International Journal of Pharmaceutics 524 (2017) 443–453

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

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

Downstream drug product processing of itraconazole nanosuspension: Factors influencing drug particle size and dissolution from nanosuspension-layered beads

Johannes Parmentier[a], En Hui Tan[b], Ariana Low[c,*], Jan Peter Möschwitzer[d]

[a] Gustav Parmentier GmbH, Eichendorffstr. 37, 60320 Frankfurt am Main, Germany
[b] AbbVie Pte Ltd, Research and Development, 9 North Buona Vista Drive, The Metropolis Tower One #19-01, Singapore 138588, Singapore
[c] AbbVie GmbH & Co. KG, Knollstrasse 50, 67061 Ludwigshafen, Germany
[d] Department of Pharmaceutical Technology, Biotechnology and Quality Management, Free University of Berlin, 14195 Berlin, Germany

ARTICLE INFO

Article history:
Received 8 December 2016
Received in revised form 4 April 2017
Accepted 5 April 2017
Available online 8 April 2017

Keywords:
Nanosuspensions
Downstream processing
Poor solubility
Nano milling
Formulation
Processing
Nanoparticles
Nanotechnology
Pellet layering
Multiparticulate oral dosage forms

ABSTRACT

There is more research required to broaden the knowledge on the downstream processing of nanosuspensions into solid oral dosage forms, especially for coated nanosuspensions onto beads as carriers. This study focuses on bead layering as one approach to solidify nanosuspensions. The aim was to systematically investigate the influence of type of coating polymer (HPMC VLV vs. copovidone), bead material and bead size (sugar vs. MCC, and small vs. large) and coating thickness (50%–150% layering level) on the properties of a dried itraconazole nanosuspension. A stable itraconazole nanosuspension with a mean particle size below 200 nm was prepared and a ratio of itraconazole and coating polymer of around 1:1 was identified. XRD and DSC scans revealed that itraconazole remained mostly crystalline after the bead layering process. The fastest dissolution rate was achieved using the small bead size, sugar beads, HPMC VLV as film-forming polymer and lowest layering level, with the best formulation releasing 94.1% (±3.45% *SD*) within the first 5 min. A deterioration of the release profile with increasing layering level was only observed for MCC beads and was more pronounced when copovidone was used as a coating polymer. It was observed that bead layering is a suitable method to process an itraconazole nanosuspension into a solid form without compromising release.

1. Introduction

Nearly 90% of small molecules in the developmental pipeline are poorly water-soluble, and the challenge faced by formulation scientists because of the increasing number of poorly water soluble drugs is well known and referred to in many publications (Dahan and Miller, 2012; Kalepu and Nekkanti, 2015; Nair et al., 2012; van Hoogevest et al., 2011). Several enabling technologies for these biopharmaceutics classification system (BCS) class II drugs were developed in the past, including lipid-based formulations, inclusion complexes, solid dispersions and nanocrystals (Alam et al., 2012; Amidon et al., 1995; Mullertz et al., 2010; Rabinow, 2004; Semalty, 2014). Williams and team has written an excellent review on poorly water soluble drugs and the technologies applied to overcome their bioavailability issues (Williams et al., 2013). Among these different methods, the nanocrystal technology plays an important role. Nanosuspensions are already used in drug product development and in marketed drugs to improve bioavailability and reduce food effect of poorly soluble drugs (Chin et al., 2014). This is achieved by reducing particle size of the crystalline drug to the submicron scale and greatly increasing the particle surface area, which results in an improved dissolution rate. It has also been proposed that the strong curvature of submicron particles also increases the solution pressure and the saturation solubility (Keck and Müller, 2006). However, increase in dissolution rate is the dominating mechanism for enhancing bioavailability of this technology.

Nanosuspensions can be administered in several ways, but most marketed products are developed as oral solid dosage forms (Malamatari et al., 2015). Many different manufacturing processes for nanocrystals are described in the literature (Chin et al., 2014),

* Corresponding author.
E-mail address: ariana.low@abbvie.com (A. Low).

http://dx.doi.org/10.1016/j.ijpharm.2017.04.012
0378-5173/

but basically all approaches result initially in an aqueous nanosuspension. Thus, drying or solidification of nanosuspensions is a necessary step in manufacturing to incorporate these resultant nanoparticles into a final solid oral dosage form. Tablets and capsules afford better patient compliance and are established manufacturing processes.

A suitable drying method should lead to an intermediate drug product, which is on the one hand stable during storage and shows the characteristics of an unmodified nanosuspension, i.e. redispersion of the nanosuspension resulting in fast drug dissolution, but is also amenable to processing into the final dosage form. A critical view through the literature reveals that spray- and freeze-drying are the most popular technologies for solidification and drying of nanosuspensions (Chin et al., 2014; Scholz and Keck, 2015; Van Eerdenbrugh et al., 2008b). Nevertheless, especially freeze-drying has some disadvantages such as poor flowability of the dried powders, which demands further unit operations such as granulation, or addition of a considerable amount of excipients to achieve blend characteristics suitable for compression (Cal and Sollohub, 2010). Furthermore, the cost, processing time and energy consumption for freeze-drying are unfavourable for commercial-scale production (Walters et al., 2014). Other drying methods might be more useful and it is therefore not surprising that none of the marketed nanosuspension formulations for oral delivery are solidified by freeze-drying and only one by spray-drying (Chin et al., 2014; Van Eerdenbrugh et al., 2008b).

Bead-layering is the coating of inert beads made of sugar, cellulose or other materials with a drug, mostly embedded in a film-forming polymer. Even though it has certain disadvantages, e.g. the limited drug load achievable, because of the inert core, and the rather long processing time (Teunou and Poncelet, 2002), this technology is already used for several oral dosage forms on the market. Furthermore, bead layering was already explored in different studies for solidification of nanosuspensions showing its principal benefits (Basa et al., 2008; Bhakay et al., 2014; De Smet et al., 2014; Luo et al., 2013; Wu et al., 2013; Yao et al., 2014). This technology can also be used to apply a second functional coating onto the beads, which could, for example, afford enteric or mucoadhesive properties (Möschwitzer and Müller, 2006, 2013). The influence of coating formulation and polymer type and/or core material and bead size on the properties of nanosuspension coated beads was previously investigated (Azad et al., 2016; Knieke et al., 2015; Li et al., 2016; Möschwitzer and Müller, 2013). In our study we aim to assess the influence of drug load, polymer type, coating thickness, bead size and type on drug dissolution and particle size of the nanocrystals after redispersion to further add to current knowledge available on the downstream processing of nanosuspension layered beads.

Itraconazole, a triazole antifungal agent, was the chosen model drug and is commercially available as capsule or solution for oral administration. It exhibits very low water solubility, strong food effect and high inter-subject oral bioavailability variability, making it a suitable candidate for enabling technologies, such as nanosizing (Van Eerdenbrugh et al., 2008a; Zimmermann et al., 1994). HPMC VLV, a very low viscosity cellulosic polymer, and copovidone (Kollidon® VA 64) were employed as film-forming polymers. Sugar and cellulose beads were used as starting cores, representing a water-soluble and a water-insoluble matrix, respectively.

In the present study, itraconazole nanosuspension was prepared by media milling. A suitable drug load in the film-forming polymers was determined in a preliminary study. Eight different coating formulations were produced and their properties including crystallinity, residual water content, particle size after redispersion and drug dissolution were assessed. In a follow-up study, the beads were blended with outer-phase excipients, compressed into tablets, and characterised for disintegration time, redispersed particle size and drug dissolution profile.

2. Materials and methods

2.1. Materials

Non-micronized itraconazole was purchased from Sequoia (Pangbourne, UK). Sodium dodecyl sulphate (SDS) was purchased from Merck (New Jersey, USA), polyethylene glycol 400 Fluka (PEG 400) from Sigma-Aldrich (Singapore) and polyethylene glycol 4000 (PEG 4000, Lipoxol 4000) from Sasol (Johannesburg, South Africa). HPMC E5 (Methocel E5 Premium LV) and HPMC VLV (Methocel Premium VLV) were obtained from Colorcon (Singapore).

Sugar spheres NF of sizes 14–18 mesh/1000–1400 μm (large) and 60–80 mesh/177–250 μm (small) were provided by Paulaur (New Jersey, USA) and cellulose spheres 14 to 18 mesh/1000–1400 μm (large) and 45 to 70 mesh/210–355 μm (small) (Cellets 1000 and 200) by Pharmatrans Sanaq (Basel, Switzerland). Yttria stabilised zirconium oxide beads (0.5 mm and 0.7 mm) were purchased from Glen Mills (New Jersey, USA).

Acetonitrile (ACN) was purchased from Romil Ups (Cambridge, UK). All other chemicals were of analytical grade and obtained from the known commercial sources.

2.2. Preparation of nanosuspensions

Formulation of the itraconazole nanosuspension was based on previous experience, where a combination of HPMC E5 (1% m/V) and SDS (0.4% m/V) produced a robust and versatile stabiliser system (Lestari et al., 2015). An overview of the prepared nanosuspension batches is given in Table 1. Prior to the main nano-milling process, the crude suspensions were pre-milled to avoid clogging of the nano-mill. During pre-milling, all components were mixed in a plastic polyethyelene (PE) bottle and either 200 g (small batch) or 500 g (large batches) of yttria stabilised zirconia beads (0.5 mm) were added and the suspensions were milled with a paddle mixer (IKA® RW20 Digital, IKA Werke GmbH, Staufen, Germany) at 2000 rpm for 24 h. Subsequently, the particle size was reduced to the submicron range in a Dynomill (Typ KDL A, Willy A. Bachofen AG, Muttenz, Switzerland) equipped with a 300 ml (small batch) or 600 ml (large batch) steel milling chamber entirely filled with yttria stabilised zirconia beads. The suspension was pumped through the milling chamber with a peristaltic pump at a speed of approximately 30 ml/min. The temperature was kept at 25 °C using an external cooling bath.

Throughout the milling process and at the end of production, particle size was measured by Dynamic Light Scattering (DLS) and Laser Diffraction (LD) as described below. The actual itraconazole concentration in the final suspension was determined by HPLC.

2.3. Optimisation of coating formulation

A suitable coating polymer should be selected to stabilise the nanosuspension during the drying process and storage as well as to allow a fast redispersion of the nanosuspension. Firstly, a suitable ratio of film-forming polymer to API was identified. Ratios of nanocrystals to polymer (either HPMC VLV or Copovidone) of 4:1,

Table 1
Composition of prepared nanosuspensions.

	Itraconazole (g)	HPMC E5 (g)	SDS (g)	Water (g)
Batch 1	100	5	2	500
Batches 2 & 3	500	25	10	2500