

UNIVERSITI TEKNOLOGI MARA

**PREDICTION OF DISSOLUTION
BEHAVIOUR OF FUMARIC ACID
(FORM B) USING MOLECULAR
MODELLING**

AMINATUZZAHARAH BINTI MUSA

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ABSTRACT

Fumaric acid is one of stable co-former used in active pharmaceutical ingredient (APIs) drug in pharmaceutical industries. As APIs drug is known for having limited dissolution bioavailability and low solubility in water, so, one method is approach which is pharmaceutical co-crystal. Pharmaceutical co-crystal is defined as a crystalline material which consists of an API and one co-former. Basically, the aim of this research is to assess the effect of number of molecules of solvent to the dissolution of Fumaric Acid (Form B) crystal by using molecular modelling. Molecular dynamic simulation is used since the visual on how the diffusion of FUM-B into ethanol solvent can be seen. The dissolution behavior of FUM-B into ethanol solvent is determined by using mean square displacement (MSD) and diffusion coefficient (D) calculations. The results shows that the dissolution of crystal first occur at facet (0 0 1) and last dissolution occur at facet (1 -3 1) with D value of 3.866×10^{-9} and 2.1×10^{-11} respectively. The higher the value of D indicates that the faster crystal can diffuse into solvent. Facet (1 -3 1) has slow dissolution behavior because it has strong hydrogen bond interaction between crystal molecules compared to other facet. The data from simulation also analyzed by using radial distribution (RDF), the result shows as same as MSD result.

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CHAPTER ONE

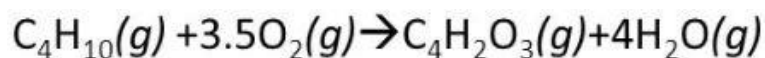
INTRODUCTION

1.1 1.1 Introduction

This chapter discussed about the research background of fumaric acid and pharmaceuticals including the definition of the fumaric acid, where it comes from, its applications and how it is related with the pharmaceuticals and dissolutions. Besides, it also discussed about the problems on why fumaric acid is chosen as a co-former and why molecular dynamic simulation has been used in this research.

1.2 1.2 Research Background

Fumaric acid is defined as a colorless crystalline chemical compound which is widely found in nature. It was first found in a plant of *Fumaria officinalis* in which it derived its name. Fumaric acid, also known as trans-1, 2-ethylenedicarboxylic acid or (E)-2 butenedioic acid, is widely used in the manufacture of drinks, medicines, food and beverage additives, unsaturated polyester, animal feed, alkyd resins, cleansing agents, printing inks, and plasticizer (A. Roa Engel, Straathof, W Zijlmans, Gulik, & Wielen, 2008). Currently, Fumaric acid is produced from maleic anhydride by maleic acid isomerization process. Below, show the reaction equation of oxidation of butane to produce maleic anhydride.



In the pharmaceutical industry, to increase the dissolution rate and solubility of co-crystal in the solvent, fumaric acid is used as a co-former in co-crystallization process. In previous studies, since 1959, fumaric acid esters (FAE) have been utilized in the psoriasis treatment, and it is known as fumarates, as its name is a fumaric acid ester, an ester is derived from fumaric acid. Although FAE is unlicensed in the UK due to the efficacy and safety, it was licensed in Germany. FAE tablets are used to treat