Prediction of Dissolution Behavior of Carbamazepine-Saccharin Co-Crystal Using Molecular Modelling Technique

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***Abstract*— The carbamazepine-saccharin (CBZ-SAC) co-crystal has poor bioavailability in pharmaceutical industry. To treat the issue to improve the bioavailability, the development of the co-crystal has been developed. To investigate the dissolution rate of co-crystal, simulation software has been used. In this study, the dissolution behavior of CBZ-SAC in ethanol was investigated using dynamic simulation by considering the transport properties of both co-crystal and solvent. In analyzing mean square displacement (MSD), high diffusion coefficient is obtained when solvent mobility increases and thus, the dissolution rate become higher. The rank of the diffusion coefficient by each facet are as follows: (0 0 1)> (1 1 -1)> (1 0 -1)> (0 1 0)> (1 0 0). In analyzing the radial distribution function (RDF) of CBZ-SAC in ethanol solution on 5 facets showed that each facet has different molecular interactions due to detachment of molecules from its crystal lattice of the respective facets. High intensity g (r) lead to higher dissolution rate as co-crystal molecules attracted to the solvent molecules.**

***Keywords*— Carbamazepine; co-crystallization; dissolution; molecular dynamic simulation; morphology; solubility; Carbamazepine-saccharin; surface chemistry.**

I. INTRODUCTION

Poor dissolution rate and solubility are a major concern in pharmaceutical industry for the development of new compounds as it can impact on bioavailability. To improve the problem, several strategies have been developed and one of them are cocrystallization.[1,2] Cocrystallization is the formation of co-crystal through hydrogen bonding between a hydrophobic drug and hydrophilic coformer. The application of co-crystal can be found in medicine and pharmaceutical industry for improving different properties. The properties can include the dissolution rate, melting point, solubility and chemical stability.[3]

The definition of co-crystal is a stoichiometric multi-component system which connected by non-covalent interactions which formed between a molecular or ionic API (Active Pharmaceutical Ingredience) and present in solid form under ambient conditions.[3–5] The function of co-crystal former in the pharmaceutical industry is helping the active drug to disintegrate into small particles so that the drug can be transported in the blood stream to where the drug intended to without effect the product's stability.[4]

Carbamazepine (CBZ) is an active API used in pharmaceutical industries as an anticonvulsant for treatment of epilepsy and trigeminal neuralgia. CBZ is belong to the biopharmaceutics classification system (BSC) class II which have low solubility and high permeability. CBZ also practically insoluble in water and has dissolution limited bioavailability.[4,6,7] Some commonly used co-formers to produce co-crystals are succinic acid, nicotinamide, salicylic acid, adipic acid, fumaric acid, succinic acid, saccharin acid and etc.[6] In this investigation, the carbamazepine-saccharin co-crystal is formed from carbamazepine (CBZ) and co-former of saccharin (SAC). This co-crystal molecular units in the stoichiometric ratio 1:1 linked through the bonds. CBZ-SAC co-crystal exists in 2 polymorphs, form I (FI) and form II (FII). [7–9]

The carbamazepine-saccharin (CBZ-SAC) co-crystal has poor bioavailability in pharmaceutical industry. To treat the issue to improve the bioavailability, the development of the co-crystal has been developed. Dissolution in the drug absorption process is where the drug molecules detach itself from the solid crystal particles and released into the surrounding gastrointestinal (GI) environment. It makes dissolution rate fundamentally important in designing pharmaceutical dosage form. Furthermore, the understanding on the molecular dissolution mechanism of solid dispersions remains unclear, even when there are many well-established reports and extensive pharmaceutical investigation conducted in the past years.[6]

So, to investigate the dissolution rate of co-crystal, simulation software has been used. Computational simulation had been a great help in crystallization study where the dissolution rate and also other crystal properties such as morphology given the condition of the research software for computational chemistry, bioinformatics, cheminformatics, molecular dynamics simulation, and quantum mechanics can be predicted. Software used for this research is Materials Studio 7.0, a software version of Accelrys for simulating and modelling materials. [6,10,11]

Dynamic simulation was used to investigate the dissolution behaviour of co-crystal in solvent, while mean square displacement (MSD) and radial distribution (RDF) analysis was conducted after a successful dynamic run. MSD data was used to calculate the diffusion coefficient, D. The diffusion coefficient, D was calculated from the slope of the linear part of the MSD versus t curve. RDF was being analyzed to identify type of interaction between co-crystal and the solvent.[6]

II. METHODOLOGY

2.1 Detail of Crystal Structure

The model of crystal structures of carbamazepine-saccharin (CBZ-SAC) co-crystal, were retrieved from the Cambridge Structural Data (CSD) with the reference code of UNEZAO. CBZ-SAC crystallizes in a monoclinic lattice with space group P .1, with cell parameters of a=7.53 Å, b = 11.15 Å, c = 15.47 Å, α= 83.6°, β= 85.7°, and γ = 75.4°. CBZ-SAC co-crystal is packed with two molecules of carbamazepine (CBZ) and two molecules of saccharin (SAC) in a unit cell (Fig. 1). Both saccharin molecules are

packed in the between two carbamazepine molecules of crystal lattice structure. Both saccharin molecules forms hydrogen bond with the hydrophilic part of carbamazepine molecules while the hydrophobic part of CBZ molecules are facing another hydrophobic part of CBZ molecules. The hydrophobic region interactions are only associated with van der Waals interaction.[12]

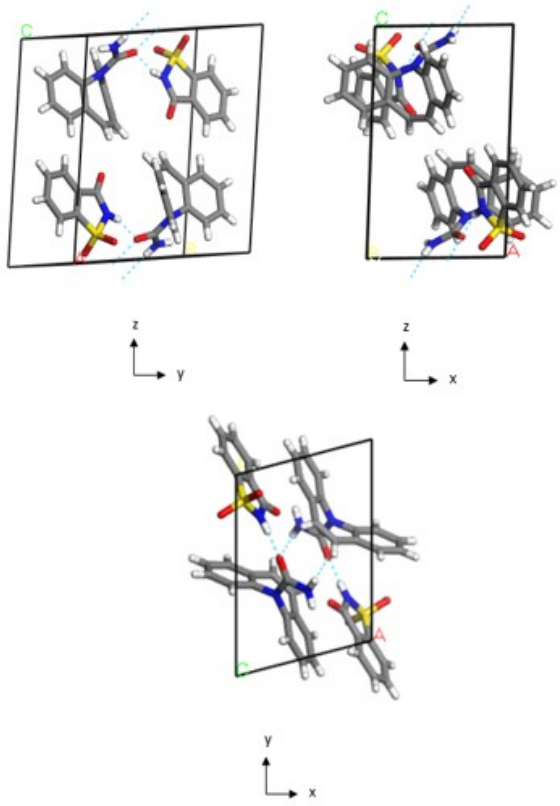


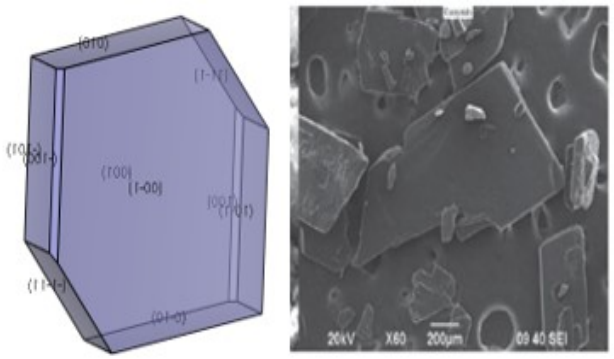
Figure 1: Molecular structure of CBZ-SAC crystal lattice in (a) x-direction, (b) y-direction and (c) z-direction.[12]

2.2 Computational methods

Molecular modelling of carbamazepine-saccharin acid (CBZ-SAC) co-crystal morphology and the dissolution behavior of CBZ-SAC in ethanol was simulated using Material Studio (MS) software version 7.0 from Accelrys. The aim to predict the dissolution behavior of CBZ-SAC co-crystal in ethanol, by looking into the mean square displacement (MSD), diffusion coefficient and also the radial distribution function (RDF) data.

Carbamazepine-saccharin (CBZ-SAC) co-crystal morphology

The predicted crystal morphology of CBZ-SAC co-crystal as shown in Figure 2. The predicted CBZ-SAC morphology shows a plate-like shape with 10 facets. Based on the morphology, the dominant facets are (0 0 1) and (0 0 -1) followed by facets (1 0 0) and (-1 0 0), while facets (0 1 0), (0 -1 0), (1 0 -1), (-1 0 1), (1 1 -1) and (-1 -1 1) are the minor facets of CBZ-SAC crystal structure. [12]



(a) (b)

Figure 2: (a) The predicted morphology of CBZ-SAC co-crystal and (b) experimental morphology of CBZ-SAC co-crystal [12]

Table 1 shows the 5 dominant crystal facets, which comprise of facets (0 0 1), (1 0 -1), (1 1 -1), (0 1 0) and (1 0 0). These facets have been chosen based on growth morphology analysis.

Table 1: Parameters of main crystal facets of CBZ-SAC co-crystal

facet	multiplicity	*d*-spacing	Attachment energy, (kcal/mol)	Slice energy, (kcal/mol)
(0 1 0)	2	10.0597	-41.52	-44.04
(0 0 1)	2	13.6103	-17.80	-55.90
(1 0 0)	2	7.4341	-47.47	-41.06
(1 0 -1)	2	7.1769	-24.51	-52.54
(1 1 -1)	2	6.4770	-40.78	-44.41

2.3 Construction of 3D periodic structures of ethanol

Ethanol molecule was constructed using the sketching tools available in MS. The structure underwent geometry optimization and minimization energy procedures using Dreiding force field. Then, a cell containing 1 molecules of ethanol was built using Amorphous Cell module. The size of ethanol size will be constructed based on the length and width of CBZ-SAC crystal slab. CBZ-SAC supercell crystal surface is in the vacuum slab. Then, ethanol molecules will be inserted. Ethanol molecules will undergo geometry optimization.

2.4 Geometry optimization of the periodic system.

The system was subjected to geometry optimization using the same forcefield as the morphology of the CBZ- SAC co-crystal used. In this case, Dreiding forcefield and current charges were used to maintain the charges from previous calculation. Atom based calculation was selected for the electrostatic and van der Waals summation method. This process sought to find the geometry of a particular arrangement of the atoms where the total energy of the system was reduced to a minimum.

2.5 Carbamazepine-saccharin acid (CBZ-SAC) co-crystal morphology prediction

Every facet of the predicted morphology of CBZ-SAC co-crystal was cleaved and extended to a 3D periodic superstructure, where the cell was extended to 3 times repetition in U or V direction depending on the configuration of the molecules on the chosen facet. Vacuum slab with the thickness of 50 Å was built above the crystal surface, to remove the additional free boundaries effect on the structure. The crystal packing diagram of CBZ-SAC as in Figure 3.

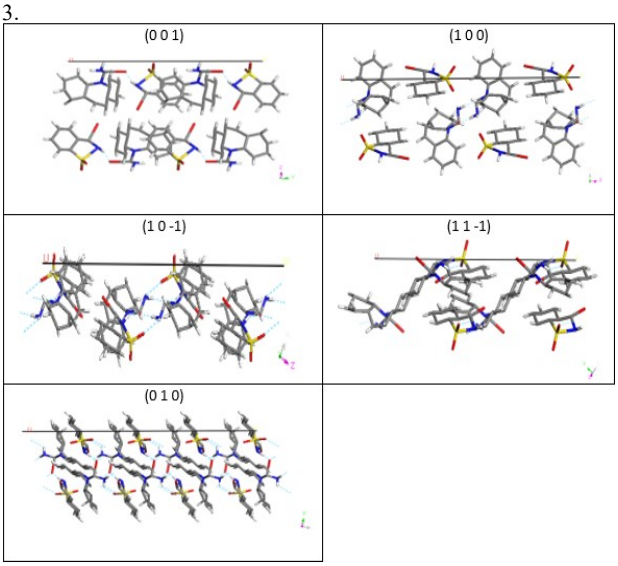


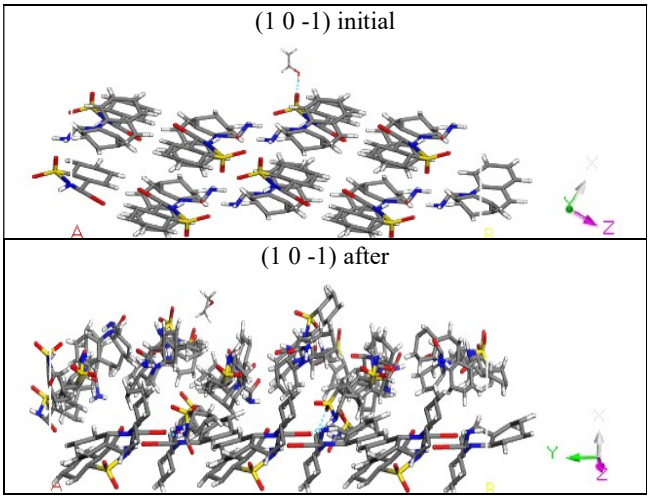
Figure 3: Crystal packing diagram of CBZ-SAC co-crystal illustrating the surface chemistry of crystal habit facets [12]

2.6 Molecular dynamics run for dissolution assessment for the periodic systems

Dynamic simulation was conducted after geometry optimization. Dynamic simulation was conducted for 1 ns with medium quality, 1 fs time step and the frame output were recorded for every 100 steps. Nose-Hoover thermostat was used to control the temperature and NVT (constant number of molecules, constant volume and constant temperature) ensemble was chosen. Universal forcefield with atom-based calculation was used for both the electrostatic and van der Waals summation method.

III. RESULTS AND DISCUSSION

3.1 Dissolution behaviour of CBZ-SAC in ethanol solution



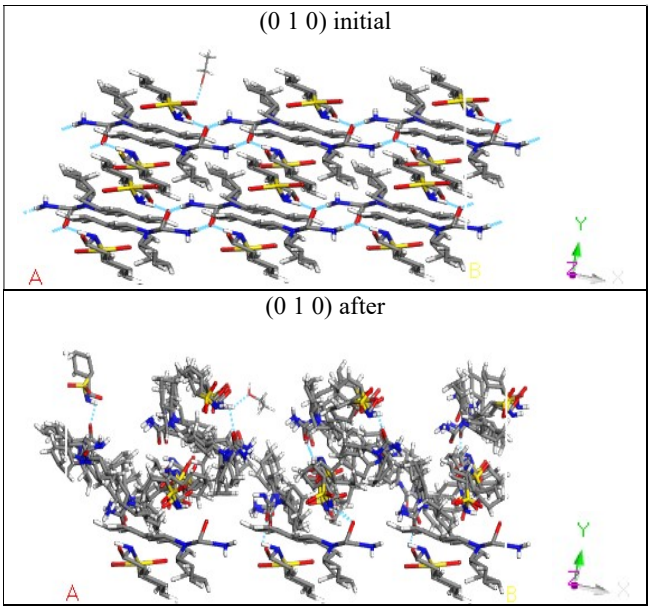


Figure 4: Interaction of CBZ-SAC co-crystal facet (1 0 -1) and (0 1 0) at initial and after dynamic simulation at 1 ns.

The interaction between CBZ-SAC co-crystal and ethanol as a solvent was conducted by running a molecular dynamic of 1ns total simulation time and summation method of Atom-based for both electrostatic and van der Waals interaction. Based on Figure 4, ethanol molecules disperse and come into contact with the co-crystal. It shows the dissolution of the CBZ-SAC co-crystal molecules in ethanol. The molecules of the co-crystal at the bottom are moving out from its original position to interact with the ethanol molecule.

The dissolution rate of co-crystal is supposed to be higher than its parent drug which is carbamazepine and it is more stable in most of dissolution medium based on the study of kinetic solubility.[13] However, the dissolution rate of the co-crystal is different in several media and is depending on its dissociation behaviour of the co-crystal into a medium of which it will be dissolved.[14] Apart from that, this phenomenon may occur because of the solvent solubilisation ability is different for certain compounds. Therefore, it can be concluded that the dissolution behaviour of CBZ-SAC co-crystal in ethanol is lower. [15]

3.2 Mean square displacement analysis

Molecular dynamic simulation was performed to model the effect of ethanol on the CBZ-SAC co-crystal morphology. It was carried out to study the interaction between crystal surface and ethanol solvent. The surface of the CBZ-SAC co-crystal inside the vacuum slab for 1 ns using dynamic simulation. After a successful dynamic simulation, the data was extracted and analysis of the trajectory data was conducted. The data was analyzed to determine the transport properties of the crystal surface. [2] Five main crystal facets were selected. The interactions were being analyzed between a rigid crystal molecule as a reference point, and molecules of 1-unit cell in the crystal surface in each facet for the mean square displacement (MSD) Figure 5,6,7,8 and 9. From the MSD trend shows the motion behavior of the crystal surface and it differs as the time increases. MSD curves show a good linearity at time < 800 ps and the linearity of some of the graph starts to become poor after 800 ps. At time < 10 ps the molecules of all facets move at the same rate and the same frequency. After 10 ps, the movement of the molecules starts to differ depending on the crystal facet.

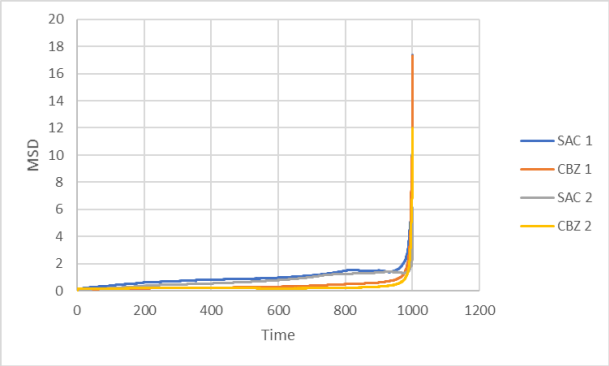


Figure 5: Motion behavior of 1-unit cell CBZ-SAC co-crystal of (1 0 -1) facet from mean square displacement (MSD) (Å^2) at different time (ps)

Table 2: Diffusion coefficient (D) of 1-unit cell (1 0 -1) crystal facet at time 1000ps

Molecule	D $\times 10^{-12}$ m^2/s
SAC 1	2.83
CBZ 1	1.67
SAC 2	2.33
CBZ 2	0.833

Facet of (1 0 -1) is a small facet at the edges of top of crystal structure. Interpretation of MSD lines in figure 4 shows that the highest diffusivity coefficient, D is molecule SAC 1. The higher diffusion coefficient value indicates a stronger movement of molecules and vice versa. The rank of the diffusion coefficient is CBZ 2< CBZ 1< SAC 2< SAC 1.

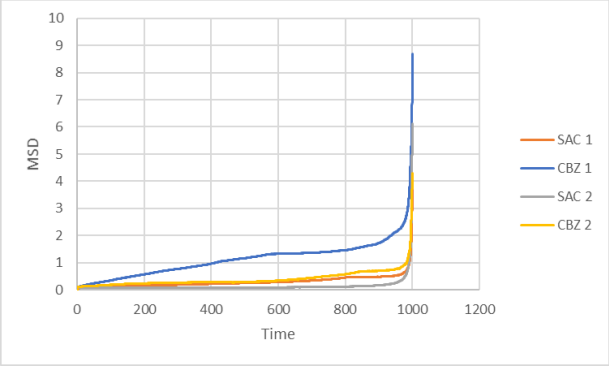


Figure 6: Motion behavior of 1-unit cell CBZ-SAC co-crystal of (1 1 -1) facet from mean square displacement (MSD) (Å^2) at different time (ps).

Table 3: Diffusion coefficient (D) of 1-unit cell (1 1 -1) crystal facet at time 1000ps

Molecule	D $\times 10^{-12}$ m^2/s
SAC 1	1.00
CBZ 1	3.33
SAC 2	0.50
CBZ 2	1.17

Facet of (1 1 -1) is a small facet at the edges of bottom of crystal structure. Interpretation of MSD lines in figure 5 shows that the highest diffusivity coefficient, D is molecule CBZ 1. Higher diffusion slope indicates higher displacement increment and hence stronger movement of molecules. The rank of the diffusion coefficient is SAC 2< SAC 1< CBZ 2< CBZ 1.

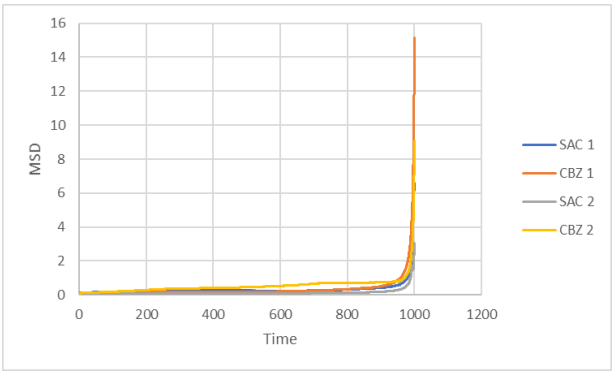


Figure 7: Motion behavior of 1-unit cell CBZ-SAC co-crystal of (0 1 0) facet from mean square displacement (MSD) (Å^2) at different time (ps).

Table 4: Diffusion coefficient (D) of 1-unit cell (0 1 0) crystal facet at time 1000ps

Molecule	D $\times 10^{-12}$ m^2/s
SAC 1	0.833
CBZ 1	1.67
SAC 2	0.50
CBZ 2	1.67

Facet of (0 1 0) is a small facet at the bottom of crystal structure. Interpretation of MSD lines in figure 6 shows that the highest diffusivity coefficient, D is molecule CBZ 1. The higher diffusion coefficient value indicates a stronger movement of molecules and vice versa. The rank of the diffusion coefficient is SAC 2< SAC 1< CBZ 2< CBZ 1.

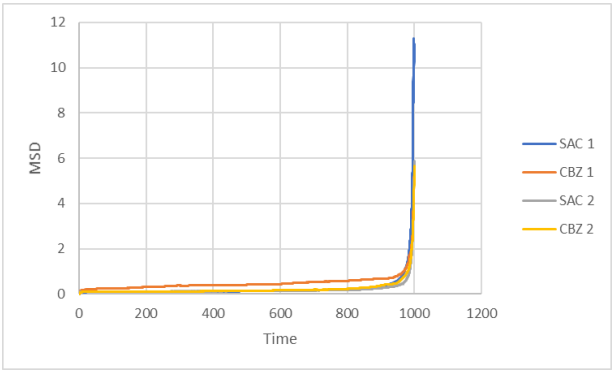


Figure 8: Motion behavior of 1-unit cell CBZ-SAC co-crystal of (1 0 0) facet from mean square displacement (MSD) (Å^2) at different time (ps)

Table 5: Diffusion coefficient (D) of 1-unit cell (1 0 0) crystal facet at time 1000ps

Molecule	D $\times 10^{-12}$ m²/s
SAC 1	1.33
CBZ 1	1.17
SAC 2	0.667
CBZ 2	0.833

Facet of (1 0 0) is a small facet at the edges of top of crystal structure. Interpretation of MSD lines in figure 7 shows that the highest diffusivity coefficient, D is molecule SAC 1. Higher diffusion slope indicates higher displacement increment and hence stronger movement of molecules. The rank of the diffusion coefficient is SAC 2< CBZ 2 < CBZ 1 < SAC 1.

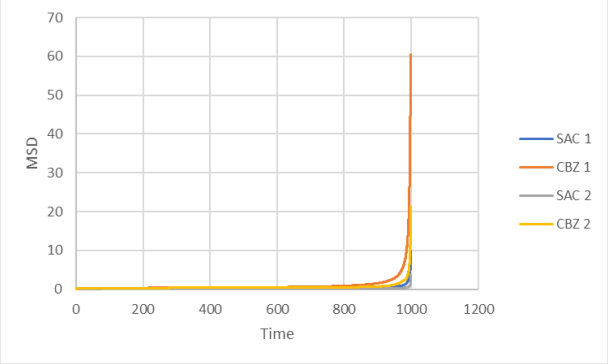


Figure 9: Motion behavior of 1-unit cell CBZ-SAC co-crystal of (0 0 1) facet from mean square displacement (MSD) (Å²) at different time (ps).

Table 6: Diffusion coefficient (D) of 1-unit cell (0 0 1) crystal facet at time 1000ps

Molecule	D $\times 10^{-12}$ m²/s
SAC 1	3.00
CBZ 1	6.50
SAC 2	0.333
CBZ 2	2.00

Facet of (0 0 1) is a dominant facet of crystal structure. Interpretation of MSD lines in figure 8 shows that the highest diffusivity coefficient, D is molecule CBZ 1. The higher diffusion coefficient value indicates a stronger movement of molecules and vice versa. The rank of the diffusion coefficient is SAC 2< CBZ 2 < SAC 1< CBZ 1.

Table 7: Diffusion coefficient (D) of main CBZ-SA crystal facet

Facet	D $\times 10^{-12}$ m²/s
(1 0 -1)	2.83
(1 1 -1)	3.33
(0 1 0)	1.67
(1 0 0)	1.17
(0 0 1)	6.50

From the analysis in table 7, it can be concluded that the diffusion coefficient of facet is in the following order: (0 0 1)> (1 1 -1)> (1 0 -1)> (0 1 0)> (1 0 0). The result indicates that the molecules of facet (0 0 1) are the first to diffuse to ethanol solvent, followed by the molecules of facet (1 1 -1) and the rest of the molecules following the order above.

3.3 Radial distribution function analysis

The radial distribution function (RDF) was being analyzed to identify type of interaction between co-crystal and the solvent. The graph of g(r) versus r measure the existence of an atom at an arbitrary reference frame origin, that there will be an atom with its center to be found in a spherical shell of infinitesimal thickness at a distance, r, from the reference atom. The RDF of CBZ-SAC for four different molecules in each 5 facets is shown in figure 10,11,12,13 and 14. The peak at lower than 3.5Å indicates the contribution of hydrogen bonding while the peak higher than 3.5 Å is mainly consists of Coulomb and van der Waals forces. [16]

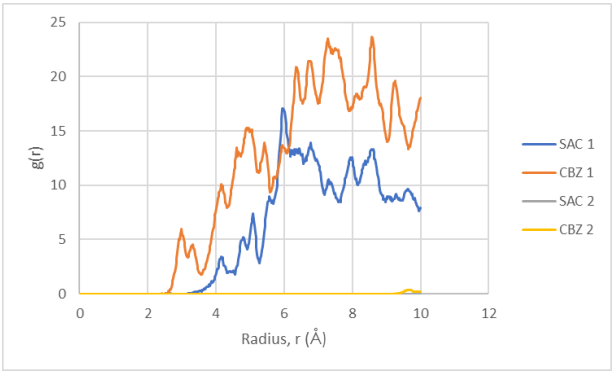


Figure 10: RDF of CBZ-SAC in ethanol solvent in (1 0 -1) facet

From figure 10 shows that the peak of molecules SAC 1, CBZ 2 are between 4.17 Å to 5.65 Å which indicate that the main interactions exist are van der Waals and Coloumbic forces. The peak of molecule CBZ 1 is 2.99 Å which indicates that the main interactions exist is the hydrogen bonding. SAC 2's curve is zero meaning that the atoms could not attracted closely to each other.

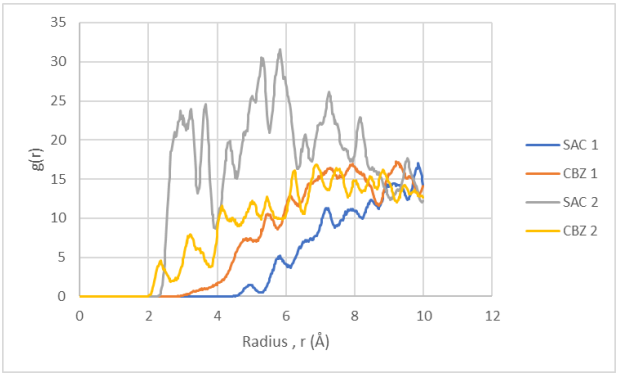


Figure 11: RDF of CBZ-SAC in ethanol solvent in (1 1 -1) facet

From figure 11 shows that the peak of molecule SAC 2 and CBZ 2 are in between 2.37 Å to 2.75 Å which indicate that the main interactions exist are hydrogen bonding. While for peak of molecules SAC 1 and CBZ 1 are 4.97 Å which indicate that the main interactions exist are van der Waals and Coloumbic forces.

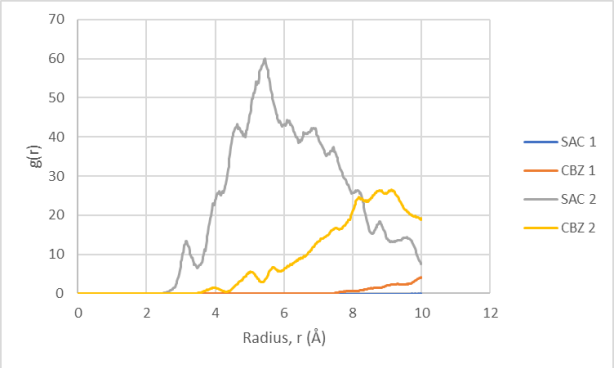


Figure 12: RDF of CBZ-SAC in ethanol solvent in (0 1 0) facet

From figure 12 shows that the peak for molecule SAC 2 is 3.17 Å indicates the contribution of hydrogen bonding. While for molecule SAC 1, CBZ 1 and CBZ 2 are in between 3.71 Å to 8.07 Å which indicate that the main interactions consist of Coulomb and van der Waals forces

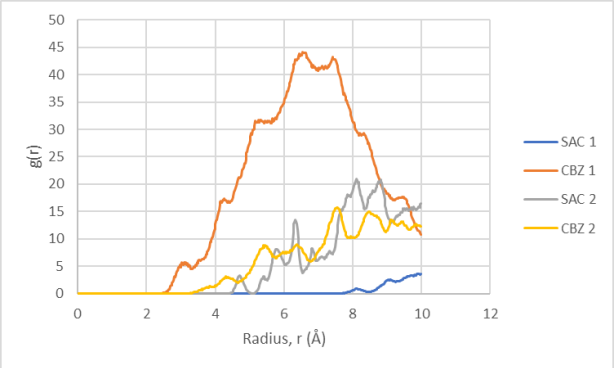


Figure 13: RDF of CBZ-SAC in ethanol solvent in (1 0 0) facet

From figure 13 shows that the peak for molecule CBZ 1 is 3.03 Å indicates the contribution of hydrogen bonding. While for molecule SAC 1, CBZ 2 and SAC 1 are in between 4.31 Å to 8.05 Å which indicate that the main interactions exist are van der Waals and Coloumbic forces.

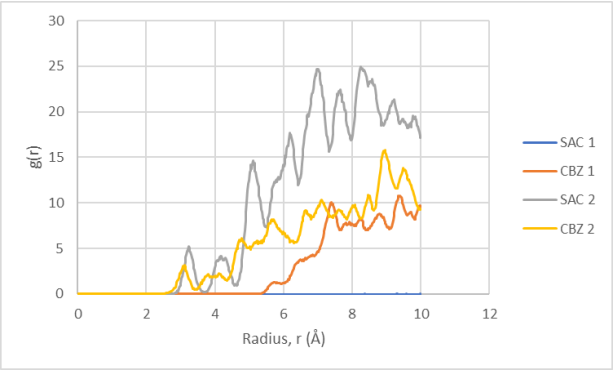


Figure 14: RDF of CBZ-SAC in ethanol solvent in (0 0 1) facet

From figure 14 shows that the peak for molecule SAC 2 and CBZ 2 is 3.23 Å and 3.11 Å respectively indicates the contribution of hydrogen bonding. For molecule SAC 1 and CBZ 1 are in between 5.45 Å to 5.73 Å which indicate that the main interactions exist are van der Waals and Coloumbic forces.

From all 5 facets of RDF result shows some peaks that show in the region of neighbour shells, the atoms approach closely and pack to each other. Then, the RDF's curve tends to downward indicates that the atoms are distributed randomly. The dissolution becomes easier when the intensity g (r) is higher as the simulation time increases. This is because the co-crystal molecules attracted to the solvent molecules as the density is higher. Facet (0 1 0) is the closest to the reference atom and the respective peak indicates the first atom/molecule found from the reference atom. Thus, from the analysis, it can be concluded that the diffusion of molecules from the facets is in the following order: (1 1 -1)< (0 0 1)< (1 0 -1)< (1 0 0)< (0 1 0)

IV. Conclusion

In conclusion, the mean square displacement (MSD) analysis through the diffusion coefficient showed that the diffusion of molecules from crystal facets were from the following order which suggested the order of strongest to the weakest movement of molecules: (0 0 1)> (1 1 -1)> (1 0 -1)> (0 1 0)> (1 0 0). Higher diffusion slope indicates higher displacement increment and hence stronger movement of molecules. Other than that, the radial distribution function (RDF) of CBZ-SAC in ethanol solution on 5 facets showed that each facet has different molecular interactions due to detachment of molecules from its crystal lattice of the respective facets. High intensity g (r) lead to higher dissolution rate as co-crystal molecules attracted to the solvent molecules.

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