Prediction of Carbamazepine-Succinic Acid Co-Crystal Dissolution in Ethanolic Solution Using a Computational Molecular Dynamic Simulation Technique

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Abstract— Co-crystallization process that comprise of APIs drug and co-crystal conformer (CCFs) is one of the method that is proven can improve the performance of the drugs in term of solubility, bioavailability, flow properties, thermal stability, and filterability [1]. In this study, co-crystal of Carbamazepine- Succinic acid (CBZ-SA) was used. The purpose of this study is to predict morphology of CBZ-SA cocrystal in vacuum and to access the dissolution behavior of CBZ-SA in ethanol solvent. The materials used in this study are (CBZ-SA) cocrystal and ethanol solvent while the method used is molecular dynamic simulation technique (theoretical method). An atomic charge calculation method was used to predict the morphology of the (CBZ-SA) cocrystal by using Dmol3 and MOPAC model. After the charged is calculated, the crystal structure was subjected to geometry optimization and then energy minimization by using the potential functions such as COMPASS, COMPASS26, COMPASS27, cvff, pcff, Universal, and Dreiding. Then, the morphology of the cocrystal was obtained. The simulated morphology of CBZ-SA co-crystals that use Dreiding force field resulted in elongated needle-like shape which shows similar shape with the experimental morphology demonstrated from previous research. For the assessment of dissolution behavior of CBZ-SA co-crystals in ethanol solvent, the mean square displacement (MSD) and radial distribution (RDF) were used to analyze the interaction between co-crystals and solvent molecules.

Keywords— carbamazepine, co-crystallization, dissolution, molecular dynamic simulation, morphology, solubility, succinic acid, surface chemistry;

1. INTRODUCTION

In the pharmaceutical industry, a major driving force that lead to new technological developments is the improvement of the properties of an active pharmaceutical ingredient (API), such as solubility, bioavailability, flow properties, thermal stability, crystallinity, particle size, and filterability are important [1]. So, it is very important to study the new solid-state forms of old active pharmaceutical ingredients to improve the performance by co-crystallization processes. Crystallization is the solidification of atoms or molecules into a highly structured form called a crystal where slow precipitation of crystals from a solution of a substance occur [2].

Crystallization process is widely used in pharmaceutical industries to produce crystal powder of drugs. The crystal drugs often show many crystalline forms called as polymorphs and the form can be solvates, hydrate, salt, amorphous, or co-crystal. Each form shows physicochemical properties that can greatly influence the bioavailability, manufacturability purification, stability and other performance characteristics of the drugs [3]. The crystal is obtained by cooling a solution, evaporating solvent, or seeding to desired polymorph of crystal. There are some crucial quality requirements for pharmaceutical crystallization that need to be considered which are yield, purity, size, morphology, polymorphism, and chirality. In pharmaceutical, there are 4 classes of drugs which are Class I, Class II, Class III, and Class IV that were classified according to the permeability and solubility level [4].

API is a central ingredient and substance in the drug that can produce the desired effect to the body. Carbamazepine (CBZ) is one of API drugs used in pharmaceuticals industries as an anti-epileptic drug and belongs to the biopharmaceutics classification system (BSC) class II (low solubility and high permeability) [5]. The API drugs is said to have problems in term of solubility, stability, and flowability and most of the API drugs are poorly water soluble [6]. So, the need for co-crystallization of the poorly water- soluble drugs with co-crystal former can be one of the ways to overcome the problem of API drugs.

Co-crystals can be defined as multi-component crystals comprised of active pharmaceutical ingredients and one or more co-crystal formers (CCFs) [7]. Co-former is a compound used to be co-crystallized with poorly water-soluble drugs of API. Some co-formers that is widely used in co-crystallization with API are succinic acid, nicotinamide, salicylic acid, adipic acid, fumaric acid, succinic acid, and so on [8]. Co-crystal of poorly water-soluble drugs have the ability to solve the physicochemical properties of the drugs by improving the solubility, stability, and dissolution rate of the drugs [9]. However, it is not easy way to cocrystal the API with co-former as co-former selection is one of the main challenge in cocrystal development that is compatible with API [10].

In this research, a molecular dynamic simulation was used as this method can provide insight in both atomic and molecular level on the interaction between crystal and solvent molecules. The methods that can be used to predict morphology of the cocrystal of CBZ-SA are by calculating atomic charge using Dmol3 and Mopac model and lattice energy using an attachment energy method. For examples of the morphology of the crystals are needle like, rod like, rhombohedral, calcite, elongated particles, and so on. This molecular dynamic simulation also was used to predict the dissolution behavior of the CBZ-SA cocrystal in ethanol solvent and the interaction between crystal faces and solvent was analyzed using RDF and MSD.

2. METHODOLOGY

2.1 Materials

In this research, all the materials which are CBZ-SA cocrystals and ethanol are obtained from Cambridge Structural Database (CSD). CSD is a highly curated and comprehensive resource where the small-molecule organic and metal-organic crystal structures is stored and managed**.** The CBZ crystals is a host molecule and SA as a co-former while ethanol act as a solvent. Succinic acid is one of the cocrystal former used in the production of cocrystal with active pharmaceutical ingredient (API) due to its high solubility in various solvents [11]. Ethanol is used to investigate the interaction on CBZ-SA cocrystals surface.

2.2 Methods

The molecular dynamic approach which is an analytical method was carried out by using Material Studio from ACCELRYS. From this computer analysis, the atomic charges and lattice energy can be calculated to predict the morphology of CBZ-SA cocrystal in ethanol solvent. Molecular dynamic simulation also reveals the interaction between the ethanol solvent and crystal faces in atomic and molecular level in order to assess the dissolution behavior of the co-crystal. Various types of forcefield were used such as COMPASS, Universal, Dreiding, cvff, and pcff and different types of forcefields used will produced different crystal morphology.

2.3 Cocrystal structure

The co-crystal structures of carbamazepine-succinic acid (CBZ-SA) was retrieved from the Cambridge Structural Data (CSD). CBZ -SA crystallizes in a monoclinic lattice with space group P2/N, and cell parameters are a = 17.729739Å, b = 5.217281Å, c = 20.753143Å, β = 103.35299, α and γ = 90. The co-crystal of CBZ-SA is packed with four molecules of carbamazepine (CBZ) and two molecules of succinic acid (SA) in a unit cell.

2.4 Atomic charges calculation

The calculation was calculated based on Density Functional Theory (DFT) which is a quantum mechanical theory that describes the nature of energy levels of atoms and subatomic particles at the smallest scales. DFT is a powerful tool in data-oriented materials research such as in Material Studio that was used to estimate more accurate the electronic structure of atoms. For the crystal structure prediction, atomic charges are often used to describe the electrostatic interactions. The first step to predict the morphology and structure of the CBZ-SA cocrystal is to extract the crystal structure from CSD. There are 2 modelling programs used to perform calculations on the crystal which are Mopac and DMol3. For Mopac, the calculation is performed using AM1, MNDO, and PM3 charge models while for DMol3, it used Mulliken, Hirshfeld, and Electrostatic potential (ESP). The charges will be calculated for different types of forcefields used. For the functional, GGA and BLYP were used. Molecular modeling really depends on the use of force fields and methods of assigning point charges to the atoms in the molecules [12]. Assigning point charges to the atoms of a molecule can help to obtain a simple description of the electrostatics that would result in fast calculations.

2.5 Prediction of Carbamazepine-Succinic acid cocrystal morphology in vacuum

The shape of the crystal is very depending on the internal structure of the crystal. So, it is very important to calculate the atomic charge and attachment energy in the molecular dynamic simulation that used Material Studio as a simulation software. In this research, the morphology of the CBZ-SA cocrystal will be investigated and predicted. The structure of CBZ-SA cocrystal which is already available obtained from Cambridge Structural Database (CSD) was subjected to geometry optimization and then energy minimization by using different types of forcefields such as COMPASS, Dreiding, pcff, Universal, and cvff. The growth rate of the crystal face is proportional to its attachment energy. For the morphology prediction, current charge was used for the calculation with medium quality while atom based was chosen for summation method, both electrostatic and Van der Waals force. The crystal face with the lowest attachment energy is the slowest growing area and has the largest surface area and the most morphological important crystal faces.

2.6 Lattice energy calculation using an Attachment energy method

In this study, Material Studio was used to calculate the lattice energy known as theoretical lattice energy (Elatt, theory) and simulate the CBZ-SA cocrystal morphology in the influence of solvent by using the attachment energy summation method. This lattice energy was obtained from the morphology prediction of CBZ-SA cocrystals in the influence of solvent where the structure of CBZ-SA cocrystals was retrieved from Cambridge Structural Database (CSD). The structure was subjected to geometry optimization and then energy minimization by using the potential functions such as COMPASS, cvff, pcff, Universal, and Dreiding. Different crystals morphology has different lattice energy values. So, in order to decide the most suitable and accurate crystal morphology, the Elatt values obtained from the simulation were then compared with the experimental lattice values until the chosen parameter values are rather close to the experimental values.

2.7 Assessment of Dissolution Behavior of Carbamazepine-Succinic Acid Cocrystal with Ethanol as Solvent

All the calculations were performed by using the Material Studio 4.4 from Accelrys. First, all the CBZ-SA cocrystal faces were cleaved. Each face will be cleaved until 3 times repetition so that there will be 3 unit cell where 1 unit cell contain 4 CBZ and 2 Succinic acid. This is done in order to make the next step in dynamic simulation faster especially in determining the rigid and unrigid part in the simulation. So, with this 3 unit cell, the top cell will be kept unrigid and lets them move freely while for the other 2 unit cell at the

bottom part will be kept as rigid to make it as a reference molecule. The faces are supercell 3 times whether in U or V direction based on the arrangement or configuration of the faces. This is because each face has different arrangement molecules of CBZ and Succinic acid. After the supercell was created, it proceeded with building the vacuum slab with constant value of slab thickness of 55 Å.

After that, ethanol molecule that act as a solvent undergoes both geometry optimization and energy minimization before an amorphous cell of the solvent is construct. The construction of the solvent is based on the a, b, and c parameters value of the vacuum slab to obtain a suitable arrangement of the 100 ethanol molecules in the vacuum slab. After construction of 100 amount of ethanol is done, ethanol is paste in the vacuum slab. All the crystal molecules in the vacuum slab is make as rigid while ethanol is allowed to move freely.

Second, the slab with rigid crystal and freely moving ethanol molecule will subjected to geometry optimization through Forcite tools to form stable conformation by using coarse quality with summation method and forcefield same as morphology calculated previously. This process seeks to find the geometry of a particular arrangement of the atoms where the total energy of the structure was reduced to minimum and by minimization, the empty space can be removed and can make the molecule distribute uniformly. In this study, atom based is used for both summation method (electrostatic and Van der Waals) with Dreiding forcefield and its charge.

After the optimization is done, it will proceed with the dynamic simulation step. Ethanol is still kept as unrigid. The first upper layer of the crystal is set as unrigid in order to let the crystal move freely and interact with the ethanol molecules while the other 2 bottom layer of the crystal is set as rigid. The dynamic simulation is run using 20 ps simulation time, medium quality, 1fs time step, 20000 number of steps, frame output every 100 steps, Berendsen thermostat, and NVT ensemble at constant T of 298K. The summation methods are both by atom based and Dreiding forcefield with its charge which is also same parameter when running morphology and geometry optimization of the crystal and ethanol in vacuum slab previously.

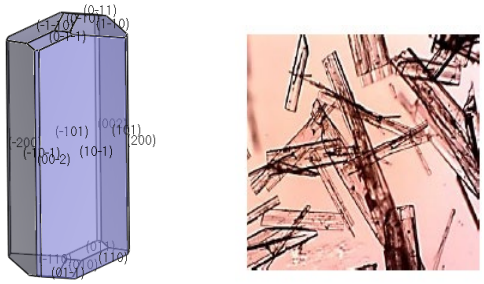
Third, after dynamic simulation is done, the interaction between crystal molecules and ethanol molecules was analyzed using RDF and MSD. One molecule whether CBZ or Succinic acid from the last layer of the crystal and at the center part of the vacuum slab is set as a reference and another set of crystal is needed in order to observe the interaction. So, one unit cell from top layer of the crystal and in the center part of the slab is set as unrigid. For RDF, it is used to relate the particles position to each other where the graph of g(r) versus r is plotted. For MSD, it is used to investigate the diffusivity of the particles in whole simulation process as well as to distinguish phases. The graph of MSD versus time (ps) will be formed. In a very short time, the slope of some point in MSD curve is directly proportional to displacement increment.

3. RESULTS AND DISCUSSION

3.1 CBZ -SA co-crystal morphology in vacuum

The morphology of the crystal was calculated from the growth morphology algorithm in morphology module which is based on an attachment energy [13]. The attachment energy model for the growth morphology of a crystal is based on the assumption that the growth rate of a face is proportional to the absolute value of the attachment energy [14]. After undergoes both geometry optimization and energy minimization, the crystal morphology of CBZ-SA in vacuum was successfully obtained. Table 1 shows the summary of lattice energy and morphology with different types of force field and charges used. Most of the force field and charges used shows flat morphology but for Hirshfeld charge, it shows elongated hexagonal flat morphology. Based on the morphology of CBZ-SA co-crystal obtained and summarized in Table 1, Dreiding force field and its charge from Hirshfeld had shown similar shape as an experimental morphology which is needle-like morphology.

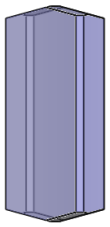
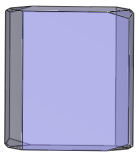
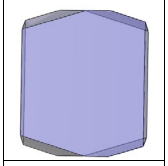
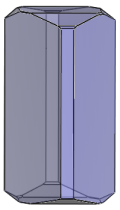
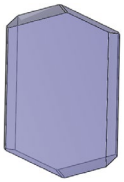
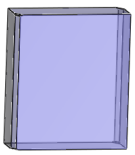
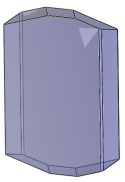
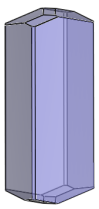
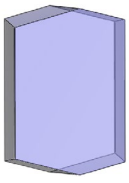
The morphology of CBZ-SA co-crystal was illustrated in Figure 1. From Figure 1, it can be proven that the prediction of CBZ-SA co-crystal shape results in a similar morphology with an experimental. Next, to proceed with the assessment of dissolution behavior of CBZ-SA co-crystal in ethanol solvent, this experiment had chosen this needle-like morphology obtained from Dreiding forcefield and its Hirsfeld charges in order to study the interaction between co-crystal faces with ethanol molecules.

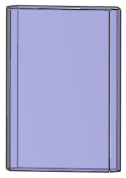
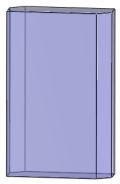
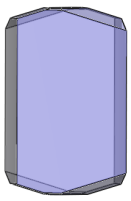
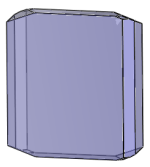
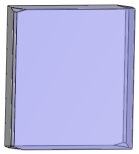
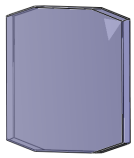
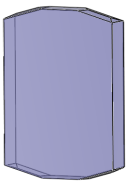


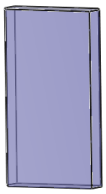
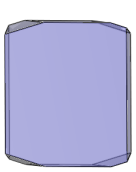
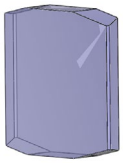
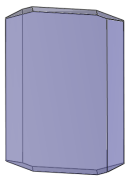
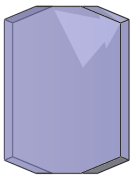
(a) **(b)**

Fig. 1. (a) The simulated morphology of CBZ-SA co-crystal in vacuum; (b) experimental morphology [8]

Table 1: Lattice energies and morphology of carbamazepine-succinic acid co-crystal using different potential function and charge types.

Forcefield	Charge	Elatt (kcal/mol)		Morphology	
		Forcefield assign	Use current	Forcefield assign	Use current
Compass	MNDO	-35.80	-52.69		
	Mulliken		-65.02		
	Hirsfeld		-37.77		
	ESP		-74.03		
Dreiding	MNDO	-	-123.56	-	
	Mulliken		-185.99		
	Hirsfeld		- 48.60		
	ESP		-173.38		

Universal	MNDO	-	-54.31	-	
	Mulliken		-60.27		
	Hirsfeld		-45.25		
	ESP		-52.87		
cvff	MNDO	-36.43	-47.15		
	Mulliken		-44.29		
	Hirsfeld		-36.74		
	ESP		-62.33		

pcff	MNDO	-39.26	-50.33		
	Mulliken		-58.76		
	Hirsfeld		-38.39		
	ESP		-56.75		

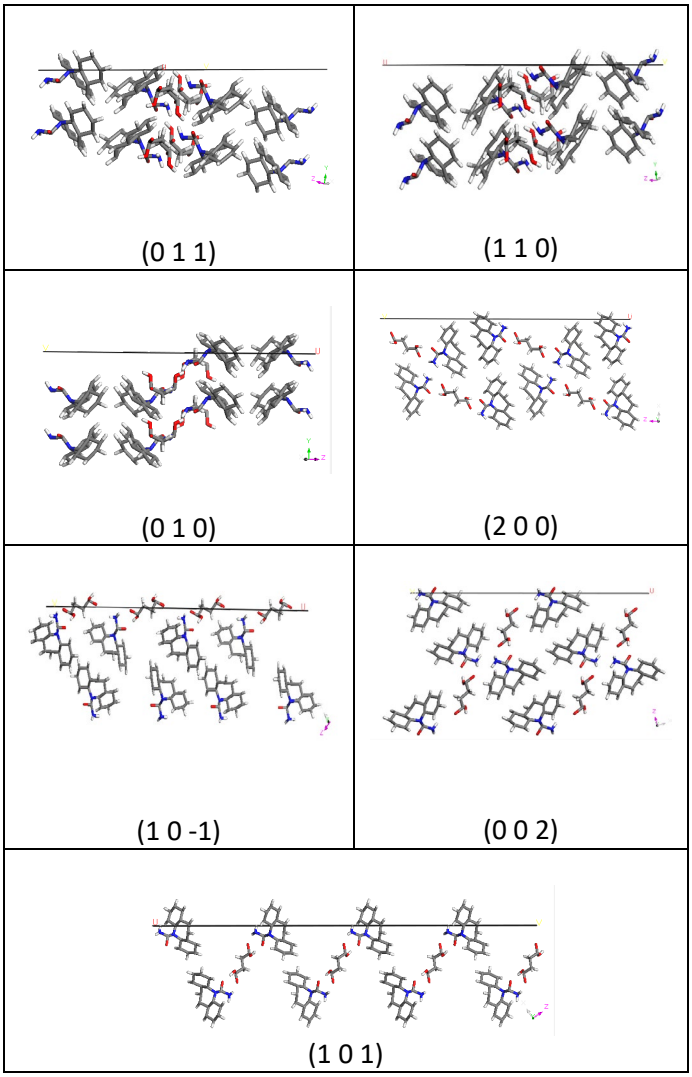


Fig 2. Molecule arrangement of morphologically important faces of CBZ-SA cocrystal

3.2 Surface chemistry analysis

Table 2 shows the number of 7 facets of the CBZ-SA co-crystal morphology and their respective slices energy calculated using an attachment energy method. According to It can be concluded that the (1 0 -1) facet is the slowest growing facet as it has the lowest attachment energy of -27.9066 kcal/mol compared to other facets. While for (0 1 1) face, it has highest attachment energy of -96.7379 kcal/mol which result in fast growing facet. Based on Figure 2, these growing facets phenomenon can be observed clearly from the surface chemistry analysis that shows an interaction between crystal facets with ethanol solvent molecules.

From Fig.2, the arrangement of molecule of morphologically important habit faces have different molecular packing orientations. The (1 0 -1), (1 0 1), (0 0 2), and (2 0 0) faces are flat surface while (0 1 0), (0 1 1), and (1 1 0) faces are rough surface at bottom and on molecular level. The nitrogen atoms can be seen on the crystal surface more clearly on (1 1 0) face which can form H-bonds with ethanol molecules. Hydrogen bonding is the most important intermolecular interaction in cocrystal design due to its strength, directionality, and universal occurrence in drug-like molecules [15]. Many cocrystals formed are linked by hydrogen bonding. For other facet, the direction and strength of H-bond formed by this nitrogen atoms are different as the nitrogen atoms present in each face have different orientations and positions.

Table 2: Face Multiplicity And d-Spacing from Growth Morphology Analysis Showing the Respective Attachment and Slice Energy Calculated Using the MS Program

Face	Multiplicity	d-spacing	Attachment energy (kcal/mol)	Slice energy (kcal/mol)
(1 0 -1)	2	14.929	-27.907	-6.898
(1 0 1)	2	11.835	-43.080	-1.840
(0 0 2)	2	10.096	-53.723	1.707
(2 0 0)	2	8.625	-43.226	-1.792
(0 1 0)	2	5.217	-93.649	15.016
(0 1 1)	4	5.051	-96.738	16.046
(1 1 0)	4	4.994	-91.338	14.246

3.3 Molecular dynamic simulation of CBZ-SA co-crystal in ethanol solvent

A molecular dynamic simulation was performed to study the effect of the any solvents on the crystal habits [16]. In other word, this molecular dynamic simulation is performed

to model the solvent effect on crystal morphology and is used as a tool to estimate the face growth rates of a crystal. It provides a better understanding to investigate the interactions of crystal faces with the pure solvent by observing what is happening between solvents and crystal molecules in both atomic and molecular level. In this study, the simulation time used is 20 ps, time step 1 fs, medium quality, 20000 number of steps, and frame output every 100 steps at constant volume and temperature (NVT) ensemble which is at 298K while the thermostat used is Berendsen. Figure 3 shows examples of molecular dynamic simulation of the CBZ-SA cocrystal-ethanol solvent interfaces, which correspond to the (1 1 0) and (1 0 -1) faces. From Figure 3, it can be observed that facet (1 1 0) has higher interaction between ethanol solvent molecules and crystal surface. While for (1 0 -1) facet, the interaction is slow compared to (1 1 0) facet. For an accurate result, the interaction between ethanol molecules with crystal surface was analyzed using RDF and MSD.

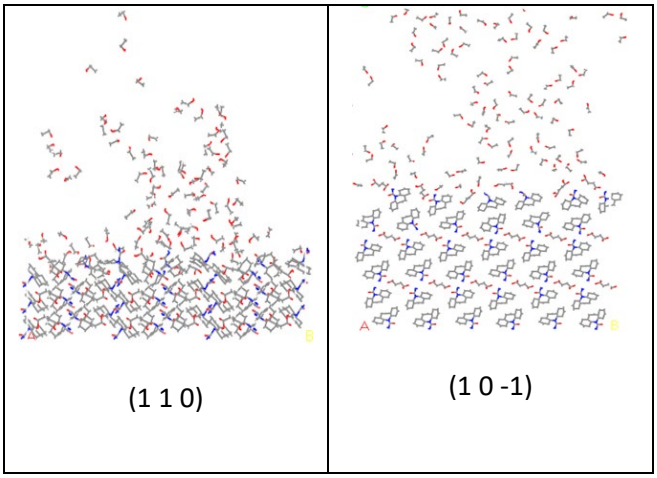


Fig. 3: Snapshots from the molecular dynamic simulation of the CBZ-SA cocrystal-ethanol solvent interfaces, which correspond to the (1 1 0) and (1 0 -1).

3.4 Radial distribution function of interfacial model

The radial distribution function (RDF) in a system of particles such as atoms, molecules, and colloids describe how density varies as a function of distance from a reference particle [17]. The radial distribution function gives the probability of finding a particle in the distance r from another particle. In RDF graph of g(r) versus r, the peak which is within 0.35nm mainly consists of chemical and hydrogen bond while for coulomb and Van Der Waals forces, the peak appears outside of 0.35nm [18]. Table 3 shows the summarization of the distance of first peak with different facet of CBZ-SA cocrystal derived from RDFs of molecular dynamic simulation.

In order to analyze the solvent-crystal interactions clearly, the interface structure between CBZ-SA cocrystal (0 1 -1) face and ethanol molecule was explored with RDF, as shown in Figure 4. Based on Figure 4, there are sharp peaks in r =11.43 Angstrom and at r = 12.99 Angstrom. This mean that, the strong hydrogen bonds exist between O, N, and H atoms. According to the graph g(r) versus r curves, wide peaks can be observed in the interval of 67.33 – 88.53 Angstrom which indicates that the Coulomb and Van der Waals forces are also formed. So, it can be said that, the adsorption of solvent molecules on the crystal faces or surface is due to both combination interaction of hydrogen bond, Coulomb and Van der Waals forces.

Table 3: Distance of first peak with different facet of CBZ-SA cocrystal derived from RDFs of molecular dynamic simulation

No	Facet	Total CBZ-SA facet-EtOH r(Å)
1	(0 1 0)	11.43
2	(0 -1 0)	11.37
3	(0 1 -1)	11.43
4	(0 1 1)	13.37
5	(0 -1 -1)	13.67
6	(0 -1 1)	13.53
7	(-1 1 0)	11.83
8	(1 1 0)	11.69
9	(1 -1 0)	11.11
10	(-1 -1 0)	11.67
11	(0 0 -2)	50.21
12	(0 0 2)	50.91
13	(-1 0 -1)	28.91
14	(1 0 1)	28.39
15	(-2 0 0)	41.87
16	(2 0 0)	42.79
17	(-1 0 1)	37.17
18	(1 0 -1)	37.29

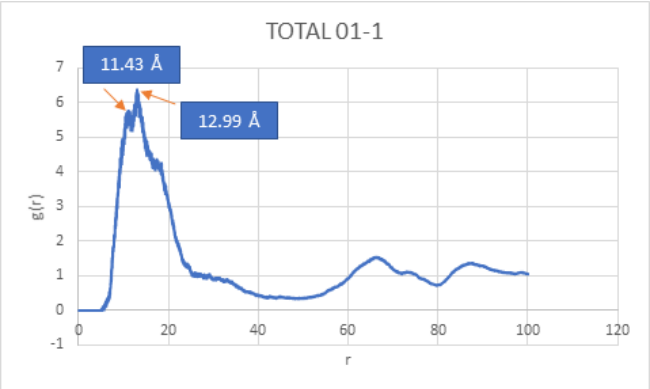


Fig. 4. RDF of the interfacial model of ethanol and CBZ-SA (0 1 -1) face.

3.5 Mean square displacement

The mean square displacement (MSD) describe an average distance of a given particle that travel in a system [19]. This analysis is used to depict the Carbamazepine-Succinic acid (CBZ-SA) cocrystal molecule's diffusion behavior. The self-diffusion coefficient which is related to the function of MSD can be calculated from the slope which is proportional to the self-diffusivity through the Einstein equation [20]. According to [21], it is said that in a very short time, the slope of some point in MSD curve is directly

proportional to displacement increment of this point from initial position. Figure 5 shows the MSD of ethanol molecules on the 18 facets. The slope which is proportional to the diffusion coefficient of ethanol molecules on all the 18 faces were estimated and summarized in Table 4. From the result obtained, it is indicated that ethanol molecules diffuse more easily on (1 0 -1), (-1 1 0), (1 -1 0), (0 -1 -1), (-1 -1 0), and (0 1 1) faces from the high slope of the MSD. There is a strong interaction between ethanol molecules and all these surfaces. In other word, the diffusion coefficient of these faces is increase with increasing slope. For (0 0 -2), (-2 0 0), (2 0 0), and (0 0 2) faces, the slope is smaller that indicate the diffusion coefficient decrease. An example of calculation on how the slope from the MSD graph is obtained is shown in Figure 6 and Figure 7 which is for (0 1 -1) face of the CBZ-SA cocrystal.

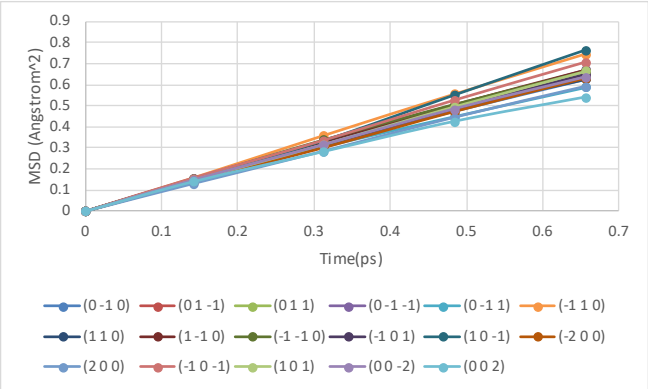


Fig. 5. MSD of ethanol molecules on the 18 facets of CBZ-SA cocrystal

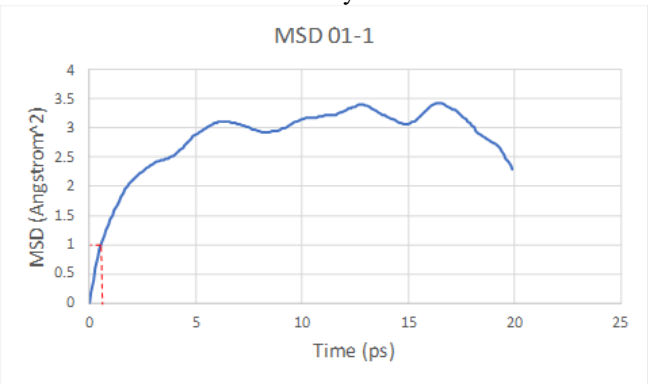


Fig. 6. MSD of ethanol molecule on (0 1 -1) face

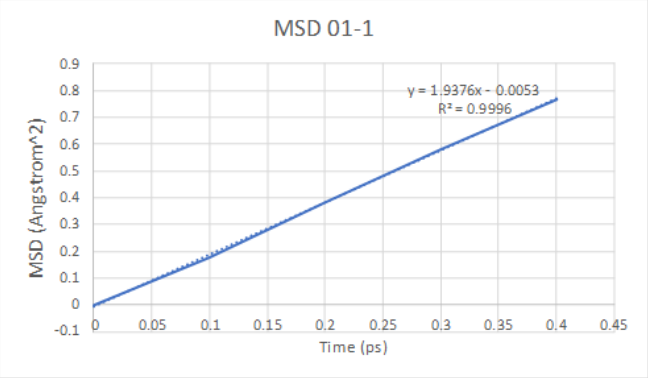


Fig. 7. Slope obtained from MSD of ethanol molecules on (0 1 -1) face

Table 4: Summary of MSD data

No	Facet	Equation of slope	Diffusion coefficient, D
1	(0 1 0)	y = 1.8451x - 0.0086	0.3075
2	(0 -1 0)	y = 2.0713x - 0.0129	0.3452
3	(0 1 -1)	y = 1.9376x - 0.0053	0.3230
4	(0 1 1)	y = 1.9721x - 0.0069	0.3287
5	(0 -1 -1)	y = 1.9715x - 0.0079	0.3286
6	(0 -1 1)	y = 1.9431x - 0.0002	0.3239
7	(-1 1 0)	y = 2.2015x - 0.0124	0.3669
8	(1 1 0)	y = 1.8291x - 0.0038	0.3049
9	(1 -1 0)	y = 1.9951x - 0.0094	0.3325
10	(-1 -1 0)	y = 1.9571x + 0.0009	0.3262
11	(-1 0 1)	y = 2.2562x - 0.0283	0.3760
12	(1 0 -1)	y = 2.2205x - 0.0284	0.3701
13	(-1 0 -1)	y = 2.0246x - 0.0162	0.3374
14	(1 0 1)	y = 2.0644x - 0.0289	0.3441
15	(-2 0 0)	y = 1.958x - 0.0122	0.3263
16	(2 0 0)	y = 1.8327x - 0.0085	0.3055
17	(0 0 -2)	y = 1.7214x - 0.0082	0.2869
18	(0 0 2)	y = 1.7227x - 0.0088	0.2871

3.6 Binding energies and the solvent effect on CBZ-SA cocrystal morphology

Binding energy can be defined as the minimum amount of energy needed to overcome the holding forces of the atoms together to separate the atoms completely into their individual component. It is the energy associated with the strong force that holds the nucleons together. In this study, binding energy was calculated to observe an interaction between crystal faces and solvent molecule which is between CBZ-SA cocrystal faces and ethanol molecules. The binding energies normally focus mainly on the formation of hydrogen bonds which is polar interactions and also Van der Waals forces between crystal faces and ethanol solvent. The solvents affect the crystal morphology by its different interaction energy with different crystal faces as most of the crystal are grown from solution [18]. A greater value of interaction energies or binding energies indicates that the interaction between crystal faces and solvent is stronger [18]. Hence, more energy is required to separate the nucleus of an atom into its component parts.

The binding energy can be calculated from the following equation;

$$E_{binding} = E_{min} - E_{surf} - E_{solv} \text{ ……..Equation 1}$$

Where E_{min} is the total energy of solvent layer and the crystal face, E_{surf} is the energy of the crystal face without solvent layer, and E_{solv} is the energy of solvent layer without crystal face.

From Table 4, it can be concluded that all the binding energies of CBZ-SA cocrystal faces-ethanol solvent system are negative that indicates the adsorption of ethanol solvent on crystal faces are thermodynamically favorable. The interaction strength of ethanol solvent with morphologically important faces of CBZ-SA cocrystal can be compared in the following sequences: (1 1 0) > (0 0 2) > (0 1 0) > (0 1 1) > (1 0 1) > (1 0 -1) > (2 0 0).

Table 5: Summarization of Binding energy for each crystal face

Facet	E_{min} (kcal/mol)	E_{surf} (kcal/mol)	E_{solv} (kcal/mol)	$E_{binding}$ (kcal/mol)
(1 1 0)	-192.644	745.631	-192.644	-745.631
(0 1 0)	-181.698	712.696	-181.698	-712.696
(0 -1 0)	-84.174	712.696	-84.174	-712.696
(-110)	-141.003	701.639	-141.003	-701.639
(0-1-1)	-174.485	712.04	-174.485	-712.04
(0-11)	-120.361	700.551	-120.361	-700.551
(1 -1 0)	-80.566	701.639	-80.566	-701.639
(-1-10)	-38.771	734.623	-38.771	-734.623
(0 1-1)	-18.839	700.551	-18.839	-700.551
(0 11)	-107.877	712.04	-107.877	-712.04
(-101)	-57.62	537.951	-57.62	-537.951
(10-1)	-199.91	537.951	-199.91	-537.951
(2 0 0)	-109.098	491.648	-109.098	-491.648
(-2 0 0)	-109.098	491.648	-109.098	-491.648
(0 0 -2)	-128.238	713.524	-128.238	-713.524
(0 0 2)	-89.115	713.524	-89.115	-713.524
(-1 0 -1)	-107.784	577.328	-107.784	-577.328
(1 0 1)	-92.835	577.328	-92.835	-577.328

4. CONCLUSION

In this study, the morphology and main co- crystal faces of CBZ-SA were successfully predicted and the main facets of CBZ-SA cocrystal was identified. The prediction of the co-crystal morphology of CBZ-SA using Dreiding forcefield with Hirshfeld charges results in a similar shape to the experimental which is elongated needle-like shape. The co-crystal morphology is dominated by seven faces which are (1 0 -1), (1 0 1), (0 0 2), (2 0 0), (0 1 0), (0 1 1), and (1 1 0). The dissolution behavior of CBZ-SA cocrystal in ethanol solvent was successfully performed and analyzed using RDF and MSD. The MSD analysis indicate that the ethanol solvent molecules diffuse more easily on (1 0 -1), (1 0 1), (0 1 1), (0 1 0) of morphologically important faces but very slow diffusion on (2 0 0), (1 1 0), and (0 0 2) faces. From binding energy calculation for (1 1 0), (0 0 2), (0 1 0), (0 1 1), (1 0 1), (1 0 -1), and (2 0 0) morphologically important faces of the cocrystal, the values of binding energy are -745.631 kcal/mol, -713.524 kcal/mol, -712.696 kcal/mol, -712.040 kcal/mol, -577.328 kcal/mol, -537.951 kcal/mol, and -491.648 kcal/mol respectively. It can be concluded that, the more negative of the binding energy, the easier for the crystal to dissolve in ethanol solvent.

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