Study on Dissolution Behavior of Saccharin in One Molecule of Ethanol Solvent Using Molecular Dynamic Simulation

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***Abstract*— Saccharin is a Food and Drug Administration (FDA)-approved sweetener and the most popular used as co-former in producing new pharmaceutical co-crystal for the development of drug. The Molecular Dynamic (MD) method was applied to analyze the behavior of five main Saccharin crystal facets with one molecule of ethanol; (1 0 0), (1 1 0), (1 0 -2), (1 1 -1), (0 1 1). The interaction of each molecule in one unit cell of the crystal was then analyzed based on Radial Distribution Function (RDF) graph and the dissolution behavior was determined by Mean Square Displacement (MSD) graph. For the RDF analysis, the highest peak of g(r) for the facet (1 0 0), (1 1 0), (1 0 -2), (1 1 -1) are from the molecules 2 at the radius of 5.91, 5.53, 5.41 and 5.19 Å respectively while for the facet (0 1 1), the highest peak was molecule 4 (SAC m4) at radius of 4.95 Å and the interactions are mainly caused by the Coulomb and Van Der Waals.**

Keywords—Dissolution Behaviour, Molecular Dynamic Simulation, Saccharin, Solubility

I. INTRODUCTION

Pharmaceutical drug or simply called as medicine is a drug that usually used to prevent or cure a disease. It is important to have drugs with various properties such as biological properties, in the latest development of them [1]. However, a significant number of drug getting approvals have poor biopharmaceutical properties such as having a problem with poor solubility and lower bioavailability of the drug resulting in drug delivery system in the human body. Therefore, it is useful for the pharmaceutical industry to manipulate and testing the properties of drug during the drug development process [2].

There are many techniques that have been used to improve the performance characteristic of drugs such as pharmaceutical co-crystal, salt formation, micronization, emulsification, and complexation [3]. One of the most popular and gained an interest for pharmaceutical research is pharmaceutical co-crystal technique because it have an ability to improve physicochemical characteristic. Pharmaceutical co-crystal is a multi-component compound combining active pharmaceutical ingredients (APIs) and appropriate co-former with specific stoichiometric coefficient by several types of interaction [4].

The main concern in pharmaceutical industry is to enhance the physical properties of an API that can result in solubility and bioavailability of the drug. In recent study, it is shown that the co-crystal of Indometachin with Saccharin (IND-SAC) exhibits higher solubility and dissolution rates compared to IND only [5]. Thus, it is important to study the dissolution behaviour of co-former used in APIs. There are many methods can be used to study the dissolution but current common tools used in dissolution research is Molecular Dynamic Simulation (MDS). Molecular Dynamic (MD) is one of the methods used to study the physical movement of particular atoms and the interaction between the molecules [6].

Co-former is specifically selected to give advantages to the API. There was a study to investigate the thermodynamic stability and interrelationship between Form I and Form II of Carbamezapine-Saccharin (CBZ-SAC) co-crystal using thermal, solubility, and slurry methods [7]. However, there is still no study from researchers about the dissolution behaviour of Saccharin as a co-former only in ethanol solvent using Molecular Dynamic Simulation (MDS) since most of the studies are focusing on the co-crystal. Therefore, before saccharin is been used in crystallization, it is important to investigate and study its dissolution behaviour. Hence, this research is prepared to study the dissolution behaviour of saccharin in solvent while the mean square displacement (MSD) and radial distribution (RDF) analysis were conducted for the analysis.

II. METHODOLOGY

A. Molecular Structure

Saccharin (SAC) co-former structures were extracted from the Cambridge Structural Data (CSD) with reference code SCCHRN03. SAC crystal is in monoclinic structure with the cell parameters of a= 10.92421, b= 6.995268, c= 10.960487, β= 105.66894°, α and γ = 90°. The crystal consists of 4 molecules of SAC in one unit cell (Figure 1) but the molecules identification (m1, m2, m3, and m4) of Saccharin for each facet is different as the conformation arrangement of molecules in the crystal is different. There are total 18 facets of SAC crystal but only 5 facets were selected for the simulation.

B. Computational Method

The dissolution behavior of SAC was simulated using Material Studio (MS) Version 7.7 from Accelrys with the aim to study the dissolution behavior of SAC co-former in ethanol. The thickness of 2 Å was used for the SAC molecules before the vacumn slab was built. Then, set up a supercell and vacumn slab of the crystal surface to be in cubic shape by adjusting the value of U and V and the thickness of vacumn slab (Figure 2). The results were analyzed by the mean square displacement (MSD) and radial distribution (RDF) data.

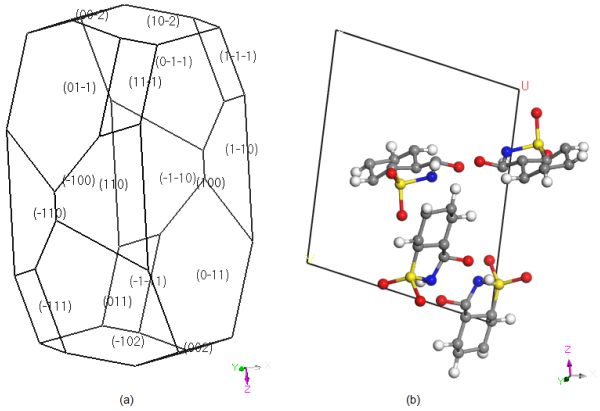


Figure 1 : Molecular structure of SAC in one unit cell

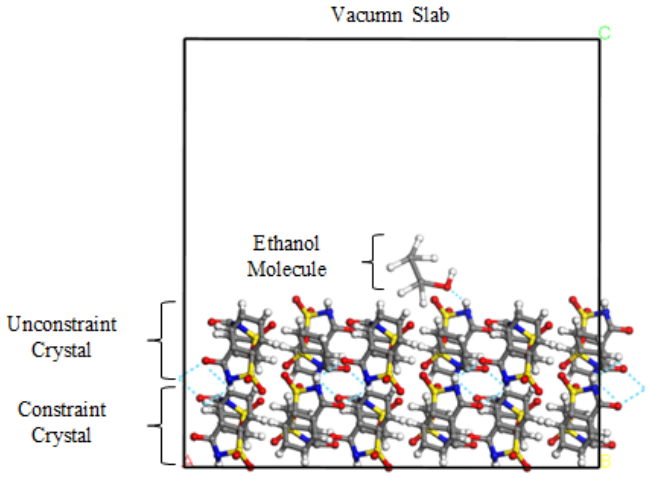


Figure 2 : SAC Crystal in Cubic ShapeVacumn Slab

C. Construction of ethanol molecule

One molecule of ethanol with density of 0.789 g/cm3 was constructed using the sketching tools available in MS. Geometry optimization is used to minimize the energy then proceed using compass forcefield. Ethanol molecule in a cell was then built using Amorphous Cell Module at 298 K. For the construction of ethanol cell, the size was based on the length and width (value of a & b) of the SAC crystal slab. Then, the ethanol molecule was inserted and allowed to be mixed in the vacuum slab containing SAC supercell surface for each main facets.

D. Energy minimization

The crystal molecules were kept constraint whilst the ethanol molecule was allowed to move for this process. The same forcefield and charge was used which is COMPASS [8] and current charge to maintain the charges from previous calculation. The process was done for each facet when the total energy of the system was reduced to a minimum which is in negative value. It is indicate that the molecules become more stable when their energy is low. The energy minimization was carried out before the dynamic simulation.

E. Molecular Dynamic run for the dissolution behavior study

After energy minimization process, dynamic simulation was conducted by unconstraint the first upper layer of the SAC crystal while the bottom layer remains constraint. This is to allow the molecules to move and interact with the ethanol molecule. The simulation was conducted for 1000 ps and 1.0 fs time steps. Nose thermostat and NVT (constant number of molecules, volume and temperature) was chosen to control the temperature. The forcefield used for the dynamic was puff with atom based calculation used for van der Waals and Ewald used for electrostatic summation method. The frame output was recorded for every 201 steps.

III. RESULTS AND DISCUSSION

A. Radial Distribution Function (RDF) analysis

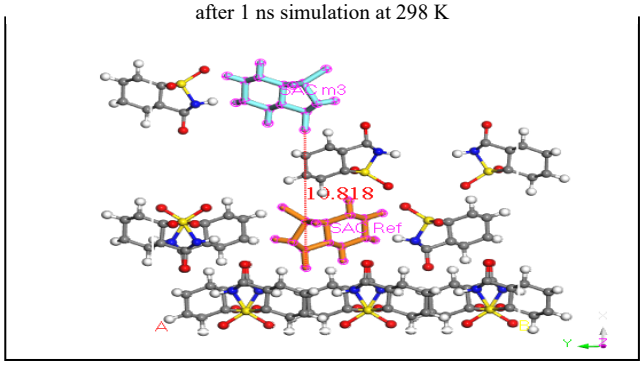
RDF helps to understand the interactions of the atoms present for small molecules in a system and the increasing in intensity of RDF is correlated to the more loosely packed atomic structure [9]. One of the studies from Samanta, they used RDF in analysing the interaction of six polymeric DNA sequence in Molecular Dynamic [10]. Figure 4 (a) – (e) shows the radial distribution function, g(r) versus distance with respect to the four molecules in one unit cell of the facets.

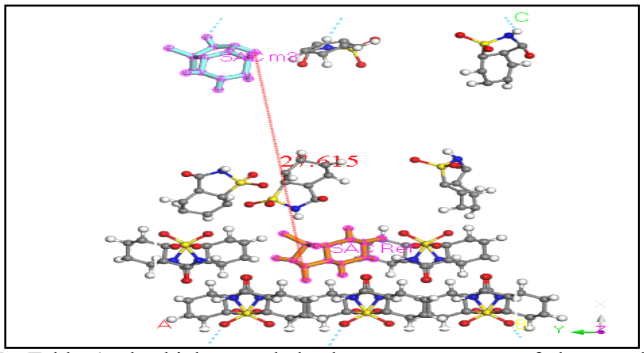
Table 1 : Percentage of the travel molecules in each facet

Molecule	Percentage of the travel molecules (%)				
	(1 0 0)	(1 1 0)	(1 0 -2)	(1 1 -1)	(0 1 1)
m1	15.25	5.27	2.81	67.83	25.34
m2	20.13	14.58	32.53	5.01	24.60
m3	60.83	7.95	39.38	17.81	0.41
m4	1.69	28.52	4.01	1.52	11.82

(a) 0 ns
(b) 1 ns

Figure 3 The detachment of SAC m3 from SAC reference in facet (1 0 0) after 1 ns simulation at 298 K





In Table 1, the highest and the lowest percentage of the travel molecules after 1 ns were 67.83% and 0.41% from facet (1 1 -1) and (0 1 1), respectively. The example of travel molecule was shown in the Figure 3 and Figure 5. In Figure 3, the molecule 3 (blue) was seen to be far from the reference atom (orange) after the simulation with the distance of 10.818 Å at 0 ns in 3(a) and 27.615 Å after 1 ns (60.83%) in 3(b). In comparison with SAC m2 in facet (1 0 0) (Figure 5), the distance becomes closer to the SAC reference after 1 ns of simulation. At 0 ns in Figure 5(a), the SAC m2 was 11.533 Å from the SAC Ref and the distance become 9.211 Å after 1 ns in Figure 5(b) which is 20.1% reduction.

Referring to Fig 4, the curve were zero at early stage means that

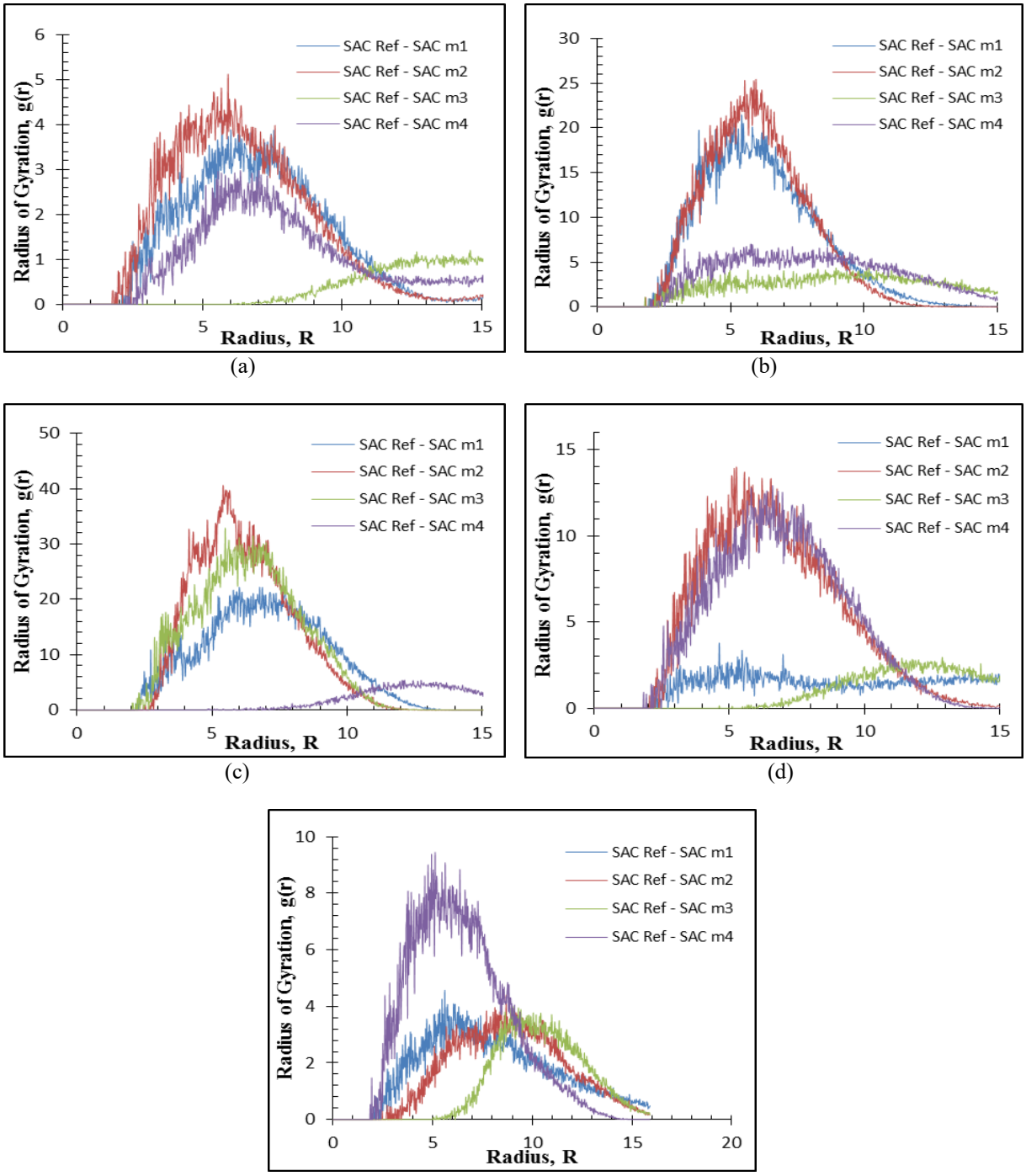
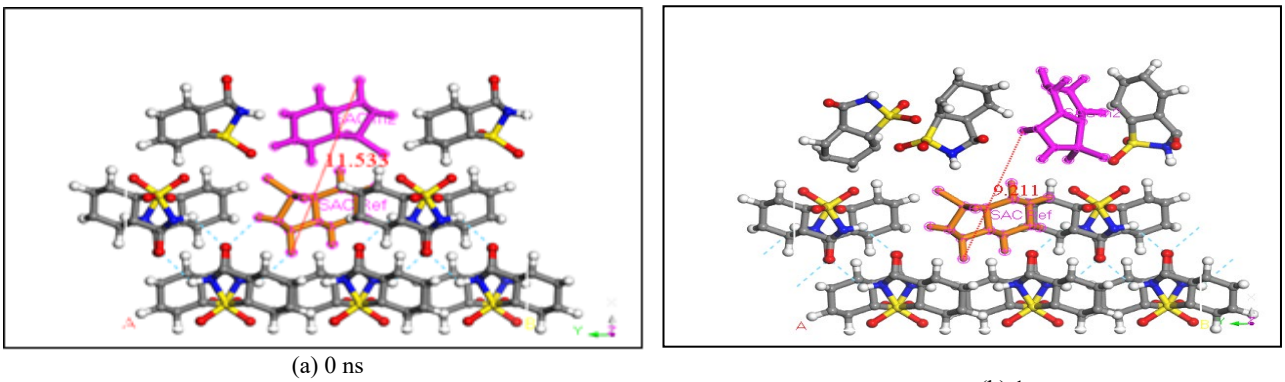


Figure 4 : Radial Distribution Function (RDF) for each molecule in each facet ; (a) (1 0 0), (b) (1 1 0), (c) (1 0 -2), (d) (1 1 -1) and (e) (0 1 1)



(a) 0 ns

(b) 1 ns

Figure 5 : The detachment of SAC m2 from SAC reference in facet (1 0 0) after 1 ns simulation at 298 K

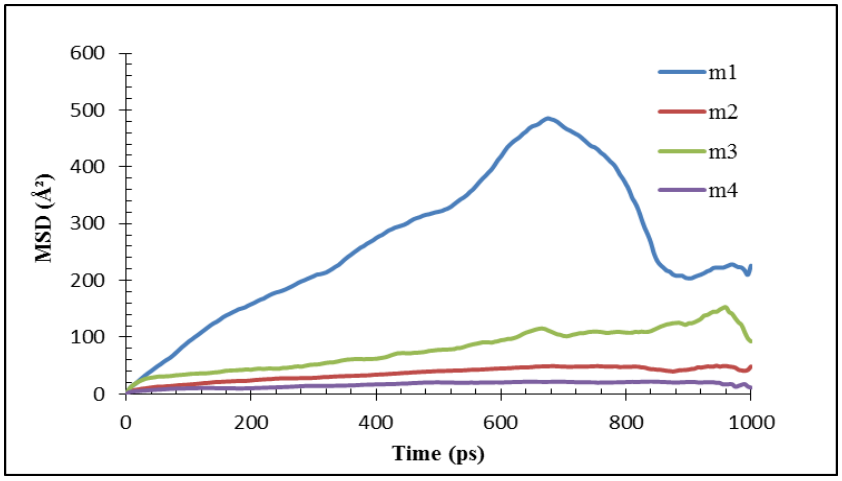


Figure 6: Motion behavior of each molecule in (1 1 -1) SAC facet

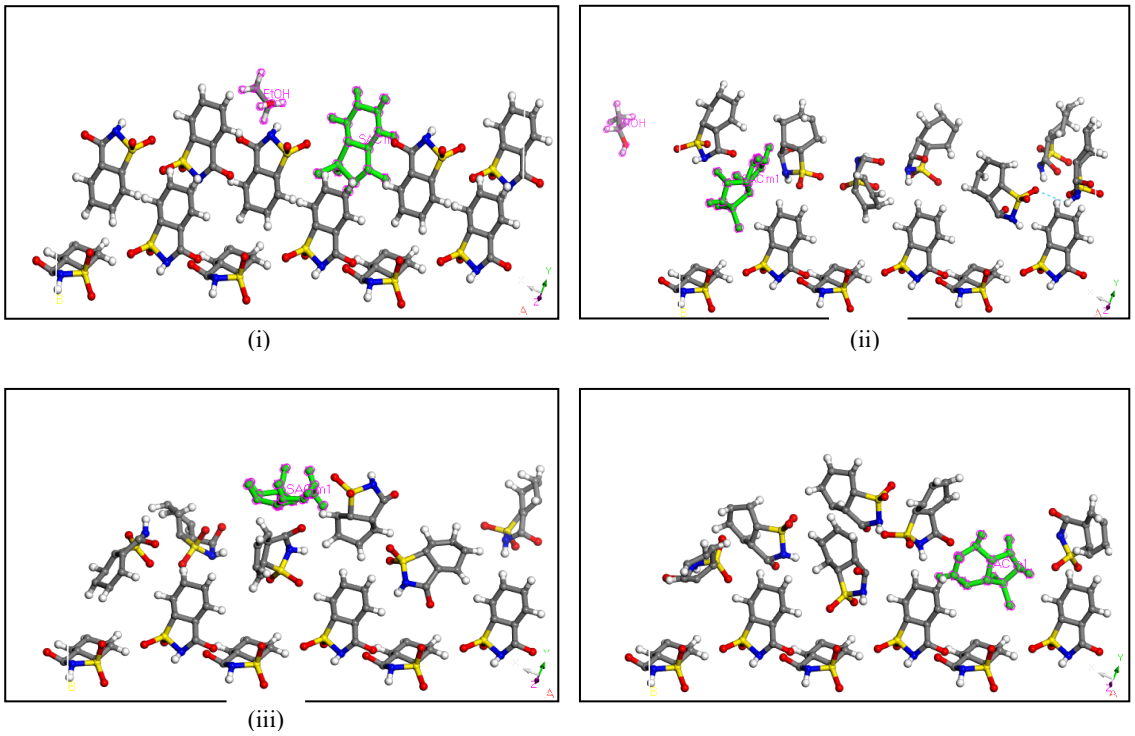


Figure 7 : The movement of molecule 1 facet (1 1 -1) of SAC at different number of frame in 1000 ps simulation; (i) 0, (ii)100, (iii)150, and (iv) 201 of frame number

the atoms could not approach closely until some peaks appeared which showed that the molecules pack around each other [11]. It is observed that no peaks occurred below the radius of 3.5 Å for all molecules in each facet because there is no hydrogen bond found. All of the Saccharin molecule 1, 2, 3 and 4 (SAC m1, m2, m3 and m4) for each facet shows the higher peaks for above 3.5 Å in radius and it is mainly caused by the Coulomb and Van Der Waals interaction [12, 13]. Based on the studied by Jing Lu et al, they also used the RDF analysis to illustrate the distribution of water layers around the 2, 3, and 4 nm of nanoparticles [14].

Furthermore, the RDF analysis also measures the detachment of the molecules from its crystal lattice. The lowest peak means that the molecule was easily to detach and it is measured by the peak from the radius of gyration g(r) because radius of gyration is defined as the distribution of atoms around its axis [9]. From Figure 4, the highest peak of g(r) for the facet (1 0 0), (1 1 0), (1 0 -2), (1 1 -1) are from the molecules 2 at the radius of 5.91, 5.53, 5.41 and 5.19Å respectively. For the facet (0 1 1), the highest peak was molecule 4 (SAC m4) at radius of 4.95 Å. From the observation also, the lowest peak was found for molecule 3 from facet (1 0 0). It means that the molecule 3 was far from the reference atom compared to other molecules after 1 ns.

B. Mean Square Displacement (MSD) Analysis

The analysis of MSD is one of an important tool to characterize the properties of irregular diffusion processes [15]. It is determined based on the position of particles over time. Each molecule in five main crystal facets was considered for the analysis. The value of diffusion coefficient of molecule 1, 2, 3 and 4 for each facet are as tabulated in Table 2 below. The molecules were calculated based on the slope of the MSD curves because it is proportional to the diffusion coefficient of the diffusing atoms [11].

According to the Table 2 below, the highest and the lowest value of diffusion coefficient were 26.64×10^{-10} and -0.007×10^{-10} which are referring to SAC m1 facet (1 1 -1) and SAC m4 facet (0 1 1), respectively. Figure 6 above shows the MSD as a function of simulation time for each molecule in (1 1 -1) SAC facet. For m1 facet (1 1 -1), the motion behavior of molecule increases as the time increases from 0 to 680 ps, while the motion decreases slowly during the end of simulation time.

Table 2 : Diffusion Coefficient of each molecules of SAC crystal facet at 0 to 1000 ps

Molecule	Diffusion, D x 10^{-10} (m2/s)				
	(1 0 0)	(1 1 0)	(1 0 -2)	(1 1 -1)	(0 1 1)
m1	14.74	3.83	-0.08	26.64	9.74
m2	1.97	0.72	0.16	3.85	0.78
m3	18.15	5.26	1.99	11.79	0.56
m4	5.91	5.03	39.5	1.42	-0.007

The m1 for the facet (1 1 -1) has the largest D value while the m4 of facet (0 1 1) has the least D value which indicates that the ethanol and SAC molecules diffuses more on facet (1 1 -1) [16]. This result also supported by the previous researchers, where their results indicate that trifluoroacetic acid molecules diffuse more easily on (1 1 0), (1 0 -1) and (1 0 0) facet because the diffusion coefficient of the solvent on (1 1 0), (1 0 -1) and (1 0 0) faces was about 2 times larger than that on the (1 1 -2) facet [17].

The visual observations in Figure 7 above help to support the finding for MSD curve. It shows the movement of molecule 1 (green) for the facet (1 1 -1) in total of 201 frame number. At 0 frame number, the molecule was at the original place and it moves around the other molecules that can be seen in Figure 7 (ii). As the time increase, the MSD (Figure 6) also increases until it decreases back after 680 ps. The trend shows similar observation with the visual observation where at 0 to 100 frame number, the molecule moves apart from its original place and the molecule moves back near to its original place after 150 to 201 frame numbers.

IV. CONCLUSION

Molecular dynamic simulation was performed to investigate the dissolution behavior and the interaction of the molecules for each facet of Saccharin. The study was based on four molecules in the five main facet of (1 0 0), (1 1 0), (1 0 -2), (1 1 -1) and (0 1 1). In conclusion, the RDF analysis has shown that no peaks occur below the radius of 3.5 Å for all molecules in each facet and mainly caused by the Coulomb and Van Der Waals interaction. The highest peak of g(r) for the facet (1 0 0), (1 1 0), (1 0 -2), (1 1 -1) are from the molecules 2 at the radius of 5.91, 5.53, 5.41 and 5.19 Å respectively while for the facet (0 1 1), the highest peak was molecule 4 (SAC m4) at radius of 4.95 Å. The MSD results concluded that the molecule 1 (1 1 -1) facet had the largest D value while disproportionally, the molecule 4 (0 1 1) facet had the least D value.

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