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A portable fiber-optic Raman analyzer for fast real-time screening and identifying cocrystal formation of drug-coformer via grinding process

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ABSTRACT

A portable Raman analyzer with a fiber-optic probe was first used to rapidly screen and identify the cocrystal formation between drug and coformer. Indomethacin (IMC) and anhydrous theophylline (TP) were selected as model drugs, but saccharin (SAC) and anhydrous citric acid (CA) were chosen as model coformers. The cocrystal formation that occurred in the solid-state IMC–SAC or TP–CA system via mechanical grinding process was investigated. Differential scanning calorimetry (DSC) was also used to investigate the possible cocrystal formation. The present study indicates that this new portable fiber-opticRaman spectroscopic technique was an easy and fast "real-time" method to screen and identify the progressive cocrystal formation in solid-state IMC–SAC or TP–CA system in the process of mechanical grinding by inserting the probe directly into the ground mixtures.

1. Introduction

It is well known that the solubility behavior of drugs is one of the most challenging aspects in formulation development and oral delivery design. More than 90% of drugs approved from 1995 and about 40% of active new chemical entities (NCEs) have been reported to have poor water solubility problems, leading to inadequate and variable absorption of these drugs [1,2]. The enhanced solubility of active pharmaceutical ingredients (APIs) critically impacts the bioavailability of orally delivered APIs from different drug dosage forms. Thus, numerous approaches have been extensively explored for optimizing the solubility of APIs such as particle size reduction, salt and polymorphic formations, micellar solubilization, cyclodextrin complexation, and solid dispersion, to enhance the solubility and bioavailability of these poorly water-soluble APIs in the pharmaceutical sciences [3–5]. However, there are several practical limitations with these techniques and the desired bioavailability enhancement may not always be achieved [6,7].

Recently, the cocrystallization is a relatively unique technology and offers a platform for improving the physicochemical and biopharmaceutical properties of APIs through the development of the new class of crystalline solids, called pharmaceutical cocrystals [8–12]. Pharmaceutical cocrystals have already been proven useful in enhancing the solubility, dissolution rate, stability, and bioavailability of APIs and recognized as the promising alternative APIs [13,14]. The cocrystals are defined as crystalline materials comprised of an API and one or more unique coformers in the solid state by constructing with noncovalent forces. Pharmaceutical cocrystals not only provide new opportunities to enhance many pharmaceutical needs of APIs, but also create the intellectual property and new patent of APIs for extending the life cycles of old APIs in the pharmaceutical industry [8–15]. As a novel research focus, the investigations of pharmaceutical cocrystals have been rapidly expanded by growing the number of research publications and patent applications [15,16]. Even the cocrystals with the same API will have strikingly different pharmaceutical properties, depending on the nature of the coformer used.

There are many methods and techniques to prepare different types of cocrystals [8–12]. Cocrystal screening methodology has attracted much attention based on a more efficient and rational basis [17–20]. Cocrystal screening methods can broadly be categorized as solid-based and liquid-based [21]. The solid-based methods belonged to mechanochemical approaches including neat or solvent assisted grinding often depend on the stoichiometric ratio of the reactants for cocrystal formation, but the liquid-based methods are a member of traditional solution crystallization approaches and can be either stoichiometric (slow evaporative crystallization, spray drying) [22] or non-stoichiometric (slurry and reaction crystallization) [19,22,23].

Although various methodologies for the preparation of pharmaceutical cocrystals have been applied [9–12], it will always take as much time as necessary to previously screen the cocrystal formation and then to identify its factuality with different analytical techniques. In our laboratory, a unique differential scanning calorimetry–Fourier transform infrared (DSC-FTIR) combined system had been first applied to simultaneously screen and detect the cocrystal formulation in real time [24]. Recently, a portable Raman analyzer with a fiber optic probe has been developed to provide greater simplicity for

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solid and liquid material analysis. This real-time Raman analyzer is a rapid, noninvasive, and nondestructive technique and can be run with an embedded computer under constant spectral resolution and precise wavelength assignment of detected peaks. This portable Raman analyzer as a potential high-throughput screening tool can provide reliable data with a minimal amount of sample and is operated reliably even in inconvenient conditions. In the present study, indomethacin and theophylline were selected as model APIs, saccharin and citric were chosen as model coformers. A new attempt by using a portable fiber-optic Raman spectrometer to quickly investigate the cocrystal formation of solid-state indomethacin–saccharin or theophylline–citric acid system via mechanical grinding process was performed.

2. Materials and methods

2.1. Materials

Four APIs, indomethacin (IMC, γ-form), saccharin (SAC), anhydrous theophylline (TP, purity > 99%) and anhydrous citric acid (CA, purity ≥ 99.5%) were commercially available from Sigma-Aldrich Chem. Co. (St. Louis, MO, USA) and used without purification. The chemical structures of these four APIs are shown in Fig. 1. These raw materials of APIs were vacuum-dried at 60 °C for 24 h before use.

2.2. Preparation of different IMC–SAC or TP–CA ground mixtures by neat grinding

The physical mixture of IMC–SAC or TP–CA (molar ratio = 1:1) was ground in an oscillatory ball mill (Mixer Mill MM301, Retsch GmbH & Co., Germany) with 20 Hz oscillation frequency, respectively. About 0.2 g of powder sample was placed into a 25 mL volume stainless steel milling jar containing two 12 mm diameter stainless steel balls by grinding for 30–40 min at ambient temperature [25,26]. At the prescribed intervals, the grinding process was stopped for a moment and the ground sample was directly detected by portable Raman analyzer with a fiber-optic probe.

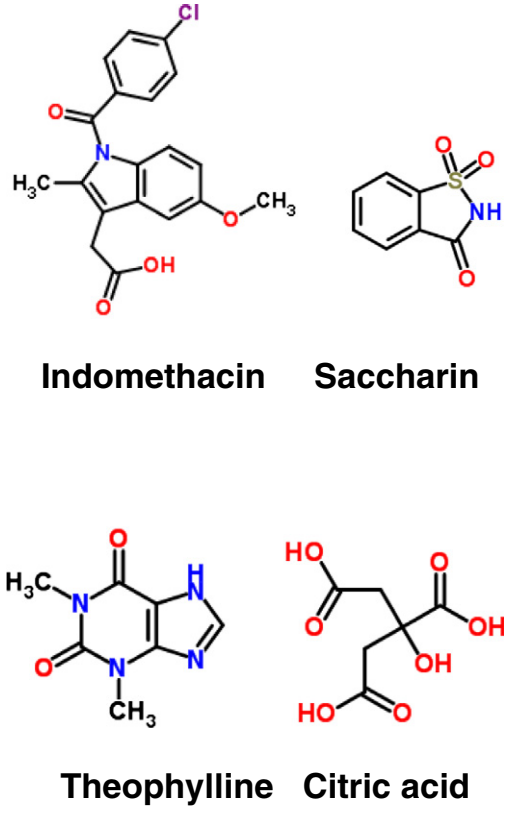

Fig. 1. Chemical structures of indomethacin (IMC), saccharin (SAC), theophylline (TP) and citric acid (CA).

2.3. Preparation of intact IMC–SAC or TP–CA cocrystal

The intact cocrystal of IMC–SAC was prepared by slow evaporation of an acetone solution containing the same molecular ratio of IMC and SAC at ambient temperature [27,28]. After evaporation for one day, the precipitates were vacuum-dried and stored at the same storage condition. The intact cocrystal of TP–CA (molar ratio = 1:1) was also obtained by slow evaporation of a solution containing anhydrous TP and anhydrous CA in a 1:1 (v/v) mixture of methanol and acetonitrile (20 mL) at ambient condition [29,30]. After slow evaporation for one week, the precipitates were vacuum-dried.

2.4. Analytical identification of different raw materials and mixtures

Each raw material of APIs, physical mixture, ground mixture and intact cocrystal of IMC–SAC or TP–CA (1:1 molar ratio) was respectively determined by thermal or portable Raman analyzer. All the samples were determined by using a DSC analytical technique (DSC, Q 20, TA Instruments, Inc., New Castle, DE, USA) at a heating rate of 3 °C/min with an open pan system in a stream of N_2 gas from 30 to 300 °C. Raman spectra of all the samples were directly recorded using portable Raman analyzer (ProTT-EZRaman-A Series, Enwave Optronics Inc., CA, USA) with a fiber optic probe. This portable Raman analyzer was equipped with a 785-nm spectrum-stabilized narrow-line diode laser fitted with a high-sensitivity CCD spectrograph cooled to −85 °C [31,32]. The average optical resolution was set at 2.5–3.0 cm^{-1}. A spectral range of 250–2000 cm^{-1} was selected.

3. Results and discussion

3.1. Identification of IMC, SAC, and IMC–SAC mixtures

The solid-phase identity of IMC, SAC, physical mixture and solvent-evaporated sample of IMC–SAC were verified using DSC and Raman spectroscopic analyses. Fig. 2-A displays the DSC curves of different samples. One endothermic peak at 163 °C with 35.39 kJ/mol (a) and another peak at 229 °C with 19.4 kJ/mol (b) were observed in the DSC curves; the former was the melting point of IMC and the latter was attributed to the fusion of SAC, respectively. While two endothermic peaks at 153 and 184 °C as well as one exothermic peak at 158 °C were also found in the DSC curve of the physical mixture of IMC–SAC (c). The peak appeared at 153 °C might be due to the fusion of eutectic mixture [21,33], but the peak at 184 °C was corresponded to the melting point of IMC–SAC cocrystal following the exothermic peak at 158 °C [24,27,34]. The exothermic peak at 158 °C was due to the molecular interaction of IMC and SAC, rather than the amorphous recrystallization since they were crystalline materials before grinding [35,36]. The solvent-evaporated sample exhibited a clear sharp endothermic peak at 184 °C with 82.8 kJ/mol (d), which was close to the melting point at 184.2 °C with 79.4 kJ/mol of IMC–SAC cocrystal reported by Basavoju et al. and us [26,27]. This indicates that the intact cocrystal of IMC–SAC was successfully prepared by slow solvent evaporation method.

The representative Raman spectra of IMC, SAC, physical mixture and intact cocrystal of IMC–SAC are also shown in Fig. 2-B. Since the cocrystal was formed between IMC and SAC after slow evaporation, a significant Raman spectral difference should be observed between the physical mixture and intact cocrystal of IMC–SAC. Fig. 2-B-a