International Journal of Pharmaceutics 428 (2012) 103–113

Contents lists available at SciVerse ScienceDirect

International Journal of Pharmaceutics

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

Solid dispersions of itraconazole for inhalation with enhanced dissolution, solubility and dispersion properties

Christophe Duret[a,*], Nathalie Wauthoz[a], Thami Sebti[b], Francis Vanderbist[b], Karim Amighi[a]

[a] Laboratoire de Pharmacie Galénique et de Biopharmacie, Université Libre de Bruxelles, Brussels, Belgium
[b] Laboratoires SMB S.A., 26-28 Rue de la Pastorale, 1080 Brussels, Belgium

ARTICLE INFO

Article history:
Received 5 January 2012
Received in revised form 4 March 2012
Accepted 5 March 2012
Available online 10 March 2012

Keywords:
Itraconazole
Pulmonary aspergillosis
Dry powder for inhalation
Spray-drying
Amorphous
Solid dispersion

ABSTRACT

The purpose of this study was to produce a dry powder for inhalation (DPI) of a poorly soluble active ingredient (itraconazole: ITZ) that would present an improved dissolution rate and enhanced solubility with good aerosolization properties. Solid dispersions of amorphous ITZ, mannitol and, when applicable, D-α-tocopherol polyethylene glycol 1000 succinate (TPGS) were produced by spray-drying hydro-alcoholic solutions in which all agents were dissolved. These dry formulations were characterized in terms of their aerosol performances and their dissolution, solubility and physical properties. Modulate differential scanning calorimetry and X-ray powder diffraction analyses showed that ITZ recovered from the different spray-dried solutions was in an amorphous state and that mannitol was crystalline. The inlet drying temperature and, indirectly, the outlet temperature selected during the spray-drying were critical parameters. The outlet temperature should be below the ITZ glass transition temperature to avoid severe particle agglomeration. The formation of a solid dispersion between amorphous ITZ and mannitol allowed the dry powder to be produced with an improved dissolution rate, greater saturation solubility than bulk ITZ and good aerosol properties. The use of a polymeric surfactant (such as TPGS) was beneficial in terms of dissolution rate acceleration and solubility enhancement, but it also reduced aerosol performance. For example, significant dissolution rate acceleration ($f_2 < 50$) and greater saturation solubility were obtained when introducing 1% (w/w) TPGS (mean dissolution time dropped from 50.4 min to 36.9 min and saturation solubility increased from 20 ± 3 ng/ml to 46 ± 2 ng/ml). However, the fine particle fraction dropped from $47 \pm 2\%$ to $37.2 \pm 0.4\%$. This study showed that mannitol solid dispersions may provide an effective formulation type for producing DPIs of poorly soluble active ingredients, as exemplified by ITZ.

1. Introduction

Active pharmaceutical ingredients (APIs) can be administered to the lung either as a solution or a suspension using nebulizer or pressurized metered dose inhalers or as a dry powder using dry powder inhalers. Pressurized metered dose inhalers and nebulizer medicines are losing interest due to their specific weaknesses, and dry powder for inhalation (DPI) medicines are currently the focus of research development in the pulmonary delivery field. The administration of an API-based dry powder formulation to the lung involves several specific considerations that can limit the design and development of a DPI medicine. Indeed, the powder must present a maximum proportion of particles with an aerodynamic diameter (d_{ae}) between 0.5 and 5 μm after being emitted from the dry powder inhaler by the inspiratory flow. This d_{ae} limitation is required because only particles within this size range will deposit in the lung. Particles over 5 μm will be stopped in the upper airways by inertial impaction, and particles smaller than 0.5 μm could be exhaled during expiration. The formulation strategies must maximize this proportion of fine particles by offering suitable particle size distributions and good flow and dispersion properties using excipient suitable for pulmonary administration (Pilcer and Amighi, 2010). Additionally, to be marketed, the manufacturing process must be easily scalable. For this purpose, the

Abbreviations: API, active pharmaceutical ingredient; CI, Carr compressibility index; d_{ae}, aerodynamic diameter; DPI, dry powder for inhalation; f_2, the similarity factor; FPD, fine particle dose; FPF, fine particle fraction; GRAS, generally recognized as safe; HPLC-UV, high performance liquid chromatography coupled to ultra-violet detection; HSM, hot stage microscopy; ITZ, itraconazole; MTDSC, modulated temperature differential scanning calorimetry; MDT, mean dissolution time; MsLI, multi-stage liquid impinger; NGI, next generation impactor; pMDI, pressurised metered dose inhaler; SD, solid dispersion; SEM, scanning electron microscopy; TPGS, tocopherol polyethylene glycol 1000 succinate; XRPD, X-ray powder diffraction.

* Corresponding author at: Laboratory of Pharmaceutics and Biopharmaceutics, Faculty of Pharmacy, ULB, Boulevard du Triomphe - CP207 Campus de la Plaine, B-1050 Brussels, Belgium. Tel.: +32 2 650 53 31; fax: +32 2 650 52 69.
E-mail address: cduret@ulb.ac.be (C. Duret).

0378-5173/$ – see front matter © 2012 Elsevier B.V. All rights reserved.
doi:10.1016/j.ijpharm.2012.03.002

production process should be as simple as possible using equipment and techniques that are readily transposable to an industrial scale.

More particularly, many existing APIs and an increasing number of new ones are often poorly water-soluble drugs. Approximately 40% of the drugs on the market and 70–90% of the drugs currently in research and development are poorly soluble in water (Zhang et al., 2011). Drug insolubility, regardless of the administration route, commonly generates bioavailability or efficacy problems. In the inhalation field, DPI formulations based on a poorly water-soluble drug should be able to provide a powder presenting a high fine particle fraction (FPF) after emission from a dry powder inhaler and to improve drug wettability, solubility and dissolution. Indeed, poor drug dissolution and wettability could induce lung irritation and therefore local side effects (Tran et al., 2000; Jones and Neef, 2012). Having a solubility and dissolution rate that are too low could also result in excessive non-absorptive clearance (macrophage phagocytosis and/or mucociliary clearance) of solid particles, leading to a rapid dose reduction in the lung (Mobley and Hochhaus, 2001). Because the activity and/or absorption of a drug are limited by the number of its molecules that are dissolved, accelerating a drug's dissolution rate could be necessary to overcome these clearance mechanisms and optimize the drug's efficacy.

Different techniques exist to increase drug dissolution and/or solubility, such as complexation within cyclodextrins (Loftsson and Brewster, 2010), particle size reduction (Van Eerdenbrugh et al., 2010), crystal engineering (Blagden et al., 2007; Hickey et al., 2007) and even the formation of a lipid-based delivery system (Porter et al., 2007). However, these strategies often require the use of specific excipients to achieve the final dissolution enhancement effect or the desired particle formation. Ideally, inhaled excipients should be chemically and physically stable and inert to the API and should not exhibit harmful effects, especially on the respiratory tract. Knowing that (i) the number of authorized inactive ingredients that can be used in the development of inhalable pharmaceutical products is quite limited (http://www.accessdata.fda.gov/scripts/cder/iig/index.cfm, 2011) and (ii) the documentation on the safety profile of potential excipients intended to be administered by the pulmonary route is usually incomplete (Pilcer and Amighi, 2010), these realities considerably reduce formulation possibilities in the development of poorly water-soluble drug-based DPIs.

Regarding problems underlying above, a formulation strategy must be set up to allow poorly water-soluble active ingredient based DPI to offer (i) a high lung deposition, (ii) an improved solubility and dissolution profile and (iii) an acceptable safety profile, in regards with excipients used. The aim of this study was to evaluate one DPI formulation strategy consisting of the formation of a poorly water-soluble drug based solid dispersions (SDs) produced by a spray-drying process to meet these needs. Indeed, the formation of a SD between a poorly water-soluble drug particle and a hydrophilic inactive ingredient that is generally recognized as safe (GRAS), such as a carbohydrate, could be an effective method of increasing the drug dissolution rate and saturation solubility while providing good aerosol and flow properties. In SD formulations, the drug dissolution rate could be improved by reducing the drug particle size to almost a molecular level and by modifying the drug crystalline state to generate a completely or partially amorphous state, both of which may increase drug saturation solubility (Serajuddin, 1999).

Itraconazole (ITZ) has previously shown interesting potential for treating pulmonary invasive fungal infection *via* inhalation (nebulization) (Hoeben et al., 2006) and was chosen in this report as a model of an insoluble API. This molecule presents very low saturation solubility (approximately 1 ng/mL at neutral pH and 4 μg/mL at pH 1) and a log *P* of 6.2. Due to its low solubility and high permeability, ITZ is a class II drug molecule according to the biopharmaceutical classification system (Amidon et al., 1995). Its low dissolution rate and saturation solubility could therefore be a limiting factor in its efficacy (Yang et al., 2010). Mannitol was chosen as the SD hydrophilic agent for its various interesting physicochemical properties and its safety profile after inhalation. Indeed, this excipient is currently recognized as safe for inhalation (Daviskas et al., 2010) and provides a sweet taste when in contact with mouth mucosa, which tends to improve patient compliance. Additionally, this carbohydrate is one of the less hygroscopic sugars, preventing excessive reuptake of water by powders during storage. Consequently, it prevents particle agglomeration and aggregation arising from the appearance of additional capillary forces between particles, which decrease DPI aerosol performance. Moreover, mannitol was also selected instead of the more classic lactose or sorbitol, which are generally used in inhalation, because of its potential to form a SD with improved solubility (Vasconcelos et al., 2007) and its ability to stabilize an amorphous drug compound (Lian, 2001), which may be both beneficial in our formulation strategy. The addition of TPGS to the formulation composition was also evaluated. TPGS is a surfactant that is potentially eligible for pulmonary administration because of its good performance and safe potential in the formulation and administration of pulmonary formulations (Yan et al., 2007; Shah and Banerjee, 2011).

2. Materials and methods

2.1. Materials

Raw ITZ was purchased from Hetero Drugs Ltd. (Hyderabad, India). This powder was micronized by jet milling (volume mean diameter, 3.5 μm; 90% of particles below 6.2 μm). Sodium lauryl sulfate and TPGS were purchased from Sigma–Aldrich (Brussels, Belgium). Pearlitol PF® (mannitol) was donated by Roquette Frères (Lestreme, France). Dipalmitoylphosphatidylcholine (DPPC) was purchased from Lipoid® (Ludwigshafen, Germany). All the solvents were analytical grade.

2.2. Methods

2.2.1. Production of SD formulations

The theoretical compositions of the formulations (A1, A2, A3, A4, A5 and A6) before and after spray-drying are described in Table 1. First, the different ingredients were dissolved under magnetic stirring (600 rpm) in a hydro-alcoholic solution of isopropanol (80%) and water (20%) heated to 70 °C. Then, the solutions containing the hydrophilic agent (mannitol), the API (ITZ) and, in some solutions, the TPGS as a surfactant were spray-dried using a Büchi Mini Spray-Dryer B-191-a (Büchi Laboratory Techniques, Flawil, Switzerland) to produce the DPI formulations in a one-step process. For each assay, the following spray-drying conditions were used: spraying air flow, 800 l/h; drying air flow, 35 m^3/h; solution feed rate, 2.7 g/min; and nozzle size, 0.5 mm. The inlet and resulting outlet spray-dryer temperatures for each formulation are reported in Table 1.

2.2.2. Particle size analysis

The particle sizes were measured using a laser diffraction based apparatus (Malvern Mastersizer 2000) equipped with a Sirocco® dry dispersion system (Malvern Instruments Ltd., Malvern, United Kingdom). A pressure of 4 bar and a feed rate vibration of 50% were used during the measurements. The very drastic dispersion conditions applied to the sample by this technique allow particle size distribution measurement of almost totally disaggregated powder particles. Particle size distributions were calculated using a refractive index of 1.61 for bulk ITZ and 1.48 for all dry powders. The