Colloids and Surfaces A: Physicochem. Eng. Aspects 510 (2016) 77–86

Contents lists available at ScienceDirect

Colloids and Surfaces A: Physicochemical and Engineering Aspects

journal homepage: www.elsevier.com/locate/colsurfa

Preparation and investigation of solid lipid nanoparticles for drug delivery

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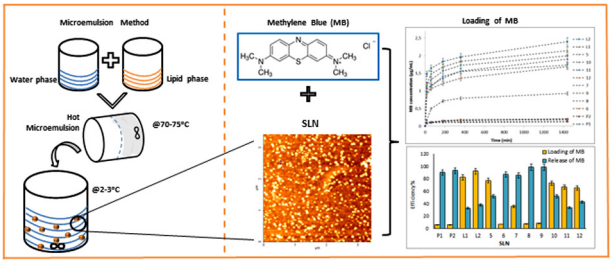
HIGHLIGHTS

- 12 newly formulated SLNs were synthesized via microemulsion method.
- Size and surface properties of SLNs were controlled by changing the composition.
- Drug entrapment and release capacities of SLNs have been investigated.
- Methylene blue have been used as model molecule in the drug incorporation studies.
- Surface charge densities were correlated with entrapment/release capacities of SLNs.

GRAPHICAL ABSTRACT



ARTICLE INFO

Article history:
Received 4 February 2016
Received in revised form 13 June 2016
Accepted 14 June 2016
Available online 21 June 2016

Keywords:
Solid lipid nanoparticle
Microemulsion
Drug delivery
Methylene blue

ABSTRACT

Solid lipid nanoparticles (SLN), a promising drug delivery vehicle, offer an alternative system to traditional colloidal carriers. In our study 12 new SLN formulations were fabricated via the "microemulsion (ME) method", each leading to a different SLN size and composition. This method is a relatively easy technique and involves biocompatible conditions. Stearic acid has been used as lipid material of which the ratio is kept under 4% to prevent particle growth. Particle size and surface properties of the synthesized SLNs were controlled using various combinations of emulsifiers such as lithocholic acid, Pluronic F127, Tween 20, lecithin and butanol. Furthermore, the mean size of the particles was adjusted by changing the ME:water ratio in the dilution step which is independent from composition. It was found that most of the SLNs were in the colloidal size range (below 100 nm) and spherical in shape, which provides high surface area to exploit, as an alternative adsorptive drug carrier system. Also, the surface charge density values of SLNs were calculated by considering size and zeta potential values which then helps in understanding the surface potential of particles. MB was chosen as a model molecule and entrapped on the surface of SLNs after the preparation, to determine the loading capacities and release efficiencies. As such, SLNs have been successfully produced which have controllable drug entrapment efficiency and release capacity according to the chosen combination of emulsifiers and dilution ratio. Thus, this study contributes to the improvement of alternative drug delivery systems with biocompatible and stable newly formulated SLNs.

1. Introduction

Solid lipid nanoparticles (SLNs), prepared using various physiological lipids, emulsifiers and water, have been used since the 1990s as colloidal nanocarrier systems, either in combination with or as

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http://dx.doi.org/10.1016/j.colsurfa.2016.06.034
0927-7757/

an alternative to liposomes, emulsions and polymeric nanoparticles [1–3]. Possessing adjustable release kinetics, determined by the method of preparation used, its level of biocompatibility, its stability and the degree to which active materials may be encapsulated within its structure, SLNs are ideal for use within the body and may be administered via different routes (parenteral, topical, ocular, etc.) [4–6]. Another advantage is that, in comparison to other systems, like the ones with liposomes for instance, SLNs have less storage and drug leakage issues. Moreover, they have good stability which they can maintain for up to 2–3 years [7,8]. To date, many hydrophobic and hydrophilic drugs, such as doxorubicin, paclitaxel, tobramycin, cyclosporine A, carmustine, pilocarpine, cortison etc. have been incorporated into SLN [9–15]. There are several methods that could be utilized to synthesize SLNs, including high pressure homogenization, high shear homogenization, etc. [16]. However, if the incorporation of selected compounds is intended, particularly drugs, genes, proteins and other biomolecules, methods such as high pressure or high shear homogenization which create harsh environments for the material, need to be avoided. By using microemulsion method, the nanoparticle formulations of interest can be prepared in vials rapidly, reproducibly and cost effectively in a two-step process involving only mild operating temperatures. Moreover, the uniform nanoparticles produced become more biocompatible due to the elimination of organic solvent use during its preparation. Furthermore the solubilization properties of hot microemulsions enable SLNs to be loaded with various drugs and is particularly useful for drugs with poor water solubility [17–19].

To our day various lipids and emulsifiers have been utilized to investigate the effect of composition on the size and surface properties of SLNs [20–22]. A large variety of compounds can be utilized as a lipid material which is used here in a broad sense such as fatty acids, triglycerides, partial glycerides and steroids. It is known that the mean diameter of SLNs is directly affected by the type and ratio of lipid in the structure. Westesen et al. have reported that the size of SLNs increase when prepared from lipids with higher melting points via the hot homogenization method [23]. In another study, the effect of lipid chain lengths on the particles produced was investigated and it was found that shorter chains make the particle more compact and reduce its size [24]. A general finding is that increasing the lipid content causes an increment in the size of particles and lowers the monodispersity [25]. Along with the choice of lipid, the type of emulsifier used also has a great impact on the SLNs fabricated. In a study reported by Cavalli et al., ionic and nonionic emulsifiers have been compared and it has been found that by using ionic emulsifiers in the microemulsion method, SLNs can be synthesized in a considerably smaller size [26]. Also, in another study focused on manipulating the surface properties of SLNs, different emulsifier concentrations were examined and it is found that increasing the amount of nonionic emulsifier resulted in the reduction of the zeta potential value of the particle [27]. In that study, Müller-Goymann et al. particularly focused on creating an alternative drug delivery system that is based on the adsorption of the material onto the particle surface. The surface properties of the particle become a vital issue which needs consideration. This remarkable approach, where the drug is loaded after the SLNs have been synthesized, helps to preserve the cargo from the conditions to which it may be exposed during the course of preparation.

As a general assessment for nanoparticles, small size is more desirable due to factors such as high surface area per mass, greater contact with surrounding materials and accessibility to target areas as drug delivery agents [28–30]. However, as the particle gets smaller it becomes harder to attain higher levels of efficiency in drug encapsulation and a sufficient release capacity. In order to overcome this problem, the active ingredients can be carried onto the surface of the particle via adsorption rather than incorporation into the structure. In this way, the drug can also be protected from a high stress environment during particle preparation. Up until today, a variety of biomolecules like BSA, HSA etc. have been successfully incorporated onto SLNs via adsorption [31–33]. Apart from simply being a means of carrying a material on the surface of a particle, protein adsorption on nanocarriers intravenously injected is an important subject, as such studies provide foresight into whether a controlled development of drug delivery agents will be possible [34]. Some proteins such as immunoglobulin induce the clearance of particles via macrophages and inhibit the transport of pharmaceutical ingredients to the target area, and others such as albumin promote a prolonged circulation time of the nanocarrier in the blood [35,36]. Thus, rather than merely aiming to develop a carrier particle, it is important to investigate the adsorptive properties of the colloidal carrier from this point of view.

Methylene blue (MB), which is a heterocyclic aromatic compound, has many uses in a number of different applications, such as redox indicators in analytical chemistry [37], as dyes or stains in biology [38], as U.S. Food and Drug Administration approved drugs for the methemoglobinemia treatment [39] and as photosensitizers in photodynamic therapy (PDT) [40]. In addition to this, MB is also an inexpensive compound which is encourages its use as a model molecule to mimic the behavior of most positively charged and aromatic drug molecules.

In the present study, 12 types of SLNs with different size and compositions were synthesized using the "microemulsion method". The effect of operational parameters such as temperature, stirring type and pH on the formation of transparent ME was investigated. Stearic acid was selected as the lipid material and the ratio was adjusted so as to not exceed 4%. Lithocholic acid, Pluronic F127, Tween 20, lecithin and butanol were used as emulsifiers and co-emulsifiers. Different combinations, concentrations and ratios of emulsifiers and co-emulsifiers were tested in order to understand the effect of both the emulsifier (in terms of its ionic charge and chemical nature), and the co-emulsifier (and its ratio) on the size and zeta potential of particles. Various techniques were used in the characterization of the SLNs. Furthermore, a stability study for the nanoparticles was performed, under room temperature conditions and over a 3 month period, on the basis of their mean diameter and zeta potential values. MB was chosen as a model molecule and its interaction with SLNs was investigated in order to obtain information about the drug entrapment capacity of these nanoparticles, as well as to observe their interaction with molecules that carry potential as drug delivery agents.

2. Materials and methods

2.1. Materials

Stearic acid, Tween 20, monosodium phosphate and disodium phosphate were purchased from Merck (Darmstadt, Germany). Pluronic F 127, lithocholic acid, soybean lecithin and butanol were obtained from Sigma-Aldrich (St. Louis, MO, USA). Methylene blue and sodium hydroxide were purchased from Fluka. These materials were obtained from the indicated sources and used without further purification. All solutions were formulated using UP (ultrapure) water (Millipore Direct-Q3 UV).

2.2. Preparation of SLN

Microemulsion method was used to prepare SLN formulations. In the first step, briefly, stearic acid as the lipid matrix was weighed and heated to ~70 °C. Various amounts of emulsifiers either Tween 20, Pluronic F 127, lithocholic acid and lecithin or sometimes combination of them were dissolved in UP water and heated to the same temperature. The hot aqueous phase was added to the lipid