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Research paper

Characteristics of indomethacin–saccharin (IMC–SAC) co-crystals prepared by an anti-solvent crystallization process

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ABSTRACT

The creation of co-crystals of various insoluble drug substances has been extensively investigated as a promising approach to improve their pharmaceutical performance. In this study, co-crystal powders of indomethacin and saccharin (IMC–SAC) were prepared by an anti-solvent (water) addition and compared with co-crystals by evaporation method. No successful synthesis of a pharmaceutical co-crystal powder via an anti-solvent approach has been reported.

Among solvents examined, methanol was practically the only one that resulted in the formation of highly pure IMC–SAC co-crystal powders by anti-solvent approach. The mechanism of a preferential formation of IMC–SAC co-crystal to IMC was explained with two aspects: phase solubility diagram and solution complexation concept. Accordingly, the anti-solvent approach can be considered as a competitive route for producing pharmaceutical co-crystal powders with acceptable properties.

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1. Introduction

Co-crystals are being studied intensively primarily due to the potential for improved pharmaceutical properties, including the dissolution behavior of BCS class-II drug substances [1,2]. Additionally, this approach has been recognized as attractive in terms of new intellectual property, based on the novelty, utility, and non-obviousness of co-crystals [3,4]. Many reviews and overview articles regarding pharmaceutical co-crystals have been published [5–8].

Pharmaceutical co-crystals are distinguished from salts by the presence/absence of proton transfer from the organic acid to the base when two or more pharmaceutical compounds are bound together as building blocks [8]. According to a survey study using 85 crystal structures, co-crystals showed predictable stoichiometric ratios versus salts, which could make the co-crystal approach especially valuable for new pharmaceutical formulations. Several drug products including meloxicam-salicylic acid have been approved in the form of co-crystal formulations. Because of the significance of co-crystals as new drug products, the US FDA recently issued draft guidance for industry [9].

Co-crystals can be prepared by various methods [10] such as solvent evaporation, vapor or solvent diffusion, cooling, anti-solvent addition, and solid-state grinding (neat and liquid-assisted). Solid-state grinding was initially performed with a mortar and pestle, and bulk pharmaceuticals [11]. This approach has attracted much attention recently due to advancements in co-crystal formation capabilities and environmental factors [12]. Several novel methods to produce pharmaceutical co-crystals have also been reported: supercritical fluid [13], solvent-mediated phase transformation [14], and ultrasound-assisted [15] processing. The feasibility of supercritical fluid technology for indomethacin–saccharin (IMC–SAC) co-crystal production was examined using three different approaches: CCS (co-crystallization with supercritical solvent), SAS (supercritical anti-solvent), and AAS (atomization and anti-solvent) [13]. With successful preparation of co-crystal particles 0.5–2 μm in size by SAS and AAS techniques, supercritical technology was demonstrated as a potential screening method for pharmaceutical co-crystals.

There have been a large number of studies on IMC–SAC co-crystals compared with other pharmaceuticals. This could be attributed to several advantages such as the distinctly improved

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dissolution behavior of insoluble IMC as well as the safety of the coformer SAC, classified as GRAS (generally regarded as safe). In this regard, SAC has been extensively studied as a coformer with many other drug substances [16].

IMC–SAC co-crystals manufactured by solution evaporation and grinding have been characterized in terms of structural and physicochemical properties [17]. It has been reported that the co-crystal structure of IMC–SAC co-crystals is formed by an interaction between the IMC carboxylic acid dimer and the SAC imide dimer synthon, through weak N—H···O bonding. Regarding evaporation, methanol, and acetone resulted in incomplete co-crystallization, whereas other solvents, such as ethyl acetate, gave pure IMC–SAC co-crystals. Additionally, a pure co-crystal was obtained with one drop of ethyl acetate or ethanol during 15 min grinding. The solubility was 2–4 times higher than IMC in phosphate buffered saline (PBS) solution, depending on the buffer concentration.

The solubility of IMC–SAC co-crystals was determined in various organic solvents to develop a model equation for solution chemistry [18]. Its solubility decreased as the SAC concentration in the solution increased, which was explained by the solubility product and solution complexation. The IMC–SAC co-crystal prepared by solvent evaporation and cooling crystallization was examined for in vivo bioavailability with a commercial product Indomee® in beagle dogs [19]. The estimated AUC value of the co-crystal turned out to be about the same as that of Indomee® but twice that of IMC alone.

In addition to X-ray diffractometry (XRD), differential scanning calorimetry (DSC) and dynamic vapor sorption (DVS) [17], near-infrared (NIR) spectroscopy was used for IMC–SAC co-crystal screening, combined with Raman spectroscopy [20]. Recently, simultaneous DSC-FTIR micro-spectroscopy was used successfully to screen the co-crystal formation of several drug substances, including IMC–SAC, in real time [21]. The IMC–SAC co-crystal formation mechanism during mechanical cogrinding was investigated using DSC and FTIR to conclude that the intermolecular interaction by hydrogen bonding between IMC and SAC was the primary root [22].

Anti-solvent crystallization has been regarded as the best method to achieve a controlled and scalable particle size distribution of drug substances [23]. Additionally, it can be operated in semi-batch or continuous fashion. The main objective of this study was to apply the anti-solvent crystallization approach to prepare IMC–SAC co-crystal powders. As described above, no successful result has been reported previously using the anti-solvent method to prepare any pharmaceutical co-crystal. Several organic solvents were examined using water as the anti-solvent for IMC and SAC. We found that methanol was the only solvent which successfully created high-quality IMC–SAC co-crystals, whereas other solvents did not work well under our experimental conditions.

2. Materials and methods

2.1. Materials

Indomethacin (IMC; 2-{1-[(4-chlorophenyl)carbonyl]-5-methoxy-2-methyl-1H-indol-3-yl}acetic acid) was purchased from Tokyo Chemical Industry (Tokyo, Japan) in a pure γ-form polymorph.

Saccharin (SAC) was from by Sigma Aldrich Co. (St. Louis, MO, USA). We examined five organic solvents, ethyl acetate (EtAc), methyl acetate (MeAc), methanol (MeOH), ethanol (EtOH), and acetone because they make a broad range of difference in water miscibility as well as in polarity. These solvents were purchased from Junsei Chem. (Tokyo, Japan). All materials were used without further purification. Water was purified using a deionizer (Human Corp., Seoul, Korea) prior to use.

2.2. Preparation of IMC–SAC co-crystal powders

We prepared pharmaceutical IMC–SAC co-crystal powders for the first time via an anti-solvent crystallization route. We also produced IMC–SAC co-crystals by an evaporation method for comparison. IMC and SAC powders in equimolar (0.034 M) amounts were dissolved in EtAc at room temperature (~25 °C). The composition used here was based on a previous study [20]. After aging for 1 h under mild agitation (@ 100 rpm; Wisetir® HT-50D, Daihan Sci., Korea), the mixture solution was evaporated by natural vaporization of the solvent overnight. When the solution evaporated leaving a dry phase, the flask was pulled by vacuum at 25 °C overnight to remove the residual solvent. The same procedures were followed for other solvents, including MeAc, EtOH, MeOH, and acetone. Each resulting solid was recovered from the flask, weighed, and characterized in various ways.

Fig. 1 illustrates a schematic diagram of our anti-solvent co-crystallization experiment. We examined various solvent-to-water volume ratios and found out 2:1 as the optimal ratio in terms of co-crystallization efficiency. The mixture solution of IMC (0.034 M) and SAC (0.05 M) was prepared in a solvent (150 mL) as described previously. After solvation at room temperature, 75 mL of purified water were added as an anti-solvent into the solution vessel using a peristaltic pump, followed by mild agitation at 300 rpm for 1 h at constant temperature (25 °C). As water was not well miscible with acetate solvents, especially EtAc, a more vigorous agitation (1000 rpm) was implemented for a sufficient homogenization. Then, each solution was filtered via aspiration using filter paper (Whatman 2.5 μm grade). The collected solid was dried in a vacuum oven at 25 °C overnight prior to subsequent characterization.

2.3. Powder characterization

The crystalline properties of all starting and resulting powders were determined using XRD (Rigaku Miniflex, Japan). Each powder specimen (200 mg) was mounted on a pan for XRD measurements with a Cu Kα source. The measurement was carried out for Bragg

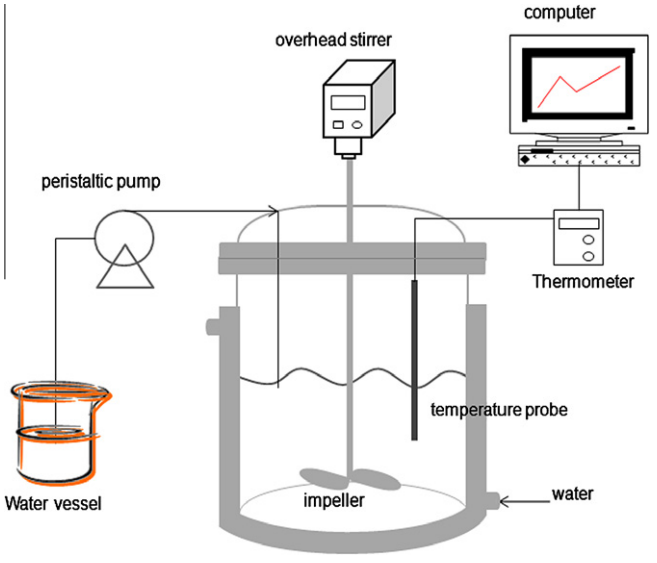

Fig. 1. Experimental apparatus for the anti-solvent co-crystallization process. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

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