CIBTech Journal of Pharmaceutical Sciences ISSN: 2319–3891 (Online)
An Open Access, Online International Journal Available at http://www.cibtech.org/cjps.htm
2018 Vol.7 (3) July-September, pp.1-8/Gazi and Krishnasailaja
Review Article

SOLID LIPID NANOPARTICLES (SLNS) APPLICATIONS: A REVIEW

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ABSTRACT
Solid lipid nanopaticles were developed in early 1990s as an substitute to other traditional colloidal carriers like liposomes, polymeric nanoparticles and emulsions as they have advantages like controlled drug release and targeted drug delivery with increased stability. Solid Lipid Nanoparticles (SLNs) as novel lipid based nanocarriers with size range between 10 to 1000nm. Solid lipid nanoparticle (SLN) dispersions have been anticipated as a new type of colloidal drug carrier system suitable for intravenous administration. The system consists of spherical solid lipid particles in the nanometer ranges, which are dispersed in water or in aqueous surfactant solution. This paper gives an overview of SLNs potential applications in pharmaceutical field, drug delivery, cosmetics, research, clinical medicine and other related sciences.

Keywords: *Solid lipid Nanoparticles (SLNs), Colloidal Carriers, Nanostructure Lipid Carrier (NLCs), Applications*

INTRODUCTION
The prefix "nano" coined from the Greek word "nanos," meaning dwarf. Prof. Norio Taniguchi at Tokyo Science University coined the term "Nanotechnology" in 1974. This term is further used by Drexler in 1986 in his book Engines of creation: The Corning Era of Nanotechnology. A variety of novel drug delivery systems prepared by polymers and solvents present in the market are still very limited in use because of their high production cost, high polymer cost, toxicity, and allergy of polymer and solvent in the body (De villiers *et al.*, 2008) . To conquer these problems related with novel drug delivery systems prepared by polymer and solvent, many researchers have diverted their attention to lipid-based nanocarrier systems such as liposomes, transfersomes, ethosomes, solid lipid nanoparticles (SLN), nanostructured lipid carriers, lipid drug conjugates, etc (Chen *et al.*, 2010). In the last decade, lipids have gained much attention as carriers for the delivery of drugs with poor water solubility. If any therapeutic agent is added into it, therapeutic usefulness of drugs will be maximized. Lipid-based nanocarriers are an acceptable approach and have gained significance in the current era because of their various prominent properties, such as low toxicity, improved bioavailability, high biocompatibility, high drug-loading efficiency, and high protection from degradation in the gastro intestinal tract (Liu *et al.*, 2010). Lipid nanocarriers can load both hydrophilic and lipophilic drugs and also be administered by various routes such as oral, topical, ocular, parenteral, and pulmonary routes. Solubility is a rate-limiting step in the case of lipophilic drugs (BCS Class II and IV), which can be greatly modified by formulation of lipid nanocarriers. Similarly, lipidic nanocarriers can also increase the permeability of most of the hydrophilic drugs (BCS Class I and III), which is the rate-limiting step this case. Novel lipid excipients used for the development of lipid nanocarriers play a very important and vital role for enhancing the therapeutic effect of various drugs. Various lipids used for the preparation of lipid nanocarriers are those which are biodegradable and showing biocompatibility in physiological media or biological fluid (Muller *et al.*, 1996).
Solid lipid nanoparticles (SLNs) are often referred to as the first generation of lipid nanoparticles. . SLNs have roused increasing attention in the scientific community as promising drug carriers due to their simplicity and versatility. By definition, they have small particle sizes and, in fact, the smaller the particle size the more likely they are to remain stable, the more likely they are to exhibit targeted responses, and the more likely they are to encapsulate large amounts of drugs. The challenge, with SLN production, is to produce a small particle size but without generating a polydisperse sample. SLNs are colloidal particles

derived from oil-in-water emulsions by replacing liquid lipids with a lipid matrix that is solid at body temperature and stabilized by the use of surfactants.SLN are prepared by a combination of lipids, fatty alcohol, wax, triglycerides and surfactants (Swathi *et al.,* 2010).

APPLICATIONS OF SOLID LIPID NANOPARTICLES

Per oral administration

Per oral administration forms of SLN may include aqueous dispersions or SLN loaded traditional dosage forms, e.g. tablets, pellets or capsules. The microclimate of the stomach favors particle aggregation due to the acidity and high ionic strength. It can be expected, that food will have a large impact on SLN performance. (Pandey *et al., 2005)* formulated and evaluated the chemotherapeutic potential of solid lipid nanoparticles incorporating antitubercular drugs following oral administration to mice and suggested that oral SLN based antitubercular drug therapy forms a sound basis for reducing dosing frequency and improving patient compliance for better management of tuberculosis . Zhang *et al.* administered orally insulin-loaded SLN and WGA-modified SLN to rats and demonstrated that both of these formulations promoted the intestinal absorption of insulin after oral administration (L.Zhang et al., 2008).

For nasal application

Nasal administration was a promising alternative noninvasive 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 (Lee *et al*., 1994). In order to improve drug absorption through the nasal mucosa, approaches such as formulation development and prodrug derivatization have been employed. SLN has been proposed as alternative transmucosal delivery systems of macromolecular therapeutic agents and diagnostics by various research groups (Muller and Keck 2004; Prego *et al.,* 2005). In a recent report, coating polymeric nanoparticles with PEG gave promising results as vaccine carriers (Vila *et al.,* 2004). 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. SLN proved to be a suitable alternative carrier for the nasal administration of the antiemetic drug ondansetron. Other more recent examples are the SLN formulations for intranasal administration with budesonide, ropinirole, alprazolam and many others. Brain targeting of the SLN was achieved by intranasal administration. An example is the risperidone loaded SLN which showed promising brain bioavailability after the nasal administration in mice (Pandey *et al., 2005)*.

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 (Agu *et al*., 2001; Banga 2003). 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-labeled SLN bio distribution has been described and the data showed an important and significant uptake of the radio-labeled SLN into the lymphatic after inhalation (Videira *et al.,* 2002). 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 (Pandey *et al.,* 2005a and 2005b). 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. SLN and NLC are suitable carriers with good tolerability and low toxicity for pulmonary application. Their small size enables their incorporation in microparticles and drops which can effectively reach the alveoli. Moreover SLN and NLC can improve the pharmacokinetic parameters after administration *via* the lungs. Various examples include itraconazole, phenethylisothiocyanate, celecoxib, beclomethasone, thymopentin. Most of these formulations are intended for use in the treatment of infectious diseases and cancer (Pardeike *et al.,* 2010).

For ocular application

Many investigations have been made to use nanoparticles for prolonged release of drugs to the eye. The basic problem of ophthalmologic formulation is the fast removal from the eye, which implies clearance of the applied drug through the nose. It could be shown for nanoparticles that an increased adhesiveness is available leading to higher drug levels at desired site of action. However, the basic problem was that the nanoparticles are of limited toxicological acceptance. It was shown by Gasco that SLN have a prolonged retention time at the eye. This was confirmed by using radiolabiled formulations and γ-scintigraphy. The lipids of SLN are easy to metabolize and open a new ways for ophthalmological drug delivery without impairing vision (Araujo J *et al.,* 2009). Delivery of drugs *via* nanotechnology-based products fulfils three main objectives, enhanced drug permeation, controlled drug release and higher targeting potential. (Attama *et al., 2008)* prepared sodium diclofenac loaded lipid nanoparticles combining the homolipid from goat (goat fat) and a phospholipid, with high encapsulation efficiency applying hot high-pressure homogenization technique. Administration of this formulation to bioengineered human cornea demonstrated sustained release of the analgesic drug. Furthermore, permeation of sodium diclofenac through the corneal construct was improved by surface tailoring of nanoparticles with phospholipid, which showed better performance for ocular administration. (Cavalli *et al.,* 2002) evaluated SLN as carriers for ocular delivery of tobramycin in rabbit eyes. Drug concentration in the aqueous humor was determined up to six hours. As a result SLN significantly enhanced the drug bioavalability in the aqueous humor**.** (Cavalli *et al.,* 1995) also studied pilocarpin 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. Another research group incorporated poorly water soluble drugs (hydrocortisone, estradiol hemihydrate and pilocarpine base) into SLN and performed in vitro drug permeation study through human organotypical cornea construct (Friedrich *et al.,* 2005). They observed high loading capacity, because drugs were nearly completely incorporated within the nanoparticles due to their high lipophilic character. Consequently, permeation studies indicated prolonged drug release in all the formulations. In industrial fields, the incorporation of several antibiotics has been attempted in SLN, due to their broad antimicrobial spectrum. For an instance, Ocusolin^{TM} from AlphaRx is a gentamicin loaded-SLN product in the form of ophthalmic solution (Friedrich *et al.,* 2005).

For parenteral application

Parenteral drug delivery took a major leap after successful development of the submicronic parenteral fat emulsion in the 1960s. Quick commercialization of submicron emulsion based products, such as Diazemuls (diazepam) and Diprivan (propofol), indicated the interest of pharmaceutical industries in colloidal carriers. (Wissing *et al.,* 2004) intensively reviewed parenteral use of SLN. SLN are very suitable for systemic delivery because they consist of physiologically well-tolerated ingredients and they have good storage capabilities after lyophilization and/or sterilization. When injected intravenously, SLN are sufficiently small to circulate in the microvascular system and prevent macrophage uptake in case of hydrophilic coating. Therefore, SLN have been suggested for viral and non-viral gene delivery. Cationic SLN has been demonstrated to bind genes directly via electrostatic interactions, and have potential benefits in targeted gene therapy in treatment of cancer. The charge of particles can also be modulated via the composition, thus allowing binding of oppositely charged molecules (Olbrich *et al.,* 2001; Tabatt *et al,.* 2004; Pedersen *et al*., 2006).

Treatment of central nervous system diseases such as brain tumors, AIDS, neurological and psychiatric disorders is often constrained by the inability of potent drugs to pass blood brain barrier (BBB). Hydrophilic coating of colloids improves the transport of these through BBB and tissue distribution (Kreuter 2001; Wang *et al.,* 2002). (Fundaro *et al*., 2000**)** prepared doxorubicin loaded stealth and non-stealth SLN and observed that the stealth nanoparticles were present in blood at higher concentrations than non-stealth SLN after 24 h following intravenous administration. (Reddy *et al.,* 2005*)* studied the influence of the route of administration on tumor uptake and biodistribution of etoposide loaded solid lipid nanoparticles in mice bearing Dalton's lymphoma after subcutaneous, intravenous and

intraperitoneal injections. It was observed that subcutaneous injection reduced the biodistribution of SLN to all the tissues studied, whereas intravenous injection resulted in lower levels of etoposide-loaded SLN in RES rich organs compared to free etoposide. SLN experienced significantly higher brain distribution after intraperitoneal injection, indicating its potential application in targeting etoposide to brain tumors. SLN products of several pharmaceutical companies can be given as follows: cationic solid lipid nanoparticles (SLN) for gene transfer namely TransoPlex^{R} was produced by PharmaSol DDS (Germany) (Olbrich *et al.*, 2001; www.pharmasol-berlin.de).AlphaRx (USA) is developing vancomycin and gentamicin products with Vansolin^{TM} and Zysolin^{TM} trade names
(www.alpharx.com). They are very effective in treatment of life-threatening infectious disease such as pneumonia. The intention of incorporating them into SLN has been to increase their efficacy while reducing their side effects. SkyePharma (UK) also has formulations of nanoparticulate technology which includes nanosuspensions and solid lipid nanoparticles under preclinical development (Powers2005; www.skyepharma.com).

For rectal application

When rapid pharmacological effect is required, in some circumstances, parenteral or rectal administration is preferred. Conventional rectal delivery of drugs is also very often used for pediatric patients all over the world due to easy application. In the meantime, plasma levels and therapeutic efficacy of rectally administered drugs were reported to be higher compared with those given orally or intramuscularly in the same dose (Kanto 1975; Sznitowska *et al.*, 2001). A few reports are available on the rectal drug administration via SLN in the literature (Sznitowska *et al.*, 2000). (Sznitowska *et al.*, 2001) incorporated diazepam into SLN for rectal administration in order to provide a rapid action. They applied SLN dispersions on rabbits and performed bioavailability studies. They found that lipid matrix which is solid at body temperature is not an advantageous system for diazepam rectal delivery. They decided to employ lipids which melt around body temperature in their next experiments. This area seems very open to investigation, especially when the benefits of rectal route are taken into consideration. PEG coating seems to be a promising approach on rectal delivery and consequently, enhancement of bioavailability.

For potential agriculture application

Essential oil extracted from *Artemisia arborescens* 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 pesticide (Lai *et al.*, 2006).

For treatment of parasitic diseases

Parasitic diseases (like malaria, leishmaniasis, and tryanosomiasis) are one of the major problems around the globe. Antiparasitic chemotherapy is the only choice of treatment for these parasitic infections, the reason for this is that these infections do not elicit pronounced immune response hence effective vaccination may not be possible. Solid lipid nanoparticles (SLNs) and nano structured lipid carriers (NLCs) represent a second generation of colloidal carriers and have emerged as an effective alternative to liposomes mainly due to their better stability profile, ease of scalability and commercialization and relative cost efficacy. Moreover, SLN and NLC due to their particulate nature and inherent structure exhibit good potential in the treatment of parasitic infections. Recent reports including our investigation have validated their usefulness at least to some extent. However, the need of hour is to undertake extensive investigations on SLN and NLC matrices in order to extend their versatility with respect to encapsulation ability and target ability and to arrive at an adaptable, effective and economical approach for the delivery of anti-parasitic drugs (Sven Gohla *et al.*, 2000).

For treatment of rheumatoid arthritis

SLNs of actarit were developed to enhance its therapeutic efficiency while decreasing its side effects, such as nephrotoxicity and gastrointestinal disorders. On intravenous injection it was found that there was a 10-fold increase in mean retention time and an increase of 1.88 times in the area under curve (MX) of actarit-containing SLNs. compared to actarit solution. A threefold increase in the targeting efficiency was observed with actarit SLNs, when compared to actarit solution (Joshi and MilIler. *et al.*, 2008).

For breast cancer and lymph node metastases

Mitoxantrone-loaded SLN local injections were formulated to reduce the toxicity and improve the safety and bioavailability of drug efficacy of doxorubicin (Dox) has been reported to be enhanced by incorporation in SLNs. In the methodology the Dox was complexed with soybean -oil-based anionic polymer and dispersed together with a lipid in water to form Dox-loaded solid lipid nanoparticles. The system has enhanced its efficacy and reduced breast cancer cells (Misra *et al.,* 2002).

For Diabetes

Diabetes mellitus is one of the most common metabolic diseases worldwide. Hyperglycemia caused by diabetes is a serious pathologic condition producing neurological and CV damage. Researchers focus considerable attention on SLNs as the carriers to protect peptides and proteins known for their sensitivity to various environmental factors such as pH, temperature, and ionic strength. Zhang et al designed SLNs coated with stearic acid octaarginine as carriers for insulin. Octaarginine is a cell-penetrating peptide that can facilitate cellular uptake of some drugs. The size and insulin encapsulation of the octaarginine-coated SLNs were 162nm and 77%, respectively. Octaarginine-coated and noncoated SLNs increased Caco-2 cell uptake by 2.3 times and 18.4 times, respectively. The SLNs containing octaarginine showed a significantly higher hypoglycemic effect (3-fold) in rats compared to noncoated SLNs. Oral delivery of insulin may significantly improve the quality of life of diabetes patients who routinely receive insulin by the subcutaneous route (Zhang *et al*., 2012).

Transdermal application

The smallest particle sizes are observed for SLN dispersions with low lipid content (up to 5%). Both the low concentration of the dispersed lipid and the low viscosity are disadvantageous for dermal ad-ministration. In most cases, 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. The incorporation step implies a further reduction of the lipid content. An increase of the solid lipid content of the SLN dispersion results in semisolid, gel-like systems, which might be acceptable for direct application on the skin (Bhaskar *et al.,* 2009).

For topical application

Regarding the regularity aspect, topical application is relatively unproblematic. The major advantages for topical products are the protective properties of SLN for chemically labile drugs against degradation and the occlusion effect due to film formation on the skin. Especially in the area of cosmetics there are many compounds such as retinol or vitamin C which cannot be incorporated because of the lack of chemical stability. Incorporation of retinol is only possible when applying certain protective measures during production (e.g. noble gasing) and using special packing materials (e.g. aluminium). SLN are a very promising tool for topical delivery and attracted a lot of attention from researchers for preparing SLNs for topical applications. SLN are prepared by nontoxic and nonirritant lipids, so they are suited for damaged or inflamed skin (Wissing and MilIler. 2003). The isotretinoin-loaded lipid nanoparticles were formulated for topical delivery of drug. Production of the flurbiprofen-loaded SLN gel for topical application offer a potential advantage of delivering the drug directly to the site of action, which will produce higher tissue concentrations. Studies reported for topical preparations are:

1. Dingier has prepared SLN and NLCs of Vitamin E (Dingier *et al.,* 1999).
2. Wissing and Muller have prepared SLN and NLCs of tocopherol acetate (Wissing and Muller, 2001).
3. Jenning and coworkers have prepared SIN and NI.Cs of retinol (Jenning *et al.,* 2000a, b).

SLNs in Cosmetics

Sln as topical vehicles for sunscreens, anti-acne and anti-ageing actives Lipid nanoparticles proved to have a synergistic effect of the UV scattering when used as vehicles for molecular sunscreens. Advantages taken from these observations are the possibility to reduce the concentration of the molecular sunscreen, consequently its potential side effects, as well as the costs of formulation of expensive sunscreens. In addition, lipid nanoparticles can be explored to formulate sunscreen products with lower and medium sun protection factor. The loading capacity of lipid nanoparticles depends mainly on the

miscibility of the active in the lipid selected for their production. It can range from about 4% (e.g. ferulic acid), 25% (e.g. tocopherol), or even up to 50% and more, in case of well lipid miscible lipophilic actives (Wissing and Muller, 2002). SLNs as topical vehicles for perfumes, fragrances and repellents prolonged release of perfumes has the advantage of creating a once-a-day application with prolonged effect over several hours. This was demonstrated to be possible with the use of lipid nanoparticles in comparison with typical o/w emulsions. The release can be slowed down by incorporating perfumes/fragrances in a SLN instead of an oil droplet. In the first 3h, similar release patterns were observed between lipid nanoparticles and oil droplets because of the release of perfume from the outer layers of the particles. During the remaining 10 h, the release from SLN was prolonged. After 6 hr 100% of perfume was released from the emulsion, but only 75% was released from SLN. This property can also be advantageous for the delivery of insect repellents to be applied onto the skin. SLN have also been employed for dermal application of cosmeceuticals like molecular sunscreens and as carriers for UV blockers. Cosmetic benefits of lipid nanoparticles include enhancement of the chemical stability of actives, film formation on skin, controlled occlusion, skin hydration, drug targeting, enhanced skin bioavailability and physical stability of lipid nanoparticles as topical formulations. An *in vivo* study showed increased skin hydration, by 31%, after 4 weeks after addition of 4% SLN to a conventional cream formulation (Muller *et al.*, 2002).

CONCLUSION

Solid Lipid Nanoparticle (SLN) Solid lipid nanoparticles (SLNs) are often referred to as the first generation of lipid nanoparticles. SLNs have roused increasing attention in the scientific community as promising drug carriers due to their simplicity and versatility. Solid lipid nanoparticle drug delivery technology presents considerable opportunities for improving medical therapeutics. This review article covers applications of solid lipid nanoparticles in different fields. Because of the SLN potential for facilitating controlled drug delivery to a target tissue and its biocompatibility, there will be much investigation in improvement of quality, efficacy, and safety profile of drugs using them in the future.

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