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Physicochemical and mechanical properties of paracetamol cocrystal with 5-nitroisophthalic acid

Stevanus Hiendrawan[a,b], Bambang Veriansyah[a], Edward Widjojokusumo[a], Sundani Nurono Soewandhi[b], Saleh Wikarsa[b], Raymond R. Tjandrawinata[a,*]

[a] Dexa Laboratories of Biomolecular Sciences, Cikarang 17550, West Java, Indonesia
[b] School of Pharmacy, Bandung Institute of Technology, Bandung 40132, West Java, Indonesia

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ABSTRACT

We report novel pharmaceutical cocrystal of a popular antipyretic drug paracetamol (PCA) with coformer 5-nitroisophthalic acid (5NIP) to improve its tabletability. The cocrystal (PCA-5NIP at molar ratio of 1:1) was synthesized by solvent evaporation technique using methanol as solvent. The physicochemical properties of cocrystal were characterized by powder X-ray diffraction (PXRD), differential scanning calorimetry (DSC), thermogravimetry analysis (TGA), fourier transform infrared spectroscopy (FTIR), hot stage polarized microscopy (HSPM) and scanning electron microscopy (SEM). Stability of the cocrystal was assessed by storing them at 40 °C/75% RH for one month. Compared to PCA, the cocrystal displayed superior tableting performance. PCA-5NIP cocrystal showed a similar dissolution profile as compared to PCA and exhibited good stability. This study showed the utility of PCA-5NIP cocrystal for improving mechanical properties of PCA.

1. Introduction

Among various pharmaceutical dosage forms, tablets represent the most popular delivery systems (Sinka et al., 2009; Mohammed et al., 2006). It offers numerous benefits in technical and economical aspects (low manufacturing cost, high production throughput, the flexibility to develop a unique product and the ease of consumption and handling for the consumer) (Perumalla and Sun, 2014; Nguyen et al., 2013). However, several problems caused by deficiency in physicochemical properties of the active pharmaceutical ingredients (APIs) such as poor mechanical properties become a hurdle in successful development of tablet formulation. This problem becomes severe especially for high doses administered drug such as paracetamol (PCA). PCA exists in three polymorphic forms, the monoclinic form (I), the orthorhombic form (II) and the third form (III). Form I, which is the commercially used form, is thermodinamically stable polymorph, however this form have poor mechanical properties (Gharaibeh and Chick Al-Ard, 2011).

Various approaches have been used to improve the mechanical properties of PCA. Several studies to prepare PCA form II which has better mechanical properties than PCA form I have been done. Di Martino et al. (1996) and Al-Zoubi et al. (2002) prepared a PCA form II (orthorhombic form) which exhibited better compressibility than PCA form I (untreated PCA). Crystal habit modifications by crystallization from different solvents have also been reported to prepare PCA crystals which have better compressibility. Fachaux et al. (1995) prepared a sintered form of PCA crystals by crystallization from dioxane solvent which showed improvement in its compressibility. Garekani et al. (1999) prepared two different crystal habits of PCA, in which the polyhedral crystals exhibited better plastic deformation than thin plate-like crystals. Preparation

Abbreviations: API, active pharmaceutical ingredient.

* Corresponding author. Fax: +62 21 898 41905.
E-mail address: raymond@dexa-medica.com (R.R. Tjandrawinata).

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of prismatic polyhedral crystals and thin plate-like crystals of PCA which have better compressibility have also been studied (Rasenack and Muller, 2002). Another approach was done using crystal habit modifier during crystallization process. Garekani et al. (2000a) studied the improvement of PCA mechanical properties by employing polyvinylpyrrolidone (PVP) as a crystal growth inhibitor. Meanwhile, Kaialya et al. (2014) reported PCA crystallization in the presence of Avicel, Brij 58 and PEG 6000. Both studies revealed that the resulting PCA particles exhibited improvement in compression properties.

Recently, modifications of compaction properties of PCA based on crystal engineering principles (salt and cocrystal) have also been investigated. Perumalla et al. (2012) reported the formation of PCA salt (PCA hydrochloride monohydrate) which exhibited superior tableting behavior than PCA form I. Alternatively, the cocrystallization approach has also been successfully utilized to alter the mechanical properties of PCA. Cocrystals of PCA with theophylline, oxalic acid, naphthalene and phenazine have been studied by Karki et al. (2009). The result from compression test demonstrated that all these four cocrystals have better compression properties compared to PCA form I. Cocrystallization of PCA with trimethylglycine, which has comparable compression and dissolution properties to that of the PCA-oxalic acid cocrystal, has also been reported (Maeno et al., 2014). From a crystal engineering viewpoint, PCA is a good API model for cocrystal design. As shown in Fig. 1, PCA contains several functional groups, i.e amide and hydroxyl groups, both are strong donors and acceptors in hydrogen-bonding (Andre et al., 2012). PCA has an ability to form cocrystals with pyridines and carboxylic acid. In particular, PCA tends to crystallize with hydrogen bond acceptor groups (Sander et al., 2010). Several multicomponents crystal forms of PCA with 1,4-dioxane, 4,4-bipyridine, *N*-methylmorpholine, *N*,*N*-dimethylpiperazine, morpholine and piperazine have been reported by Oswald et al. (2002). They explained that the main hydrogen bond interactions responsible for their formation are not only O—H···O and N—H···O, but also N—H···N and O—H···N (Oswald et al., 2002). Elbagerma et al. (2011) studied the formation of PCA-citric acid cocrystal. Detailed analysis of the cocrystal formation was performed using raman spectroscopy analysis. Another study demonstrated the formation of three new cocrystals of PCA with trans-1,4-diaminocyclohexane, 1,2-bis(4-pyridyl) ethane and trans-1,4-di(4 pyridyl) ethylene (Srirambhatla et al., 2012).

In this study, cocrystal screening process by solvent evaporation methods was performed with several coformers (4-hydroxybenzoic acid, sorbic acid, pimelic acid, glycolic acid, glutaric acid, 2.4-dihydroxybenzoic acid and 5-nitroisophthalic acid) which have functional groups that are able to generate hydrogen bond motifs (supramolecular synthons) with PCA. Based on the screening process, cocrystal was only obtained using coformer 5-nitroisophthalic acid (5NIP). As can be seen in Fig. 1, 5NIP contains two carboxylic acid groups that can act as hydrogen-bond donors and acceptor, respectively. It is expected that PCA and 5NIP can interact via formation of heterosynthons between amide···carboxylic acid functional groups or other interactions. To our knowledge, only three references involving the use of 5NIP as coformer in cocrystalization of APIs, specifically, cocrystallization of 5NIP with carbamazepine, dapsone, etiracetam and levetiracetam (Fleischman et al., 2003; Smith and Wermuth, 2013; George et al., 2014). Solid-state material characterization techniques such as powder X-ray diffraction (PXRD), differential scanning calorimetry (DSC), fourier transform infrared spectroscopy (FTIR), laser diffractometry (LD) analysis, polarized light microscopy (PLM) and scanning electron microscopy (SEM) were performed for PCA-5NIP cocrystal characterization. Their solubility, dissolution rate, stability and tabletability study were also investigated.

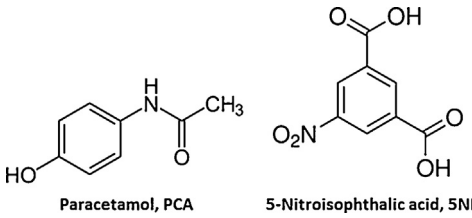

Fig. 1. Chemical structure of paracetamol (PCA) and 5-nitroisophthalic acid (5NIP).

2. Materials and methods

2.1. Materials

Paracetamol (PCA) was purchased from Zhejiang Kangle Pharmaceutical Co., Ltd. (Wenzhou, China). 5-Nitroisophthalic acid (5NIP) was obtained from Sigma–Aldrich, Co. (MO, USA). Methanol (ACS grade), potassium dihydrogen phosphate (KH_2PO4) and sodium hydroxide (NaOH) were obtained from Merck KGaA (Darmstadt, Germany). Acetonitrille (HPLC grade) was obtained from J.T. Baker, Inc. (NJ, USA).

2.2. Cocrystallization by rapid evaporation process

Equimolar (1:1 mol ratio) quantities of PCA and 5NIP were dissolved in 20 mL of methanol and mixed under sonication at 40 °C for 10 min. The resulting solution was then placed into crystallizing disk and heated at 70 °C for 5 h using hot plate to evaporate the solvent. The dried solid was collected and placed in the glass vial for further analysis. The cocrystal product from this experiment was further namely as PCA-5NIP.

2.3. Characterization of cocrystal

2.3.1. Powder X-ray diffraction (PXRD)

The PXRD patterns were collected by a Rigaku Ultima IV X-ray diffractometer (Rigaku Co., Tokyo, Japan) using Cu Kα radiation (λ = 1.54 Å), a tube voltage of 40 kV and a tube current of 40 mA. Data were collected from 2 to 40° at a continuous scan rate of 4°/min.

2.3.2. Differential scanning calorimetry (DSC)

Thermal analysis of the samples was performed on a DSC Q20 (TA Instruments, DE, USA) which was calibrated for temperature and cell constants using indium. Samples (1–3 mg) crimped in aluminum pan were analyzed from 50 to 300 °C with heating rate of 10 °C/min. Samples were continuously purged with nitrogen at 50 mL/ min.

2.3.3. Thermogravimetric analysis (TGA)

TGA was performed on a TGA Q50 (TA Instruments, DE, USA) instrument. Approximately 1–5 mg sample was heated from 50 to 300 °C in open aluminium pan at the rate of 10 °C/min under nitrogen purge at flow rate of 50 mL/min.

2.3.4. Polarized light microscopy (PLM)

All PLM experiments were performed using BX-50 polarizing microscope (Olympus, Tokyo, Japan) equipped with home-made Mk3-OMROM EcK5 hot stage. Photomicrographs were captured using Olympus SC-30 digital color camera and analyzed using AnalySIS getIT software.