

REVIEW ARTICLE

SOLID LIPID NANOPARTICLES: AN EMERGING NOVEL DRUG DELIVERY SYSTEM

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ABSTRACT

The solid lipid nanoparticles (SLNs), a type of lipid nanoparticles (LNPs), is a special field of interest that has emerged during the last few decades as a potential colloidal carrier delivery system. They have gained great attention in controlling the drug release, increasing the bioavailability and attaining a sustain release profile of entrapped drug substance with fewer side effects as compared to traditional dosage forms. They serve as a promising system in various pharmaceutical fields such as cosmetics, research, clinical medicine and other allied sciences. SLNs have also been identified as a substitute to carrier systems such as liposomes, emulsions and polymeric nanoparticles. In the present review, the structure, advantages and applications of SLNs are focused which would provide an idea of global scenario of SLNs.

Keywords: Solid lipid nanoparticles, lipids, sustain release, bioavailability.

1. INTRODUCTION

The lipid-based formulations, also known as liposomes, were discovered in 1965¹. A liposome is composed of spherical vesicle with an aqueous internal cavity, which is enclosed in a lipid bilayer membrane. Liposomes offer great advantages such as protection of drug by degradation, low toxicity, high flexibility, biocompatibility, biodegradability and non-immunogenicity²⁻⁴. However, the limitations of having short shelf-life, poor stability, low encapsulation efficacy, rapid removal by reticuloendothelial system (RES), cell interactions or adsorption and intermembrane transfer⁵ leads to the development of advanced approaches for control over drug release and its delivery. The lipid nanoparticles (LNs) are of two types i.e. solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs). Both of them have been identified as substitute to carrier systems such as liposomes, emulsions and polymeric nanoparticles^{1,6-8}.

In pharmaceutical industry, SLNs are used to control the drug release and increase the bioavailability of the entrapped drug substance. They were developed in the early 1990s and since then they have been considered as promising drug carrier systems

particularly when intended to achieve a sustained release profile of the incorporated active substance. SLNs can be used as colloidal drug carriers for incorporating both hydrophilic as well as lipophilic drugs. The encapsulation may provide effective means for administering chemotherapeutic agents with minimal targeting barriers such as physical stability, protection of the active substance, controlled release, biocompatibility and selective orientation⁹⁻¹¹. On large scale, SLNs can be easily produced in industries as they are physicochemically stable and the production techniques are relatively cost effective^{12,13}.

2. COMPOSITION AND STRUCTURE

The SLNs are nanoparticles of aqueous colloidal dispersions which comprises of a core solid biodegradable lipid^{14,15} with a bioactive material creating a part of the lipid matrix (Fig. 1). The average diameter ranges between 50 and 1000 nm along with surfactants and water^{12,13}. The lipids used may be triglycerides, partial glycerides, fatty acids (stearic acid, palmitic acid), steroids (cholesterol) and waxes (cetyl palmitate). Different emulsifiers and their combinations (Pluronic F68, F127) have also been used to stabilize the lipid dispersion and

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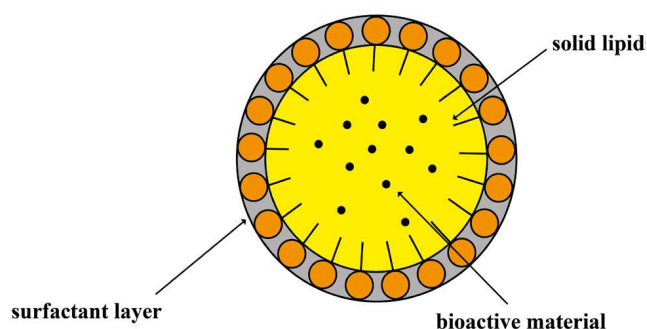


Fig. 1. Structure of solid lipid nanoparticles¹⁰.

A number of other ingredients such as counter-ions and surface modifiers may also be used in LNs formulations. The cationic, water-soluble drugs encapsulated as LNs may also contain counter-ions such as organic anions or anionic polymers¹⁸⁻²⁰. On the basis of incorporated drug molecule location, SLNs have three different morphologies²¹ (Fig. 2) and are as follows:

(a) Drug-enriched shell model

Where a solid lipid core forms when the recrystallization temperature of the lipid is achieved and the drug concentrate surrounds the core²².

(b) Drug-enriched core model

Where recrystallization of the lipid takes place and surrounds the drug as a membrane²².

(c) Homogenous matrix model

Where the drug is molecularly dispersed throughout the lipid matrix²².

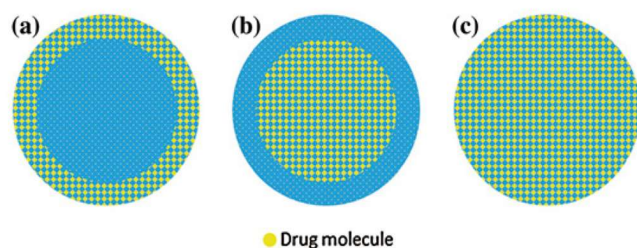


Fig. 2. Drug incorporation models of SLNs.

- (a) Drug-enriched shell model;
 (b) Drug-enriched core model;
 (c) Homogenous matrix (solid solution) model²².

3. PREPARATION TECHNIQUES OF SLNs

Different methods are reported for the preparation of SLNs such as ultrasonication², high shear homogenization (HSH)^{13,16,23}, microemulsion based

SLNs preparation^{12,24}, precipitated lipid particles¹³, lipid nanopellets and lipospheres¹³, spray drying¹⁵, solvent emulsification / evaporation¹⁵, supercritical fluid technology^{25,26}, solvent emulsification-diffusion²⁷, double emulsion²⁸, solvent injection^{29,30}.

4. ADVANTAGES AND DISADVANTAGES OF SLNs

The advantages of polymeric nanoparticles, fat emulsions and liposomes are combined in SLNs and are summarized as follows:

- i) Decreased risk of toxicity due to the use of biodegradable physiological lipids and production methods devoid of the use of organic solvents³¹.
- ii) Better bioavailability of poorly water soluble molecules³².
- iii) Increased drug penetration due to dermal application¹⁵.
- iv) Targeted drug delivery¹⁵.
- v) Chemical agents as well as sensitive molecules can be protected against chemical degradation and environmental stress¹⁵.
- vi) Better stability as compared to liposomes¹⁵.
- vii) Functional compounds can be incorporated in high concentration¹⁰.
- viii) Can also be used as potential UV blockers, sunscreens or in combination with other sun protective substances³³.
- ix) Are capable of incorporating both lipophilic and hydrophilic substances and are convenient to be produced on large scale¹⁰.

The potential disadvantages of SLNs are as follows:

- i) The drug loading capacity of conventional SLNs is dependent on the solubility of drug in the lipid melt, structure of the lipid matrix and polymeric state of the lipid matrix^{10,15}.
- ii) Expulsion of the drug after polymeric transition during storage^{10,15}.
- iii) Relatively high water content of the dispersions (70–99.9%)^{10,15}.

5. APPLICATIONS OF SLNs

SLNs possess remarkably wide range of pharmaceutical applications along with the delivery of food, cosmetics and pesticides. Some of the

important applications are as follows:

5.1. Pharmaceutical Applications

5.1.1. Oral applications

Tablets, pellets or capsules are included in the aqueous dispersions or SLNs loaded dosage forms for oral administration¹. The selection of suitable surfactant with appropriate concentration is the key step in the preparation of physicochemically stable LNs³⁴. Since poorly water soluble drugs are not preferred to be administered orally, the lipid based delivery systems such as SLNs and NLCs have played a vital role to overcome this limitation. The structure of these systems is based on the drug dissolution in the lipid phase (which contains the aqueous vesicle) which improves the bioavailability of poorly soluble drugs in water and hence become beneficial for increased dissolution, residence time and lymphatic uptake of drug without any toxicity^{34,35-37}. Later the lipid matrices, which are made up of triglycerides, are digested by pancreatic lipases that convert the triglycerides into mono- and di-glycerides. Different fluorescent dyes have been used for the detection and confirmation of the lymphatic uptake of SLNs³⁸. The controlled lymphatic uptake can also be obtained by particle size reduction but this may also result in higher uptake³⁹.

The bioavailability and stability of proteins after oral administration may efficiently be increased by forming SLNs⁴⁰⁻⁴² such as the insulin loaded SLNs have shown improved stability against proteolytic enzymes⁹. Similarly, in another study the chemotherapeutic potential of oral SLNs of antituberculosis drugs i.e. rifampicin, isoniazid and pyrazinamide have been measured. The emulsion solvent diffusion technique was employed for the preparation of SLNs which had an encapsulation efficiency of $51 \pm 5\%$ for rifampicin, $45 \pm 4\%$ for isoniazid and $41 \pm 4\%$ for pyrazinamide. The results of the study indicated better management of tuberculosis due to reduced dosing frequency and improved patient compliance⁴³.

5.1.2. Parenteral applications

Since protein and peptidal drugs cannot be formulated

for oral administration due to their instability to gastrointestinal tract enzymes, the SLNs parenteral formulations are found to minimize the instability as well as side effects of such drugs and also causes increase in the bioavailability². On the contrary, in some cases SLNs have proved to be a limiting formulation against the fast drug expulsion from parenteral nanoemulsions⁴⁴. The SLNs may also provide in vivo chemical stability and controlled drug release of active pharmaceutical substances⁴⁵. "Stealth" particles⁴⁶ or targeted drug deliveries are some of the other aspects that need to be considered regarding SLNs and NLCs as they may selectively reach lung⁴⁷, spleen⁴⁸, brain^{48,49}, liver^{50,51} tumors or other damaged organs and tissues.

5.1.3. Dermal / cosmetic / topical applications

SLNs are a potential system for improving dermatological as well as cosmetological factors such as controlled release of active, drug targeting, occlusion, penetration and increased hydration of the skin⁵². A novel SLNs semisolid dosage form showed superior results in terms of therapeutic activity as compared to nanoparticles incorporated in a conventional semisolid form i.e. plain carbopol gel⁵³. Similarly, a SLNs based gel of meloxicam (an anti-inflammatory drug) was prepared and an increase in its penetration was observed⁵⁴.

The skin atrophy caused by long-term treatment of glucocorticoid is considered as a major limitation for its use. A comparative study was conducted to overcome the problem by incorporating a corticosteroid, prednicarbate (0.25%), into SLNs of various compositions and tested against conventional form of prednicarbate cream and ointment taken as reference. Since the purpose of the study was to formulate an epidermal targeting novel dosage form, prednicarbate SLNs induced a localized effect on epidermal layer for 6 hours and later declined. Thus suggesting that SLNs may prove as an advancement in the topical therapy with low risks⁵⁵. Similar type of SLNs have also been studied for epidermal targeting of podophyllotoxin (a lignan) and exhibited useful results⁵⁶.

5.1.4. Pulmonary applications

SLNs have small size, therefore, they can be well contained in microparticles which reaches the alveoli more efficiently. The SLNs and NLCs can also improve the pharmacokinetic parameters of the drug after pulmonary administration through the lungs⁵⁷. A potent non-halogenated corticosteroid, i.e. budesonide, with high anti-inflammatory effects was incorporated in SLNs by the emulsification-solvent diffusion method and exhibited high encapsulation efficiency with controlled release profile⁵⁸. In another study, phospholipid and triglyceride in the ratio of 30:70 were incorporated in SLNs for advanced pulmonary applications. The in vitro, ex vivo and in vivo models for toxicity studies and cytokine activation measurements indicated no activation of pro-inflammatory cytokines after nebulizing the mice with SLNs⁵⁹⁻⁶¹. Doxorubicin, an anti-cancer drug, was prepared in the form of SLNs. This drug contains polyunsaturated fatty acid such as docosahexaenoic acid and triethanolamine to increase the encapsulation efficiency and solubility, respectively. The doxorubicin SLNs resulted in maximum uptake by lungs with enhanced cytotoxic effect and encapsulation efficiency that increased from 36 to 99%^{61,62}.

5.1.5. Intranasal applications

The intranasal route is one of the most advantageous routes due to non-invasiveness, neutral pH environment, high permeability of the nasal mucosa than gastrointestinal tract. The olfactory epithelium of the nasal mucosa acts as a connection between brain and itself promoting the substances to absorb through it⁶³⁻⁶⁶. A haloperidol loaded SLNs when tested against intranasal and intravenous solutions of the drug showed better brain-blood ratio and bioavailability⁶⁷. The SLNs have also been studied as an alternative transmucosal delivery system of macromolecular therapeutic agents and diagnostics⁶⁸⁻⁷⁰. Budesonide⁷¹, ropinirole⁷², alprazolam⁷³, raloxifene hydrochloride⁷⁴ and many other drugs have been formulated as transnasal SLNs formulations and are found effective for their respective purposes.

5.1.6. Intraocular and intrarectal applications

Little information is available on the ocular and rectal applications of SLNs. Tobramycin and pilocarpine when prepared in the form of SLNs for ocular delivery in rabbit eyes resulted in enhanced drug bioavailability^{18,19}. Similarly, diazepam loaded SLNs have been prepared in order to achieve rapid action of the drug⁷⁵.

5.2. Food and Agricultural Applications

SLNs have been used as vehicles for food bioactives such as nisin which is used as a preservative in heat processed and low pH foods^{76,77}. The formulation of SLNs containing essential oil of *Artemisia arborescens* resulted in a huge decrease in the quick evaporation of the pesticidal drugs in comparison with the systems already being used in agriculture^{15,78}.

6. CONCLUSION

SLNs have a wide range of applications in pharmaceutical sciences in order to deliver a variety of drugs through oral, parenteral, topical, respiratory, nasal, ocular and rectal route of administration. Since drug targeting is the main focus for the pharmaceutical formulators and researchers to develop a promising dosage form with maximum benefits and minimum limitations, the development of SLNs offers a new drug prototype which may eventually lead to a controlled and site specific drug delivery. Further research in the field of SLNs to understand their structure and dynamics on molecular level may create various possibilities to treat many complex diseases. The problems associated with the conventional chemotherapy can also be minimized by encapsulating the drugs as SLNs to reduce the frequency of dosing and improve patient compliance for better disease management.

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