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Review Article

A Review: Solid Lipid Nanoparticle A Potential Drug Delivery Carrier

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ABSTRACT
Solid Lipid Nanoparticle (SLN) have emerged as potential drug delivery system with wide application in the several fields including pharmaceutical, cosmetics, research along with other allied sciences. The prime use of SLN in several fields is as colloidal drug carriers for incorporation of several hydrophilic and lipophilic drugs including proteins and antigens. The several routes of drug administration like parentral routes along with oral, nasal and pulmonary has been utilized for further administration of SLN along with drug. Specially, proteins and antigens with therapeutics purposes may be incorporated or adsorbed onto SLN. The several problems related with conventional chemotherapy may be partially overcome with the encapsulation of them as SLN. This present review largely deals with advantages, method of production and characterization along with applications of SLN in several areas.

Key words: Solid lipid Nanoparticle, Carrier, Nanotechnology.

1. INTRODUCTION

The one of the challenging research area in the pharmaceutical sciences is to deliver drug molecule to specific organ sites for targeted delivery. For this purpose several colloidal delivery systems including liposomes, micelles and nanoparticles have been utilized in the improvement of drug delivery. Nanoparticles are solid colloidal particles having size from 10 to 1000 nm in which the active moieties are dissolved, entrapped and or to which the active material is adsorbed. Recent years the research has been focus especially on delivery of large macromolecules like proteins or genes to cells along with tissues. Other advantages of it include the prevention of macromolecules from the enzymatic degradation. There are several advantages of nanoparticles as drug delivery systems are that they are biodegradable, non toxic along with their ability to remain stable for longer period of time. Since, a decade trails are being made to use solid lipid nanoparticles as alternative drug delivery system to colloidal drug delivery system like lipid emulsions, liposomes along with polymeric nanoparticles. SLN combines the advantages of several colloidal carriers along with the avoidance of some disadvantages. SLN has potential application in improvement of drug bioavailability of drugs like cyclosporine A along with to obtain sustained release of lipophilic drugs like camptothecin [1-4].

Solid lipid nanoparticles are aqueous colloidal dispersions including matrix of solid biodegradable lipids. This system provides several advantages like physical stability, protection of incorporated labile drugs from degradation, controlled release along with excellent tolerability. SLN can be administered via various routes including parentral, oral, dermal, ocular, pulmonary along with rectal too[5-7].

2. ADVANTAGES OF SLN

- It consists of biodegradable physiological lipids which diminishes the danger of acute along with chronic toxicity as well as avoidance of organic solvents in production methods.
- It improved the bioavailability of poorly water soluble drugs along with gives site specific delivery of drugs as well as enhanced drug penetration inside the skin via dermal application.
- It also provides protection of chemically labile agents from degradation inside the guts along with sensitive molecules from outer environment.
- It shows better stability as compared to liposomes and it also includes inclusion of high concentration of functional compound.

3. DISADVANTAGES OF SLN

- It suffer from poor drug loading capacity
- The drug which has been entrapped may show expulsion after polymeric transition during storage.
- It generally consists of high water content of the dispersions (70% to 99.9%) [8-10].

4. METHOD OF PREPARATION

4.1 High shear homogenization

Initially utilized for the production of solid lipid nanoemulsions, consist of the high pressure homogenization which pushes the liquid with high pressure (100 to 2000 bar) via a narrow gap ranging a few microns. The fluid accelerates to a very short distance at very high viscosity of over 1000 km/h along with inclusion of 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 and there are two general approaches to achieve HSH. The first one is hot homogenization and second is cold homogenization. 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 as shown in fig 1 and 2.

Cold homogenization has been induced to overcome the temperature related degradation problems along with loss of drug into the aqueous phase as well as partitioning associated with hot homogenization method.

Unpredictable polymeric transitions of the lipid due to complexity of the crystallization step of the nanoemulsions results in production of several modifications and/or super cooled melts.

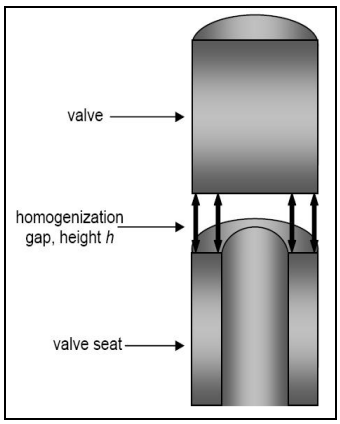

Figure 1: The geometry of the homogenization valve (valve and valve seat) and the resulted homogenization gap between them.

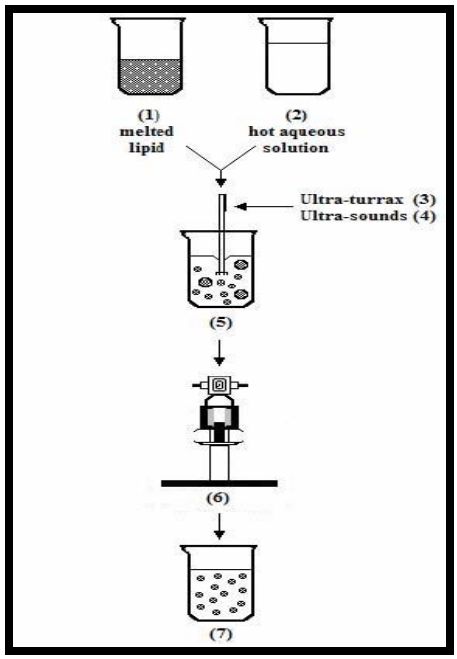

Figure 2: Schematic representation of the production of lipid nanoparticles by hot HPH method.

Here, drug is incorporated into melted lipid and the lipid melt is cooled rapidly with the help of 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 along with that the temperature should be regulated effectively for assurance of the solid state of the lipid during homogenization as shown in fig 3.

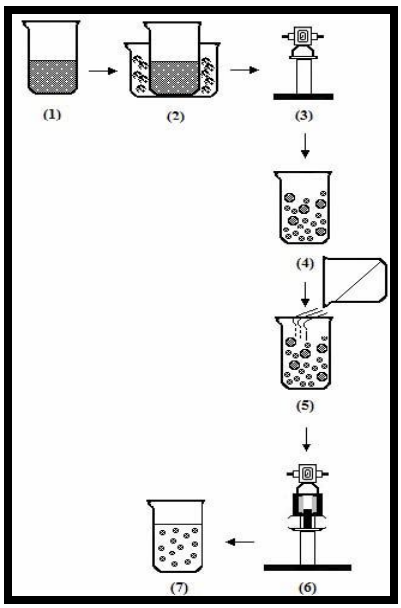

Figure 3: Schematic representation of the production of lipid nanoparticles by cold HPH method.

4.2 Ultrasonication

Ultrasonication or high speed homogenization is other method for the generation of SLNs. The advantage of this method is that the equipment utilized is commonly available at lab scale. But, this method suffers from problems like broader size distribution ranging inside micrometer range along with Potential metal contaminations; physical instability including particle growth upon storage is other drawbacks related with this technique.

4.3 Microemulsion based SLN preparation

Gasco and coworkers (1997) developed SLNs depend on the dilution of microemulsions. These are produced by stirring an optically transparent mixture at 65-70°C which is generally composed of a low melting fatty acid such as stearic acid, an emulsifier (e.g. polysorbate 20, polysorbate 60, soyaphosphatydylcholine along with taurodeoxycholic acid sodium salt), co-emulsifiers (e.g. butanol, sodium monooctylphosphate) and water. The hot microemulsion is dispersed inside cold water (2-3°C) under stirring. Typical volume ratios of the hot microemulsion to that of the cold water are in the range of 1:25 to 1:50. The dilution process is critically determined with the help of the composition of the microemulsion. The SLN dispersion can be utilized as granulation fluid for transferring in to solid product such as tablets and pellets through granulation process, however in case of low particle content too much of water required to be removed. The nanoparticles were generated only with solvents which distribute very rapidly inside the aqueous phase (acetone), while larger particle sizes were produced with more lipophilic solvents as shown in fig. 4.

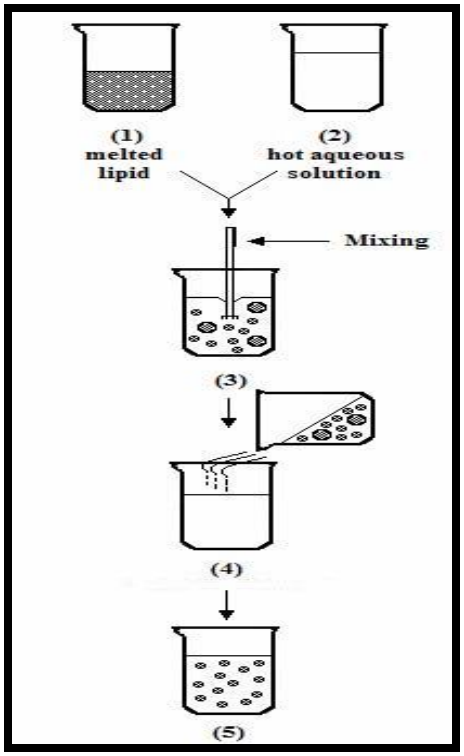

Figure 4: Schematic representation of the production of lipid nanoparticles via microemulsions.

4.4 Supercritical Fluid technology

This is a novel technique now a day's utilized for the production of SLNs. A fluid is called as supercritical when its pressure along with temperature exceed their respective critical value along with that the ability of the fluid to get dissolve compounds enhances. This technology consist of several processes for nanoparticle production like rapid expansion of supercritical solution (RESS), particles obtained from gas saturated solution (PGSS), aerosol solvent extraction solvent (ASES) and supercritical fluid extraction of emulsions (SFEE). The several advantages of this technique involves avoidance of the utilization of solvents, particles obtained as a dry powder, instead of suspensions, needs mild pressure along with temperature conditions. Carbon dioxide solution is the excellent choice as a solvent for such type of method [11-21].

4.5 Solvent emulsification/evaporation

For the generation of nanoparticle dispersions via precipitation in o/w emulsions, the lipophilic component is dissolved in water-immiscible organic solvent (cyclohexane)

which get emulsified in an aqueous phase. Upon evaporation of the solvent nanoparticle dispersion is produced by precipitation of the lipid in the aqueous medium; however the mean diameter of the obtained particles was 25 nm in the case of cholesterol acetate as model drug along with lecithin/sodium glycocholate blend apply as emulsifier. The reproducibility of the result was confirmed by Siekmann and Westesen (1996), who generated the cholesterol acetate nanoparticles having mean size of 29 nm. The method is generally done as shown in fig.No. 5.

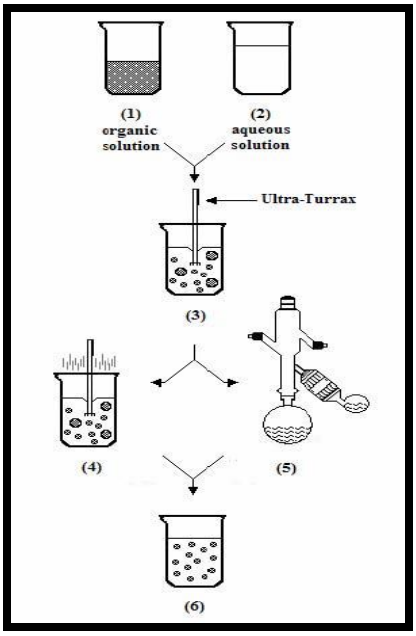

Figure 5: Schematic representation of the production of lipid nanoparticles by solvent emulsification-evaporation method.

4.6 Solvent emulsification-diffusion

SLNs can also be generated through solvent emulsification-diffusion technique. The mean particle size based upon lipid concentration inside the organic phase along with the emulsifier used. Particles with average diameters of 30-100 nm can be generated by application of this technique. The heat is not be used during the preparation is the most important advantage of this technique. [22-33] In this method the lipid matrix is dissolved in water-immiscible organic solvent followed by emulsification in an aqueous phase along with that the solvent is evaporated under reduced pressure result in formation of nanoparticles dispersion via precipitation of the lipid in aqueous medium as shown in fig. no.6.

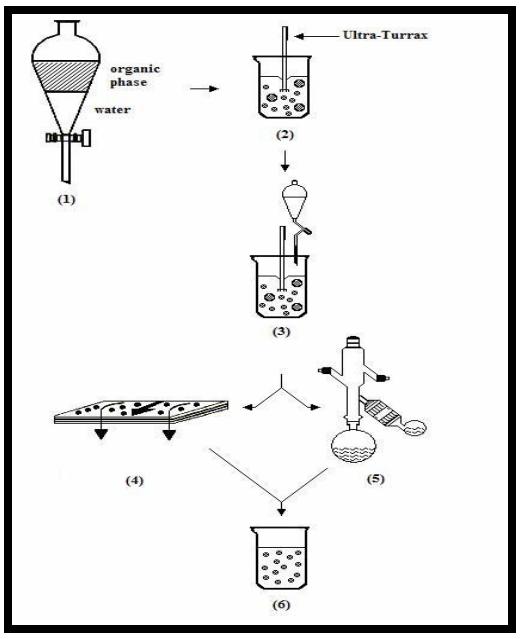

Figure 6: Schematic representation of the production of lipid nanoparticles by emulsification-diffusion method.

4.7 Double Emulsion

This method involved drug which 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. Li et al. (2010) prepared solid lipid nanoparticles consist of active of bovine serum albumin (BSA) with the help of double emulsion method [34-39].

4.8 Spray Drying

Spray drying is an alternative method to lyophilization in order to transform an aqueous SLN dispersion into a drug product. This technique is a cost-effective as compared to lyophilization along with that it recommends the use of lipid with melting point >70°C. This method induces particle aggregation because of high temperature shear forces and partial melting of the particle. According to Freitas and Mullera (1998) best results were produced with SLN concentration of 1% in a solution of trehalose in water or 20% trehalose in ethanol-water mixtures (10/90 v/v).

4.9 Solvent injection technique

In this method the solid lipid is dissolved in water miscible solvent along with that the lipid solvent mixture is injected into stirred aqueous phase with or without surfactant. At last the dispersion filtered to remove excess lipid. Emulsion

within the aqueous phase helps to induce lipid droplets at the site of injection as well as stabilize SLNs until solvent diffusion gets completed. Mishra et al. (2010) prepared and evaluated SLNs with the help of Solvent injection method for delivery of Hepatitis B surface antigen for vaccination utilizing subcutaneous route [40-45].

5. CHARACTERIZATION OF SLN's

Adequate along with proper characterization of the SLNs is need for its quality control. But the characterization of SLN is a serious challenge because of the colloidal size of the particles and the complexity along with dynamic nature of the delivery system. The vital parameters evaluated for the SLNs involves particle size, size distribution kinetics (zeta potential), degree of crystalinity along with lipid modification (polymorphism), coexistence of additional colloidal structures (micelles, liposome, super cooled melts, drug nanoparticles), time scale of distribution processes, drug content, in-vitro drug release and at last surface morphology.

5.1 Particle size and Zeta potential

The physical stability of SLNs is based on their particle size. Photon correlation spectroscopy (PCS) along with laser diffraction (LD) is the most powerful techniques for determination of particle size. PCS (also known as dynamic light scattering) utilized for the measurement of the fluctuation of the intensity of the scattered light, which is induced by particle movement. The particle size determination via photon correlation spectroscopy (PCS) which detects the size range of 3nm to 3µm along with laser diffraction in size range of 100 nm to 180 µm. Although PCS is a good technique to characterize nanoparticles, but it have ability for the detection of larger microparticles. The LD method is depend on the diffraction angle on the particle size. Smaller particles cause large intense scattering at high angles as compared to the larger ones.

Zeta potential measurement can be done by utilizing zeta potential analyzer or zetameter. Prior to measurement, SLN dispersions are diluted 50-fold with the original dispersion preparation medium for size determination along with that of zeta potential measurement. Larger value of zeta potential may lead to deaggregation of particles in the absence of other complicating factors like steric stabilizers or hydrophilic surface appendages. A zeta potential measurement is capable of assurance about the storage stability of colloidal dispersions.

5.2 Electron microscopy

Scanning electron microscopy (SEM) along with transmission electron microscopy (TEM) provides way to directly observe nanoparticles. SEM is generally better for morphological examination while TEM has a small size limit of detection.

5.3 Atomic force microscopy (AFM)

This method involves the probe tip with atomic scale sharpness is rastered across a sample to produce a topological map depend on the forces at play between the tip and the surface. The probe can be dragged across the sample (contact mode), along with that it allowed to hover just above (non contact mode), with the exact nature of the particular force employed helping to distinguish among the sub techniques. That ultra-high resolution is obtainable with this technique, which along with the capability to map a sample according to properties in addition to size, e.g., colloidal attraction along with resistance to deformation, makes AFM a vital tool.

5.4 Dynamic light scattering (DLS)

It is also called as PCS or quasi-elastic light scattering (QELS) records the differentiation in the intensity of scattered light on the microsecond time scale. This variation induced from interference of light scattered via individual particles under the coverage of Brownian motion, along with that it is quantified by compilation of an autocorrelation function. The benefits of the method are the speed of analysis, lack of required calibration along with sensitivity to submicrometer particles.

5.5 Differential scanning calorimetry (DSC)

DSC along with powder X-ray diffractometry (PXRD) is performed for the determination of the degree of crystalinity of the particle dispersion while the rate of crystalinity utilizing DSC is estimated by comparison of the melting enthalpy/g of the bulk material to that of the melting enthalpy/g of the dispersion.

5.6 Acoustic methods

The acoustic spectroscopy involves the measurement of the attenuation of sound waves as a means of determining size via the fitting of physically relevant equations. In addition, the oscillating electric field produced by the movement of charged particles under the impact of acoustic energy can be detected to give information on surface charge.

5.7 Nuclear magnetic resonance (NMR)

NMR can be applying for the determination of both the size and the qualitative nature of nanoparticles. The selectivity provided by chemical shift complements the sensitivity to that of molecular mobility to give information on the physicochemical status of components within the nanoparticle.

5.8 Static light scattering (SLS)

It involves the studies regarding the pattern of light scattered from a solution of particles is collected as well as fit to fundamental electromagnetic equations in which size is the primary variable. It is quick and rugged method; however it requires more cleanliness than DLS, and advance knowledge of the particles' optical qualities [46-50].

6. APPLICATIONS OF SLN's

6.1 SLN for Parentral Application

Wissing et al. (2004) largely reviewed parentral application of SLN. SLN are very useful for systemic delivery due to their ability for physiologically well-tolerated ingredients and they have good storage capabilities later to that of lyophilization and/or sterilization. When injected intravenously, SLN are sufficiently small to get circulate in the microvascular system along with it prevents macrophage uptake in case of hydrophilic coating. Hence, SLN have been suggested for viral along with non-viral gene delivery. Cationic SLN has been demonstrated to bind genes directly through electrostatic interactions, and have potential profits in targeted gene therapy in treatment of cancer. The charge of particles can also be modulated through the composition, thus allowing binding of oppositely charged molecules.

Treatment of central nervous system diseases like brain tumors, AIDS, neurological and psychiatric disorders is generally constrained by the inability of potent drugs to pass blood brain barrier (BBB). Hydrophilic coating of colloids enhances the transport of these via BBB along with tissue distribution. Fundaro et al, 2000, prepared doxorubicin loaded stealth along with non-stealth SLN and observed that the stealth nanoparticles were present in blood at larger concentrations than non-stealth SLN after 24 h following intravenous administration.

6.2 SLN for Nasal Application

Nasal administration was a vital alternative noninvasive route of drug administration because of fast absorption and rapid onset of drug action, avoiding degradation of labile drugs (like peptides and proteins) in the GI tract along with insufficient transport across epithelial cell layers. To get enhanced drug absorption through the nasal mucosa, approaches like formulation development along with prodrug derivatization have been employed. SLN has been proposed as alternative transmucosal delivery systems regarding macromolecular therapeutic agents along with diagnostics by various research groups. In a recent study, coating polymeric nanoparticles to that of PEG gave promising results as vaccine carriers. The role of PEG coating of polylactic acid nanoparticles in enhancement of the transmucosal transport of the encapsulated bioactive molecule showed to be successful by Tobio et al, 1998. This concept can be applied for solid lipid nanoparticles.

6.3 SLN for Respiratory Application

The lungs having high surface area for drug absorption by inhibiting first-pass effects. Rapid drug absorption via aerosolization of drugs (in the 1-3 μm size range) induces since the walls of alveoli in the deep lung are extremely thin. Lymphatic drainage plays a vital role in the uptake of particulates in the respiratory system. SLN can be utilized as carriers of anti-cancer drugs in lung cancer treatment or peptide drugs to enhance their bioavailability. Assessment of inhaled radio-labeled SLN bio distribution has been given and the data showed an important along with significant uptake of the radio-labeled SLN inside the lymphatic after inhalation. The recent study reported the antitubercular drugs (like rifampicin, isoniazid and pyrazinamide) were incorporated into several formulations of solid lipid particles having range from 1.1–2.1 μm along with that formulations were nebulized to guinea pigs via mouth for direct pulmonary delivery. Nebulization of solid lipid particles carrying antitubercular drugs was observed to be successful in enhancement of drug bioavailability along with reduction of the dosing frequency for excellent management of pulmonary tuberculosis.

6.4 SLN for Ocular Application

Ocular drug administration through SLN has been reported several times and bio-compatibility along with mucoadhesive properties of SLN enhances their interaction with ocular mucosa and prolongs corneal residence time of the drug, with the object of ocular drug targeting. Cavalli et al., (2002) evaluated SLN as carriers for ocular delivery related to tobramycin inside rabbit eyes. As a result SLN significantly improves the drug bioavailability in the aqueous humor. Cavalli et al., (1995) also studied pilocarpine loaded SLN, which is commonly utilized in glaucoma treatment, earlier. They reported very same results in order to improve the ocular bioavailability of drug.

6.5 SLN for Rectal Application

A few reports are majorly focused on the rectal drug administration through SLN in the literature. Sznitowska et al., 2001 prepared diazepam loaded SLN for rectal administration in order to give a rapid action. They applied SLN dispersions on rabbits along with performed bioavailability studies. They found that lipid matrix which is generally solid at body temperature is not a profitable system for diazepam rectal delivery. They decided to apply lipids which melt around body temperature in their next experiments. This area seems very open to investigation, especially when the profits of rectal route are taken into consideration. PEG coating seems to be a promising tool on rectal delivery along with enhancement of bioavailability.

6.6 SLN for Topical application

SLN and NLC are very vital colloidal carrier systems regarding skin applications due to their various desirable effects on skin besides the characteristics of a colloidal carrier system. They are well suited for application on damaged or inflamed skin due to their dependence on non-irritant along with non-toxic lipids. Researchers have reported largely on the topical application of SLN. During the last few years, SLN and NLC have been studied with active compounds like Vitamin E, tocopherol acetate, retinol, ascorbyl palmitate, clotrimazole, triptolide, phodphyllotoxin and a nonsteroidal antiandrogen RU 58841 regarding topical application. A completely new, recently discovered section of application is the application of SLN in sun-protective creams.

6.7 SLN in Cancer chemotherapy

From the last two decades major chemotherapeutic agents have been encapsulated in SLN and their in-vitro along with in-vivo efficacy have been evaluated. Tamoxifen, an anticancer drug have been incorporated in SLN to delay the release of drug following i.v. administration in breast cancer. Tumor targeting has been achieved by SLN loaded with drugs such as methotrexate and camptothecin. Metoxantrone SLN local injections were formulated to deduce the toxicity along with improves the safety and bioefficacy of the drug in treating breast cancer as well as lymph node metastases [51-59].

6.8 Oral SLN in antitubercular chemotherapy

Antitubercular drugs like rifampsin, isoniazide, pyrazinamide-loaded SLN systems were able to deduce the dosing frequency and improve patient compliance. Antitubercular drugs loaded SLNs were prepared by utilizing the solvent diffusion technique.

6.9 SLN for potential agriculture application

Essential oil extracted to that from *Artemisia arborescens* L. when incorporated in SLN, were able to deduce the rapid evaporation compared to that of emulsions and the systems have been utilized in agriculture as a suitable carrier of ecologically safe pesticide [60-61].

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