# Molecular Dynamic Investigation on the Dissolution Behavior of Fumaric Acid Crystal (Form B) in Ethanol Solution

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Abstract— The objectives of this study are to analyse the morphology of fumaric acid crystal (form B) and to access dissolution behaviour of fumaric acid crystal (form B) in ethanol solution. For this study, the predicted morphology obtained from the simulation using Material Studio 4.4 by ACCELERYS. The combination hirshfield charges with dreiding potential function gave the morphology (small needle shape) for the crystal with lattice energy of -31.039 kcal/mol and the percentage error is 1.46% when compare with the experimental value, -31.50 kcal/mol. The morphology consists of 10 main facets which are (0 1 0), (0 1 -1), (1 -1 0), (0 0 1), (1 - 2 1), (1 0 0), (1 -2 0), (1 0 -1), (0 2 -1) and (1 -3 1). RDF and MSD analysis show that facet (0 1 -1) is interact and dissolve first in ethanol solution.

*Keywords*—Molecular dynamic simulation, Dissolution, Morphology prediction, Fumaric acid (Form B)

# I. INTRODUCTION

acid Fumaric is the chemical compound with the formula C4H4O4 has been widely used as cocrystal former (CCF) in pharmaceutical industry. CCF from carboxylic acid group was used to change homosynthon form the carboxamide in order to 2015) supramolecular heterosynthon. (Roberts CCF will combine with active pharmaceutical ingredient (API) to form co-crystal.

pharmaceutical, In co-crystals have gain considerations pharmaceutical industry due manv in their ability to improve the biological properties to physicochemical free active and of pharmaceutical (Zhang et al. 2016). A co-crystal is ingredient (API). the combination of two or more different molecules that are in solid state at room temperature in a crystal lattice and the hydrogen bond help to stabilised the structure. (Tomaszewska et al. 2013).

of Co-crystals the major is one pharmaceutical materials use to improve the solubility and dissolution rate.(Rahman et al. 2017) Solubility known as the main the is factors in performance of the drugs and the improvement of its compulsory solubility the pharmaceutical is in

industry. The study on the crystal morphology must be done before the analysis on its dissolution due to the changes of the crystal morphology during the The of crystallization process. growth surface morphology is crucial on the interaction between the and environment crystals their and also on the solubility.(Li of crystal formation mechanisms and its et al. 2000)

Molecular dynamics methods have been used widely as an advance technology to obtain important information about the process of dissolution at the microscopic level and then compare with the experimental results. Molecular dynamics determining been used have also have in the biological function such protein-folding as thermodynamics and kinetics, self-assembly in difficult fluids biological lipid bilaver process, profiles for pharmaceutical uses pressure related to lipids, nucleic acids and proteins.(Toroz et al. 2014)

# II. METHODOLOGY

this work. morphology prediction and study In on dissolution behaviour were done hv using Material Studio 4.4 by ACCERLYS.

## A. Crystal Structure

The crystal structure of fumaric acid (Form B) was obtained the Cambrigde from Structural Database (ref FUMAAC002). (CSD) code: Fumaric acid (Form B) crystallizes in triclinic lattice with space group 2 P-1, and lattice paremeters 5.264, a= b= 7.618, c = 4.487,  $a = 106.85^{\circ}$ ,  $b = 86.34^{\circ}$ ,  $c = 134.93^{\circ}$ 

### **B.** Computational Methods

The prediction of morphology and dissolution of fumaric acid (Form B) crystal was carried out by using Material Studio 4.4 from ACCERLYS.

# C. Atomic Charges

Atomic charges be determined mol<sup>3</sup> can by using calculation by using Material Studio. There are three charges that can be obtained from this method which are mulliken. hirsfield and electrostatic potential fitting (ESP). The setup for DMol<sup>3</sup> calculation used for this study is the combination of GGA and BLYP. The task for this calculation is set as geometry optimization with medium quality.

#### **D.** Lattice Energy Determination and Morphology Prediction

In Material Studio, the potential functions used were Compass26. Compass27, Dreiding, Compass. CVFF, PCFF and PCFF30. Universal, Each of potential functions was combined with different type of charges to obtain the value of lattice energy for fumaric acid crystal (Form B). All the values of lattice energy from different combination of potential functions and charges from the mulliken, hirshfeld, ESP and charges from the forcefield compared with experimental value of lattice energy of fumaric acid crystal (Form B) which is -31.50kcal/mol. The atomic charges were assigned to the molecules and with the selected potential functions were used to predict the morphology. The structure was subjected to geometry then energy optimization minimization. Then, and calculation on the value of lattice, also morphology prediction.

#### E. Dissolution Prediction between Crystal and Solvent

Dissolution behaviour between fumaric acid crystal and ethanol solvent is determined by using molecular dynamic simulation by Material Studio 4.4. Ethanol structure was taken from the structure file in Material Studio. Then, the ethanol structure is optimized by using force field and same setting as the morphology prediction. After that, 3002 molecule of ethanol is constructed in amorphous cell. Fumaric acid crystal was fixed in the centre of the ethanol solvent and optimization is carried out to standardize the energy between the crystal and solvent. Finally, dynamic was run with setting 20 ps to observed the interaction of the crystal with ethanol solvent.

## **RESULTS AND DISCUSSION**

#### A. Atomic Charges and Lattice Energy

Hirshfield and Electrostatic potential Mulliken, (ESP) are the charges that used in calculating the lattice The combination of hirshfield charges energy. and dreiding give the nearest value to the experimental value. The value lattice energy obtained from the simulation is -31.04 kcal/ mol and the percentage experimental error when compared with values, -31.50kcal/mol (derissen 1978) is 1.46%. Table 1 shows the comparison of the values for lattice energy from the calculation with the experimental value.

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Potential	charge type	Elatt (kcal/mol)	Percentage
Function			error (%)
Experimental	-	-31.50	-
Compass	Mulliken	-35.51	-12.74
	Hirsfield	-16.69	47.02
	ESP	-45.90	-45.70
Dreiding	Mulliken	-69.18	-119.63
	Hirsfield	-31.04	1.46
	ESP	-72.28	-129.46
Universal	Mulliken	-23.94	23.99
	Hirsfield	-15.79	49.87
	ESP	-25.03	20.53
CVFF	Mulliken	-25.92	17.71
	Hirsfield	-16.13	48.87
	ESP	-27.99	11.13
PCFF	Mulliken	-24.97	20.72
	Hirsfield	-18.59	40.99
	ESP	-26.28	16.61



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Figure 1: Morphology for fumaric acid crystal (Form B)

Based on Bednowitz et al, 1966 the experimental shape for fumaric acid (Form B) crystal is a small needle-shaped. The space group for the crystal is P1 with lattice parameter a = 5.264 A, b = 7.618 A, c = 4.487 A,  $a = 106.85^{\circ}$ ,  $B = 86.33^{\circ}$ ,  $y = 134.94^{\circ}$ , Z = 1. From the simulation work, the combination hirsfield charges with dreiding as the potential function give the small needle-shaped morphology for the crystal. The morphology has 10 unique numbers of facets. The numbers of facets that contribute to the morphology are (0 1 0), (0 1 -1), (0 0 1), (1 -2 1), (1 0 0), (1 -1 0), (1 -2 0), (1 0 -1), (0 2 -1) and (1 -3 1).

C. Surface analysis for the crystal 1) 0 1 0 2) 0 1 -1



Figure 2: Cleaved crystal surface for morphology

(1 -2 0), (0 2 -1) and (1 -3 1) have high potential to react first with ethanol due to the fumaric acid molecule position on the surface. Fumaric acid from functional group of carboxylic acid will interact with ethanol (alcohols) to form esters. For surface (1 -2 0), the OH- molecule from fumaric acid molecule is above the surface will form bond with the H+ from ethanol to form water. molecule Oxygen molecule has two lone pairs of electrons will form hydrogen bonds with two molecule of hvdrogen. Then, the fumaric acid molecule will react with R-O of ethanol to form esters. Same with surface (0 2 -1) and (1 -3 1) that have same position of fumaric acid different orientation will but with have high possibilities for interaction to occur. For surface (0 0 1) and (1 0 0) it can be predict that it will difficult for the fumaric acid molecule to interact with the ethanol because this two surface contribute a high total facet area on the crystal morphology. The high total facet for the both of the surface is contributed by high value in lattice energy which are -8.34kcal/mol and -8.55kcal/mol respectively.

D.Solvent Interaction with Fumaric Acid Crystal (Form B)

Radial distribution functions (RDF) is used to observe the interaction between crystal facet and solvent molecules through the interfacial models of fumaric acid (form B) crystal surface or facet and the ethanol molecules. Figure 3 show the molecule that has high possibilities to interact first with ethanol at different frames: frame 1(3a), frame 2 (3b), frame6 (3c) and frame 11(3d). There are three molecules that observe to be interacted first with ethanol and the molecules is set as set 1, set 2 and set 3. Set 1 is molecule form facet (1 0 -1) while set 2 and set 3 are from facet (0 1 - 1)



Figure 3a:Fumaric acid crystal in ethanol solution at frame 1



Figure 3b: At frame 2



RDF analysis at selected molecule of fumaric acid crystal

RDF analysis were plotted to show the intermolecular interaction between oxygen from fumaric acid molecules and hydrogen from ethanol. Based figure 4, graph of RDF for set 1 (facet -1 0 1) it can be observed that the pattern of the graph is sharp peak at range from 0.9A to 1.5A and after that the graph show the intensity pattern until the end. The sharp indicates the strong hydrogen bond peak exist between O and H. Figure 5 show the RDF graph for set 2 of fumaric acid and the pattern of the graph is sharp peak is range between r=0.9A and r=1.4A but after that it can observe the intensity shape of the graph. Figure 6 based on RDF graph of set 3 from fumaric acid crystal. This graph show that the sharp peak start at range same as set 1 and set 2 and also intensity pattern of graph after the sharp peak formation on the graph. The formation of peak on all the graph is same but the difference that we can observe is the g(r). The g(r) for set 1 (facet -1 0 1) is 25000 while 40000 and 20000 for facet (0 1 -1) which contain set 2 and set 3 respectively. This show that set 3 from facet (0 1 -1) of the crystal have more possibilities to interact first with ethanol solution. For the sharp peak it can be said that there is strong hydrogen bond presence between O and H. Strong van der Waals forces and the electrostatic interactions between fumaric acid molecules and ethanol is shown at wide peak.



Figure 4: RDF graph at set 1



Figure 5: RDF graph at set3



Figure 6: RDF graph at set 3

E. Dissolution Behaviour of Fumaric Acid Crystal (Form B) in Ethanol Solution

The dynamic simulation is run at 20.0 ps to observe the interaction more clearly. After the simulation is successful, we observe the interactions between crystal and the ethanol solution. The interactions for this simulation time is still fast but we can observe a few molecules that can be said have high possibilities to interact first with ethanol solution. Figure 7 below show the interaction between fumaric acid crystal and ethanol solution at 20.0 ps. At 20.0 ps, the mean square displacement (MSD) is analysed to determine the selected fumaric acid crystal molecule interaction in ethanol solution. Figure 8 show the MSD graph for set 1, molecule from facet (1 0 -1) and can be observe that the crystal is dissolved into the ethanol solution at 2.0 ps and the dissolution rate kept increase until 14.0 ps before it is gradually decrease at 16.0 ps showing that the dissolution rate decreased. For facet  $(0 \ 1 \ -1)$  represent by set 2 and set 3. For set 2, the MSD graph shown on figure 9 shown that the dissolution of the crystal can be observe at 4.0 ps but then dissolution start to decrease after that and the pattern of the graph is same until 20.0 ps. For set 3 the pattern of the MSD graph at figure 10 show that the dissolution for the molecule is slow at the starting the simulation but then the dissolution rate of increased rapidly starting 16.0 ps until the simulation finished. From the slope of the graph, the diffusion coefficient value can be obtained. Table 2 show the diffusion values for facet (-1 0 1) and (0 1 -1).

Table 2:Self-diffusion of the interfacial model of ethanol and fumaric acid.

Components	Facet,hkl	Diffusion cm <sup>2</sup> . S <sup>-1</sup>	coefficient,
Fumaric Acid	(-1 0 1)	0.1997	
	(0 1 -1)	0.2973	



Figure 7: Dynamic simulation interactions at 20.0 ps







Figure 9: MSD for set 2



#### III. CONCLUSION

The modelling process has been proven have high pharmaceutical industry potential in and very to determine the crystal behaviour important at the molecular level. In this research, material studio 4.4 is used to determine the morphology of the fumaric acid crystal (Form B) and its dissolution behaviour in ethanol solution. The predicted morphology using combination Hirshfeld of charges and dreiding produced forcefield small needle shape.The dissolution of fumaric acid crystal in ethanol solution can be observed by dynamic simulation at 5.0 ps and 20.0 ps but the RDF and MSD analysis are observe at 20.0 ps to see the clear interaction of fumaric acid crystal and ethanol. Facet (0 1 -1) is observed to dissolve first in ethanol solution based on RDF and MSD analysis. So, the dynamic simulation time can increase so that we can clearly observe the be movement of fumaric acid crystal to interact with the ethanol solution.

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