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Optimization and scaling-up of ITZ-based dry powders for inhalation

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ABSTRACT

Dry powders for inhalation with amorphous itraconazole (ITZ) dispersed in a hydrophilic matrix were previously obtained by the spray-drying technique. This gave interesting aerodynamic and dissolution characteristics leading to promising lung pharmacokinetic and prophylaxis efficacy in a preclinical model of invasive pulmonary aspergillosis. The spray-drying allows dry powder to be obtained in a one-step process; nonetheless, the scale-up still presents a challenge in maintaining the main particle characteristics. This study aimed to investigate the feasibility of obtaining similar powder characteristics from concentrated solutions using laboratory-scale and pilot-scale spray dryer equipment. ITZ was solubilized in a solvent mixture (ethanol/ethyl acetate/water mixture 40:40:20 v/v/v) in mannitol solutions or suspensions. These mixtures were spray dried at laboratory scale to produce a solid dispersion for inhalation (SDI) containing amorphous ITZ dispersed in a mannitol matrix. A solution of 35% (So1) w/w ITZ was chosen to evaluate the scale-up process. This formulation was chosen for its high yield (60%), its amorphous ITZ content (100%), its good aerodynamic behavior (fine particle fraction - FPF = 33± 2%) and its increased dissolution profile compared to bulk ITZ. The scale-up process showed pilot-scale dry powders with a higher yield than lab-scale dry powders and similar aerodynamic performance and equivalent dissolution profiles. Moreover, all SDIs displayed improved release kinetics in comparison with bulk ITZ. Despite the slight differences between lab- and pilot-scale SDIs, this study shows that the scaling-up process allowed interesting ITZ-based SDIs to be obtained, in order to achieve pilot-scale production.

1. Introduction

Itraconazole (ITZ) is an antifungal agent with poor water solubility and high membrane permeation (class II of BCS) [1]. For pulmonary fungal infections, ITZ is recognized as a first-line treatment for chronic cavitary pulmonary aspergillosis and allergic bronchopulmonary aspergillosis or a second-line treatment for invasive pulmonary aspergillosis with a minimal inhibitory concentration (MIC) of 2 μg/mL against *Aspergillus fumigatus* species [2,3].

Currently ITZ administration to patients is mainly carried out through IV or oral treatment [4]. Administration of ITZ by the pulmonary route could be a promising alternative for targeting fungal lung infections. Targeting lungs allows the hepatic first pass to be avoided, unlike oral administration. Indeed, ITZ is metabolized to its active metabolite (hydroxy-itraconazole) by the liver, which increases the randomness of the bioavailability, while with lung administration, drug is directly available to act on its target. This decreases the dose that needs to be delivered in comparison to systemic routes (i.e. the oral or IV route) [5]. These effects allow drug to reach the MIC faster and more easily while reducing the risk

Table of abbreviations: AI, aggregation index; BCS, biopharmaceutics classification system; DPI, dry powder inhaler; d_{ae}, aerodynamic diameter; FSI, fast screening impactor ; FPD, fine particle dose; FPF, fine particle fraction; GRAS, generally recognized as safe; ITZ, itraconazole; MIC, minimum inhibitory concentration; MMAD, mass median aerodynamic diameter; NGI, next generation impactor; PSD, particle size distribution; PXRD, powder x-ray diffraction; SEM, scanning electron spectroscopy; SDI, solid dispersion for inhalation; TGA, thermogravimetric analysis.

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of side effects and drug-drug interactions [6,7].

Usually, nebulizers, pressurized metered dose inhalers and dry powder inhalers (DPIs) are employed to deliver drugs through the lung. Despite the need for cleaning, in the case of non-disposable devices, and the reliance on the patient's inhalation rate, dry powders delivered by DPI seem to be the most appropriate way to deliver high doses of poorly soluble drugs such as ITZ. Indeed the advantages of DPIs comprise the absence of liquid propellants, no need for hand-lung coordination and the ability to deliver a high dose compared to pressurized metered dose inhalers. Moreover, the compact design, the ease of use, the absence of maintenance requirements and the ability to deliver poorly water-soluble drug is more suitable compared to nebulizers [8]. Therefore, ITZ-based-strategies in developing solid dispersion for inhalation (SDI) have consisted in the production of solid dispersions presenting aerodynamic behavior appropriate to reaching the MIC in the lung and with improved ITZ dissolution properties to optimise its pharmacokinetic profiles [9] and therefore its pharmacological action. In SDIs, ITZ is in amorphous state dispersed in a hydrophilic mannitol matrix responsible for the improved ITZ dissolution rate [9–11]. These innovative SDIs have been produced using a scalable spray-drying process and using mannitol, a generally recognized as safe excipient (GRAS) for administration by the inhalation route [12,13].

During pharmaceutical development, the production step is evaluated from laboratory scale (lab-scale) to pilot-scale and finally to industrial-scale. Moreover, pilot-scale spray-drying is also necessary for powder production for clinical trials. From an economic point of view, the scaling up should allow a high productivity rate with a high yield. For this reason, previous SDI formulation and manufacturing parameters used at the lab-scale have to be robust but also be optimized to increase the efficiency of the production process. An important concern is the total dry component content in solution or suspension before the spray-drying. This because the greater the total component contents is, the less solvent there is to evaporate, which therefore generates lower economic and environmental costs. Nevertheless, these productivity benefits should not be at the expense of the product's quality or its main properties, i.e. the amorphous state of ITZ, aerodynamic particle sizes and the ITZ dissolution rate obtained with lab-scale SDIs. Indeed, between each scale, and in particular between lab-scale and pilot-scale spray dryers, there are some differences in the feeding system, the nature of wall components (e.g. glass in lab-scale or stainless in large-scale spray dryers), the nature of the drying gas, the chamber dimensions and the droplet trajectories. Moreover, the evaporation rate could induce some changes in the residual solvent content, particle surface area, density, roughness or porosity, particle size distribution (PSD) or crystalline properties of the drug or excipients [14]. Therefore the scaling up of a spray-drying process is established well empirically as well as with thermodynamic models to assess the drying kinetics governing the structural arrangement of particles [14–18].

The aim of this study was to evaluate the ability to scale up these lab-scale produced formulations while keeping their main properties i.e. i) ITZ in amorphous state, ii) a fine particle dose (FPD) allowing the MIC to be reached using a single capsule filled with 10–20 mg of SDI, and iii) an improved ITZ dissolution rate compared to bulk ITZ.

In the first instance, this study focused on the formulation optimization before spray-drying. It looked at the increase in component content for spray-drying solutions or suspensions of ITZ and mannitol. Then, this study explored how the ITZ SDI properties varied with the change of scale from a laboratory Mini Spray-Dryer B-290 (Büchi, Switzerland) to a pilot Mobil Minor Spray-Dryer (GEA Niro, Denmark). The lab-scale and the pilot-scale produced SDIs were evaluated on their crystalline forms of ITZ, their polymorph forms of mannitol, their aerodynamic behavior and their drug release kinetics, as well as on their PSD, morphology and residual solvent content.

2. Materials and methods

2.1. Materials

Raw ITZ was provided by Hetero Drugs Ltd (India). Sodium lauryl sulfate was purchased from Sigma-Aldrich (Belgium). Sodium chloride, disodium hydrogen phosphate, potassium dihydrogen phosphate, potassium chloride, chloride calcium and magnesium chloride were purchased from VWR (Belgium). Mannitol (Pearlitol® 25C) was donated by Roquette Frères (France). All solvents used were of analytical grade.

2.2. Methods

2.2.1. Solvent mixture determination

To determine the optimal solvent mixture, different combinations of organic solvents and water were evaluated. Binary, ternary and quaternary mixtures with isopropanol, ethyl acetate, ethanol and water were evaluated. For each mixture, at the temperature fixed, ITZ was added until an opalescent suspension was obtained under magnetic stirring for 24 h. The solubilized ITZ concentration was determined after filtration (0.45 μm pores, Millipore, Germany) using HPLC-UV analysis.

2.2.2. Production of dry powder for inhalation

At the lab-scale, dry powders were produced by spray-drying a solution or a suspension using a Mini Spray Dryer B-290 (Büchi laboratories, Switzerland). For the solutions, mannitol and ITZ were successively dissolved in a mixture of ethanol, ethyl acetate and water (40:40:20) at 60 °C before being spray dried. For the suspensions, aqueous mannitol solution (10% w/v) was first spray dried at an inlet temperature of 130 °C with a feed rate of 270 g/h using a 0.7 mm nozzle, drying air flow of 35 m^3/h and compressed air at 800 L/min, inducing an outlet temperature of 43 °C. Then, the spray-dried mannitol was suspended in an ITZ solution composed of ethanol, ethyl acetate and water (40:40:20). Finally, the suspensions obtained were homogenized by means of a high-speed homogenizer (Ultra Turrax, IKA, Germany) at 21 500 rpm for two steps of 10 min before the spray-drying process. During the pumping step, solution temperatures slightly decreased in the pipe, causing mannitol precipitation when the component content was higher than 4.5% w/v. This precipitation produced pipes and spray nozzle obstruction. Therefore an insulation system surrounding the pipes was established allowing a constant temperature to be maintained throughout the whole process and mannitol precipitation to be avoided. At the pilot-scale, dry powders were produced by spray-drying a solution using a Mobil Minor Spray Dryer (GEA Niro, Denmark) with a specific spraying air flow, drying gas flow, feed rate and inlet temperature to allow an outlet temperature of 50 °C. In the pilot spray dryer, two collections could be made: i) at the end of the cyclone (CY) or ii) in the bag filter (BF) (see Table 1).

Table 2 presents the expected composition of each solution (So) and suspension (Su) spray-dried with the laboratory-scale (100 mL) and pilot-scale spray dryers (2000 mL).

2.2.3. Residual solvent content determination

The amount of residual solvents (organic and/or aqueous solvents) was assessed by thermogravimetric analysis (TGA) using a Q500 apparatus (TA instruments, Belgium) and Universal Analysis 2000 version 4.4A software (TA Instruments, Belgium). About 10 mg of powder was placed on the platinum cup and was