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Formulation and drying of miconazole and itraconazole nanosuspensions

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ABSTRACT

Miconazole and itraconazole possess adequate membrane permeability, but only slight water solubility, which limits their bioavailability and antifungal effect. To increase their dissolution rate, the compounds were nanoground by media milling to produce nanosuspensions with mean particle size of approximately 210 nm and stabilized with sodium dodecylsulfate (SDS) in combinations with either cellulose ethers (HPC or HPMC) or poloxamers. During storage for 3 months at 25 °C, HPC/SDS stabilized more efficiently miconazole nanoparticles, while poloxamer 407/SDS performed better with itraconazole nanosuspensions. The stabilizing efficiency of the excipients was explained by physical–chemical drug–excipients interactions. The HPC/SDS-stabilized nanosuspensions were spray-dried or freeze-dried with and without the matrix formers mannitol or microcrystalline cellulose (MCC). In absence of matrix former, itraconazole particles agglomerated more extensively than miconazole particles, resulting in a low dissolution rate. Dissolution of the spray- or freeze-dried miconazole nanosuspension was enhanced in presence of mannitol or MCC (drug substance:excipient ratio of 1:1, w/w), as compared to the coarse drug suspension (twice the amount dissolved after 10 and 20 min). Spray-drying itraconazole nanosuspension in presence of mannitol or MCC also yielded fast dissolution (60% dissolved in less than 10 min as compared to 30–45 min with the coarse suspension). Freeze-dried itraconazole nanosuspensions did generally not dissolve substantially faster than freeze-dried coarse suspension. In conclusion, we were able to process miconazole and itraconazole successfully and under similar conditions into dry nanoparticulate drug products with enhanced in vitro performance.

1. Introduction

Nanoparticle technology has gained wide interest in the medicinal and pharmaceutical sciences as it has numerous applications; nanoparticles can be designed to target and/or sustain the delivery of drugs, to improve oral bioavailability, or for pulmonary, ocular, or parenteral delivery (Patravale et al., 2004; Mishra et al., 2009; Müller et al., 2011; Merisko-Liversidge and Liversidge, 2011; Shegokar and Singh, 2011; Gao et al., 2012). For very slightly water-soluble or practically water-insoluble drug substances, nanosuspensions are of great interest, as they can be formulated with up to 40% drug content in either aqueous or mixed aqueous-organic solvents, require only small amounts of non-toxic excipients, and may preserve drug stability better than other formulations (Patravale et al., 2004). As a consequence, several nanosuspension products have become available, with most of them being manufactured by media milling and intended for oral administration.

The current engineering processes to obtain nanosuspensions are divided into bottom-up processes such as nanoprecipitation or nanocrystallization (Chan and Kwok, 2011; D'Addio and Prud'homme, 2011; Dandagi et al., 2011) and top-down processes such as high pressure homogenization (Keck and Müller, 2006) and media milling (Merisko-Liversidge et al., 2003; Merisko-Liversidge and Liversidge, 2011). In media milling (nanogrinding), for example, desired particle size range and particle stability may be achieved by optimizing the formulation (e.g., type and concentration of excipients and concentration of drug substance) (Wu et al., 2011) as well as the process parameters (e.g., size of grinding beads and specific energy input) (Cerdeira et al., 2011; Merisko-Liversidge and Liversidge, 2011; Juhnke et al., 2012).

Whereas process parameters can be optimized relatively easily (Cerdeira et al., 2011; Hennart et al., 2012), the selection of adequate excipients remains an important challenge that has to be addressed mostly empirically (Merisko-Liversidge and Liversidge, 2011; Wu et al., 2011); the latter is due to lack of basic knowledge of exact mechanisms of nanosuspension stabilization upon nanogrinding (Lee et al., 2005, 2008; Merisko-Liversidge and Liversidge, 2011). Nanosuspension formulation generally requires addition of appropriate stabilizers to lower the free surface energy

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of the nanoparticles and prevent particle aggregation and/or particle growth. The high surface free energy of nanoparticles is readily lowered by lowering the solid–liquid interfacial tension upon addition of surfactants (Rabinow, 2004). Particle aggregation or growth may be efficiently prevented or at least slowed down through adsorption of stabilizers that form electrostatically repulsive or steric barriers (Merisko-Liversidge and Liversidge, 2011; Wu et al., 2011). So far, only relatively few compounds have proven to be suitable for nanosuspension stabilization, as for example, sodium dodecylsulfate (SDS), polysorbates, povidones, poloxamers, and cellulose derivatives (Van Eerdenbrugh et al., 2009a). Surfactant/polymer mixtures have often shown synergistic effects (Lee et al., 2008; Cerdeira et al., 2010).

To enhance long-term stability, nanosuspensions can be converted into dry form, typically by freeze-drying or spray-drying (Liu et al., 2010; Chaubal and Popescu, 2008; Van Eerdenbrugh et al., 2008a; Choi et al., 2005). However, drying of nanosuspensions may negatively affect nanoparticle size and dispersibility (Van Eerdenbrugh et al., 2008a; Chaubal and Popescu, 2008). The generation of aggregates likely causes alteration of disintegration and dissolution, which may subsequently cause changes in bioavailability (Chaubal and Popescu, 2008). Therefore, particle size distribution of dried nanosuspensions is a critical quality attribute, which is primarily affected by the formulation.

Particle aggregation upon drying of nanosuspensions can be minimized by adding so-called matrix formers such as sugars or sugar alcohols (e.g., sucrose, lactose, mannitol) or insoluble excipients (e.g., microcrystalline cellulose, colloidal anhydrous silica) (Van Eerdenbrugh et al., 2008c); matrix formers fill the gaps between nanoparticles upon water removal and thereby prevent undue close contacts between the particles (Kim and Lee, 2010). To select appropriate excipients both for nanogrinding and subsequent drying it is important to consider drug substance properties and their potential role in the manufacturing process and final product quality attributes. For example, in a study on nine drug compounds, which were media-milled in presence of the stabilizer D-tocopheryl polyethylene glycol 1000 succinate (TPGS) and subsequently freeze-dried or spray-dried, Van Eerdenbrugh et al. (2008a) demonstrated that the drug substance hydrophobicity plays a major role in these processes; more hydrophobic drug substances, including itraconazole, were found to be more difficult to stabilize against irreversible particle aggregation during drying.

Drying of itraconazole nanosuspensions, obtained by bottom-up or top-down processes, has been studied by different authors (Chaubal and Popescu, 2008; Lee et al., 2008; Van Eerdenbrugh et al., 2008b; Liu et al., 2010; Mou et al., 2011). For example, Van Eerdenbrugh et al. (2008b) reported that microcrystalline cellulose was superior to sucrose as matrix former to avoid agglomeration upon freeze-drying of itraconazole nanosuspensions stabilized with 10% TPGS. Contrarily to itraconazole, miconazole nanosuspensions have, to our knowledge, only scarcely been considered (Cerdeira et al., 2010, 2011, 2012). Itraconazole and miconazole are imidazole derivatives of low solubility (BCS II) and used as antifungals (Piel et al., 1998; Tsutsumi et al., 2011; Van Eerdenbrugh et al., 2009a). The two drug substances differ, however, in their molecular weight (miconazole: 416.1 g/mol; itraconazole: 705.6 g/mol), melting temperature (miconazole: 83–87 °C for polymorph I; itraconazole: 168 °C), and water-solubility (miconazole: ≈1 mg/l; itraconazole: ≈0.1 mg/l, both in unbuffered water and pH 7 buffer). Therefore, comparison between the two drug substances in nanogrinding and subsequent drying appeared to be of interest, as compounds with of higher molecular weight and melting point, and lower aqueous solubility (itraconazole) were reported to be easier to formulate as nanosuspensions (Lee et al., 2008).

In the present study, we first aimed at relating the stability of miconazole and itraconazole nanosuspensions, obtained by media milling, with the adsorption of various stabilizers. Further, we assessed various matrix formers in spray-drying and freeze-drying of the obtained nanosuspensions in terms of nanoparticle stability and dissolution.

2. Materials and methods

2.1. Materials

Miconazole (diameter $D_{4,3} \approx 20\,\mu m$; lot # R018134PUC701, Janssen Pharmaceutica N.V., Geel, Belgium) and itraconazole (diameter $D_{4,3} \approx 20\,\mu m$; lot # ZR051211PUK401, Janssen Pharmaceutica N.V., Geel, Belgium) were used as received. All other materials were also used as received: sodium dodecyl sulfate [SDS] (Texapon® K12P, Cognis, Düsseldorf, Germany); hydroxypropylcellulose [HPC] (type LF, Hercules, Doel, Belgium); hydroxypropylmethylcellulose [HPMC] (Hypromellose 2910, E15 LV, Colorcon, Dow Chemicals, Dartford, UK); poloxamers [poloxamer 188 and 407] (Pluronic® F68 and F127; BASF, Ludwigshafen, Germany); mannitol (Pearlitol 160C®, Roquette, Lestrem, France); microcrystalline cellulose (Avicel PH-105®, FMC BioPolymer, Brussels, Belgium); croscarmellose sodium (Ac-Di-Sol®, FMC, Philadelphia, PA, US); gelatine capsules (size 0, Capsugel®, Bornem, Belgium).

2.2. Nanogrinding of the drug substances

Formulation and process parameters for this work were selected according to previous experiments (Cerdeira et al., 2010, 2011). A first series of experiments aimed at screening polymeric excipients for their suitability for nanogrinding and stabilizing the two drug substances. For this, HPC, HPMC, or the poloxamers 188 or 407 were used at a concentration of 5% (w/w) and each in combination with 0.05% (w/w) SDS. The concentration of drug substance in the suspensions was kept at 20% (w/w). HPC without SDS was also tested as a stabilizer for itraconazole to compare with previous experiments with miconazole (Cerdeira et al., 2010). A second series of experiments examined the effect of the quantitative composition of the formulations on the particle size reduction using 5, 12.5, or 20% miconazole or itraconazole, along with 0.05, 0.125 or 0.2% SDS, and 1.25, 3.125 or 5% HPC.

For preparing the nanosuspensions, SDS was dissolved in purified water, and the polymer added under mechanical agitation. The drug substance was then dispersed in the stabilizer solution and kept under mechanical stirring for 60 min. The suspensions were left overnight to reduce the air incorporated before starting the nanogrinding process. Nanogrinding was performed in a high-energy mill (LabStar LS1 MiniCer, Netzsch, Selb, Germany) filled to 83% (v/v; apparent volume of grinding beads relative to the volume of the grinding chamber) with yttrium-stabilized zirconium oxide beads (0.8 mm or 0.4 mm in diameter). The suspension was first circulated through the milling chamber to adjust the flow to 113 g/min, before turning on the stirrer. Nanogrinding was performed in circulation mode using 300 g of suspension, a pump-speed of 41 rpm (113 g/min), and a stirrer-tip speed of 3400 rpm (10 m/s). The stirrer speed was gradually increased during 5 min from 1000 to 3400 rpm; the duration of the process lasted 60 min. The nanosuspensions that were further dried (see below) were all milled with beads of 0.4 mm in diameter.

2.3. Spray-drying and freeze-drying of coarse drug suspensions and nanosuspensions

Amounts of suspension (drug substance 20%/HPC 5%/SDS 0.05%, w/w) equivalent to 8 g of drug substance were diluted with water to obtain drug substance concentration of 10% (w/w). For spray