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Research paper

Solid lipid nanodispersions containing mixed lipid core and a polar heterolipid: Characterization

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Abstract

This paper describes the characterization of solid lipid nanodispersions (SLN) prepared with a 1:1 mixture of theobroma oil and goat fat as the main lipid matrix and Phospholipon 90G® (P90G) as a stabilizer heterolipid, using polysorbate 80 as the mobile surfactant, with a view to applying the SLN in drug delivery. The 1:1 lipid mixture and P90G constituting the lipid matrix was first homogeneously prepared by fusion. Thereafter, the SLN were formulated with a gradient of polysorbate 80 and constant lipid matrix concentration by melt-high pressure homogenisation. The SLN were characterized by time-resolved particle size analysis, zeta potential and osmotic pressure measurements, differential scanning calorimetry (DSC) and wide angle X-ray diffraction (WAXD). Transmission electron microscopy (TEM) and isothermal heat conduction microcalorimetry (IMC) which monitors the in situ crystallization were also carried out on the SLN containing P90G and 1.0 % w/w of polysorbate 80. The results obtained in these studies were compared with SLN prepared with theobroma oil with and without phospholipid. Particle size analysis of SLN indicated reduction in size with increase in concentration of mobile surfactant and was in the lower nanometer range after 3 months except SLN prepared without P90G or polysorbate 80. The lipid nanoparticles had negative potentials after 3 months. WAXD and DSC studies revealed low crystalline SLN after 3 months of storage except in WAXD of SLN formulated with 1.0 % w/w polysorbate 80. TEM micrograph of the SLN containing 1.0 % w/w polysorbate 80 revealed discrete particles whose sizes were in consonance with the static light scattering measurement. In situ crystallization studies in IMC revealed delayed crystallization of the SLN with 1.0 % w/w polysorbate 80. Results indicate lipid mixtures produced SLN with lower crystallinity and higher particle sizes compared with SLN prepared with theobroma oil alone with or without P90G, and would lead to higher drug incorporation efficiency when used in formulation of actives. Mixtures of theobroma oil and goat fat would be suitable for the preparation of nanostructured lipid carriers. SLN of theobroma oil containing phospholipid could prove to be a good ocular or parenteral drug delivery system considering the low particle size, particle size stability and in vivo tolerability of the component lipids. SLN prepared with lipid admixture, which had higher increase in $d_{90\%}$ on storage are suitable for preparation of topical and transdermal products.

Keywords: Mixed lipid; Theobroma oil; Phospholipon 90G®; Solid lipid nanoparticles; Nanostructured lipid carriers; Characterization; Drug delivery

1. Introduction

Nanosized controlled drug delivery devices consisting mainly of nanoemulsions, liposomes and lipid nanoparticles have been proposed recently for oral, topical and parenteral administration of drugs. Solid lipid nanoparticles (SLN) consist of solid lipids in nanosized range dispersed in aqueous medium. SLN combine the advantages and avoid the disadvantages of other colloidal carrier systems, and are regarded as an alternative carrier system to other colloidal drug delivery systems [1–3]. When optimised, SLN exhibit high physical stability, protection of incorporated labile actives against degradation and excellent in vivo tolerability [4–6]. However, these systems generally exhibit a low drug pay-load capacity and drug

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expulsion during storage due to transition to highly ordered lipid particles [7].

Crystallinity of lipid matrices affects the functional properties of SLN derived therefrom. Lipid mixtures can result in increased or decreased crystallinity. Directly after preparation, lipids crystallize partially in higher energy modifications (α, β') with more imperfections in the crystal lattice [8–10]. If however, a polymorphic transition to β modification takes place during storage, any incorporated drug could be expelled from the lipid matrix and it can then neither be protected from degradation nor released in a controlled manner. To overcome such phenomenon, use of mixtures of lipids which do not form highly ordered crystalline arrangement is needed. Such lipid matrix could be achieved by using solid lipid and liquid lipid [11] or solid lipid mixtures of complex nature such as mono-, di- or triglycerides of different chain lengths [7]. Mixture of lipids also modifies the polymorphic properties of the individual lipids, and has been shown to generate lipid matrices of low crystallinity [12]. Lipid nanoparticles produced from such lipid mixtures involving solid lipid and liquid lipid have been termed nanostructured lipid carriers [10,11].

It was the objective of this study to formulate and characterize SLN from physically structured lipid matrix composed of 1:1 mixture of theobroma oil and goat fat. This lipid matrix has been characterized in an earlier study [13]. The SLN were compared with those formulated with theobroma oil alone. As adjuncts, Phospholipon 90G® and polysorbate 80 were used to further stabilize the formulated SLN for improved performance as drug delivery systems. Use of Phospholipon 90G® as lipid nanoparticle surface modifier has been reported [14,15]. However, in this study a lipid matrix composed of the 1:1 mixture of theobroma oil and goat fat, and Phospholipon 90G® was first formulated and used in the formulation of SLN. For the SLN, characterization procedures such as static light scattering, differential scanning calorimetry (DSC), wide angle X-ray diffraction (WAXD), transmission electron microscopy (TEM) and isothermal heat conduction microcalorimetry (IMC) were employed to investigate the colloidal lipid dispersion.

Theobroma oil obtained from the seeds of *Theobroma cacao* is a lipid with many applications in pharmaceutical and food industries. The polymorphic transformation in theobroma oil is well documented [16,17]. Goat fat on the other hand is extracted from *Capra hircus*, an animal domesticated for meat purposes. This fat is easily sourced in Nigeria and represents a potential for drug delivery applications because of its crystal properties [13]. Goat fat consists mainly of triglycerides of C16, C18 and C18:1 fatty acids which are somewhat similar to the fatty acid profile of theobroma oil [18]. However, the location of these fatty acids in their triglycerides differs, with theobroma oil being more homogeneous. A 1:1 binary mixture of these two lipids resulted in mixture of crystals with high degree of disorder that may be favourable for drug loading [13]. Despite possessing good crystal properties, natural lipids are better tolerated in vivo than semi-synthetic lipids. Goat fat has been used in the formulation of self-emulsifying drug delivery systems and has been shown to be stable to rancidity after degumming and deodorization [19,20].

2. Materials and methods

2.1. Materials

Phospholipon 90G® (P90G) (Phospholipid GmbH, Köln, Germany) is a purified, deoiled and granulated soy lecithin with a phosphatidylcholine content of at least 90%. Thimerosal (Synochem, Germany), sorbitol, theobroma oil (Caesar & Loretz, Germany) and polysorbate 80 (Tween 80®) (Across Organics, Germany) were used as procured from their manufacturers without further purification. Goat fat was obtained from a batch processed according to earlier procedure [19]. Bidistilled water was used for nanoparticle preparation.

2.2. Formulation of the lipid matrix

The lipid matrix used in SLN formulation corresponded to 30 % w/w of P90G in 1:1 mixture of theobroma oil and goat fat was prepared by fusion. This concentration of P90G has been shown to produce nanoparticles with good qualities [15]. The lipids were weighed with an electronic balance (Type L2200P-xD2, Sartorius AG, Göttingen, Germany), melted together at 60 °C on a hot plate (RCT basic, IKA®, Staufen, Germany) and stirred until solidification.

2.3. Formulation of solid lipid nanoparticles (SLN)

SLN were formulated to contain 5 % w/w of lipid matrix (30 % w/w of P90G in 1:1 mixture of theobroma oil and goat fat), 0.0, 0.1, 0.5 or 1.0 % w/w of polysorbate 80 (corresponding, respectively, to SLN-0M, SLN-1M, SLN-2M and SLN-3M), 4 % w/w of sorbitol, 0.005 % w/w of thimerosal and enough bidistilled water to make 100 % w/w. SLN containing 1.0 % w/w polysorbate 80 but no P90G (SLN-4M) was also prepared ('M' stands for mixed lipid). The hot homogenisation technique was adopted. In each case, the lipid matrix was melted at 60 °C and the water containing polysorbate 80, thimerosal and sorbitol at the same temperature was added to the molten lipid matrix with gentle stirring with a magnetic stirrer. The mixture was further dispersed with a mixer (Ultra-Turrax T25 basic, Ika Staufen, Germany) at 24,000 rpm for 5 min to produce the hot primary emulsion. The hot primary emulsion at 60 °C was immediately passed through a heated high pressure homogeniser (EmulsiFlex-C5, Avestin, Canada) at a pressure of 1000 bars for 20 cycles to produce the nanoparticles, which were collected in a hot container and allowed to recrystallize at room temperature. For comparison, SLN containing