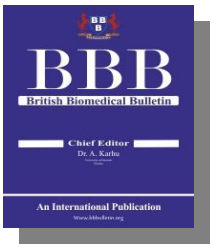
Journal Home Page www.bbbulletin.org

BRITISH BIOMEDICAL BULLETIN



Original

Applications of Solid Lipid Nanoparticle in Novel Drug Delivery System

Jagdevappa Patil*[1], Prashant Gurav[1], Ravindra Kulkarni[2], Sachin Jadhav[1], Satish Mandave[1], Meghanath Shete[1] and Vaibhav Chipade[2]

[1]*Department of Pharmaceutics,SVERI's College of Pharmacy, Gopalpur-Ranjani Road, P.B.No.54,Gopalpur, Pandharpur-413 304, Maharashtra, India.*
[2]*Department of Pharmaceutical Chemistry,SVERI's College of Pharmacy, Gopalpur-Ranjani Road, P.B.No.54,Gopalpur, Pandharpur-413 304, Maharashtra, India.*

ARTICLE INFO

Received 06 Nov. 2013
Received in revised form 10 Nov. 2013
Accepted 15 Nov. 2013

Keywords:
Colloidal system,
Nanoparticles,
Lipospheres,
Nanospheres,
Nanotechnology,
Novel drug delivery,
Solid lipid.

Corresponding author: Department of Pharmaceutics,SVERI's College of Pharmacy, Gopalpur-Ranjani Road, P.B.No.54, Gopalpur, Pandharpur-413 304, Maharashtra, India.
E-mail address:
pharmajspatil@gmail.com

ABSTRACT

Nanotechnology is rapidly expanding research area, encompassing the development of man-made materials in nanometer size range. Nanoscale drug delivery system using various nanomaterials is emerging technology for the rational delivery of many chemotherapeutic agents. Nanoparticles attracted the scientists across many disciplines to engineer many desired properties that might otherwise be incompatible on a single device. Formulation scientists are facing the challenges such as poor solubility and bioavailability of the newly invented drugs. One of the approaches to face the above challenge is to develop the particulate carrier system. Solid lipid nanoparticle or liposphere or nanosphere system is the most feasible particulate carrier system which is an alternative to nanoemulsions, liposomes and polymeric nanoparticles. This system offers added advantages in comparison to other related particulate drug delivery systems. The present review emphasizes on various basic and applied aspects of solid lipid nanoparticles in novel drug delivery system especially techniques involved in their production, characterization and various applications. It also focuses on the drug loading capacity, drug incorporation and factors affecting drug release from this colloidal system.

Introduction

In the current domain of science, specially drug delivery areas and even in our everyday life, nanotechnology has become a commonly used buzzword.[1,2] Numerous definitions have been coined for nanoscience and nanotechnology which are often used interchangeably and the former can be defined as the study of activity of natural laws at a nanoscale and latter can be defined as the novel and practical applications of this scientific knowledge to change the world we live in. [3] Nanotechnology is the area of science, which deals with developing and producing extremely small tools and machines by controlling the arrangement of individual atoms based on the needs. Several restrictions have been placed on what exactly nanotechnology is. It has been described as the exploitation of materials with structural features at the intermediate range between atoms and the molecular scale with the important prerequisite that at least one dimension is in the nanometer length scale.[4-6]

Particles lie between 10-1000 nm with mean correlation spectroscopy diameter are usually prepared from synthetic or natural polymers and designed to deliver the drug in an optimized manner with reduced toxicity. The first practical applications of nanotechnology can be found in the areas communications, engineering, physics, chemistry, biology, robotics and medicine. Applications of nanotechnology can be explored in medicine for therapeutic drug delivery and development of treatments for a many disease and disorders. Nanoparticles attracted scientists of many disciplines due to the scope to engineer many properties such as relevant attachment of biologically active molecules, targeting sequences, biocompatible coatings and others.[7]

Over the decades, nanoparticles have emerged as an alternative particulate drug carrier system for liposomes. Successful use of nanoparticles mainly depends on their ability to penetrate through various biological barriers, controlled fashion of drug release and their stability in the nano range. However, high cost of approved polymers has restricted the wide spread application of nanoparticles in the clinical medicine.[8] Polymeric nanoparticles are generally prepared with suitable polymers, which have been shown to prolong the release of encapsulated drug[9] a typical SLN is depicted in **Figure 1**. The polymer system has an advantage to provide chemical modifications, however, lack of large scale production methods to yield acceptable polymers for regulatory registration, cost of the polymer, toxic solvent residues and cytotoxicity of some polymers are the major limitations associated with polymeric nanoparticles.[10]

During the last twenty years, solid lipid nanoparticles (SLN) system emerged as an alternative particulate drug carrier to suite the development of dosage forms for lipophilic and poor water soluble drugs.[11-18] SLN are highly biocompatible with better bioavailability and control release property. The system protects the incorporated labile drug from degradation and also got excellent tolerability with safer ease of administration through multiple routes.[19-24] This also offers unique features such as large surface area, high drug loading and interaction of phases at the interfaces, and is attractive for their potential to improve performance of pharmaceuticals, neutraceuticals and other materials.[25] The present review is aimed to focus on various fundamental and applied aspects of SLN in the field of novel drug delivery system especially techniques involved in their production, characterization methods and different applications.

Historical Background of Sln

The history of SLN starts from middle of late 90s. Solid lipid system is explored and modified from the original concept into more complex systems, such as nano-structured carriers (NLC) or lipid drug conjugates (LDC) since then.[26-29] At the beginning of the SLN research, only few groups were working in this area. Later on, this system found more attention which was clearly documented in the increase of research groups and the number of published papers, a first review being published in 1995. The research work on SLN continued further and focused almost exclusively on pharmaceutical applications this has been observed in recent available data about the patents related to SLN as depicted in **Figure 2.**[30] The SLN system has been emerged as a promising alternative to other novel drug delivery systems such as emulsions, liposomes, microparticles and polymeric nanoparticles which suffer with the drawbacks such as instability and non-biodegradability.[31]

Drug Loading Capacity and Drug Incorporation in SLN

Many different drugs have been incorporated in SLN. A very important point to judge the suitability of a carrier system is its loading capacity. The loading capacity is generally expressed in percent related to the lipid phase. Major disadvantages of SLN system is poor drug loading capacity and drug expulsion after polymeric transition during storage have been observed. Properties such as solubility of drug in lipid melt, physical and chemical structure of lipid matrix, miscibility of drug and lipid melt and polymeric state of lipid matrix have been considered to be the parameters which limit the drug loading capacity of conventional SLN. It is essential to obtain a sufficiently high solubility of the drug in the lipid melt and typically, the solubility should be higher than required because it decreases when cooling down the melt and it requires putting some suitable solubilizers. In addition, the presence of mono and diglycerides in lipids used as matrix material promotes drug solubilization. The chemical nature of lipids is also important because lipids which form highly crystalline particles with a perfect lattice leads to drug expulsion.[32] Two approaches have been reported to overcome such drawbacks which are nanostuctured lipid carriers (NLC) and lipid drug conjugates (LDC). In the NLC approach, the first model includes mixture of spatially arranged different lipids (glycerides) composed of different fatty acids which leads to larger distance between fatty acid chains of the glycerides and general imperfections in the crystal thus provides more room for inclusion of guest molecules. The maximum drug load could be achieved by mixing solid lipids with small amount of liquid lipids. This model is called as imperfect type NLC. The drug shows higher solubility in liquid lipids than in solid lipids can be dissolved in the oils and yet to be protected by the surrounding solid lipids. This model is called as multiple types NLC, are analogous to w/o/w emulsions since it is an oil-in-solid lipid-in-water dispersion. The drug expulsion is generally caused by ongoing crystallization or transformation of the solid lipid; this can be prevented by third amorphous type model of NLC. In this model the particles are solid but crystallization upon cooling is avoided by mixing special lipids like hydroxyl octacosanyl. The NLC have mainly been investigated in the topical and dermatological preparations in the delivery of clotrimazole.[33,34]

The drug loading capacity of SLN for hydrophilic drugs is very less due to partitioning effect during the production process. Certain highly potent hydrophilic drugs which have low dose may be suitably

incorporated in the solid lipid matrix.[35] In order to overcome this problem, the so called LDC nanoparticles with better drug loading capacities have been developed. The LCD with insoluble drug is first prepared either by salt formation with fatty acids or by covalent linking with ester or ethers. Thus obtained LDC nanoparticles are then processed with an aqueous surfactant solution to a nanoparticle formulation using high pressure homogenization. Such matrices may have potential application in brain targeting of hydrophilic drugs in serious protozoal infections.[36]

Preparation Techniques for Sln

Preparation of SLN mainly depends on the top-down techniques that divide the lipids with drugs dispersed in them after heat melting or dissolving with the aid of solvents with high pressure homogenization method and the solvent emulsification/evaporation method, followed by cold congealing and/or solvent evaporation. SLN can be produced by following advanced techniques.

High pressure homogenization technique

High pressure homogenization technique is initially employed for the production of solid lipid nanodispersions in which SLN produced by melt emulsification method.[37] The two basic production methods for SLN are, the hot and cold homogenization techniques.[38, 39] In both techniques the lipid is melted little above its melting point and drug to be used is dissolved in the molten mass of lipid. For the hot homogenization technique, the drug lipid melt is dispersed under stirring in hot aqueous surfactant solution of same temperature. Thus obtained pre-emulsion is homogenized using a piston-gap homogenizer. The nano emulsion thus obtained is cooled down to room temperature which recrystallizes the lipid and leads to formation of solid lipid nanoparticles.[40] In cold homogenization technique the drug lipid melt is cooled and solid lipid is ground to microparticles which are then dispersed in a cold surfactant solution to yield a pre-suspension. This pre-suspension is then homogenized below the room temperature, in which the cavitation forces are strong enough to break lipid microparticles into solid lipid nanoparticles.[41] This process minimizes the melting of lipid and reduces loss of hydrophilic drugs to the water phase.

Microemulsion technique

Microemulsions are slightly bluish or clear solutions composed of a lipid phase in water. Addition of a microemulsion to water leads to precipitation of lipids into the fine particles. This effect is exploited in the preparation of SLN as developed by Gasco.[42] Microemulsion is formed at a temperature above the melting point of the lipid which remains solid at room temperature. Lipid is heated to melt, a mixture of water, co-surfactant and the surfactant is heated to the same temperature as the lipid and added under mild stirring to the lipid melt. A transparent, thermodynamically stable system is formed when the compounds are mixed in the correct ratio of microemulsion formation. This product is then dispersed in a cold aqueous medium at 2-3ºC temperature under mild mechanical mixing, thus small sized particles are precipitated out.[43,44]

Solvent emulsification/evaporation technique

Lipid material is dissolved in water immiscible organic solvent that is emulsified in an aqueous phase. Upon evaporation of the solvent, nanoparticle dispersion is formed due to the precipitation of lipid in the aqueous phase. The size of particle thus obtained would be in the range of 20-25 nm. This method is based on precipitation of

lipid component of emulation upon evaporation of continuous phase.[45]

Double emulsion technique

Hydrophilic drug loaded SLN are prepared by a novel double emulsion method based on solvent emulsification/evaporation technique.[46] In this method, a drug is encapsulated with a stabilizer to prevent drug partioning into external water phase during solvent evaporation in w/o/w emulsion system.

Ultrasonication technique

Lipid nanopellets for oral delivery can be produced by dispersing a lipid melt in a surfactant solution by sonication.[47] To obtain nanoparticles preferentially, relatively high surfactant concentrations are employed and even lipospheres can also be developed by this method. These lipospheres are solid water insoluble microparticles that have a layer of a phospholipid embedded on their surfaces.[48-50] Lipospheres comprise a hydrophobic core solid at room temperature and phospholipid coat surrounding the core. Particles are prepared by melting the core material and dispersing in the aqueous phospholipid medium at elevated temperature by sonication and cooling leads to solid lipospheres.

Spray drying technique

A cheaper and alternative method to convert the colloidal SLN into solid lipid particulate system instead of lyophilization is spray drying technique. Aggregated particles are obtained with this method due to the use of high temperature, shear forces and partial melting of the particles. Use of high melting lipids is recommended in order to avoid such particle aggregation problem.[51]

Supercritical fluid technique

This is an alternative and very attractive new method of preparing SLN from gas saturated solution. The main component of this technique is said to be supercritical fluid when pressure and temperature exceed its respective critical value. Above the critical temperature it is not possible to liquefy a gas by increasing the pressure. However, the super critical fluid has a unique thermo-physical property. As the pressure increased, the density of gas increases without significant increase in viscosity while the ability of the fluid to dissolve compounds also increases. This method offers mild pressure and temperature conditions for the production and also gives option to use carbon dioxide solution instead of toxic as well as costly organic solvents. This method yields dry particulate mass instead of suspension[52] and the method can also be modified into two ways as gas/supercritical antisolvent technique and gas saturated solution technique. In the former method, the supercritical fluid is used due to its ability to dissolve in organic solvents and reduce the salvation power of solid in solution thus causing the precipitation of solid. The precipitator is partially filled with the drug solution. Carbon dioxide is then pumped at desired pressure and introduced in the vessel preferably from the bottom to achieve a better mixing. The expanded solution is made to pass after a holding time through valve present above the precipitator under isobaric condition to wash and clean the precipitated particles. This method suffers with the lack of control on particle formation.[53] In the latter method, the supercritical fluid is dissolved in liquid substrate in solvent or a suspension of substrate in solvent followed by a rapid depressurization of this mixture through a nozzle causing the formation of SLN. A great verity of substances which are not

soluble in supercritical fluid can be used to produce the particles by this method. Insulin SLN of size less than 500 nm was produced by this technique.[54]

Membrane contactor technique

This technique was developed aiming at large scale production of SLN. Here, the liquid phase is pressed at a temperature above the melting point of the lipid through the membrane pores on to moving aqueous phase to allow the formation of small droplets. The aqueous phase is stirred continuously and circulated tangentially inside the membrane module. This aqueous phase sweeps away the droplets being formed at the pore outlets. The product is cooled at the room temperature or placed in the thermostated water bath of required temperature to obtain SLN.[55,56] This process offer advantages of its facility of use, control of particle size, versatility in preparing polymeric nanoparticles and its scaling up ability.[57]

Solvent injection technique

This is a novel technique to produce SLN owing to its unique advantages over other methods such as use of pharmacologically acceptable organic solvents, easy handling and fast production without technically sophisticated equipment. The basic principle involved in this method is precipitation of dissolved lipid in a solution. A solid lipid is usually dissolved in a water miscible solvent or a mixture. This mixture is injected through an injection needle into stirred aqueous phase with or without surfactant. The resultant dispersion is filtered in order to remove any excess lipid. The emulsifier present within the aqueous phase helps to produce lipid droplets at the site of injection and stabilize SLN until solvent diffusion completes by reducing the surface tension between water and solvent.[58]

Microchannel/Microfluidic technique

This novel method involves passing of a lipid solution prepared with water miscible organic solvent through the main channel of equipment, while an aqueous surfactant solution is introduced into the branches simultaneously. These two liquids meet together at the cross-shaped junction and passes along the main channel. The solvent diffuse from the lipid solution stream into the aqueous phase which results in the local supersaturation of lipid and thus lead to the formation of SLN.[59, 60] All the types of manufacturing techniques and lipid employed for formulation of SLN have been listed in **Table 1**.

FACTORS AFFECTING DRUG RELEASE FROM THE SLN

The data available on method of drug incorporation into SLN are plenty, however, there are distinctly few data available about the mechanisms of drug release. A prolonged drug release was exhibited when studying the incorporation of prednisolone. This demonstrated the principle suitability of SLN system for prolonged drug release.[61, 62] *In vitro* drug release could be achieved for up to 5-7 weeks. The profiles could be modulated with prolonged release pattern without any burst at all, but also generating systems with different percentage of burst followed by prolonged release. The burst can be exploited to deliver an initial dose when desired. It is very important that the drug release patterns are not or only slightly affected by the particle size and shape but also by various production parameters such as surfactant concentration, temperature employed and nature of the lipid matrix. The extent of burst release can be controlled via the solubility of the drug in water phase during production through the control of temperature and surfactant concentration. Higher temperature and surfactant concentrations increase the burst. Production

of SLN at room temperature avoids partitioning of drug into the water phase and subsequent repartitioning to oil phase, thus showing burst at all. To avoid or minimize such burst effect, SLN can be produced by devoid of surfactant.

CHARACTERIZATION OF SLN

SLN are characterized adequately in order to control the quality of final product. The characterization of SLN is really a challenging task for investigators due to the complexity of this system which also includes dynamic phenomena and particularly when the size of particles is very small. The characterization parameters which show direct impact on the stability and release kinetics of incorporated drugs have to be considered and assessed suitably.

Particle size and zeta potential

Particle size is measured usually with powerful techniques such as photon correlation spectroscopy or dynamic light scattering, laser diffraction, coulter counter, phase sensitivity diffraction scattering, atomic force microscopy, field flow fractionation and cryo-field emission scanning electron microscopy. All the techniques have their own merits and demerits. Based on the need, a suitable method is selected for particle size analysis of SLN. In the polyphasic systems the electrical properties of particles at the interface are unique and decide the storage stability of system. Zeta potential is an important and useful parameter which deals with the particle surface charges of multiphase system which can be utilized to predict and control the storage stability.[63] Prediction of zeta potential is often a key parameter which explains the dispersion and aggregation processes. The particle aggregation is less likely to occur for charged particles which show high zeta potential due to electric repulsion.[64]

Polymorphic form and degree of crystallinity

To analyze the quality of SLN system, it is not only sufficient to determine the particle size but a special attention also to be paid to predict the degree of crystallinity of the lipid and its modification, as these parameters are equally correlated with drug incorporation and release kinetics. Polymorphism is an important route of physical deterioration which affects the stability of a solid system, though polymorphs are chemically similar but exhibit different thermodynamic properties such as melting point, X-ray diffraction pattern and solubility.[65,66] The lipid state can be investigated by differential scanning calorimetry and X-ray scattering techniques. Former method gives an idea about different melting points and enthalpies for different lipid modifications and later technique reveals about length of the long and short spacings of the lipid lattice. Infrared and Raman spectroscopy are useful tools to investigate structural properties of lipids from their vibrational transitions.[66-68]

Co-existence and dynamic phenomena

Co-existence of additional colloidal structures like micelles, liposomes, supercooled melts and drug nanoparticles which also show profound influence on lipid crystallization. NMR and ESR, are powerful tools to investigate dynamic phenomena and characteristics of nanocompartments in colloidal lipid dispersion. The potential of NMR has scarcely been used in SLN field, although it will provide unique insights into the structure and dynamics of SLN dispersions. ESR requires the addition of paramagnetic spin probes to study the SLN system and corresponding ESR spectra reveal about microviscosity and micropolarity of the SLN system.

Drug incorporation and entrapment efficiency

The status of drug incorporation into the carrier matrix and its expulsion are mainly depends on lipid crystalline structure. The highly crystalline state with a perfect lattice of lipid in the nanoparticle structure would lead to drug expulsion. In contrary, the imperfect lattice of the lipid structure offers space to accommodate the drugs and this result in structure of less ordered arrangement which is beneficial to the drug loading capacity in nanoparticles. Entrapment efficiency is normally determined by spectrophotometrically after centrifugation of the aqueous dispersion. SLN of mefepristone which is prepared by ultrasonification and homogenization technique showed more than 83 percent entrapment efficiency and also demonstrated relative long term stability as the leakage was very negligible after being stored for one month.[69]

APPLICATIONS OF SLN

Cancer chemotherapy

From the last twenty years many anticancer agents have been formulated into SLN system that resulted in improvment of efficiency with significant decrease in associated side effects. Such chemotherapeutic agents when encapsulated into SLN system has augmented stability and pharmacokinetics with reduced toxicity which proved the SLN to be a suitable carrier for delivery of such agents. Not only small anticancer molecules but also macro molecules like antsense oligonucleotides have been delivered to liver cancer cells by lipid coated particles. [70] SLN was also employed as a targeted carrier for anticancer drugs to solid tumor, as exemplified by Tamoxifen SLN prolonged the release of drug after IV administration in breast cancer. The advantage of using SLN containing anticancer drug is passive targeting property due to enhanced permeability and retention (EPR) effect in which particles are shielded by surface coating using poly ethylene glycol/oxide (PEG/PEO) system which enhances the circulation time.[71] Other drugs used in the similar manner are methotrixate and camptothesin.[52] In similar fashion, SLN have been employed in treatment of colorectal and lung cancer. Doxorubicin and paclitaxel were loaded in SLN and evaluated for colorectal cancer treatment however doxorubicin is not an ideal drug candidate for the same cancer.[72]

Brain drug delivery

Extremely fine particles of SLN with diameter less than 50 nm offer advantages in drug targeting drugs to brain this could be attributed to enhance the drug penetration through blood brain barrier especially SLN coated with polysorbate surfactants demonstrated increased transport of drugs.[73] SLN system also favors reduced uptake by reticuloendothelial system which leads to lower cytotoxicity and enhanced drug loading ability thus making them preferred over polymeric nanoparticles.[74] SLN offers high capacity to load the drugs and at the same time avoids drug degradation and releases the unaltered drug within tumor cells which is due to the lipid components used for surface coating.[75] Though nanotechnology gained momentum in targeting drugs to brain, several formulations showed reduced presence of drugs in brain which is attributed to swift clearance from reticuloendothelial system. This clearance from reticloendothelial system consists of opsonization, phagocytosis and reuptake. This could be overtaken by inserting hydrophilic groups at the surface of particles. Such modifications in the formulations of SLN for targeting brain tumor aided to deliver drugs including

peptides, cytokines, antibodies and ferromagnetic agents.

Parasitic diseases

SLN and nanostuctured lipid carriers (NLC) are particulate in nature and inherent structure exhibit good potential in the treatment of parasitic infections.[76] With respect to encapsulation ability and target ability, it requires extensive investigations on these systems to arrive at a versatile, effective and economical approach for the delivery of anti-parasitic drugs.

Ultrasonic drug and gene delivery

Ultrasonic drug and gene delivery by nanocarriers has tremendous potential because of the wide variety of drugs and genes could be delivered to targeted tissues by fairly noninvasive means.[74] Liquid emulsions and solid nanoparticles are used with ultrasound to deliver genes *in vitro* and *in vivo*.

Pulmonary disorders

Nano particles with their special characteristics have numerous merits in targeted drug delivery compared with other systems. Targeted nanoparticle delivery to the lungs is an emerging area of interest.[77] SLN powders can be used in dry powder inhaler form by spray-drying with lactose as an excipient.

Topical applications

In future, it is expected that SLN replace other carriers for tropical formulations, SLN are usually prepared from well tolerated excipients and possess adhesive properties which helps in the formation of film on the skin due to their small particle size which may assist the drug penetration through stratum corneum. SLN and NLC have been used for topical applications for various drugs such as tropolide and glucocorticoids.[78,79] Numerous hydrophilic and hydrophobic drugs including corticosteroids and anticancer agents like doxorubicin and paclitaxel have been delivered through SLN.[80] In the treatment of aczema, SLN formulations consisting glucocorticoids and calcinuerin inhibitors were tried, in the similar lines, glucocorticoids were formulated in lipid nanoparticles which showed skin atrophy in long term use. Muller et al exhibited sustained release of prednisolone from SLN consistently for weeks.

The existing cotrimazole creams though treated effectively the topical fungal infections but upon discontinuation of the cotrimazole application, dermal fungal re-inflection was observed. This defect of such formulations has been overcome by incorporating clotrimazole in SLN and NLC. Encouraged by such developments in antifungal drug delivery, SLN has also reduced the toxicity of few antifungal drugs, to exemplify this ketoconazole which is potent antifungal agent, developed as SLN for tropical fungal infections, minimized the adverse effects of ketoconazole and also provided control release.[81]

Cosmeceuticals

SLN have been applied in the preparation of sunscreens.[79] SLN & NLC have proved as controlled release innovative occlusive topical.[82] It has been reported that, 31% increase in the skin hydration upon addition of 4% SLN to a conventional cream.[78] Better localization of vitamin A with glyceryl behenate SLN was reported in comparison to conventional formulations.[83]

Oral administration

SLN can also be administered by oral route in an aqueous dispersion form rather than its traditional solid forms. The aqueous SLN dispersion can be used as a granulating fluid in the granulation process or alternatively, the spray-dried powder can

be added to the tableting powder mixture. During the preparation of pellets by extrusion process, SLN dispersion can be used as a wetting agent.[84]

Parenteral administration

A study on intravenous administration of SLN has been reported by Yang *et al.*[85] The intravenous administration of SLN led to elevated and prolonged plasma levels of paclitaxel and interestingly increased uptake by brain was observed along with low uptake by liver and spleen.[86] This study demonstrates nicely the potential of SLN to achieve prolonged drug plasma levels. SLN are also useful in delivery of peptides and protein based drugs which enhances the bioavailability by avoiding degradation when given by oral route.

Agricultural applications

Some of the essential oils after incorporating in SLN system exhibited reduction in rapid evaporation when compared to emulsion system and have been used as a suitable carrier of ecologically safe pesticides.[87]

DEMERITS OF SLN

Numerous research and review publications already reported large side advantages of SLN, however, only few reports cited the problems associated with SLN as a carrier and such drawbacks require special attention to improve the SLN formulation. We here wish to bring some of such difficulties associated with SLN during its formulation as carriers.

Formulation based drug degradation

Reports suggest that large molecular weight and long chain molecules like DNA and peptides have demonstrated greater sensitivity than low molecular weight drugs or drugs having spherical shape during SLN production in bulk scale.[88] Different techniques are known for the production of SLNs in laboratory scale and large scale. High pressure homogenization technique if employed in the production of SLN in bulk quantity in which high shear is produced which may be responsible for degradation of aforementioned drugs, although shear may not be a significant problem for majority of drugs.[89]

Lipid Modifications

Selection of lipids for the formulation of SLN is vital because the efficiency of SLN in terms of drug loading and its release depend on lipid used and how much modifications needed. Lipids possess thermodynamical mobility which attributes for stable and unstable configuration. Such themodynamic stability and lipid packing pose serious challenge for formulation scientists and the incorporation rate decrease in the following order, Super cooled melt < α-modification < β9-modification < β-modification. During storage, the lipid structure changes from unstable configuration to stable configuration due to which rapid expulsion of drug occur which hinder the high drug loading capacity of SLN. This drawback of lipid configuration requires modification during the course of storage. DSC and X- ray scattering are successfully employed to inspect the status of the lipid. DSC reveals the lipid modification based on principle that different structures of lipids possess different melting points and melting enthalpies. Infrared and Raman spectroscopy are also effective tools for exploring structural properties of lipids.[90]

Conclusion

According to Paul Ehrlich's concept of magic bullet, which emphasized the idea of delivery of the drug to the specific site, at specific time, in appropriate concentration and to avoid the systemic side effects, SLN

are considered as potential drug carriers to achieve aforementioned broad objectives apart from controlled drug delivery. A detailed survey over SLN disclosed that plentiful academic groups are involved in SLN development which could be attributed to lack of drug formulation in the market. The broad applications of this system can be expected only when pharmaceutical companies come forward and carry research based studies which yield prolific and cost effective formulation containing SLN. Still SLN is a premature drug delivery system and in infancy stage however has gained primary attention in the last two decades. Active involvement of pharmaceutical industries will gradually shift attention and future holds great promise for SLN development and rightful exploitation. Hope such momentum results in new SLN based formulations in market in future.

Acknowledgement

The authors express thanks to Dr. B P Ronge, Founder Secretary and Principal, SVERI's College of Engineering, Pandharpur for providing all necessary facilities. Also all the Management trusties are extended with sincere thanks for their encouragements.

CONFLICT OF INTEREST

None

References

1. Dosch H. Some general aspects of confinement in nanomaterials. Appl Surf Sci.2001; (82):192–195.
2. Navrotsky A. Calorimetry of nanoparticles, surfaces, interfaces, thin films, and multilayers. *J Chem Thermodyn*. 2007; (39): 2–9.
3. Balzani V. Nanoscience and nanotechnology: a personal view of a chemist. Small. 2005; (1): 278–283.
4. Rao CNR, Cheetham AK. Science and technology of nanomaterials: current status and features. *J Mater Chem*. 2001; (11): 2887–2894.
5. Rao CNR, Kulkarni GU, Thomas PJ, Edwards PP. Size-dependent chemistry: properties of nanocrystals. Chemistry – A. *Eur J*. 2002;(8): 28–35.
6. Jortner J, Rao CNR. Nanostructured advanced materials. Perspectives and directions. Pure Appl Chem. 2002; (74): 1491–1506.
7. Amir HF, Peter W. Nanoparticles in cellular drug delivery. *Bioorg Med Chem*. 2009;(17) :2950-2962.
8. Scheffel U, Rhodes BA, Natarajan TK, Wagner HN. Albumin microspheres for study of the reticuloendothelial system. *J Nucl Med*. 1972; (13) : 498-503.
9. Blasi P, Giovagnoli S, Schoubben A, Ricci M, Rossi C. Solid-lipid nanoparticles for targated brain drug delivery. Adv Drug Deliv Rev. 2007; (59): 454-477.
10. Date AA, Joshi MD, Patravale VB. Parasitic diseases: Liposomes and polymeric nanoparticles versus lipid nanoparticles. *Adv Drug Deliv Rev*. 2007; (59): 505-521.
11. Seikmann B, Westesen K. Sub-micron sized paraetral carrier systems based on solid lipids. *Pharm pharmacol Letters*. 1992; (1) :123-126.
12. Schwarz C, Mehnert W, Lucks JS, Muller RH. Solid lipid nanoparticles (SLN) for controlled drug delivery. I. Production, characterization and sterilization. *J Control Rel*. 1994; (30): 83-96.
13. Westesen K, Seikmann B, Koch MHJ. Investigations on the physical state of lipid nanoparticles by synchroton radiation X-ray diffraction. *Int J Pharm*.1993; (93): 189-199.
14. Bunjes H, Westesen K, Koch MHJ. Crystallization tendency and polymeric transitions in triglyceride nanoparticles. *Int J Pharm*. 1996; 12 (9): 159-173.
15. Gasco MR. Solid lipid nanospheres from warm microemulsions. *Pharm Technol Eur*. 1997; (9): 52-58.
16. Heiati H. Phillips MC, Tawashi R. Evidence for phospholipid bilayer formation in solid-lipid nanoparticles formulated with phospholipid and triglyceride. *Pharm Res* 1996; (13):1406-1410.

17. Vringer T, Ronde HAG. Preparation and structure of water-in-oil cream containing lipid nanoparticles. *J Pharm Sci*. 1995; (84): 466-472.
18. Sjostrom B, Kaplun A, Talmon Y, Cabane B. Structure of nanoparticles prepared by oil-in-water emulsions. *Pharm Res*. 1995; (12): 39-48.
19. Pinto JF, Muller RH. Pellets as carriers of solid-lipid nanoparticles (SLN) for oral administration of drugs. *Pharmazie*. 1999; (54):506-509.
20. Wissing SA, Muller RH. Solid-lipid nanoparticles as carrier for sunscreens: *in vitro* release and in vivo skin permeation. *J Control Rel*. 2002; (81) : 225-233.
21. Liu W, Hu M, Liu W, Xue C, Xu H, Wang X. Investigation of the carbopol gel of solid lipid nanoparticles for the transdermal iontophoretic delivery of triamcinolone acetonide acetate. *Int J Pharm*. 2008; (364): 135-141.
22. Cavalli R, Gasco MR, Chetoni P, Burgalassi S, Saettone MF. Solid-lipid nanoparticles (SLN) as ocular delivery system for tobramycin. *Int J Pharm*. 2002; (238) : 241-245.
23. Rapolu K, Aatipamula V, Reddy KJ, Voruganti S. Cyclodextrins: Nanocarriers for Novel Drug Delivery. *Int J Pharm*. 2012; (2) :109-116.
24. Gasco MR. Solid-lipid nanoparticles for ocular delivery. Pharm Tech Eur. 2001; (13): 32-41.
25. Cavalli R, Caputo O, Gasco MR. Solid lipospheres of doxorubicin and idarubicin. *Int J Pharm*. 1993; (89):R9-R12.
26. Muller RH, Mehnert W, Lucks JS. Solid-lipid nanoparticles (SLN): an alternative colloidal carrier system for controlled drug delivery. *Eur J Pharm Biopharm*. 1995; (41): 62-69.
27. Muller RH, Lucks JS. Medication vehicles made of solid lipid particles (solid lipid nanospheres-SLN). 1996; *Eur Patent* N0.605, 497.
28. Muller RH, Radtke M, Wissing SA. Nanostructured lipid materials for improved microencapsulation of drugs. *Int J Pharm*. 2002; (242):121-128.
29. Muller RH, Keck CM. Challenges and solutions for the delivery of biotech drugs-a review of drug nanocrystal technology and lipid nanomaterials. *J Biotech*.2004; (113): 151-170.
30. www.patentlens.net (US/WIPO and Europe-Patents Grants And Applications Data)
31. Muller RH, Mader K, Gohla S. Solid-lipid nanoparticles (SLN) for controlled drug delivery-a review of the state of the art. Eur J *Pharm Biopharm*. 2000; (50):161-177.
32. Westesen K, Bunjes H, Koch MHJ. Physicochemical characterization of lipid nanoparticles and evaluation of their drug loading capacity and sustained release potential. *J Control Rel*. 1997; (48):223-236.
33. Souto EB, Wissing SA, Barbosa CM, Muller RH. Development of controlled release formulation based on SLN and NLC for topical clotrimazole delivery. *Int J Pharm*. 2004; (278):71-77.
34. Souto EB, Muller RH. Investigation of the factors influencing the incorporation of clotrimazole in SLN and NLC prepared by hot high-pressure homogenization. Microencapsule. 2006; 23(4); 377-378
35. Morel S, Terreno E, Ugazio E, Aime S, Gasco MR. NMR relaxometric investigations of lipid nanoparticles (SLN) containing gadolinium (III) complexes. *Eur J Pharm Biopharm*. 1998; (45):157-163.
36. Olbrich C, Gessner A, Kayser O, Muller RH. Lipid-drug conjugate (LDC) nanoparticles as novel carrier system for the hydrophilic antitrypanosomal drug diminazene-diaceturate. *J Drug Target*. 2002; (10):387-396.
37. Ahlin P, Kristl J, Kobar S. Optimization of procedure parameters and physical stability of solid lipid nanoparticles in dispersion. Acta Pharm. 1998; (48):257-267.
38. Muller RH, Lucks JS. Arzeistofftager aus fasten lipidteilchen, Feste lipidnanospharen (SLN). (1996), European Patent No. 0605497.
39. Muller RH, Schwarz C, Mehnert W, Lucks JS. Production of solid lipid nanoparticles (SLN) for controlled drug delivery. Proc Int Symp Control Rel Bioact Mater. 1993; (20) :480-481.

40. Lander R, Manger W, Scouloudis M, Ku A, Davis C, Lee A. Gaulin homogenization: a mechanistic study. *Biotechnol Prog*. 2000; (16):80-85.
41. Jahnke S. A theory of high pressure homogenization. In: Muller RH, Benita S, Bohm B, Eds. Emulsions and nanosuspensions for the formulation of poorly soluble drugs, Stuttgart: *Medpharm Scintific Publishers* 1998; 177-200.
42. Gasco MR. Method for producing solid lipid microspheres having a narrow size distribution. US Patent. 5 250 236.
43. Gasco MR. Solid lipid microspheres from warm microemulsions. Pharm Tecnol Eur. 1997; (9) : 52-58.
44. Boltri L, Canal T, Esposito PA, Carli F. Lipid nanoparticles: evaluation of some critical formulation parameters. *Proc Int Symp Control Rel Bioact Mater*. 1993; (20): 346-47.
45. Sjostrom B, Bergenstahl B. Preparation of submicron drug particles in lecithin-stabilized o/w emulsions. I. Model studies of the precipitation of cholesterol acetate. *Int J Pharm*. 1992; (88):53-62.
46. Cortesi R, Esposito E, Luca G, Nastruzzi C. Production of lipospheres as carriers for bioactive compounds. Biomater 2002; (23): 2283-94.
47. Weyhers H. Feste lipid-nanopartikel (SLN)furdiege websspezifischearzneistofa applikation. Ph. D. thesis. Free University of Berlin. 1995.
48. Domb AJ. Lipospheres for controlled delivery of substances. 1993; US Patent. (5) 188 837.
49. Domb AJ, Marlinsky A, Maniar M, Teomim L. Insect repellant formulations of N,N-diethyl-m-tolumide (deet) in a liposphere system: efficacy and skin uptake. J Am Mosquito Control Assoc. 1995; (11):29-34.
50. Domb AJ. Long acting injectable oxytetracycline liposphere formulations. *Int J Pharm*. 1995; (124):271-278.
51. Freitas C, Muller RH. Spry-drying of solid lipid nanoparticles (SLN). Eur J Pharm Biopharm. 1998; (46):145-51.
52. Ekambaram P, Abdul HAS, Priyanka K. Solid lipid nanoparticles: A review. *Sci Revs Chem Commun*. 2012; (2): 80-102.
53. Rabinarayan P, Suresh P. Preparation and characterization of solid lipid nanoparticles-A review. *Curr Drug Descov Technol*. 2012; (9):2-16.
54. Almeida AJ, Souto E. Solid lipid nanoparticles as a drug delivery system for peptides and proteins. *Adv Drug Deliv Rev*. 2007; (59):478-490.
55. Charcosset C, El-Harati A, Fessi H. Preparation of solid lipid nanoparticles using a membrane contactor. *J Control Rel*. 2005; (108):112-120.
56. El-Harati A, Charcosset C, Fessi H. influence of the formulation for solid lipid nanoparticles prepared with a membrane contactor. *Pharm Devel Tech*.2006; (11): 53-57.
57. Charcosset C, El-Harati A, Fessi H. A membrane contactor for the preparation of solid lipid nanoparticles. Desalination. 2006; (200): 570-571.
58. Schubert MA, Muller-Goymann CC. Solvent injection as a new approach for manufacturing lipid nanoparticles-evaluation of method and process parameters. *Eur J Pharm Biopharm*. 2003; (55): 125-131.
59. Zhang S, Yun J, Shen S, Chen Y, Chen C. Formation of solid lipid nanoparticles in a microchannel system with a cross-shaped junction. *Chem Eng Sci*. 2008; (63): 5600-5705.
60. Zhang S, Shen S, Chen Z, Yao Z, Chen C. Preparation of solid lipid nanoparticles in coflowing microchannels. *Chem Eng J*. 2008; (144): 324-328.
61. Zur Muhlen A, Mehnert W. Drug release and release mechanism of prednisolone loaded solid lipid nanoparticles. Pharmzie. 1998; (53): 552-558.
62. Cavalli R, Peira E, Caputo O, Gasco MR. Solid lipid nanoparticles as carriers of hydrocortisone and progesterone complexes with β-cyclodextrins. *Int J Pharm*. 1999; (182): 59-69.
63. Muller RH. Zetapotential und partikelladung-Kurze theorie, parktische Meβdurchfuhrung, Deteninterpretation. Wissenschaftiche Verlagsgesellschaft. Stuttgart.(1996).
64. Ney P. Zetapotentiale und flotierbarkeit von mineralien. New York: Springer. (1973).

65. Martin A, Swarbrick J, Cammarata A. Physical pharmacy. In: Lea, Febiger. Eds. States of matter and phase equilibria Philadephia. 1983; p. 62-92.
66. Libster D, Aserin A, Wachtel E, *et al.* Surfactant Science Series. In: Garti N, Sato K, Eds. Crystallization and polymorphism of fats and fatty acids. New York: Marcel Dekker 1988; p.3-87.
67. Prativi D, Fawcet JP, Gordon KC, Rades T. Quantitative analysis of polymorphic mixture of ranitidine hydrochloride of Raman spectra and principal component analysis. *Eur J Pharm Biopharm*. 2002; (54): 337-41.
68. Tandon P, Forster G, Neubert R. Phase transition in oleic acid as studied by X-ray diffraction and FT- Raman spectroscopy. *J Mol Struct*. 2005; (524):201-15.
69. Hou DZ, Xie CS, Huang KJ, Zhu CH. The production and characterization of solid lipid nanoparticles (SLNs). Biomater. 2003; (24): 1781-85.
70. Bartsch M, Weeke KAH, Hoenselaar EP, Stuart MC, Meijer DK, Scherphof GL, et al. Stabilized lipid coated lipoplexes for the delivery of antisense oligonucleotides to liver endothelial cells *in vitro* and *in vivo***.** *J Drug Target*. 2004; (12):613–21.
71. Yang T, Cui FD, Choi MK, Cho JW, Chung SJ, Shim CK, et al. Enhanced solubility and stability of PEGylated liposomal paclitaxel: in vitro and in vivo evaluation. *Int J Pharm*. 2007; (338):317–26.
72. Nielsen D, Marre C, Skovsquard T. Cellular resistance to anthracyclines. Gen Pharmacol. 1996; (27):251–55.
73. Kreuter J. Influence of the surface properties on nanoparticle-mediated transport of drugs to the brian. *J Nanosci Nanotechnol*. 2004; (4): 484–88.
74. Wolfgang M, Karsten M. Solid lipid nanoparticles production, characterization and applications. *Adv Drug Delv Rev*. 2001; (47): 165-96.
75. Wissing SA, Muller RH, Kayser O. Solid lipid nanoparticles for parenteral drug delivery. *Adv Drug Deliv* Rev. 2004; (56) : 1257–72.
76. Venkateshwaralu V, Manjunath K. preparation, characterization and *in vitro* release kinetics of lozapine solid lipid nanoparticles. *J Control Rel*. 2004; (95) : 627-38.
77. Jain NK. Controlled and novel drug delivery. 1st ed. New Delhi: CBS Publishers and distributors; 1997. p.3-28.
78. Mei Z, Wu Q. Triptolide loaded solid lipid nanoparticle hydrogel for topical application. *Drug Dev Ind Pharm*. 2005; (31):161-168.
79. Wissing SA, Muller RH. Solid lipid nanoparticles (SLN) a novel carrier for UV blockers. Pharmazie. 2001; (56):783-786.
80. Souto EB, Müller RH. The use of SLN® and NLC® as topical particulate carriers forimidazole antifungal agents. Pharmazie. 2006; (61):431-437.
81. Elmadfa J, Bosse W. Vitamin E. Stuttgart: Wissenschaftliche Verlagsgesellschaft. 1985.
82. Wissing SA, Lippacher A, Muller RH. Investigations on the occlusive properties of Solid lipid nanoparticles (SLN). *J Cosmet Sci*. 2001; (52):313-324.
83. Jenning V, Gycler A, Schafer-Korting M, Gohla SH. Vitamin A loaded solid lipid nanoparticles for topical use: occlusive properties and drug targeting to the upper skin. *Eur J Pharm Biopharm*. 2000; (49): 211-218.
84. Pinto JF, Muller RH. Pellets as carriers of solid lipid nanoparticles (SLN) for oral administration of drugs. Die Pharmazie. 1999; p.506-09.
85. Yang SC, Lu LF, Cai Y, Zhu JB, Liang BW, Yang CZ. Body distribution in mice of intravenously injected camptothecin solid lipid nanoparticles and targeting effect on brain. *J Control Rel*. 1999; (59): 299-307.
86. Fundaro A, Cavalli R, Bargoni A, Vighetto D, Zarg GP, Gasco MR. Non-stealth and stealth solid lipid nanospheres carrying doxorubicin: pharmacokinetics and tissue distribution after i.v. administration to rats. *Pharm Res*. 2000; (42): 337-43.
87. Lai F, Wissing SA, Muller RH, Fadda AM. Artemisia arborescens L essential oil-loaded solid lipid nanoparticles for potential agriculture application: preparation and characterization. *AAPS Pharm Sci Tech*. 2006; 7: E2.
88. Boistelle R. Fundamentals of nucleation and crystal growth. in: N. Garti, K. Sato (Eds.)

Crystallization and Polymorphism of Fats and Fatty Acids. Marcel Dekker Inc., New York, Basel. 1988; p.189–226.
89. Almeidea AJ, Runge S, Muller RH. Peptide-loaded solid lipid nanoparticles (SLN) influence of production parameters. *Int. J. Pharm.* 1997; (149): 255-65.
90. Westesen K, Siekmann B. Investigation of the gel formation of phospholipid-stabilized solid lipid nanoparticles. *Int. J. Pharm.* 1997; (151):35–45.

Table 1. Types of preparation methods and ingredients used for formulation of SLN[74]

Different methods of SLNs preparation	Name of the ingredients	
	Lipids	**Emulsifiers /Coemulsifiers**
▪ High shear homogenization ▪ Ultrasound High shear homogenization ▪ Probe ultrasonication ▪ Bath ultrasonication ▪ Hot homogenization ▪ Cold homogenization ▪ Solvent emulsification ▪ Solvent evaporation ▪ Microemulsion method	Triglycerides • Tricaprin • Trilaurin • Trimyristin • Tripalmitin • Tristearin • Hydrogenated co-glycerides (Softisan 142) Hard fat types ➢ Witepsol W 35 ➢ Witepsol H 35 ➢ Witepsol H 42 ➢ Witepsol E 85 ➢ Glyceryl monostearate (Imwitor 900) ➢ Glyceryl behenate (Compritol 888 ATO) ➢ Glyceryl palmitostearate (Precirol ATO 5) ➢ Cetyl palmitate ➢ Stearic acid ➢ Palmitic acid ➢ Decanoic acid ➢ Behenic acid ➢ Acidan N12	• Soybean lecithin • (Lipoid S 75, Lipoid S 100) • Egg lecithin (Lipoid E 80) • Phosphatidylcholine • (Epikuron 170, Epikuron200) • Poloxamer 188 • Poloxamer 182 • Poloxamer 407 • Poloxamine 908 • Tyloxapol • Polysorbate 20 • Polysorbate 60 • Polysorbate 80 • Sodium cholate • Sodium glycocholate • Taurocholic acid sodium salt • Taurodeoxycholic acid sodium salt • Butanol • Butyric acid • Dioctyl sodium sulfosuccinate • Monooctylphosphoric acid sodium

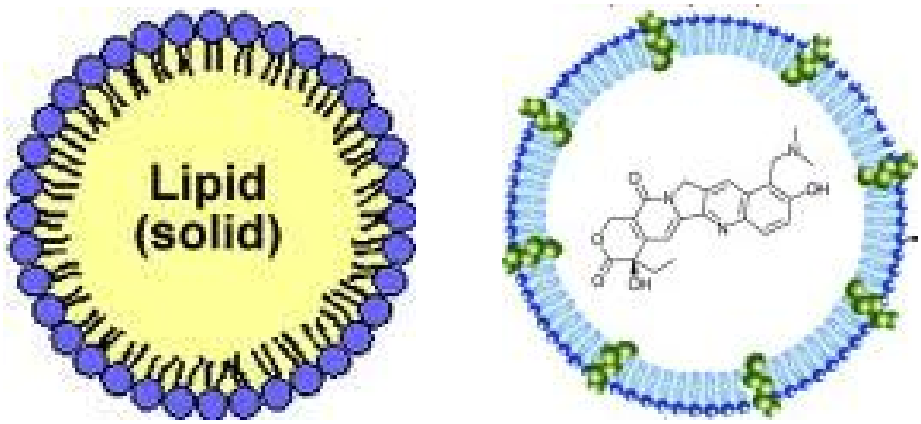


Figure 1. Typical solid lipid nanoparticles

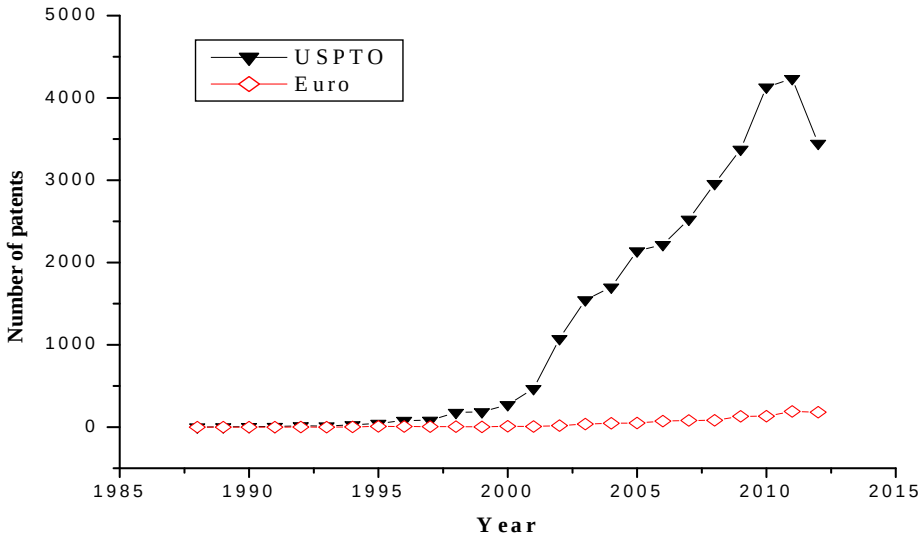


Figure 2. Shows the comparative patents published in United State of America

Legends:

USPTO-

EURO -