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# SOLID LIPID NANOPARTICLES : A PROMISING AND NOVEL DRUG DELIVERY SYSTEM - A REVIEW

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## ABSTRACT

Solid lipid nanoparticles is the rapidly emerging field of nanotechnology with numerous potential applications in drug delivery, clinical medicine, cosmetics and research, as well as in other varied sciences. Solid lipid nanoparticles, colloidal drug carrier for incorporating hydrophilic or lipophilic drugs, the ability to incorporate drugs into nano-carriers offers a new prototype in drug delivery that could be used for secondary and tertiary levels of drug targeting. Due to their unique size-dependent properties, lipid nanoparticles hold great promise for reaching the goal of controlled and site specific drug delivery and hence have attracted wide attention of researcher. This article gives an outline about the potential advantages and disadvantages of solid lipid nanoparticles, the excipients and all the different methods involved in the production. The characteristic of SLN stability and secondary steps involved in their stabilization like freeze drying, sterilization etc. Analytical methods involved in SLN evaluations are discussed in detail. The route of administration and current applications are mentioned in the article.

**KEY WORDS :** Solid lipid nanoparticles, homogenization, drug delivery, targeting, TEM.

## INTRODUCTION

The field of novel drug delivery system is emerging at an exponential rate with the deep understanding gained in diversified fields of biotechnology, biomedical engineering and nanotechnology.[1] Targeted delivery to the diseased lesions is one of the most important

aspects of drug delivery system. To convey the accurate desired dose of the drug and diagnostic agent to the lesions, suitable carriers are required. Nanoparticles have important potential applications for the administration of therapeutic and diagnostic agents.[2] Many of the recent formulation approaches utilize nanotechnology that is the preparation of nanosized structures containing the API.[3]

Nanotechnology, as defined by the National Nanotechnology Initiative (NNI), is the study and use of structures roughly in the size range of 1 to 100 nm. The overall goal of nanotechnology is the same as that of medicine: to diagnose as accurately and early as possible and to treat as effectively as possible without any side effects using controlled and targeted drug delivery approach.[4]

Nanoparticulate drug delivery system may offer plenty of advantages over conventional dosage forms which include improved, reduced toxicity, enhanced biodistribution and improved patient compliance. Some of the important drug delivery system which has been developed using Nanotechnology principles are nanoparticles, solid lipid nanoparticles, nanosuspension, nanoemulsion, nanocrystals.[5]

In this article the main focus is on solid lipid nanoparticles (SLNs).

**Solid lipid nanoparticles (SLN)**

SLNs, introduced in 1991 represent an alternative and better carrier system to traditional colloidal carriers such as emulsions, liposomes and polymeric micro and nanoparticles.[6] Solid lipid nanoparticles(SLN) are colloidal carriers , they are made up of solid hydrophobic core having 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.[6]

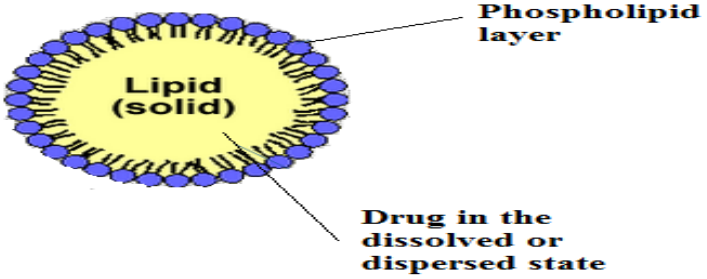


**Fig. 1: Structure of solid lipid nanoparticle**

SLNs are in the submicron size range of 50-1000 nm and composed of physiologically tolerated lipid components which are in solid state at room temperature. They have many advantages such as good biocompatibility, low toxicity. Lipophilic drugs are better delivered by solid lipid nanoparticles and the system is physically stable.[7] Solid lipid nanoparticles may be a promising sustained release and drug targeting system for lipophilic CNS antitumor drugs.[2,8]

**Advantages of SLN**

1. Small size and relatively narrow size distribution, which provide biological opportunities for site, targeting brain for enhanced penetration of drug into brain.[9]
2. Preparation of biodegradable physiological lipids which decrease the danger of acute and chronic toxicity and avoidance of organic solvent in production method.[10]
3. SLNs have better stability compared to liposomes.
4. Enhances the bioavaibility of bioactive and chemical production of labile incorporated compound.
5. Easy to scale up and sterilize.
6. Protection of chemically liable agents from degradation in the gut and sensitive molecules from outer environment.
7. Much easier to manufacture than biopolymeric nanoparticles.
8. Improves bioavaibility of poorly water soluble molecules.[11]
9. It can be subjected to commercial sterilization procedure.
10. Incorporation of drug can reduce distinct side effects of drug, Thrombophlebitis that is associated with i.v injection of diazepam or etomidate.
11. No toxic metabolites are produced.
12. Conventional emulsion manufacturing methods are applicable.
13. No organic or other special solvent required.
14. Surface modification can easily be accomplished and hence can be used for site specific drug delivery system.[12]

**Disadvantages of SLN**

1. Limited drug loading capacity due to solubility of drug in the lipid melt, the structure of the lipid matrix and the polymeric state of lipid matrix. If the lipid matrix consists of especially similar molecules (i.e. tristearin or tripalmitin), a perfect crystal with few imperfections is formed. Since incorporated drugs are located between fatty acid chains,

between the lipid layers and also in crystal imperfections, a highly ordered crystal lattice cannot accommodate large amount of drug.[13]

2. Drug expulsion during storage due to the formation of perfect crystal.
3. Particle growing, unpredictable gelation tendency.
4. Unexpected dynamics of polymorphic transition.
5. High water content of SLN dispersion (70-99.9%).[14]
6. Adjustment of drug release profile.

**Aims of solid lipid nanoparticles**[15,16]

1. Possibility of controlled drug release[17]
2. Increase drug stability
3. High drug pay load
4. No biotoxicity of the carrier
5. Avoidance of organic solvent
6. Incorporation of lipophilic and hydrophilic drugs
7. No problem with respect to large scale production and sterilization
8. Increased bioavaibility of entrapped bioactive compound.[18]
9. Enhanced penetration of medicine through biological barrier

**Nanostructured lipid carrier (NLC)**

NLC have been introduced at the end of 1990s in order to overcome the potential difficulties of SLNs.[19,20] The goal was to increase the drug loading and prevent drug expulsion. This could be visualized in three ways. In the first model, spatially different lipids (like glycerides) composed of different fatty acids are mixed. The use of spatially different lipids leads to larger distances between the fatty acid chains of the glycerides and general imperfections in the crystal and thus provides more room for accommodation of guest molecules. The highest drug load could be achieved by mixing solid lipids with small amount of liquid lipids (oils). This model is called imperfect type NLC. In the second model, drugs showing higher solubility in oils than in solid lipids, can be dissolved in the oil and yet be protected from degradation by the surrounding solid lipids. These types of NLC called multiple type NLC, and are analogous to w/o/w emulsion since it is an oil-in-solid-in-water dispersion.[13] Since drug expulsion is caused by ongoing crystallization or transformation of the solid lipid, this can be prevented by the formation of a third type, the amorphous type NLC. Here the particles are solid but crystallization upon cooling is avoided by mixing special lipids like

hydroxyl octacosanyl, hydroxyl stearate, isopropyl myristate. The NLCs have mainly been investigated in the topical and dermatological preparation,[21] in the delivery of clotrimazole,[22, 23] ketoconazole,[23] other antifungal imidazoles[23] and ascorbic palmitate.[24]

**Lipid drug conjugates (LDC)**

A major problem of SLNs is the low capacity to load hydrophilic drugs due to partitioning effects during the production process. Only highly potent low dose hydrophilic drugs may be suitably incorporated in the solid lipid matrix.[25] In order to overcome this limitation, the so called LDC nanoparticles with drug loading capacities up to 33% have been developed.[21] An insoluble drug-lipid conjugate bulk is first prepared either by salt formation (e.g. with fatty acid) or by covalent linking (e.g. to ester or ethers). The obtained LDC is then processed with an aqueous surfactant solution (such as Tweens) to a nanoparticle formulation using high pressure homogenization (HPH). Such matrices may have potential application in brain targeting of hydrophilic drugs in serious protozoal infection.[26]

**Table 1: List of excipients used in SLN preparation** [18, 27, 28]

| Lipids | Surfactants |
|---|---|
| **Triglycerides**<br>Tricaprin, Trilaurin,<br>Trimyristin (Dynasan 114),<br>Tripalmitin (Dynasan 116),<br>Tristearin (Dynasan 118),<br>Hydrogenated coco-glyceride (SoftisanÒ142)<br>**Hard fat types**<br>WitepsolÒ W 35, WitepsolÒ H 35,<br>WitepsolÒ H 45, WitepsolÒ E 85<br>**Acyl glycerols**<br>Glyceryl monostearate (ImwitorÒ 900),<br>Glyceryl distearate (Precirol),<br>Glyceryl monooleate (Peceol),<br>Glyceryl behenate (CompritolÒ 888 ATO),<br>Glyceryl palmitostearate (PrecirolÒ ATO 5).<br>**Waxes**<br>Cetyl palmitate, Fatty Acids, Stearic acid,<br>Palmitic acid, Decanoic acid, Behenic acid,<br>Acidan N12.<br>**Cyclic complexes**<br>Cyclodextrin, *para*-acyl-calix-arenes | **Phospholipids**<br>Soy lecithin (LipoidÒ S 75, LipoidÒ S 100)<br>Egg lecithin (LipoidÒ E 100) ,<br>Phosphatidylcholine (Epikuron 170,<br>Epikuron 200)<br>**Ethylene oxide/propylene oxide copolymers**<br>Poloxamer 188, Poloxamer 182,<br>Poloxamer 407, Poloxamine 908<br>**Sorbitan ethylene oxide/propylene oxide copolymers**<br>Polysorbate 20, Polysorbate 60,<br>Polysorbate 80<br>**Alkylaryl polyether alcohol polymers**<br>Tyloxapol<br>**Bile salts**<br>Sodium cholate, Sodium glycocholate,<br>Sodium taurocholate, Sodium<br>taurodeoxycholate<br>**Alcohols**<br>Ethanol, Butanol, Butyric acid,<br>Dioctyl sodium sulfosuccinate,<br>Monooctylphosphoric acid sodium |

**Solid lipid nanoparticles production procedure**

The major problem for the SLNs to be introduced to the market is the use of excipients having no accepted status. For topical SLN, all excipients used in current topical cosmetic and dermal pharmaceutical products can be used. 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 used in many oral products and accepted as excipients by the regulatory authorities. The situation is different for parenteral administration as solid lipids have not yet been administered parenterally before-in contrast to liquid lipids. However, the glycerides used for SLN production are composed of compounds (glycerol, fatty acids), which are also present in emulsions for Parenteral nutrition.[21]

The general excipients used in any SLN formulation are solid lipids, emulsifiers, co-emulsifiers and water. The lipid is used here in broader sense and examples of lipids are given in the Table 1. All the classes of emulsifier (with respect to charges and molecular weight) have been used to stabilize the lipid dispersion. It has been found that the combination of emulsifiers might prevent particle agglomeration more efficiently.[18]

**Influence of various excipients used on product quality**

**Influence of lipid**

The difference in the chemical nature of the lipid matrix will influences the overall hydrophobicity which in turn influences particle size distribution. This is a crucial parameter for the nanoparticle formation that may have potential impact not only on the physical stability but also on drug loading capacity, drug release rate, rate of drug hydrolysis as well as *in-vivo* fate.[29] In hot homogenization, it can be seen that average particle size of SLN dispersion is increasing with higher melting lipids and this is because of higher viscosity of dispersed phase.[18, 30]

**Influence of emulsifier**

Various emulsifiers (surfactants) and their combination (Pluronic F 68, Pluronic F 127), have been used to stabilize the lipid dispersion. The combination of emulsifier might prevent particle agglomeration more efficiently.[31] Choice of emulsifier has a great impact on quality of SLN. Reduction in surface tension and particle partitioning during homogenization is facilitated by increasing the emulsifier concentration. Reduction in particle size leads to increased surface area.[28] Surfactants decrease the surface tension between the interface of

the particles causing portioning of the particles and thereby increasing the surface area.[6] During SLN preparation the primary dispersion must contain excessive emulsifier to rapidly cover the new surfaces formed during High Pressure Homogenization; otherwise it will lead to agglomeration of uncovered new lipid surfaces. The addition of some co-emulsifying agent like Sodium Glycocholate further decreases the particle size.[18]

**Method of preparation of solid lipid nanoparticles**

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

In this technique lipids are pushed with high pressure (100-200 bars) through a narrow gap of few micron ranges. So shear stress and cavitations are the forces which cause the disruption of particle to submicron range. The fluid accelerates to a very short distance at very high viscosity of over 1000 km/h. In contrast to other preparation technique high pressure homogenization does not show scaling up problem.[19, 32] HPH is of two type-hot homogenization and cold homogenization.

**A. Hot homogenization**

Hot homogenization is generally carried out at temperature above the melting point of the lipid. A pre-emulsion of the drug loaded lipid melt and the aqueous emulsifier phase (same temperature) is obtained by high shear mixing device. The resultant product is hot o/w emulsion and the cooling of this emulsion leads to crystallization of the lipid and the formation of SLNs. Smaller particle size obtained at higher processing temperatures because of lowered viscosity of the lipid phase. However, high temperature leads to degradation rate of the drug and carrier. Generally, 3-5 homogenization cycles at a pressure of 500-1500 bar are used.[33] The primary product is a nanoemulsion due to the liquid which on cooling at room temperature leads to solid particles. Due to the small particle size and the presence of emulsifier, lipid crystallization may be highly retarded and sample may remain as a super cool melt for several months.[4,6,18, 34, 35]

**B. Cold homogenization**

Cold homogenization has been developed to over-come the temperature related degradation problems, loss of drug into the aqueous phase and partitioning associated with hot homogenization method. The first preparatory step is the same as in the hot homogenization procedure and includes dispersion or solubilisation of drug into melted lipid and the lipid melt is cooled rapidly using dry ice or liquid nitrogen. The solid material is ground by a mortar mill/ball mill. The prepared lipid microparticles are in the range of 50-100 microns

and then dispersed in a cold emulsifier solution at or below room temperature. However, compared to hot homogenization, larger particle sizes and a broader size distribution are typical of cold homogenization samples.[6, 33]

2. **Ultrasonication /High speed homogenization**

SLNs are also prepared by ultrasonication or high speed homogenization techniques. For smaller particle size, combination of both ultrasonication and high speed homogenization is required. The particles are prepared by melting the core material, adding phospholipids along with an aqueous medium and dispersing the melted material at increased temperature by mixing techniques, such as mechanical stirring or sonication.[36, 37] The advantage of this method is that the equipment used is commonly available at lab scale. It reduces shear stress but has some disadvantages like potential mental contamination, physical instability like particle growth upon storage.[38]

**3. Solvent evaporation method/Solvent emulsification evaporation technique**

For the production of nanoparticles dispersions in o/w by precipitation in o/w.[39] 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 with cholesterol acetate as model drug and lecithin/sodium glycocholate blend as emulsifier. To improve the efficiency of fine emulsification, the coarse emulsion was immediately passed through the Homogenizer.[40] The organic solvent is removed from the emulsion by evaporation under reduced pressure (40–60 mbar) (e.g. Rotary evaporator) leaving lipid precipitates nanoparticles. The reproducibility of the result was confirmed by Siekmann and Westensen, who produced the cholesterol acetate nanoparticles of mean size 29 nm.[6, 41]

**4. Solvent diffusion method/Solvent emulsification-diffusion method**

The particles with average diameters of 30-100 nm can be obtained by this technique. Avoidance of heat during the preparation is the most important advantage of this technique. In this technique, the solvent used (e.g. benzyl alcohol, butyl lactate, ethyl acetate, isopropyl acetate, methyl acetate) must be partially miscible with water and this technique can be carried out either in aqueous phase or in oil.[42] In this technique lipid is, are generally dissolved in the organic phase in water bath at 50 °C and used an acidic aqueous phase in order to adjust the zeta potential to form coacervation of SLN, and then easy separation by

centrifugation. The SLN suspension was quickly produced. The entire dispersed system can then be centrifuged and re-suspended in distilled water.[6,43, 45]

**5. Supercritical fluid method**

This is a relatively new technique for SLN production and has the advantage of solvent-less processing. A fluid is termed supercritical when its pressure and temperature exceed their respective critical value. The ability of the fluid to dissolve compounds increases. This technology comprises of several processes for nanoparticles production such as rapid expansion of supercritical solution (RESS), particles from gas saturation solution (PGSS), aerosol solvent extraction solvent (ASES) and supercritical fluid extraction of emulsions (SFEE).[46] SLN can be prepared by the rapid expansion of supercritical carbon dioxide solutions (RESS) method. Carbon dioxide (99.99%) is the good choice as a solvent for this method.[6, 47]

**6. Microemulsion based method**

Gasco and co-workers developed SLN preparation techniques which are based on the dilution of microemulsions. By stirring at 65-70°C an optically transparent mixture is obtained which is typically composed of a low melting fatty acid (stearic acid), an emulsifier (polysorbate 20, polysorbate 60, soy phosphatidylcholine, and sodium taurodeoxycholate), co-emulsifiers(sodium monooctylphosphate) and water. The hot microemulsion is dispersed in cold water (2-3°C) under stirring. The dilution process is critically determined by the composition of the microemulsion.[6, 48, 49]

**7. Double emulsion method**

For the preparation of hydrophilic drug loaded SLN, a novel method based on solvent emulsification – evaporation has been used.[12] Warm w/o/w double microemulsions can be prepared in two steps. Firstly, w/o microemulsion is prepared by adding an aqueous solution containing drug to a mixture of melted lipid, surfactant and co-surfactant at a temperature slightly above the melting point of lipid to obtain a clear system. In the second step, formed w/o microemulsion is added to a mixture of water, surfactant and co-surfactant to obtain a clear w/o/w system. SLNs can be obtained by dispersing the warm micro double emulsions in cold then washed with dispersion medium by ultra filtration system.[6, 50] Li et al. prepared solid lipid nanoparticles loaded with bovine serum albumin (BSA) using double emulsion method.[51]

### 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.[6,52]

### 9. Film ultra sound dispersion

The lipid and the drug are 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 is added. Using the ultrasound with the probe to diffuser at last, the SLN with the little and uniform particle size is formed.[6, 53]

### 10. Solvent injection technique

In this technique, the solid lipid is dissolved in water-miscible solvent (eg. ethanol, acetone, isopropanol) or a water miscible solvent mixture. Then this lipid solvent mixture is injected through an injection needle into stirred aqueous phase with or without surfactant. The resultant dispersion was then filtered with a filter paper in order to remove any excess lipid. The presence of emulsifier within the aqueous phase helps to produce lipid droplets at the site of injection and stabilize SLN until solvent diffusion is completed by reducing the surface tension between water and solvent.[6, 54, 55] Mishra et al., prepared and evaluated SLNs using solvent injection method for delivery of Hepatitis B surface antigen for vaccination using subcutaneous route.[56]

### 11. Using membrane contractor

The lipid phase is pressed, at a temperature above the melting point of the lipid, through the membrane pores allowing the formation of small droplets. The aqueous phase circulates inside the membrane module, and sweeps away the droplets forming at the pore outlets. SLNs are formed by the following cooling of the preparation to room temperature. Also, vitamin E loaded SLNs are prepared, and their stability is demonstrated.[57]

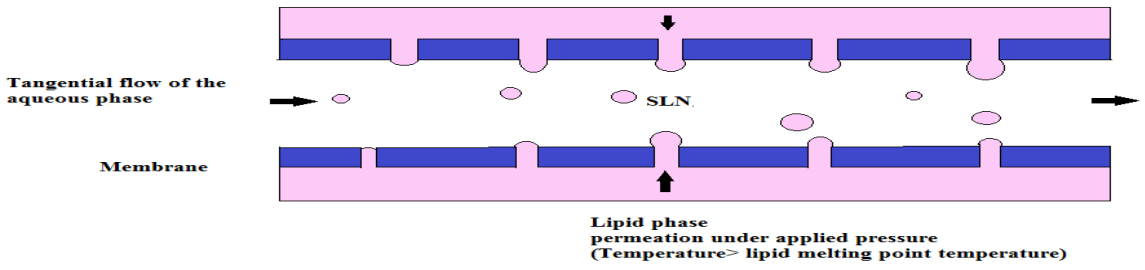


**Fig. 2: Schematic diagram of membrane contractor for preparation of SLN**

**12. Spray drying method**

It is an alternative and cheaper technique to the lyophilization process. This recommends the use of lipid with melting point more than 70$^{o}$C. The addition of carbohydrates and low lipid content favor the preservation of the colloidal particle size in spray drying. The melting of the lipid can be minimized by using ethanol–water mixtures instead of pure water due to cooling leads to small and heterogeneous crystals, the lower inlet temperatures.[6,18, 58, 59] This method causes particle aggregation due to high temperature, shear forces and partial melting of the particle.[6,12]

**Secondary production steps**

**Sterilization**

Sterilization of the nanoparticles is desirable for parenteral administration and autoclaving, which is applicable to formulations containing heat-resistant drugs. Effects of sterilization on particle size have been investigated and it is found to cause a distinct increase in particle size. Critical parameters include sterilization temperature and SLN composition. The correct choice of the emulsifier is of significant importance for the physical stability of the sample at high temperatures. Increased temperatures affect the mobility and the hydrophilicity of all emulsifiers to a different extent. Steam sterilization causes the formation of an o/w-emulsion due to the melting of the lipid particles. Solid particles are formed after recrystallization. γ-irradiation could be an alternative method to steam sterilization for temperature sensitive samples.[18, 52, 60, 61]

**Lyophilization**

Lyophilization is a promising way to increase the chemical and physical stability over extended periods of time for a product containing hydrolysable drugs or a suitable product for per-oral administration. Transformation into the solid state would prevent the Oswald ripening and avoid hydrolytic reactions. An adequate amount of cryoprotectant can protect the aggregation of solid lipid nanoparticles during the freeze drying process.[18,52, 60, 61]

**Characterization of SLNs**

Characterization of SLNs is necessary for its quality control.

**Particle size and Zeta potential**

The physical stability of SLNs depend on their particle size. Photon correlation spectroscopy (PCS) and laser diffraction (LD) are the most powerful techniques for determination of

particle size. PCS (also known as dynamic light scattering) measures the fluctuation of the intensity of the scattered light, which is caused by particle movement. The particle size determination by photon correlation spectroscopy (PCS) detects size range of 3nm to 3µm and by laser diffraction in size range of 100nm to 180µm.[62] The Coulter method is rarely used to measure SLN particle size because of difficulties in the assessment of small nanoparticles and the need of electrolytes which may destabilize colloidal dispersions.[13] Zeta potential measurement can be carried out using Zeta Potential Analyzer or Zetameter.[63] Higher value of zeta potential may lead to disaggregation of particles in the absence of other complicating factors such as steric stabilizers or hydrophilic surface appendages. Zeta potential measurements allow predictions about the storage stability of colloidal dispersions.

**Drug content and drug release**

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 + drug). Factors determining the loading capacity of drug in the lipid are, for example:[64] Solubility of drug in melted lipid, miscibility of drug melt and lipid melt, chemical and physical structure of solid lipid matrix and polymorphic state of lipid material.

**Electron microscopy**

Scanning electron microscopy (SEM) and transmission electron microscopy (TEM) provide way to directly observe nanoparticles. SEM is however better for morphological examination. TEM has a small size limit of detection.[65]

**Atomic Force Microscopy (AFM)**

That ultra-high resolution is obtainable with this approach, which along with the ability to map a sample according to properties in addition to size, e.g., colloidal attraction or resistance to deformation, makes AFM a valuable tool.[66]

**Dynamic Light Scattering (DLS)**

DLS, also known as PCS or quasi-elastic light scattering (QELS) records the variation in the intensity of scattered light on the microsecond time scale. This variation results from interference of light scattered by individual particles under the influence of Brownian motion, and is quantified by compilation of an autocorrelation function.[32]

**Differential Scanning Calorimetry (DSC)**

DSC and Powder X-ray Diffractometry (PXRD) is performed for the determination of the degree of crystallinity of the particle dispersion. The rate of crystallinity using DSC is estimated by comparison of the melting enthalpy/g of the bulk material with the melting enthalpy/g of the dispersion.[68]

**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 nanoparticles.[32]

**Crystallinity and lipid modifications**

Special attention must be paid to the characterization of the degree of lipid crystallinity and the modification of the lipid, because these parameters are strongly correlated with drug incorporation and release rates. Due to the small size of the particle and the presence of emulsifiers, lipid crystallization and modification changes might be highly retarded.[12]

**Sterilization of SLNs**

For intravenous and ocular administration SLN must be sterile. The high temperature reach during sterilization by autoclaving presumably causes a hot o/w microemulsion to form in the autoclave, and probably modifies the size of the hot nanodroplets. On subsequent slow cooling, the SLN reformed, but some nanodroplets may coalesce, producing larger SLN than the initial ones.[68] For parenteral administration, SLN dispersions must be sterile. Aseptic manufacturing processes following sterilization of the starting materials (gamma or e-beam irradiation of the final dispersion) or exposure to ethylene oxide gas (EO).[69]

**Stability of SLN**

The physical properties of SLNs during prolonged storage can be determined by monitoring changes in zeta potential, particle size, drug content, appearance and viscosity as the function of time. The zeta potential should be in general, remain higher than -60mV for a dispersion to remain physically stable. 4°C - most favorable storage temperature, 20°C - long term storage did not result in drug loaded SLN aggregation or loss of drug and 50°C - a rapid growth of particle size was observed.[28]

**Route of administration and their biodistribution**

**Per oral administration**

Per oral administration forms of SLN may include aqueous dispersions or SLN loaded traditional dosage forms, e.g. tablets, pellets or capsules. The microclimate of the stomach favors particle aggregation due to the acidity and high ionic strength. It can be expected, that food will have a large impact on SLN performance.[6]

**Parenteral administration**

SLN has 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. In addition, incorporation of the drug into SLN might reduce irritancy compared to injecting drug micro particles.[6]

**Rectal administration**

When rapid pharmacological effect is required, in some circumstances, parentral or rectal administration is preferred. This route is used for pediatric patients due to easy application.[6]

**Nasal administration**

Nasal route is preferred due to its fast absorption and rapid onset of drug action also avoiding drug degradation of labile drugs in the GIT and insufficient transport across epithelial cell layers.[6]

**Respiratory delivery**

Nebulisation of solid lipid particles carrying anti tubercular drugs, anti-asthematic drugs and anti cancer is observed to be successful in improving drug bioavaibility and reducing the dosing frequency for better management of pulmonary action.[6]

**Transdermal application**

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. 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.[70]

**Topical application**

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.[71]

**Ophthalmic administration**

Many investigations have been made to use nanoparticles for prolonged release of drugs to the eye. The basic problem of ophthalmologic formulation is the fast removal from the eye, which implies clearance of the applied drug through the nose. It could be shown for nanoparticles that an increased adhesiveness is available leading to higher drug levels at desired site of action.[72]

**Pulmonary administration**

SLN powders cannot be administered to the lung because the particle size is too small and they will be exhaled. A very simple approach is the aerosolization of aqueous SLN dispersions. The aerosol droplets were collected by collision of aerosol with a glass wall of a beaker. This basically demonstrates that SLNs are suitable for lung delivery.[6]

**Applications**[73, 74, 75]

**SLN as potential new adjuvant for vaccines**

The safer new subunit vaccines are less effective in immunization and therefore effective adjuvants are required. 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.

**Solid lipid nanoparticles in cancer chemotherapy**

From the last two decades several chemotherapeutic agents have been encapsulated in SLN and their *in-vitro* and *in-vivo* efficacy have been evaluated. Several obstacles frequently encountered with anticancer compounds, such as normal tissue toxicity, poor specificity and stability and a high incidence of drug resistant tumor cells, are at least partially overcome by delivering them using SLN. The rapid removal of colloidal particles by the macrophages of the RES is a major obstacle to targeting tissues elsewhere in the body, such as bone marrow and solid tumors.

**SLN as targeted carrier for anticancer drug to solid tumor**[76, 77, 78, 79]

SLN has been to be useful as drug carriers. Tamoxifen is an anticancer drug incorporated in SLN to prolong the release of drug after IV administration in breast cancer. Tumor targeting has been achieved with SLN loaded with drugs like methotrexate and camptothecin.

**SLN in breast cancer and lymph node metastases**

Mitoxantrone SLN local injections were formulated to reduce the toxicity and improve the safety and bioavailability of the drug.[79]

**Solid lipid nanoparticles for delivering peptides and proteins**

Solid lipid particulate systems such as solid lipid nanoparticles (SLN), lipid microparticles (LM) and lipospheres have been sought as alternative carriers for therapeutic peptides, proteins and antigens. The research work developed in the area confirms that under optimized conditions, they can be produced to incorporate hydrophobic or hydrophilic proteins and seem to fulfill the requirements for an optimum particulate carrier system. Formulation in SLN confers improved protein stability, avoids proteolytic degradation, as well as sustained release of the incorporated molecules. Important peptides such as cyclosporine A, insulin, calcitonin and somatostatin have been incorporated into solid lipid particles and are currently under investigation.

**Solid lipid nanoparticles for targeted brain drug delivery**[73]

The extremely small particle size of solid lipid nanoparticles, which are less than 50 nm, might be beneficial with respect to drug targeting. Small carrier size generally favors reduced uptake by the reticuloendothelial system. Drug targeting might also be possible by surface modification of solid lipid nanoparticles. 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.[80] The state of the art on surfactant coated poly (alkylcyanoacrylate) nanoparticles specifically designed for brain targeting is given by emphasizing the transfer of this technology to solid lipid matrices. The potential advantages of the use of solid lipid nanoparticles over polymeric nanoparticles are accounted on the bases of a lower cytotoxicity, higher drug loading capacity, and best production scalability.

**Solid lipid nanoparticles for parasitic diseases**[73, 74, 38]

Parasitic diseases (like malaria, leishmaniasis, tryanosomiasis) are one of the major problems around the globe. Antiparasitic chemotherapy is the only choice of treatment for these

parasitic infections, the reason for this is that these infections do not elicit pronounced immune response hence effective vaccination may not be possible. Solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs) represent a second generation of colloidal carriers and have emerged as an effective alternative to liposomes mainly due to their better stability profile, ease of scalability and commercialization and relative cost efficacy.

**Solid lipid nanoparticles for ultrasonic drug and gene delivery**[73]

Drug delivery research employing micelles and nanoparticles has wide application in ultrasonic drug and gene delivery in recent years. Ultrasound, traditionally used in diagnostic medicine, is finding a place in drug delivery in connection with these nanoparticles. In addition to their non-invasive nature and the fact that they can be focused on targeted tissues, acoustic waves have been credited with releasing pharmacological agents from nanocarriers, as well as rendering cell membranes more permeable. Ultrasonic drug delivery from micelles usually employs polyether block copolymers and has been found effective in vivo for treating tumors. Ultrasound releases drug from micelles, most probably via shear stress and shock waves from the collapse of cavitation bubbles. Liquid emulsions and solid nanoparticles are used with ultrasound to deliver genes *in vitro* and *in vivo*.[80]

**SLN applications for improved delivery of antiretroviral drugs to the brain**[74]

Human immunodeficiency virus (HIV) can gain access to the central nervous system during the early course of primary infection. Current antiretroviral drugs (ARVs) often fail to effectively reduce the HIV viral load in the brain. This, in part, is due to the poor transport of many ARVs, in particular protease inhibitors, across the blood brain barrier (BBB) and blood-cerebrospinal fluid barrier (BCSBF). Studies have shown that nanocarriers including polymeric nanoparticles, liposomes, solid lipid nanoparticles (SLN) and micelles can increase the local drug concentration gradients, facilitate drug transport into the brain via endocytotic pathways and inhibit the ATP-binding cassette (ABC) transporters expressed at the barrier sites.

**SLN applied to the treatment of malaria**[74]

The main drawbacks of conventional malaria chemotherapy are the development of multiple drug resistance and the nonspecific targeting to intracellular parasites, resulting in high dose requirements and subsequent intolerable toxicity. Nanosized carriers have been receiving special attention with the aim of minimizing the side effects of drug therapy, such as poor

bioavailability and the selectivity of drugs. Several nanosized delivery systems have already proved their effectiveness in animal models for the treatment and prophylaxis of malaria.[81]

**Targeted delivery of solid lipid nanoparticles for the treatment of lung diseases**

Nanoparticles with their special characteristics such as small particle size, large surface area and the capability of changing their surface properties have numerous advantages compared with other delivery systems. Targeted nanoparticle delivery to the lungs is an emerging area of interest.[82]

**Solid lipid nanoparticles in tuberculosis disease**

SLN have been used to encapsulate Anti Tubercular Drugs (ATD) and were proved to be successful in experimental tuberculosis. Antitubercular drugs such as rifampicin, isoniazid, and pyrazinamide SLN systems are able to decrease the dosing frequency and to improve patient compliance.[73, 74]

**Transfection agent**

PCS showed that the prepared SLNs were smaller in diameter than the corresponding liposomes while AFM supported the expected structural differences. DNA binding differed only marginally. Cationic lipid composition governs the *in vitro* transfection performance than the colloidal structure it is arranged in. Hence, cationic SLN extends the range of highly potent non-viral transfection agents by one with favorable and distinct technological properties. Combination of cationic SLN with the nuclear localization signal TAT2 increased transfection efficiency hundredfold.[83]

**SLN in cosmetic and dermatological preparations**

An area of big potential for SLN and with a short time-to market are topical products based on the SLN technology, that means pharmaceutical but also cosmetic formulations. Due to the lower risk of systemic side effects topical treatment of skin disease appears favorable, yet the stratum corneum counteracts the penetration of xenobiotics into viable skin. The lipid nanodispersion applied to the skin surface, lipid particles form an adhesive layer occluding the skin surface. Then hydration of the stratum cornea may increase by which reducing corneocyte packing and widening of the inter-corneocytes gaps can facilitate drug penetration into deeper skin strata.[84]

**Solid lipid nanoparticles for lymphatic targeting**

The solid lipid nanoparticles (SLN) are developed and evaluated for the lymphatic uptake after intraduodenal administration to rats.[73]

**SLN for potential agriculture applications**

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.[85]

## CONCLUSION

Lipid based nano carriers have the greater importance in developing field of nanotechnology with several advantages apart from various carriers. Lipid based carriers are a promising nanoscale delivery system for the pharmaceutical industry. Solid lipid nanoparticles have combined advantages of other colloidal drug carriers and avoid disadvantages of them. The advantages of SLN include the composition (physiological compounds), the rapid and effective production process including the possibility of large scale production, the avoidance of organic solvents, the possibility to produce carriers with higher encapsulation efficiency and its ability to deliver the drugs to specific sites. Disadvantages include low drug loading capacities, the presence of alternative colloidal structures (micelles, liposomes, mixed micelles, drug nanocrystals) etc. SLN constitutes attractive colloidal drug carrier system due to successful incorporation of active compounds and their related benefits. SLN offers an effective, promising, economical and patient friendly dosage form for administration of drugs by various routes. The biocompatibility of lipid nanoparticles with blood components and other tissues is essential for successful regulatory clearance of lipid nanoparticles. This necessitates the need for studying the toxicological implications of lipid nanoparticles.

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