Prediction of Energetic Surface Interaction of Aspirin-Aspirin Crystals Using Grid-Based Search Method

Norhafizah Binti Ismail Nasiruddin, Dr. Siti Nurul 'Ain Yusop

Faculty of Chemical Engineering, Universiti Teknologi Mara

***Abstract*—Shape and morphology of crystals is needed to be identified to make sure the crystals produce are the good crystals. Other than that, crystal is tends to agglomerated which will affect the production in industries. Thus, energy interaction studies were done to overcome this problem. Therefore, computational method was used to predict the morphology and surface energy interaction for aspirin crystal. In this research, HABIT98 program was used to predict the morphology of aspirin crystal and SYSTSEARCH program to predict the surface energy interaction of aspirin facet to aspirin molecule. As the result from this research, lattice energy for three different types of charges was obtain. Lattice energy from PM3 charges have nearest value compare with computational method done by Hammond et al which was -27.39 kcal/mol. Other than that, face of aspirin that have high surface energy interaction was (100). This due to this faces can form hydrogen bond with other molecules which hydrogen bond will give strong interaction and resulting in high surface energy.**

Keywords— Morphology, surface energy interaction, attachment energy, lattice energy, HABIT98, grid-search method, SYSTSEARCH.

I. INTRODUCTION

The morphology of crystals is needed to be identified to make sure the crystals produce are good crystals. It is important to identify because the morphology of crystals will influence the physical and chemical properties of the crystals. The change in morphology also will disturb the efficiency of manufacturing process. Other than that, morphology and stability of the crystals will also affect surface energy of crystals. Different faces of crystals will have different value of surface energy due to different molecular arrangement at the surface [1]. Some crystals also tend to agglomerated between each other. This condition will affect downstream process in industries at filtration process. To overcome this problem, morphology and surface interaction of crystals can be determine via laboratory experiments but this method is expensive and time consuming [2]. Therefore, many researchers was tried new way to study the morphology and surface interactions of the crystals which by using computational method.

A. Crystal Morphology

Morphology of the crystals can be affected by internal factor and external factor such as type of solvent used, temperature, super saturation and impurities. Morphology of the crystals can be predicted by calculating the lattice energy and attachment energy of the crystals using molecular modeling method. Morphology of the crystals relatively very related to growth rate of the crystals faces. Growth rate of every faces of the crystals can be differed to another. The growth rate of the crystals will differ in different condition such as type of solvent, temperature, super saturation and impurities. This cause the morphology of the crystals produce in different condition will vary [3].

For example, in case of Aspirin that was crystallized in different polarity of the solvent which is polar solvent and nonpolar solvent. The result shows unpaired (100) surface of Aspirin favor in the interaction with polar solvent while surface (100) has unfavorable interaction with polar solvent and (010) surface was stable both in polar and nonpolar solvent [4].

B. Crystal Faces

Different type of crystals has different faces form. In complete growing crystals, there are three different type of crystal faces possibly can be form. According to Periodic Bond Chain (PBC) theory that has been develops by Hartman and Perdok, the three types of faces are flat faces that also known as F-faces, stepped faces or S-faces and kink faces or K-faces. These three types of faces are categories based on the number of broken periodic chain at the facet. All of this type of crystals faces have different growth rate. In most cases that had been studied, F-faces have slowest growth rate between the two other faces which give this F-face have largest morphology importance (MI). Meanwhile, S-face and F-face have fast growing rate [5]. Crystal faces also can be representing in miler indices {hkl}.

C. Bonding Forces of Crystals

Bonding forces in crystal is very important for determining the crystal structure. Bonding forces of crystals hold atoms of the crystals in the arrangement of atomic packing. These bonding forces are important because the bonding forces will determine the arrangement of crystal packing and stability of the crystal packing. There are several types of crystal bonding forces which are hydrogen bonding force, covalent bonding force, ionic bond force and Van der Waal force.

Ionic bonding will produce two opposite charged ion. Ionic bonding involves electrostatic attraction between two type of ion which is anion and cation. Other than that, other type of forces is covalent bond. Covalent bond is also known as molecular bond which sharing electrons between atom. Van der Wall forces also one of the forces in intermolecular interaction of crystals. Van der Waal force is an attractive and repulsive force between atoms or molecules in crystal structure. Van der Wall force is weaker forces in crystals intermolecular interaction [6].

Hydrogen bonding is very important in crystals. This is because hydrogen bond will determine the strength of molecule in crystal lattice which also can affect the crystal structure. In polymorphism, hydrogen bond will link two molecules at their functional group [4].

For example in crystal packing of Aspirin, Hydrogen bond was link two respective carbonyl group of Aspirin molecule that formed dimer. This two of molecule was held together by strong Van der Waal forces [4].

D. Molecular Modeling

Molecular modeling is a computational technique to predict the physical and chemical properties of target molecules. Molecular modeling is also one of the ways that can be used to predict the morphology of crystal and predict the surface energy interaction of crystals. Researchers have developed molecular modeling technique to improve the performance and change the properties of desired material to meet the need of industries [8].

In molecular modeling to predict the morphology of crystal, there are several method that can be use which is attachment energy method and using Bravais-Friedel-Donnay-Harker (BFDH) method. Attachment energy method was developed by Hartman and Bennema [9]. In attachment energy method, there are several parameters that need to be calculated in order to obtain the morphology of the crystal. The parameters are lattice energy, attachment energy and slice energy. Attachment energy method gives that lattice energy is the summation of slice energy and attachment energy [1]. Bravais-Fridel-Donnay-Harker (BFDH) method, the faces that have the greatest interplanar spacing is low morphology importance faces which have high growth rate. From this method the growth rate is related with crystal form {hkl} and lattice geometry [10].

Other than that, surface interaction of crystal also can be determined using molecular modeling method. In molecular modeling method that used to predict the surface interaction between crystals, there are several characteristic that will be use which is appropriate potential force field and distance constrains [11].

II. METHODOLOGY

A. Materials

In this research, material used was Aspirin which also known as Acetylsalicylic acid. Aspirin is one type of non-steriodal anti-inflammatory drug which use to treat pain, fever, inflammation and also prevent heart attacks, stroke and blood clot [12]. Aspirin molecule has three different functional groups which are carbonyl group, phenyl group and acetyl group. Figure 2.1 shows the molecular structure of Aspirin. Aspirin crystal structure is monoclinic P21/c space group which has unit cell parameters of a=11.433 Å, b=11.395 Å, c=11.395 Å and β=95.68° which obtain from experimental finding. Aspirin crystal has four molecules per unit cell as shown in Figure 2.2.

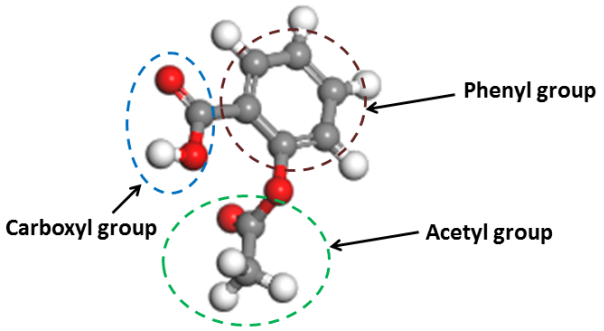


Figure 2.1: Molecular structure of Aspirin. The red color indicate Oxygen atom, grey color indicate Carbon atom and white color indicate Hydrogen atom.

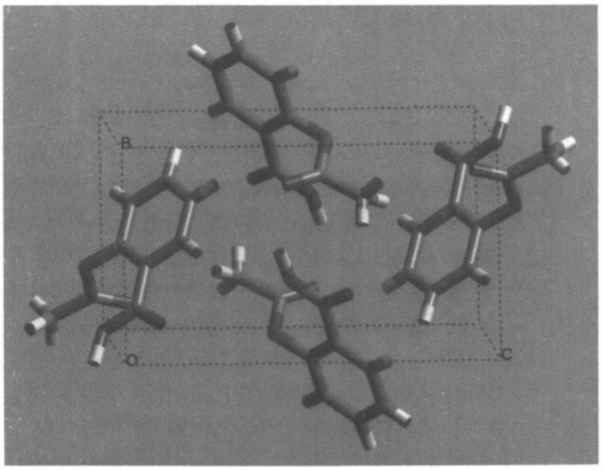


Figure 2.2: Unit cell of Aspirin [15].

B. Methodology

In this research, prediction of aspirin morphology was done first in other to predict the surface energy interaction between aspirin molecules and aspirin facets. To predict the morphology of the crystal, HABIT98 program was used and Systsearch program was used to predict the surface energy interaction between aspirin molecules to aspirin facets.

1) Prediction of Crystal Morphology using HABIT98

HABIT program was developed by Clydesdale et al. in 1996 [13]. From HABIT98 program, the crystal morphology was predicted using attachment energy method which the intermolecular interaction of the crystal was calculated. The intermolecular interaction of the crystals was consider the crystallographic structure and habit planes {hkl} that derives from Bravais-Friedel-Donnay-Harker (BFDH) rules [1].

Crystallographic Information File (CIF file) was used in HABIT98 program in other to predict the crystal morphology. The Crystallographic Information File (CIF file) was obtains from Cambridge Structure Database (CSD). From information of crystal in the CIF file, the atomic charges that obtain from quantum chemistry calculation was used to calculate the energies between the molecules of the crystal and symmetry operation of the crystal was also used. Atomic charges of the crystal were obtained using MOPAC. Potential function used was Mommany force field and atom-atom method was used to calculate the intermolecular force of the crystal which was attachment energy and lattice energy [14]. Summation of intermolecular forces was calculated within the thickness of d_{hkl} which lattice energy was considered within the radius limit of central molecules to surrounding molecules. Limiting radius used for the calculation was 30 Å. Lattice energy was calculated by selecting lattice (LATT) mode and information of bonding analysis and attachment energy was calculated by selecting FULL mode in HABIT98 program [6]. Ten possible faces was selected from Material Studio (MS) and used in HABIT98 to obtain the attachment energy of the selected faces. Then, central distance was calculated by using attachment energy for every faces that already obtained from HABIT98. Morphology of the crystal was visualized using SHAPE program by referring the central distance that had already been calculated.

2) Charges Calculation

In this research, charges of the Aspirin crystal were very important to be determined. This crystal charges is important to obtain because the crystal charges was used in calculation of lattice energy and attachment energy of the crystal. The charges of the crystal determined by using MOPAC with different Hamilton parameters which are AM1, MNDO and PM3 will differ [6]. The

different in attachment energy and lattice energy calculated with different MOPAC charges based on the way of every MOPAC charges were calculate. AM1 charges that also known as Austin Model 1. The charges were calculated based on Gaussian functions centered with various distances which the force between two atoms was modified. Other than that, MNDO charges were calculated based on orbital ionization potential and electrostatic interaction. PM3 charges than were calculated based on two Gaussian functions per atom [17].

3) *Surface energy determination*

Total surface energy of the crystal is proportional to surface area of the faces of the crystal. Specific surface energy was differs for different crystal faces due to molecular arrangement at the surface as the function of crystal orientation {hkl} is different. Dynamic molecular calculation was used to predict the surface energy of the crystal and simpler method by Walton was also used which was bond breaking model. Surface energy was calculated by using Equation 2.1 below [1].

$$\gamma_{hkl} = \frac{ZE_{att}d_{hkl}}{2V_{cell}N_A} \qquad \text{(Equation 2.1)}$$

Where, γ_{hkl} = surface energy of (hkl) face,
Z = number of molecules in the unit cell,
V_{cell} = unit cell volume,
E_{att} = attachment energy,
D_{hkl} = d spacing,
N_A = Avogadro's constant.

4) *Energy Interaction Determination*

Energy interaction of Aspirin crystals was determined by using SYSTSEARCH program. In this program, grid-based search method was used to the surface energy interaction of the crystals. To determine surface energy interaction using SYSTSEARCH program, input file was created. In input file, position of slab boundaries along x axis was stated which is in range -2.0 to 0.0 from the x axis. Other than that, step sizes for center of coordinates for probe molecules in Cartesian coordinate (xyz) were also stated in input file. Then, the energy interaction was calculated by using SYSTSEARCH program. The crystal slab has been created and the position of probe relative with slab was visualized in Material Studio. The energy interaction was then tabulated and graph was plotted [16].

III. RESULTS AND DISCUSSION

A. *Morphology Prediction of Aspirin*

In prediction for morphology of Aspirin, lattice energy and attachment energy was calculated. Morphology of Aspirin crystal was predicted using three different types of charges which calculated using MOPAC. The three different charges are AM1, MNDO and PM3. The morphology of the Aspirin crystal was obtained based on attachment energy that had been calculated for every faces. The attachment was calculated for ten predicted faces. The calculated lattice energy and morphology of the Aspirin crystal for every type of charges and experimental value was show in Table 3.1.

Based on Table 3.1, the value of lattice energy that that been calculated by using HABIT98 with force field Mommany was closed to computational method that had been done by Hammond et al and experimental method. Lattice energy calculated using PM3 charges has the most nearest value with computational method which done by Hammond et al. Other than that, morphology obtains from this method also closed to the experimental method and method done by Hammond et al. Figure 3.1 shows the morphology of Aspirin crystal obtain from experimental method which have calculated lattice energy -30.03 kcal/mol while Figure 3.2 shows the morphology of Aspirin crystal obtain by computational method done by Hammond et al with lattice energy -27.42 kcal/mol. Thus, percentage error of lattice energy for every type of charges are 1.75% error for AM1 charges, 2.92% error for MNDO charges and 0.109% error for PM3 charges.

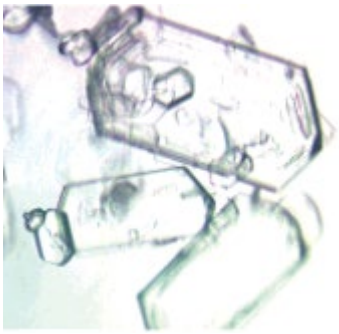


Figure 3.1: Morphology of Aspirin crystal obtains by experimental method [1].

Figure 3.2: Morphology of Aspirin crystal obtains by computational method done by Hammond et al [1].

Table 3.2 shows the comparison of attachment energy of Aspirin crystal for 10 predicted faces by using PM3 charges and experimental method. From this attachment energy, central distance was calculated to be used for obtain the morphology of the Aspirin crystal. As shown in Table 3.2, the attachment energy of Aspirin crystal that had been calculated no more less the same with attachment energy that obtain from experimental.

Table 3.1: Lattice energy and morphology of Aspirin crystal calculated with different MOPAC charges.

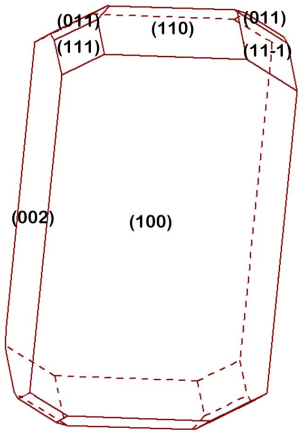
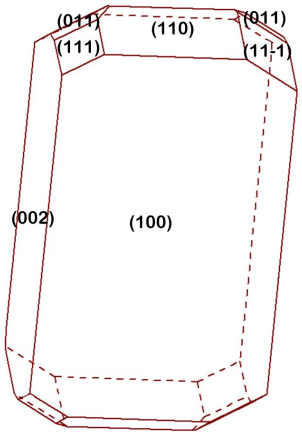
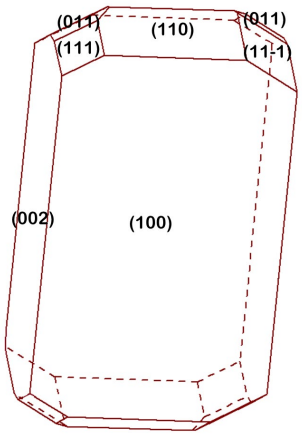
Parameter	Lattice energy (kcal/mol)	Morphology
AM1	-27.90	
MNDO	-26.60	
PM3	-27.39	

Table 3.2: Comparison of attachment energy of Aspirin with different type of charges.

Faces	PM3	Experimental
(1 0 0)	-4.48	-4.49
(1 1 0)	-15.78	-15.46
(0 1 1)	-18.23	-16.82
(0 0 2)	-9.67	-9.86
(1 0 -2)	-12.45	-
(1 1 -1)	-16.74	-
(1 1 1)	-16.61	-16.59
(1 0 2)	-18.40	-
(2 1 0)	-18.50	-
(0 1 2)	-20.40	-

Based on morphology obtain by using attachment energy calculated, the dominant faces present were (100), (110), (011), (002), (11-1) and (111). (110) face shows the biggest surface area and also has lowest attachment energy. Therefore, (100) was the most stable faces because it has lowest attachment energy. Face (100) also was the most morphological important compare to other faces and have slowest growth rate. Thus, this morphology and lattice energy obtain from molecular modeling was have good agreement with experimental method and other computational method done by other researchers. Morphology and attachment energy obtain by using PM3 charges was used in predicting surface interaction energy due to it has lower percentage error of lattice energy which was by comparing with lattice energy obtain by Hammond et al.

B. Surface interaction of Aspirin Crystal

Surface interaction of Aspirin crystals was determined by using grid-search method. In grid-search method, energy interaction of Aspirin molecules at every faces of Aspirin was calculated. Figure 3.3 shows the graph of population of Aspirin molecule attach at different range of interaction energy that had been plotted.

Based on Figure 3.3, at face (100) and (002) the highest population of the interaction is occur at binding energy in range of -59 to -60 kcal/mol while for other faces, (110), (011) and (111), the highest population of interaction was occur at binding energy below the range of -59 to -60 kcal/mol. This shows that face (100) and (002) have strongest surface interaction due to the most interaction was occur at lowest binding energy. Other than that, at face (100) the interaction was occurred at lowest binding energy compare to others faces. The lowest binding energy was the most stable interaction which will make the face was the strongest interaction. Thus, the strongest interaction of Aspirin crystals was occurred at face (100) and face (100) also more favorable to interact with other Aspirin molecule. The interaction of the Aspirin crystal also can be determined based on surface energy. Table 3.3 shows the comparison between attachment energy, interaction energy and surface energy of Aspirin crystal. As shown in Table 3.3, when the interaction energy decreases, the surface energy will increase. Face (100) has highest surface energy because it has lowest interaction energy. Thus, the most interaction will occur at face (100).

Table 3.3: Comparison between attachment energy, interaction energy and surface energy of Aspirin crystal.

Face	Interaction energy, kcal/mol	Attachment energy, kcal/mol	Surface energy, kcal/m^2 (10^{-27})
(100)	-88.6	-4.48	-3.99
(110)	-73.8	-15.78	-49.14
(002)	-68.8	-9.67	-18.38
(011)	-67.5	`-18.23	-65.64
(111)	-78.2	-16.61	-54.41

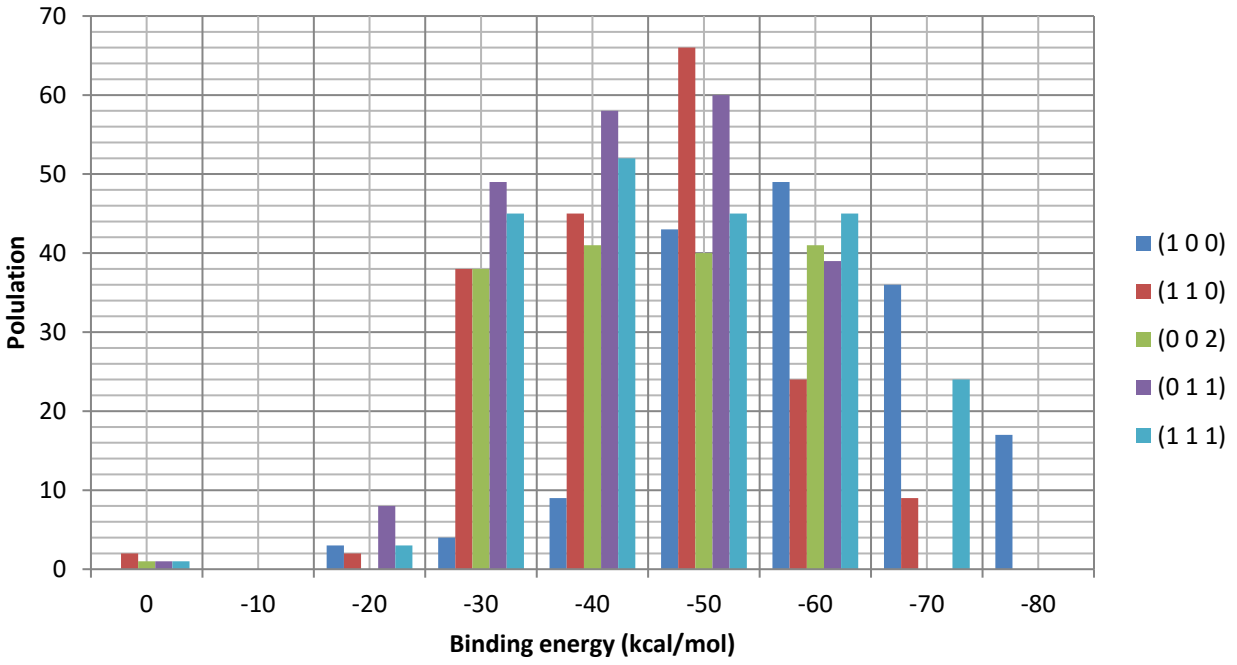
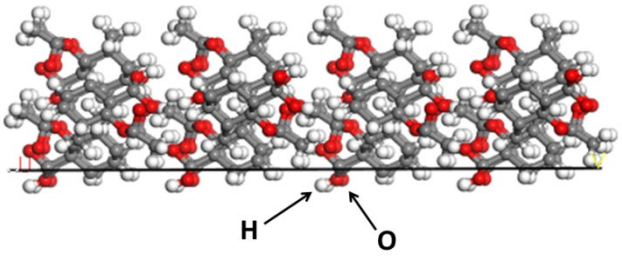


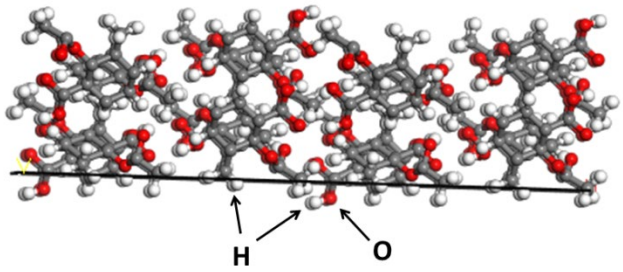
Figure 3.3: Graph of population of Aspirin molecule attach at different range of interaction energy.

Interaction energy of Aspirin crystals can be determined by referring the cleave surface for every faces of Aspirin crystal. This cleave surface can be obtain from morphology of the Aspirin crystal. At cleave surface of every faces of Aspirin crystal, type of atom that present at the cleave surface was determined. From this cleave and type of atom present, the surface that will have high energy interaction can be determined by obtain the atom that can produce hydrogen bonding with other Aspirin molecules.

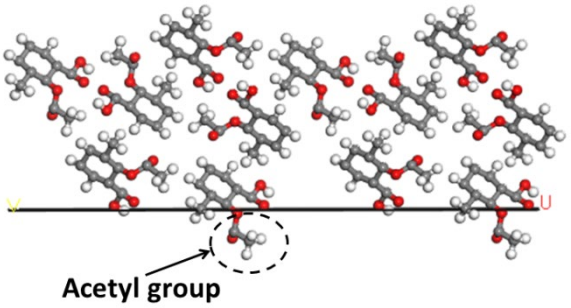
Figure 3.1 shows the cleave surface for every faces of Aspirin crystal



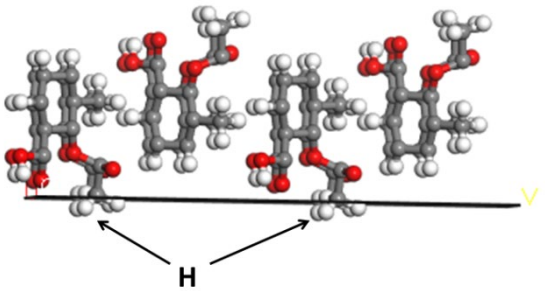
(a)



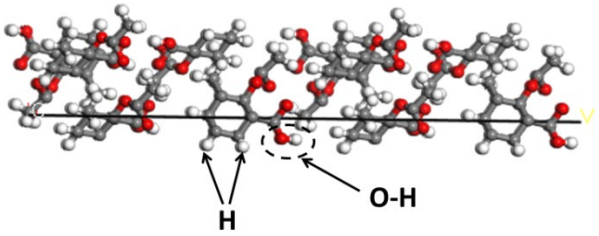
(b)



(c)



(d)



(e)

Figure 3.4: Cleave surface of Aspirin for (a) (100) face, (b) (110) face, (c) (011) face, (d) (002) face, (e) (111) face.

Figure 3.4 (a) shows (100) face which the most morphological important face and have strongest interaction energy. This face have strongest interaction energy due O-H atoms from carbonyl group were exposing at the surface. This hydrogen atom that expose at the surface of (100) face will give the hydrophilic characteristic to the surface. Other molecule that comes to this surface will provide hydrogen bond to the atom at this surface. This make this face has strong interaction and high surface energy due to the present of hydrogen bond. Face (002) also have strong interaction because hydrogen atoms from acetyl group was present in this surface which also can provide hydrogen bonding to other molecule that approach this surface which also will resulting in high surface energy at this face but face (002) has weaker surface interaction and surface energy if compare to face (100). Meanwhile, face (110) and (111) have low interaction energy. This is because at face (110), atoms that present at the surface were hydrogen atoms from acetyl group and O-H atoms from carbonyl group while at face (111) only hydrogen atoms from aromatic group and O-H atoms from carboxyl group were present at the surface. Both this surface cannot form hydrogen bond if other molecules approach the surface which will make the interaction low and surface energy at this face was low. Therefore, (100) face have higher surface interaction due to O-H atom from carbonyl group was expose at the surface of this face which can from strong hydrogen bind with other molecule which also resulting in high surface energy and high attachment energy. Thus, face (100) is the most stable face.

IV. Conclusion

In this research, I was studying the prediction of morphology of Aspirin crystal and to predict the surface energy interaction of Aspirin-Aspirin crystals. From the result that obtain, lattice energy for different type of charges which was AM1, MNDO and PM3 that have been calculated using HABIT98 program was -27.90 kcal/mol, -26.60kcal/mol and -27.39 kcal/mol respectively. Value of lattice energy for PM3 charges that had been calculated was closed to other computational method that had been done by Hammond et al. Surface energy interaction that had been obtain by using SYSTSEARCH program shows that face (100) have the highest energy interaction due to the faces can form hydrogen bond that will give high interaction and high surface energy. The objective was achieved.

Acknowledgment

In preparing this research, I was in contact with many people, researchers, academicians and practitioners. They have contributed towards my understanding and thought to obtain the finding of this research. In particular, I wish to express my sincere to my main research supervisor, Dr. Siti Nurul ‘Áin Yusop, for encouragement, guidance, critics and friendship. Other than that, I also want ti thank Universiti Teknologi Mara (UiTM) to give an opportunities for me doing this research. Lastly, I also want to thanks all people that involve during my journey in finishing this research project.

References.

[1] Robert B. Hammond, Klimentina Pencheva & Kevin J. Roberts. (2006). A Structural-Kinetic Approach to Model Face-Specific Solution/Crystal Surface Energy Associated with the Crystallization of Acetyl Salicylic Acid from Supersaturated Aqueous/Ethanol Solution. *Crystal Growth & Design*, 1324-1334

[2] C. Schmid, J. Ulrich. (2012). Morphology Prediction of Crystals Grown in The Presence of Impurities and Solvent - An Evaluation of The State of The Art. *Journal of Crystal Growth*, 168-173.

[3] Sendhil K. Poornachary, Pui Shan Chow & Reginald B. H. Tan. (2012). Application of Molecular Modeling in Pharmaceutical Crystallization and Formulation. In B. Rai, *Molecular Modeling for the Design of Novel Performance Chemicals and Materials* (pp. 157-186). London: CRC Press Taylor & Francis Group.

[4] T. Li, B. Li, M. S. Tomassone. (2006). Surface Characterization of Aspirin Crystal Planes Using Molecular Dynamic Simulations. *Chemical Engineering Science*, 5159-5169.

[5] Singh, M. K. (2006). First Principle Study of Crystal Growth Morphology: An Application to Crystalline Urea. *Cornel University Library*.

[6] Yusop, S. N. (2014). *Characterisation of the Morphological and Surface Properties of Organic Micro-Crystalline Particles.* England : University of Leeds.

[7] Houcine Ghalla, N. R. (2010). Theoritical modeling of infrared spectra of the hydrogen and deuterium bond in aspirin crystal. *Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy*, 37-47.

[8] Rai, B. (2012). Basic Concepts in Molecular Modeling. In B. Rai, *Molecular Modeling for the Design of Novel Performance Chemicals and Material* (pp. 1-26). New York: CRC Press Taylor & Francis Group.

[9] Fanfan Shen, Penghao Lv, Chenghui Sun, Rubo Zhang & Siping Pang. (2014). The Crystal Structure and Morphology of 2,4,6,8,10,12-Hexanitro-2,4,6,8,10,12-hexaazaisowurtzitane (CL-20) p-Xylene Solvate: A Joint Experimental and Simulation Study. *Molecules* , 18574-18589.

[10] G. Clydesdale, R. Docherty & K.J. Roberts. (1991). HABIT - a program for predicting the morpholdgy of molecular crystals. *Computer Physics Communications* , 311-328.

[11] R. B. Hammond, K. Pencheva, and K. J. Roberts. (2007). Molecular Modeling of Crystal-Crystal Interactions between the r- and â-Polymorphic Forms of L-Glutamic Acid Using Grid-Based Methods. *Crystal Growth & Design*, 875-884.

[12] C. Muthuselvi, M. Dhavachitra, S. Pandiarajan. (2016). Growth and Characterization of Aspirin Crystal in the Phosphoric acid Medium. *Journal of Chemical and Pharmaceutical Research*, 806-814.

[13] Sendhil K. Poornachary, P. S. (2008). Impurities effect on the growth of molecular crystals: experiments and modeling . *Advance Power Technology*, 459-473.

[14] G. Clydesdale, K. J. Roberts & R. Docherty. (1996). HABIT95 - a program for predicting the morphology of molecular crystals as a function of the growth environment. *Journal of Crystal Growth*, 78-83.

[15] Meenan, P. (1997). Crystal Morphology Predictive Techniques To Characterize Crystal Habit: Application to Aspirin (C9H8O4).

[16] Hammond, R. B. (2011). Surface Systematic Search Program Manual.

[17] Cramer, C. J. (2004). *Essentials of Computational Chemistry (Second Edition) Theories and Models.* England: John Wiley & Sons Ltd.