Journal of Thermal Analysis and Calorimetry
https://doi.org/10.1007/s10973-024-13379-y

Impact of the SAC:CBZ ratio on polymorphic transformation and morphology of carbamazepine-saccharin co-crystals using fast cooling crystallization

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Received: 26 October 2023 / Accepted: 9 June 2024

Abstract
Carbamazepine-saccharin (CBZ-SAC) co-crystal is one of the most studied co-crystals to date. It is proven to be polymorphic, consisting of Form I (plate-like shape) and Form II (needle-like shape), which is rarely reported by researchers. The present study aimed to study the effect of SAC:CBZ ratio on the polymorphic transformation and morphology of CBZ-SAC co-crystals using ice bath fast cooling crystallization. A series of CBZ-SAC co-crystals were produced from different SAC:CBZ mol ratios (1:1, 2:1, 3:1, 4:1, 5:1, 6:1) and were compared in terms of their crystal form and morphology under microscope. The polymorphic changes were also studied from the CBZ-SAC suspension during co-crystallization process. The polymorphs of CBZ-SAC co-crystals were identified using PXRD, DSC, ATR-FTIR. The results showed that at lower ratio (1:1, 2:1, 3:1), only plate-like shaped crystals (Form I) was present. For higher mol ratio (4:1, 5:1, 6:1), mixture of Form I and II of CBZ-SAC co-crystals were observed and further confirmed by DSC and ATR-FTIR. The nucleation process showed that Form II could convert to Form I when varying the SAC:CBZ ratio. Hence, it is proven that SAC:CBZ mol ratio can affect the polymorphic transformation and morphology of CBZ-SAC co-crystals. Nonetheless, other parameters should be used to further study the formation of CBZ-SAC co-crystals since pure CBZ-SAC Form II co-crystals were not obtained in this study.

Keywords Carbamazepine · Saccharin · Co-crystals · Polymorphic · Morphology · Fast cooling

Introduction

Pharmaceutical co-crystals are a subset of co-crystals which show promising improvements in dissolution, compressibility, physical stability and bioavailability of pharmaceutical solids [1]. To date, carbamazepine-saccharin and carbamazepine-nicotinamide are the most studied co-crystal model.

Carbamazepine drug (CBZ) is a neurological drug that has four anhydrous polymorphic forms [2–4]. It is a Biopharmaceutics Classification System (BCS) Class II drug and often given in high dose to compensate for its low solubility problem [5–7]. Saccharin (SAC) is commonly known as an artificial sweetener and widely used as a co-crystal former (CCF) in co-crystallization technology [8–10].

Carbamazepine-saccharin (CBZ-SAC) co-crystal exists in two forms of polymorphs after co-crystallization: one form is stable (Form I) while another form (Form II) is metastable [11]. Form I exists in plate-like shape whereas Form II exists in needle shape [12, 13]. Previous studies have reported that Polymorph II could be converted to Polymorph I during solution-mediated polymorphic transformation (SMPT) [14]. The selection between CBZ-SAC Form I and Form II co-crystals is influenced by factors related to stability, pharmacokinetic properties, and drug development. Form I, characterized by its stability, exhibits consistent dissolution rates and bioavailability [13].

SAC:CBZ mol ratio is one of the factors affecting the formation of different co-crystal forms [15]. Different ratio values can impact the polymorphic changes and final morphology of CBZ-SAC co-crystals [16]. Co-crystallization method is also crucial in screening formation of co-crystals [17, 18]. Previously, studies have suggested slurry, slow evaporation [19], slow cooling [20], spray drying [11],

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Published online: 15 July 2024