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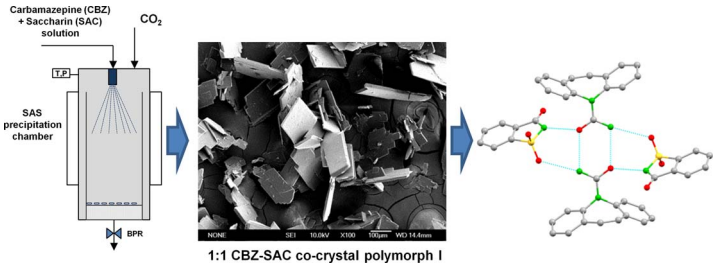
Polymorphism in the co-crystallization of the anticonvulsant drug carbamazepine and saccharin using supercritical CO_2 as an anti-solvent

Isaac A. Cuadra, Albertina Cabañas, José A.R. Cheda, Concepción Pando*

Departamento de Química Física I, Universidad Complutense, E-28040 Madrid, Spain

GRAPHICAL ABSTRACT



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ABSTRACT

1:1 Co-crystals of carbamazepine (CBZ) and saccharin (SAC) were obtained for the first time through the supercritical anti-solvent (SAS) technique based on using supercritical CO_2 as anti-solvent. The capability of SAS to produce the desired polymorphic form (two polymorphs are known) was assessed. Operational conditions investigated were temperature (40.0 and 60.0 °C), pressure (10.0 and 15.0 MPa), solvent choice and coformer concentration in the organic solution (CBZ: 30 and 15 mg/mL; SAC: stoichiometric ratio). Co-crystals were characterized in terms of crystallinity and coformers interactions. No homocrystals were present. Using methanol, at 40.0 °C polymorph I was obtained with yields up to 65%; whilst at 60.0 °C a mixture of polymorphs was obtained. Mixtures of polymorphs were also obtained in the ethanol and dichloromethane experiments at the studied conditions while the dimethylsulfoxide experiments failed to produce any co-crystal polymorph. For comparison purposes, pure CBZ and SAC were also processed by SAS.

1. Introduction

The production of co-crystals is reaching a major importance in the pharmaceutical industry not only to overcome some crucial drawbacks of new produced drugs such as poor solubility, inadequate dissolution profiles or short shelf-life, but also to improve the drug organoleptic and mechanical properties [1]. Moreover, multidrug co-crystallization is becoming an important field of research in the treatment of some complex disorders [2]. A broad and generally accepted definition of co-crystal would be “a stoichiometric multi-component system connected by non-covalent interactions where all the components present are solid under ambient conditions” [3]. A pharmaceutical co-crystal would therefore involve a bonding through supramolecular synthons of at least an active pharmaceutical ingredient (API) and another API (in

Abbreviations: API, active pharmaceutical ingredient; BCS, Biopharmaceutics Classification System; BPR, back pressure regulator; CBZ, carbamazepine; CSS, co-crystallization with supercritical solvent; DCM, dichloromethane; DSC, differential scanning calorimetry; DMSO, dimethylsulfoxide; EMA, European Medicines Agency; FDA, Food and Drug Administration; FTIR, Fourier transform infrared; GAS, gas anti-solvent; HPLC, high performance liquid chromatography; P, pressure; T, temperature; SAC, saccharin; SAS, supercritical anti-solvent; SEA, supercritical fluid enhanced atomization; SEM, scanning electron microscopy; PXRD, powder X-ray diffraction

* Corresponding author at: Departamento de Química Física I, Facultad C. Químicas, Universidad Complutense, E-28040 Madrid, Spain.
E-mail address: pando@quim.ucm.es (C. Pando).

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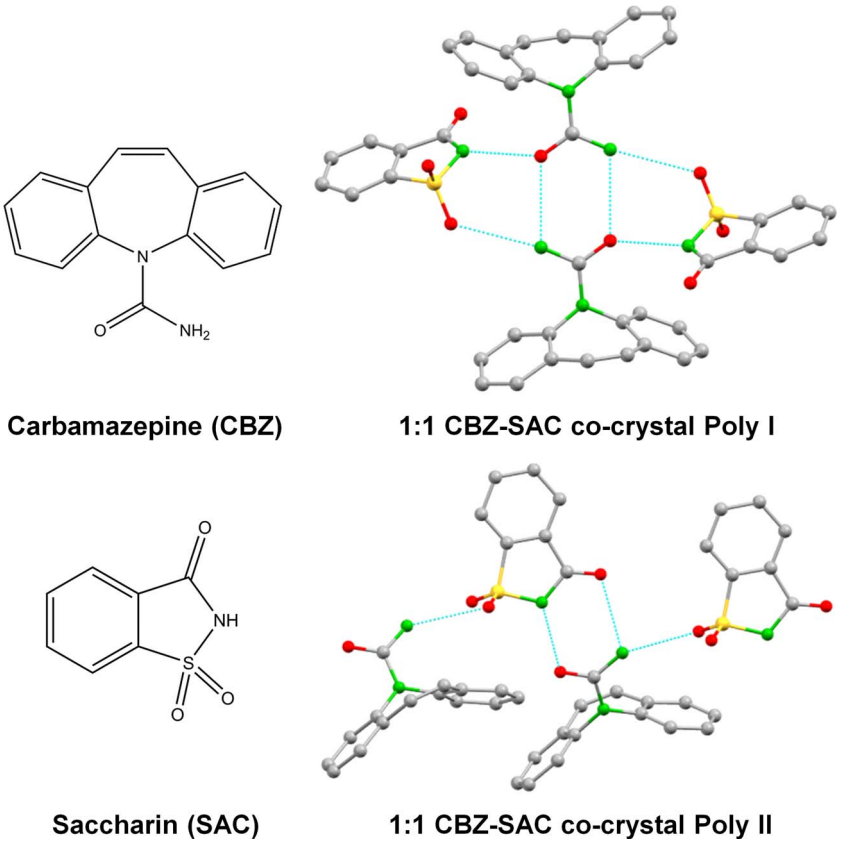

Fig. 1. Molecular structures of carbamazepine, saccharin, and the two polymorphs of the 1:1 carbamazepine-saccharin co-crystal showing the supramolecular synthons involved.

case of multidrug co-crystals), or a suitable coformer. A guidance and regulatory classification for pharmaceutical co-crystals has been recently given by the European Medicines Agency (EMA) [4] and the United States Food and Drug Administration (FDA) [5]. According to the recent rules, co-crystals are considered a drug polymorph rather than a new API and drug development and regulatory submissions are simplified [6].

In this study, we investigate the production of the 1:1 co-crystal of carbamazepine (CBZ) and saccharin (SAC) using the supercritical antisolvent (SAS) technique; this co-crystal consists of CBZ and SAC molecular units in the stoichiometric ratio 1:1 linked through the bonds shown in Fig. 1. CBZ (molar mass = 236.27 g mol^{-1}) is a poorly water-soluble drug used primarily in the treatment of epilepsy and trigeminal neuralgia that belongs to BCS class II. CBZ has five known anhydrous polymorphs [7–19] (at room temperature the most stable polymorph is polymorph III, an enantiotropic pair of polymorph I), and several dihydrate and solvate polymorphs. CBZ solubilities in water and simulated gastric fluid may be found in Refs. [20,21]. CBZ major problems are its slow rate of absorption when administered through oral route, and its tendency to adopt the dihydrate form, which reduces its solubility in water to nearly a half of that of its anhydrous form. Therefore, larger doses of the drug are required in order to be effective. Aiming to improve CBZ performance, the co-crystallization of CBZ with coformer SAC has been widely studied during the last decade. Saccharin (molar mass = 183.18 g mol^{-1}) is widely used as coformer in the preparation of pharmaceutical salts (acting as a weak acid when combined with a sufficiently basic molecule), or co-crystals (remaining then a neutral molecule). SAC has one known polymorph [22] and good water solubility [21]. The first published structure of the CBZ-SAC co-crystal reported by Fleischman et al. [23] corresponds to the more stable polymorph I [24] and was produced by slow evaporation from an equimolar solution of CBZ and SAC in ethanol. The structures of CBZ and SAC along with the co-crystal polymorphs are shown in Fig. 1. In polymorph I, the CBZ molecules are bond to each other through an amide–amide homosynthon and the saccharin molecules bond through a pyridine-carbonyl oxygen H-bond to a CBZ molecule and through a sulfonyl oxygen-amide H-bond to another CBZ molecule. The polymorph II of the co-crystal was discovered later by Porter et al. [25] using evaporation crystallization from an ethanol solution with the aid of functionalized cross-linked polymers. In polymorph II, the amide–amide homosynthon of polymorph I established between the two CBZ molecules disappears and each molecule of CBZ bonds through a pyridine–carbonyl oxygen and an amide–carbonyl oxygen H-bond to one saccharin molecule; and through an amide–sulfonyl oxygen to another saccharin molecule (see Fig. 1). Huskić et al. [26] and Maeshwari et al. [27] reported the formation of other polymorphs, but no crystallographic information file of these polymorphs is available yet and most authors only take into account the co-crystal polymorphs I and II.

A co-crystal can be prepared by several conventional methods with the aid of solvents (evaporative or cooling crystallization and reaction crystallization), directly from the solid state (mechanical grinding or melt crystallization) or using some more novel co-crystallization methods [6]. The use of conventional methods often presents scaling-up difficulties, leads to the presence of crystals of the individual components (homocrystals) in the final product and often involves post purification steps to eliminate solvents [1,28–30]. To overcome these difficulties several processes using supercritical CO_2 have been developed for the preparation of pharmaceutical co-crystals [6,31]. These processes generally involve fewer steps, reduced amounts of organic solvents, and use CO_2 that is considered a green solvent [32] because this fluid is innocuous, non-flammable, may be recycled and has readily accessible critical parameters (31 °C and 7.4 MPa). Thus, the sustainable process requirements of the pharmaceutical industry can be fulfilled using supercritical CO_2 based processes. The CBZ-SAC co-crystal has already been produced using two supercritical techniques: supercritical fluid enhanced atomization (SEA) [33] and co-crystallization