UNIVERSITI TEKNOLOGI MARA

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

NURFATIHAH SYAMIMI BINTI MOHAMAD SAM

BACHELOR OF ENGINEERING (HONS.)
CHEMICAL

July 2019

ABSTRACT

Carbamazepine (CBZ) famously known to be analgesic and anticonvulsant with solubility and polymorphism problem had become a great challenge to crystal engineers since their crystal packing were unpredictable. CBZ forms supramolecular complexes with co-crystal former, succinic acid (SA) which are complementary with each other in terms of hydrogen bonding. This approach thoroughly modifies the crystal packing and affect the physical and pharmaceutical properties of CBZ. The interaction occur between carbamazepine and the succinic acid can be predicted by using a molecular dynamic simulation technique. Carbamazepine-succinic acid (CBZ-SA) co-crystal morphology that consist of seven dominant facets was cleaved to gain better insights on the interaction, which later affects the dissolution behaviour of the crystal. Hydrogen bonding is the key of interaction in the crystal engineering. Thus, accessing the interaction between one reference atom and ethanol with one unit cell of carbamazepine-succinic acid (CBZ-SA) co-crystal was the main objective. The plate-like shape morphology of CBZ-SA co-crystal consist of seven dominant facets which were (1 0 -1), (1 0 1), (1 1 0), (0 1 1), (0 1 0), (2 0 0) and (0 0 2). In order to study the stability phenomenon, two aspects were analyzed: (1) Radial distribution function (RDF), (2) Mean square displacement (MSD). Each molecules in each facets exhibit different type of interaction with the reference molecule and ethanol molecule.

ACKNOWLEDGEMENT

I would like to take this opportunity to thank those who helped make this thesis and my four years at the Universiti Teknologi Mara (UiTM) Shah Alam a reality. I am grateful for everyone's dedication and support throughout these four years.

First and foremost, I thank my research supervisors, Dr Nornizar Anuar, Sir Muhamad Fitri Othman and Dr Nurul Ain' Yusop. They are the model of inspiration! Their excitement and interest about supramolecular chemistry and modelling approach are really admirable. I am thankful being the student under their supervision.

The love and support from my family and friends have encouraged me throughout these four years. My mom and dad, and Mohamad Sam were always there for me if I need to talk, no matter what time of the day. Thank you to my brothers, grandmother, uncles and aunties that always giving me motivational quotes and support me during my bad time of the day. This piece of victory is dedicated to all of you. Alhamdulilah.

Lastly, I would like to thank all of my friends-Aniza, Najihah and Darwina -who have provided much need outlets along the way.

TABLE OF CONTENTS

SUPERVISOR'S CERTIFICATION iii
COORDINATOR'S CERTIFICATION iv
AUTHOR'S DECLARATION v
ABSTRACT vi
ACKNOWLEDGEMENT vii
TABLE OF CONTENTS viii-ix
LIST OF TABLES x
LIST OF FIGURE xi-xii
LIST OF SYMBOLS xiii
LIST OF ABBREVIATIONS xiv

CHAPTER ONE: INTRODUCTION **2**

1.1 Research Background 2-3
1.2 Problem statement 4
1.3 Objectives 4
1.4 Significance of study 5

CHAPTER TWO: LITERATURE REVIEW **6**

2.1 Crystallization 6-7
2.2 Solubility 7-8
2.3 Cocrystallization 8-10
2.4 Carbamazepine (CBZ) 10-12
2.5 Succinic acid (SA) 12-13
2.6 Assessment for the solubility of CBZ-SA in ethanol solvent 14-16
2.7 Molecular modelling approach 16
2.8 Dissolution behaviour in solvent using molecular modelling approach 17-18
2.9 Radial distribution function (RDF) 18-19
2.10 Mean square displacement (MSD) 19
2.11 Binding energies 20

CHAPTER ONE

INTRODUCTION

1.1 Research background

During the years, crystallization technique is important in the production of pharmaceuticals, dyestuffs, pigments, foodstuffs, chemicals, cosmetics and others as it exist as a molecular crystal with determined characteristics. Crystallization can be categorized as an old technique in the process of formation of crystalline solid from a supersaturated solution, melt or vapor phase. It is a supramolecular reaction and the heart of crystal engineering. Nowadays, crystal growth has become an important and attractive research field. There are different crystalline phase or polymorphs that can be obtained from crystallization technique. The arrangement and the formation of the molecules in the crystal lattice has made the polymorph differs from one another. The first case is called packing polymorphs while the second case is called conformational polymorphs (S. Redinha, Lopes Jesus, Pais, & Almeida, 2013). Packing polymorph happens when the molecules share the same molecular conformation while the conformational polymorph happen when different conformation of same molecules occur in different crystal forms (Lee, 2014).

Drugs can be classified into crystalline, solvates, hydrates and amorphous forms. Crystalline solid and amorphous solid are the common type of solid that usually discussed (G. G. Z. Zhang & Zhou, 2017). Crystalline solid comprise of a long order arrangement of their particles that will show same arrangement indefinitely, whereas amorphous solid comprise of a short order arrangement that has a variety arrangement. The changes in internal packing of the solid will give rise to changes in bulk properties. The difference in properties of the solid form affect the later drug processing and the solubility will have an impact on the absorption of the active drugs. Dissolution rate and the mass transport of the molecules may also be affected by the various types of form (Jacob, Nair, Pn, & Panda, 2011). Figure 1.1 shows the solid state arrangements that are applicable to polymorph and cocrystals.