European Journal of Pharmaceutical Sciences 83 (2016) 175–183

Contents lists available at ScienceDirect

European Journal of Pharmaceutical Sciences

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

Nanonized itraconazole powders for extemporary oral suspensions: Role of formulation components studied by a mixture design

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ARTICLE INFO

Article history:
Received 29 July 2015
Received in revised form 26 December 2015
Accepted 27 December 2015
Available online 30 December 2015

Keywords:
Nanosuspensions
Itraconazole
High pressure homogenization
Spray drying
Mixture design
Mathematical model

ABSTRACT

Itraconazole (ITZ) nanocrystal-containing powders were prepared through the combined use of high pressure homogenization (HPH) and spray drying (SD). These powders were intended as base materials for the preparation of extemporary oral suspensions of the drug. The role and the effect of stabilizers on the size of re-dispersed particles were studied using a mixture design and a Scheffé model relating the dried nanosuspension composition to the mean particle diameters. The homogenization process required a surface active agent (Tween 20) to obtain the efficient comminution of itraconazole micronized powder. SD was carried out on ITZ nanosuspensions after addition of a cellulose derivative (Methocel® E5) that allowed the prompt re-dispersion of nanoparticles under "in use" conditions. The powders obtained by drying of homogenized systems showed *in vitro* dissolution profile faster than that of the micronized drug, suggesting a potential ameliorated GI absorption of itraconazole released from the nanosuspensions.

1. Introduction

Among different strategies that can be used for enhancing the dissolution rate of poorly water-soluble drugs and leading to an ameliorated bioavailability, particle size reduction to sub-micron range (typically 100–200 nm) seemed to be the simplest way to face the formulation challenges (Mou et al., 2011; Möschwitzer, 2013; Gao et al., 2012; Plakkot et al., 2011).

In the last ten years, many efforts have been spent in developing pharmaceutical nanosuspensions and now some nanocrystal-based products are available on the market (Rapamune®, Emend®, Tricor® and Megace® ES) and others are currently being evaluated in clinical trials (Baert et al., 2009; Hanafy et al., 2007; Shrewsbury et al., 2009; Tuomela et al., 2014; Kumar and Burgess, 2012). Nanosuspensions are biphasic systems constituted of nanocrystals, with dimensions ranging between 10 and 1000 nm, dispersed in a liquid containing stabilizer agents that lower the free surface energy of the nanoparticles and prevent particle aggregation and/or particle growth.

Several processes can be used for the nanosuspension production; they can be classified into "Bottom-up" such as nanoprecipitation or nanocrystallization (Chan and Kwok, 2011; D'Addio and Prud'homme, 2011; Dandagi et al., 2011) and "Top-down" such as high pressure homogenization (Keck and Müller, 2006) and media milling (Merisko-Liversidge et al., 2003; Merisko-Liversidge and Liversidge, 2011). Each of these technologies possesses advantages and disadvantages; among the major drawbacks, the use of organic solvents and the possible degradation of the active molecule can be cited.

Independently from the strategy adopted for the nanosuspension production, the final product is invariably a system that suffers from physical instability, linked to sedimentation, agglomeration/aggregation of particles and/or Ostwald's ripening phenomena. To avoid such instability issues, the nanosuspension can be converted into a dry powder. This solid material can be conveniently handled and used, either as dosage form or as pre-formulate in the production of granules, tablets, capsules or pellets (Cerea et al., 2015; Dolenc et al., 2009; Pinto and Müller, 1999). Freeze drying (FD) and spray drying (SD) are techniques of first choice to convert solutions and suspensions to powder and their application to this purpose has been extensively investigated (Abdelwahed et al., 2006; Lee, 2003; Vehring, 2008; Yin et al., 2005).

At time of use, the obtained dried nano-particulate systems should be able to give aqueous dispersions characterized by particle size similar to that of the original nanosuspension. To reach this goal, appropriate stabilizers are added to the nanosuspension to lower the free surface energy of the nanoparticles. The high surface free energy of nanoparticles can be readily lowered by stabilizers that decrease the solid–liquid interfacial tension (Rabinow, 2004), while particle aggregation may be efficiently prevented or slowed down through adsorption of

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http://dx.doi.org/10.1016/j.ejps.2015.12.030
0928-0987/

substances that form electrostatic repulsion or steric barriers (Wu et al., 2011). Surfactants (sodium dodecylsulphate, polysorbates, poloxamers), polymers (cellulose derivatives, povidones) and sugars have been employed, in many cases in mixture, to exploit their synergistic stabilizing effect (Van Eerdenbrugh et al., 2009).

The development of a dried nanosuspension containing itraconazole was the objective of the present study: itraconazole, an antifungal drug for the treatment of local and systemic mycoses, belongs to BCS class II, having high permeability, but a very poor water solubility (less than 1 ng mL^{-1} at pH 7.0) (Peeters et al., 2002). The poor aqueous solubility and high hydrophobicity limit its therapeutic efficiency and consequently it has been object of many studies (Chaubal and Popescu, 2008; Cerdeira et al., 2013; Kumar et al., 2014; Segale et al., 2015) devoted to develop pharmaceutical dosage forms with ameliorated biopharmaceutical characteristics. The reduction of the particle size is one of the strategies pursued for ITZ to improve its solubility and dissolution rate with a view to increasing its bioavailability. Our interest was focused on a dried product containing a high amount of ITZ in form of nanocrystals and able to promptly re-form a nanosuspension in contact with water. Further aims were to model the ITZ particle diameter as a function of system composition, and to investigate the role played by the excipients on the comminution of ITZ particles and on the redispersibility of dried suspension in water.

2. Materials and methods

2.1. Materials

Itraconazole (ITZ) was kindly donated by Chemo Group (E). Hydroxypropylmethylcellulose Benecel® E50 (E50) was provided by Ashland Inc. (KY, USA) and Methocel® E5 (E5) by Colorcon (UK). Sodium carboxymethylcellulose (Blanose® 7 LF — CMC) and hydroxyethylcellulose (Natrosol® 250 HX — HEC) were provided by Hercules (USA). Polyethoxylated sorbitan esters (Tween 20 — TW20 and Tween 60 — TW60), sorbitan monoesters (Span 20 — SP20 and Span 80 — SP80) and sodium lauryl sulfate (SLS) were purchased from Sigma-Aldrich (USA). Poly(ethylene oxide)/poly(propylene oxide) block copolymer (Pluronic® F127 — poloxamer, PLX) and macrogolglycerol ricinoleate (Cremophor® ELP — CRM) were obtained from BASF (D).

2.2. Evaluation of dispersion stability

A set of experiments was performed for selecting the stabilizer or the stabilizer mixture to be used for the production of the nano-powdered formulation.

An amount of 0.125 g of each stabilizer (both surfactant and polymer) was added to a water dispersion (10 mL) containing 1.25 g ITZ and the system was treated by a disperser (UltraTurrax T25 IKA®, D) at 24,000 rpm for 5 min. The suspensions were transferred in a graduated cylinder and visually inspected for homogeneity after 15 min, 1 h and 24 h using an arbitrary 4 points rating scale (see Table 1). An analog arbitrary scale was used at time 24 h for evaluating the consistency of the cake at the bottom of the cylinder (see Table 1).

2.3. High pressure homogenization

In exploratory tests, 3 different systems (100 mL) constituted of water and ITZ alone, ITZ/Tween 20 (10/1 weight ratio) and ITZ/Tween 20/E5 (10/1/1 weight ratio) respectively were processed by a high pressure homogenizer (Microfluidizer M-110L, Microfluidics®, USA). The coarse dispersions were pre-treated by a disperser (UltraTurrax T25 IKA®, 6500 rpm for 1 min) before applying the HPH process. In the high energy process, pressure was set to 1000 bar, temperature at 25 °C and process time at 10 min. After HPH treatment, the suspensions were immediately analyzed for the particle size (Z_{ave}) and surface charge (zeta potential, Z_{pot}) by PCS.

Table 1
Preliminary experiments for component screening: low energy process of drug/stabilizer aqueous dispersion.

System	Homogeneity			Cake aspect
	After 15 min	After 1 h	After 24 h	
ITZ-SLS	+++	++	+	+
ITZ-TW20	++++	++++	+	+
ITZ-TW60	++	++	+	++
ITZ-SP20	−	−	−	+++
ITZ-SP60	−	−	−	+++
ITZ-CRM	+++	++	+	+++
ITZ-E50	−	−	−	+
ITZ-E5	+	−	−	+
ITZ-PLX	+++	++	+	+
ITZ-CMC	−	+	+	+
ITZ-HEC	−	+	+	+

Homogeneity scale. −: absent; +: poor; ++: discrete; +++: good; ++++: very good.
Cake scale. −: absent; +: loose; ++: solid; +++: very solid.

In the body of the experimental work, HPH process was carried out by the following procedure. ITZ coarse powder was dispersed by UltraTurrax (6500 rpm for 1 min) in water containing an appropriate amount of Tween 20. The suspension was transferred to the homogenizer hopper and treated at constant temperature (25 °C) under 1200 bar for the different times (1 cycle lasted about 15 s). The nanosuspension was recovered and immediately analyzed for particle size determination.

Two sets of experiments were carried out: in the first, three suspensions constituted of coarse ITZ in different amounts (corresponding to 3, 10 and 15% *w*/*v*) and TW20 in a fixed ratio with the drug (drug/TW20 = 10/1 *w*/*w*) were submitted to HPH process. At pre-selected time intervals (1, 2, 5, 10, 12, 20, 25, 40 and 60 min), samples (1 mL) were withdrawn and immediately analyzed by PCS for particle size determination. A second set of experiments (see 2.7. Mixture design) was accomplished on systems composed of 10% *w*/*v* coarse ITZ and different percentages of Tween 20 (ranging from 0.7 and 2.42% *w*/*v*): they were homogenized for 25 min and, after withdrawal of 1 mL sample for PCS analysis, the prescribed amount of E5 was added to the suspension, which was dried as below described.

2.4. Spray drying

Nanosuspensions were dried by a Mini Spray Dryer B-290 (Buchi® Labortechnik, CH). The drying conditions were the same for all the formulations (Cerea et al., 2015): inlet temperatures of 160 °C; air flux at 742 L/h, nozzle 0.6 mm diameter and a feeding rate of 4 mL/min. Before drying, the equipment was equilibrated using deionized water. The dried powders were recovered only from the collection chamber.

2.5. Morphology and size of particles

The morphological properties of spray dried powders were investigated using a scanning electron microscope (SEM; Sigma, Carl Zeiss, D). Before scanning, the samples were coated with gold using a plasma evaporator under vacuum. SEM images were acquired at an accelerated voltage of 10 kV using different magnifications.

Particle size of micronized-ITZ was measured on SEM pictures using an image analysis software (Seneco, Motic Image Plus, Ver. 2.0 ML) analyzing 20 particles on two different pictures for each sample.

The average size (Z_{ave}) and size distribution (Polydispersity Index—PI) of nanoparticles were investigated by Photon Correlation Spectroscopy (PCS) with a Zetasizer 3000HS (Malvern instrument, UK) after HPH and after the spray drying process. Liquid formulations were diluted with deionized water to obtain reproducible