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Review

Solid lipid nanoparticles as attractive drug vehicles: Composition, properties and therapeutic strategies

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ABSTRACT

This work briefly reviews up-to-date developments in solid lipid nanoparticles (SLNs) as effective nanocolloidal system for drug delivery. It summarizes SLNs in terms of their preparation, surface modification and properties. The application of SLNs as a carrier system enables to improve the therapeutic efficacy of drugs from various therapeutic groups. Present uses of SLNs include cancer therapy, dermatology, bacterial infections, brain targeting and eye disorders among others. The usage of SLNs provides enhanced pharmacokinetic properties and modulated release of drugs. SLN ubiquitous application results from their specific features such as possibility of surface modification, increased permeation through biological barriers, resistance to chemical degradation, possibility of co-delivery of various therapeutic agents or stimuli-responsiveness. This paper will be useful to the scientists working in the domain of SLN-based drug delivery systems.

Contents

1. Introduction

During last three decades, nanotechnology has been introduced as a novel interdisciplinary field of science which initiated the explosion of research on the development of nanostructures. Most attractive area of research is the development of nanomaterials with potential applications in biomedical and pharmaceutical fields, specifically in drug delivery, biosensing and bioimaging. Nanomaterial-based drug delivery systems (DDSs) are known to have potential to provide controlled drug release and targeted delivery of active agents. Additionally, the minimization of numerous pharmaceutical limitations of the drug used can be achieved. Nanomaterials which have been greatly interested to be used in nanomedicine are quantum dots [1], carbon nanotubes [2], graphene derivatives [3], polymeric nanoparticles [4], dendrimers [5], metal and metal oxide nanoparticles [6], liposomes [7], nanoporous materials [8] and many others.

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In the early 1990s, the attention of three research groups of Müller [9,10], Gasco [11,12] and Westesen [13] has focused on the development of alternative carrier system to liposomes, emulsions and polymeric nanoparticles, the so-called solid lipid nanoparticles (SLNs). SLNs represent a class of colloidal particles composed of lipids being solid at both room and body temperatures [14]. The scientists have exploited the fact that the usage of solid lipids instead of liquid oils may provide controlled drug release as the mobility of the drug in a solid lipid matrix is substantially lower as compared to a liquid oil [15]. The average diameter of SLNs is in the submicron range from 50 to 1000 nm [16]. They are composed of physiologically tolerated lipids dispersed in an aqueous surfactant phase [17]. Over the last two decades, SLNs have attracted increasing attention as a colloidal carrier system for cosmetic active ingredients [18] and biologically active food components [19]. Particularly, these nanoparticles exhibit great potential as suitable drug delivery system [16,17,20,21]. This paper presents an overview of the recent literature about SLNs for medical applications. It will provide the reader with some background information for SLN, *i.e.* composition and production methods. Special attention is paid to the particle surface modification and drug incorporation. Aspects of SLN properties including stability, drug loading and drug release behavior are discussed. Finally, chosen features of SLNs determining their medical application are demonstrated.

2. Fabrication and characterization of SLN dispersions

A number of formulation techniques have been employed in SLN preparation with high pressure homogenization and microemulsion being the most commonly used [22,23]. In the former, the molten lipid is combined with an aqueous surfactant solution followed by high pressure homogenization. Subsequent cooling down of the mixture results in recrystallization of nanoemulsion and SLN formation. The latter method consists of dispersion of warm microemulsion of molten lipid and surfactant in cold water [15,22]. SLNs can be also prepared using solvent emulsification method followed by solvent evaporation or diffusion. In the emulsification and solvent evaporation method, usually water-immiscible organic solvents such as chloroform [24] are employed while the emulsification and solvent diffusion technique involves the usage of ethanol, acetone or dimethyl sulfoxide as the solvents [25,26]. Subsequent addition of water results in diffusion of organic solvent to water phase and SLN precipitation. Furthermore, SLNs can be prepared using a double emulsion technique in which primary emulsion formed by homogenization of lipid and aqueous phases is mixed with emulsifier forming w/o/w double emulsion [27–29]. Fig. 1 describes the most common methods used for SLN preparation. It should be pointed out that the active compound is usually added to the oil phase [30–35] and rarely to the aqueous phase [27,36]. Interestingly, it is worth to note that microemulsion and emulsification techniques are ease to handle. Moreover, an obvious advantage of emulsification techniques is the avoidance of elevated temperatures. Meanwhile, high pressure homogenization technique reveals no problem with scaling up. Although there exist a vast array of improvement approaches, some of nowadays used SLN preparation techniques still suffer from a number of drawbacks and limitations. An important disadvantage of emulsification and solvent evaporation and double emulsion techniques is the usage of water-immiscible solvents such as chloroform, dichloromethane or toluene which are harmful to human and to the environment. Especially, the use of chloroform and dichloromethane which are known to be potentially carcinogenic should be avoided. The methods of melt-emulsification and hot melt homogenization require the usage of high temperatures which can destroy the incorporated active substances such as thermolabile drugs or proteins. The high pressure homogenization technique involves the use of expensive apparatus and causes a mechanic stress on the resulting product.

The appropriate characterization of SLN dispersion gives detailed information about prepared formulation [37]. In-depth examination of the nanocolloidal carriers plays a key role in the formulation of SLN-based DDSs allowing us to predict the drug loading capacity, drug release kinetics, stability of dispersion and behavior of nanoparticles in biological systems. Table 1 lists the most common analytical techniques used for evaluation of particle size and shape, polydispersity, zeta potential and crystallinity of the system.

SLNs are prepared using various solid lipids such as mono-, di- and triglycerides, fatty acids, waxes and steroids [22,64]. Numerous surfactants providing sterical stabilization of nanoparticles including phospholipids, Poloxamers, and Polysorbates are employed for SLN formulation [22]. The variety of components used for SLN fabrication is listed in Table 2. Obviously, the composition of ingredients has great influence on quality of the SLN dispersion [15,65]. Moreover, different lipids and emulsifiers might require different methods and parameters of homogenization. It should be taken into consideration that frequently the lipid phase is composed from various chemical compounds and that the stability of the drugs may differ between the lipids used. Meanwhile, the accurate selection of the emulsifier is of considerable importance for the physical stability of the formulation which is indispensable for the process of sterilization. It has been noted that higher concentration of emulsifier results in the decrease of particle size which is desirable for intravenous administration. Whereas, the increase of lipid content in most cases results in larger particle size and broader particle size distribution [15,65]. Recently, cationic SLNs combining the advantages of lipid matrix and hydrophilic layer have focused increasing research attention [26,66]. In comparison to traditional SLNs, the surface of cationic SLNs is positively charged as they contain cationic lipids or surfactants [67]. Cationic lipids are composed of the hydrophilic head, the linker and the hydrophobic chain [68]. The hydrophilic head of the lipid often consists of quaternary ammonium salt characterized by the positively charged nitrogen atom or it can constitute a primary, secondary or tertiary amine. In this case, the positive charge results from protonation of amine groups at appropriately low pH. The lipid core of cationic SLNs serves as a reservoir for hydrophobic drugs while positively-charged surface enables better cellular internalization [26,67] which is necessary in the cases of increasing tumor targeting, penetrating the blood-brain barrier (BBB) and promoting gene transfection [69].

SLNs have gained increasing attention as colloidal carriers for various active substances. The choice of the lipids for the SLN formulation should be based on drug solubility in the lipid material [57]. The active substance may be located in the particle core [90], shell [45] or can be dispersed within the whole lipid matrix [28,72]. Models of drug distribution in SLN particle are demonstrated in Fig. 2. The particle outer shell can be modified with various biomolecules including proteins [51], oligosaccharides [91], ligands for receptors [24] or antibodies [82], providing their specific activity when administered to the body.

3. Properties of SLNs

Used as the carriers for various active substances SLNs may provide numerous advantages of as-prepared systems. Table 3 summarizes main advantages and drawbacks resulting from application of SLNs as the carriers in drug delivery systems (DDSs) meanwhile broader characteristics and benefits resulting from application of SLN formulations in biomedical field will be discussed in Section 4.

Nanometric dimensions of SLNs and the usage of lipids and surfactants approved by Food and Drug Administration (FDA) or of GRAS (Generally Recognized As Safe) status while their manufacturing allow their application *via* different routes including intravenous [46], oral [86], ocular [40,98], dermal [18,42,48], inhalatory [71], intranasal [14], rectal [76,89], subcutaneous [99], intramuscular [30] administration. An appropriate modification of SLNs and the fact that they are made from physiological compounds help them to overcome various biological barriers and to be delivered to the targeted site minimizing the risk of acute and chronic toxicity [84,87]. Furthermore, suitable surface modification of SLNs can significantly reduce the initial rapid release