UNIVERSITI TEKNOLOGI MARA

PREDICTION OF DISSOLUTION OF CARBAMAZEPINE- FUMARIC ACID CO- CRYSTAL FORM B POLYMORPH IN ETHANOLIC SOLUTION THROUGH MOLECULAR MODELLING APPROACH

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B. Eng. (Hons) Chemical and Bioprocess

July 2017

ABSTRACT

The main objectives of this study are to predict the dissolution of carbamazepine- fumaric acid (CBZ- FUM) Form B polymorph in ethanolic solution by using molecular modelling approach and to establish the interaction of ethanol molecule with co- crystal carbamazepine- fumaric acid (CBZ- FUM). In order to achieve the objectives of the research, the simulation was carried out by using Material Studio (MS) 4.4 software. The dissolution behavior of CBZ- FUM in ethanol solvent was simulated by molecular dynamic (MD) simulation. MD simulations were carried out at 571 ^{o}C and 788 ^{o}C in the NVT ensemble with simulation time of 5 ps and time step 0.1 fs, using the Berendsen thermostat. The predicted morphology has a good agreement to the experimental morphology of CBZ- FUM with 0.0020% deviation of lattice energy value between the predicted and the experimental lattice energy. For this work, the results show that the dissolution favours to occur first at the corners and edges of the crystal morphology followed by the flat surfaces of the crystal. Facet (1 1 -2) molecules located at the corner edges leave the crystal surface first into ethanol solvent phase followed by facet (1 0 -2) and lastly facet (0 1 2), and this result signifies the favourable interactions between the morphology of the crystal and the solvent is the major contributor to the dissolution process. The dissolution result also supported by coefficient diffusion and surface energy result calculated.

ACKNOWLEDGEMENT

"In the name of Allah, the Most Merciful and the Most Compassionate"

First and foremost, I would like to express my deepest gratitude to Allah S.W.T for giving me the strength and patience to complete this research studies. A special of appreciation also goes to my supervisor, Dr. Nornizar Anuar and also to my co- supervisors, Mrs. Umi Rafiah Shukri and Ms. Nik Salwani Md Azmi for their encouragement, guidance as well as support in completing this research. This research studies would not be able to be completed successfully on time without their constant encouragement, guidance and support.

Next, a special of appreciation also goes to my family especially my parents, who are my biggest supporters and also to my course mates that for their supports as well as valuable advices and tips that help me a lot in completing this research studies. This research studies would not be able to be completed without their prayers and supports. I also would like to thank the Faculty of Chemical Engineering, UiTM for the facilities support given for this work

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CHAPTER ONE
INTRODUCTION

1.1 BACKGROUND STUDY

Solubility is a crucial property of drugs as the drugs must be dissolved so that they can reach the site of action by absorption mechanism through membranes. Drug solubility is one of the most crucial parameter influencing the drug bioavailability, the availability of drugs in a correct concentration at the site action (Khadka et al, 2014). However, amongst major problems arise during the development of new drugs in pharmaceutical industry nowadays is poor aqueous solubility. In recent years, poor water solubility number of drugs has increased for about 70% (Censi et al, 2015). This problem becomes the main reason why pharmaceutical compounds introduced into the marketplace are less than 1% (Abd Rahim et al, 2015). The drug substances are classified into four classes according to Biopharmaceutical Classification System (BCS), based on their aqueous solubility and intestinal permeability (Khadka et al, 2014) as follows:

Table 1.1: *The classification of drugs solubility according to BCS*

BCS Class	Solubility	Permeability
1	High	High
2	Low	High
3	High	Low
4	Low	Low

The pharmaceutical co- crystal is a single crystalline solid that combines two neural molecules, which are an active pharmaceutical ingredient (API) and a co-crystal former (Khadka et al, 2014) that are constructed through several types of interaction such as hydrogen bonding, pi- stacking, and van der Waals forces (Sekhon, 2009). Co- crystal former may be an excipient or another drug (Khadka et al, 2014). This method is an effective mean in modifying the physical and chemical properties of drugs including solubility and dissolution rate but not altering their pharmacological