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

Aminatuzzaharah Musa, Siti Nurul 'Ain Yusop, Nornizar Anuar, Muhammad Fitri Othman and Syarifah Abdul Rahim

Faculty of Chemical Engineering, Universiti Teknologi Mara

***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 3.866x10-9 and 2.1x10-11 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.**

Keywords*— Dissolution, Molecular Dynamic Simulation, Active Pharmaceutical Ingredients (APIs), Fumaric Acid B, Pharmaceutical Co-Crystal

I. INTRODUCTION

Fumaric acid is one of stable co-former used in active pharmaceutical ingredient (APIs) drug in pharmaceutical industries. APIs is a main ingredient in a pharmaceutical drug that have the low solubility, stability and flowability [1]. As APIs drug is known for having limited dissolution bioavailability and low solubility in water [2], 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. In co-crystallization process, fumaric acid is used as a co-former to increase the dissolution rate and solubility of co-crystal in solvent. Basically, the dissolution behavior of drug in solvent have become an issue, approximately, about 70% of new drug molecules have been discovered by scientists that have low solvent solubility [3] [4]. The low solubility and stability could result in a low effectiveness when consume in human body. Generally, the increment in solubility and stability is credit to the intermolecular interactions, for example, hydrophobic interactions between API and co-former or between the two APIs, hydrogen bonding, and van der Waals interaction. However, for this research, focused is on fumaric acid. Fumaric acid is used in helping the APIs to break up into small parts or particles [5] and transport it into a blood stream without decreasing the performance or stability of the drug [1] [6].

Dissolution is a process where the drug molecules are removed from the solid crystal particles and released into gastrointestinal (GI) environment surrounding, therefore, the removal of ions in solvents could give positive resulted in pharmaceutical dosage form design [7]. The understanding on how a drug molecules removes itself from a crystalline phase is quite poor even though many mathematical models and experimental methodologies were established. This is because of the difficulties of dissolution mechanism in solvent. To overcome these problem, and due to the revolutionary advances in computer technology and algorithmic improvements, the computational methods especially molecular dynamic (MD) simulation had been used [8]. MD simulation has become a valuable tool in area of physics and chemistry besides, it is a system that have ability to determine the physicochemical properties of drug without costly experiments [9]. Then, MD simulation is used due to the high cost in developing a novel drug candidate, which is about US$800 million and increase at an annual rate of 7.6 %[10]. In recent decades, the MD simulations have reported largely changed the process of drug development and retarding the growth of non-clinical costs in pharmaceutical industry [10]. Based on the previous research, the researcher highlight the close interaction between experimental and simulation techniques in which the crystallization may lead to drawbacks in drug activity [10]. Basically, MD simulation is a powerful tool that can help in gaining insight of the mechanism at both atomic and molecular level of Fumaric Acid (Form B) as this research is focused on the dissolution behavior of Fumaric Acid (Form B) in ethanol. Then, by using MD simulation, it also can evaluate the interactions between molecules using mean square displacement (MSD) and radial distribution (RDF) analysis right after the simulation is run [11].

MSD analysis is used to measures the distance of molecules from its original position and the diffusion coefficient of molecules is calculated by increased of mean squared displacement (MSD) with time. The MSD is calculated by using equation below [12]:

$$D = \lim_{t \to \infty} \frac{\langle |\vec{r}(t) - \vec{r}(0)|^2 \rangle}{6t} \quad (1)$$

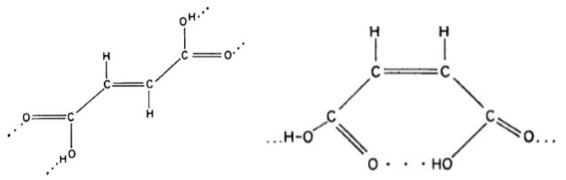
Meanwhile, RDF is used to investigate specific interactions such as hydrogen bonding. It also measures the probability of an atom or molecule found from a reference atom at a distance, then, RDF values is calculated by using equation below [13]:

$$x_\alpha x_\beta \rho g_{\alpha\beta}(r) = \frac{1}{N}\left\langle \sum_{i=1}^{N_\alpha}\sum_{i=1}^{N_\beta} \delta(r - r_i + r_j) \right\rangle \quad (2)$$

II. METHODOLOGY

A. Molecular structure

This Carboxylic acid is defined as an organic compounds where carbon (C) atom is bonded with an oxygen (O) atom by double bond and also to a hydroxyl group (-OH) by single bond. The fourth bond links carbon atom to a hydrocarbon group (R). Meanwhile, dicarboxylic acid is an any carboxylic acid that contain two carboxyl (COOH) groups. The dicarboxylic acid with chemical structure HOOCCH = CHCOOH occurs in two isomeric forms which are trans and cis isomer where it is known as fumaric acid and maleic acid respectively [14]. There are two form of fumaric acid which is α-Fumaric (Form A) and β-Fumaric (Form B). β-Fumaric crystallizes in a triclinic lattice with space group PI, with one molecule per unit cell, Z = 1, with cell parameters of a = 5.264 ± 0.003 Å, b = 7.618 ± 0.003 Å, c = 4.487 ± 0.002 Å, α = 106.85 ± 0.05°, β = 86.33 ± 0.05° and γ = 134.94 ± 0.08° [14]. Figure 1 shows the fumaric acid (a) and maleic acid (b) molecular structure. β-Fumaric acid crystal only has one molecule of fumaric acid (Form B) in a unit cell. Each β-Fumaric acid consist of hydrophobic and hydrophilic part. The hydrogen bonds form between hydrophilic part of FUM-B and ethanol molecules, while it is also form between hydrophobic part of FUM-B and another hydrophobic part of FUM-B.



(a) (b)

Figure 1: Fumaric acid (a) and maleic acid (b) molecular structure

B. Construction of 3D period structures of ethanol

The ethanol molecules are constructed using sketching tools which is available in Material Studio version 7.0. The square cell and ethanol solvent molecules are built using Amorphous Cell module which ethanol molecules will be interact with a fumaric acid crystal. The ethanol molecules are going to be inserted into the vacuum slab which containing Fumaric Acid (Form B) crystal surface.

C. Geometry optimization of the periodic system

After construction of ethanol molecules, the cell which containing ethanol molecules and Fumaric Acid crystal are optimized using dreiding forcefield and summation method to form stable conformation where the total energy of the system is reduced to a minimum as the initial structure of Fumaric Acid in ethanol solvent is not stable. Besides, the forcefield used for geometry optimization must be the same as the morphology of Fumaric Acid crystal.

D. Molecular dynamics simulation for dissolution assessment

Molecular dynamic simulation is running after geometry optimization of the molecules by using the same combination of forcefield and summation method. Then, as three layers of Fumaric Acid crystal used, the first upper surface of the Fumaric Acid crystal is uncontrolled to allow the crystal to interact with ethanol solvent molecules. While the other two layer of crystal at the bottom is controlled by intermolecular forces where the detachment of ions occur when the interaction between crystal faces and ethanol solvent is stronger at the upper surface of crystal. The Nose-Hoover thermostat is used to control the temperature at 298K.

E. Selection of facets

Fumaric acid (Form B) have 20 facet in total, however, only 5 facet was chosen for molecular dynamic simulation analysis which are (1 -2 1), (0 0 1), (0 1 0), (0 1 -1) and (1 -3 1). The selection of facets involved are based on the percentage of total facet area, polar energy, attachment energy (van der waals) and distance between ethanol and Fumaric acid crystal molecule. Facet (0 0 1) was chosen due to the highest percentage of total surface area, while facet (1 -3 1) has the lowest attachment energy (van der waal) and percentage of total surface area. (0 1 -1) has the least negative value of attachment energy (van der waal) which is -4.8918 kcal/mol, while for facet (0 1 0), it was chosen due to the polar energy value. The more negativity the value of polar energy, the more electrostatic charges produces in this facet. So, this situation lead to the increasing of solubility of fumaric acid in ethanol solvent. Figure 2 shows the morphology of fumaric acid (Form B).

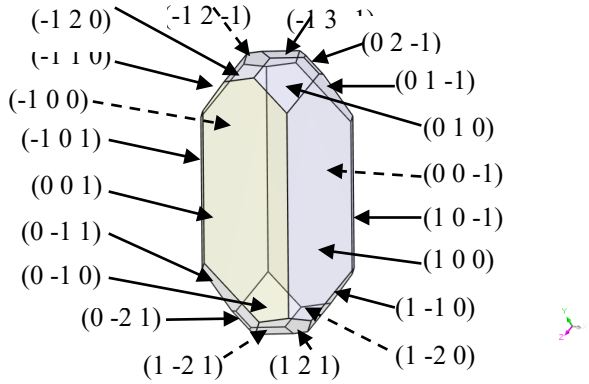
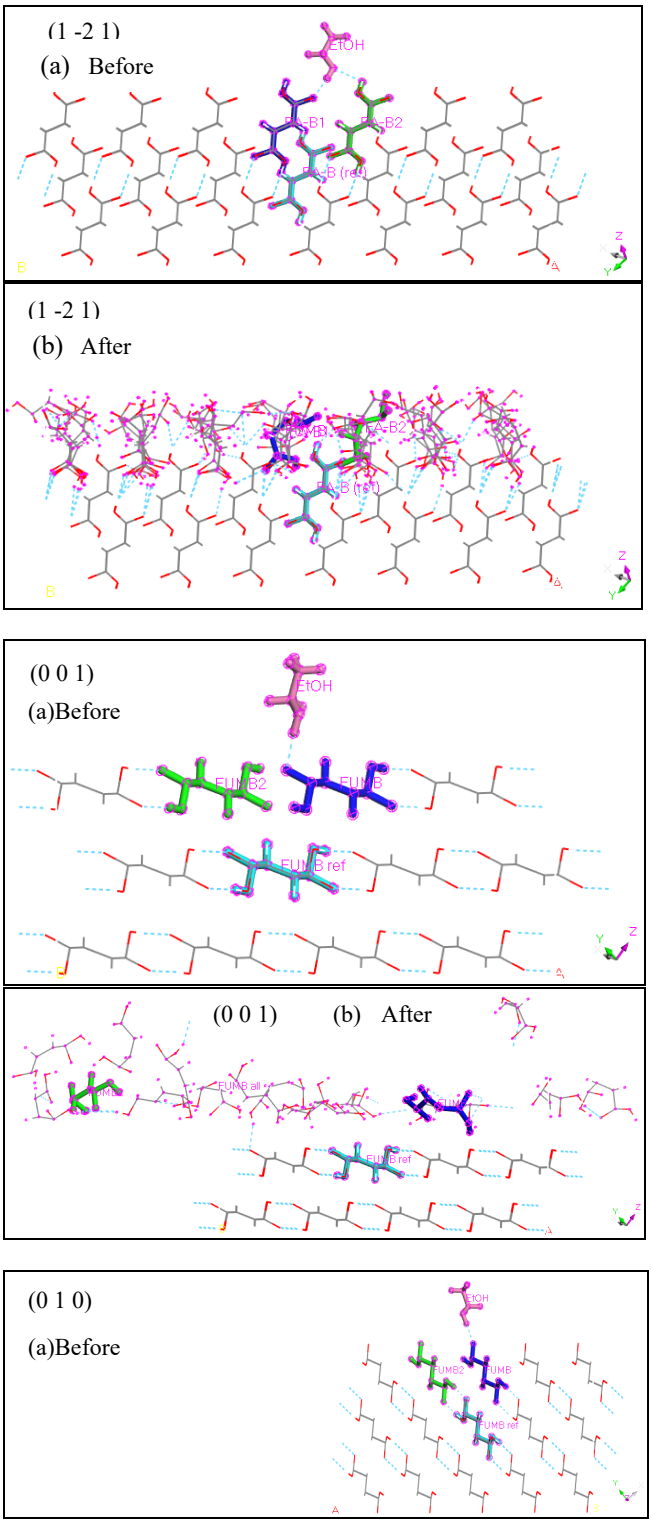


Figure 2: The morphology of fumaric acid (Form B)

III. RESULTS AND DISCUSSION

Dissolution and transport properties of FUM-B in ethanol solvent

Molecular dynamic simulation is used to study the effect and solubility of fumaric acid B in ethanol solvent. It also can provide a better understanding as the interaction of fumaric acid crystal and ethanol solvent can be observed. Figure 3 shows the molecular interactions between fumaric acid molecules and ethanol before and after simulation. Purple colour molecule represent ethanol molecule, light blue represent FUM-B reference, dark blue represent FUM-B and yellow/green represent FUM-B2. From figure 2, in which after dynamic simulation is run, it shows that the first layer of FUM-B detach from bulk crystal surface and moves into solvent. For facet (1 -3 1), none of hydrogen bonding visible, this situation occur might be due to the arrangement of molecules on crystal facet. Due to strong hydrogen bonding interaction between crystal molecules, the crystal molecules are difficult to detach and diffuse into ethanol solvent. Then, data from successful simulation are analyzed by using MSD to determine the diffusivity of each facet.results section is where you will describe the main findings from your research study. You may feel free to use tables, charts, and figures to illustrate your results. Be sure to include the findings from all your analysis of data.



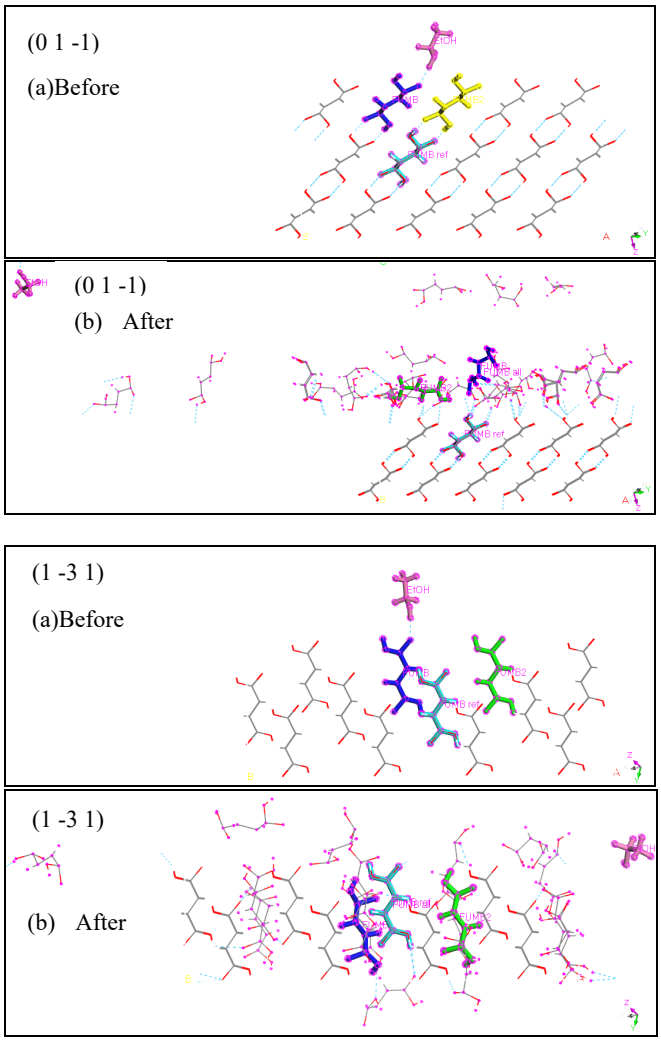


Figure 3: Molecular interactions between fumaric acid molecules and ethanol before and after simulation

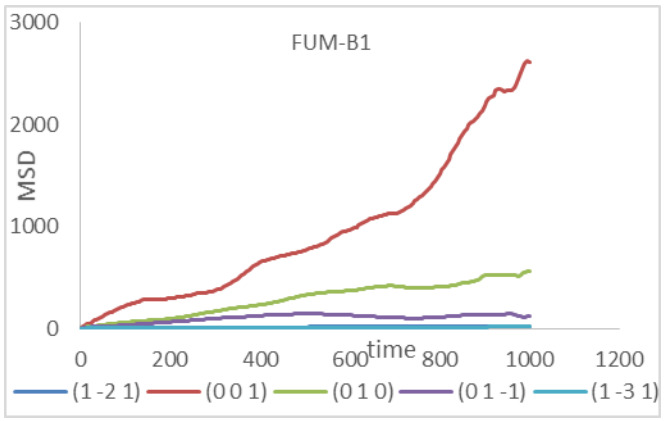


Figure 4: MSD graph for FUM-B1 molecule for each facet

Table 1: Diffusion coefficient (D) of FUM-B1 molecule for each facet for 1000ps

Facets	D (diffusion coefficient) A◦	$Dx10^{-10}$ (diffusion coefficient) m^2/s
(1 -2 1)	0.002483	0.2483

(0 0 1)	0.3866	38.66
(0 1 0)	0.0916	9.16
(0 1 -1)	0.0170	1.7
(1 -3 1)	0.0021	0.21

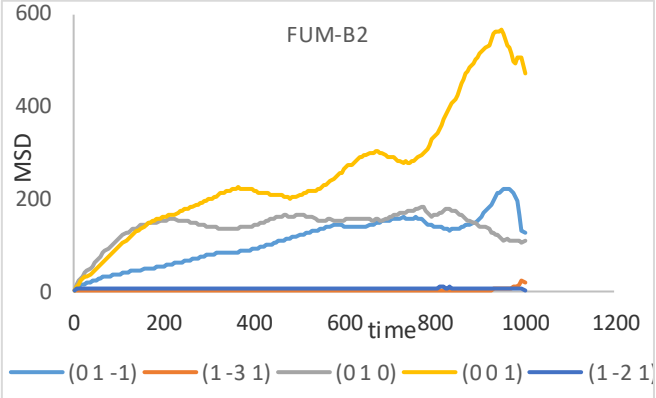


Figure 5: MSD graph for FUM-B2 molecule for each facet

Table 2: Diffusion coefficient (D) of FUM-B2 molecule for each facet for 1000ps

Facets	D (diffusion coefficient) A◦	Dx10^{-10} (diffusion coefficient) m^2/s
(1 -2 1)	0.0000667	0.00667
(0 0 1)	0.0727	7.27
(0 1 0)	0.00865	0.865
(0 1 -1)	0.0285	2.85
(1 -3 1)	0.000717	0.0717

Figure 4 and 5 shows the MSD graph of fumaric acid molecules for five facets while table 1 shows the diffusion coefficient values calculated from the slopes of the plotted graphs for each facets. Based on the graph, the value of MSD increases when time increase. The slope of MSD curve is used to calculate the value of diffusion coefficient,D of crystal surface. The higher the value of diffusion slope indicates that the higher the displacement increment or the molecule travel from their origin place. So, the situation where the stronger movement of molecules occur shows that the molecules dissolve in ethanol solvent. So, for MSD, can be concluded that the higher the value of D, the higher the diffusion rate of FUM-B into ethanol solvent. Based on the result from the figure 4 and table 1, the diffusion coefficient, D of FUM-B1 for facet (0 0 1) > (0 1 0) > (0 1 -1) > (1 -2 1) > (1 -3 1). Meanwhile, for MSD of FUM-B2, the result from figure 4 shows that after 935 ps, the curve for all facet start to decrease. This situation may be cause by the interaction of FUM-B2 with ethanol molecule where FUM-B2 cannot diffused more in ethanol solvent due to the stronger hydrogen bond interaction between these two molecules. Based on the figure 5 and table 2, it shows that the diffusion coefficient, D for facet (0 0 1) > (0 1 -1) > (0 1 0) > (1 -3 1) > (1 -2 1) where this results indicate that facet (0 0 1) will diffuse first, followed by facet (0 1 -1) and the rest facets followed the order above.

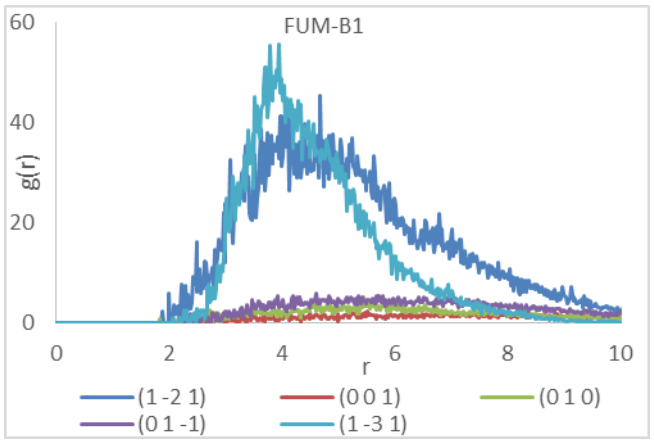


Figure 6: RDF graph of FUM-B1 molecule for each facet

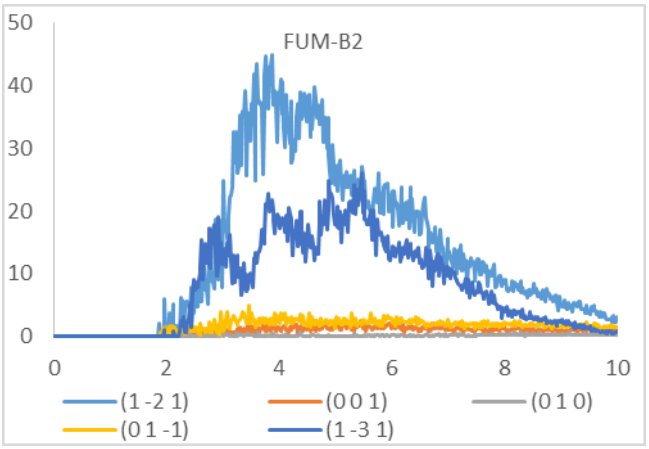


Figure 7: RDF graph for FUM-B2 molecule for each facet

RDF is used to measure specific interactions between molecules such as hydrogen bonding. It also measures the distance of probability of an atom or molecule to be found from a reference atom. Based on figure 2, light blue color molecule is a FUM-B reference molecule. It means that the distance of FUM-B and FUM-B2 from FUM-B reference molecule are calculated. This kind of distance measure the diffusion rate of FUM-B into ethanol solvent. Based on the figure 6 and 7 above, the peak also indicate the diffusion rate of crytstal molecule into solvent. The hydrogen bonds will appears betweeen molecules if the first peak is located at r < 3.5, while if the first peak is located at r > 3.5, it is due to the van der waals and coulomb interactions [15]. Based on figure 6, there is no first peak appears at r < 3.5. The first peak for facet (1 -3 1), (1 -2 1), (0 1 -1), (0 1 0) and (0 0 1) are found at radius 3.95, 4.69, 4.61, 5.45 and 6.51 respectively. From the result above, facet (1 -3 1) is the closest to the reference atom, so here means that facet (1 -3 1) has the slowest diffusion rate of FUM-B1 into ethanol solvent. Meanwhile, facet (0 0 1) has the highest diffusion rate. It can be concluded that the diffusion of molecule into ethanol solvent are following this order which is (0 0 1) > (0 1 0) > (0 1 -1) > (1 -2 1) > (1 -3 1). Eventhough facet (0 0 1) has large surface area compared to facet (1 -3 1), the diffusion rate of facet (0 0 1) is higher than facet (1 -3 1). This result shows that the diffusion rate does not depends on the surface area of facet. Besides, the first peak for FUM-B2 does appears at r < 3.5. Based on figure 7, the first peak for facet (1 -3 1), (1 -2 1), (0 1 -1), (0 1 0) and (0 0 1) are found at radius 4.89, 3.87, 3.47, 1.99 and 5.45 respectively. Based on the radius, facet (0 1 -1) and (0 1 0) should have the slowest rate of diffusion due to the presence of hydrogen bond and molecule close to the reference atom. From figure 7, the result shows that the diffusion rate of FUM-B2 into ethanol solvent for facet (0 1 0) > (0

0 1) > (0 1 -1) > (1 -3 1) > (1 -2 1). It can be seen that the result from figure 7 does not compatible with the theory of the presence of hydrogen bond (hydrogen bond interaction between crystal molecule) with r < 3.5 cause the crystal molecule having low rate of diffusion. This situation occurred because there is no interaction between ethanol molecule and crystal molecule. However, as there is interaction between FUM-B1 with ethanol molecule, from the result obtained from figure 6, figure 4 and table 1, it can be concluded that the higher the first peak, the slowest the diffusion rate of crystal molecule into ethanol solvent.

IV. Conclusion

Both MSD and RDF analysis result shows that the diffusion behaviour of crystal facet follow this following order: facet (0 0 1) > (0 1 0) > (0 1 -1) > (1 -2 1) > (1 -3 1). Basically, the slope of MSD curve is used to calculate the value of diffusion coefficient,D of crystal surface. The diffusion coefficient result shows that the diffusion behaviour of crystal facet also follow those order with value 3.866x10-9, 9.16x10-10, 1.7x10-10, 2.483x10-11 and 2.1x10-11 respectively. It can be concluded that the higher the value of diffusion coefficient, the higher the diffusion rate of facet. The analysis carried out in this research shows there is a relationship between RDF and MSD analysis since both analysis shows the same result which is the first facet to diffuse into ethanol solvent is (0 0 1) and the last facet diffused is (1 -3 1).

Acknowledgment

Thank you to my supervisor, Dr. Siti Nurul ‘Ain Yusop for her guidance, support, suggestion and recommendation in completing my final year project. Thank you also to Dr. Nornizar Anuar, Mr. Muhammad Fitri Othman and my friends for your guidance and knowledge that contributed to the completing this project and also Universiti Teknologi Mara.

References

[1] N. Blagden, M. d. Matas, P. Gavan and P. York, "Crystal engineering of active pharmaceutical ingredients to improve solubility and dissolution rates," *Advanced Drug Delivery Reviews 59,* p. 617–630, 2007.

[2] Z. Jianping, W. Aimin, G. Xuedong, C. Jingwen, C. Song and X. Feng, "Molecular Dynamics Simulation of Diffusion of Vitamin C in Water Solution," *chinese journal of chemistry,* vol. 30, pp. 115-120, 2012.

[3] S. Kalepu and V. Nekkanti, "Insoluble drug delivery strategies: review of recent advances and business prospects," *Acta Pharmaceutica Sinica B,* pp. 1-12, 2015.

[4] Y. Kawabata, K. Wada, M. Nakatani, S. Yamada and S. Onoue, "Formulation design for poorly water-soluble drugs based on biopharmaceutics classification system: Basic approaches and practical applications," *International Journal of Pharmaceutics 420,* p. 1–10, 2011.

[5] A. LEMMERER, C. ESTERHUYSEN and J. BERNSTEIN, "Synthesis, Characterization, and Molecular Modeling of a Pharmaceutical Co-Crystal: (2-Chloro-4-Nitrobenzoic Acid):(Nicotinamide)," *Journal of Pharmaceutical Sciences,* p. 4054–4071 , 2010.

[6] K. T. Savjani, A. K. Gajjar and J. K. Savjani, "Review Article: Drug Solubility: Importance and Enhancement Techniques," *International Scholarly Research Network Pharmaceutical,* pp. 1-10, 2012.

[7] R. Sharma, S. Jain and R. Tiwari, "NANOPARTICLE TECHNOLOGY: FORMULATING POORLY WATER-SOLUBLE COMPOUNDS: A REVIEW," *international journal of pharmaceutical sciences and research ,* vol. 6(1), pp. 57-71, 2015.

[8] G. Yi and O. K. W., "Molecular Dynamics of Drug Crystal Dissolution: Simulation of," *molecular pharmaceutics,* pp. 905-917, 2013.

[9] T. Chan and D. Ouyang, "Investigating the molecular dissolution process of binary solid dispersions by molecular dynamics simulations," *asian journal of pharmaceutical sciences ,* p. 248–254, 2018.

[10] R. Gholizadeh, Y. Wang and Y.-X. Yu, "Molecular dynamics simulations of stability at the early stages of silica materials preparation," *Journal of Molecular Structure,* pp. 198-207, 2017.

[11] M. Greiner, E. Elts, J. Schneider, K. Reuter and H. Briesen, "Dissolution study of active pharmaceutical ingredients using molecular dynamics simulations with classical force fields," *Journal of Crystal Growth,* p. 122–130, 2014.

[12] N. Anuar, N. S. Pauzi, S. N. ‘. Yusop, N. S. M. Azmi, S. A. Rahim and M. F. Othman, "Prediction of Carbamazepine-Succinic Acid Co-Crystal Dissolution in Ethanolic Solution using a Computational Molecular Dynamic Simulation Technique," *International Journal of Engineering & Technology,* pp. 1-7, 2018.

[13] H.-M. Shim, J.-K. Kim, H.-S. Kim and K.-K. Koo, "Molecular Dynamics Simulation on Nucleation of Ammonium Perchlorate from an Aqueous Solution," *Crystal Growth & Design,* p. 5897−5903, 2014.

[14] A. Bednowitz and P. B, "Direct Determination of the Crystal Structure of I}-Fumarie Add," *Acta Cryst,* pp. 566-571, 1966.

[15] s. hossain, A. Kabedev, A. Parrow, C. A. Bergstom and P. Larsson, "Molecular simulation as a computational pharmaceutics tool to predict drug solubility, solubilization processes and partitioning".