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# SOLID LIPID NANOPARTICLES; A REVIEW

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**ABSTRACT**: Solid lipid nanoparticles (SLN) are at the forefront of the rapidly developing field of nanotechnology with several potential applications in drug delivery and research. Due to their unique size dependent properties, lipid nanoparticles offer possibility to develop new therapeutics. The ability to incorporate drugs into nanocarriers offers a new prototype in drug delivery that could use for drug targeting. Hence solid lipid nanoparticles hold great promise for reaching the goal of controlled and site specific drug delivery and hence attracted wide attention of researchers. This review presents a broad treatment of solid lipid nanoparticles discussing their aims, production procedures, advantages, limitations and their possible remedies. Appropriate analytical techniques for the characterization of SLN like Photon Correlation Spectroscopy (PCS), Scanning Electron Microscopy (SEM), and Differential Scanning Calorimetry are highlighted. Aspects of SLN route of administration and the *in vivo* fate of the carriers are also discussed.

**INTRODUCTION:** Solid lipid nanoparticles (SLN) introduced in 1991 represent an alternative carrier system to tradition colloidal carriers such as - emulsions, liposomes and polymeric micro and nano particles [1].

Nanoparticles made from solid lipids are attracting major attention as novel colloidal drug carrier for intravenous applications as they have been proposed as an alternative particulate carrier system.

SLN are sub-micron colloidal carriers ranging from 50 to 1000 nm, which are composed of physiological lipid dispersed in water or in aqueous surfactant solution. SLN offer unique properties such as small size, large surface area, high drug loading and the interaction of phases at the interface and are attractive for their potential to improve performance of pharmaceuticals [2, 5, 6].

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

1. Lipids enhance oral bioavailability and reduce plasma profile variability.
2. Better characterization of lipoid excipients.
3. An improved ability to address the key issues of technology transfer and manufacture scale-up.

Solid lipid nanoparticles are one of the novel potential colloidal carrier systems as alternative materials to polymers which is identical to oil in water emulsion for parenteral nutrition, but the liquid lipid of the emulsion has been replaced by a solid lipid shown on **Fig. 1**.

They have many advantages such as good biocompatibility, low toxicity and lipophilic drugs are better delivered by solid lipid nanoparticles and the system is physically stable.

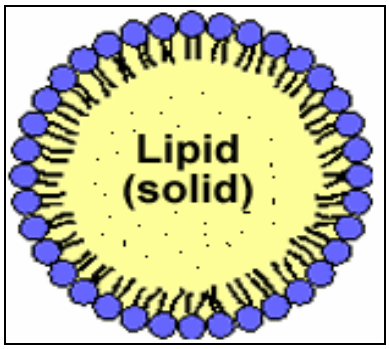


**FIG. 1: STRUCTURE OF SOLID LIPID NANOPARTICLE (SLN)**

Solid lipid nanoparticles (SLNs) are considered to be the most effective lipid based colloidal carriers, introduced in early nineties. This is the one of the most popular approaches to improve the oral bioavailability of the poorly water soluble drugs. SLNs are in the submicron size range of 50-1000 nm and are composed of physiologically tolerated lipid components which are in solid state at room temperature.

The schematic representation of different particulate drug carriers such as emulsions and liposomes and their advantages are compared with SLNs in **Fig. 2**. SLNs combine all the advantages of polymeric nanoparticles, fat emulsions and liposomes.

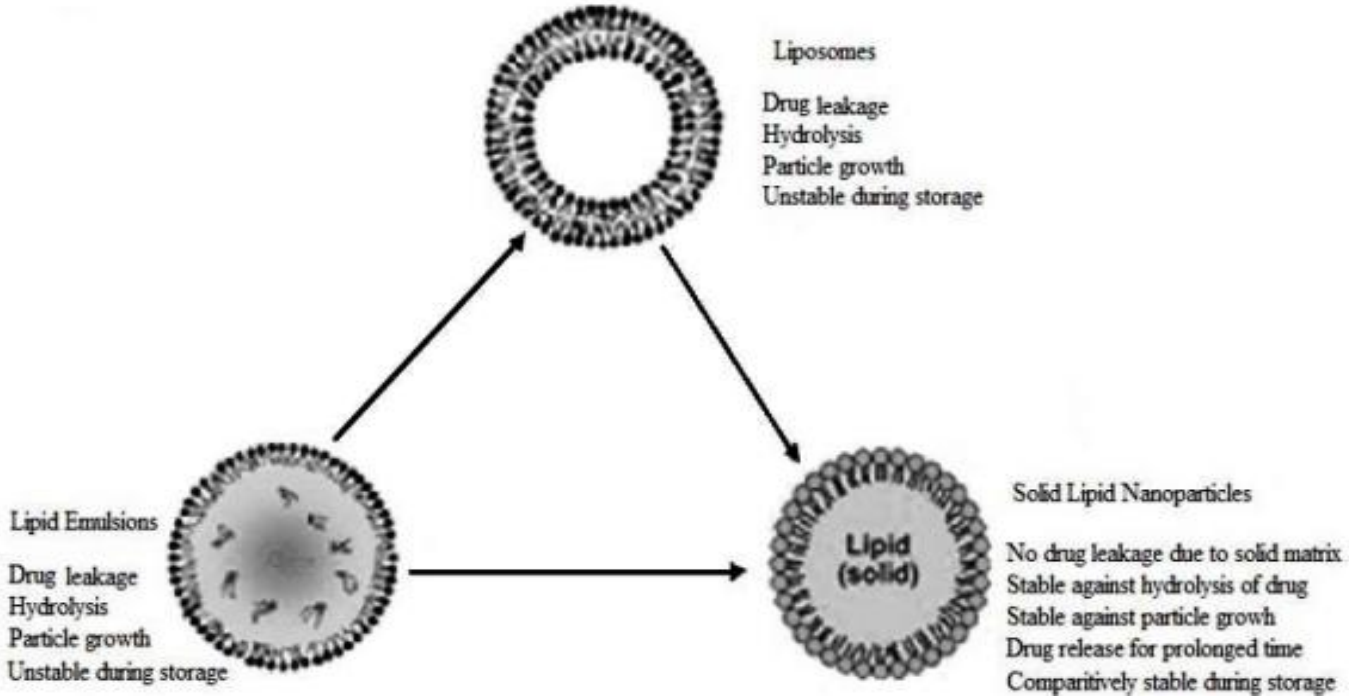


**FIG. 2: A DIAGRAMMATIC REPRESENTATION ON SLN OVER EMULSIONS AND LIPOSOMES**

**Advantages of SLN [1-4]:**

- Control and / or target drug release.
- Excellent biocompatibility[5].
- Improve stability of pharmaceuticals[4].
- High and enhanced drug content.
- Easy to scale up and sterilize.
- Better control over release kinetics of encapsulated compounds.
- Enhanced bioavailability of entrapped bioactive compounds.
- Chemical protection of labile incorporated compounds.
- Much easier to manufacture than biopolymeric nanoparticles.
- No special solvent required.
- Conventional emulsion manufacturing methods applicable.

- Raw materials essential the same as in emulsions.
- Very high long-term stability.
- Application versatility.
- Can be subjected to commercial sterilization procedures.

**Disadvantages of SLN [4, 6]:**

- Particle growth.
- Unpredictable gelation tendency.
- Unexpected dynamics of polymeric transitions.

**Aims of solid lipid nanoparticles [6, 9]:**

- Possibility of controlled drug release[5].
- Increased drug stability.
- High drug pay load[5].
- No bio-toxicity of the carrier.
- Avoidance of organic solvents.
- Incorporation of lipophilic and hydrophilic drugs.

**Preparation of Solid Lipid Nanoparticles [1-4, 6, 22, 23, 24]:** SLNs are prepared from lipid, emulsifier and water/solvent by using different methods and are discussed below.

**Methods of preparation of Solid Lipid Nanoparticles:**

1. High pressure homogenization:
   A. Hot homogenization.
   B. Cold homogenization.
2. Ultrasonication/high speed homogenization:
   A. Probe Ultrasonication.
   B. Bath Ultrasonication.
3. Solvent evaporation method.
4. Solvent emulsification-diffusion method.
5. Supercritical fluid method.
6. Microemulsion based method.
7. Spray drying method.
8. Double emulsion method.
9. Precipitation technique.
10. Film-ultrasound dispersion.

1. **High Pressure Homogenization (HPH):** It is a reliable and powerful technique, which is used for the production of SLNs. High pressure homogenizers push a liquid with high pressure (100–2000 bar) through a narrow gap (in the range of few microns). The fluid accelerates on a very short distance to very high velocity (over1000Km/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. 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.

a. **Hot homogenization:** Hot homogenization is carried out at temperatures above the melting point of the lipid and can therefore be regarded as the homogenization of an emulsion. A pre-emulsion of the drug loaded lipid melt and the aqueous emulsifier phase (same temperature) is obtained by high-shear mixing device. HPH of the pre-emulsion is carried out at temperatures above the melting point of the lipid. In general, higher temperatures result in lower particle sizes due to the decreased viscosity of the inner phase. However, high temperatures increase the degradation rate of the drug and the carrier. Increasing the homogenization pressure or the number of cycles often results in an increase of the particle size due to high kinetic energy of the particles.

b. **Cold Homogenization:** Cold homogenization has been developed to overcome various problems associated with hot homogenization such as; Temperature-induced drug degradation, drug distribution into the aqueous phase during

homogenization, Complexity of the crystallization step of the nano emulsion leading to several modifications and/or super cooled melts. In this technique the drug containing lipid melt is cooled, the solid lipid ground to lipid microparticles and these lipid microparticles are dispersed in a cold surfactant solution yielding a pre-suspension. Then this pre-suspension is homogenized at or below room temperature, the gravitation force is strong enough to break the lipid microparticles directly to solid lipid nanoparticles.

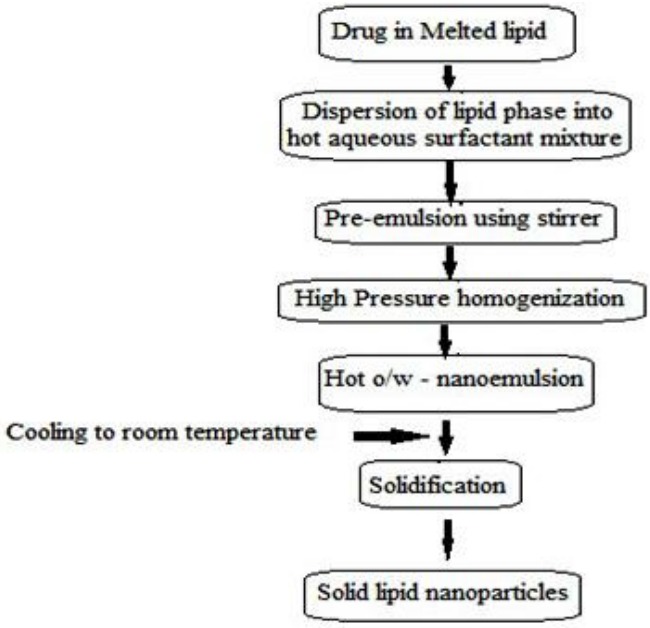


**FIG. 3: SOLID LIPID NANOPARTICLES PREPARATION BY HOT HOMOGENIZATION PROCESS**

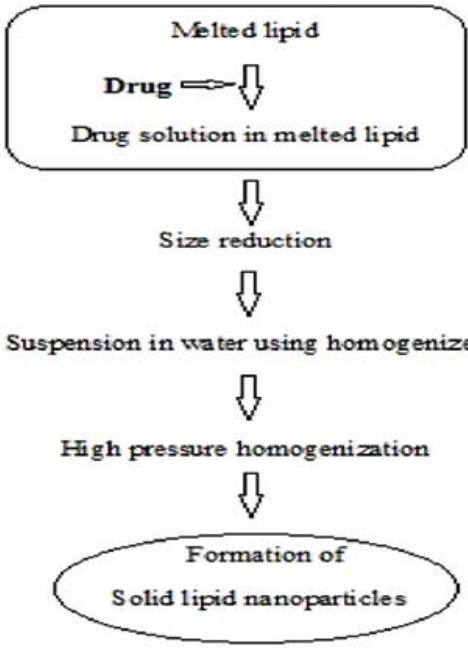


**FIG. 4: SOLID LIPID NANOPARTICLES PREPARATION BY COLD HOMOGENIZATION PROCESS.**

**Advantages:**

- Low capital cost.
- Demonstrated at lab scale.

**Disadvantages:**

- Energy intensive process.
- Demonstrated at lab scale Bio molecule damage.
- Polydisperse distributions.
- Unproven scalability.

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.

**Advantages:**

- Reduced shear stress.

**Disadvantages:**

- Potential metal contamination.
- Physical instability like particle growth upon storage.

3. **Solvent evaporation:** SLNs can also prepared by solvent evaporation method. 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. The solution was emulsified in an aqueous phase by high pressure homogenization. The organic solvent was removed from the emulsion by evaporation under reduced pressure (40–60 mbar).

**Advantages:**

- Scalable.
- Mature technology.
- Continuous process.
- Commercially demonstrated.

**Disadvantages:**

- Extremely energy intensive process.
- Polydisperse distributions.
- Bio molecule damage.

4. **Solvent emulsification-diffusion method:** The particles with average diameters of 30-100 nm can be obtained by this technique. Voidance of heat during the preparation is the most important advantage of this technique.

5. **Supercritical fluid method:** This is an alternative method of preparing SLNs by particles from gas saturated solutions (PGSS).

**Advantages:**

- Avoid the use of solvents.
- Particles are obtained as a dry powder, instead of suspensions.
- Mild pressure and temperature conditions.
- Carbon dioxide solution is the good choice as a solvent for this method.

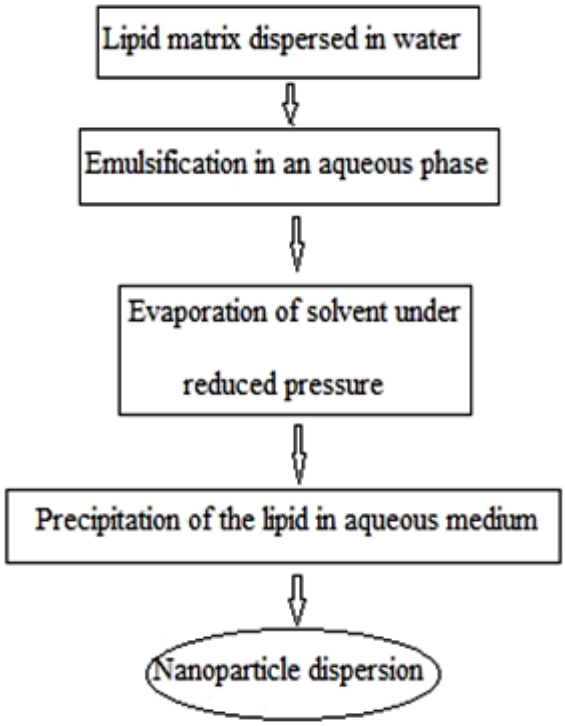


**FIG. 5: SYSTEMATIC REPRESENTATION FOR EMULSIFICATION-DIFFUSION METHOD.**

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

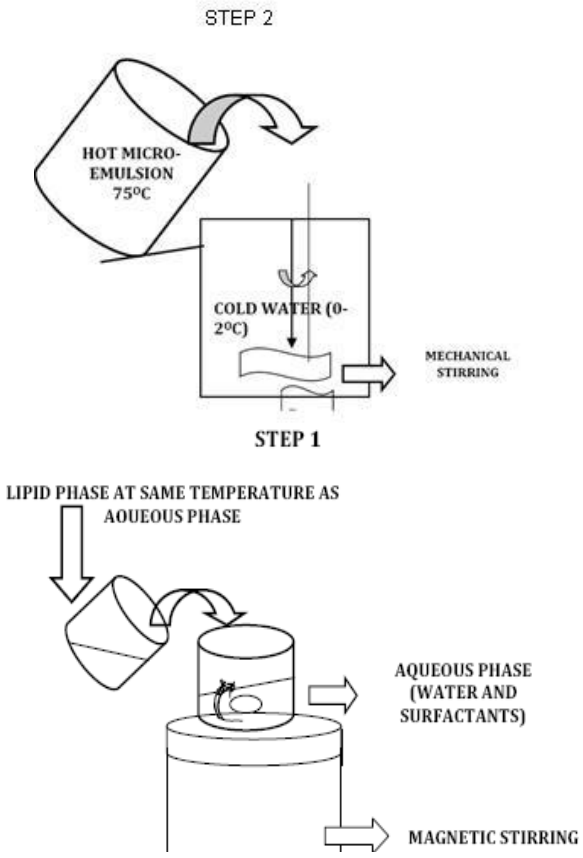


**FIG. 6: MICROEMULSION METHOD**

**Advantages:**

- Low mechanical energy input.
- Theoretical stability.

**Disadvantages:**

- Extremely sensitive to change.
- Labour intensive formulation work.
- Low nanoparticle concentrations.

7. **Spray drying method:** It is an alternative technique to the lyophilization process. This recommends the use of lipid with melting point more than70$^{0C}$. The best results were obtained with SLN concentration of 1% in a solution of trehalose in water or 20% trehalose in ethanol-water mixture.

8. **Double emulsion method:** Here the drug is encapsulated with a stabilizer to prevent the partitioning of drug in to external water phase during solvent evaporation in the external water phase of w/o/w double emulsion.

9. **Precipitation method:** The glycerides are 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.

10. **Film-ultrasound dispersion:** The lipid and the drug were put into suitable organic solutions, after decompression, rotation and evaporation of the organic solutions, a lipid film is formed, then the aqueous solution which includes the emulsions was added. Using the ultrasound with the probe to diffuser at last, the SLN with the little and uniform particle size is formed.

**Secondary Production Steps:**

1. **Freeze drying:** Lyophilization is a promising way to increase the chemical and physical stability over extended periods of time. Lyophilization had been required to achieve long term stability for a product containing hydrolysable drugs or a suitable product for per-oral administration. Transformations into the solid statewould prevents the Oswald ripening and avoid hydrolytic reactions. In case of freeze drying of the product, all the lipid matrices used, form larger Solid Lipid Nanoparticles with a wider size distribution due to presence of aggregates between the nanoparticles. Theconditions of the freeze drying process and the removal of water promote the aggregation among SLNs. An adequate amount of cryoprotectant can protect the aggregation of solid lipid nanoparticles during the freeze-drying process.

2. **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 was found to cause a distinct increase in particle size.

3. **Spray drying:** Spray drying might be an alternative procedure to lyophilization in order to transform an aqueous SLN dispersion into a dry product. This method has been used scarcely for SLN formulation, although spraydrying is cheaper as compared to lyophilization. The lipids with melting points at temperature >70°C had been recommended for spray drying.

**Influence of excipients [4, 10, 25]:**

**Formulation variables in the Product Quality:**

1. **Particle size:** Alteration of the size significantly affects the physical stability, bio fate of the lipid particles, and release rate of the loaded drug. Hence the size of the SLNs has to be controlled within reasonable range. Well formulated systems (liposomes, nanospheres and nanoparticles) should display a narrow particle sizedistribution in the submicron size range (as having size below 1µm), according to the definition of colloidal particles.

2. **Influence of the ingredients on Product Quality:** The particle size of lipid nanoparticles is affected by various parameters such as composition of the formulation (such as surfactant/ surfactant mixture, properties of the lipid and the drug incorporated), production methods and conditions (such as time, temperature, pressure, cycle number, equipment, sterilization and lyophilisation). Large particle size is obtained at lower processing temperature.

The hot homogenization technique gives a smaller particle size, generally below 500 nm, and a narrow particle sizedistribution as compared to cold homogenization. Mean particle size as well as polydispersity index (PI) values are reported to be reduced at increasing homogenization pressure up to 1500 bar and number of cycles (3-7 cycles).

3. **Influence of the Lipids:** Using the hot homogenization, it has been found that the average particle size of SLN dispersions is increasing with higher melting lipids. However, other critical parameters for nanoparticle formation will be different for the different lipids. The examples include the velocity of lipid crystallization, the lipid hydrophilicity (influence on self-emulsifying properties and the shape of the lipid crystals (and therefore the surface area). Further, increasing the lipid content over 5-10% resulted in larger particles (including microparticles) and broader particle size distribution in most cases.

4. **Influence of the Emulsifiers:** The concentration of the surfactant/surfactant mixture strongly affects the particle size of the lipidnanoparticles. In general, smaller particle sizes were observed when a higher surfactant/lipid ratio was chosen. The decrease in surfactant concentration resulted in increase of particle size during storage.

   Surfactants decrease the surface tension between the interface of the particles causing portioning of the particles and thereby increasing the surface area.

**Characterization of Solid Lipid Nanoparticles (SLNs):** The methods for the characterization should be perceptive to the key parameters of the performance of SLNs. Several parameters which have to be considered in characterization are as follows

1. **Particle size and Zeta Potential:** Size of nanoparticles can be determined by several methods such as photon-correlation spectrometry (PCS), transmission electron microscopy (TEM), and scanning electron microscopy (SEM), SEM combined with energy-dispersive X-RAY spectrometry, scanned probe microscopy and fraunhofer diffraction. Among these, the most widely used techniques are PCS and electron microscopy methods. SEM and TEM are very useful in determining the shape and morphology of lipid nanoparticles and also allow determination of particle size and distribution.

Another advanced microscopic technique used for characterization of nanoparticles is atomic force microscopy (AFM). This is a new tool to image the original unaltered shape and surface properties of the particles. In this technique, the force acting between the surface and probing tip results in a spatial resolution up to 0.01µm. Laser diffraction technique could also be used which is applicable for sub micrometer range particles and calculations are based on the refractive index of the dispersion medium water (1.33) and on the lipid particles [11].

The particle size depends on the matrix constituents as well as on the type and amount of emulsifying agents and lipids. It has been reported that increase in amount of emulsifier decreases the mean diameter of the bulk [12]. The size and structure of incorporated drug also affects average diameter of the SLNs [13]. Photon correlation spectroscopy (PCS) is also known as dynamic light scattering. This method measures the fluctuation of the intensity of the scattered light which is caused by particle movement and gives a size range from 3 nanometres to 3 microns [14, 15].

The PCS device consists of a light source, a temperature-controlled sample cell, and a photomultiplier for detection of the scattered light.

Zeta potential is measure of the charge on the particles. It helps in designing particles with reduced reticuloendothelial uptake. In order to divert SLNs away from the RES, the surface of the particles should be hydrophilic and free from charge. Structure of the SLNs can be determined by nuclear magnetic resonance (NMR) technique after $Mn^{+2}$ or $Pr^{+3}$ ion complication.

2. **Determination of Incorporated Drugs:** The amount of drug incorporated is determined after separation of the free drug and solid lipids from the aqueous medium and the separation carried out by ultracentrifugation, centrifugation filtration or gel permeation chromatography. Drug content can also be determined directly by extracting the drug with suitable solvent under optimum conditions and then analysis of resulted product in SLNs.

   Models have been proposed to describe the localization of drug molecules in SLNs [16]. The enriched shell model is characterized by drug selectively locating at the interface, either by fast solidification of the matrix lipid or by successful competition of the drug for the interface. Drug dispersed by such a model might exhibit a successful burst effect during drug release. The homogeneous matrix model is characterized by drug dispersed evenly throughout the matrix, much like a solid solution.

   The enriched core model is characterized by drug selectivity located at the core of the solid lipid nanoparticles, perhaps due to more rapid solidification of the drug relative to the matrix material. The enriched core model would be useful to produce a membrane controlled release pattern. Although the chemical stability and the release kinetics of drugs are largely related to localization of drugs within the aggregates, more research is still required to validate these models.

3. ***In-vitro* Drug Release Studies:** *In-vitro* drug release studies are mainly useful for quality control as well as for the prediction of in-vivo kinetics. Release profile of drug can be conducted in dialysis tubing or without tubing. In dialysis, the SLNs dispersion is introduced into prewashed dialysis tubing, which is then hermetically sealed and then dialyzed against dissolution medium at constant temperature with constant stirring. Samples were taken at different times, centrifuged and assayed for drug content. Levy and Benita (1990) have reported a new technique which avoids the enclosure of the colloidal drug carrier in a dialysis sac and is based on reverse dialysis. This method is not sensitive enough to characterize rapid release rate of drug from colloidal carrier [17].

4. **Storage stability:** The physical stability of the SLNs during prolonged storage can be determined by monitoring changes in particle size, drug content, appearance and viscosity. This can also be done by thin layer chromatography [18, 19].

5. **Crystallization tendency and polymorphic behaviour of SLNs:** Special consideration must be given to crystallization of lipids because this is associated with drug incorporation and release rates. The solid state of the particles is of major importance, as it reduces the mobility of incorporated drugs and thus preventing drug leakage from the carrier. Basic techniques to establish the physic-chemical state of particles include thermal analysis and X-ray diffraction [20, 21]. In thermal analysis most commonly used techniques are differential thermal analysis (DTA) and differential scanning Calorimetry (DSC).

**Routes of administration and their Biodistribution [2, 3, 7, 23, 26]:** The *in vivo* behaviour of the SLN particles will mainly depend on the following points:

**Administration route:** Interactions of the SLN with the biological surroundings including: distribution processes (Adsorption of biological material on the particle surface and desorption of SLN components into to biological surroundings) and enzymatic processes. Various administration routes are:

1. **Parenteral administration:** Peptide and proteins drugs are usually available for parenteral use in the market. Since their Conventional oral administration is not possible due to enzymatic degradation in GI tract. Parenteralapplication of SLN reduces the possible side effects of drug incorporated with the increased bioavailability. These systems are very suitable for drug targeting.

2. **Oral administration:** Controlled release behaviour of SLNs is reported to enable the bypass of gastric and intestinal degradation of the encapsulated drug, and their possible uptake and transport through the intestinal mucosa. However, the assessment of the stability of colloidal carriers in

GI fluids is essential in order to predict their Suitability for oral administration.

3. **Rectal administration:** When rapid pharmacological effect is required, in some circumstances, parenteral or rectal administration is preferred. This route is used for pediatric patients due to easy application.

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

5. **Respiratory delivery:** Nebulisation of solid lipid particles carrying anti-tubercular drugs, anti-asthmatic drugs and anticancer was observed to be successful in improving drug bioavailability and reducing the dosing frequency for better management of pulmonary action.

6. **Ocular administration:** Biocompatibility and muco-adhesive properties of SLN improve their interaction with ocular mucosa and prolong corneal residence time of the drug, with the aim of ocular drug targeting.

7. **Topical administration:** SLN are very attractive colloidal carrier systems for skin applications due to their various desirable effects on skin besides the characteristics of a colloidal carrier system. They are well suited for use on damaged or inflamed skin because they are based on non-irritant and non-toxic lipids.

**Applications of SLN** [4, 26, 27]**:** There are several potential applications of SLNs some of which are given below:

1. **SLN as potential new adjuvant for Vaccines:** Adjutants are used in vaccination to enhance the immune response. The safer new subunit vaccines are less effective in immunization and therefore effective adjuvants are required. New developments in the adjuvant area are the emulsion systems. These are oil-in-water emulsions that degrade rapidly in the body. Being in the solid state, the lipid components of SLNs will be degraded more slowly providing a longer lasting exposure to the immune system.

2. **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. Outcomes of these studies have been shown to improve the efficacy of chemotherapeutic drugs, simultaneously reduction in side effects associated with them.

   Improved stability of drugs, encapsulation of chemotherapeutic agents of diversified physico-chemical properties, enhanced drug efficacy, improved pharmacokinetics and less *in-vitro* toxicity are the important features of SLN which make them a suitable carrier for delivering chemotherapeutic drugs.

   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 the musing 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.

a. **SLN as Targeted Carrier for Anticancer drug to Solid Tumor** [28-30, 31]**:** SLN have 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 [27]**.**

b. **SLN in breast cancer and lymph node metastases** [31]**:** Mitoxantrone SLN local injections were formulated to reduce the toxicity and improve the safety and bioavailability of the drug.

3. **Solid Lipid Nanoparticles for delivering Peptides and Proteins** [32]: Solid lipid particulate systems such as solid lipid nanoparticles (SLN), lipid microparticles (LM) andlipospheres 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 fulfil the requirements for an

optimum particulate carrier system. Proteins and antigens intended for therapeutic purposes may be incorporated or adsorbed onto SLN, and further administered by parenteral routes or by alternative routes such as oral, nasal and pulmonary.

Formulation in SLN confers improved protein stability, avoids proteolysis 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. Several local or systemic therapeutic applications may be foreseen, such as immunisation with protein antigens, infectious disease treatment, chronic diseases and cancer therapy [33].

4. **Solid Lipid Nanoparticles for Targeted Brain Drug Delivery [4]:** 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 thereticuloendothelial system. Drug targeting might also be possible by surface modification of solid lipidnanoparticles. SLNs can improve the ability of the drug to penetrate through the blood-brain barrier and is promising drug targeting system for the treatment of central nervous system disorders.

   In a study to overcome the limited access of the drug 5-fluoro-2'-deoxyuridine (FUdR) to the brain, 3',5'-dioctanoyl-5-fluoro-2'deoxyuridine (DO-FUdR) was synthesized and incorporated into solid lipid nanoparticles (DOFUdR-SLN) **[22]**.

   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 physicochemical characteristics are also particularly regarded in order to address the critical issues related to the development of suitable brain targeting formulations [4].

5. **Solid Lipid Nanoparticles for Parasitic Diseases [4, 27, 34]:** Parasitic diseases (like malaria, leishmaniasis, tryanosomiasis) are one of the major problems around the globe. Ant parasitic 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 nanostructure 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.

   Moreover, SLN and NLC due to their particulate nature and inherent structure exhibit good potential in the treatment of parasitic infections. Recent reports including our investigation have validated their utility at least to some extent. However, the need of hour is to undertake extensive investigations on SLN and NLC matrices in order to extend their versatility with respect to encapsulation ability and target ability and to arrive at a versatile, effective and economical approach for the delivery of anti-parasitic drugs.

6. **Solid Lipid Nanoparticles for Ultrasonic drug and Gene Delivery** [4]: Drug delivery research employing micelles and nanoparticles has wide application in ultrasonic drug and gene delivery in recent years. Of particular interest is the use of these nanovehicles that deliver high concentrations of cytotoxic drugs to diseased tissues selectively, thus reducing the agent's side effects on the rest of the body. 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 fromnanocarriers, 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 ofcavitation bubbles.

Liquid emulsions and solid nanoparticles are used with ultrasound to deliver genes *invitro* and *in vivo*. The small packaging allows nanoparticles to extravagate into tumor tissues. Ultrasonic drug and gene delivery from nanocarriers has tremendous potential because of the wide variety of drugs and genes that could be delivered to targeted tissues by fairly non-invasive means [35].

7. **SLN applications for improved delivery of antiretroviral drugs to the brain** [27]: Human immunodeficiency virus (HIV) can gain access to the central nervous system during the early course of primary infection. Once in the brain compartment the virus actively replicates to form an independent viral reservoir, resulting in debilitating neurological complications, latent infection and drug resistance. 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 bloodbrainbarrier (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. By delivering ARVs withnanocarriers, significant increase in the drug bioavailability to the brain is expected to be achieved. Recent studies show that the specificity and efficiency of ARVs delivery can be further enhanced by usingnanocarriers with specific brain targeting, cell penetrating ligands or ABC transporters inhibitors. Future research should focus on achieving brain delivery of ARVs in a safe, efficient, and yet cost-effective manner [27].

8. **SLN applied to the treatment of Malaria** [27]: Despite the fact that we live in an era of advanced technology and innovation, infectious diseases, like malaria, continue to be one of the greatest health challenges worldwide. 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. A number of strategies to deliver antimalarials using nanocarriers and the mechanisms that facilitate their targeting to Plasmodium spp-infected cells are discussed in this review. Taking into account the peculiarities of malaria parasites, the focus is placed particularly on lipid-based (e.g., liposomes, solid lipid nanoparticles and nano and microemulsion) and polymer-based nanocarriers (Nanocapsules and nanospheres) [23].

9. **Targeted delivery of Solid Lipid Nanoparticles for the treatment of Lung Diseases** [4]: Targeted delivery of drug molecules to organs or special sites is one of the most challenging research areas in pharmaceutical sciences. By developing colloidal delivery systems such as liposomes, micelles andnanoparticles a new frontier was opened for improving drug delivery. 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 [36].

10. **Solid Lipid Nanoparticles in Tuberculosis Disease** [4, 27]: SLN have longer stability and better encapsulation efficiency than liposomes and, as opposed to polymeric nanoparticles, the production process involves minimal amounts of organic solvents.

SLN have been used to encapsulate Anti Tubercular Drugs (ATD) and were proved to be successful in experimental tuberculosis. Anti tubercular drugs such as rifampicin, isoniazid, and pyrazinamide SLN systems were able to decrease the dosing frequency and to improve patient compliance. ATD were co-incorporated into SLN to evaluate the potential of these carriers in tuberculosis chemotherapy via the oral route. The finding of this study suggested that SLN have great potential in the delivery of ATD by reducing frequency of doses and improving patient compliance by better management of tuberculosis.

11. **Transfection Agent** [37]: Cationic SLNs for gene transfer are formulated using the same cationic lipid as for liposomal transfection agents. The differences and similarities in the structure and performance between SLN and liposomes were investigated. 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 transfect ion performance than the colloidal structure it is arranged in. Hence, cationic SLN extends the range of highly potent non-viral transfectionagents by one with favorable and distinct technological properties. Combination of cationic SLN with the nuclear localization signal TAT2 increased transfection efficiency hundredfold.

12. **SLN in Cosmetic and Dermatological preparations** [38]: 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. SLN are considered as being the next generation of delivery system after liposomes.[39] Due to the lower risk of systemic side effects topical treatment of skin disease appears favourable, yet the stratum corneum counteracts the penetration of xenobiotics into viable skin. Particulate carrier systems may mean an option to improve dermal penetration. Since epidermal lipids are found in high amounts within the penetration barrier, lipid carriers attaching themselves to the skin surface and allowing lipid exchange between the outermost layers of the stratum corneum and the carrier appear promising. Besides liposomes, solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC) have been studied intensively [40].

    Following the evaporation of water from the lipid nanodispersion applied to the skin surface, lipid particles form an adhesive layer occluding the skin surface. Then hydration of the stratum corneum may increase by which reducing corneocyte packing and widening of the inter-corneocytes gaps can facilitate drug penetration into deeper skin strata. Occlusive effects appear strongly related to particle size. Nanoparticles have turned out 15-fold more occlusive than microparticles, and particles smaller than 400 nm in a dispersion containing at least 35% lipid of high crystallinity has been most potent.

13. **Solid lipid nanoparticles for lymphatic targeting** [4]: The solid lipid nanoparticles (SLN) were developed and evaluated for the lymphatic uptake after intraduodenal administration to rats.

14. **SLN for potential agriculture applications** [41]: 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.

**CONCLUSION:** Solid lipid nanoparticles do not, as proposed, ‘‘combine the advantages of other colloidal drug carriers and avoid the disadvantages of them’’. The results cannot simply be regarded as nanoemulsions with a solid core.

Clear 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 and the possibility to produce carriers with higher encapsulation efficiency.

Disadvantages include low drug-loading capacities, the presence of alternative colloidal structures (micelles, liposomes, mixed micelles, drug nanocrystals), the complexity of the physical state of the lipid (transformation between different modifications) and the possibility of super cooled melts which cause

stability problems during storage or administration (gelation, particle size increase, drug expulsion). Sample dilution or water removal might significantly change the equilibria between the different colloidal species and the physical state of the lipid.

The appropriate characterization of the complex surfactant/lipid dispersions requires several analytical methods in addition to the determination of the particle size kinetic aspects to be taken into account. NMR, ESR and synchrotron irradiation will help the drug nanosuspensions coexist in the sample. Unfortunately, these aspects have not always been considered and the terminus 'drug incorporation' in the SLN literature is often misleading.

In summary, SLN are very complex systems with clear advantages and disadvantages to other colloidal carriers. Further work needs to be done to understand the structure and dynamics of SLN on molecular level *in vitro* and *in vivo* studies.

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**Reviewers Recommendations:**

1. **Figures 3-6 not mentioned in text.**
2. **Check for grammar, spelling and punctuation errors.**
3. **Check references in reference section (Out of format, marked in red).**