SOLID LIPID NANOPARTICLES (SLN): APPROACH AND APPLICATIONS

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ABSTRACT

Solid lipid nanoparticles (SLN) have emerged as a next-generation drug delivery system with potential applications in pharmaceutical field, cosmetics, research, clinical medicine and other allied sciences. Recently, increasing attention has been focused on these SLN as colloidal drug carriers for incorporating hydrophilic or lipophilic drugs. Proteins and antigens intended for therapeutic purposes may be incorporated or adsorbed onto SLN, and further administered by parenteral routes or be alternative routes such as oral, nasal and pulmonary. Therefore SLNs are reaching the goal of controlled and site specific drug delivery system. In this article we discussed the preparation method, characterization, route of administration of SLNs, advantages, different preparation method which are suitable for large scale production and application of SLNs.

KEYWORDS: Solid lipid nanoparticles (SLN).

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 nanoparticles.[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. 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.\textsuperscript{[2]} SLNs are developed as an alternative system for polymeric nanoparticles, liposome and emulsion. SLNs have unique property like small size, large surface area, high drug loading and interaction of phase at the interphase.\textsuperscript{[3]} SLNs are attracting major attention in novel colloidal carrier for intravenous application. SLNs are a new generation of submicron-sized lipid emulsions where the liquid lipid (oil) has been substituted by a solid lipid. SLNs are sub-micron colloidal carrier composed of physiological lipid, dispersed in water or in an aqueous surfactant solution.\textsuperscript{[4]} Solid lipid nanoparticles (SLN) are aqueous colloid-al dispersions, the matrix of which comprises of solid biodegradable lipids.\textsuperscript{[5]} SLNs combine the advantages and avoid the drawbacks of several colloidal carriers of its class such as physical stability, protection of incorporated labile drugs from degradation, controlled release, excellent tolerability.\textsuperscript{[6]} SLN formulations for various application routes (parenteral, oral, dermal, ocular, pulmonary, rectal) have been developed and thoroughly characterized in vitro and in vivo.\textsuperscript{[7]}

\textbf{Advantage}

1. Use of biodegradable physiological lipids which decreases the danger of acute and chronic toxicity and avoidance of organic solvents in production methods.\textsuperscript{[8]}
2. Improved bioavailability of poorly water soluble molecules.\textsuperscript{[9]}
3. SLNs have better stability and ease of upgradability to production scale as compared to liposome.
4. In SLNs the lipid matrix is made from physiological lipid which decreases the danger of acute and chronic toxicity.
5. Very high long-term stability.
6. It is easy to manufacture than bipolymeric nanoparticles.
8. SLNs can be enhancing the bioavailability of entrapped bioactive.
9. Chemical protection of labile incorporated compound.
10. Raw material which are to be required are same as that of emulsion.
11. Large scale production is possible.
12. High concentration of functional compound can be achieved.
13. Lyophilization possible.
Disadvantage
1. Poor drug loading capacity.
2. Drug expulsion after polymeric transition during storage.
3. Relatively high water content of the dispersions (70-99.9%).\cite{10}
4. The low capacity to load hydrophilic drugs due to partitioning effects during the production process.

Preparation of Solid Lipid Nanoparticles
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
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 Presser Homogenization (HPH)
Initially used for the production of solid lipid nanoemulsions, this method is reliable. It involves high pressure homogenization which pushes the liquid with high pressure (100-2000 bar) through a narrow gap ranging a few microns. The fluid accelerates to a very short distance at very high viscosity of over 1000 km/h. Very high shear stress and cavitation forces disrupt the particles down to submicron range. As low as 5% to as high as of 40% lipid content has been investigated. Two general approaches to achieve HPH are hot homogenization and cold homogenization.
A. Hot homogenization is generally carried out at temperatures 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 sizes are obtained at higher processing temperatures because of lowered viscosity of the lipid phase. However, high temperature leads to the degradation rate of the drug and the carrier. Increasing the homogenization temperature or the number of cycles often results in an increase of the particle size due to high kinetic energy of the particles. Generally, 3-5 homogenization cycles at a pressure of 500-1500 bar are used.\textsuperscript{11,12}

B. Cold homogenization has been developed to overcome the temperature related degradation problems, loss of drug into the aqueous phase and partitioning associated with hot homogenization method. Unpredictable polymeric transitions of the lipid due to complexity of the crystallization step of the nanoemulsion resulting in several modifications and/or super cooled melts. Here, drug is incorporated 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. The prepared lipid microparticles are then dispersed in a cold emulsifier solution at or below room temperature. The temperature should be regulated effectively to ensure the solid state of the lipid during homogenization. However, compared to hot homogenization, larger particle sizes and a broader size distribution are typical of cold homogenization samples.\textsuperscript{13}

2. Ultrasonication or High Speed Homogenization
Ultrasonication or high speed homogenization is another method for the production of SLNs. The advantage of this method is that the equipment used is commonly available at lab scale. However, this method suffers from problems such as broader size distribution ranging into micrometer range. Potential metal contaminations, physical instability like particle growth upon storage are other drawbacks associated with this technique.\textsuperscript{14}

3. Solvent Emulsification/Evaporation
For the production of nanoparticle dispersions by precipitation in o/w emulsions, the lipophilic material is dissolved in water-immiscible organic solvent (cyclohexane) that is emulsified in an aqueous phase.\textsuperscript{15} Upon evaporation of the solvent nanoparticle dispersion is formed by precipitation of the lipid in the aqueous medium. The mean diameter of the obtained particles was 25 nm with cholesterol acetate as model drug and lecithin/sodium
glycocholate blend as emulsifier. The reproducibility of the result was confirmed,\textsuperscript{[16]} who produced the cholesterol acetate nanoparticles of mean size 29 nm.

4. Solvent Emulsification-Diffusion
SLNs can also be produced by solvent emulsification-diffusion technique. The mean particle size depends upon lipid concentration in the organic phase and the emulsifier used. 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. Here, the lipid matrix is dissolved in water-immiscible organic solvent followed by emulsification in an aqueous phase. The solvent is evaporated under reduced pressure resulting in nanoparticles dispersion formed by precipitation of the lipid in aqueous medium.\textsuperscript{[17,18]}

5. Supercritical Fluid Technology
This is a novel technique recently applied for the production of SLNs.\textsuperscript{[19]} 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 nanoparticle production such as rapid expansion of supercritical solution (RESS), particles from gas saturated solution (PGSS), aerosol solvent extraction solvent (ASES), supercritical fluid extraction of emulsions (SFEE). The advantages of this technique includes avoidance of the use of solvents, particles obtained as a dry powder, instead of suspensions, requires mild pressure and temperature conditions. Carbon dioxide solution is the good choice as a solvent for this method.\textsuperscript{[20]}

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 (polysorbate20, polysorbate 60, soy phosphatidylcholine, and sodium taurodeoxycholate), co-emulsifiers(sodium monooyctylphosphate) and water. The hot microemulsion is dispersed in cold water (2-3°C) under stirring. Typical volume ratios of the hot microemulsion to cold water are in the range of 1:25 to 1:50. The dilution process is critically determined by the composition of the microemulsion. According to the literature, the droplet structure is already contained in the microemulsion and therefore, no energy is required to achieve submicron particle sizes. Fessi produced polymer particles by dilution of polymer solutions in water.
According to,\textsuperscript{[21]} the particle size is critically determined by the velocity of the distribution processes.

Nanoparticles were produced only with solvents which distribute very rapidly into the aqueous phase (acetone), while larger particle sizes were obtained with more lipophilic solvents. The hydrophilic co-solvents of the microemulsion play a similar role in formation of lipid nanoparticles as acetone for formation of polymer nanoparticles.

7. Spray Drying
It is an alternative technique to lyophilization in order to transform an aqueous SLN dispersion into a drug product. This is a cost-effective method than lyophilization and recommends the use of lipid with melting point $>$70$^\circ$C. This method causes particle aggregation due to high temperature shear forces and partial melting of the particle. According to Freitas and Mullera\textsuperscript{[22]} best results were obtained with SLN concentration of 1\% in a solution of trehalose in water or 20\% trehalose in ethanol-water mixtures (10/90 v/v).

8. Double Emulsion
In this method, 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\textsuperscript{[23]} prepared solid lipid nanoparticles loaded with bovine serum albumin (BSA) using double emulsion method.

9. 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.\textsuperscript{[24]}

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.\textsuperscript{[24]}
Drug Release from SLn

There are mainly three drug incorporation models which describe the incorporation of drug into SLN\(^{[25]}\)

1. Homogenous matrix model.
2. Drug enriched shell, core shell model.
3. Drug enriched core, core shell model.

Homogenous matrix model or solid solution model with drug being present in amorphous clusters or molecularly dispersed is mainly obtained when incorporating highly lipophilic drugs into SLN with using hot homogenization technique or applying cold homogenization method or by avoiding potentially drug solubilizing surfactants. In the cold homogenization technique the drug (in molecularly dispersed form) is dispersed in bulk of melted lipid, then the mechanical force of high pressure homogenization leads to the breakdown of molecular form to nanoparticles and giving rise to homogenous matrix. Etomidate SLN represents the homogenization matrix model.

The drug enriched shell with core shell model will be obtained when performing the production. During the production, the drug partitioned to water phase. Upon cooling, the lipid precipitates first, forming a practically drug free lipid core due to phase separation. At the same time, the drug re-partitions into the remaining liquid-lipid phase and drug concentration in the outer shell increasing gradually. Finally drug enriched shell crystallizes as depicted. The amount of drug partitioning to the aqueous phase will increases with the increase of solubility of drug in the aqueous phase. Mainly two factors, increasing temperature of the aqueous phase and increasing surfactant concentration, are increasing the saturation solubility of drug in water phase. Tetracaine SLN were prepared by hot HPH shows drug enriched shell model.

A drug enriched core obtained when dissolving a drug (e.g. glimepiride) in the lipid melts at or close to its saturation solubility. In this model, cooling of the formed nanoemulsion will lead to supersaturation of drug in melted lipid and it further leads drug precipitation prior to lipid precipitation. Further cooling will lead to precipitation of lipid surrounding the drug enriched core as a membrane. Due to increased diffusional distance and hindering effect of surrounding solid lipid shell, the carrier system shows sustained release profile.
Characterization of SLNs

Characterization of the SLNs is necessary for its quality control. Characterization of SLN is a serious challenge due to the colloidal size of the particles and the complexity and dynamic nature of the delivery system. Parameter which are to be evaluated: Particle size, zeta potential, drug release, surface morphology. Polymorphism, degree of crystallinity, time scale of distribution processes.

Particle Size and Zeta Potential

There are so many techniques for the particle size and zeta potential (size distribution) like photon correlation spectroscopy (PCS), transmission electron microscopy (TEM), scanning electron microscopy (SEM), atomic force microscopy (AFM), scanning tunneling microscopy (STM) or freeze fracture electron microscopy (FFEM). For the routine measurement of particle size Photon correlation spectroscopy (PCS) and laser diffraction (LD) are important techniques used. Coulter counter are rarely used to measure particle size because of difficulties in the assessment of small nanoparticle. Photon correlation spectroscopy (PCS) is not able to detect larger microparticles. Difficulties may arise both in PCS and LD measurements for samples which contain several populations of different size. Therefore, additional techniques might be useful like light microscopy it gives fast indication of the presence and character of microparticles. Electron microscopy provides, in contrast to PCS and LD, direct information on the particle shape. However, the investigator should pay special attention to possible artifacts which may be caused by the sample preparation. For example, solvent removal may cause modifications which will influence the particle shape. Zeta potential is an important product characteristic of SLNs since its high value is expected to lead to deaggregation of particles in the absence of other complicating factors such as steric stabilizers or hydrophilic surface appendages. It is usually measured by zetameter.

Static Light Scattering/Fraunhofer Diffraction

The method is fast and rugged, but requires more cleanliness than DLS, and advance knowledge of the particles’ optical qualities 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.
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. 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 submicrometer particles.\textsuperscript{[26]}

Electron Microscopy

Scanning electron microscopy (SEM) and transmission electron microscopy (TEM) provide a way to directly observe nanoparticles and physical characterization of nanoparticles. TEM has a smaller size limit of detection, is a good validation for other methods and one must be cognizant of the statistically small sample size and the effect that vacuum can have on the particles.\textsuperscript{[29]}

Nuclear Magnetic Resonance (NMR)

NMR is used to determine both size and nature of nanoparticles. The selectivity afforded by chemical shift complements the sensitivity to molecular mobility to provide information on the physicochemical status of components within the nanoparticle.

Atomic Force Microscopy (AFM)

In this technique, a probe tip with atomic scale sharpness is kept 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.\textsuperscript{[29]} That ultrahigh resolution is obtainable with this approach, which along with the ability to map a sample according to properties in addition to size.

Acoustic Methods

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.

**X-Ray Diffraction and Differential Scanning Calorimetry (DSC)**

The geometric scattering of radiation from crystal planes within a solid allows the presence or absence of the former to be determined thus permitting the degree of crystallinity to be assessed. DSC can be used to determine the nature and speciation of crystallinity within nanoparticles through the measurement of glass and melting point temperatures and their associated enthalpies.\(^\text{[27]}\)

**Advantage**

1. Very high long-term stability.
2. It is easy to manufacture than bipolymeric nanoparticles.

**Disadvantage**

1. Poor drug loading capacity.\(^\text{[28]}\)
2. Relatively high water content of the dispersions (70-99.9\%)\(^\text{[29]}\)
3. The low capacity to load hydrophilic drugs due to partitioning effects during the production process.\(^\text{[30]}\)

**Routes of Administration and Their Biodistribution**

The *in vivo* behavior of the SLN particles will mainly depend on the following points: 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.\(^\text{[31; 32]}\)

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. Parenteral application 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 behavior 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\[^{33,34,40}\]
There are several potential applications of SLNs some of which are given below

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

A) SLN as targeted carrier for anticancer drug to solid tumor

SLN have been 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.

B) 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.

3. 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. 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 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. Several local or systemic therapeutic
applications may be foreseen, such as immunisation with protein antigens, infectious disease treatment, chronic diseases and cancer therapy.\cite{39}

4. Solid Lipid Nanoparticles for Targeted Brain Drug Delivery\cite{40}

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. 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).\cite{41}

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.\cite{40}

5. Solid Lipid Nanoparticles for Parasitic Diseases\cite{40,33,42}

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, thereason 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. 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 inorder 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**[^40]

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 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*. The small packaging allows nanoparticles to extravasate 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.[^43]

7. **SLN Applications for Improved Delivery of Antiretroviral Drugs to the Brain**[^33]

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 blood-brain barrier (BBB) and blood-cerebrospinal fluid barrier (BCSFB). 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 endocytic pathways and inhibit the ATP-binding cassette (ABC) transporters expressed at the barrier sites. By delivering ARVs with nanocarriers, significant increase in

[^40]: Reference for solid lipid nanoparticles
[^33]: Reference for SLN applications for improved delivery of antiretroviral drugs to the brain
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 using nanocarriers 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.\[33\]

8. SLN Applied to the Treatment of Malaria\[33\]
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 malarial parasites, the focus is placed particularly on lipid-based (e.g., liposomes, solid lipid nanoparticles and nanoand microemulsions) and polymer-based nanocarriers (Nanocapsules and nanospheres).\[44\]

9. Targeted Delivery of Solid Lipid Nanoparticles for the Treatment of Lung Diseases\[40\]
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 and nanoparticles 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.\[45\]

10. Solid Lipid Nanoparticles in Tuberculosis Disease\[40,33\]
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. Antitubercular 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\cite{46}
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 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.

12. SLN in Cosmetic and Dermatological Preparations\cite{47}
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\cite{41}. Due to the lower risk of systemic side effect, 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\cite{42}. Following the evaporation of water from the lipid nano dispersion 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-corneocyte 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

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

14. SLN for Potential Agriculture Applications

Essential oil extracted from *Artemesia arborea sens L* when incorporated into SLN, were able to reduce the rapid evaporation compared with emulsions and the systems have been used in agriculture assuitable carrier of safe pesticides.

CONCLUSION

SLN as colloidal drug carrier combines the advantage of polymeric nanoparticles, fat emulsions and liposome; due to various advantages, including feasibility of incorporation of lipophilic and hydrophilic drugs, improved physical stability, low cost, ease of scale-up, and manufacturing. SLNs are prepared by various advanced techniques. The site specific and sustained release effect of drug can better achieved by using SLNs. Nanoparticles have been used extensively for applications in drug discovery, drug delivery, and diagnostics and for many others in medical field. They are relatively novel drug delivery systems, having received primary attention from the early 1990s and future holds great promise for its systematic investigation and exploitation. We can expect many patented dosage forms in the form of SLNs in the future.

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