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Pharmaceutical co-crystals of the anti-inflammatory drug diflunisal and nicotinamide obtained using supercritical CO_2 as an antisolvent

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ABSTRACT

A method based on using supercritical CO_2 as an antisolvent (SAS method) is explored as a co-crystallization technique. Co-crystallization is an emerging and powerful technique to improve the physicochemical properties of an active pharmaceutical ingredient. The solid-state and solution co-crystallization methods usually employed present several disadvantages. The one-step SAS method has a low environmental impact and overcomes some of the difficulties associated to conventional methods. The 2:1 co-crystals of the anti-inflammatory drug diflunisal (DIF) and nicotinamide (NIC) are prepared for the first time by SAS. Drug concentrations corresponding to the co-crystal stoichiometric composition are used. The influence of the SAS parameters temperature (35 and 40 °C), pressure (10.0 and 12.0 MPa), drug concentration (two levels) and solvent (acetone and ethanol) in the co-crystal formation is studied. A crystalline material in the form of needles of uniform width and more variable length is obtained. For comparison purposes, pure DIF and NIC are also processed by SAS. Co-crystals are characterized in terms of crystallinity, thermal behavior, coformer interactions and drug release; their dissolution rate improves with respect to that of pure DIF. SAS co-crystals exhibit the same crystal structure, melting point and FTIR spectrum as those previously obtained by liquid assisted ball mill grinding and solution crystallization.

1. Introduction

A key issue in the field of pharmaceuticals is the improvement of the active pharmaceutical ingredient (API) physicochemical properties. To this end, co-crystallization is an emerging and powerful technique that enables to modify properties such as the solubility and chemical stability by establishing a new solid form through the interaction with a coformer [1]. Coformers are usually molecules included on the Generally Recognized as Safe (GRAS) list [2]. Nevertheless, in some cases pharmaceutical co-crystals consist of two different APIs, thus providing new dual-drugs [3]. A co-crystal may be defined as a multiple component crystal that consists of two or more solid components in a definite stoichiometric ratio held together via noncovalent interactions. The co-crystal structure is the result of weak but directional molecular recognition events. Based on these interactions, crystal engineering provides strategies to search for new co-crystals of a given API. However, the discovery and preparation of a new co-crystal is still to a great extent a matter of trial and error [4,5]. As to the experimental methods, co-crystals can be prepared by solution methods, evaporative or cooling crystallization or solid-state grinding and mixing [5]. Solution co-crystallization is the method preferred if single crystals are desired for crystal structure elucidation although sometimes this method fails in the preparation of a co-crystal already obtained by a mechanochemical method. Phase solubility diagrams are required in order to understand the mechanism of a solution co-crystallization [5,6]. The solution initial composition plays a key role in the process. The different solubilities of the co-crystal components in the chosen solvent may pose a problem. Using a solvent mixture has been suggested to overcome this difficulty [7]. If the desired co-crystal is

Abbreviations: API, active pharmaceutical ingredient; BPR, back pressure regulator; *C*, solution concentration; DIF, diflunisal; DSC, differential scanning calorimetry; FTIR, Fourier transform infrared; GAS, gas antisolvent; GRAS, generally recognized as safe; NIC, nicotinamide; NSAID, non-steroidal anti-inflammatory drug; *P*, pressure; *T*, temperature; T_m, melting point; SAS, supercritical antisolvent; SEM, scanning electron microscopy; XRD, X-ray diffraction.

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metastable, kinetics must be taken into account and supersaturation has to be achieved by rapid cooling, fast solvent removal or anti-solvent addition. To overcome some of the difficulties presented by solution and solid state methods, we propose to use a co-crystallization method based on the utilization of supercritical CO_2 as an antisolvent, the supercritical antisolvent (SAS) technique [8–10]. To test this method, the 2:1 co-crystal involving diflunisal (DIF) and nicotinamide (NIC) will be prepared.

Carbon dioxide is the most commonly used supercritical fluid because it is nontoxic, non-flammable, has moderate critical temperature and pressure (31 °C and 7.4 MPa) and is considered a green solvent [10]. Supercritical CO_2 densities and solvation power are intermediate between those of gases and liquids and can be easily modified with small changes in temperature and pressure; meanwhile the fluid maintains good transport properties. The utilization of CO_2 in the SAS method is also based on its relatively low solvent power for solutes such as polymers or pharmaceuticals and its good miscibility with many organic solvents. The solvent-free particles exhibit narrow size distributions. Other advantages are operation at moderate temperatures in an inert atmosphere thus avoiding the drug degradation and the possibility of tuning the fluid properties through changes in temperature and pressure that enable control of particle size and/or morphology.

Pharmaceutical companies are urged to develop production processes with very low environmental impact, processes with fewer steps and a reduced used of organic solvents. Therefore, the SAS method has been frequently used to precipitate drugs alone or to coprecipitate them in combination with a carrier [8–12]. For instance, at our laboratory the non-steroidal anti-inflammatory drug (NSAID) diflunisal was micronized alone and later composite particles formed by the drug and the biocompatible polymer polyvinylpyrrolidone were also obtained [13]. The coprecipitates showed a dissolution rate enhancement. However, the SAS method or the closely related gas antisolvent (GAS) methods have been seldom used to obtain co-crystals [14–20]. Diflunisal, Fig. 1, belongs to class II of the Biopharmaceutical Classification System (low aqueous solubility, high membrane permeability as most NSAIDs) [21], has been approved worldwide and is frequently used [22]. Nicotinamide, a water soluble component of the vitamin B family whose structure is also shown in Fig. 1, is generally regarded as a safe substance and has been used to obtain several co-crystals [23–25] because the nitrogen atom at the pyridine group can interact with APIs through carboxylic acid–pyridine or amide–pyridine interactions, and the amide can also participate in amide–amide or carboxylic acid–amide interactions. In this case, carboxylic acid–amide and carboxylic acid–pyridine nitrogen bonds are established (see Fig. 1) and the co-crystal solubility is expected to improve with respect to that of pure DIF. On the other hand, nicotinamide has shown an ability to restore cognition in Alzheimer's disease transgenic mice [26]. Therefore, this co-crystal may offer additional or synergistic therapeutic benefits.

Our aim in this paper is to explore the possibilities of SAS as a co-crystallization method and to examine the possible differences among the SAS co-crystals and those prepared by traditional methods. Recently, the 2:1 co-crystal involving diflunisal and nicotinamide has been prepared by liquid assisted ball mill grinding and by solution crystallization from ethanol by two different groups [24,25]. These co-crystals were characterized by powder X-ray diffraction, differential scanning calorimetry, and Fourier transform infrared spectroscopy, and dissolution rates were also reported. Evora et al. [24] also obtained the solid + liquid DIF + NIC binary phase diagram that pointed out the formation of the 2:1 DIF-NIC co-crystal.

2. Materials and methods

2.1. Materials

The materials employed were CO_2 (Air Liquide 99.98 mol% pure), diflunisal (Fluka, analytical standard), nicotinamide (Fluka, ≥99.5 mol% pure), acetone (Sigma–Aldrich, ≥99.8 mol% pure) and ethanol (PanReac 99.5 v/v% pure). All water used was pretreated using the Milli-Q Elix water purification system (Millipore Ibérica, Madrid, Spain).

2.2. Supercritical Fluid Antisolvent (SAS) precipitation and design of experiments

The application of the method to prepare the DIF-NIC co-crystal is illustrated in Fig. 2. The API and the coformer are simultaneously dissolved in a polar organic solvent such as ethanol or acetone. Supercritical carbon dioxide is introduced in a precipitation chamber using a high-pressure pump at constant flow rate. Then the organic solution containing the drugs is fed through a second pump also at a constant flow rate reaching steady state operating conditions and an adequate supercritical fluid/solvent ratio. A given amount (30 mL) is sprayed in the precipitation chamber through a thin stainless steel nozzle. This single nozzle is drilled in a sapphire plate. The height of the cylindrical basket shown in Fig. 2 is 39.14 cm and the values for its internal and external diameter are 6.65 and 7.59 cm, respectively. The chamber is heated and both temperature and pressure are controlled. When the fluid

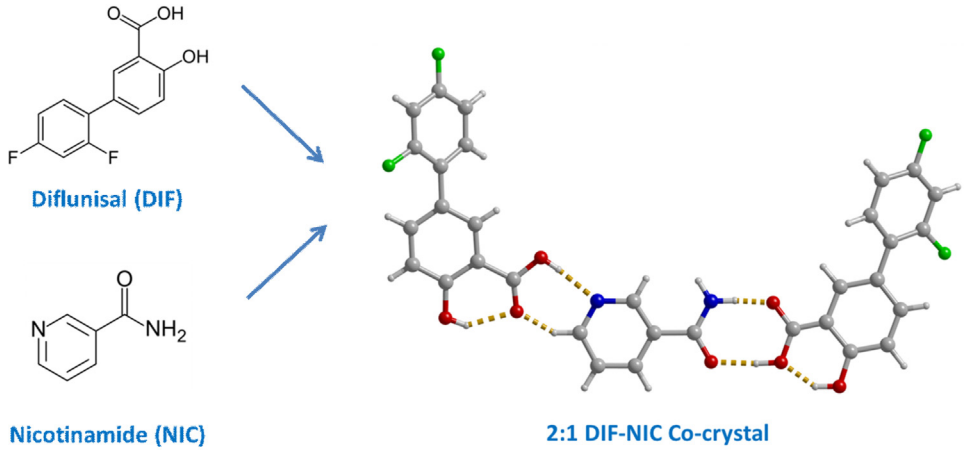

Fig. 1. Molecular structures of diflunisal, nicotinamide, and the 2:1 diflunisal-nicotinamide co-crystal showing the supramolecular heterosynthons involved.