UNIVERSITI TEKNOLOGI MARA

PREDICTION OF CARBAMAZEPINE-SUCCINIC ACID CO-CRYSTAL DISSOLUTION IN ETHANOLIC SOLUTION USING A COMPUTATIONAL MOLECULAR DYNAMIC SIMULATION TECHNIQUE

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Abstract

In the pharmaceutical industry, it is very important to study the new solid-state forms of old APIs to improve the performance of the drugs in term of solubility, bioavailability, and stability. One of the method used is by co-crystallization processes that comprise of APIs drug and co-crystal conformer (CCFs). In this study, co-crystal of Carbamazepine- Succinic acid (CBZ-SA) was used. CBZ is a poorly water-soluble drug that is classified as Class II drugs based on Biopharmaceutics Classification System (BCS). It is an anti-epileptic drug that is used for the treatment of seizure disorders and neuropathic pain. SA is a dicarboxylic acid that is used as a chemical intermediate (solvents and lubricants), food additives, corrosion inhibitor, perfumery, and in the preparation of fine chemicals such as pharmaceuticals, antibiotics, and vitamins. The purpose of this study is to predict morphology of CBZ-SA cocrystal and to access the dissolution behavior of CBZ-SA in ethanol solvent. The materials used are CBZ-SA cocrystal and ethanol solvent while the method used is molecular dynamic simulation technique (theoretical method). An atomic charge is calculated by using Dmol3 and MOPAC model to predict the morphology of the cocrystal. After the charged was calculated, the crystal structure was subjected to geometry optimization and then energy minimization by using the potential functions such as COMPASS, COMPASS26, COMPASS27, cvff, pcff, Universal, and Dreiding. Then, the morphology of the cocrystal was obtained. Next, the lattice energy was calculated by using an attachment energy method. For the assessment of dissolution behaviors of the cocrystal in ethanol solvent, first a unit cell was constructed containing both crystal and solvent structure. Then, crystal and solvent structure was also subjected to geometry optimization and then energy minimization using a suitable forcefields so that an empty space inside the cell can be eliminated. The simulation was started and the interaction between cocrystal and solvent was analyzed using RDF and MSD. As a result, the prediction of the co-crystal shape of CBZ-SA in vacuum using Dreiding forcefield and Hirshfeld charges results in a shape similar to the experimental which is elongated needle-like shape. The co-crystal morphology is dominated by seven faces which are (1 0 -1), (1 0 1), (0 0 2), (2 0 0), (0 1 0), (0 1 1), and (1 1 0). The MSD analysis indicate that the ethanol solvent molecules diffuse more easily on (1 0 -1), (1 0 1), (0 1 1), (0 1 0) of morphologically important faces but very slow diffusion on (2 0 0), (1 1 0), and (0 0 2) faces.

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CHAPTER 1

INTRODUCTION

1.1 Research background

In the pharmaceutical industry, a major driving force that lead to new technological developments is the improvement of the properties of an active pharmaceutical ingredient (API), such as solubility, bioavailability, flow properties, thermal stability, crystallinity, particle size, and filterability are important (Vioglio et al., 2017). So, it is very important to study the new solid-state forms of old active pharmaceutical ingredients to improve the performance by co-crystallization processes. Crystallization is when a slow precipitation of crystals from the solution of a substance occur. It also can be defined as the phase change of matter such as atoms or molecules into a solid form called as a crystal (Helmenstine, 2017).

Crystallization process is widely used in pharmaceutical industries to produce crystal powder of drugs. The crystal drugs often show many crystalline forms called as polymorphs and the form can be solvates, hydrate, salt, amorphous, or co-crystal. The crystal is obtained by cooling a solution, evaporating solvent, or seeding to desired polymorph or form of crystal. There are some crucial quality requirements for pharmaceutical crystallization that need to be considered which are yield, purity, size, morphology, polymorphism, and chirality. In pharmaceutical, there are 4 classes of drugs which are Class I, Class II, Class III, and Class IV that were classified according to the permeability and solubility level (Papich et al., 2015).

API is a central ingredient and substance in the drug that can produce the desired effect to the body. For examples of API drugs in pharmaceuticals industries are Carbamazepine (CBZ), Itraconazole, Ibuprofen, acetaminophen, and so on. CBZ is classified as a class II drug that has low solubility and high permeability according to biopharmaceutics classification system (BSC) (Ali et al., 2014). It is used as an anti-epileptic drug. Common side effects of Carbamazepine include