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ORIGINAL ARTICLE

Diflucortolone valerate loaded solid lipid nanoparticles as a semisolid topical delivery system

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Abstract Solid lipid nanoparticles (SLNs) are promising delivery carriers that have been utilized for formulation and delivery of various drugs. For topical administration, they are usually incorporated into gel or cream to increase their residence time, which is time-consuming process and could affect their stability and characteristics. Preparation of solid lipid nanoparticles based semisolid formulations could have potential pharmaceutical applications. The aim of this study was to formulate the corticosteroidal drug, diflucortolone valerate (DFV) into topical semisolid SLN formulations using a rapid cheap one-step process. SLN formulations were developed using a high-shear homogenization combined with sonication, using different types of solid lipids (*e.g.*, Geleol®, Precirol® ATO5, Tristearin® and Compritol® 888ATO) and Poloxamer® 407 as a surfactant. Selection of the lipids and using high lipid concentration were the key elements to get semisolid formulation immediately after sonication without incorporating the nanoparticles into a gel or a cream base.
DFV SLN formulations possessed average particle size ranging from 203.71 ± 5.61 to 1421.00 ± 16.32 nm with a narrow size distribution and possessed shear thinning behavior. Incorporation of lipid based surfactants (Labrasol® or Labrafil®) was found to significantly increase DFV encapsulation efficiency (up to 45.79 ± 4.40%).
Semisolid DFV-loaded SLN with high drug encapsulation efficiency and acceptable rheological behavior for topical preparation could be prepared in a one-step process.

1. Introduction

Solid lipid nanoparticles (SLNs) are the first generation colloidal drug carrier systems developed at the beginning of the 1990s.[1] SLNs are similar to nanoemulsions, although liquid lipids used in emulsions are replaced by solid lipids, such as,

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glycerides or waxes.[2] In particular, SLNs are suitable for topical drug delivery, due to their ability to reduce skin irritation, protect the encapsulated active ingredients and allow for controlled release of the drugs.[3] In addition, they are well-suited for inflamed skin because they are composed of physiologically tolerated lipids.[4] Usually, lipid nanoparticle dispersions are incorporated into commonly used dermal carriers (*e.g.*, gels or creams) to obtain semisolid formulations. This multiple step production process is time-consuming, and incompatibilities between nanoparticles and gel or cream components may occur.[5,6] To overcome the previously mentioned challenges, we applied a one-step process to produce semisolid SLN formulations, using the high-shear homogenization and ultrasonication techniques.[5,6]

Topical corticosteroids are widely used for the treatment of skin disorders that require anti-inflammatory and immunosuppressive regimens.[7] They alleviate inflammation by inhibiting vasodilatation and increasing vascular permeability that occurs following inflammation, and they also decrease leukocyte emigration into inflamed sites.[8] Immunosuppressive corticosteroids reduce the response to delayed and immediate hypersensitivity reactions by inhibiting the toxic effect of antigen–antibody complexes that precipitate in vessel walls creating cutaneous allergic vasculities.[9]

Diflucortolone valerate (DFV) is a potent corticosteroid esterified with valeric acid.[10] It is insoluble in water, freely soluble in dichloromethane, 1,4-dioxane, slightly soluble in methanol, and sparingly soluble in ether. It is commercially available in the form of 0.1 and 0.3% cream, oily cream and ointment.[11] DFV is characterized by rapid onset of action and good tolerability in the treatment of cutaneous diseases[12] such as, eczema, psoriasis, and discoid lupus erythematosus.

Hence, development of lipid nanoparticles that can be loaded with the lipophilic drug, DFV, and applied topically as semisolid formulations could be promising in the treatment of several skin disorders. In addition, simplification of the preparation procedures will be extremely useful for scale-up of various pharmaceutical products which are based on these kinds of nanoparticles. Therefore, the aim of this work was the preparation of SLNs semisolid formulations with acceptable rheological properties, small particle size and low polydispersity index, in addition to high drug entrapment efficiency, using high-shear homogenization and ultrasonication techniques.

2. Materials and methods

2.1. Materials

Diflucortolone valerate (DFV) was purchased from Chemical Industries Development (CID) (El Ahram, Giza, Egypt) which was obtained from Bayer Schering Pharma, Germany. Geleol® (glyceryl monostearate 40–55%), Precirol® ATO5 (glyceryl distearate), Compritol® 888 ATO (glyceryl behenate), Capryol™ 90 (propylene glycol monocaprylate), Labrasol® (caprylocaproyl macrogol-8 glycerides EP) and Labrafil® (oleoyl macrogol-6 glycerides EP) were kindly donated by Gattefosse′ (St Priest, Cedex, France). Tristearin® (glyceryl tristearate), Poloxamer® 407 (pluronic F-127; a triblock copolymer of polyoxyethylene–polyoxypropylene) were purchased from Sigma Chemical Company (St. Louis, USA) and methanol used was of analytical reagent grade.

2.2. Preparation of diflucortolone valerate solid lipid nanoparticles

Blank and drug loaded solid lipid nanoparticles were prepared following the one step production method, as previously reported.[5,6] Briefly, solid lipid was melted at 10 °C above its melting point, then, DFV was dispersed in the melted lipid. The melted lipid phase was dispersed in the hot surfactant solution (Poloxamer® 407, 10% *w*/*w*) using high-shear homogenizer (Silent crusher homogenizer, Heidolph Instrument, Schwabach, Germany) at 26,000 rpm for 5 min at 70 °C, keeping hot condition during the process using a water bath. This o/w pre-emulsion was sonicated for 10 min using digital ultrasonicator (Model SH150-4L, MTI Corporation, California, USA) maintaining temperature 10 °C above the melting point of the lipid, and the cycle was repeated twice. The produced DFV dispersion was left to cool at room temperature.

2.3. Modification of diflucortolone valerate-loaded solid lipid nanoparticles using lipid-based surfactants

Modified SLN formulations were prepared using lipid-based surfactant aiming at increasing the solubility of the drug in the lipid phase, and hence increasing its EE%. The added percentage of lipid-based surfactant replaced an equal amount of the water content of each formula. Two lipid-based surfactants were investigated, namely, Labrasol® and Labrafil®. Each of them was tested at three concentration levels of 2.5, 5 and 10% *w*/*w*. DFV was dissolved in the lipid-based surfactant prior to the addition of the solid lipid then the mixture was heated to 10 °C above the lipid melting point. The drug lipid mixture was dispersed in an aqueous surfactant solution at the same temperature and then the high-shear homogenization and ultrasonication techniques were proceeded, as previously explained.

2.4. Characterization of DFV-loaded solid lipid nanoparticles

2.4.1. Particle size analysis

Mean particle size and polydispersity index (PDI), which is a measure of the distribution of nanoparticles population, were determined using Zetasizer Nano ZS (Malvern instruments, UK). Samples were prepared by diluting 0.2 g of the semisolid preparation with 10 ml distilled water, then, vortexed for 30 s and subsequently analyzed. Each sample was measured thrice.

2.4.2. Rheological studies

The rheological measurements were performed with a plate and plate rheometer (Anton Paar® GmbH, Ostfildern, Germany). Up and down portions of the flow curves were determined using parallel plate geometry (50 mm diameter), where, the gap between the two plates was 1 mm. About 0.5 g of the tested formulation was applied to the plate and left until the temperature of the plate reached 25 ± 1 °C. The measurements were made over the whole range of speeding setting from 0.5 to 350 rpm with 20 s between each two successive speeds. The rheological behavior of each formulation was evaluated by plotting the shear stress *versus* the obtained shear rate values. The flow behavior was studied according to Farrow's equation[13]: