Journal of PharmaSciTech
ISSN: 2231 3788 (Print)
2321 4376 (Online)
Review Article

Solid Lipid Nanoparticles (SLN): A Nano-Drug Delivery System

Sagar K. Savale

Mylan Laboratories Ltd, Sinnar, Nashik, Maharashtra 422113, India

Correspondence: avengersagar16@gmail.com (Tel.: +91 9960885333)

Article Info:
Received: 25.11.2018
Accepted:12.12.2018
Available online:14.2.2019

Abstract

Solid Lipid Nanoparticles (SLN) is recently developed technique, in which the size ranges from 1 to 1000 nm particles can use for drug delivery system (DDS). It is basically a colloidal carrier. In this review based on the latest research and development of SLN according to the modern literature are cited. The ability to incorporate drugs into Nanoparticulate system offers a new prototype in drug delivery that could use for drug targeting. The preparation techniques for production of SLN are Novel and more efficient. Appropriate analytical techniques for the characterization of SLN. Solid lipid nanoparticles (SLN) have emerged as a next-generation drug delivery system with potential applications in pharmaceutical field, cosmetics, research, clinical medicine and other allied sciences. Recently, increasing attention has been focused on these SLN as colloidal drug carriers for incorporating hydrophilic or lipophilic drugs.

Keywords: Nanoparticles, Solid lipid nanoparticles, drug delivery, targeting, drug release

Introduction

Nanoparticle is a novel versatile drug delivery approach having targeted and site specific activity. Many of the recent formulation approaches utilize Nanotechnology that is the preparation of Nanosized structures containing the active pharmaceutical material. Nanoparticle is a nanosized particle having the size range of 1 to 1000 nm. Some of the important Drug Delivery System developed using Nanotechnology principles are, Nanoparticles, Solid Lipid Nanoparticles, Nanosuspension, Nanoemulsion, Nanocrystals. In this review article mainly focus on Solid Lipid Nanoparticles (SLN). SLN alternative and better modern colloidal carrier system to traditional colloidal carriers such as emulsions, liposomes and polymeric micro and nanoparticles [1]. In nanoparticulate system, nanosuspensions are colloidal dispersions of nanosized drug particle that are produced by suitable method and stabilized by suitable stabilizer [2]. Nanoparticles are solid colloidal particles sized from 1-1000 nm [3]. Nanospheres are the polymer matrices in which drug is dissolved or dispersed [4]. Nanocapsules Consists of polymer wall entrapping an oily core in which the drug is dissolved [5]. Nanoparticles as a drug delivery vehicle were first developed by Spieser and co-workers in the late 1960. In early 1970 the cross linked polyacrylamide Nanoparticles were produced [6, 7]. Nanoparticles are particles made of natural or synthetic polymers ranging in size from 1 to 1000 nm. They consist of macromolecular materials containing active principle (pharmaceutical or biologically active material) is dissolved, entrapped, and or to which the active principle is adsorbed or attached [8, 9].Nanoparticles are mainly divide by two types (Nanospheres and Nanocapsules), first is Nanospheres are solid core spherical particulates, which contain drug embedded within the matrix or adsorbed onto the surface. (Matrix type) [10]. Second is Nanocapsules are vesicular system in which drug is essentially encapsulated within the central core surrounded by a polymeric sheath. (Reservoir type) [11]. They Improved Efficacy, Reduced Toxicity, Enhanced Distribution and Improved Patient Compliance [12].

Types of Nanoparticles

Nanoparticle is a nano sized particle is mainly divided by thirteen types,Polymeric Nanoparticles [13], Solid Lipid Nanoparticles [13], Nanosuspension [13], Polymeric Micelles [13], Ceramic Nanoparticles [14], Liposome [14], Dendrimers [14], Magnetic Nanoparticles [15], Nanoshells Coated With Gold [15], Nanowires [15], Nanopores [16], Quantum Dots [16], Ferrofluids [16].

Solid Lipid Nanoparticles (SLN)

The solid lipid nanoparticles (SLN) are submicron colloidal carriers which are composed of physiological lipid, dispersed in water or in an aqueous surfactant solution. Nanoparticles are particles made of natural or synthetic polymers ranging in size from 50 to 500 nm. No potential toxicity problems as organic solvents are not used.SLN are new generation of submicron sized lipid emulsion where the liquid lipid (oil) has been substituted by a solid lipid [16, 17]. The Structure of Solid Lipid Nanoparticle (SLN) along with Liposomes and nanoemulsion is shown in Figure1.

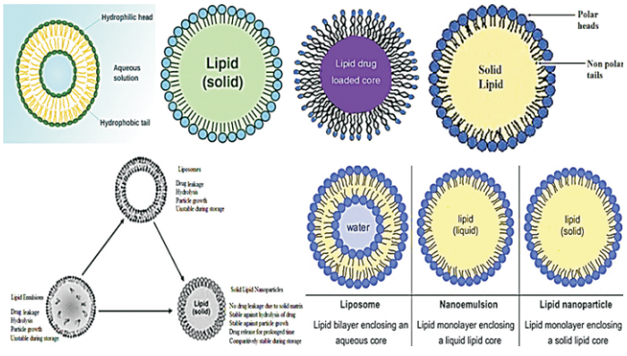

Figure1: Structure of SLN along with Liposomes and nanoemulsion

Principles of Drug Release

There is an inverse relationship between drug release and the partition co-efficient of the drug [17]. Higher surface area owing to smaller particle size in the nanometre size range gives higher drug release [17]. Slow drug release can be achieved when drug is homogenously dispersed in the lipid matrix, it depends on the type and the drug entrapment model of SLN [18]. Crystallinity behaviour of the lipid and high mobility of the drug lead to fast drug release. There is an inverse relationship between crystallization degree and mobility of drug [19]. Factors contributing to a fast release are the large surface area, a high diffusion co- efficient due to small molecular size, low viscosity in the matrix and a short diffusion distance for the drug [19].

Advantages of SLN

i.Small size and narrow size distribution provides for site specific drug delivery by SLN [20].
ii.Controlled release of active drug over a long period can be achieved [21].
iii.Protection of incorporated drug against chemical degradation [22].
iv.SLNs can be lyophilized and spray dried [23].
v.No toxic metabolites are produced [24].
vi.Sterilization can be done by autoclaving or gamma irradiation [25].
vii.Surface modification can be easily done [26].

Disadvantages of SLN

i.Drug loading capacity is limited [27].
ii.High pressure induces drug degradation [28].
iii.Coexistences of several colloidal species [29].
iv.Lipid crystallization and drug incorporation, super cooled melts, gelation phenomenon [30].
v.Drug expulsion [31].

Disadvantages of SLN

i.Drug loading capacity is limited [27].
ii.High pressure induces drug degradation [28].
iii.Coexistences of several colloidal species [29].
iv.Lipid crystallization and drug incorporation, super cooled melts, gelation phenomenon [30].
v.Drug expulsion [31].

Composition of SLN

General ingredients include solid lipid, surfactant, co-surfactant and water. Lipid used may be triglycerides (Tristearin, Tripalmitin and Trimyristin). Partial glycerides (glyceryl monostearate).Fatty acids (e.g. stearic acid, Lauric acid), waxes (carnauba wax). Charge modifier (Stearylamine) Combination of surfactant enhances stability by preventing particle agglomeration. Surfactant (soybean lecithin, egg lecithin, Poloxamers) [32, 33, 34, 35].

Aim of Solid Lipid Nanoparticles (SLN)

i.Possibility of controlled drug release [36].
ii.Increased drug stability [37].
iii.High drug pay load [38].
iv.No bio-toxicity of the carrier [39].
v.Avoidance of organic solvents [40].
vi.Incorporation of lipophilic and hydrophilic drugs [41].

Types of Solid Lipid Nanoparticles (SLN)

According to drug incorporation mechanism, SLN based system can be classified into Three Types they as follow (Figure 2).

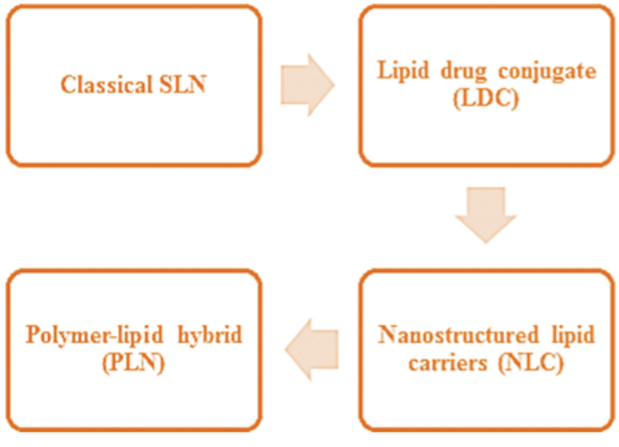

Figure 2: Types of SLN

Classical SLN

Based on the difference melting point (MP) between drug and lipid matrix together with consideration on the release kinetics of SLN [42], Solid solution model: M.P. drug $\approx$ M.P. lipid [42]. Core-shell model, drug enriched shell: M.P. drug $<$M.P. lipid [42]. Core-shell model, drug-enriched core: M.P. drug $>$ M.P. lipid [42].

Lipid Drug Conjugates (LDC)

It should similar to classical SLN with the loaded drug evenly distributed within the lipid matrix because they are directly bonded to the lipid molecule [43].

Nanostructured Lipid Carriers (NLC)

In this case, the lipid matrix is composed of binary mixture of a solid lipid and a medium chain triglyceride or liquid oil. Based on the lipid matrix of NLC [44]. Drug model: In the first model, liquid oil molecularly dispersed within the solid lipid matrix when the concentration of the liquid oil is below its solubility in the liquid [45]. In the second model, liquid oil is distributed in the solid lipid in droplet form. In order to deliver the hydrophilic drugs with a high drug loading capacity and simultaneously control the kinetics of SLN [46].

Polymer lipid hybrid (PLN)

In PLN, water soluble polymer lipid counter polymer nanoparticle under reaction with water soluble ionic drugs to from the drug – polymer complex and drug loaded Polymer hybrid was formed [46, 47].

Method of preparation

Solid lipid Nanoparticulate system is Novel drug delivery system is prepared by using following method they as follows (Figure 3):

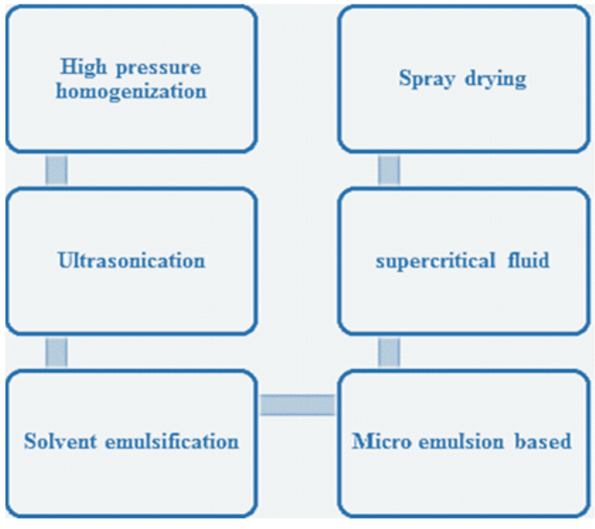

Figure 3: Method of preparation

High Pressure Homogenization

It pushes the liquid with high pressure (100-200 bar) through a hollow gap of some few microns. With nearly 100Km/h rate and with high viscosity the fluid accelerates to a very short distance. Very high pressure stress and cavitations force interrupt the particle down to submicron size range with 5-40% lipid content. In HPH two different approaches with same principle were established [47]. First was hot homogenization: The Melting of the lipid and dissolving/dispersing of the drug in the lipid, dispersing of the drug loaded lipid in a hot aqueous surfactant mixture. Premix the Prepared Mixture using a stirrer to form a Coarse pre-emulsion. High pressure homogenization at a temperature above the lipid M.P. and to form Hot O/W nanoemulsion generate the Solid Lipid Nanoparticles [47, 48].

Second was cold homogenization: The melting of lipid & dissolving/dispersing of the drug in the lipid, Under Solidification of the drug loaded lipid in liquid nitrogen or dry ice. Grinding in a powder mill and dispersing the powder in an aqueous surfactant dispersion medium. High pressure homogenization at room temperature or below and to from Solid Lipid Nanoparticles [48, 49].

Ultrasonication/ High Speed Homogenization

SLN are also prepared by Ultrasonication orhigh speed homogenization techniques. To achievesmaller particle size, combination of both Ultrasonication and high speed homogenization is required [50].

Solvent emulsification/ evaporation

SLN can be prepared by solvent evaporation method. The lipophilic material is dissolved in a water immiscible organic solvent (cyclohexane) that is emulsified in an aqueous phase. Upon evaporation of the solvent, nanoparticles dispersion is formed by precipitation of the lipid in the aqueous medium by giving the nanoparticles of 25 nm mean size. The solution was emulsified in an aqueous phase by high pressure homogenization. The organic solvent was removed from the emulsion by evaporation under reduced pressure (40-60 mbar) [51-53].

Micro emulsion based SLN preparations

Preparation by stirring optically transparent mixture at 65-70oc composed of a low melting fatty acid, emulsifier, coemulsifier and water.This hot microemulsion dispersed in cold water (2-3 °C) and stirring [54, 55].

Supercritical fluid method

This is a novel technique recently applied for the production of SLN. A fluid is termed supercritical when its pressure and temperature exceed their respective critical value. The ability of the fluid to dissolve compounds increases. This technology comprises of several processes for nanoparticle production such as rapid expansion of supercritical solution (RESS), particles from gas saturated solution (PGSS), aerosol solvent extraction solvent (ASES), supercritical fluid extraction of emulsions (SFEE). The advantages of this technique includes avoidance of the use of solvents, particles obtained as a dry powder, instead of suspensions, requires mild pressure and temperature conditions. Carbon dioxide solution is the good choice as a solvent for this method [56-58].

Spray drying method

This is conceder to be the best alternative technique for Lyophollization technique. Lipid with melting point above 70 ºC was best suitable for this method. The best results were obtained with SLN concentration of 1% in a solution of trehalose in water or 20% trehalose in ethanol-water mixture [59, 60].

Sterilization of SLN

i.For parenteral and ocular administration SLN must be sterile [61].

ii.For lecithin stabilized SLN autoclaving is possible & it is not possible for sterically stabilized polymers [62].

iii.Physical stability during autoclave cannot be stated, it depends on composition [62].

iv.SLN dispersion can also be sterilized by filtration [62].

Route of administration

Solid Lipid Nanoparticle (SLN) are given by following route of administration (Figure 4)

Oral administration

The Formation of SLNs preparation which are given by oral route are aqueous dispersions. SLNs loaded dosage form such as tablets, pellets and capsule. The microclimate of the stomach favours particle aggregation due to the acidity and high ionic strength. It is to be expected that food will have a large impact on SLN performance [63].

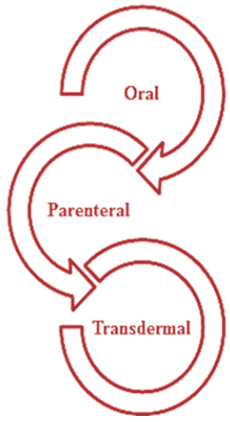

Figure 4: Route of administration (SLN)

Parenteral administration

SLN generally administered intravenously to animals. Distribution of SLN was found to have higher drug concentrations in lung, spleen and brain, while the solution led to more distribution into liver and kidneys. SLN showed higher blood levels in comparison to a commercial drug solution after intravenous [64].

Transdermal application

The smallest particle sizes are observed for SLN dispersions with low lipid content (up to 5%). Disadvantages of dermal administration are low concentration of the dispersed lipid and the low Viscosity. The incorporation of the SLN dispersion in an ointment or gel is necessary in order to achieve a formulation which can be administered to the skin [65].

Characterization of Solid Lipid Nanoparticle (SLN)

Measurement of particle size and zeta potential

Photon Correlation Spectroscopy (PCS) and Laser Diffraction (LD) are the most powerful techniques for routine measurements of particle size. PCS (also known as dynamic light scattering) measures the fluctuation of the intensity of the scattered light which is caused by particle movement. This method covers a size range from a few nanometers to about 3 microns. PCS is a good tool to characterize nanoparticles, but it is not able to detect larger micro particles. Electron Microscopy provides, in contrast to PCS and LD, direct information on the particle shape. The physical stability of optimized SLN dispersed is generally more than 12 months. ZP measurements allow predictions about the storage stability of colloidal dispersion [66, 67].

Photon Correlation Spectroscopy (PCS)

It is an established method which is based on dynamic scattering of laser light due to Brownian motion of particles in solution/suspension. This method is suitable for the measurement of particles in the range of 3 nm to 3 mm. The PCS device consists of laser source, a sample cell (temperature controlled) and a detector. Photomultiplier is used as detector to detect the scattered light. The PCS diameter is based on the intensity of the light scattering from the particles [68].

Electron Microscopy

Electron Microscopy methods such as Scanning Electron Microscopy (SEM) and Transmission Electron Microscopy (TEM) are used to measure the overall shape and morphology of lipid nanoparticles. It permits the determination of particle size and distributions. SEM uses electrons transmitted from the surface of the sample while TEM uses electrons transmitted through the sample [69].

Atomic Force Microscopy (AFM)

It is an advanced microscopic technique which is applied as a new tool to image the original unchanged shape and surface properties of the particles. AFM measures the force acting between surface of the sample and the tip of the probe, when the probe is kept in close proximity to the sample which results in a spatial resolution of up to 0.01 nm for imaging [70, 71].

Drug content determination

1ml of the formulation is diluted with 5ml 0.5% Surfactant solution and made to undergo sonication in a bath sonicator. Thereafter, the preparation is subjected to centrifugation at 12,000 rpm for 30 minutes at 4 °C. The supernatant is collected and absorbance is measured at the corresponding lambda max 430nm. The entrapment efficiency for the SLN was studied by taking 1ml of the formulation and subjected to centrifugation at 2000 rpm for 5 minutes. The supernatant was collected and the settled particles were washed with Polar Solvent. Again, the centrifuges and the supernatant were added together and the absorbance was measured at the Corresponding lambda max of in nm in particular drug by using ultraviolet-visible spectrophotometer [72]. The Entrapment Efficiency was measured by using the following formula: Drug concentration per ml of SLN X Total volume of dispersion / Total drug incorporated X 100.

Differential Scanning Calorimetric (DSC)

The geometric scattering of radiation from crystal planes within a solid allow the presence or absence of the former to be determined thus the degree of crystallinity to be assessed. DSC can be used to determine the nature and the speciation of crystallinity within nanoparticles through the measurement of glass and melting point temperature. The geometric scattering of radiation from crystal planes within a solid allow the presence or absence of the former to be determined thus the degree of crystallinity to be assessed. DSC can be used to determine the nature and the speciation of crystallinity within nanoparticles through the measurement of glass and melting point temperature [73, 74].

In vitro release

In vitro release was evaluated using a dialysis bag diffusion technique. Drug loaded solid lipid nanoparticles (2 mg) were placed in dialysis bags. The dialysis bag was tied at both ends. The dialysis bag was then placed 100 ml phosphate buffer solution (pH 7.4) at 37±1 ºC and under 100 rpm stirring. Samples (5 ml) were withdrawn at predetermined time interval and replaced with the same volume of fresh dialyzing medium and the withdrawn samples were assayed for drug content by measuring absorbance at 254 nm for ARM against the blank using UV spectrophotometer [75, 76].

Stability studies

For both SLNs dispersion and lyophilized SLNs, were stores at refrigerated condition(2-8 ºC) and at room temperature, 25 °C ± 2 °C (ambient) for 1 month and assay were evaluated immediately after production of the SLN and during one month (after 7, 15and 30 days) of storage at different temperature conditions. The final formulations were also examined visually for the evidence of caking and discoloration [77].

Application of Solid Lipid Nanoparticle (SLN)

Targeted drug delivery

A key area in drug delivery is the accurately targeting of the drug to cells or tissue of choice. Drug targeting systems should be able to control the fate of a drug entering the body. Today's delivery technologies are far away from the design of the so called "magic bullet", proposed by Paul Ehrlich at the beginning of the 20th century, in which the drug is precisely targeted to the exact side of action. Nanotechnology offers here another challenge to come to this goal a bit closer, to deliver the drug in the right place at the right time. Nanotechnology is expected to bring a fundamental change in manufacturing in the next few years and will have an enormous impact on Life Sciences, including drug delivery, diagnostics, nutraceuticals and the production of biomaterials. Targeting is the ability to direct the drug-loaded System to the site of interest. Two major mechanisms can be distinguished for addressing the desired sites for drug release: passive and active targeting [78, 79].

Health implication of SLN

It is important to differentiate between 'free' and 'fixed' nano particles. The formers pose a direct health threat because they are more difficult to contain due to airborne and can be inhaled. Nanoparticles can enter the human body in several ways via the Lungs where a rapid translocation through the blood stream to vital organ is possible, including crossing the BBB and absorptions by the intestinal tract and skin [79].

Lungs

Based on three particle types titanium dioxide (TiO2) carbon black and the diesel particles, hazards studies in rats, demonstrate that ultrafine nanoparticles administration to the lung produce more potent adverse effect in the form of inflammation and subsequent tumors compared with larger sized particles, of identical chemical composition at equivalent mass concentration. Surface properties such as surface chemistry may play a significant role in nanoparticles toxicity [79, 80].

Intestinal tract

The epithelium of the small and large intestinal is in close contact with ingested material so that nutrients can be utilized. A mixture of disaccharides, peptides, fatty acids and mono-glycerides generated but digestion in small intestine are further transformed and taken in the villi. Charged particles like carboxylated polystyrene nano particles or those composed of positively charged polymer exhibit poor oral bioavailability through electrostatic repulsions and means entrapment. The smaller the particles diameter the faster they could penetrate the mucus to reach the colonic enterocytes; 14nm diameter permeated within 2 mints, 415 nm particles look 30 mints while 1000 nm particles were unable to translocate this barrier [79, 80].

Skin

Particles 500-1000 nm in size theoretically beyond the realms of nano technology can penetrate and reach the lower levels of human skin, 128 and smaller particles are likely to deeper into the skin [79, 80].

SLN for cancer chemotherapy

In recent time chemotherapeutic drugs are vastly encapsulate in SLN. Developed cationic core-shell nanoparticles with carmustine contained with o6–Benzyl guanine shell for glioma therapy. On the other side, Xin-Hua Tian et al. (2011) did research on enhanced brain targeting of Temozolomide in polysorbate-80 coated poly-butyl-cyano-acrylate nanoparticles. In both the cases enhancement of bioavailability and less cytotoxicity was observed for chemotherapeutic agents. 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. 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 [81, 82].

SLN has targeted carrier for anticancer drug to solid tumour

Tamoxifen is an anticancer drug incorporated in SLN to prolong the release of drug after IV administration in breast cancer. Tumour targeting has been achieved with SLN loaded with drugs like Methotrexate and Camptothecin [81, 82].

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 [81, 82].

SLN applied to the treatment of malaria

The main disadvantages of conventional chemotherapeutic drugs in malaria treatment are development of multi drug resistance, and nonspecific targeting to inter cellular parasites. Nano sizer carriers have been receiving special attention with the aim of minimizing the side effects of drug therapy, such as poor bioavailability and the selectivity of drugs. Several nanosizer delivery systems have already proved their effectiveness in animal models for the treatment and prophylaxis of malaria [83, 84].

SLN for nasal application

Nasal administration was a promising alternative non-invasive route of drug administration due to fast absorption and rapid onset of drug action, avoiding degradation of labile drugs (such as peptides and proteins) in the GI tract and insufficient transport across epithelial cell layers. In order to improve drug absorption through the nasal mucosa, approaches such as formulation development and prodrug derivatisation have been employed. SLN has been proposed as alternative Tran's mucosal delivery systems of macromolecular therapeutic agents and diagnostics by various research groups. In a recent report, coating polymeric nanoparticles with PEG gave promising results as vaccine carriers. The role of PEG coating of Polylactic acid nanoparticles in improving the Trans mucosal transport of the encapsulated bioactive molecule reported to be successful by Tobio et al. 1998. This concept can be useful for solid lipid nanoparticles [85].

SLN for respiratory application

The lungs offer a high surface area for drug absorption by avoiding first-pass effects. Rapid drug absorption by aerosolization of drugs (in the 1-3 µm size range) occurs since the walls of alveoli in the deep lung are extremely thin. Lymphatic drainage plays an important role in the uptake of particulates in the respiratory system. SLN can be proposed as carriers of anti-cancer drugs in lung cancer treatment or peptide drugs to improve their bioavailability. Assessment of inhaled radio-labelled SLN bio distribution has been described and the data showed an important and significant uptake of the radio-labelled SLN into the lymphatic after inhalation. In a recent study, antitubercular drugs (rifampicin, isoniazid and pyrazinamide) were incorporated into various formulations of solid lipid particles ranged from 1.1–2.1 µm and formulations were nebulized to guinea pigs by mouth for direct pulmonary delivery. Nebulization of solid lipid particles carrying antitubercular drugs was observed to be successful in improving drug bioavailability and reducing the dosing frequency for better management of pulmonary tuberculosis [86, 87].

SLN for ocular application

Ocular drug administration via SLN has been reported several times. Bio-compatibility and mucoadhesive properties of SLN improve their interaction with ocular mucosa and prolong corneal residence time of the drug, with the aim of ocular drug targeting. Evaluated SLN as carriers for ocular delivery of Tobramycin in rabbit eyes. As a result SLN significantly enhanced the drug bioavailability in the aqueous humour. Also studied Pilocarpine delivery via SLN, which is commonly used in glaucoma treatment, earlier. They reported very similar results in order to enhance the ocular bioavailability of drug [88].

SLN for topical application

SLN are very attractive colloidal carrier systems for skin applications due to their various desirable effects on skin besides the characteristics of a colloidal carrier system. They are well suited for use on damaged or inflamed skin because they are based on non-irritant and non-toxic lipids. Researchers have reported intensively on the topical application of SLN. During the last few years, SLN have been studied with active compounds such as Vitamin E, Tocopherol acetate, Retinol, Ascorbyl palmitate, Clotrimazole, Triptolide, Podophyllotoxin and a nonsteroidal anti androgen RU 58841 for topical application. A completely new, recently discovered area of application is the use of SLN in sun-protective creams [89].

SLN 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 fulfil the requirements for an optimum particulate carrier system. Proteins and antigens intended for therapeutic purposes may be incorporated or adsorbed onto SLN, and further administered by parenteral routes or by alternative routes such as oral, nasal and pulmonary. Formulation in SLN confers improved protein stability, avoids proteolytic degradation, as well as sustained release of the incorporated molecules. Important peptides such as cyclosporine A, insulin, calcitonin and somatostatin have been incorporated into solid lipid particles and are currently under investigation. Several local or systemic therapeutic applications may be foreseen, such as immunisation with protein antigens, infectious disease treatment, chronic diseases and cancer therapy [90].

SLN as gene vector carrier

SLN can be used in the gene vector formulation. There are several recent reports of SLN carrying genetic/peptide materials such as DNA, plasmid DNA and other nucleic acids. The gene transfer was optimized by incorporation of a diametric HIV-1 HAT peptide (TAT 2) into SLN gene vector. The lipid nucleic acid nanoparticles were prepared from a liquid nanophase containing water and a water miscible organic solvent where both lipid and DNA are separately dissolved by removing the organic solvent, stable and homogeneously sized lipid-nucleic acid nanoparticle (70-100 nm) were formed. It's called genospheres. It is targeted specific by insertion of an antibody-lipo polymer conjugated in the particle [91, 92].

SLN for potential agriculture application

Essential oil extracted from *Artemisia arboreseens* L when incorporated in SLN, were able to reduce the rapid evaporation compared with emulsions and the systems have been used in agriculture as a suitable carrier of ecologically safe pesticides [93-97].

Conclusion

The main Application of SLNs are large scale up is possible and drug can be effective with in less dose incorporation. Moreover SLNs particles are in sub-micron size due to this, more effective surface area and good bioavailability is possible. Recent studies on brain targeting, lungs targeting, ophthalmic delivery provides significant cellular uptake of drugs with less cytotoxicity. Nanotechnology-enabled drug delivery is opening prospective future in pharmaceutics. The emergence of nanotechnology is likely to have a significant impact on drug delivery sector, affecting just about every route of administration from oral to injectable. Nanotechnology focuses on the very small and it is uniquely suited to creating systems that can better deliver drugs to tiny areas within the body. Nano-enabled drug delivery also makes it possible for drugs to permeate through cell walls, which is of critical importance to the expected growth of genetic medicine over the next few years. High physical stability and drug loading are advantageous to SLN.

Acknowledgement

All the peers, who are involved directly or indirectly for compilation of this article. It has been a great honor to work with such professionals.

Conflicts of interest

The author declares no conflict of interest.

References

[1]De Labouret A, Thioune O, Fesii H, Devissaguet JP, Puiseieux F. Application of an original process for obtaining colloidal dispersion of some coating polymers, preparation, characterization, industrial scaling up. Drug Develop Ind Pharm 1995; 21:229-41.

[2]Dingler A, Blum RP, Niehus H, Müller RH, Gohla S. Solid lipid nanoparticles (SLN™/Lipopearls™) – a pharmaceutical and cosmetic carrier for the application of vitamin E in dermal products. J Microencapsul 1999; 16(6):751-67.

[3]Ekambaram P, Sathali A, Priyanka K. Solid lipid nanoparticles: A review. Sci Revs Chem Commun 2012; 2(1):80-102.

[4]Elldem T, Speiser P, Hineal A. Optimization of spray-dried and congealed lipid microparticles and cha-racterization of their surface morphology by scanning electron microscopy. Pharm Res 1991; 8:47-54.

[5]Fahr A. and Liu X. Drug delivery strategies for poorly water soluble drugs. Exp Opin Drug Del 2007; 4(4):403-16.

[6]Freitas C. and Mullera RH. Spray drying of solid lipid nanoparticles (SLN TM). Eur J Pharm Biopharm 1198; 46(2):145-51.

[7]Friedrich I, Reichl S, Müller CC. Drug release and permeation studies of nanosuspensions based on solidified reverse micellar solutions (SRMS). Int J Pharm 2005; 305(1-2):167-75.

[8]Fundaro A, Cavalli R, Bargoni A, Vighetto D, Zara GP, Gasco MR. Non-stealth and stealth solid lipid nanoparticles (SLN) carrying doxorubicin: pharmacokinetics and tissue distribution after i.v. administration to rats. Pharm Res 2000; 42(4):337-43.

[9]Gasco MR. Method for producing solid lipid nanospheres with warm microemulsions. Pharm Tech Eur 1997; 9:52-58.

[10]Jenning V, Gysler 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(3):211-18.

[11]Jenning V, Lippacher A, Gohla SH. Medium scale production of solid lipid nanoparticles (SLN) by high pressure homogenization. J Microencapsul 2002; 19:1-10.

[12]Kreuter J. Peroral administration of nanoparticles. Adv Drug Del Rev 1991; 7:71-86.

[13]Kreuter J. Nanoparticulate systems for brain delivery of drugs. Adv Drug Deliv Rev 2001; 47(1):65-81.

[14]Lai F, Wissing SA, Muller RH, Fadda, A.M. Essential oil-loaded solid lipid nanoparticles for potential agriculture application: prepa-ration and characterization. AAPS Pharm Sci Tech 2006; 7(1):E2-E12.

[15]Mukherjee S, Ray S, Thakur RS. A review solid lipid nanoparticle. J Pharm Sci 2009; 22(2):131-38.

[16]Hu EQ, Yuan H, Zhang HH, Fang M. Nanoparticulate system of nanotechnology. Int J Pharm 2002; 239:121-28.

[17]Reddy B AK, Debnath S, Babu MN. Nanoemulsion: A novel approach for lipophilic drugs -a review. Asian J Pharm Res 2013; 3(2):84-92.

[18]Mishra RK, Soni GC, Mishra R. Nanoemulsion: A novel drug delivery tool. Int J Pharm Res Rev 2014; 3(7):32-43.

[19]Sessa M, Luisa MB, Ferrari G, Servillo L, Castaldo D, D'Onofrio N, et al. Bioavailability of encapsulated resveratrol into nanoemulsion-based delivery systems. Food Chem 2014; 147:42-50.

[20]Shah P, Bhalodia D, Shelat P, Nanoemulsion: A pharmaceutical review. Sys Rev Pharm 2010; 1(1):24.

[21]Debnath S, Gampa VK. Nanoemulsion-A method to improve the solubility of lipophilic drugs. Pharmanest-An Int J Adv Pharm Sci 2011; 2(3):72-83.

[22]Sharma1 N, Bansa M, Visht S, Sharma PK, Kulkarni GT. Nanoemulsion: A new concept of delivery system. Chron Young Scientists. 2010; 1(2):2-6.

[23]Dhas A, Deshmulkh G, Andhale V, Patil P, Pansare S, Mundke S. Review on Nanoemulsion: A Novel Drug Delivery System. Ejbps. 2016; 3(4):156-66.

[24]Khasia HV and Khasia VD. A review on self emulsifying drug delivery system. Int J Pharm Chem Sci 2012; 1(1):353-59.

[25]Voorham J, Haaijer-Ruskamp FM, Stolk RP. For the groningen initiative to analyze type 2 diabetes treatment group. influence of elevated cardiometabolic risk factor levels on treatment changes in type 2 diabetes. Diabetes Care 2008; 31:501-03.

[26]Harris SB, Kapor J, Lank CN. Clinical inertia in patients with T2DM requiring insulin in family practice. Can Fam Physician 2010; 56:418-24.

[27]Zafar A, Davies M, Azhar A, Khunti K. Clinical inertia in management of T2DM. Prim Care Diabetes 2010; 4:203-07.

[28]David S, Michael F. Preclinical evaluation of pharmacokinetic pharmacodynamic rationale for oral CR metformin formulation. J Control Rel 2001; 71:107-15.

[29]Vidon N, Chaussade S. Metformin in the digestive tract. Diabetes Res Clin Pract 1988; 4:223-29.

[30]Wajchenberg BL. Beta-cell failure in diabetes and preservation by clinical treatment. Endocr Rev 2007; 28(2):187-218.

[31]Van BR, Gorter K, Stolk R. Clinical inertia in general practice: widespread and related to the outcome of diabetes care. Fam Pract 2009; 26:428-36.

[32]Ebenezer AN, Terri WJ. Management of type 2 diabetes. Metab Clin Expert 2011; 60:1-23.

[33]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; 50:161-77.

[34]Hoffman A, Ziv E. Pharmokinetic considerations of new insulin formulations and routes of administration. ClinPharmacokinet 1997; 33:285-301.

[35]Mugumu H. Transdermal delivery of CaCO3- Nanoparticles Containing Insulin. Diabetes Technol Ther 2006; 8(3):369-74.

[36]Michael UA, Yukako Y. Pharmacodynamic, pharmacokinetic profiles of metformin hydrochloride from a mucoadhesive formulation of a polysaccharide with antidiabetic property in streptozotocin-induced diabetic rat models. Biomat 2004; 25:3041-48.

[37]Ekambaram P, Sathali A, Priyanka K. Solid lipid nanoparticles: A review. Sci Rev Chem Commun 2012; 2(1):80-102.

[38]Elldem T, Speiser P, Hineal A. Optimization of spray-dried and congealed lipid microparticles and cha-racterization of their surface morphology by scanning electron microscopy. Pharm Res 1991; 8:47-54.

[39]Muller RH, Mäder K, Gohla SH. Solid lipid nanoparticles for controlled drug delivery- A review of the state of the art. Eur J Pharm Bio Pharm 2000; 50(1):161-77.

[40]Trotta M, Debernardi F, Caputo O. Preparation of solid lipid nanoparticles by a solvent emulsification-diffusion technique. Int J Pharm 2003; 257:153-60.

[41]Chouksey R, Jain AK, Pandey H, Maithil A. Development and bioavailability studies of Atorvastatin nanoemulsion. Int J Pharm Life Sci 2011; 2(8):982-88.

[42]Kaur G, Chandel P, Harikumar SL. Formulation development of self nanoemulsifying drug delivery system (snedds) of Celecoxib for improvement of oral bioavailability. Pharmacophore 2013; 4(4):120-33.

[43]Makadia HA, Bhatt AY, Parmar RB, Paun JS, Tank HM. Self-nano emulsifying drug delivery system (SNEDDS): Future aspects. Asian J Pharm Res 2013; 3(1):21-27.

[44]Gadhave AD. Nanoemulsions: Formation, stability and applications. Int J Res Sci Adv Tech 2014; 2(3):38-43.

[45]Wooster TJ, Matt G, Peerasak S. Impact of oil type on nanoemulsion formation and ostwald ripening stability. Langmuir 2008; 24:12758-65.

[46]Jincy J, Krishnakumar K, Anish J, Dineshkumar B. Nano-Emulsion in Pharmaceuticals: A Review. Curr Res Drug Target 2015; 5(1):1-4.

[47]Kumar A, Sharma S., Kamble R. Self-Emulsifying Drug Delivery System (Sedds): Future Aspects. Int J Pharm Pharm Sci 2010; 2(4):7-13.

[48]Nazzal S, Smalyukh II, Lavrentovich OD, Khan MA. Preparation and in vitro characterization of a eutectic based Semisolid self-nanoemulsified drug delivery system (SNEDDS) of ubiquinone: mechanism and progress of emulsion formation. Int J Pharm 2012; 235:247-65.

[49]Uner M, Yener G. solid lipid nanoparticles overview. Int J Nanomed 2007; 5(1):289-300.

[50]Tian XT, Lin XN, Wei F, Huang ZC, Wang P, Ren L, Yi D. Enhanced brain targeting of Temozolomide in polysorbate-80 coated polybutyl cyanoacrylate nanoparticles. Int J Nano Med 2011; 6:445-52.

[51]Arora P, Sharma S, Garg S. Permeability issues in nasal drug Delivery. Drug Discov Today (DDT). 2002; 7(18):967-75.

[52]Pagar S, Dattatraya MS, Bhanudas SR. A Review on Intranasal Drug Delivery System. J Adv Pharm Edu Res 2013; 3(4):333-46.

[53]Kumar PT, Sirisha BP, Narayana RK. & Reddy GN. Nasal Drug Delivery: A Potential Route for Brain Targeting. The Pharm Innov J 2013; 2(1):77-85.

[54]Vila A, Gill H, McCallion O, Alonso MJ. Trans-port of PLA-PEG particles across the nasal mucosa: effect of particle size and PEG coating density. J Control Release 2004; 98(2):231-44.

[55]Videira MA, Botelho MF, Santos AC, Gouveia LF, de Lima JJ, Almeida AJ. Lymphatic uptake of pulmonary delivered solid lipid nanoparticles. J Drug Target 2002; 10(8):607-13.

[56]Dingler A, Blum RP, Niehus H, Müller RH, Gohla S. Solid lipid nanoparticles (SLN™/Lipopearls™) – a pharmaceutical and cosmetic carrier for the application of vitamin E in dermal products. J Microencapsul 1999; 16(6):751-67.

[57]Ahlin P. Optimization of procedure parameters and physical stability of solid lipid nanoparticles in dispersions. Acta Pharm 1998; 48:257-67.

[58]Siekmann B, Westesen K. Submicron-sized parenteral carrier systems based on solid lipids. Pharm Pharmacol Lett 1992; 1:123-26.

[59]Vivek K, Reddy H, Murthy RSR. Investigations of the effect of the lipid matrix on drug entrapment, in vitro release, and physical stability of olanzapine loaded solid lipid nanoparticles. AAPS PharmSciTech 2007; 8(4):E1-E9.

[60]Zimmermann E, Muller RH, Madar K. Influence of different parameters on reconstitution of lyophilized SLN. Int J Pharm 2000; 196:211-13.

[61]Illum L. Nasal drug delivery-possibilities, problems and solutions. J Control Release 2010; 87:187-98.

[62]Misra A, Kher G. Drug delivery systems from nose to brain. Curr Pharm Biotech 2012; 13:2355-79.

[63]Falcao A, Pires A, Fortuna A. & Alves G. Intranasal drug delivery: how, why and what for. J Pharm Pharm Sci 2009; 12(3):288-311.

[64]Bahadur S, Pathak K. Physicochemical and physiological considerations for efficient Nose-to-brain targeting. Expert Opin Drug Deliv 2012; 9(1):19-31.

[65]Jadhav KR, Gambhire MN, Shaikh IM, Kadam VJ, Pisal SS. Nasal drug delivery system-factors affecting and applications. Curr Drug Ther 2007; 2(1):27-38.

[66]Soeda A, Inagaki A, Oka N, Ikegame Y, Aoki H, Yoshimura Si, Nakashima S, Kunisada T, Iwama T. Epidermal Growth factor plays a crucial role in mitogenic regulation of human brain tumor stem cells. The J Biol Chem 2008; 283(16):10958-966.

[67]Basu S & Bandopadhyay AK. Nasal drug delivery: An overview. Int J Pharm Sci Tech 2010; 1:1-20.

[68]Pandey R, Khuller GK. Solid lipid particle based inhalable sustained drug delivery system against experimental tuberculosis. Tuberculosis 2005; 85(4):227-34.

[69]Cavalli R, Gasco MR, Chetoni P, Burqalassi S, Saettone MF. Solid lipid nanoparticles (SLN) as ocular delivery system for tobramycin. Int J Pharm 2002; 238(1-2):241-45.

[70]Cavalli R, Marengo E, Rodriguez L, Gasco MR. Effects of some experimental factors on the production process of solid lipid nanoparticles. Eur J Pharm Biopharm 1996; 42(2):110-15.

[71]Sznitowska M, Gajewska M, Janicki S, Radwanska A, Lukowski G. Bioavailability of diazepam from aqueous-organic solution, submicron emulsion and solid lipid nanoparticles after rectal administration in rabbits. Eur J Pharm Biopharm 2001; 52(2):159-63.

[72]Sznitowska M, Janicki S, Gajewska M, Kulik M. Investigation of diazepam lipospheres based on Witepsol and lecithin for oral or rectal delivery. Acta Pol Pharm 2000; 57(1):64.

[73]Wissing SA, Muller RH. Cosmetic applications for solid lipid nanoparticles (SLN). Int J Pharm 2003; 254(1):65-68.

[74]Dingler A, Blum RP, Niehus H, Muller RH, Gohla S. Solid lipid nanoparticles (SLN™/Lipopearls™) a pharmaceutical and cosmetic carrier for the application of vitamin E in dermal products, J Microencapsul 1999; 16(6):751-67.

[75]Wissing SA, Muller RH. A novel sunscreen system based on tocopherol acetate incorporated into solid lipid nanoparticles. Int J Cosmet Sci 2001; 23(4):233-43.

[76]Rainer H, Karsten M, Sven G. Solid lipid nanoparticles (SLN) for controlled drug delivery -a review of the state of the art. Eur J Pharm Biopharm 2000; 50(1): 161-77.

[77]Melike U, Gulgun Y. Importance of solid lipid nanoparticles (SLN) in various administration routes and future perspectives. Int J Nanomedicine 2007; 2(3):289-300.

[78]Pal K, Bhandari R, Bhandari S, Kakkur L. Potential of solid lipid nanoparticles in brain targeting. J Cont Rel 2008; 127:97-109.

[79]Sailaja A, Amareshwar P, Chakravarty P. Formulation of solid lipid nanoparticles and their applications. CPR 2011; 1(2):197-203.

[80]Ireson CR. Metabolism of the cancer chemopreventive agent curcumin in human and rat intestine. Cancer Epidemiol Biomarkers Pre 2002; 11:105-11.

[81]Korsmeyer RW, Gurny R, Docler E, Buri P, Peppas NA. Mechanism of solute release from porous hydrophilic polymers. Int J Pharm 1983; 15:25-32.

[82]Li HL, Zhao XB, Ma YK, Zhai GX. Enhancement of gastrointestinal absorption of quercetin by solid lipid nanoparticles. J Control Release 2009; 133:238-44.

[83]Luo YF, Chen DW, Ren LX, Zhao XL. Solid lipid nanoparticles for enhancing vinpocetine's oral bioavailability. J Control Release 2006; 114:53-59.

[84]Rahman SMH, Telny TC, Ravi TK, Kuppusamy S. Role of surfactant and pH in dissolution of curcumin. Ind J Pharm Sci 2009; 71:139-42.

[85]Ranajit KB, Ishita C, kaushik B, Uday B. Turmeric and curcumin: Biological actions and medicinal applications. Curr Sci 2004; 87:44-53.

[86]Rao CV, Rivenson A, Simi B, Reddy BS. Chemoprevention of colon carcinogenesis by dietary curcumin, a naturally occurring plant phenolic compound. Cancer Res 1995; 55:259-66.

[87]Sargent JM. The use of the MTT assay to study the drug resistance in fresh tumor samples. Recent Results Cancer Res 2003; 161:13-25.

[88]Schwarz C. Mehnert W. Freeze-drying of drug free and drug loaded solid lipid nanoparticles. Int J Pharm 1997; 157:171-79.

[89]Shaikh J, Ankola D, Beniwal DV, Singha D. Nanoparticle encapsulation improves oral bioavailability of curcumin by at least 9-fold when compared to curcumin administered with piperine as absorption enhancer. Eur J Pharm Sci 2009; 37:223-30.

[90]Pal I, Kaur A. Potential of solid lipid nanoparticles in brain targeting. Science direct, Journal of control release 2008; 127:97-109.

[91]Pawar R, Gopalakrishnan C, Bhutani KK. Dammarane triterpene saponin from Bacopa monniera as the superoxide Inhibitor in polymorph nuclear cells. Planta Medica 2001; 67:752-54.

[92]Rai D, Bhatia G, Palit G, Pal R, Sinhg S, Singh HK. Adaptogenic effect of Bacopa monniera. Pharmacol Biochem Behave 2003; 75(4):823-83.

[93]Rahman Z. Non-destructive methods of characterization of Risperidone solid lipid nanoparticles. Eur J Pharm Biopharm 2010; 4(8):88-92.

[94]Roodenrys S, Booth D, Bulzomi S, Phipps A, Micallef C, Smoker J. Chronic effects of Brahmi (Bacopa monnieri) on human memory. Neuro Psychopharmacol 2002; (27):279-81.

[95]Sarachandan M. A review on nanotechnology in solid lipid nanoparticles. IJPDT 2012; 2 (1):45-64.

[96]Mark R and Gilbert Md. Designing clinical trials for brain tumors: The next generation. Curr Oncol Report 2007; 9:49-54.

[97]Pardeike J, Hommoss A, Muller RH. Lipid nanoparticles in cosmetic and pharmaceutical dermal products. Int J Pharm 2009; 366(1-2):170-84.