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Solid Lipid Nanoparticles (SLN's): A Promising Drug Delivery Approach

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ABSTRACT

Solid lipid nanoparticles (SLN) have emerged as a next-generation drug delivery system with potential applications in the 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. The obstacles associated with conventional chemotherapy may be partially overcome by encapsulating them as SLN. The present review focuses on the utility of SLN in terms of their advantages, production methodology, characterization, and applications. If properly investigated, SLN's may open new vistas in the therapy of complex diseases.

INTRODUCTION

Solid lipid nanoparticles (SLN's) 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 the 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 an aqueous surfactant solution. Generally, they are made of the 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.[2] SLN's are developed as an alternative system for polymeric nanoparticles, liposome, and emulsion. SLN's have the unique property of the small size, large surface area, high drug loading and interaction of phase at the interphase.[3] SLN's are attracting major attention in the novel colloidal carrier for intravenous application. SLN's are a new generation of submicron-sized lipid emulsions where the liquid lipid (oil) has been substituted by a solid lipid. SLN's are sub-micron colloidal carrier composed of physiological lipid, dispersed in water or in an aqueous surfactant solution.[4] Solid lipid nanoparticles (SLN) are aqueous colloidal dispersions, the matrix of which comprises of solid biodegradable lipids.[5] SLN's 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.[6] SLN formulations for various application routes (parenteral, oral, dermal, ocular, pulmonary, rectal) have been developed and thoroughly characterized in vitro and *in vivo*.[7]

ADVANTAGES OF SOLID LIPID NANOPARTICLES (SLN's)

- Use of biodegradable physiological lipids which decreases the danger of acute and chronic toxicity and avoidance of organic solvents in production methods [8]
- Improved bioavailability of poorly water soluble molecules [9]
- Site specific delivery of drugs, enhanced drug penetration into the skin via dermal application

- The possibility of scaling up.
- Protection of chemically labile agents from degradation in the gut and sensitive molecules from outer environment
- SLN's have better stability compared to liposomes
- Enhance the bioavailability of entrapped bioactive and chemical production of the labile incorporated compound.
- High cc ncentration of functional compound achieved.
- Lyophilization possible

DISADVANTAGES OF SOLID LIPID NANOPARTICLES (SLN's)

- Poor drug loading capacity,
- Drug expulsion after polymeric transition during storage
- Relatively high water content of the dispersions (70-99.9%) [10]

AIMS OF SOLID LIPID NANOPARTICLES (SLN's) [11,12]

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

PREPARATION OF SOLID LIPID NANOPARTICLES (SLN's)

SLN's are prepared from lipid, emulsifier and water/solvent by using different methods and are discussed below.

METHODS OF PREPARATION OF SOLID LIPID NANOPARTICLES (SLN's)

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 SLN's. High-pressure homogenizers push a liquid with high pressure (100–2000 bar) through a narrow gap (in the range of a few microns). The fluid accelerates on a very short distance to very high velocity (over 1000 Km/h). Very high shear stress and cavitation forces disrupt the particles down to the sub-micron 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 the 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 the high kinetic energy of the particles. [13,14]

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 nanoemulsion 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. [15]

Advantages

- Low capital cost.
- Demonstrated at lab scale.

Disadvantages

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

2. Ultrasonication/high-speed homogenization

SLN's 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. [16]

3. Solvent evaporation

SLN's can also prepare 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 bar).

Advantages

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

Disadvantages

- Extremely energy intensive process.
- Polydisperse distributions.

- Biomolecule damage. [17]

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.

Advantages

- Reduced shear stress.

Disadvantages

- Potential metal contamination.
- Physical instability like particle growth upon storage. [18,19]

5. Supercritical Fluid Technology

This is a novel technique recently applied for the production of SLN's.[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 include 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.[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 mono octyl phosphate) and water. The hot micro emulsion is dispersed in cold water (2-3°C) under stirring. Typical volume ratios of the hot micro emulsion to cold water are in the range of1:25 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,[21] the particle size is critically determined by the velocity of the distribution processes.

7. Spray drying method

It is an alternative technique to the lyophilization process. This recommends the use of lipid with the melting point more than 70^0C. The best results were obtained with SLN concentration of 1% in a solution of trehalose in water or 20% trehalose in the 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 the diffuser, at last, the SLN with the little and uniform particle size is formed.

DRUG RELEASE FROM SOLID LIPID NANOPARTICLES (SLN's)

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 the 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 homogeneous 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 the water phase. Upon cooling, the lipid precipitates first, forming a practical 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 increase with the increase of solubility of the drug in the aqueous phase. Mainly two factors, increasing temperature of the aqueous phase and increasing surfactant concentration, are increasing the saturation solubility of the drug in the 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 SOLID LIPID NANOPARTICLES (SLN's)

Characterization of the SLN's 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. The parameter which is to be evaluated: Particle size, zeta potential, drug release, surface morphology. Polymorphism, a 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). F or the routine measurement of particle size Photon correlation spectroscopy (PCS) and laser diffraction (LD) are important techniques used. Coulter counter is 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 size29. Therefore, additional techniques might be useful like light microscopy it gives the 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 SLN's since its high value is expected to lead to disaggregation of particles in the absence of other complicating factors such as steric stabilizers or hydrophilic surface appendages. It is usually measured by zettameter.

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 the 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, the 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.[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.[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 (non-contact mode), with the exact nature of the particular force employed serving to distinguish among the sub techniques.[29] That ultra-high resolution is obtainable with this approach, which along with the ability to map a sample according to properties in addition to size.

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.[27]

Rheology

Rheological measurements of formulations can perform by Brookfield Viscometer, using a suitable spindle number. The viscosity depends on the dispersed lipid content.As the lipid content increases, the flow becomes non-Newtonian from Newtonian.

Dialysis tubing

In vitro drug release could be achieved using dialysis tubing. The solid lipid nanoparticle dispersion is placed in pre-washed dialysis tubing which can be hermetically sealed. The dialysis sac then dialyzed against a suitable dissolution medium at room temperature; the samples are withdrawn from the dissolution medium at suitable intervals, centrifuged and analyzed for the drug content using a suitable analytical method.

Reverse dialysis

In this technique, a number of small dialysis sacs containing 1 mL of dissolution medium are placed in SLN dispersion. The SLN's are then displaced into the medium

APPLICATIONS OF SOLID LIPID NANOPARTICLES (SLN's) [3,4,8,11,23,28,30,32]

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 SLN's 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 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 has been to be used 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. The formulation in SLN confers improved protein stability, avoids proteolytic degradation, as well as the 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 immunization with protein antigens, infectious disease treatment, chronic diseases and cancer therapy.

4. Solid lipid nanoparticles for targeted brain drug delivery

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. SLN's 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 (DO-FUdR-SLN).

5. Solid lipid nanoparticles for parasitic diseases

Parasitic diseases (like malaria, leishmaniasis, trypanosomiasis) are one of the major problems around the globe. Antiparasitic chemotherapy is the only choice of treatment for these parasitic infections, the reason for this is that these infections do not elicit pronounced immune response hence effective vaccination may not be possible. Solid lipid nanoparticles (SLN's) and nanostructured lipid carriers (NLCs) represent the 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.

6. Solid lipid nanoparticles for ultrasonic drug and gene delivery

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 nano vehicles that deliver high concentrations of cytotoxic drugs to diseased tissues selectively, thus reducing the agent's side effects on the rest of the body.

7. SLN applications for improved delivery of antiretroviral drugs to the brain

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 with nanocarriers, the 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 using nanocarriers with specific brain targeting, cell penetrating ligands or ABC transporters inhibitors.

8. SLN applied to the treatment of malaria

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.

9. Transfection agent

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.

10. Targeted delivery of solid lipid nanoparticles for the treatment of lung diseases

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.

11. Solid lipid nanoparticles for lymphatic targeting

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

12. SLN in cosmetic and dermatological preparations

SLN is considered as being the next generation of delivery system after liposomes. Due to the lower risk of systemic side effects, topical treatment of skin disease appears favorable, yet the stratum corneum counteracts the penetration of xenobiotics into the viable skin.

13. SLN for potential agriculture applications

The essential oil extracted from Artemesia arborescent Lwhen incorporated into SLN were able to reduce the rapid evaporation compared with emulsions and the systems have been used in agriculture as the suitable carrier of safe pesticides.

14. Solid lipid nanoparticles in tuberculosis disease

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.

CONCLUSION

SLN as colloidal drug carrier combines the advantage of polymeric nanoparticles, fat emulsions, and liposome; due to various advantages, including the feasibility of incorporation of lipophilic and hydrophilic drugs, improved physical stability, low cost, ease of scale-up, and manufacturing. SLN’s are prepared by various advanced techniques. The site specific and sustained release effect of the drug can better achieve by using SLN's. Nanoparticles have been used extensively for applications in drug discovery, drug delivery, and diagnostics and for many others in the 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 SLN’s in the future.

Conflict of Interest

There are no conflicts of interest.

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