European Journal of Pharmaceutics and Biopharmaceutics xxx (2013) xxx–xxx

Contents lists available at SciVerse ScienceDirect

European Journal of Pharmaceutics and Biopharmaceutics

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

Research paper

High-shear granulation as a manufacturing method for cocrystal granules

Sönke Rehder [a,b], Niels Peter Aae Christensen [a], Jukka Rantanen [a], Thomas Rades [a,c], Claudia S. Leopold [b,*]

[a] University of Copenhagen, Faculty of Health and Medical Sciences, Dept. of Pharmacy, Copenhagen, Denmark
[b] University of Hamburg, Dept. of Chemistry, Hamburg, Germany
[c] University of Otago, School of Pharmacy, Dunedin, New Zealand

ARTICLE INFO

Article history:
Received 16 January 2013
Accepted in revised form 29 April 2013
Available online xxxx

Keywords:
Cocrystal
Piracetam
Tartaric acid
High-shear granulation
Compactability
Drug release

ABSTRACT

Cocrystal formation allows the tailoring of physicochemical as well as of mechanical properties of an API. However, there is a lack of large-scale manufacturing methods of cocrystals. Therefore, the objective of this work was to examine the suitability of high-shear wet granulation as a manufacturing method for cocrystal granules on a batch scale. Furthermore, the cocrystal granules were characterized regarding their mechanical properties as well as their dissolution behavior.

High-shear wet granulation was found to be a feasible manufacturing method for cocrystal granules. Cocrystal formation depended on the exposure time of the solids to the granulation liquid (water), the amount of liquid, the impeller speed of the granulator, and on the excipients (hydroxyl propylcellulose, microcrystalline cellulose, calcium hydrogenphosphate) used in the formulation. Storage stability was strongly influenced by the excipients, since in presence of calcium hydrogenphosphate, the poorly water-soluble salt calcium tartrate monohydrate was formed at high relative humidity. Interestingly, compactability was increased by cocrystal formation compared to that of the reference granules (piracetam and the respective excipients). The drug release was slightly decreased by cocrystal formation, most likely due to the lower solubility of the cocrystal. In the presence of calcium hydrogenphosphate however, no influence of cocrystal formation on either compactability or on drug release were observed, compared with the reference tablets.

It was concluded that high-shear wet granulation is a valuable, however complex, manufacturing method for cocrystals. Cocrystal formation may influence compactability and drug release and thus affect drug performance and should be investigated during pre-formulation.

1. Introduction

The most common orally administered drug formulations are solid dosage forms such as capsules and tablets, as their manufacture is fast, inexpensive, and straight-forward. Usually, the active pharmaceutical ingredient (API) is processed in its crystalline form, most preferably as the stable polymorph, salt, or hydrate. In recent years, another solid-state form has attracted interest, namely the cocrystal systems. These systems can be defined as a stoichiometric multicomponent system, formed by an API and a cocrystal former, which both are solid under ambient conditions [1]. Cocrystals offer multiple options to vary the physicochemical properties of an API such as stability [2,3], dissolution behavior [4], bioavailability [5], hygroscopicity [6], and mechanical properties [7], without chemical modification of the API [8]. The API and cocrystal former molecules interact via van-der-Waals forces, π–π interactions, and, most commonly, hydrogen bonds [9,10]. Although a better understanding of cocrystal formation allowed a more specific cocrystal design by predicting the intermolecular interactions by modeling approaches [11], cocrystal formation is not yet fully predictable and has to be confirmed experimentally. Cocrystals may be prepared for example by solvent evaporation [12], slurrying [13], liquid-assisted grinding [14–16], and dry-grinding [17,18]. To differentiate between solution-based and mechano-chemical preparation methods, Friščić introduced the empirical parameter η (µl/mg), defined as the ratio of the volume of the grinding liquid V (µl) and the sum of the masses of the API and cocrystal former m (mg):

$$\eta = \frac{V(granulation\ liquid)}{m(API + cocrystal\ former)} \quad (1)$$

An η value of zero represents dry-grinding, η between zero and 2 liquid-assisted grinding, between 2 and 12 slurrying, and larger

* Corresponding author. University of Hamburg, Dept. of Chemistry, Div. Pharmaceutical Technology, Bundesstraße 45, 20146 Hamburg, Germany. Tel.: +49 40 42838 3480; fax: +49 40 42838 6519.
E-mail address: Claudia.leopold@pharmaceutical-technology.de (C.S. Leopold).

0939-6411/$ - see front matter © 2013 Published by Elsevier B.V.
http://dx.doi.org/10.1016/j.ejpb.2013.04.022

than 12 solution synthesis [19]. In the past years, liquid-assisted grinding has emerged to the method of choice for cocrystal preparation, exhibiting significant advantages over the other techniques, including an increased formation rate, higher yields, and higher crystallinity of the product [15,18]. The mechanistic role of the grinding liquid however is not yet fully understood. While in some cases, the liquid appears to act as a lubricant and increases molecular mobility during cocrystallization [18]; in other cases, the properties of the liquid seem to have an impact on the cocrystal formation process [16]. In 2007, Zhang et al. reported a solution-mediated cocrystal formation mechanism, which was developed based on the mechanism suggested for hydrate formation of an anhydrous API, for example baclofen [20]. Zhang et al. assumed a critical cocrystal former activity (αCCF_c), at which the API and the cocrystal are in equilibrium, showing the same thermodynamic stability. If the API is exposed to an environment with a higher αCCF than αCCF_c, the cocrystal is more stable than the API and is therefore formed. The same assumption is true with respect to the activity of the API. In a slurry where both portions of the API and the cocrystal former remain solid, the activities of both are higher than their critical activities, leading to formation of the respective cocrystal. Upon nucleation, the remaining API and the cocrystal former will dissolve and crystallize as the cocrystal until the activities of the cocrystal former or the API fall below the critical activity [21–23]. Mechanical agitation such as sonicating or vortexing may facilitate the solution-mediated cocrystal formation process [22].

While the above-mentioned preparation methods are well-suited for lab-scale experiments, up-scaling of these processes is limited [24]. A few attempts have been undertaken to produce cocrystals on a large-scale by pharmaceutical standard operations. Hot-melt extrusion, using a combination of controlled heat and shear deformation, has recently been used for cocrystal preparation [24–26]. Alhalaweh and Velaga spray-dried solutions of various APIs and cocrystal formers as stoichiometric mixtures to obtain the respective cocrystals [27]. In their review regarding pharmaceutical cocrystals, Miroshnyk et al. explicitly suggest the performance of detailed studies to investigate cocrystal formation during agglomeration techniques [28]. However, high-shear granulation as a cocrystal manufacturing method has not been extensively investigated [29].

High-shear granulation is a common manufacturing process in the pharmaceutical industry where small particles are agglomerated by means of a granulation liquid. The main reasons are to improve flowability, increase uniformity in drug distribution, prevent segregation, and reduce dust exposure to the environment [30]. The high-shear granulation process can be divided into three different steps: first, the materials are mixed and the granulation liquid is added. Subsequently, the moist mixture is wet-massed, followed by a drying step [30]. During every step, process-induced solid-state transformations [31] can occur, which may be examined by XRPD [32], near infrared [33], and Raman spectroscopy [34]. These process-induced transformations can result from water exposure and thermal as well as mechanical stress. They are usually undesired, as they are difficult to control and may alter the physicochemical properties of the API [35].

Nevertheless, the objective of this work was to examine cocrystal formation during high-shear granulation by means of at-line Raman spectroscopy in combination with multivariate data analysis and to investigate its suitability as a manufacturing method for the well-described piracetam–tartaric acid cocrystal (Cambridge Structural Database (CSD) reference code: RUCDUP) [36] on a batch scale. Furthermore, the influence of different excipients on the cocrystallization process was examined. The manufactured cocrystal granules were characterized with regard to their mechanical properties as well as their dissolution behavior by comparison with piracetam reference granules.

2. Materials and methods

2.1. Materials

Piracetam (Pir) was kindly donated by the Northeastern Pharmaceutical Group, China. L-tartaric acid (TA) was purchased from Carl Roth, Germany. Hydroxypropyl cellulose (HPC) and calcium hydrogenphosphate anhydrate ($CaHPO_4$) were supplied by Nycomed, Denmark. Microcrystalline cellulose (MCC) was donated by Lehmann and Voss, Germany. All substances were of pharmaceutical grade.

2.2. Methods

2.2.1. Manufacturing of the granules

Three different granule formulations (Table 1) were prepared. Each mixture contained a 1:1 M ratio of Pir and TA with HPC as binder. 30.0 g of each mixture were granulated with 4.0 ml of purified water as granulation liquid.

The components of the three formulations were mixed in a Turbula mixer (Bachofen, Switzerland) for 10 min. Granules were manufactured with a Bohle Mini Granulator (Bohle, Germany). The volume of the granulation jar was 300 ml. Two different factors were analyzed at two levels with respect to the response (cocrystal formation), the impeller speed, and the granulation period. While the chopper speed was constant during granulation with 1000 rpm, two different impeller speed levels were applied: low (100 rpm) and high impeller speed (800 rpm). Furthermore, cocrystal formation over two different granulation time levels was investigated, at a low (15 min) and at a high level (60 min) after the water was added drop-wise with a pipette. As categorical variable, three different excipients were used in the granule formula. After the granulation process, large agglomerates were disassembled by a sieve with a mesh size of 800 μm. Each granulation procedure was performed in duplicate.

For comparative purposes, Pir/HPC and Pir/HPC/$CaHPO_4$ granules were prepared as described for the Pir/TA/HPC and Pir/TA/HPC/$CaHPO_4$ granules, but without the addition of TA. All granules were stored for 2 days at 21 °C and 45% RH.

2.2.2. Preparation of the cocrystal reference

The cocrystal reference was prepared by grinding 600 mg of a 1:1 M ratio of Pir and TA and addition of 20 μl of water in a 25 ml milling jar with two 9 mm stainless steel balls for 15 min using a Retsch ball mill 200 (Retsch, Germany). The milling frequency was 25 Hz [36,37].

2.2.3. Characterization of the granules

2.2.3.1. Raman spectroscopy. The amount of cocrystal formed during granulation was determined at-line using a Raman spectrometer (Control Development, USA) equipped with a thermostatically cooled CCD detector and a fiber optic sampling probe (RamanProbe™, InPhotonics, USA). Samples were excited using a laser with a wavelength of 785 nm and a laser power of 300 mW (Starbright 785S, Torsana Laser Technologies, Denmark). For each spectrum, 8 scan interferograms were recorded from 81 to 2209 cm^{-1} with a resolution of 8 cm^{-1} and 1 s integration time. Spectra were

Table 1
Formulas of the investigated granules.

	Pir (%)	TA (%)	HPC (%)	MCC (%)	$CaHPO_4$ (%)
Pir/TA/HPC	47.5	47.5	5	–	–
Pir/TA/HPC/MCC	27.5	27.5	5	45	–
Pir/TA/HPC/$CaHPO_4$	27.5	27.5	5	–	45

Please cite this article in press as: S. Rehder et al., High-shear granulation as a manufacturing method for cocrystal granules, Eur. J. Pharm. Biopharm. (2013), http://dx.doi.org/10.1016/j.ejpb.2013.04.022