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

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Abstract— Carbamazepine(CBZ) famously known to be analgesic and anticonvulsant with solubility and polymorphism problem had become a great challenge to crystal engineers since their crystal packing were unpredictable. CBZ forms supramolecular complexes with co-crystal former, succinic acid(SA) which are complementary with each other in terms of hydrogen bonding. This approach thoroughly modifies the crystal packing and affect the physical and pharmaceutical properties of CBZ. The interaction occur between carbamazepine and the succinic acid can be predicted by using a molecular dynamic simulation technique. Carbamazepine-succinic acid(CBZ-SA) co-crystal morphology that consist of seven dominant facets was cleaved to gain better insights on the interaction, which later affects the dissolution behaviour of the crystal. Hydrogen bonding is the key of interaction in the crystal engineering. Thus, accessing the interaction between one reference atom with one unit cell of carbamazepine-succinic acid (CBZ-SA) co-crystal was the main objective. The plate-like shape morphology of CBZ-SA co-crystal consist of seven dominant facets which were (1 0 -1), (1 0 1), (1 1 0), (0 1 1), (0 1 0), (2 0 0) and (0 0 2). In order to study the stability phenomenon, two aspects were analyzed: (1) Radial distribution function (RDF), (2) Mean square displacement (MSD). Each molecules in each facets exhibit different type of interaction with the reference molecule.

I. Introduction

Nowadays, the ability of pharmaceutical co-crystals on improving solubility and dissolution behaviour of poorly water soluble drug had gained interest among the researchers. Co-crystal can be introduced as the formulation of the stoichiometric ratio of crystal or active pharmaceutical ingredient (API) which is carbamazepine and coformer which is primarily known as succinic acid. A crystalline solid can be characterized by definite internal and external structure. Habit describes the external structure while polymorphic refers to internal structure of the crystal. Different crystal form have different internal structure. However, metastable crystalline form have been provided with enhanced dissolution behaviour. The greater solubility of the metastable form can only be achieved when large energy differences were exist between the polymorphs [1]. Co-crystallization technique was used as an approach that allows the binding of active pharmaceutical ingredients(API) with one or more components of co-crystal former(CCF) without breaking or making new covalent bond within one periodic crystalline lattice [2].

This combination actually proved that the solubility and dissolution behaviour can be enhanced and their physical stability is much better than in their pure state. Aqueous dissolution rate will increase up to 18 times when co-crystal was being used as compared to the homomeric crystalline form of the same drug [3]. Carbamazepine(CBZ) belong to BCS Class II drug which can be categorized as having low solubility and high permeability. The bioavailability of the drugs is likely to be dissolution rate limited. But, solubility enhancement researches had been developed excessively due to their high permeability characteristic. High soluble drugs are the drugs that soluble in 250 mL of aqeous media in gastrointestinal area with pH range of 1.2 to 7.4 while high permeable drugs are the drugs that the extent of absorption is greater than 90% of the dose administered [4]. Carbamazepine is a weak acid and base which exhibit good oral absorption even though it was poorly soluble at pH conditions. Carbamazepine along with other co-crystal former will help CBZ to disintegrate into small particles so that it could be easily transported throughout the blood stream in human bodies. The choice of the coformer is succinic acid that had been restricted to generally regarded as safe(GRAS) in the pharmaceutical industry [5]. Succinic acid was chosen as coformer because of its ability to donate or accept atoms that can form hydrogen bonds. Solubility, dissolution and gastrointestinal permeability are the fundamental parameters that control rate and extent of drug absorption and bioavailability. In the drug discovery, there are about 70% of new drug candidates showing poor water solubility. Poor aqueous solubility is mainly caused by two factors which are high lipophilicity and it has strong intermolecular interactions which make the solubilization of the solid costly. Thus, predictive models based on molecular dynamic simulation technique can guarantee success of work and help to understand the dissolution behaviour and interaction exhibited by the molecules. Detachment of the drug molecules from the solid particles and then entering the surrounding gastrointestinal(GI) milieu is defined as dissolution while phenomenan of the dissolution of solute in solvent giving a homogenous system is called as solubility [6]. In order to study the nature of interaction exist, carbamazepine-succinic acid(CBZ-SA) co-crystal morphology had been scaled down into seven dominant facets only. Molecular modelling is a feasible approach to analyze the intermolecular interactions [7] by radial distribution function (RDF) analysis by giving a measure of the probability $g(r)$ of a particle appearing at a distance r from the reference atom [7] while mean square displacement (MSD) can show the distance travelled

by molecule in the system or in other words is the activity of the molecules in the system [8]. The MSD data was used to calculate the diffusion coefficient, *D* by Einstein relation where the value comes from the slope of the graph MSD versus t curve [9].

$$D = \frac{1}{6}\lim_{t\to\infty}\frac{d}{dt}(|r_i(t) - r_i(0)|^2) \quad (1)$$

Where $r_i(t)$ and $r_i(0)$ stand for the molecular coordinates of particle *i* at *t* and intial time, respectively. $|r_i(t) - r_i(0)|^2$ is the mean squared displacement of coordinates.

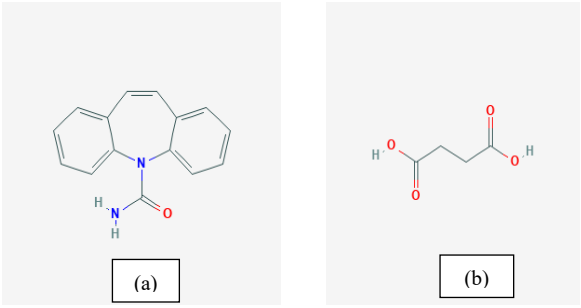


Fig. 1: Molecular structure of the studied (a) Carbamazepine and (b) Succinic acid

II. METHODOLOGY

A. Molecular structures

With the reference code XOBCIB, carbamazepine-succinic acid(CBZ-SA) co-crystal structures were extracted from Cambridge Structural Data(CSD). CBZ-SA crystallizes in a monoclinic lattice with a space group P2/N, with cell parameters of a=17.729739 Å, b=5.217281 Å, c=20.753143 Å, β=103.35299°, α and γ=90°. Four molecules of Carbamazepine(CBZ) and two molecules of succinic acid(SA) were packed as a CBZ-SA co-crystal in a unit cell. In the middle of crystal lattice structure, both succinic acid molecule were packed in between two carbamazepine molecules. Hydrophilic part of carbamazepine molecules were forming hydrogen bond with both succinic acid molecules while hydrophobic parts of carbamazepine molecules were forming Van Der Waals interaction with the other hydrophobic parts of carbamazepine molecules [10]. Each facets had different number of molecules in one unit cell and the orientation varied.

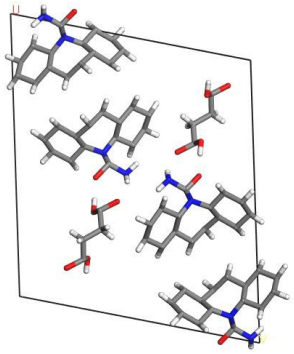


Fig. 2: Molecular structure of one unit cell of CBZ-SA co-crystal in y-direction of facets (1 1 0)

B. Computational methods

Co-crystal morphology and dissolution behaviour of Carbamazepine-succinic acid(CBZ-SA) was simulated using Material Studio Software version 7.0 from Accelrys. Radial distribution function(RDF) and mean square displacement(MSD) data were retrieved from the molecular dynamic simulation in order to predict the dissolution behaviour of CBZ-SA co-crystal facets in ethanol. By using the co-crystal morphology, seven dominant facets were cleaved and the thickness of each slice was set as two and each slice was expanded in different multiples. Table 1 shows the crystal thickness and layer for each facets were differ due to some circumstances which were limitation on each facets as the crystal-crystal interaction that should be observed have different one unit cell of CBZ-SA molecules. The arrangement for one unit cell of CBZ-SA co-crystal can include four molecules of CBZ with two molecules of SA or two molecules of CBZ with one molecule of SA for each different facets. Next, the crystal layer for each facet have different value of U x V to ensure the shape is in cubic form.

Table 1: Thickness and crystal layer of each facet

Crystal facets	Thickness	U x V
(1 0 -1)	3	9 x 3
(1 0 1)	3	5 x 3
(0 0 2)	3	3 x 7
(2 0 0)	2	3 x 4
(0 1 0)	2	3 x 3
(0 1 1)	2	3 x 3
(1 1 0)	2	3 x 3

Meanwhile, the orientation and origin of the slice was reset to make the V axis along the Y axis, and the U axis was in the XY plane. Then, vacuum slab was built accordingly to obtain the cubic boxes as shown in Figure 3. Then, from one unit cell, the molecules were arranged and denoted as CBZ 1, CBZ 2, CBZ 3, CBZ 4, SA 1 and SA 2 differently for each facet.

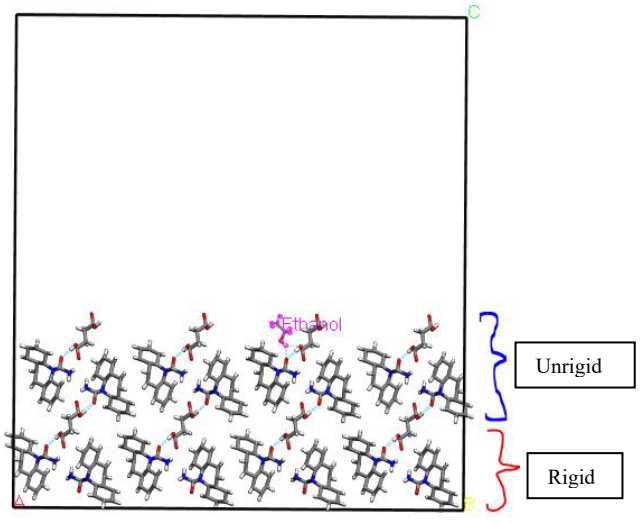


Fig. 3: The schematic view of CBZ-SA co-crystal and ethanol interface model

C. Construction of 3D periodic structures of ethanol

Ethanol molecule was constructed by using the sketching tools available in the Material Studio. One number of molecules of ethanol was built using Amorphous cell module. The ethanol molecule was inserted into the empty vacuum slab. Then, the structure underwent geometry optimization using polymer

consistent forcefield (pcff) to obtain the stable low-energy structure cell [11]. Atom based calculation was selected for the electrostatic and Van Der Waals summation method.

D. Geometry optimization of the periodic system

In this process, for each facets, the crystal surface supercell were kept constraint. The ethanol molecule that had been optimized were allowed to move freely. Then, the system was subjected to geometry optimization using the same forcefield as the ethanol molecules. In this case, polymer consistent forcefield (pcff) and forcefield assigned charges were used and atom based calculation was selected for the electrostatic and Van Der Waals summation method.

E. Molecular dynamic simulation for dissolution assessment of periodic systems

Dynamic simulation was conducted once geometry optimization had been done. In order to run the dynamic simulation, the first and second upper layers of the CBZ-SA co-crystal were kept unrigid while the bottom layer remained rigid. The simulation was conducted for 1000 ps with medium quality at 298 K and 1 fs time step. Nose-Hoover thermostat was used to control the temperature and NVT ensemble was chosen to control the constant number of molecules, volume and temperature. Dynamic simulation ran by using pcff and use current charges with Ewald calculation for both electrostatic and Van Der Waals summation method.

F. Radial distribution function(RDF) and Mean square displacement(MSD)

Radial distribution function (RDF) analysis and mean square displacement was done by using Forcite calculation to study the interaction between carbamazepine reference which was located at the center and rigid with one unit cell of carbamazepine-succinic acid (CBZ-SA) co-crystal. Mean square displacement (MSD) analysis also was done for one unit cell of CBZ-SA co-crystal.

III. RESULTS AND DISCUSSION

A. *Carbamazepine-succinic acid (CBZ-SA) co-crystal facets*

According to [10], the predicted carbamazepine-succinic acid co-crystal morphology was shown as Figure 4. The co-crystal have 18 developed facets with major ones (1 0 -1), (1 0 1), (1 1 0), (0 1 1), (0 1 0), (2 0 0) and (0 0 2). Hartman and Perdok have developed a theory that relates crystal morphology to the crystal graph. They conclude that crystals were bounded by facets called flat facets that are parallel to at least two intersecting periodic bond chains. Flat facets have a non-zero step energy in any direction. The step energy were closely related to E_{hkl}^{slice}. Flat facets which have larger value of slice energy grow generally slow and have small attachment energy. The most prominent facets on a growing crystal were the facets that have small growth rate and therefore it have high morphological importance [12].

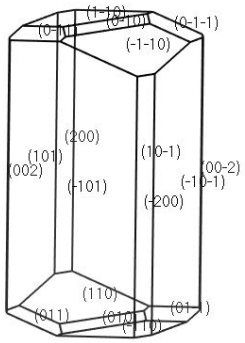
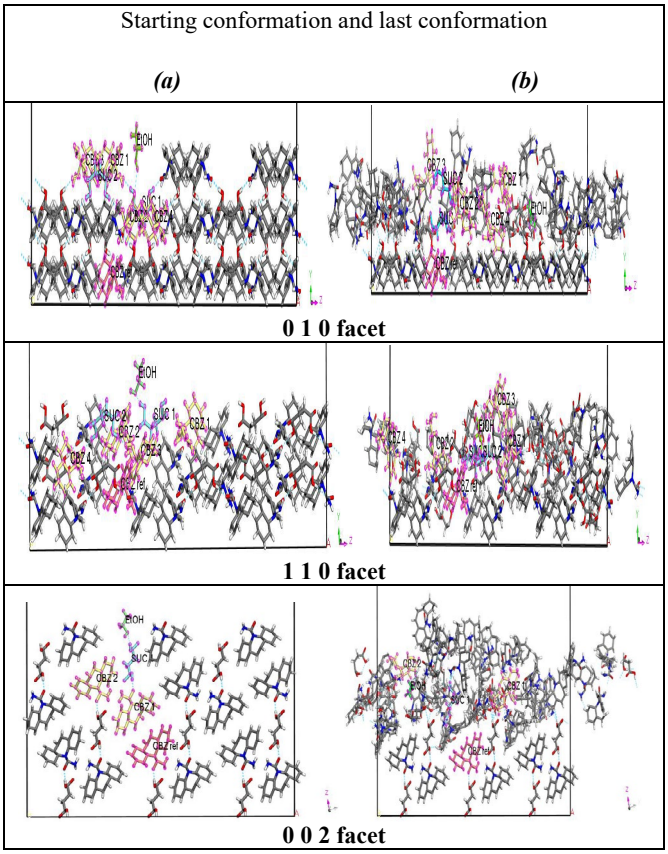


Fig. 4: Morphological prediction of carbamazepine-succinic acid (CBZ-SA) co-crystal [10]

Figure 4 shows the morphological prediction of CBZ-SA co-crystal have a plate-like shape structure[10]. From the results, the (1 0 -1) facets has the strongest morphological importance because of the largest interplanar distance ($d_{1\,0-1}$ =14.929 Å) and total habit facet area (47.89%). The (1 0 1) facet possess the second largest facet area while (0 0 2) facets have the lowest morphological importance with surface area 1.97 %. The dominant facets consist of facets (1 0 -1), (1 0 1), (1 1 0), (0 1 1), (0 1 0), (2 0 0) and (0 0 2).

2.1 Dissolution behavior and transport properties for each facets

The analysis for one unit cell of CBZ-SA co-crystal shows that the patterns of hydrogen bonds occur very frequently. Carbamazepine has carboxamide groups to be invoked for rational design of novel co-crystal. The synthons that may formed in CBZ co-crystal consist of amide-acid heterodimer, amide-amide homodimer and amide-acid-H2O heterosynthon. Carbamazepine and succinic acid exhibit amide-acide heterodimer with 2:1 stoichiometric ratio [13]. The heterosynthon formation is more preferable compared to homosynthon if both components for heterosynthon complement each other [14]. The application of the RDF was used to study the specific interactions of the hydrogen bond. In radial distribution function graph g(r)-r, chemical bond and hydrogen bond exist when the peak is within 3.5 Å while Coulumb and Van der Waals forces prevail when the peak is greater than 3.5 Å [15]. In order to understand the interactions of reference molecules with one unit cell of molecules of facets, the co-crystal schematic view of starting and last frame of CBZ-SA habit facets are explored and displayed in Figure 5. This figure shows the movement and distance of one unit cell of CBZ-SA co-crystal from the carbamazepine reference molecule.



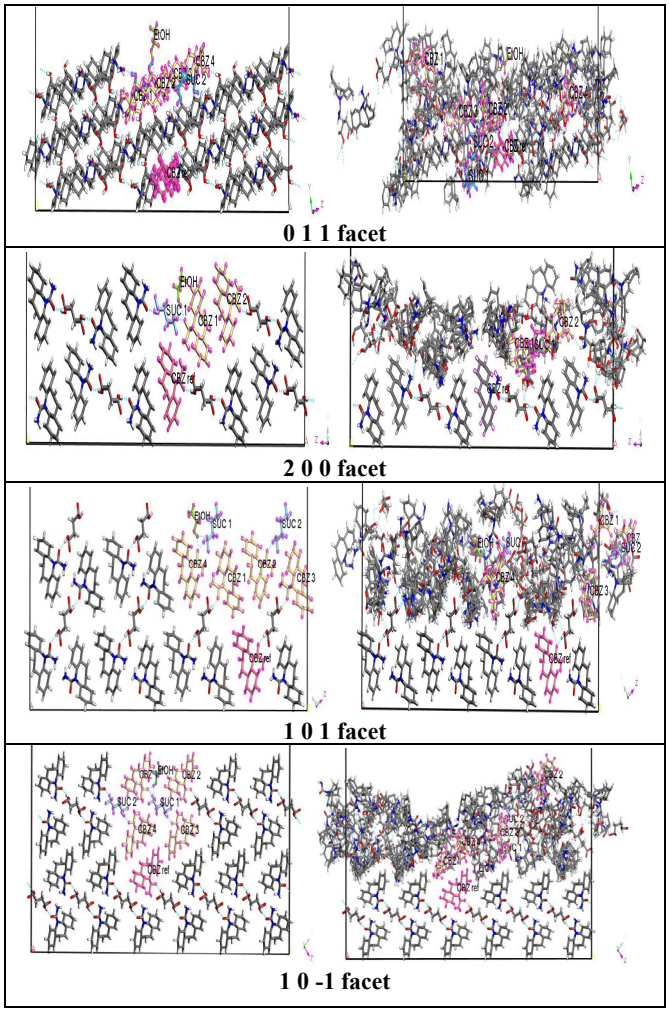
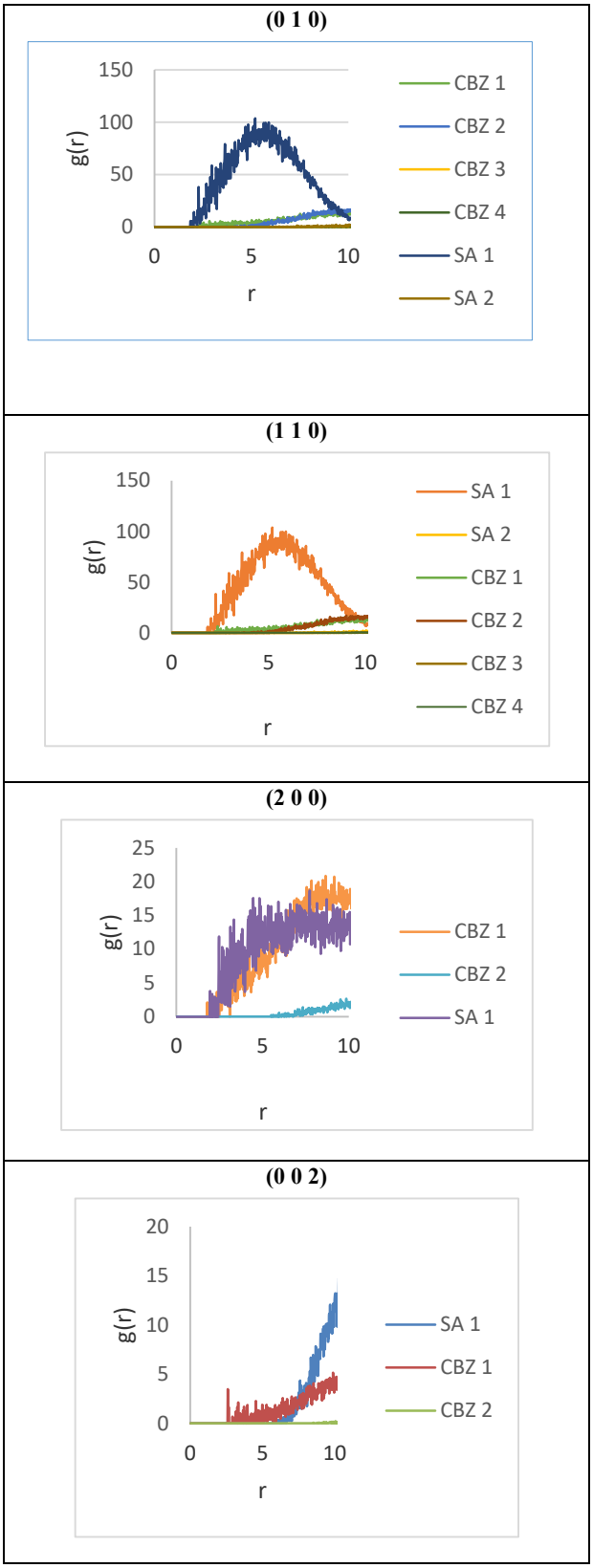


Fig. 5: Schematic view of (a) starting conformation and (b) last conformation of seven dominant facets of CBZ-SA co-crystal



2.2 Radial distribution function (RDF) analysis for each molecules in a facet

Hydrogen bonds play an essential role in numerous chemical, biochemical and biological processes and provide stability in many systems. Thus, radial distribution function (RDF) analysis had been conducted to examine the strength of hydrogen bonding interaction within the CBZ reference with one unit cell of CBZ-SA co-crystal. The correlation function g(r) reflects the distribution and correlation of atoms in the system. To explain the interaction between the crystal surface and reference molecule, the first peak for each molecule of the seven important crystal facets were studied from the graph. For the interaction that occur between carbamazepine with the carbamazepine reference molecule, r value for each facets that are less than 3.5 Å indicating the presence of hydrogen bond. Hydrogen bonds energy is larger than Van der Waals energy, thus the formation of hydrogen bond is the main contributor to the growth rate of crystal facets which then influence morphology of the crystal [16]. In order to clarify the interaction in CBZ-SA co-crystal molecules, an analysis had been carried out on carboxamide groups of carbamazepine and carboxyl group of succinic acid in the co-crystal system. The asymmetric unit of co-crystal consist of the carbamazepine and succinic acid molecules being connected forming a supramolecular heterosynthon. The strongest hydrogen bond donor which is (acid O-H) should form a hydrogen bond with the best acceptor atom which is (amide C=O). Slightly weaker donor which is (amide N-H) will form a hydrogen bond with the weaker acceptor group (acid C=O) [14]. For the interaction of reference atom with carbamazepine molecules, hydrogen bonding exist in all seven facets. The RDF analysis for each facets were provided in Figure 6.

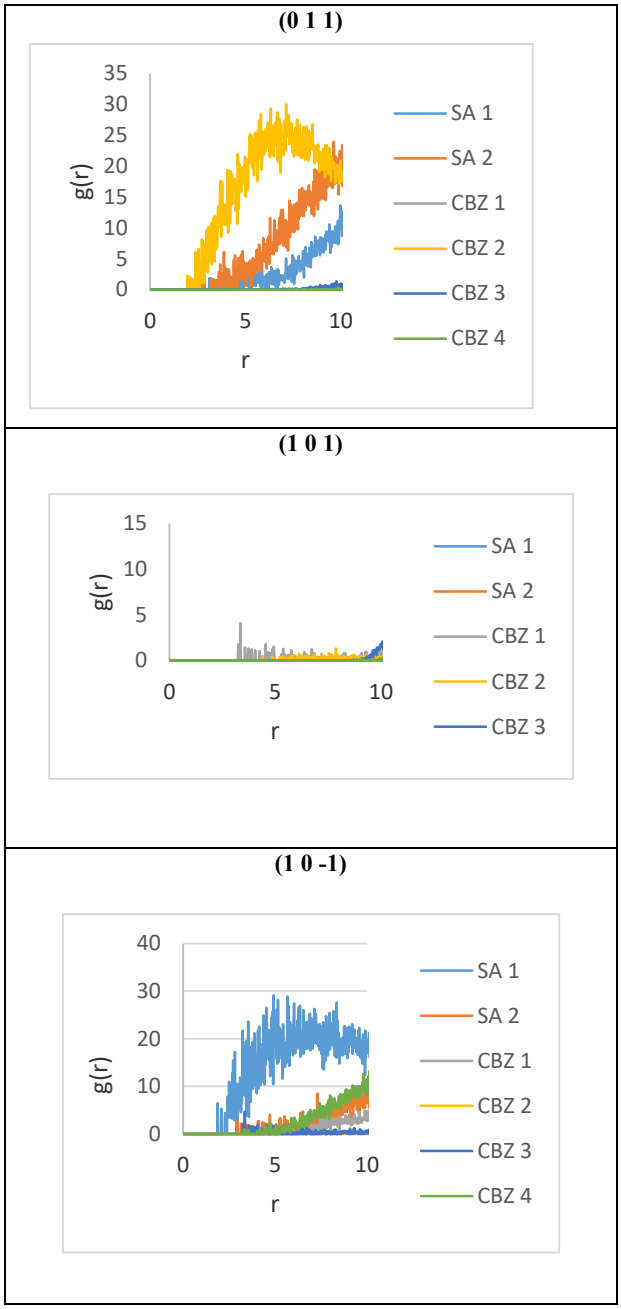
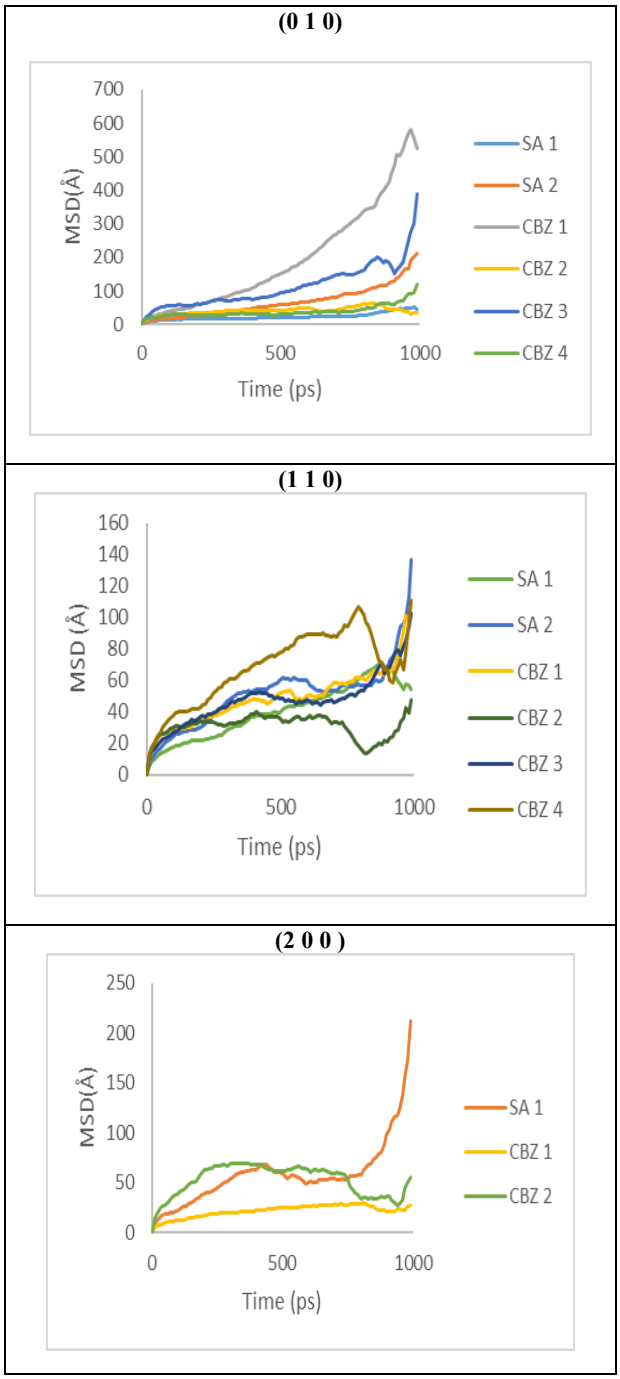


Fig. 6: Radial distribution function (RDF) graph

Figure 6 shows the molecule-molecule interactions analyzed by RDF graph and it will quantify the distributions of carbamazepine(CBZ) reference with one unit cell of unconstraint molecules. Only the molecules which were nearest to ethanol solvent was considered as one unit cell that will have interaction within the reference atom. For facets (0 1 0) and (1 1 0), the first peak of SA 1 molecule appear at 1.85 Å with the g(r) value of 5.74. This amide-acide heterodimer supramolecular synthon between CBZ reference and SA 1 shows that it is stronger compared to the amide-amide supramolecular synthon. This interaction is the good chemical combination as it is suitable for the co-crystal formation [17]. Molecules for facet (2 0 0) and facet (1 0 -1) also exhibit the same interaction as the first peak of CBZ 1 is at 1.95 Å and SA 1 is at 1.87 Å with the g(r) value of 5.74 and 6.47 respectively. Thus, stronger intermolecular hydrogen bond interactions that exist between carboxamide group of carbamazepine and adjacent hydrogen of succinic acid are the primary driving forces for the formation of co-crystal that can lead to the stability of the crystal structure [18]. Next, molecules for facet (0 0 2), (0 1 1) and (1 0 1), their first peak of CBZ 1 is at 2.59 Å, CBZ 2 is at 1.95 Å and CBZ 1 is at 3.25 Å respectively. The interaction that occur between the CBZ reference with CBZ molecules from each facet are amide-amide homodimer supramolecular synthon. This synthon interaction have weak interaction compared to the acide-amide interaction. Thus, it will lead to non-stability of crystal formation and subsequently affect the dissolution and solubility behavior of the crystal.

2.3 Mean square displacement method (MSD) for selected molecules in a facet

The dynamics of molecule has the colliding and recolliding with each other. Although there is no directed motion, a molecule will not remain indefinitely in the circle of their present position. The mean square displacement (MSD) is a measure of the average distance a molecule can travels [19]. Diffusion coefficient is employed to evaluate the surface diffusion of carbamazepine and succinic acid molecules at each crystal facets which can be measured by the derivative of the mean square displacement method (MSD) with respect to time with the help of Einstein relation [20]. The trend of the graph from the MSD method for each facets was interpreted in Figure 7.



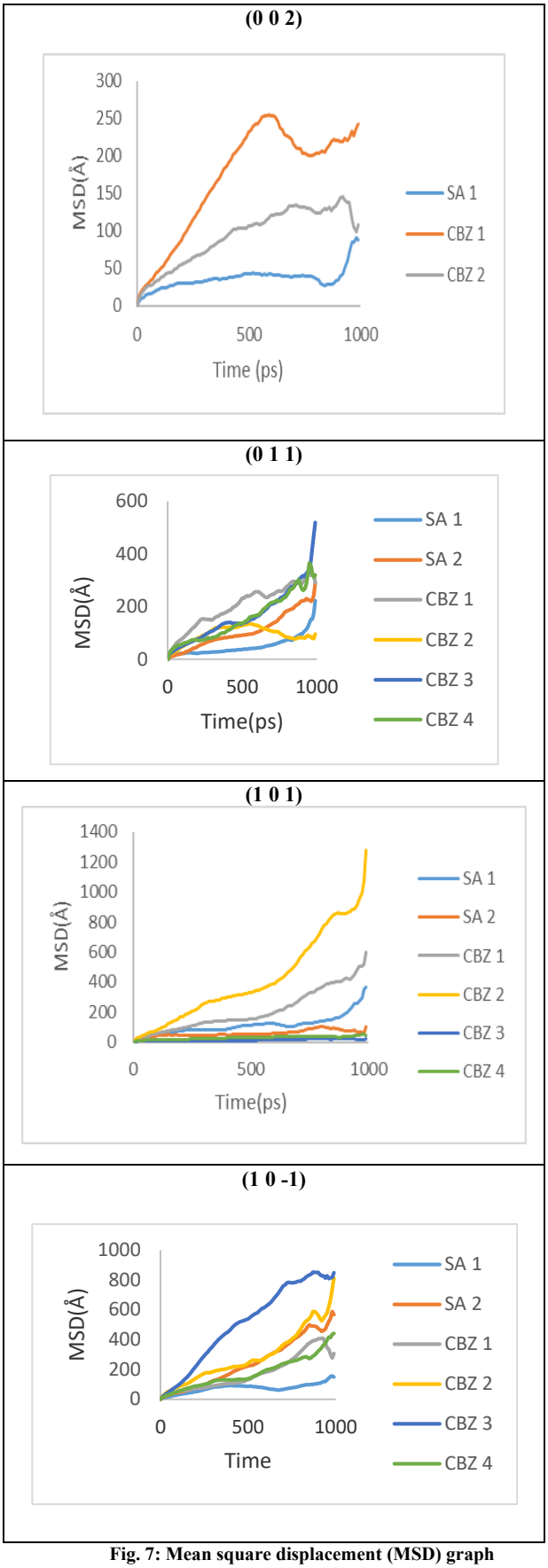


Fig. 7: Mean square displacement (MSD) graph

Figure 7 displays the MSD results of carbamazepine molecules as a function of simulation time. This results is proportional to the diffusion coefficient of the diffusing atoms. Particle movement was being affected by the displacement of the molecules. Thus, the larger value of slope demonstrate the stronger movement of the molecule [21]. Table 2 shows the diffusion coefficient value of molecules in each facets. The larger value of diffusion coefficient shows that weaker interaction of CBZ reference with crystal molecules exist. Diffusion coefficient for facet (0 1 0) and (1 1 0) is in the order of CBZ 1 > CBZ 3 > SA 2 > CBZ 4 > SA 1 > CBZ 2. CBZ 1 can be easily diffuse to the surrounding molecule because of the distance from the reference molecule is nearer compared to other molecules. For facets (2 0 0) and (0 0 2), one unit cell of the CBZ-SA co-crystal consist of two carbamazepine molecules and one succinic acid molecules. The hierarchy for the diffusivity of facets (2 0 0) and (0 0 2) are SA 1 > CBZ 1 > CBZ 2 and CBZ 1 > CBZ 2 > SA 1 respectively. The distance of each molecules with the reference molecule is very important as it greatly affect the diffusivity of the molecules. The farther the distance between each molecules, the type of interaction occur will become insignificant as the stronger hydrogen bond may be hard to form within the surrounding. For facet (0 1 1), (1 0 1) and (1 0 -1), the trend for the diffusion coefficient are CBZ 3 > CBZ 4 > CBZ 1 > SA 2 > SA 1 > CBZ 2, CBZ 2 > CBZ 1 > SA 1 > SA 2 > CBZ 4 > CBZ 3 and CBZ 3 > CBZ 2 > SA 2 > CBZ 1 > CBZ 4 > SA 1 respectively showing the molecules that will first to diffuse is the one with largest value of diffusion coefficient.

Table 2: Diffusion coefficient of molecules for each dominant facets

Molecules/ Facets	Diffusion coefficient, $m^2/s(x\ 10^{-10})$						
	0 1 0	**1 1 0**	**0 0 2**	**0 1 1**	**2 0 0**	**1 0 1**	**1 0 -1**
SA 1	3.25	5.99	3.43	10.76	8.57	19.21	8.68
SA 2	14.7	6.31	NA	22.62	NA	6.39	55.95
CBZ 1	50.8	5.65	21.7	27.34	1.71	45.98	38.29
CBZ 2	2.72	11.0	12.2	4.13	0.51	96.29	59.05
CBZ 3	19.8	4.97	NA	33.37	NA	1.74	91.67
CBZ 4	5.0	6.67	NA	29.95	NA	3.13	34.97

*NA= Not Available

IV. Conclusion

In this research work, MD simulation was used to achieve more knowledge about the interaction within the CBZ-SA co-crystal. Understanding the interaction exist between carbamazepine (CBZ) and succinic acid(SA) molecules with the reference atom increases the knowledge to describe the mechanism of stability of the co-crystal. The findings were two types of supramolecular synthon between amide-amide homodimer and acid-amide heterodimer generally formed between the molecules in one unit cell and reference. Acid-amide heterodimer formed by CBZ-SA molecules while amide-amide homodimer consist of CBZ-CBZ molecules interaction. Radial distribution function (RDF) analysis was done to examine the existence of hydrogen bonding in the co-crystal. It was shown that for the first peak of RDF analysis, SA 1 is exist for facet (0 1 0), (1 1 0) and (1 0 -1), CBZ 1 for facet (2 0 0), (0 0 2) and (1 0 1) and CBZ 2 for facet (0 1 1). It can be concluded that the stability of formation of the co-crystal was influenced by the type and strength of the hydrogen bond. Mean square displacement (MSD) method was being implemented in order to identify the distance between the reference molecules and the other molecules while highlighted the diffusion coefficient of each molecule in each facets. CBZ 1 for facets (0 1 0) and (0 0 2), CBZ 2 for facets (1 1 0) and (1 0 1), CBZ 3 for facets (0 1 1) and (1 0 -1) and SA 1 for facets (2 0 0) were the molecules that likely to be the first to diffuse because of the weak interaction that exist between the molecules with the reference.

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