Journal of Controlled Release 180 (2014) 109–116

Contents lists available at ScienceDirect

Journal of Controlled Release

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

Nanocrystal-based per-oral itraconazole delivery: Superior *in vitro* dissolution enhancement *versus* Sporanox® is not realized in *in vivo* drug absorption

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ARTICLE INFO

Article history:
Received 4 November 2013
Accepted 15 February 2014
Available online 22 February 2014

Keywords:
Solid oral nanocrystal formulation
Wet milling
Poorly water soluble drugs
Bioavailability
Dissolution
In vivo studies

ABSTRACT

Nanoscience holds true promise in enabling efficient formulation development and *in vivo* delivery of poorly water soluble drugs. The objective of this study was to formulate solid oral nanocrystal delivery systems of itraconazole, and thus enhance the oral bioavailability of the very poorly soluble drug. Nanocrystal suspensions were prepared by a rapid wet milling technique, after which the suspensions were transformed into solid dosage forms by both freeze drying and granulating. Finally, the obtained nanocrystalline powders were capsule-packed as well as compacted to tablets. After *in vitro* analysis, the formulations (nanocrystal suspension (NPs), freeze dried NPs, granulated NPs) were tested *in vivo* in a rat model, and compared with commercial itraconazole formulation (Sporanox). Importantly, the results indicated rapid dissolution of the nanocrystalline itraconazole with enhanced bioavailability compared to physical mixture. Drug dissolution *in vitro* was immediate from NPs and freeze dried powder, and differed significantly from the marketed product ($P = 0.004$ and 0.002, correspondingly) until 30 min. Freeze drying was detected to be especially advantageous for the solid dosage forms. It is possible to maintain the original character of the nanocrystals, *e.g.* rapid dissolution, even after tableting of the nanocrystalline powders. Interestingly, the marketed product out-performed the nanocrystalline formulations *in vivo*, even though the nanocrystals provided reasonable bioavailability of itraconazole absorption as well. The efficient *in vitro* dissolution enhancement of the nanocrystalline formulations compared to Sporanox® was not realized in *in vivo* drug absorption.

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1. Introduction

Pharmaceutical research and formulation development is continuously struggling with problems related to poor oral bioavailability of the new drug candidates. The oral bioavailability problem arises often from the low aqueous solubility limiting the dissolution rate [1]. Compounds expressing aqueous solubility lower than 100 μg/ml commonly exhibit dissolution-limited absorption [2]. Therefore, there exists a strong emphasis to enhance the solubility, the dissolution rate, and thus the oral bioavailability of drug candidates.

The biopharmaceutics classification system (BCS) categorizes drugs (classes I–IV) according to their solubility and permeability characteristics [3]. Compounds of BCS class II express potential targets for formulation development, since dissolution is the bioavailability rate-limiting factor. The dissolution rate is affected by the effective surface area, the diffusion coefficient, the thickness of the diffusion layer, the saturation solubility, the amount of the dissolving drug, and the volume of the dissolution medium [2]. According to the Noyes–Whitney equation, by increasing the saturation solubility and the effective surface area, the dissolution rate can be enhanced. These parameters can be affected by the means of preformulation and formulation designs. In the preformulation research phase, crystal modifications such as salt formation of ionizable drugs, co-crystal formation, and utilization of metastable crystalline forms, are methods to be applied [4–6]. In the phase of formulation design, different approaches are utilized; amorphization, pH-modification, self-emulsification, and cyclodextrin complexation are worthy options [1,2,7–10]. Particle

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http://dx.doi.org/10.1016/j.jconrel.2014.02.016
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size reduction has been proven as a highly effective tool in enhancing the dissolution behavior of the BCS class II poorly soluble drugs [11].

The Noyes–Whitney and Prandtl equations describe how the reduction of the particle size facilitates an increase of the surface area and a decrease of the diffusion layer thickness, and thus provides an enhanced dissolution rate [2,12]. Additionally, according to Ostwald–Freundlich equation, increased saturation solubility can be achieved by reducing the particle size below 1 μm, to nanoscale [13]. Enhanced oral bioavailability by nanoscience exploitation has been well demonstrated [11,14,15]. Especially the approach of formulating drug nanocrystals has rapidly gained a proven record, although the number of marketed and clinically used oral solid nanocrystal products is relatively limited [1]. Currently the established key methods in nanocrystallization involve either bottom-up (chemical precipitation) or top-down (high-pressure homogenization and media milling) techniques [16]. Media milling, which is the most utilized nanocrystallization method in the industry, provides high capacity and rapid production with low costs. Majority of the approved solid nanocrystal formulations are based on media milling [17].

Until recently, research on further processing of nanocrystals, like granulation and tableting, have been largely ignored [17]. Furthermore, the *in vivo* characterization of the different developed solid dosage forms has been missing [18]. There exists a need for information about the *in vivo* performance of nanocrystals, which cannot be covered *i.e.* by modeling. This knowledge is for instance essential in order to solve the problems related to the formation of *in vitro*–*in vivo* correlations. Solid oral formulation is the preferred but also challenging goal of formulation development. Patient compliance and physical (*e.g.* Ostwald ripening, agglomeration) and chemical (*e.g.* hydrolysis) stability issues associated in the suspended state support the approach of the solid dosage form [17,19]. The objective of the present study was to examine formulation approaches for solid oral itraconazole nanocrystal formulations by a rapid wet milling technique, and evaluate their bioavailability *in vivo*. Itraconazole, categorized into BCS class II, exhibits extremely poor aqueous solubility (~1 ng/ml at neutral pH and ~4 μg/ml at pH 1; *logP* 5.66) but good permeability behavior [3,20,21]. Thus, the absorption is limited by the solubility of the compound resulting in low oral bioavailability [20]. After the optimization of the milling process parameters, the obtained nanocrystal suspensions were further processed by freeze drying and granulating, after which capsules were packed and tablets compacted. The *in vivo* behaviors of the formulations were studied in a male Sprague–Dawley rat model.

2. Materials and methods

2.1. Materials

Itraconazole (ITC), used as the model substance, was generously provided by Orion Pharma Oy (Espoo, Finland). Poloxamer 407 (Lutrol® F127, BASF Co., Ludwigshafen, Germany), microcrystalline cellulose (MCC, Avicel PH-101 and PH-102 (Ø ~ 50, 100 μm), FMC International, Cork, Ireland), polyvinylpyrrolidone (PVP, povidone, Kollidon K25 (Ø ~ 50, 250 μm), BASF Co., Ludwigshafen, Germany), lactose monohydrate (Pharmatose® 80 M (Ø ~ 200–800 μm), DMW International, Veghel, the Netherlands), cross-linked povidone (cross-linked PVP, Kollidon CL SF (Ø < 250 μm), BASF Co., Ludwigshafen, Germany), colloidal silicon dioxide (CSD, Aerosil® 200, Orion Pharma Oy, Espoo, Finland) and magnesium stearate (Orion Pharma Oy, Espoo, Finland) were used in the preparation of the nanocrystal formulations and the negative control, *i.e.* physical mixture. Commercial oral Sporanox® capsules (inc. ITC 100 mg, sucrose, starch, hypromellose and polyethylene glycol (PEG) 20,000 in a hard gelatin capsule, Janssen-Cilag S.p.A., Borgo San Michele, Lazio, Italy) were used as reference. Methanol (HPLC grade, VWR International, Leuven, Belgium), hydrochloric acid aqueous solution (1 M, HCl, VWR International, Fontenay-sous-Bois, France), acetonitrile (CAN) (HPLC grade, VWR International, Pennsylvania, USA) and trifluoroacetic acid (Sigma-Aldrich Chemie GmbH, Steinheim, Germany) were used in the characterization of the nanocrystal formulations. Water used throughout the study was ultra-purified Milli-Q®-water (Millipore SAS, Molsheim, France). Soft gelatin capsules (size 9, Torbac Inc., Fairfield, USA) were used to administer the itraconazole samples in the *in vivo* experiments.

2.2. Methods

2.2.1. Development of the nanocrystal formulations

Five different oral ITC nanocrystal formulations were developed (Supplement 1). The nanocrystal suspensions were prepared using a rapid top-down wet milling technique [22]. The milling was performed using a planetary ball mill (Pulverisette 7 Premium, Fritsch Co., Idar-Oberstein, Germany) with the following parameters: 20 ml milling bowl (zirconium oxide) including 30 g of milling pearls (ø 1 mm, zirconium oxide) and the drug/stabilizer suspension (ITC, 1 g; poloxamer F127, 0.80 g; water, 5 ml). The suspension was grinded (1100 rpm) for ten 3 min milling cycles. After each milling cycle there was a 15 min pause for the system to cool down. Finally, the nanocrystal suspension was separated from the milling pearls by pipetting. The nanocrystal suspension was used as such (No. 1).

The prepared nanocrystal suspensions were freeze-dried (72 h, LyoPro 3000, Heto-Holten A/S, Allerød, Denmark) and the freeze dried nanocrystal suspensions were manually compacted to tablets (m = 25 mg) with a single-punch tablet press (Korsch, EK-0, Korsch, Germany) for *in vitro* characterization and *in vivo* testings (Nos. 2 and 3). The ITC amount of the compacts was optimized to maintain the sink conditions in the dissolution experiments. The excipients (Supplement 1) and the freeze-dried nanocrystal powder were manually mixed to a homogenous mass and inserted on the tablet mold. Rounded surface punches with a diameter of 5 mm were used. The tablet press was instrumented and the compression force of the upper press was monitored (Single Station DAAS Measure, software version 1.2) and kept as even as possible (≈4000 N). The average mass and crushing strength (Schleuniger-2E, Schleuniger & Co., Thun, Switzerland) of the compacts were investigated. Both the freeze dried powder and the compacts were stored in closed vials protected from light at room temperature (19–22 °C).

The nanocrystal suspension was also used as a granulation medium in producing fast dissolving micro-granules. An exact amount of fresh nanocrystal suspension was inserted into a mixing bowl including PVP, manually grinded, and the PVP was let to absorb the suspension and swell. MCC was added and the mixture was again manually grinded. The granules were obtained by wet sieving (mesh size 1.4 mm (w); 0.71 mm (d)), after which they were allowed to dry at room temperature, protected from light for 24 h. Finally, the dry mass was sieved using the same mesh size (No. 4). The granulated nanocrystals were also compacted to tablets (No. 5) like the freeze dried nanocrystals for further analysis and testing. The amounts of the granules and excipients were adjusted to maintain the constant compact concentration and mass (25 mg), equal to the compacts of the freeze dried powders. The same parameters as used with the freeze dried powders were applied in the compaction. Both the granules and compacts were stored in closed vials protected from light at room temperature (19–22 °C).

Prior to the *in vivo* experiments, both the freeze dried nanocrystals (No. 2) and granules (No. 4) were packed into soft gelatin capsules (size 9) using the Torbac® ProFill capsule filling system (Fairfield, USA). The selection of the solid nanocrystal formulations for the *in vivo* studies was based both on comparable capsulated system Sporanox® and on the excessively large size of the compressed tablets to be administered to rats. Based on the *in vivo* pilot studies, the ITC dose was determined to be 2 mg to achieve high analytical sensitivity and precision. The administered dose was constant (ITC; 2 mg) for all the animals. The solid formulations were administered *in vivo* in two

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