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Mini Review

Solid Lipid Nanoparticles for Poorly Water-Soluble Drugs

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Abstract

The problem of poor water-solubility has remained as a significant challenge in pharmaceutical industry. The emergence of solid lipid nanoparticles (SLNs) from former colloidal system proposes several advantages namely encapsulation of lipophilic agents, nano-sized particles, absence of organic solvents, and ease of large-scale production. This review aims to provide readers an overview regarding the feasibility and recent applications of SLNs as drug delivery systems for different administrations including oral, skin, ocular, pulmonary and parenteral routes. Researches about SLNs are predicted to continually flourish for an enormous contribution to the fields of medicine.

INTRODUCTION

Significant amounts of current pharmaceutical products are found to possess unfavorable characteristics of poor water-solubility, which are major challenges for pharmaceutical industry since they exhibit low bioavailability leading to limited efficiency or therapy failure at treatment site. Specifically, the obstacles lie in inadequate drug concentration because of poor absorption, rapid metabolism and elimination as well as uncontrollable fluctuations in plasma level. Hence, along with novel drug discoveries, several suitable drug delivery systems have been contemporaneously investigated in the attempts to facilitate solubility and controlled release properties of therapeutic agents [1]. The problem of poor water-solubility arises from the natural occurrence of drugs such as crystallinity [2], lipophilicity [3], large particle size [4], etc., making them hard to be dissolved in the biofluids. In this regards, the employment of lipid nano-carriers has drawn significant attention from scientists.

The development of solid lipid nanoparticles (SLNs) which was emerged in 1990s incorporated the advantages of solid particles with those of emulsions and liposome's [5]. SLNs consist of dispersed systems of lipid phase in aqueous solution, which are stabilized by surfactants [6]. They have been fabricated using well-established excipients namely fatty acids (palmitic acid, stearic acid), triglycerides (tristearin), steroids (cholesterol), waxes (cetyl palmitate), and emulsifiers (pluronic F68, F127) [7,8]. Although SLNs have proven the capability in encapsulating lipophilic compounds in their structure, challenges still remain for distributing hydrophilic materials in lipid matrix because of the tendency to separate towards the aqueous phase [9,10]. The particle size of SLNs is distributed in the submicron range from 50 to 1000 nm [11]. An interesting improvement of SLNs over other systems of liquid oil is its sustainable drug mobility due to the substitution of liquid lipid by solid components [12]; thus, protecting active compounds from potential chemical degradation. Other advantages of SLNs are the ease of large-scale production, low biotoxicity, and avoidance of organic solvents.

SLNs are conventionally prepared by high pressure homogenization techniques [13,14]. The principle of SLNs formation is basically based on the incorporation of drug melted in molten lipid and aqueous surfactant solution followed by homogenization and immediate cooling for lipid recrystallization. Solvents are then completely removed from resulting products for dry oral dosage design by spray drying [15] or lyophilization [16]. Other approaches include ultrasonication/high speed homogenization [17,18], micro emulsion based SLNs preparation [19,20] solvent emulsification/evaporation [21-23].

SLNs have been investigated for several different applications due to their outstanding characteristics. The aim of this review is to provide an overview about the feasibilities of SLNs in several routes of administration for poorly water-soluble drugs and highlight their potential in fabricating multi-combined systems of SLNs for maximizing therapeutic efficiency in treatment.

Oral delivery of SLNs

Oral is not only recognized for its natural and fast drug

administration but also for its high patient compliance. However, the oral route conquers various difficulties including permeability and stability in the gastrointestinal (GI) environment [24]. To this regard, SLNs offer a protection against biodegradation in GI tract owing to the large surface area of physiological compatible lipid matrix [25]. The protection ability is found to be susceptible to the degree of protein trapped inside the nanostructures [26]. Additionally, their nano-sized particles can promote the penetration across epithelial cells; hence, increasing cellular uptake of therapeutic agents. Researches regarding the use of SLNs in oral administration have been momentously developed for both aqueous dispersions and solid dosage forms such as powders, tablets, capsules, pellets [27].To be more specific, SLNs can be transformed into powder by complete sublimation of solvents using spray drying or lyophilization for tablets, and hard gelatin capsules formation.

Early *in vitro* studies by R.H. Müller et al. [28], Investigated cyclosporine A (CycA) loaded aqueous SLN dispersion for enhancing its solubility and prolonging release time. The crystallinity of CycA disappeared upon incorporating into SLNs. Additionally; relatively high drug loading was obtained (20%). Extensive characterization methods were performed; however, limited drug release results were reported. Later studies have drawn decisive evidence on the oral bioavailability of CycA loaded SLNs [29]. It was found that the drug particles were released from lipid matrix by enzymatic degradation together with optimized range in blood concentration profile. CycA loaded SLNs achieve better bioavailability as compared to CycA nanocrystals in the same testing conditions. Other recent applications of SLNs in enhancing oral absorption of poorly water-soluble drugs namely curcumin [30-32], camptothecin [33], paclitaxel [34], and antihypertensive drugs [35]etc. have been widely reported, which showed promising findings. Furthermore, SLNs have been employed for successful transporting peptides and proteins such as to bramycin [36,37], rifampicin [38], isoniazid and pyrazinamide [39]. SLNs have opened up a novel approach for an efficient delivery of therapeutic agents via oral administration. The applications of SLNs are predicted to continue to flourish in the future.

Skin delivery of SLNs

The implications of SLNs in skin delivery of pharmaceutical molecules and cosmetic products have gained considerable interests among scientists. Due to the lipophilicity and small particle size, SLNs exhibit great permeation through skin membrane in controlled manner; thus, preventing sudden systemic absorption and potential toxicity [40,41]. Moreover, SLNs offer a protection to active drug compounds through the incorporation of various well-tolerated excipients which also reduce the risks of irritation or bio-incompatibility [5,42].

A study by Jie Liu and co-workers [43] designed skin targeting formulations for topical delivery of isotretinoin loaded SLNs. Significant particle size reduction ranging from 30 to 50 nm with high entrapment efficiency up to 100% and good stability were achieved. *In vitro* evaluation using Franz diffusion cells fitted with rat skins demonstrated the permeation rate of 0.76 ± 0.30 μg cm^{-2} h^{-1} through skins alongside with the absence of systemic uptake. Other interests in this concern include clotrimazole [44], prenicarbate and betamethasone 17-valerate [45], tretinoin [46].

SLNs have brought numerous advantages to the field of cosmetics and dermatology [47]. One of interesting features is occlusion of SLNs which can increase skin hydration through increased water content [48]. Moreover, SLNs exhibit a physical UV-blocking property individually or combining with molecular sunscreens for maximizing photo protecting effects [49]. The use of SLNs as pharmaceutical and cosmetic carriers for skin delivery is still on the promising road of development.

Ocular delivery of SLNs

The complexity of ocular structure has presented several physiological barriers namely efflux transporters, tear dynamics, epithelium membranes, and non-specific absorption which significantly regulate the penetration and bioavailability of drugs [50]. The employment of SLNs in ocular delivery has been documented for their remarkable advantages over conventional ophthalmic formulations. SLNs are able to entrap lipophilic drugs in their amphiphilic structure for extending release rate and protection against eye enzymatic degradation [51]. Exceptional nano-sized, shape, and surface charge properties of SLNs improve adhesion and interaction to the epithelial ocular surface as well as prolong pre-corneal retention in the conjunctiva sac by interacting with the lipid layer of tear film; thus, enhancing bioavailability of therapeutic agents [52]. SLNs have been applied to improve ocular bioavailability of poorly water-soluble drugs including levofloxacin [53], Cyclosporine A [54,55], anti-inflammatory drugs [56].

Parenteral delivery of SLNs

Structure of SLNs makes them advantageous for their extreme physical stability in parenteral applications. Similar to other routes of administration mentioned above, SLNs provide a protection to encapsulated drug against potential biodegradation as well as exhibit specific site targeting and controlled release model. Wissing et al. [57], closely investigated the profile of SLNs in parenteral route. The disadvantages of SLNs lie mostly in insufficient drug loading capacity that importantly depend on the choice of suitable lipid carriers [58]. SLNs have desired particle sizes that permit circulation in microvascular system. Moreover, the possibility for hydrophilic coating prevents SLNs from macrophage uptake; thus, prolonging blood circulation [59]. Efforts in formulating PEG-modified SLNs, alternatively known as stealth SLNs, have been taken into considerations [60] as promising alternatives.

Studies of doxorubicin loaded SLNs injected on rats illustrated higher blood levels as compared to commercial drug solution [61]. Higher drug concentrations were found in lung, spleen, and brain. In another study by Cavalli et al., a sustained release of doxorubicin was obtained [62]. Also, cardiotoxic side effects of doxorubicin in rats were remarkably reduced. Pharmacokinetic profile of paclitaxel was further conducted [63], which draw similar findings. Considering the transportation of therapeutics to central nervous system [64], as hydrophilic coating SLNs enhance the absorption across the blood brain barrier, more optimized drug concentrations were obtained following the intravenous injection [65].

Pulmonary delivery of SLNs

The systemic administration through pulmonary route demonstrates its feasibility for treatment of cancer, diabetes, immune deficiencies, and infection, listed as exhibiting large vascularized surface area, thin alveolar epithelium, and the easily permeable membrane [66]. Due to the low extracellular and intracellular enzyme activity, drug degradation rate in lung remains slow [67]. Pulmonary route favors both rapid onset action and prolonged release patterns. A review by Weber et al. [68], extensively discussed the use of SLNs for pulmonary applications. SLNs are found to be distributed in deep lungs because of their ability to be fabricated into inhalable particles with extremely small sized, good muco adhesion, and non-biotoxicity. Researches in the field are still on the urge of development of the delivery system [69-71].

Conclusions and future perspectives

SLNs have attracted significant concerns from scientists for their outstanding advantages over other colloidal carriers in terms of solubilized feature, high stability, low bio-toxicity, and large-scale production. Therefore, applications of SLNs for oral, skin, ocular, pulmonary and parenteral administrations have been widely developed, some of which present interesting results. Disadvantages remain for SLNs include entrapment efficiency and encapsulation of hydrophilic materials. Lately, the novel idea of combining methods of SLNs and other polymeric systems has been initiated. In a study published by Casadei et al. [72], the lipophilic drug (ibuprofen) was capable of being incorporated into modified hydrophilic system for oral administration by coupling SLNs and hydrogels. SLNs were prepared by hot homogenization followed by mixing with dextran methacrylate (DEX-MA) prior to UV irradiation. The combined system eliminated the use of organic solvents in fabricating lipophilic drug loaded hydrogels through solubilizing active compounds in lipid phase of SLNs. Additionally; hydrogels offer a better modified release profile as compared to SLNs alone. To this regard, SLNs loaded hydrogels for topical delivery were also investigated [73]. The future perspectives of these combined SLNs systems are encouraged to be promoted.

Recently SLNs have been developed as an interesting approach of anti-bacterial surface coating for invasive medical devices such as endo tracheal tubes in order to prevent bacterial infections and avoid the use of anti-biotic solutions [74,75]. Membrane disruptive lipophilic compounds namely free fatty acids and monoglycerides could be encapsulated inside SLNs structure. Taylor et al. [76], conducted research on Pseudomonas aeruginosa and showed that bacterial adhesion was reduced by 99% along with bacterial growth inhibitory effect. Other attempts in this concern include S. epidermidis, P. acnes, and S. aureus [77], Nisin [78]. Overall, several potential applications of SLNs in pharmaceutical research have been investigated, which importantly contribute to the work of enhancing bioavailability of poorly water-soluble drugs. Researches regarding to the work of developing alternative routes of administration or towards broad-spectrum treatment of viral infections still remain to be further explored in near future [79].

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