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Kinetics and nucleation mechanism of carbamazepine–saccharin co-crystals in ethanol solution

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Abstract This study aimed to investigate the metastable zone width (*MSZW*) and the nucleation order of carbamazepine–saccharin (CBZ–SAC) co-crystals via slow cooling crystallisation, to obtain the kinetic value using Kashchiev–Borissova–Hammond–Roberts (*KBHR*) technique and to deduce the induction time, the radius of the critical nucleus and the interfacial energy of the CBZ–SAC co-crystals via fast cooling. Slow cooling experiments with cooling/heating rates of 0.8, 0.6, 0.4 and 0.2 °C min^{-1} were applied to determine the crystallisation and the dissolution temperature of CBZ–SAC co-crystals at SAC:CBZ ratios of (3.5, 3.0, 2.5, 2.0 and 1.0) and CBZ concentrations of 19.14, 17.96, 17.06 and 15.83 mg mL^{-1}. Then, fast cooling experiments were run at CBZ concentration of 17.96 mg mL^{-1} and SAC:CBZ mole ratio of 2.0. Nucleation kinetics, such as *MSZW*, nucleation order, nucleation kinetic constant and interfacial energy, was determined and analysed. *KBHR* method was applied to analyse the kinetics value and compared with isothermal method. The nucleation orders obtained from slow cooling method were in between 1.65 and 4.9, which were within the range for nucleation of organic compounds. The results of *KBHR* method in determining the kinetic values of CBZ–SAC co-crystals were similar to those of the isothermal method.

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Introduction

Metastable zone is the area between solubility and supersolubility curves, where a solution is supersaturated and spontaneous crystallisation is unlikely to occur. This region is vital for crystallisation process because the supersaturation can be controlled within this region to obtain the desired crystal properties. The optimisation of a crystallisation process and the quality of the formed crystal can be controlled when the crystallisation occurs within the metastable zone [1, 2]. The factors affecting the metastable zone width (*MSZW*) are cooling/heating rates, solution temperature, impurities or seeds, stirring rate, and solvent [3–5].

In the recent decade, co-crystal has been one of the major interesting research subjects due to its ability to enhance the physicochemical properties of active pharmaceutical ingredients (APIs), such as solubility, stability, dissolution rate, bioavailability and compressibility [6–8]. Co-crystals are defined as "solids that are crystalline single-phase materials composed of two or more different molecular and/or ionic compounds generally in a stoichiometric ratio which are neither solvates nor simple salts" [9]. Co-crystal is known as pharmaceutical co-crystal when one of the co-formers is an API [8, 10]. In pharmaceutical industry, the physicochemical properties of the API play an important role to ensure that the drug is a cost-effective, safe and efficient [11–13]. The study of kinetics and nucleation mechanism is surely important in designing and controlling of the shape and size of the final crystalline product. Therefore, by understanding the fundamental of co-crystal nucleation

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