid content is used but up to 40% lipid content has also been investigated [26]. Two general approaches of HPH are hot homogenization and cold homogenization; work on the same concept of mixing the drug in bulk of lipid melt [27].

2. **Hot Homogenization** [28, 29]**:** Hot homogenization is carried out at temperatures above the melting point of the lipid and can therefore it is similar to the homogenization of an emulsion. A pre-emulsion of the drug loaded lipid melt and the aqueous emulsifier phase (same temperature) is obtained by high shear mixing device. The product of this process is hot o/w emulsion and the cooling of this emulsion leads to crystallization of the lipid and the formation of solid lipid nanoparticle.

   High pressure homogenization of the pre-emulsion is done above the lipid melting point. The quality of the pre-emulsion affects the quality of the final product to a great extent and it is desirable to obtain droplets in the size range of a few micrometers.

   Lower particle sizes are obtained at higher processing temperatures because of lowered viscosity of the lipid phase. However, high temperatures increase the degradation rate of the drug and the carrier. High pressure processing always increases the temperature of the sample (approximately 10° at 500 bar). In most cases, 3-5 homogenization cycles at 500-1500 bar are sufficient. 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.

3. **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 [30]. Polymorphic transitions of the lipid due to complexity of the crystallization step of the nanoemulsion leading to several modifications and/or super cooled melts. Drug is incorporated into melted lipid and the lipid melt is cooled upto solidification. Solid material is ground by a mortar mill. Obtained lipid microparticle is dispersed in a cold surfactant solution at room temperature or even at temperature distinctly below room temperature. To ensure the solid state of the lipid during homogenization, effective temperature regulation is needed. However, compared to hot homogenization, larger particle sizes and a broader size distribution are typical of cold homogenized samples [31].

4. **Ultrasonication/High Speed Homogenization** [32, 33]: SLNs are also prepared by ultrasonication or high speed homogenization techniques. The problem of this method is broader particle size distribution ranging into micrometer range. Potential metal contamination and physical instability like particle growth upon storage are the major drawbacks of this technique.

5. **SLNS prepared by Solvent Evaporation/ Emulsification:** SLNs are also prepared by solvent evaporation method. Sjostrom and Bergenstahl described a production method to prepare nanoparticle dispersions by precipitation in o/w emulsions [34].

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 [35, 36]. Siekmann and Westesen also prepared solid lipid nanoparticles of 30 to 100 nm by dissolving tripalmitin in chloroform. This solution was emulsified in an aqueous phase by high pressure homogenization. The organic solvent was removed from the emulsion by evaporation under reduced pressure (40–60mbar) [37].

6. **Microemulsion based Method:** This method is based on the dilution of microemulsions [38]. As microemulsions 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 is typically composed of a low melting fatty acid (e.g. stearic acid), an emulsifier (e.g. polysorbate 20, polysorbate 60, soy phosphatidylcholine 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 [39]. The precipitation of the lipid particles in water is the dilution of the system that leads to reduction of solid content of SLN dispersion. The SLN dispersion can be used as granulation fluid for transferring into solid product (tablets, pellets) by granulation process, but in case of low particle content too much water needs to be removed. In microemulsions, the temperature gradient and the pH value fix the product quality in addition to the composition of the microemulsion [40].

7. **Spray Drying Method:** It's an alternative procedure to lyophilization in order to transform an aqueous SLN dispersion into a drug product. 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 >70° for spray drying. The best result was obtained with SLN concentration of 1% in a solution of trehalose in water or 20% trehalose in ethanol-water mixtures (10/90 v/v) [41].

8. **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 [42, 43].

9. **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 [44].

Characterization of SLNS [45, 46, 47]: Characterization of solid lipid nanoparticles is a serious challenge due to the small size of the particles andcomplexity of the system. The important parameters which need to be evaluated for the SLNs are, particle size, size distribution kinetics (zeta potential), degree of crystallinity and lipid modification (polymorphism), coexistence of additional colloidal structures (micelles, liposome, super cooled, melts, drug nanoparticles), time scale of distribution processes, drug content, in vitro drug release and surface morphology.

1. **Particle Size and Zeta Potential:** Particle size may be determined by photon correlation spectroscopy (PCS), transmission electron microscopy (TEM), scanning electron microscopy (SEM), atomic force microscopy (AFM), scanning tunneling microscopy (STM), freeze fracture electron microscopy (FFEM) and laser diffraction (LD).

2. **Measurement of Particle Size and Zeta Potential:** Photon correlation spectroscopy (PCS) and laser diffraction (LD) are the most powerful techniques for routine measurements of particle size. The Coulter method is rarely used to measure SLN particle size because of difficulties in the assessment of small nanoparticle and the need of electrolytes which may destabilize colloidal dispersions. PCS (also known dynamic light scattering) measures the fluctuation of the intensity of the scattered light which is caused by

the particle movement. This method covers a size range from a few nanometers to about 3 microns. This means that PCS is a good tool to characterize nanoparticles, but it is not able to detect larger microparticles. They can be visualized by means of LD measurements. This method is based on the dependence of the diffraction angle on the particle radius (Fraunhofer spectra). Smaller particles cause more intense scattering at high angles compared to the larger ones.

A clear advantage of LD is the coverage of a broad size range from the nanometer to the lower millimeter range. It should be kept in mind that both methods are not measuring particle sizes; rather they detect light scatting effects which are used to calculate particle sizes. Difficulties may arise both in PCS and LD measurements for samples which contain several populations of different size. Therefore additional techniques may also be used. For example, light microscopy is recommended, although it is not sensitive to the nanometer size range. It gives a fast indication of the presence and character of micro particles (micro particles of unit form or micro particles consisting of aggregates of smaller particles).

Electron microscopy provides, in contrast to PCS and LD, direct information on the particle shape . Zeta potential is an important product characteristic of SLNs since its high value is expected to lead to de aggregation of particles in the absence of other complicating factors such as steric stabilizers or hydrophilic surface appendages. It is usually measured by zeta meter.

3. **Dyanamic Light Scattering (DLS):** DLS, also known as PCS or quasi-elastic light scattering (QELS) records the variation in the intensity of scattered light on the microsecond time scale. This variation results from interference of light scattered by individual particles under the influence of Brownian motion, and is quantified by compilation of an autocorrelation function. This function is fit to an exponential, or some combination or modification thereof, with the corresponding decay constant(s) being related to the diffusion coefficient. 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 sub micrometer particles.

4. **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.

5. **Electron Microscopy:** SEM and TEM provide a way to directly observe nanoparticles, physical characterization of nanoparticles with the former method being better for morphological examination. TEM has a smaller size limit of detection, is a good validation for other methods, and affords structural required, and one must be cognizant of the statistically small sample size and the effect that vacuum can have on the particles.

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

7. **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.

8. ***In-vitro* and *Ex-vivo* methods for the assessment of Drug Release from SLN [48-51]:**

a. ***In-vitro* Drug Release Dialysis Tubing:** In-vitro drug release could be achieved using dialysis tubing. The solid liquid nanoparticle dispersion is placed in a prewashed dialysis tubing which can be hermetically sealed. The dialysis sac is then dialyzed against a suitable dissolution medium at room temperature, the samples are withdrawn from the dissolution medium at suitable intervals, centrifuged and analysed for drug content using a suitable analytical method (U.V. Spectroscopy, HPLC etc.). The maintenance of sink condition is essential. This method however suffers from the limitation of a lack of direct dilution of the SLNs by the dissolution medium.

b. **Reverse Dialysis:** In this technique a number of small dialysis sacs containing 1ml of dissolution medium are placed in SLN dispersion. The SLNs are then displaced into the dissolution medium. The direct dilution of SLNs is possible with this method; however the rapid release cannot be quantified using this method.

c. **Franz Diffusion Cell:** The solid liquid nanoparticle dispersion is placed in the donor chamber of a Franz diffusion cell fitted with a cellophane membrane. The dispersion is then dialyzed against a suitable dissolution medium (simulated gastric medium/simulated intestinal medium/ simulated plasma) at room temperature, the samples are withdrawn from the dissolution medium at suitable intervals and analysed for drug content using suitable instrumental method. The maintenance of sink condition is essential and the method suffers from the limitation of lack of direct dilution of SLNs by the dissolution medium.

9. ***Ex-vivo* model or determining Permeability across the Gut:** Ahlin *et al*., demonstrated passage of Enalaprit SLNs across rat jejunum. In short, the rat jejunum was excised from the rats after sacrificing the animal. The jejunum 20-30 cm distal from the pyloric sphincter was used. The jejunum was rinsed to remove the luminal contents after washing with ice cold standard ringer solution. The tissue was then cut into segments, opened up along the mesenteric border and placed between two Easy Mount side-y-side diffusion chambers with an exposed tissue are of 1 cm2. The mucosal side was bathed with Ringer buffer containing 10mM mannitol and the serosal side Ringer buffer containing 10mM glucose. The enalprilat loaded nanoparticles were placed on the mucosal side, dispersed in Ringer containing paracellular transporter sodium fluorescein confirming for tissue integrity.

Animals and administration of Drug Formulation: Male Wistar rats and Swiss Albino mice are used for pharmacokinetic and tissue distribution studies, respectively.

1. **Intravenous Administration:** Rats are anesthetized and the selected samples are given. Time taken for administration is 30 sec. blood samples are withdrawn by retro-orbital venous plexus puncture at 15, 30,45, 60, 90, 120, 240 and 480 min post i.v. dose. The samples are centrifuged (5000xg, 15 min) and serum are collected and started at -20 °C until analysis.

2. **Intradeuodenal Administration:** Rats are anesthetized by intraperitoneal injection of 60mg/kg of thiopentone sodium (short acting anaesthetic agent). Small incisions are made at abdomen, duodenum is located and similar formulations are administered directly into the duodenum with syringe. Blood samples are collected and processed as described in intravenous route.

3. **Biodistribution Studies:** Tissue distribution studies are carried out in Swiss albino mice after 7-day acclimatization period. At predetermined time points (like 15, 30, 45, 60, 90, 120, 180, 360 and 720 min) three animals at each time point from each group is given anaesthesia and blood is collected via cardiac puncture. Tissues of interest brain, liver, spleen, kidney, and heart) are collected immediately after at different time

points cervical dislocation at different time points and they were blotted dry with tissue paper. Serum and tissue samples are frozen at -20°c until analysis.

Applications of Solid Lipid Nanoparticles [52, 53]:

1. **Oral Delivery:** Oral administration of SLNs is possible as aqueous dispersion or after transforming in to dosage form i.e. tablets, pellets, capsules or powder in sachets. For the production of the 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. For the production of pellets the SLN dispersion can be used as wetting agent in the extrusion process. SLN powder can be used for the filling of hard gelatine capsules; or the SLN can be produced directly in liquid PEG 600 and filled in to soft gelatin capsules. Sachets are also possible using spray dried or lyophilized powers. The microclimate of the stomach favours particle aggregation due to the acidity and high ionic strength. It can be expected, that food will have a large impact on SLN performance, however no experimental data have been publish on this issue to our knowledge.

2. **Topical Delivery:** Topical applications of lipid nanoparticles have been used with promising results either for therapeutic or cosmetic purposes. SLN have shown some protective activity on skin surface, such as a UV-blocking potential. SLN may be formulated in creams, gels, sprays. The smallest particle sizes are observed for SLN dispersions with low lipid content (up to 5%). Both the low concentration of the dispersed lipid and the low viscosity are disadvantageous for dermal administration. In most cases, the incorporation of the SLN dispersion in an ointment or gel is necessary in order to achieve a formulation which can be administered to the skin. The incorporation step implies a further reduction of the lipid content. An increase of the solid lipid content of the SLN dispersion results in semisolid, gel-like systems, which might be acceptable for direct application on the skin.

3. **Parenteral Delivery:** SLNs can be administered intravenously, intramuscularly, subcutaneously or to the target organ, because of their small size. The particles are cleared from the circulation by the liver and the spleen. SLN formulations can be used for systemic body distribution with a minimized risk of blood clotting and aggregation leads to embolism. SLNs formulations also provide a sustained release depot of the drug when administered subcutaneously or intramuscularly. SLNs have been administered intravenously to animals.

   Pharmacokinetic studies of doxorubicin incorporated into SLNs showed higher blood levels in comparison to a commercial drug solution after i.v. injection in rats.Concerning the body distribution, SLNs were found to cause higher drug concentrations in lung, spleen and brain, while the solution led to a distribution more into liver and kidneys.

   Yang *et al.,* reported on the pharmacokinetics and body distribution of camptothecin after i.v. injection in mice. In comparison to a drug solution SLN was found to give much higher AUC/dose and mean residence times (MRT) especially in brain, heart and reticuloendothelial cells containing organs.

   The highest AUC ratio of SLN to drug solution among the tested organs was found in the brain. Paclitaxel containing solid lipid nanoparticles (SLNs) were prepared and studied in culture of macrophage.

4. **Transdermal Application:** The smallest particle sizes are observed for SLN dispersions with low lipid content (up to 5%). Both the low concentration of the dispersed lipid and the low viscosity are disadvantageous for dermal administration. In most cases, the incorporation of the SLN dispersion in an ointment or gel is necessary in order to achieve a formulation which can be administered to the skin. The incorporation step implies a further reduction of the lipid content of the SLN dispersion resulting in semisolid, gel-like systems, which might be acceptable for direct application on the skin.

5. **Pulmonary Delivery:** Unique features that can facilitate systemic delivery via pulmonary administration of drugs are large surface area, good vascularisation, large capacity for solute exchange, ultra-thinness of the alveolar epithelium (0.1-0.5 mm) and first-pass metabolism is avoided. To demonstrate the

6. Suitability in principle of SLN for pulmonary delivery, aqueous SLN dispersions were nebulized with a Pari-Boy, the aerosol droplets were collected and the size of SLN are analysed. It could be shown that the particle size distributions of SLN before nebulization and after nebulization were almost identical, only very little aggregation could be detected which is of no significance for pulmonary administration. Alternatively the SLN powders might be used in dry powder inhalers. SLN could be spray-dried using, e.g. lactose as excipient in the spray drying process.

7. **SLNs as Gene Vector Carrier:** SLN can be used in the gene vector formulation. In one work, the gene transfer was optimized by incorporation of a diametric HIV-1 HAT peptide (TAT 2) into SLN gene vector. There are several recent reports of SLN carrying genetic/peptide materials such as DNA, plasmid DNA and other nucleic acids. The lipid 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.

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.

Methods like high pressurized homogenization has shown excellent reproducibility and cost effective. On the other hand the use of solid lipids as matrix material for drug delivery is well known from lipid pellets for oral drug delivery (Runge S et al., 1996). So SLNs is a new technology which has been taken over by the pharmaceutical industry.

The possibility of incorporating both the lipophillic and hydrophilic molecules and the possibility of the intravenous and intradeuodenal administration make the SLNs delivery system all the more promising. SLNs will open a new channel for an effective delivery of a vast variety of drug molecules including analgesics, antitubercular, anticancerous, antiaging, antianxiety, antibiotics, and antiviral agents to the target site.

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