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Formulation and nebulization of fluticasone propionate-loaded lipid nanocarriers

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ABSTRACT

Inhaled fluticasone propionate (FP) is often prescribed as a first-line therapy for the effective management of pulmonary diseases such as asthma. As nanocarriers offer many advantages over other drug delivery systems, this study investigated the suitability of lipid nanocapsules (LNCs) as a carrier for fluticasone propionate, examining the drug-related factors that should be considered in the formulation design and the behaviour of LNCs with different compositions and properties suspended within aerosol droplets under the relatively hostile conditions of nebulization.

By adjusting the formulation conditions, particularly the nanocarrier composition, FP was efficiently encapsulated within the LNCs with a yield of up to 97%, and a concentration comparable to commercially available preparations was achieved. Moreover, testing the solubility of the drug in oil and water and determining the oil/water partition coefficient proved to be useful when assessing the encapsulation of the FP in the LNC formulation.

Nebulization did not cause the FP to leak from the formulation, and no phase separation was observed after nebulization. LNCs with a diameter of 100 nm containing a smaller amount of surfactant and a larger amount of oil provided a better FP-loading capacity and better stability during nebulization than 30 or 60 nm LNCs.

1. Introduction

Pulmonary diseases such as asthma and chronic obstructive pulmonary disease (COPD) affect millions of people worldwide. Inhalation is the preferred route of drug administration for asthma treatment (Borgström, 2001). Pulmonary administration offers many advantages for the treatment of respiratory diseases compared with other routes of delivery. Inhalation therapy allows for the direct application of a drug within the lungs (Beck-Broichsitter et al., 2009). Direct delivery of the active substances to the lung enables the administration of lower doses compared with other routes of administration (i.e., oral, buccal, or rectal delivery) with an equivalent therapeutic response and lower systemic exposure (Arzhavitina and Steckel, 2010). Inhaler devices are commonly used for the local delivery of drug molecules to treat pulmonary diseases such as COPD and asthma. Four broad classes of inhalation devices are used to administer these drugs, including pressurized metered dose inhalers, nebulizers, soft mist inhalers, and dry powder inhalers (Cipolla et al., 2014). Nebulizers are recommended for children and adults have difficulty coordinating inspiration and aerosol actuation and in acute severe episodes of bronchospasms. Nebulization can also be indicated when a patient requires large doses of inhaled drugs (Arzhavitina and Steckel, 2010).

Inhaled glucocorticosteroids are often prescribed as the first-line therapy for the effective management of persistent asthma (Dahl, 2006). The most commonly prescribed inhaled corticosteroid is fluticasone propionate (FP), a highly potent anti-inflammatory drug with good pharmacokinetic and pharmacodynamic properties (Chiang et al., 2010). Compared with other inhaled corticosteroids (triamcinolone acetonide, flunisolide, beclomethasone dipropionate, and budesonide), FP has the highest affinity to the corticosteroid receptor relative to dexamethasone (RRA = 1800) and the lowest systemic bioavailability (<1%). Reports have indicated that 80% of FP is bound to plasma proteins (Derendorf et al., 1998).

Drug absorption and retention in the lungs is dependent on many factors such as the physico-chemical properties of the drug,

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the formulation and the method of delivery (Yang et al., 2008). Fluticasone for inhalation is available as a dry powder inhaler, an inhalation aerosol (a suspension of FP with suitable propellants in a pressurized container) and a micronized suspension for nebulization.

Recently, the use of nanoparticles for drug delivery has received a great deal of attention from researchers due to their efficacy and safety, and the advantages offered by nanoparticles are widely accepted by industry (Chiang et al., 2010). Nanoparticles offer numerous advantages over other delivery systems due to their special characteristics including their small particle size and large surface area and the ability to control their surface properties (Azarmi et al., 2008). Drug encapsulation within nanocarriers protects the encapsulated molecules from direct biological interactions, protects them from degradation, and reduces their potential systemic toxicity. Encapsulation can also improve the therapeutic efficiency by controlling the biodistribution and release kinetics of the active pharmaceutical ingredient (API; Delmas et al., 2012). Nanoscale suspensions offer several advantages compared with solutions and dry powder formulations including their suitability for poorly soluble crystalline compounds (therefore eliminating the need for solubilization), the ease of dosing with a syringe-type delivery device in animal studies (leading to more consistent drug distribution in the lung compared with dry powder formulations), and the ability to control the particle size (reducing the variability in drug absorption) (Yang et al., 2008).

The fate of inhaled nanomaterials depends on regional distribution in the lung (Sakagami, 2006). The inertial impaction and sedimentation occur during the passage through the oropharyngeal region or the bronchial region, respectively, and it affects particles larger than 10 μm in diameter. At the other extreme, particles smaller than 1 μm are likely to reach the alveolar region, but they are expected to be exhaled rather than deposited. Particles with aerodynamic diameters between 1 and 5 μm are likely to be deposited in the lung periphery (Bailey and Berkland, 2009). Individual nanoparticles are too small to be deposited in the alveoli and the majority of the administered dose is exhaled. The nanoparticles are most often delivered to the lungs via nebulization of colloidal suspensions (Sung et al., 2007), and in this case it is the size of the aqueous droplet that determines the fate of the inhaled nanocarriers. To administer the nanoparticles in the solid state form, Trojan particles (nanoparticles incorporated into microparticles) can be employed (Tsapis et al., 2002).

Lipids have been widely used in a variety of drug delivery systems such as liposomes, emulsions, solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs). These formulations were not developed specifically for pulmonary applications, but they have since been used for respiratory delivery as scientists have explored novel applications in various pharmaceutical areas (Cipolla et al., 2014). A number of pharmaceutical liposome formulations have reached the market, and many liposome formulations have shown promise as inhaled products (Cipolla et al., 2014). In contrast, the evaluation of the potential of SLNs and NLCs to provide therapeutic benefit as inhaled products is at an earlier stage (Weber et al., 2014). Lipid nanocarriers can be used to solubilize poorly water-soluble drugs. One major advantage of these systems is that their solubilization capacity is retained on administration, in contrast to formulations based on conventional solubilization approaches. Formulations containing cosolvents or surfactant micelles may partially lose their solubilization potential upon dilution with aqueous media (Bunjes, 2010).

A broad range of drugs, mainly drugs with lipophilic properties, has already been incorporated into lipid nanocapsules (LNCs), including ibuprofen (Lamprecht et al., 2004), etoposide (Lamprecht and Benoit, 2006), paclitaxel (Hureaux et al., 2009), and amiodarone (Lamprecht et al., 2002). LNCs can be considered as drug carriers for various routes of administration, including oral and local delivery (Huynh et al., 2009). Recently, researchers have investigated pulmonary administration of LNCs (Hureaux et al., 2009). Hureaux et al. (2009) examined the nebulization of drug-free and paclitaxel-loaded LNCs. That study focused on the selection of the nebulizer device and the properties of the resulting aerosol. However, the influence of nanoparticle characteristics and concentration were not investigated, with only 50 nm LNCs tested at one concentration. The characteristics of nanoparticles and liposomes including their composition have been shown to exert an important influence on their stability and possible aggregation upon nebulization (Dailey et al., 2003; Kleemann et al., 2007). Indeed, the performance of liposomes during nebulization strongly depended on the composition of the lipids and the drug, with characteristics such as particle size and surface charge exhibiting significant effects (Niven and Schreier, 1990; Niven et al., 1991; Desai et al., 2002). As the size and composition of LNCs can vary (Heurtault et al., 2002; Lamprecht et al., 2002; Huynh et al., 2009), it is important to examine the influence of these factors on the behaviour of nanocarriers during nebulization.

The objective of this study was to investigate the suitability of LNCs as carriers for fluticasone propionate and to determine which drug factors should be considered in the formulation design. Another important goal of this work was to examine the behaviour of the different LNCs suspended within aerosol droplets under the relatively aggressive conditions of nebulization.

2. Materials and methods

2.1. Materials

Labrafac® CC (caprylic/capric acid triglycerides-C8/C10-TG) was kindly provided by Gattefossé S.A. (France). Lipoid® S75-3 (hydrogenated lecithin) and Solutol® HS15 (macrogol 15 hydroxystearate, polyoxyl 15 hydroxystearate) were kindly provided by Lipoid Gmbh (Germany) and BASF (Germany), respectively. Fluticasone propionate was purchased from Kemprotec (UK). All other chemicals and solvents were of analytical grade. Amicon Ultra-4 centrifugal filter devices were obtained from Millipore (USA).

2.2. Solubility in oil and in water

In a glass scintillation vial, 50 mg of FP and 10 ml of C8/C10-TG, water or a 0.5% (w/v) aqueous solution of polyoxyl 15 hydroxystearate were heated up to 95–100 °C for 5 min. Samples were cooled down to room temperature and centrifuged (16,000 × *g*, 5 min) to remove undissolved FP, and the supernatant was diluted with acetonitrile (1:20 and 1:1 volume ratios for the C8/C10-TG and aqueous solutions, respectively). The solubility of FP was determined by measuring the absorbance at an operating wavelength of 250 nm in optically homogenous quartz cuvettes (Hellma) with a light path of 10 mm, with mixtures of C8/C10-TG/acetonitrile, water/acetonitrile, and polyoxyl 15 hydroxystearate solution/acetonitrile used as references. The absorbance measurements were performed using a UV-2600 spectrophotometer (Shimadzu).

2.3. Thermal stability of FP

1 mg of FP dissolved in 10 ml of C8/C10-TG was heated up to 95–100 °C and then cooled to 60 °C; this cycle was repeated three times, and after the final cycle the dispersion was cooled down to room temperature. Then, 0.2 ml of the solution of FP in C8/C10-TG was mixed with 1.8 ml of acetonitrile (1:10 v/v dilution, 10 μg of FP/ml). As a control, FP was dissolved in acetonitrile and mixed with C8/C10-TG without heating. Due to the high absorbance of the