MOLECULAR DYNAMICS SIMULATION OF IBUPROFEN CRYSTAL POLYMORPH

MOHAMMAD SAFUAN BIN MAT NOOR

UNIVERSITI MALAYSIA PAHANG

MOHAMMAD SAFUAN MAT NOOR BACHELOR OF CHEMICAL ENGINEERING 2013 UMP

SUPERVISOR'S DECLARATION

I hereby declare that I have checked this thesis and in my opinion, this thesis is adequate in terms of scope and quality of the award of the degree of Bachelor of chemical engineering

Signature:…….

Name of Supervisor: DR. FATMAWATI BINTI ADAM

Position: LECTURER

Date: 27 JANUARY 2013

STUDENT'S DECLARATION

I hereby declare that the work in this thesis is my own except for quotations and summaries which have been duly acknowledged. The thesis has not been accepted for any degree and is not concurrently submitted for award of another degree.

Signature:……

Name: MOHAMMAD SAFUAN BIN MAT NOOR

ID Number: KA09134

Date: 27 JANUARY 2013

MOLECULAR DYNAMICS SIMULATION OF IBUPROFEN CRYSTAL POLYMORPH

MOHAMMAD SAFUAN BIN MAT NOOR

Thesis submitted in partial
fulfillment of the requirements for the award of the
degree of Bachelor of Chemical Engineering

Faculty of Chemical and Natural Resources Engineering
UNIVERSITI MALAYSIA PAHANG

FEBRUARY 2012

Dedicated to my parents

Mr Mat Noor Bin Mat Yatim and Mrs Raimi Binti Yahaya,

my family and friends

ACKNOWLEDGEMENTS

I am grateful and would like to express my sincere gratitude to my supervisor Dr. Fatmawati Adam for her germinal ideas, invaluable guidance, continuous encouragement and constant support in making this research possible. She has always impressed me with her outstanding professional conduct, her strong conviction for science. I appreciate her consistent support from the first day I applied to graduate program to these concluding moments. I am truly grateful for her progressive vision about my training in science, her tolerance of my naïve mistakes, and her commitment to my future career.

My sincere thanks go to master student, Mrs. Siti Hana Abu Bakar for helping me to understand the fundamental of molecular dynamics simulation. Not to forget all my lab mates and members of the staff of the Faculty of Chemical & Natural Resources, UMP, who helped me in many ways and made my stay at UMP pleasant and unforgettable.

I acknowledge my sincere indebtedness and gratitude to my parents, Mr. Mat Noor Bin Mat Yatim and Mrs Raimi Binti Yahaya for their love, dream and sacrifice throughout my life. I cannot find the appropriate words that could properly describe my appreciation for their devotion, support and faith in my ability to attain my goals until I achieve this level of education. Also thanks to my siblings Mr. Mohd Zulkipeli, Mr Mohamad Rizal, Mrs. Siti Rosmawati, Mrs. Roziana, Mrs Siti Noor Ain, Mr. Mohd Firdaus, Mr. Muhammad Khairul Azam and Ms. Nurul Fatihah for their contribution for me and their support. Special thanks should be given to my committee members. I would like to acknowledge their comments and suggestions, which was crucial for the successful completion of this study.

MOLECULAR DYNAMICS SIMULATION OF IBUPROFEN CRYSTAL POLYMORPH

ABSTRACT

Ibuprofen (iso-butyl-propanolic acid) is one of the Active Pharmaceutical Ingredients (API) that uses to treat a symptom of rheumatism, arthritis, fever, as an analgesic (pain reliever). This study aims to identify which solvents should affect the polymorph of ibuprofen begins from the crystallization solution. The Molecular Dynamics Simulation and Fourier transform infrared (FTIR) is used to recognize which molecules that form hydrogen bond in the ibuprofen crystal polymorph. The study analysis has shown that the higher hydrogen bond between the atoms will contribute to the ibuprofen crystal polymorph. As the conclusion, only the selected atoms will contribute in the formation of desired crystal polymorph of ibuprofen.

Keywords : radial distribution function, diffusion coefficient, hydrogen bonding

SIMULASI DINAMIK MOLEKUL IBUPROFEN KRISTAL POLIMORF

ABSTRAK

Ibuprofen (iso-butil-propanolic asid) adalah salah satu daripada Ramuan Aktif Farmaseutikal (API) yang digunakan untuk merawat gejala penyakit reumatisme, artritis, demam, sebagai analgesik (pelega kesakitan). Kajian ini bertujuan untuk mengenal pasti pelarut mana akan menjejaskan polimorf ibuprofen bermula dari larutan kristal. Simulasi Dinamik Molekul dan Jelmaan Fourier Inframerah (FTIR) digunakan untuk mengiktirafkan molekul yang membentuk ikatan hidrogen di ibuprofen Kristal polimorf. Analisis kajian telah menunjukkan bahawa hidrogen yang lebih tinggi ikatan antara atom akan menyumbang kepada ibuprofen kristal polimorf. Sebagai kesimpulan, hanya atom yang dipilih akan menyumbang dalam pembentukan diingini kristal polimorf ibuprofen.

Katakunci: fungsi agihan jejarian, pekali resapan, ikatan hidrogen

TABLE OF CONTENT

		Page
SUPERVISOR'S DECLARATION		i
STUDENT'S DECLARATION		ii
TITLE PAGE		iii
ACKNOWLEDGEMENT		v
ABSTRACT		vi
ABSTRAK		vii
LIST OF TABLES		xii
LIST OF FIGURES		xiii
LIST OF SYMBOLS		xviii
LIST OF ABBREVIATIONS		xix
CHAPTER 1 BACKGROUND OF THE RESEARCH		
1.1	Introduction	1
1.2	Background of Proposed Study	1
1.3	Problem Statements	2
1.4	Research Objectives	3
1.5	Research Questions/ Hypothesis	3

1.6 Scope of Study 3

1.7 Expected Outcome 4

1.8 Significance of Study 4

1.9 Conclusion 5

CHAPTER 2 LITERATURE REVIEW

2.0 Introduction 5

2.1 Crystallization 7

2.2.1 Crystallization of Active Pharmaceutical Ingredients (APIs) 9

2.2.2 Crystallization of Ibuprofen 11

2.2 Polymorphism 12

2.2.1 Polymorphism of Active Pharmaceutical Ingredients (APIs) 13

2.2.2 Polymorphism of Ibuprofen 15

2.3 Iso-Butyl-Propanolic Acid (Ibuprofen) 19

2.4 Solvent 23

2.5 Molecular Dynamic Simulation 25

2.5.1 Molecular Dynamic Simulation Of Active Pharmaceutical Ingredients (APIs) 27

2.6 Radial Distribution Function 29

2.7 Diffusion 31

2.8 Fourier transform infrared (FTIR) 33

CHAPTER 3 METHODOLOGY

3.1 Computer Simulation 35

3.1.1 Simulation Work 35

3.1.2 Molecular Labeling 39

3.2 Experimental Work 40

CHAPTER 4 RESULTS AND DISCUSSION

4.1 Simulation Data 42

4.1.1 Pure system 44

4.1.1.1 Ibuprofen 44

4.1.1.2 Ethanol 46

4.1.1.3 Ethyl Acetate 49

4.1.2 Binary system of solute solvent 51

4.1.2.1 Ethanol Mixture 51

4.1.2.2 Ethyl Acetate Mixture 56

4.2 Experimental data 61

4.2.1 Discussion 61

4.2.1.1 Pure system 61

4.2.1.2 Binary System of solute solvent 64

4.2.2 Solubility 67

CHAPTER 5 CONCLUSION AND RECOMMENDATIONS

5.1 Conclusions 69

5.2 Recommendations for Future Research 70

REFERENCES 71

APPENDIX

APPENDIX A Snapshots of Pure System 75

APPENDIX B Snapshots of Binary System 77

APPENDIX C Infrared Absorption Frequencies 78

APPENDIX D Experimental Instruments 82

LIST OF TABLES

		Page
Table 2.1	Mean aspect ratio of ibuprofen crystals from various solvents	17
Table 2.2:	Properties of Ibuprofen	20
Table 3.1	Molecular dynamics simulation details for the pure methanol, ethanol and p-xylene using the COMPASS force field.	38
Table 3.2	Molecular dynamic simulation details for 2,6-DHB in methanol, ethanol and p-xylene mixtures using the COMPASS force field.	38
Table 4.1	Ibuprofen in solvents	67
Table C.1	Characteristic Infrared Absorption Frequencies	78
Table C.2	Characteristic Ir Absorption Frequencies Of Organic Functional Groups	79
Table C.3	Ir Absorption Frequencies Of Functional Groups Containing A Carbonyl (C=O)	81

LIST OF FIGURES

Page

Figure 2.1 SEM-photograph of ibuprofen tablet surface. (a) Ibuprofen control; (b) ibuprofen crystallized in the presence of sucrosemonolaurate and dextran. 16

Figure 2.2 SEM photographs of the ibuprofen crystals. (a) Control; (b) crystallized without additives; (c) crystallized in the presence of polysorbate 80; (d) crystallized in the presence of sucrosemonolaurate; (e) crystallized in the presence of hydroxypropyl cellulose; (f) crystallized in the presence of sucrosemonolaurate and dextran 200; (g, h) crystallized in the presence of sucrosemonolaurate and hydroxypropyl cellulose. 18

Figure 2.3 Ibuprofen molecular structures 19

Figure 2.4 ibuprofen optimized structures of (a) neutral ground state ibuprofen. (b) radical anion (A^-), (c) radical cation (A^+), and (d)the deprotonated from (A^-). 21

Figure 2.5 Snapshots from the molecular dynamics simulations of the HMX–acetone solvent interfaces. (a), (b), (c), (d) and (e) correspond to (1 0 0), (0 1 1), (1 0 $\bar{2}$), (1 1 $\bar{1}$) and (0 2 0) crystal faces, respectively. 27

Figure 2.6 Space for the evaluation of radial distribution function 29

Figure 3.1 Snapshot from Material Studio (Pure System) of the initial configuration of molecular dynamics simulation 36

Figure 3.2 Molecular structure defining the atomic number for molecular recognition.The figure shows that the molecular labeling for solute and solvents. 39

Figure 3.3 Fourier transform infrared (FTIR) 41

Figure 3.4 Thermomixer 41

Figure 4.1(a) RDF graph for O1-H33 in pure ibuprofen represents the hydrogen bonding 44

Figure 4.1(b) RDF graph for O2-H33 in pure ibuprofen represents the hydrogen bonding 45

Figure 4.2 Atoms interaction between O1-O1, H33-H33 and O2-O2 in pure ibuprofen 46

Figure 4.3(a) RDF graph for interaction between ethanol's oxygen with H3 and H6 ethanol in pure system 47

Figure 4.3(b) RDF graph for oxygen interaction in pure ethanol between COMPASS and OPLS (Saiz, et al, 1997) 48

Figure 4.4 Atoms interaction for O1-O1 and H6-H6 in pure ethanol 49

Figure 4.5 RDF graph for O1-H10, O1-H13, O2-H10 and O2-H13 interaction in pure ethyl acetate 50

Figure 4.6 Atoms interaction for O1-O1, O2-O2 and H13-H13 in pure ethyl acetate 51

Figure 4.7(a) RDF graph for O ethanol with H6 ethanol and H33 ibuprofen in binary system and between O ethanol and H6 ethanol in pure system 53

Figure 4.7(b) RDF graph for O1 ibuprofen with H6 ethanol and H33 ibuprofen in binary systems and between O1 ibuprofen and H33 ibuprofen in pure system 54

Figure 4.7(c) RDF graph for O2 ibuprofen with H6 ethanol and H33 ibuprofen in binary systems and between O2 ibuprofen and H33 ibuprofen in pure system 55

Figure 4.8 Atoms interaction between O1ibuprofen with O ethanol and O2 ibuprofen with O ethanol in ethanol mixture 56

Figure 4.9(a) RDF graph for O1 ethyl acetate with H33 ibuprofen and H13 ethyl acetate in binary system and between O1 ethyl acetate and H13 ethyl acetate in pure system 58

Figure 4.9(b) RDF graph for O2 ethyl acetate with H33 ibuprofen and H13 ethyl acetate in binary system and between O2 ethyl acetate and H13 ethyl acetate in pure system 58

Figure 4.9(c) RDF graph O1 ibuprofen with H11 ethyl acetate and H33 ibuprofen in binary system and between O1 ibuprofen and H33 ibuprofen in pure system 59

Figure 4.9(c) RDF graph O1 ibuprofen with H11 ethyl acetate and H33 ibuprofen

in binary system and between O1 ibuprofen and H33 ibuprofen in pure system 59

Figure 4.9(d) RDF graph for O2 ibuprofen with H11 ethyl acetate and H33 ibuprofen in binary system and between O2 ibuprofen and H33 ibuprofen in pure system 59

Figure 4.10 Atoms interaction between O1 ibuprofen with O1 ethyl acetate, O1 ibuprofen with O2 ethyl acetate, O2 ibuprofen with O1 ethyl acetate and O2 ibuprofen with O2 ethyl acetate in ethyl acetate mixture 60

Figure 4.11(a) Ethanol infrared FTIR analysis pattern 62

Figure 4.11(b) Ethyl acetate infrared FTIR analysis pattern 62

Figure 4.11(c) Hexane infrared FTIR analysis pattern 63

Figure 4.12(a) Ethanol mixture infrared FTIR analysis pattern 64

Figure 4.12(b) Ethyl acetate mixture infrared FTIR analysis pattern 65

Figure 4.12(c) Hexane infrared FTIR analysis pattern 65

Figure A.1 Ibuprofen 75

Figure A.2 Ethanol 75

Figure A.3 Ethyl Acetate 76

Figure B.1 Ethanol Mixture 77

Figure B.2 Ethyl Acetate Mixture 77

Figure D.1 Thermomixer 82

Figure D.2 Vacuum Pump 82

LIST OF SYMBOLS

t	Time
D	Diffusion coefficient
Å	angstrong
C	Concentration
r	Radius
ρ	Density
N	Number of molecules
r	radial
ps	pico second
ns	nano second
g (r)	Radial distribution function

LIST OF ABBREVIATIONS

DHB	Dihydroxybenzoic Acid
COMPASS	Condensed-phase optimized molecular potential for atomistic simulation studies
NVE	Microcanonical Ensemble
NPT	Isobaric-Isothermal Ensemble
RDF	Radial distribution function
MSD	Mean square displacement
OPLS	Optimized Potentials for Liquid Simulations

CHAPTER 1

INTRODUCTION

In this chapter, its cover why the ibuprofen is used as the main element in the active pharmaceutical ingredients for the research. In this chapter also cover what are the problems in the pharmaceutical industry and to be specified the problem in the crystallization of ibuprofen polymorph. Besides that, the chapter will cover all the objectives in this study and what are the significances of this study toward our future development in the pharmaceutical sector.

1.1 Background of Study

Ibuprofen is one of the famous active pharmaceutical ingredients (API) in the current pharmacy industry. Ibuprofen or iso-butyl-propanoic phenolic acid is of being a

well known drug that used to treat a symptom of rheumatism, arthritis, fever, as an analgesic (pain reliever), especially where there is an inflammatory component and dysmenorrhea. It is also applicable to use for pericarditis and patent ductus arteriosus (Derksen, 1995). Ibuprofen is a common non-steroidal anti-inflammatory drug (NSAID). NSAID can be described as the drugs with analgesic and antipyretic (fever reducing) effects and which have higher dose anti-inflammatory effects. Besides that, the ibuprofen is known to have an effect of antiplatelet, though it is relatively mild and somewhat short-lived if compare with others API such as aspirin and others better known antiplatelet drugs. Aspirin breaks down in the solution which completely different with the ibuprofen. Ibuprofen in which state is stable and that makes the ibuprofen available in the topical gel form thus can be absorbed by the skin, and can be used for the sports injuries that theoretically have the least risk of digestion problem. Besides this properties of the ibuprofen, ibuprofen is classified as an important part or core in the medicine of the World Health Organization's" WHO Model List of Essential Medicines", which is a list of minimum medical needs for basic health care system (Kouimtzi, 2009).

1.2 Problem Statement

Polymorphism and solvate formation represents a major issue in pharmaceutical crystallization to the pharmaceutical industry and in terms of patent establishment and protection, reliability of production, and stability on storage and in processing. So, it is very compulsory to study the method in order to solve the problem in the pharmaceutical crystallization. Different types of solvent used will affect the interaction between the

solute-solvent and how do solute-solvent interactions to reflect the polymorphism due to the different solubility. The chosen of solvent also will be considered in this research for the ibuprofen crystal polymorph.

1.3 Research Objectives

This study aims to identify which solvent should affect the polymorph of ibuprofen begin with the crystallization solution and to investigate the correlation between the intermolecular forces of the molecules by the radial distribution function and hydrogen bond existing in the structure.

1.4 Research Questions/Hypothesis

The research question in this study is to identify which solvent will affect the polymorph of ibuprofen by the crystallization solution and to relate between inter-atomic distances between specified atoms in solute molecules that is ibuprofen.

1.5 Scope of Study

The study covers the research by the molecular dynamics simulation and by the experimental analysis. The molecular dynamics simulation consists of 2 systems which pure and binary system at 298.15K. It is will include the system for ethanol and ethyl

acetate. For the experimental analysis, the study will cover by the molecular recognition by using the Fourier transform infrared (FTIR) for the ethanol, hexane and ethyl acetate at saturated solution at 298.15K.

1.6 Expected Outcome

The expected outcome of this study is to clearly understand on how the solute-solvent interaction influences the crystallization by the analysis through the experimental study and also through a simulation study. Another outcome predicted is how the different solvent used affects the solubility of an ibuprofen by study of experiment and by the simulation.

1.7 Significance of Study

There are 4 significance of this study which towards our medical, engineering, economics and environment. For the medical aspects, the efficiency of the drug depends on its solubility which strongly influence by the choice of crystal structure used in processing the drug. For the second aspect which the engineering aspect, this study will able fully understand the correlations in the inter-atomic distances between specified atoms in solute molecules by determine the of Radial Distribution Function (RDF). And in the economic aspect, by using the molecular dynamic simulation all the new therapies and to develop the existing one can only be done by using the molecular dynamic simulation since the price for the active pharmaceutical ingredients is expensive.

Meanwhile, in the environmental aspect, the simulation will prevent the dispose of hazardous waste to the environment.

1.8 Conclusion

At the conclusion, in this chapter able to identify why this study has been proposed and what is the problem with this study. All the scope of study must fully cover in order to achieve our objective in this study and what will it's done towards our future in terms of medical, engineering, economics and environment.

CHAPTER 2

LITERATURE REVIEW

2.1 Introduction

This chapter is the review of previous research on the related topic with this study and by this literature review, helps fully understand that study that had been done and also the problem that current researcher try to solve for the benefit of the human kind and also all the living things in the earth. One of the objectives of this chapter is to understand the full concept and ideas about the ibuprofen, crystallization, active pharmaceutical ingredients (APIs), dynamic simulation and also all the aspects related to the topic of research. It will explain the application of the ibuprofen in the current pharmacy industry and also the important aspect that need to be considered in the producing the crystal

ibuprofen. Besides that, it will also explain about the polymorphism also for the ibuprofen.

The literature review is done based on the journals that are related ibuprofen crystal polymorph and also the dynamic simulation of it. The literature review will cover the characteristic of ibuprofen. This chapter will also cover the active pharmaceutical ingredients (APIs). The software used in the simulation also will be considered to gain the most accurate result for the simulation of the compound. This chapter will let the reader know the importance of ibuprofen. The concept of crystallization method used in obtains the crystal structure of ibuprofen.

2.2 Crystallization

Crystal that obtains from the solution by the process called crystallization, Crystallization is a procedure used in the chemical industries for the preparation of the many types of solid (e.g. pharmaceutical products, chemical intermediates, specialty chemicals, catalyst) (Micheal et al. 2008) and it's widely used for the purification of drugs during the final stages of the process under the pharmaceutical products industries (Garekani and Sadeghi, 2001). Many drugs exist in the crystalline solid form because of the stability and ease handling during the various stages of the process and development. Crystalline solid can appear in the form of polymorph, solvates or hydrates (Jacob et al. 2011). Several key properties of the resultant materials originate from this process,

including chemical purity and composition, internal structure (polymorph state), size and shape distribution and detect density (crystallinity).

It is very significant to control the crystal form of the drug during the different stages of process because any phase changes due to the polymorph interconversions, desolvation of solvates, formation of hydrates and changes in the degree of crystallinity can alter the bioavailability of the drug. The solid drug may experience a change in the thermodynamic properties during the phase transition, with consequent changes in the transport characteristics and its dissolution (Vippagunta et al. 2001). The solvent use will have a larger impact on the resulting morphology by the process crystallization but the consistent prediction not yet can be determined (Horst et al. 2001). Even the chemical composition of the crystalline polymorph is the same but it gives different in the internal crystal structures and therefore, posses' different physic-chemical properties (Borka and Haleblian, 1990).

Few models exist for predicting the morphology of crystal grown from solution. The solvent - crystal interface of the molecular level simulation have been successfully used to predict the shapes of several organic crystal systems. This method makes us use of pure solvent properties and does not require molecular level fluid-phase simulations for designing solvents for crystallization process that related to the hydrogen bonding solubility parameter of solvent and crystal morphology that resulting the desire crystal polymorph (Acquah et al. 2008). And for this study, the researcher has already highlighted the solvent as the parameters in the crystallization process since they solvents play a significant role in the crystalline of the solid.

2.1.1 Crystallization of Active Pharmaceutical Ingredients (APIs)

Active pharmaceutical ingredients (APIs) are defined as the any substance or combination of substances used in a finished pharmaceutical product, intended to furnish pharmacological activity or otherwise have direct effect in the diagnosis, cure, mitigation, treatment or prevention of disease or to have a direct effect in restoring, correcting or modifying physiological functions in- human beings . It is frequently delivered to the patient in the solid-state as part of the approved dosage form (e.g. tablets, capsules, etc..) and each form will display a unique physicochemical properties that can profoundly influence the bioavailability, manufacturability purification, stability and other performance characteristics of the drug (Sherry and Matthew, 2003). Advances in the pharmaceutical sciences have shown and significant impact in the increasing of the number of approaches for addressing the issues of low aqueous solubility. These strategies for improving and maximize the dissolution rate include micronisation to produce higher surface area for dissolution, the use of salt forms with enhanced dissolution profiles, solubilisation of drugs in co-solvents and micellar solutions, complexation with Cyclodextrins and the use of lipid systems for the delivery of lipophilic drugs (Blagden and Matas, 2007).

Many compounds of pharmaceutical interest have the ability to exist in more than one crystal structure or crystalline form. The commonest crystal forms are polymorph and solvates, that the different polymorph will have a differential in the internal crystal structure and therefore possess different physicochemical properties (Jacob et al. 2011). The differences of the properties make the crystal polymorph are difficult to control in

order to get the most suitable and stable crystal polymorph. This different crystal polymorph will they affect the formation of the tablet and also eventually affects the efficiency of the drug itself. Besides that, the size and shape contribute a great impact to the various solid properties including end-use efficacy, flowability, wettability and adhesion. This desired size and shape will effect on the production of crystal depending on its application (Micheal et al. 2008). For example, the needle shaped crystals are well known to harden in the process making them undesirable for the pharmaceutical application (Micheal et al. 2008). And usually, for the pharmaceutical products crystal that have the higher in the aspect ratio (ration between the two major dimensions of the crystal) are preferred to crystal that have low in aspect ratio, because of reasons related to efficient down-stream process (Karunanithi et al. 2008).

The common crystalline forms found in the pharmaceutical products for a given drug substance are polymorph and solvates (Kuhnert-Bradstatter, 1971). The crystallization skills can make a difference in such of crystal properties as habit, polymorphism, and crystal size. The extent of these changes depends on the crystallization factor itself, for example the presence of the impurities, types of solvents, and cooling rate (Mullin, 1993). For the conclusion in the pharmaceutical products, the largest in size and lower in aspect ratio (ratio between the two major dimensions of the crystal) for crystal are preferred because of reasons related to efficient downstream processing.

2.1.2 Crystallization of Ibuprofen

Crystallization is a complicated kinetic process where in current research it is not fully study (Weissbuch et al. 2003). Desupersaturation rate is one of the kinetic factors that have a significant effect on the polymorph appearance but cannot include in the solvent property analysis. Crystallization in the diversified solvent environment may then increase the success rate of discovering polymorph. Also from the analysis of the types solvents use will provide the guideline for the similar solvent selection for the optimization process (Gu et al. 2004). The types of solvent use can help in controlling the extent of the crystal morphology. The extents of crystal morphology are affecting the physicomechanical property of solute crystal such as the bulk density, mechanical strength, wettability, flowability, stability and bioavailability.

From the ibuprofen previous study, the ibuprofen's crystals were found that the types of solvent whether the polar or non-polar solvent will give the crystal in different aspect ratios. It shows also that the methanol or ethanol will produce the crystal in isometric structure and the ethyl acetate or isopropanol will produce crystal in elongated structure. Meanwhile, the needle-like crystals were produced by the hexane or diethyl ether (Acquah et al. 2009). From this, can say that the ibuprofen can form different crystal forms with different in terms of properties. The shape of the crystal whether the needle like, elongated or isometric will affects its tabletability (Rasenack and Muller, 2002).

It can be concluded that, the crystallization of the ibuprofen is mostly affected by the selection of solvents. And this selection will decide what types of crystal ibuprofen will be produced whether the high aspect ratio or low aspect ratio. It is also will contribute to the forms of crystal will produce whether the needle like, elongated or isometric crystal.

2.2 Polymorphism

Polymorphisms in crystalline solid form define that the material's ability to that have the same chemical composition but possess a different in lattice structure and/or different molecular conformations. Pseudopolymorphism is a term that analysis the crystalline form with solvent molecules as an integral part of the structure. In a supramolecular sense, the existence of more than one type of network superstructure in the same molecular building block is called polymorphism and pseudopolymorphism is the case where a molecular component of the network consists of solvent structure (Rodriquez-Spong et al. 2004). However, the experimental transition temperature may be higher than the theoretical one due to the high energy barrier of the transformation. It is even possible that form Imelts without transformation. If the polymorphs are monotropically related, the stability order is always the same below their melting temperatures. Heating of metastable form II may or may not cause polymorphic transitions (Kohsaku, 2011).

Selection of appropriate crystal polymorph is necessary for the industrial process and for the product storage because the failure in choosing the suitable crystal polymorph will be a negative impact to the process or product storage (Shan et al. 2002). Under the mixed solvent conditions or appropriate solvent only one polymorph might precipitate and thus exceeding other polymorph. And if the several polymorph that a precipitate is not stable which might be in metastable form, the solvent-mediated polymorph transformations must be completely suppressed in order to avoid contamination of the stable polymorph crystals (Shan et al. 2002). At the conclusion, the crystal polymorph of the sample are needed to fully study in order to prevent any failure selection of the crystal polymorph that probably only will affect the industries process that will contribute to the lost of money or worse, the company will bankrupt.

2.2.1 Polymorphism of Active Pharmaceutical Ingredients (APIs)

Polymorphisms normally happen to the Active Pharmaceutical Ingredients (APIs). Most of the APIs compound can exist more than one crystal structure but remain the same molecular structure which normally well known as “polymorphism”. Polymorphism may also be observed for amorphous forms, for which it is called polymorphisms. Detailed investigation on this subject has been done for water to show that high-density and low-density ices exist (Jayasankar and Rodríguez-Hornedo, 2004). Although this notion may be applicable to pharmaceutical compounds as well, strong evidence for polymorphisms has not been presented in this field. Polymorphism is suggested when lot-to-lot differences in dissolution or crystallization behavior are observed for amorphous forms. However, these differences can be explained in terms of

other factors as well including the existence of nuclei or solvent, and relaxation. Because water is known to exhibit many exceptional behaviors, it is doubtful to apply the notion made for water to other compounds. Discussion on polymorphisms in pharmaceutical field requires caution (Kohsaku, 2011).

Choosing the suitable polymorphic form will affect the properties of the drug or in other word by choosing the appropriate crystal habit will affect in the drug properties in terms of efficiency of the drugs (Rasenack and Muller, 2002). There are a few ways to improve the solubility of the drug. For instance, particle size reduction or micronizations increase the specific surface area, modification of the structure of particles by increasing the amorphous fraction (Pharm, 2010). The selection of a suitable type and appropriate solvent may play a significant role in the production of a desirable polymorph or solvate by affecting the polymorphic selectivity and resulting crystal polymorph (Adam et al. 2012) and also the crystal polymorph also can be controlled (Sabiruddin and Miroshnyk, 2008). From that review, it can be say that the key point to the processing of the drug is by the selection of the appropriate solvent and the proper selection of the solvents will give a higher efficiency of the drugs.

Polymorph screening is routinely conducted from the different solvent by crystallization process using either of the conventional or high throughput crystallization technology. The specific solvent will produce a specific crystal polymorph (Gu et al. 2004). Because of this phenomena, the researcher nowadays are trying to control the effect of solvent-solute interactions on the nucleation, crystal growth and solvent-mediated polymorph transformation which eventually affect the appearance of

polymorphs. The solvent properties may be described by solvent property parameters, including molecular descriptors e.g. hydrogen bond donor or acceptor propensity descriptors (Gu et al. 2004).

2.2.2 Polymorphism of iso-butyl-propanolic Acid (Ibuprofen)

One of the ability of the ibuprofen it is, it can possess a different properties of a crystal by the different crystal that form. And this shape of crystal will affect the tabletability. The shape of crystal polymorph of ibuprofen is depending on the solvent, powder flow and compatibility. From the review, it said that the appropriate selection of solvents will affect the tablettability even more or in different word improve the efficiency of the drug (Rasenack and Muller, 2002). Ibuprofen single crystal unit cell four ibuprofen molecules are attached with two hydrogen bonding. The growth rate is controlled by the non-polar surface variant but the strong hydrogen bonding and difficult displacement of the solvent can change the growth rate as the kinetics is transferred to the polar surface (Rasenack and Muller, 2002). Since the effect of which crystal is compressed into tablets also influence in the crystal morphology. The tablets size and shape should be reconsidered seem its play an important role in ibuprofen's tendency to stick to the faces of the tablet punches and dies during compressing and its tendency to laminate during decompression (Vippagunta et al. 2001). Figure 2.1 shows the SEM-photograph of ibuprofen tablet surface (Rasenack and Muller, 2002).

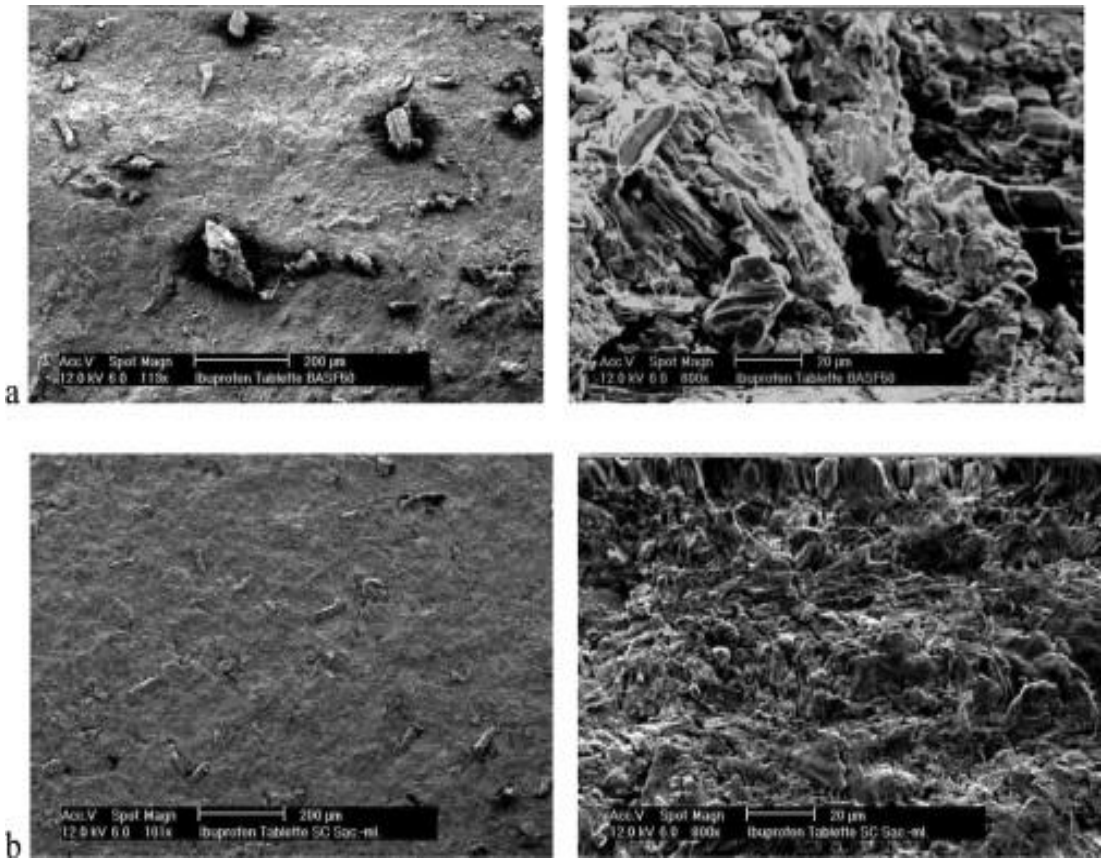


Figure 2.1 SEM-photograph of ibuprofen tablet surface. (a) Ibuprofen control; (b) ibuprofen crystallized in the presence of sucrosemonolaurate and dextran.

(Source : Rasenack and Muller, 2002)

In addition, ibuprofen crystallized from solvents with high hydrogen bonding ability will form plate-like crystal with low aspect ratio and large size due to the polar solvents would have less interaction with the non-polar of the ibuprofen dimmer because of the resulting in uniform growth of all units (Gordon and Amin, 1984). High aspect ratio crystals were observed when ibuprofen was grown from non-polar hexane such as ethanol and methanol (Gordon and Amin, 1984). Due to the good flow and improved compaction, methanol once used to produce ibuprofen crystals (Gordon and Amin, 1984). Figure 2.1 shows the SEM photographs of the ibuprofen crystals (Rasenack and Muller, 2002). In Table 2.1, the experimental of the mean aspect ratio are summarize and corresponding

standard deviation. Figure 2.2, shows the optical microscope images of ibuprofen crystals grown (Acquah et al. 2009).

Table 2.1 Mean aspect ratio of ibuprofen crystals from various solvents

Solvent	AR_{expt}
n-Hexane	7.23 ± 0.83
Carbon tetrachloride	4.81 ± 0.78
Ethyl acetate	4.65 ± 0.41
Acetonitrile	3.01 ± 0.26
Sulfolane	4.05 ± 0.13
Methlylene dichloride	3.20 ± 0.22
Isopropanol	3.10 ± 0.20
Ethanol	2.85 ± 0.34
Proppylene glycol	3.02 ± 0.18
Methanol	1.85 ± 0.35
Ethylene glycol	2.20 ± 0.16
Cyclohexane	5.64 ± 0.47
Acetone	4.27 ± 0.82
t-Amyl alcohol	3.21 ± 0.48
Benzyl alcohol	2.63 ± 0.43
Toluenne	4.94 ± 0.30

(Source: Rasenack and Muller, 2002)

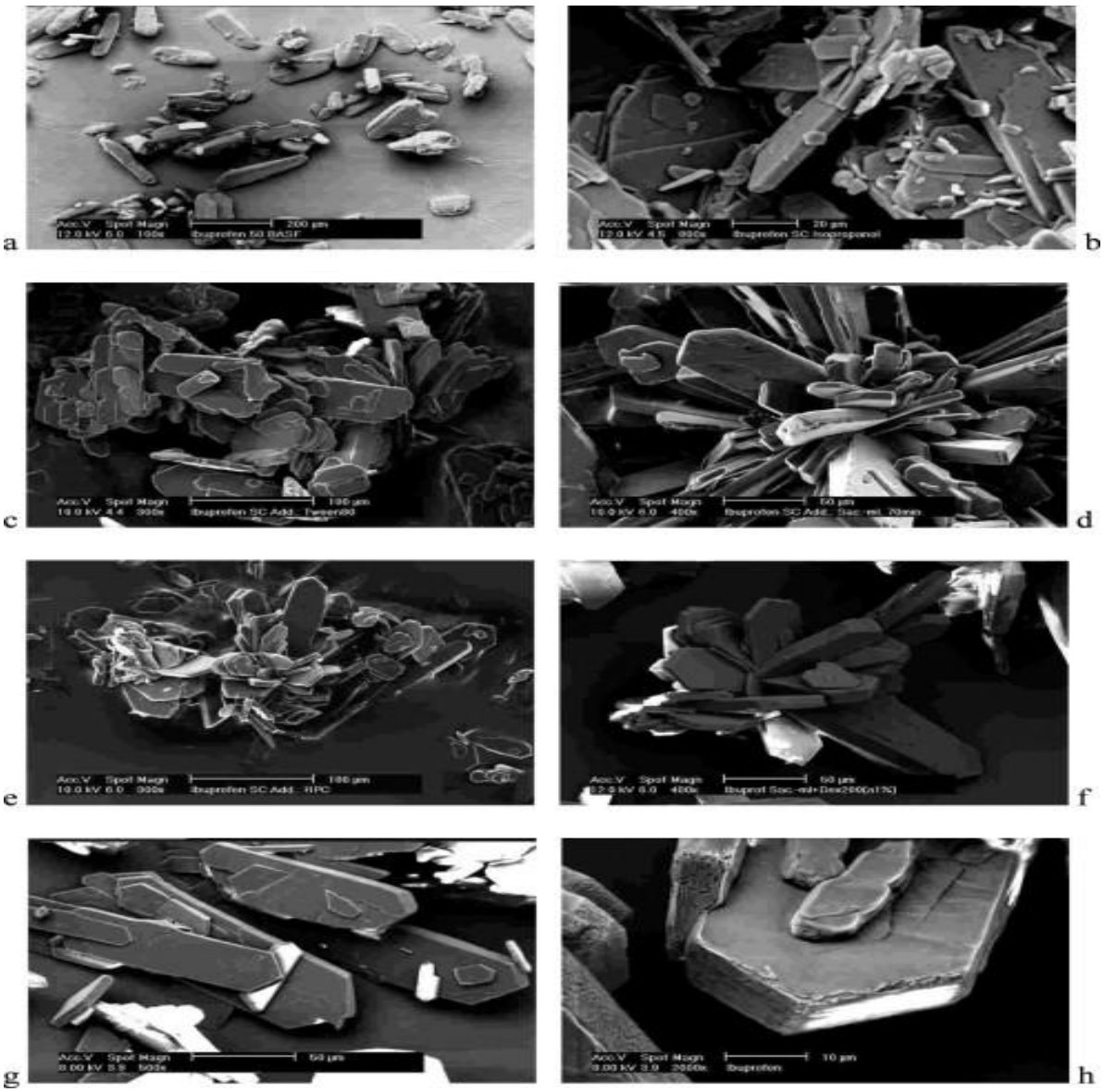


Figure 2.2 SEM photographs of the ibuprofen crystals. (a) Control; (b) crystallized without additives;(c) crystallized in the presence of polysorbate 80; (d) crystallized in the presence of sucrosemonolaurate; (e) crystallized in the presence of hydroxypropyl cellulose; (f) crystallized in the presence of sucrosemonolaurate and dextran 200; (g, h) crystallized in the presence of sucrosemonolaurate and hydroxypropyl cellulose.

(Source: Acquah et al. 2009)

2.3 Iso-Butyl-Propanolic Acid (Ibuprofen)

Ibuprofen or in the nomenclature iso-butyl-propanolic acid is a well known drug. That's means this compound contains an aryl group (the benzene ring), joined to a carboxylic acid derived from propane (3 carbons). In Figure 2.3 it's shows the molecular structure of ibuprofen.

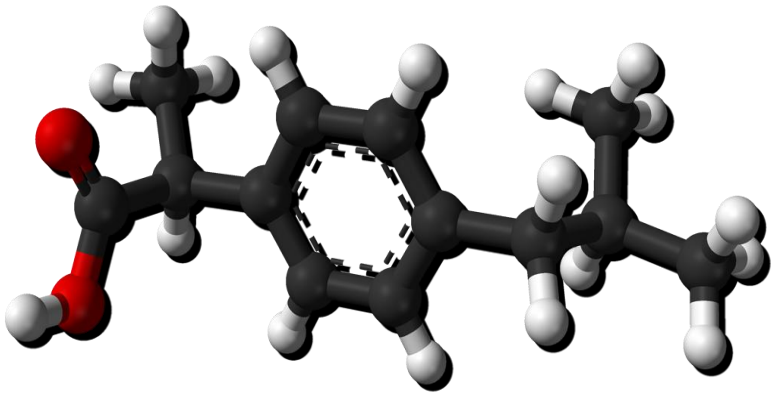


Figure 2.3 Ibuprofen molecular structure

(Source: http://www.chemspider.com, 2012)

The properties of the ibuprofen are shown in the Table 2.2 which listed are a few properties of the ibuprofen which believe can give a little information that will helps in order to solve the problem face in this research study.

Table 2.2 Properties of Ibuprofen

Ibuprofen	
IUPAC name	(*RS*)-2-(4-(2-methylpropyl)phenyl)propanoic acid
Pharmacokinetic data	
Bioavailability	49-73%
protein binding	99%
Metabolism	Hepatic
Half life	1.8 - 2.0 hours
Chemical Data	
Formula	$C_{13}H_{18}O_2$
Molecular Mass	206.29 g/mol
Physical Data	
Melting Point	157°C
Boiling Point	215°C

(Source: http://www.wikipedia.org, 2012)

Other drugs which have approximately the same structure with the ibuprofen's molecular structure is naproxen (which more powerful than ibuprofen because part of its molecular structure is from the ibuprofen's structure itself) and fenoprofen. In Figure 2.4, show the figure of optimized molecular structure of ibuprofen (Musa and Eriksson, 2007).

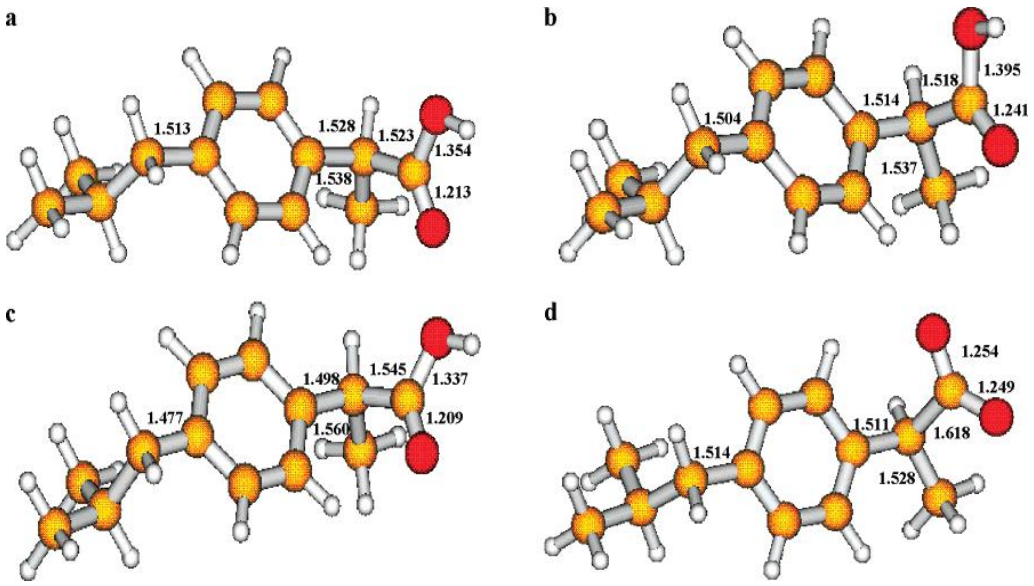


Figure 2.4 Ibuprofen optimized structure of (a) neutral ground state ibuprofen. (b) radical anion (A^-), (c) radical cation (A^+), and (d) the deprotonated from (A^-).

(Source: Musa and Eriksson, 2007)

Ibuprofen is a well known drug that used to treat a symptom of rheumatism, arthritis, fever, as an analgesic (pain reliever), especially where there is an inflammatory component and dysmenorrheal (Martin et al. 2009). It is also applicable to use for pericarditis and patent ductus arteriosus (Derksen, 1995). Ibuprofen is a common non-steroidal anti-inflammatory drug. Nonsteroidal anti inflammatory drug (NSAID) here defines that the compounds used as analgesics, constitute one of the most important groups of pharmaceuticals worldwide, estimated that the annual production of several kilotons (Musa and Eriksson, 2007). NSAIDS also classified from a heterogeneous group of compound that exhibit favorable anti-inflammatory, analgesic, and antipyretic properties (Musa and Eriksson, 2007). In the World Health Organization's" WHO Model List of Essential Medicines", ibuprofen had classified as the important parts in the world of medicine because a list of minimum medical needs for basic health care system

(Kouimtzi, 2009). That means ibuprofen is the most convenient medicine for a healthy lifestyle. In fact, 7 0f the top 100 best selling drugs in the world are anti-inflammatory drugs of this type. For instance, ibuprofen an anti-inflammatory drugs (NSAD) belong to the class II, i.e. permeate membranes but have a lower solubility in water (Custodio, et al, 2008).

The low solubility of this acid can limit the dissolution and absorption rates into an organism (Martin et al. 2009). The classification of the ibuprofen from class II to class I am affected by the increasing in the solubility in water is paramount to increase the dissolution rate of ibuprofen from solid dosage forms. An easier and more obvious relationship between the drug's properties and its therapeutic activity becomes possible. Racemic ibuprofen is known to form eutectic mixtures with a wide range of additives included polyethylene glycol (Mura, 1987, Shebab and Richards, 1996). In the case of racemic ibuprofen, Zhang et al have described there are three different polymorph. The thermodynamically stable form was termed the ɣ-form, α-form and β-form. Which only ɣ-form is stable (Martin et al. 2009).

The dose-dependent duration of action for ibuprofen is longer than suggested by its short half-life which approximately four to eight hours. The advised dose varies with the indication and body mass. 1200mg is considered the maximum daily dose for OTC (Over The Counter) use (U.S. Food And Drug Administration), under the medical direction. And 800miligrams per dose or 3200miligrams per day is the maximum amount of ibuprofen for adults (Ibuprofen Drugs.com). Different from aspirin, which breaks down in solution, ibuprofen is stable. Thus, ibuprofen can be available in topical gel form,

which absorbed through the skin, and can be used for sports injuries but yet have a less risk of aggressive problems (Plasma and Tissues concentration, bandolier).

2.4 Solvent

A solvent is classified as the substance that can dissolve in a solute which in our study is the Active pharmaceutical ingredients (APIs), resulting in a solution. Normally, the solvent is in the liquid state but also available in the gaseous or solid state. The maximum amount that can dissolve in a specific volume of solvent varies with temperature. The use of inorganic solvents (other than water) is typically limited to research chemistry and some technological processes. The solvent properties can be classified based on the solvent property parameters, including molecular descriptors such as hydrogen bond donor or acceptor propensity descriptors and bulk property parameters such as viscosity (Gu et al. 2004).

The selection of solvents is an important area at industrial companies by applying the thermodynamics. Over 30% of the work of thermodynamics group can be related to the selection of the solvent (Kolar et al. 2002). The typical tasks included the selections of solvents for selective absorption, crystallizations solvents and anti-solvents, extraction solvent, co-solvents for supercritical extractions, reaction solvents, catalyst solvents, solvents for coating and formulations and cleaning solvents (Kolar et al. 2002). The solvent selection is important in a thermodynamics task because most of the solvent

selection problem can be formulated using thermodynamics criteria which contains basic physical properties and phase equilibrium relationships.

There are few types of molecular structure of the solvent such as polar protic, dipolar aprotic and non-polar solvents. These 3 different structures of solvents give a different in the properties which for the polar protic solvents consists of a polar group OH and non-polar tail. It is dissolving with other substances with polar protic molecular structure. For the dipolar aprotic solvents, this type of solvents posses a larger bond dipole moment which the measurement of the polarity of molecule chemical bond. And for the last types of solvents which the non-polar solvents, an electric charge in the molecules of non-polar solvents are evenly distributed, therefore the molecules possess a low dielectric constant (Gu et al. 2004).

From the previous study of solvent effect on the crystallization, the solvents proposed are ethyl acetate, hexane and also ethanol as the selected solvents for this study on the crystal polymorph of the ibuprofen. The ethyl acetate is an organic compound which classified as an ester of ethanol and acetic acid. Ethyl acetate also categorizes as dipolar aprotic solvents. For the second solvent selection which the hexane, hexane is hydrocarbon that classified under the alkane group which consists of 6 carbon atoms. Non-polar solvent is the hexane solvent type. And the last one is the ethanol, ethanol also well known as ethyl alcohol is the volatile, flammable and colorless liquid which classified as the polar protic solvent.

2.5 Molecular Dynamic Simulation

Computer simulation is a modern and powerful tool for solving scientific problem and also powerful to study a new scientific research as numerical experiments can be performed for new materials without synthesizing them. One of the targets of computer simulation is to reproduce experiment to elucidate the invisible microscopic details and further explain the experiments. On the other hand, simulation can also be used as a useful predictive tool. The most widely used simulation methods for molecular systems are Monte Carlo, Brownian dynamics and molecular dynamics (Kolar et al. 2010).

A Molecular dynamics simulation is one of the computer simulations of physical movements of atoms and molecules. The atoms and molecules are allowed to interact for a period of time which can give a view on the movements of the molecules and atoms. In the most common version of molecular dynamics simulation such as Material Studio, the trajectories of atoms and molecules are determined by the Newton's equations of motion for a system of interacting particles where forces between the particles and potential energy are defined by molecular mechanics force field. The trajectory is obtained by solving the differential equations embodied in Newton's second law, the formula is shown in Equation 2.1 and Equation 2.2.

Newton's second law, $F = ma$: (2.1)

$$\frac{d^2y}{dt^2} = \frac{F_{x_i}}{m_i} \quad (2.2)$$

This equation describes the motion of a particle of mass m_i along one coordinate (x_i) with F_{xi} being the force on the particle in that direction (Andrew, 1996). Besides that, to investigate the structure, dynamic and thermodynamics of materials and biological systems, the molecular dynamic simulation can say a the most common software to investigate these things. It is also can be classified as the computer experiment that's available for the test of new theoretical result (Frenkel et al. 2002). By this simulation, the effect of the parameter can be clearly understood which normally temperature and the types of solvent use. The information on the intermolecular and intermolecular interactions can be obtained by this simulation.

Compass is a powerful force field supporting atomistic simulations of condensed-phase materials and stands for condensed-phase optimized molecular potentials for atomistic simulation studies. For the potential-energy calculations, the coulombic and Van Der Waals interactions are calculated by employing the standard Ewald method (Kolar et al. 2010). Figure 2.4(a) shows the snapshots from the molecular dynamics simulations of the HMX–acetone solvent interfaces (Kolar et al. 2010).

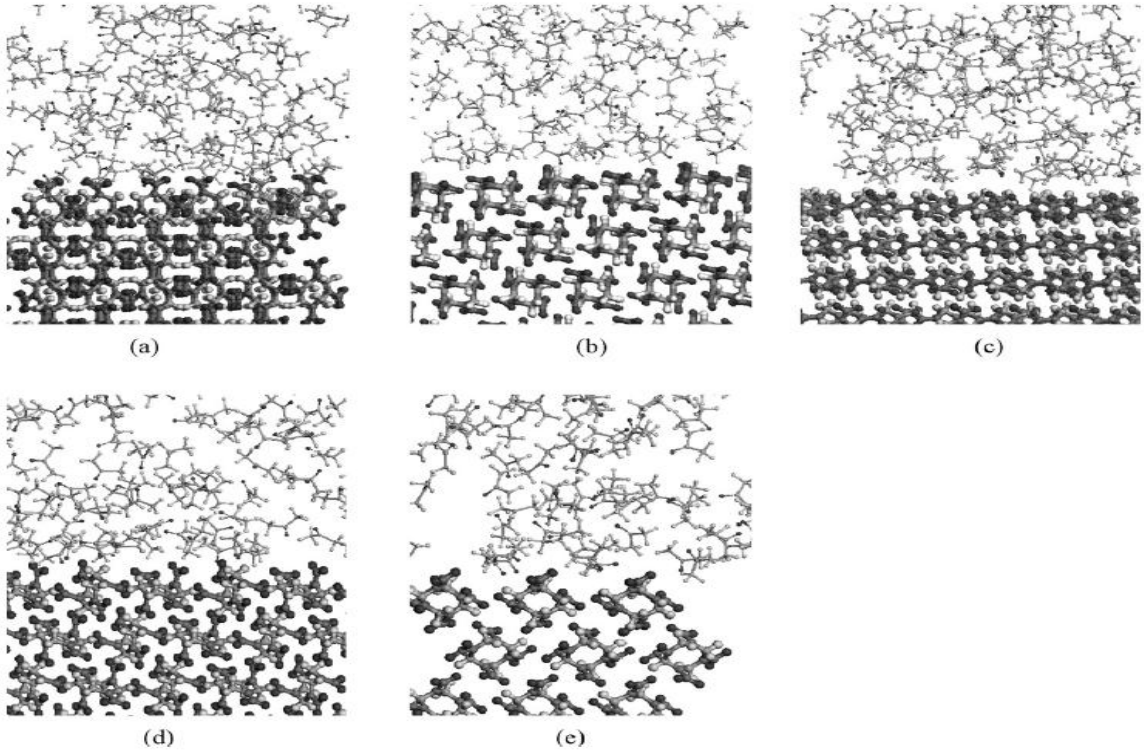


Figure 2.5 . Snapshots from the molecular dynamics simulations of the HMX–acetone solvent interfaces. (a), (b), (c), (d) and (e) correspond to (1 0 0), (0 1 1), (1 0 $\bar{2}$), (1 1 $\bar{1}$) and (0 2 0) crystal faces, respectively.

(Source: Kolar et al. 2010)

2.5.1 Molecular dynamics simulation of Active Pharmaceutical Ingredients (APIs)

Molecular dynamics (MD) simulations are being increasingly partnered with experiments in nowadays research because of the simulation ability which can track system behavior a vast spatiotemporal domain. Novel computational methods which in other hand include MD simulations, have assumed an ever growing role in drug discovery over the past quarter century. The molecular dynamics simulation methods have been applied to the direct prediction of solubility of pharmaceuticals. Commercial packages

principally differ in their treatment of the effect of solute polarization and salvation technique is currently available (Kolar et al. 2002). Each of the techniques has distinct advantages for a certain types of molecules only. This method also available to determine the parameters of activity coefficient models from quantum-mechanical calculations. A significant feature of molecular simulations is that they provide insight into interactions and local structures in the solvent-solute systems.

Molecular dynamics simulation such as Material Studio and Compass force field are used to predict the principle behavior of the drug products, especially miscibility and glass transition temperature (Tg). Different products containing Active Pharmaceutical Ingredients (APIs) such ibuprofen and water soluble or water insoluble were studied. Applied the highly develop the force field as the basis of any Molecular Dynamics Simulation software helps in the calculation of the parameters solubility with a highly accurate comparable to those measured experimentally by inverse gas chromatography and an increasing number of other statistical quantitative by inverse gas chromatography and an increasing number of other statistical quantitative property relationship (SQPR) between simulated and experimental values are established. Force Field based calculation of the cohesive energy densities of single constituents led to a qualitative approach according to Hanson describing the solid state of the mixture to the further calculation on the basis of the theory of free energy of mixing facilitated a semi quantitative prediction.

2.6 Radial Distribution Function

Radial distribution (pair correlation) functions (RDF) are the primary link between the intermolecular interactions of fluid and fluid mixture and also between the macroscopic thermodynamic properties. The idea can get on the how is the mass transfer behavior of the molecules or targeted molecules via the diffusion coefficients. Mean square displacement at time average of simulation can be calculated by the diffusion coefficient. While the intermolecular forces such as hydrogen bonding will be able to describe the salvation strength of the solvent molecules towards the targeted molecule. Measurement of the salvation strength can be measured through calculation of the radial distribution function (RDF) (Suchocki, 2000).

From Figure 2.6, considering a homogeneous distribution of the atoms or molecules in space, the radial distribution function represents the probability to find an atom in a shell *dr* at the distance *r* of another atom chosen as a reference point.

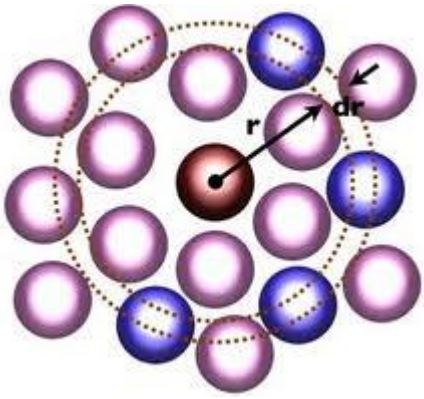


Figure 2.6: Space for the evaluation of radial distribution function.

(Source: http://www.wikipedia.org, 2012)

In the simple word, it is about the measurement of the probability of finding a particle at a distance of *r* away from a given reference particle, relative for an ideal gas. The mathematically, this involves determining how many particle is within a distance of *r* and *r+dr* away from the particle. Meanwhile, in modern theories of fluid and fluid mixture have a great deal to the concept of radial distribution functions (RDF). And from the research, the radial distribution function (RDF) is shown a quite successful in describing the behavior of the simple liquid and liquid mixture (Matteoli and Mansoori, 1995). Many interesting correlation functions can also be measured in a simulation. An important example is the pair correlation function.

$$g(r) = \frac{V}{N^2}\langle \sum_{I=1}^{N} \sum_{I=1}^{N} \delta^3[r - (r_i - r_j)]\rangle \qquad (2.3)$$

This basically measure the probability that two particles are a distance r apart relative to a uniform random distribution of non-interacting point particles. The average of this function over angular directions

$$g(r) = \frac{1}{4\pi r^2}\int_o^{\pi} \sin\theta d\theta \int_0^{2\pi} d\emptyset g(r) \qquad (2.4)$$

It is called the radial distribution function. It can be measured experimentally by light, light, x-ray or neutron scattering from the system.

The radial distribution function (structural property) correlated to the existence of dimmers in the salvation from the trajectory frames as described in the Equation 2.5.

$$g_{xy}(r) = \frac{\langle N_r(r,r+dr)\rangle}{\rho_y 4\pi r^2 dr} \quad (2.5)$$

The formula for radial distribution function are shown in Equation 2.5 where the r represent the spherical radius, ρ_y represent the density of y atom and N_y represent the number atom of y. Investigation of the structure of disordered systems can be performed directly by diffraction methods. Fourier inversion of diffraction data gives the radial distribution function (RDF) with a spatial resolution inversely proportional to the maximum value of the scattering vector attained in the experiment. The radial distribution function (RDF) provides information about the probability of finding an atom. Successive peaks correspond to the nearest, the second and the next neighbor atomic distribution.

2.7 Diffusion

Diffusion is the process of the movement of matter from one part of a system to another part of system, and it is mainly due to random molecular motions. Diffusion is also one of several transport phenomena that occur in nature. It is distinguished feature of diffusion resulting from the mixing or mass transport without requiring bulk motion. These are the different characteristics between the diffusion and others transport phenomena that required bulk motion to move a particle from one to another place such as the convection or advection. Both of this transport process required a bulk motion to move it is particle to move. Diffusion processes are faster in gases (10 cm/min) liquid (0.05 cm/min) is much slower than gases and follows by solids (0.00001 cm/min).

According to Cussler (Masaro, 1990), diffusion in both gases and liquids can be successfully predicted by theories.

There are few factors affecting the diffusion such as temperature, pressure, solute size and viscosity. Diffusion has a much larger range of values in solids, where diffusion coefficients can differ by more than a factor of 10^{10}. Therefore, diffusion in solids is difficult to estimate with theoretical models (Cussler, 1999). Diffusion in polymers is complex and the diffusion rates should lie between those in liquids and in solids. The diffusion of the polymer depends strongly on the concentration and the degree of swelling. Consequently, it remains a challenge to understand, predict and control the diffusion of small and large molecules in polymer systems. The theories and physical models of diffusion may help to realize these goals.

The formula for diffusion was established by Fick (Masaro, 1999) who developed a law of diffusion in one dimension. This equation is also known as Fick's first law.

$$J = -Aj = -AD\frac{\delta c}{\delta z} \tag{2.6}$$

Where J is the flux, j the flux per unit area, A the area across which diffusion occurs, D the diffusion coefficient, c the concentration, z the distance and $\frac{\delta c}{\delta z}$ the gradient of the concentration along the z axis. The diffusion flux is proportional to the minus gradient of concentration. It goes between the higher concentration regions to the lower region of concentration. From the atomistic point of view, diffusion is considered as a result of the

random walk of the diffusion particles. In the molecular diffusion, the moving molecules are self-propelled by thermal energy.

2.8 Fourier transforms infrared (FTIR) analysis

Fourier transform infrared spectroscopy (FTIR) is a technique which has been known about more than a century and used to obtain an infrared spectrum of absorption, emission, photoconductivity or Raman scattering of a solid, liquid or gas. FTIR spectrometer fundamentals are by collecting the simultaneously spectral data in a wide spectral range. This confers a significant advantage over a dispersive spectrometer which measures intensity over a narrow range of wavelengths at a time. FTIR has made dispersive infrared spectrometers all but obsolete (except sometimes in the near infrared), opening up new applications of infrared spectroscopy. It is functioning by measuring the interference between light paths at right angles; one could find the direction & speed of the ether. An electronic computer was needed to perform the required Fourier transform and this only became practicable with the advent of minicomputers, such as the PDP-8 which became available in 1965 (Griffiths and Hasseth, 2007).

The low energy light of the infrared radiation is representing the temperature of the object that will affect the wavelength of infrared radiation are well known as black body radiation. Achieves maximum results, the temperature source suggested being as high as possible. There is little consideration needed to be considered in choosing the IR. The first one is the material should be thermodynamically stable to prevent break down and need replacing. There is also the possibility that the source may produce an excess of

IR radiation. This would saturate the detector and possibly overload the analog-to-digital converter (Rossini, 2007).

CHAPTER 3

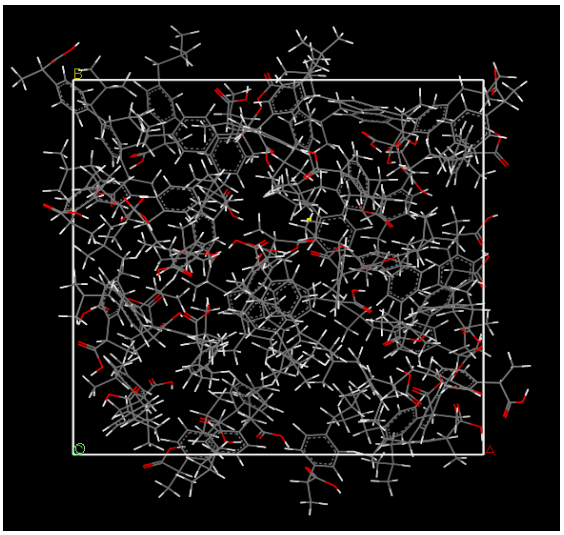
METHODOLOGY

3.1 Computer Simulation

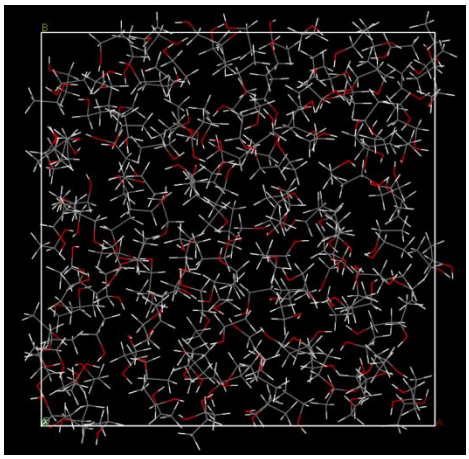
3.1.1. Simulation Work

The molecular dynamics simulation technique applied in this work was the same employed in earlier MD studies of 2,6-DHB in toluene and chloroform solvent (F. Adam et al). Prior to simulation, the pure system of ethanol and ethyl acetate were optimized and minimized using the generic COMPASS force field in Material Studio. The cubical boxes which containing the number of molecules by 200 for ethanol and ethyl acetate pure system of solvents were created using the Amorphous Cell in the Material Studio. By using the same technique, the binary system which combination of the API which ibuprofen were mixed with the solvent, in this study the ethanol and ethyl acetate respectively created containing about 200:13 of solvent: solute ratio for ethanol, and 200:106 of solvent: solute ratio for ethyl acetate. Then, the simulation boxes were applied

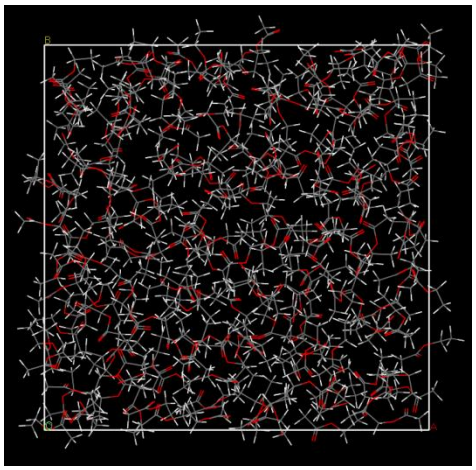
by technique of energy minimization. The box of the pure and the binary system of solute (ibuprofen) and solvents (ethanol and ethyl acetate) is shown in Figure 3.1.



(a) Pure Ibuprofen



(b) Pure Ethanol



(c) Pure Ethyl Acetate

Figure 3.1 Snapshot from Material Studio (Pure System) of the initial configuration of molecular dynamics simulation.

Initially, the boxed were equilibrated using Forcite Module by performing the molecular dynamics simulation in NVE ensemble for 200ps and followed by the NPT

ensemble for 500ps with the total of 1ns simulation time at the set point of 298.15K and 1.00 atm. These methods only apply to the pure system which for the pure ibuprofen, pure ethanol and pure ethyl acetate. For the ethanol mixture, the NPT ensemble to 500ps. Meanwhile for ethyl acetate mixture, NPT ensemble only to 100ps. The ethyl acetate mixture only ensemble to 100ps in the NPT system due to the computer capability. The molecular dynamics simulation should have higher performance in the term of graphic and processor.

For the dynamics run in the NVE ensemble, the temperature and pressure of the system are scaled down until the values achieved are consistent with the setting conditions in order to get a reasonable total energy for the system. In addition, dynamics run in the NPT are ensemble will maintain the pressure and the temperature of the system and control the simulation of box size to achieve the density of the real system. Once the pressure, temperature and energy of the system were in equilibrium at the desired values, the radial distribution function of the system was calculated and analyzed from the trajectory files. For analyzing, cutoff for half of A length with 0.5 intervals were chosen to perform the trajectory files. The radial distribution function depends on the density and temperature. Therefore, it serves as an indicator of the nature of phase assumed by the simulated system. The radial distribution function, $g_{xy}\ (r)$ gives the probability or occurrence of atoms with types y at a distance r from atoms of type x in the liquid are given in the Section 2.6.

The summary of the molecular dynamics simulation method is shown in Table 3.1 and Table 3.2.

Table 3.1 Molecular dynamics simulation details for the pure ibuprofen, ethanol and ethyl acetate using the COMPASS force field.

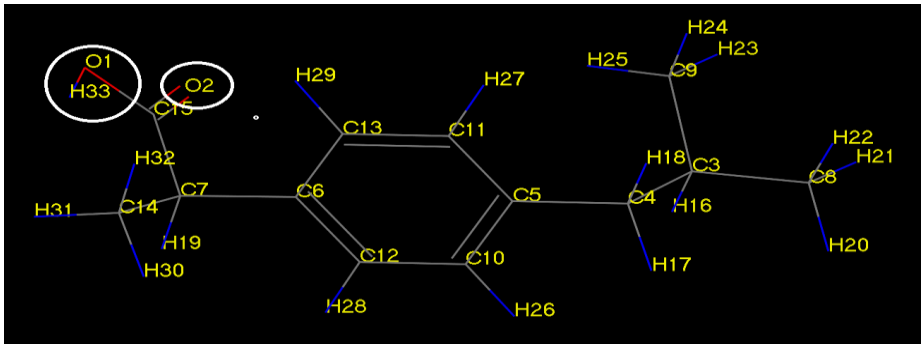
System	Ibuprofen	Ethanol	Ethyl acetate
Number of molecules	50	200	200
NVE (ps)	200	200	200
NPT (ps)	500	500	500
Simulation time (ps)	700	700	700
Timesteps (fs)	1	1	1
Cut off (Å)	12.9	13.5	16.1
Interval (Å)	0.5	0.5	0.5
Simulated density (g/cm^3)	1.001	0.777	0.883
Measured density (g/cm^3)	1.03	0.789	0.897

Table 3.2 Molecular dynamic simulation details for ibuprofen in ethanol and ethyl acetate mixture using the COMPASS force field.

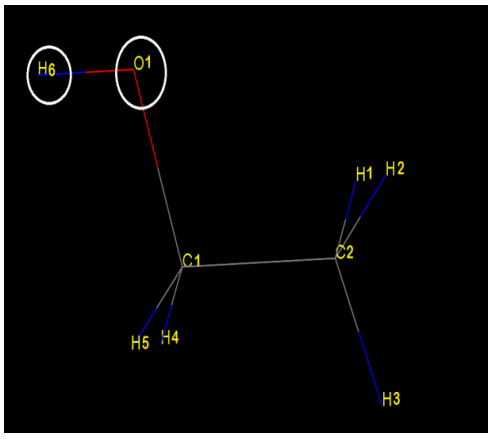
System	Ethanol mixture	Ethyl Acetate mixture
Number of solute molecules	200	200
Number of solvent molecules	13	120
Equilibration time in NVE ensemble (ps)	200	200
Equilibration time in NPT ensemble (ps)	500	100
Total simulation time (ns)	700	300
Timestep (fs)	1	1
Cutoff (Å)	14.4	20.7
Interval (Å)	0.5	0.5
$\rho_{simulated}$ (g/cm^3)	0.823	0.964
$\rho_{theoretical}$ (g/cm^3)	0.813	0.97

3.1.2 Molecular Labeling

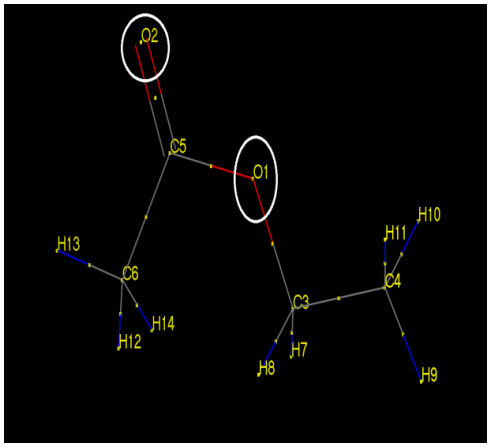
From the Figure 3.2, the molecular structures were labeled by naming every single atom in the molecules. It is because all the atoms play a significant role in the polymorphism of ibuprofen based on their ability to form hydrogen bonding with particular neighboring atoms in the solution system. The labels for ibuprofen structure were adopted from the previous MD study in order to facilitate in performing the comparison between this researches with the previous one.



(a) Ibuprofen molecular structure



(b) Ethanol molecular structure



(c) Ethyl acetate molecular structure

Figure 3.2 Molecular structure defining the atomic number for molecular recognition The figure shows that the molecular labeling for solute and solvents.

The circle indicates the main key in the crystal polymorph which interacts with different atoms to form hydrogen bond.

3.2 Experiment Work

Based on the article review, the analysis for the solubility of the solute: solvents were done by the use of the thermomixer. The experiments were conducted by placing the samples of solvents which the ethanol, ethyl acetate and hexane in the test tube for 3ml. Then, the solute is added which in our case in the ibuprofen. Ibuprofen is added until the solution becomes a saturated solution. The saturated solution will have an excess of the solute where the mixture of solvent and solute have already reached it is limit to react with the solvents. The excess of this solvent shows the differences of solvent will affect the reaction of the ibuprofen towards our selection of solvent. Then, the solution is undergoing the process in the thermomixer for the 2 hours in the speed of 300-400rpm. Then, the pH of the mixture was measured using the pH paper to make sure it is compatible to use with the Fourier transform infrared (FTIR) analysis. For the solubility, the calculation method is shown in Equation 3.1.

$$x_A = \frac{\frac{m_A}{M_A}}{\frac{m_A}{M_A} + \frac{m_B}{M_B}} \quad (3.1)$$

Where the x_A represent the solubility of the system, m_A and m_B represent the mass of the solute and solvents respectively. M_A for the molecular weight of the solute and M_B for the molecular weight of the solvents.

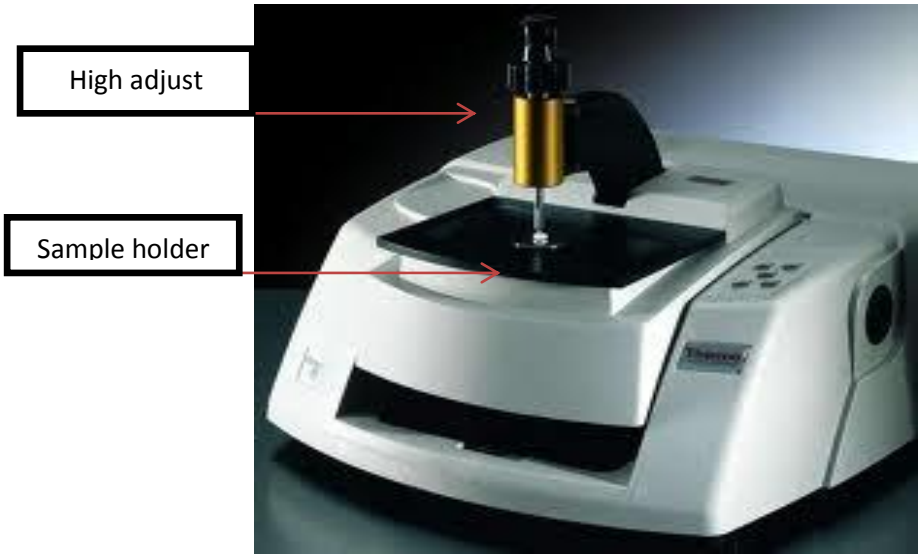
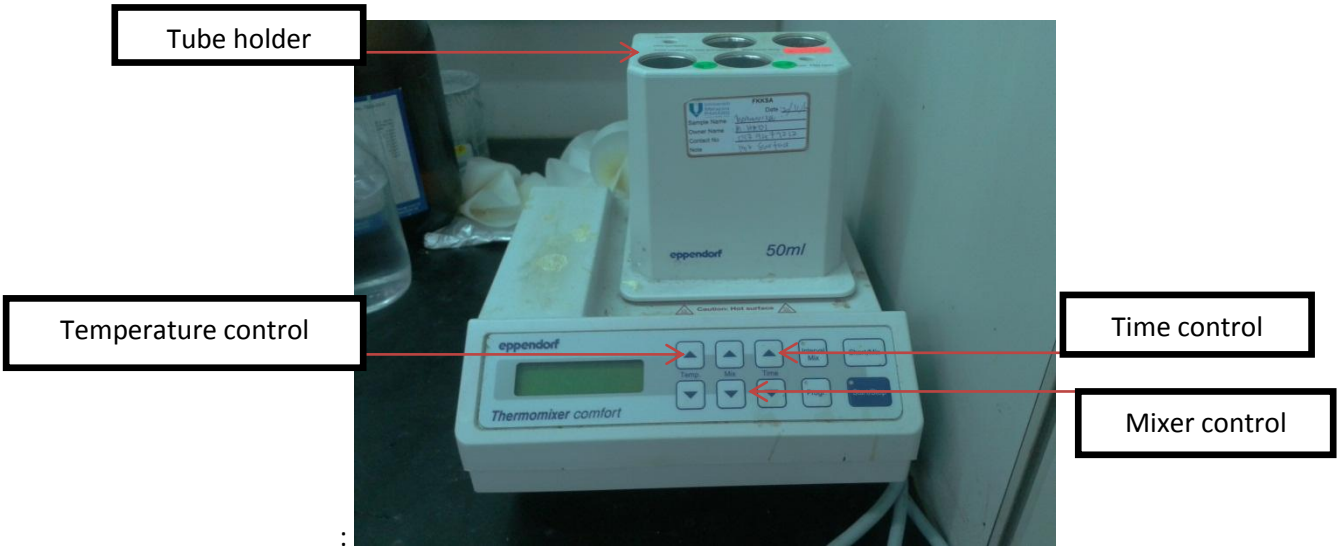


Figure 3.3 Fourier transform infrared (FTIR)



:

Figure 3.4 Thermomixer

CHAPTER 4

RESULT AND DISCUSSION

4.1 Simulation Data

The molecular dynamics simulations for the study have done by the use of Material Studio software which one of the most efficient molecular simulation. The simulations of the study have been done for different systems which pure and solute solvent systems. The solvent system has chosen is ethanol and ethyl acetate.

From the simulation table shown in Table 3.1, the simulated density for the pure ibuprofen, ethanol and ethyl acetate are respectively good and shows acceptable agreement with experimentally determined from the simulation analysis, the value for

ibuprofen, ethanol and ethyl acetate are 1.001 g/cm^3, 0.777 g/cm^3 and 0.883 g/cm^3 respectively. When compared with the measured density, the differences between the simulated and experimental data are 0.19% for ibuprofen, 1.52% for ethanol and 1.56% for the ethyl acetate by using the COMPASS force field respectively.

In the binary system, the results were shown in Table 3.2, the simulated density of the binary system which for binary ibuprofen and ethanol obtained is 0.823 g/cm^3 and for the binary ibuprofen and ethyl acetate are 0.964 g/cm^3. From this simulated result, the differences between the simulated and experimental data are 1.23% and 0.62% respectively for ethanol mixture and ethyl acetate mixture.

Based on the trajectory files obtained from this research, the diffusion coefficient and radial distribution function of the system were calculated and analyzed. The intermolecular forces in the pure system for ibuprofen, ethanol and ethyl acetate were done to compare the previous studies using different force field types to ensure radial distribution function obtained from this research is in good agreement with those findings. The results presented in this research indicate that the character of the intermolecular interaction plays an important role in the crystallization process.

4.1.1 Pure System

4.1.1.1 Ibuprofen

Figure 4.1 shows the radial for the O1 with the H33 is 9.00Å and at 5.00Å for radial between the O2 with H33. The radial distance of this oxygen atom shows that, the hydrogen bond is stronger between the O2 and H33 bond. The O2 represents the carboxyl group which acts as hydrogen bond acceptors which more it more attractive to attach with the nearest hydrogen atoms which the H33.

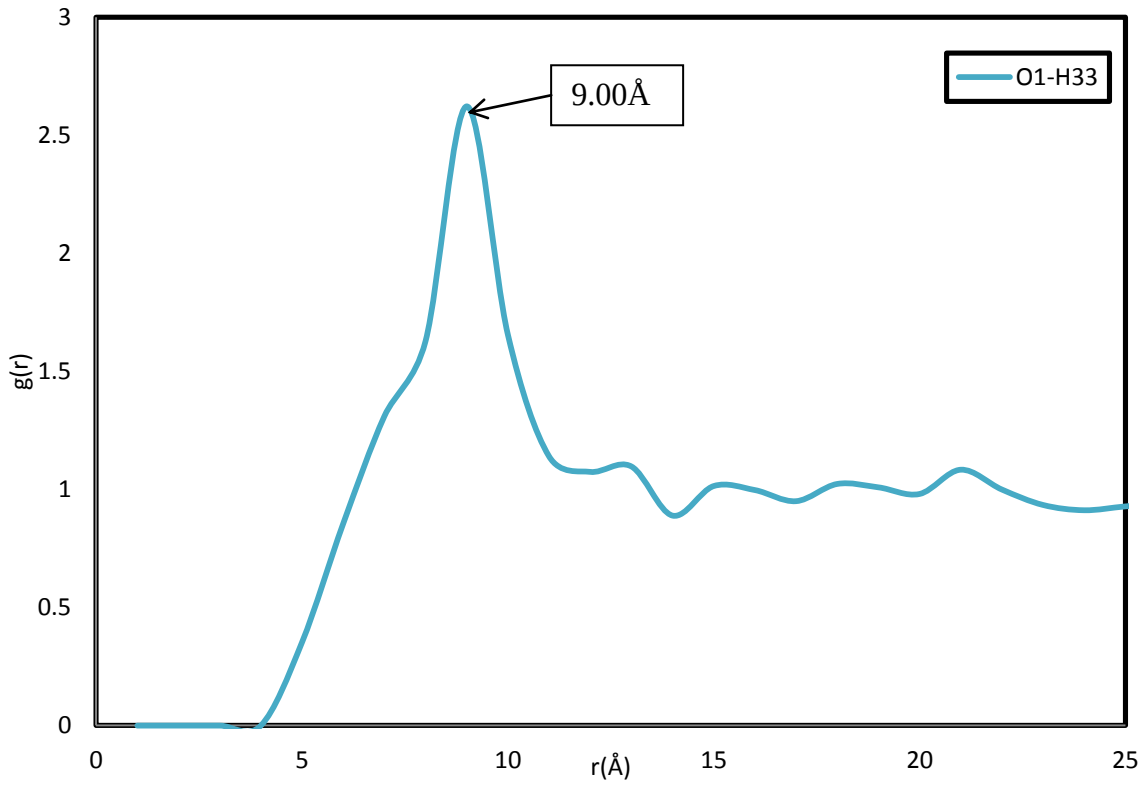


Figure 4.1 (a) RDF graph for O1-H33 in pure ibuprofen represents the hydrogen bonding

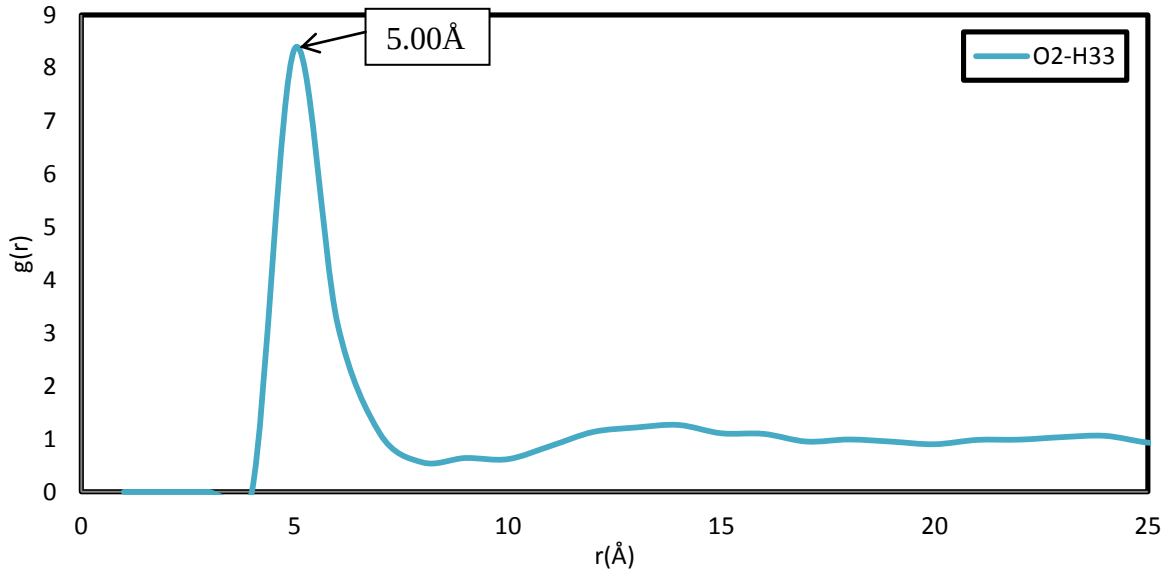


Figure 4.1 (b) RDF graph for O2-H33 in pure ibuprofen represents the hydrogen bonding

Based on the Figure 4.2, the radial distribution function of the atoms is stronger for O1---O1 interaction. And the weak interactions are between the H33---H33 and O2---O2. This is due to the repulsion of the atoms with the same electronegativities.

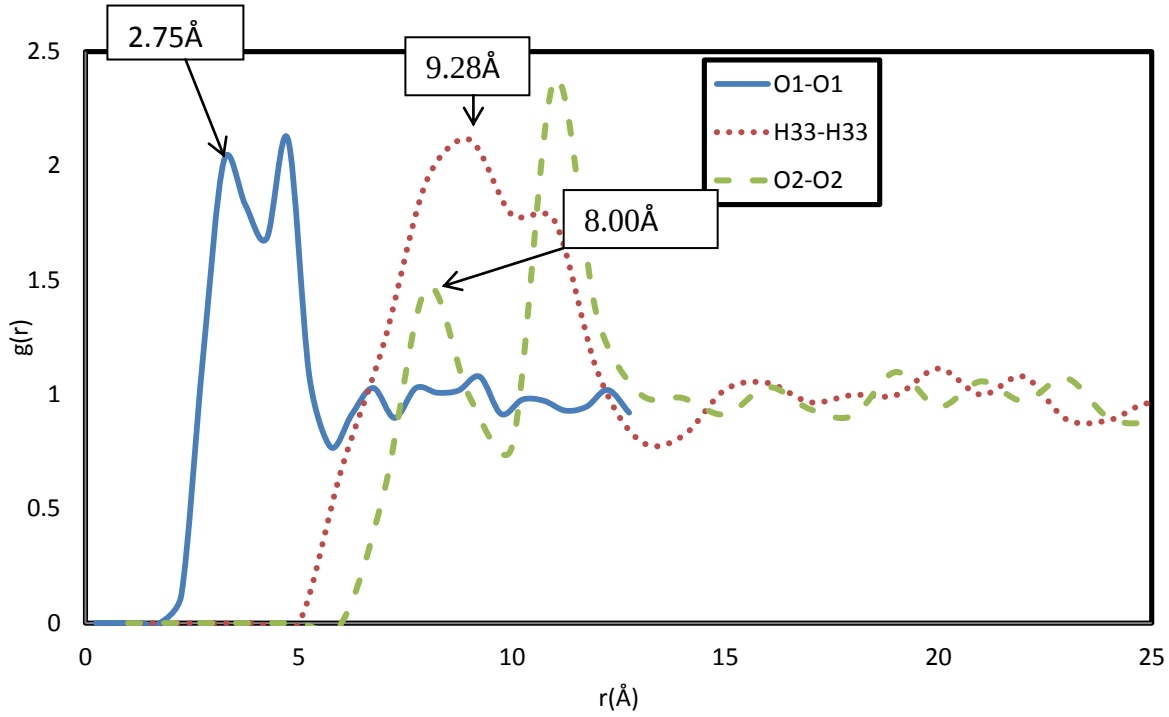


Figure 4.2 Atoms interaction between O1-O1, H33-H33 and O2-O2 in pure ibuprofen

4.1.1.2 Ethanol

The Figure 4.3 (a) shows the radial distribution functions of pure ethanol in the pure system. The radial is higher between the O1---H6 at 1.75Å while the radial for the O1 with H3 are at 5.25Å. This presented the hydrogen bonding between the oxygen atom are stronger with H6. This situation probably because of hydroxyl groups in the molecular structure of ethanol makes it dominant in making the hydrogen bond. In the Figure 4.3 (b), the graph shows that the differences between the peak of the oxygen interaction by using the COMPASSS and by using the OPLS. It is shown that the radial distribution functions for this study are not in good agreement with the previous study data. (Saiz, et al, 1997). Since the portability of this study shows a lower peak compare with the

previous study, it is suggested that the simulation should be run in more period of time where the molecules that reach its equilibrium state.

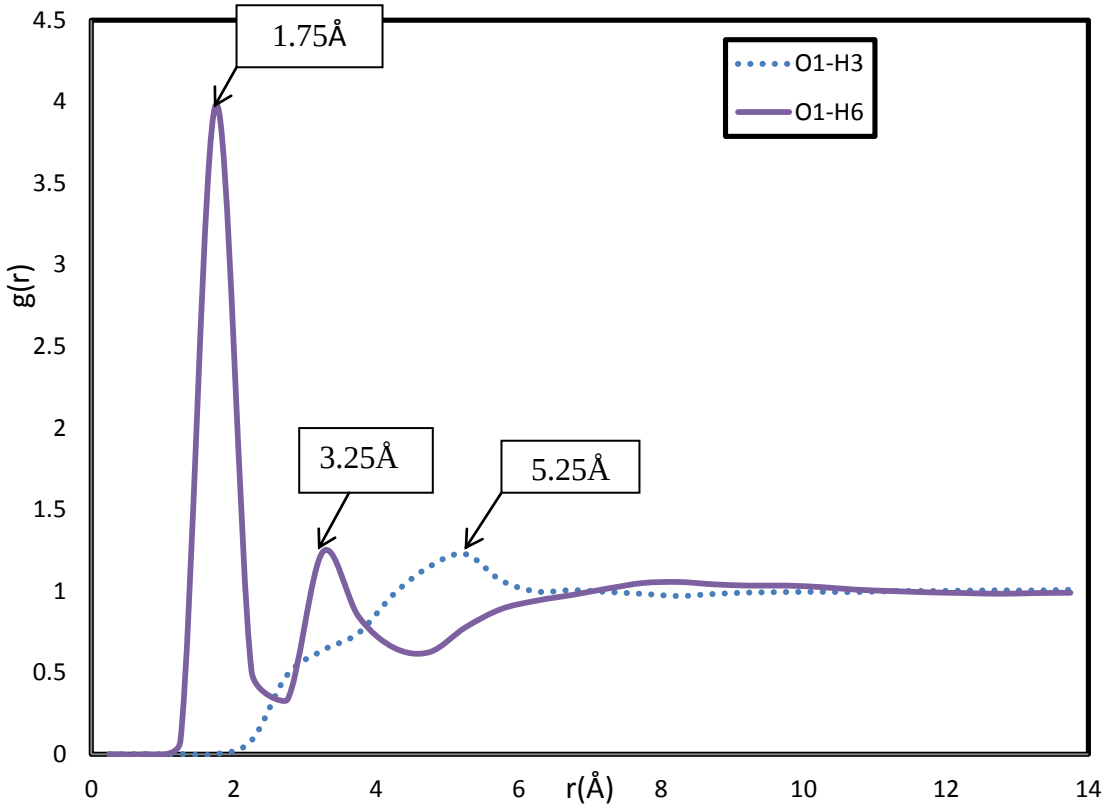


Figure 4.3 (a) RDF graph for interaction between ethanol's oxygen with H3 and H6 ethanol in pure system

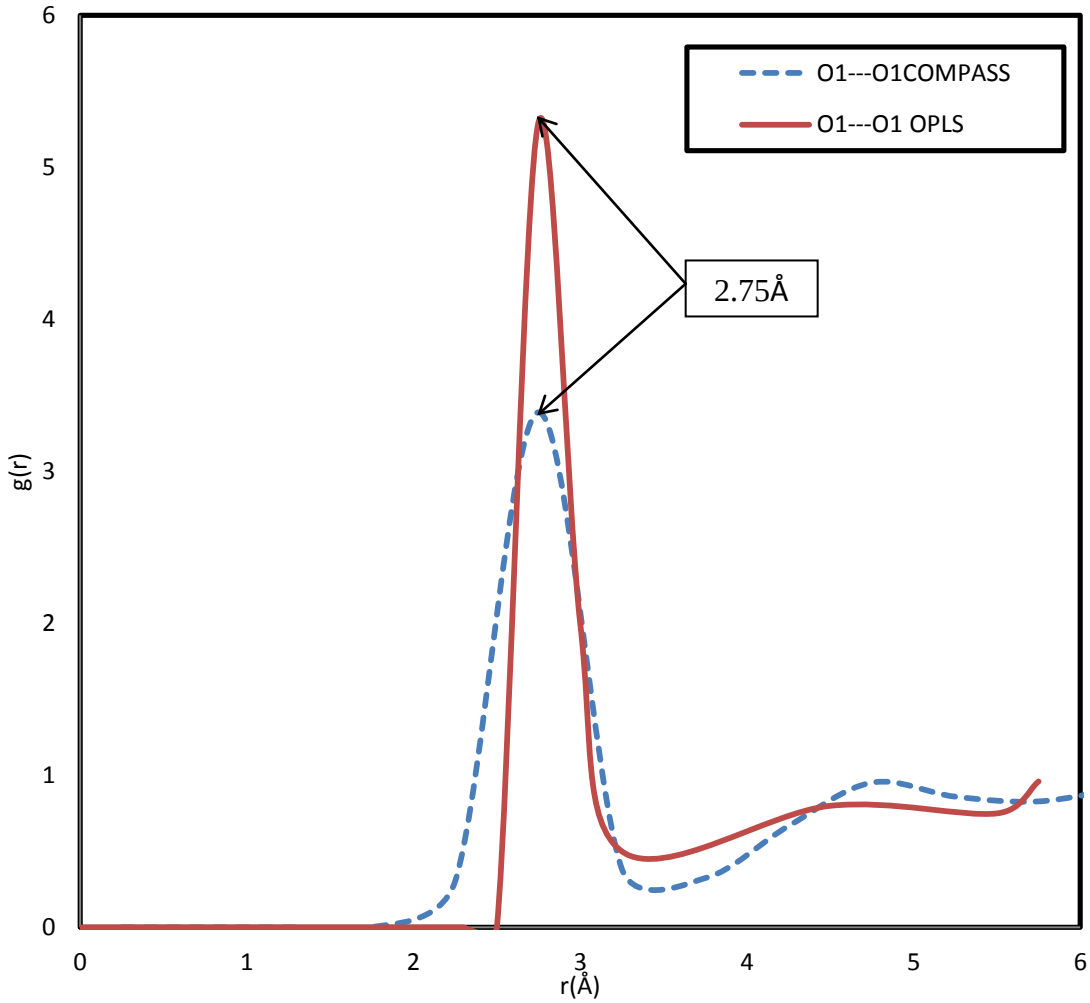


Figure 4.3 (b) RDF graph for oxygen interaction in pure ethanol between COMPASS and OPLS (Saiz, et al, 1997)

Based on the Figure 4.4, it shows that the radial distribution function for O1---O1 and H6---H6 are stronger for both atom interactions. This situation probably because the ability of the ethanol molecule which acts as a hydrogen bond donor.

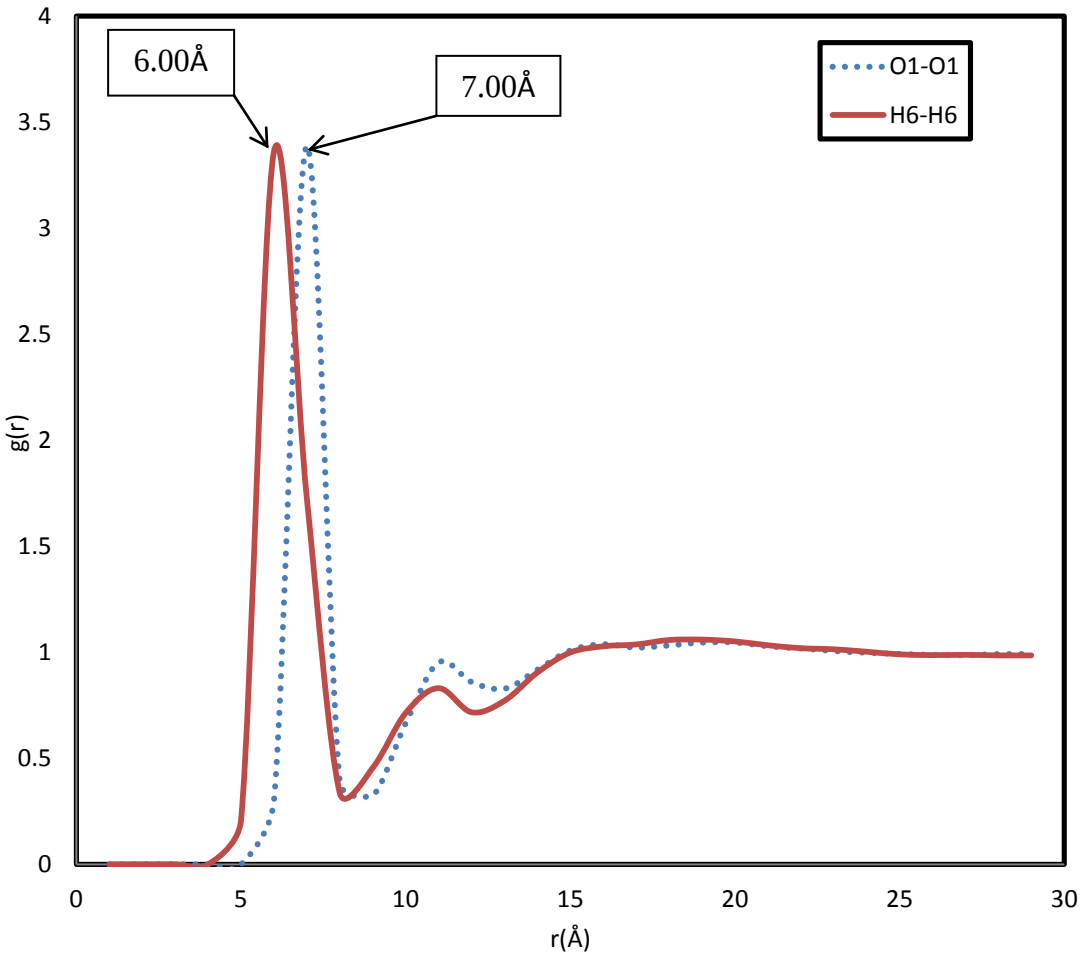


Figure 4.4 Atoms interaction for O1-O1 and H6-H6 in pure ethanol

4.1.1.3 Ethyl Acetate

From the Figure 4.5, the radial distance between the both oxygen atoms with the selected hydrogen atoms in the ethyl acetate are bigger. The radial distance for all the atom interaction shows a great distance which between 10.00Å to 13.00Å. This shows that the hydrogen bonding doesn't form in the ethyl acetate pure system. This situation probably because of the functional group in the ethyl acetate only can act as the hydrogen bond acceptors.

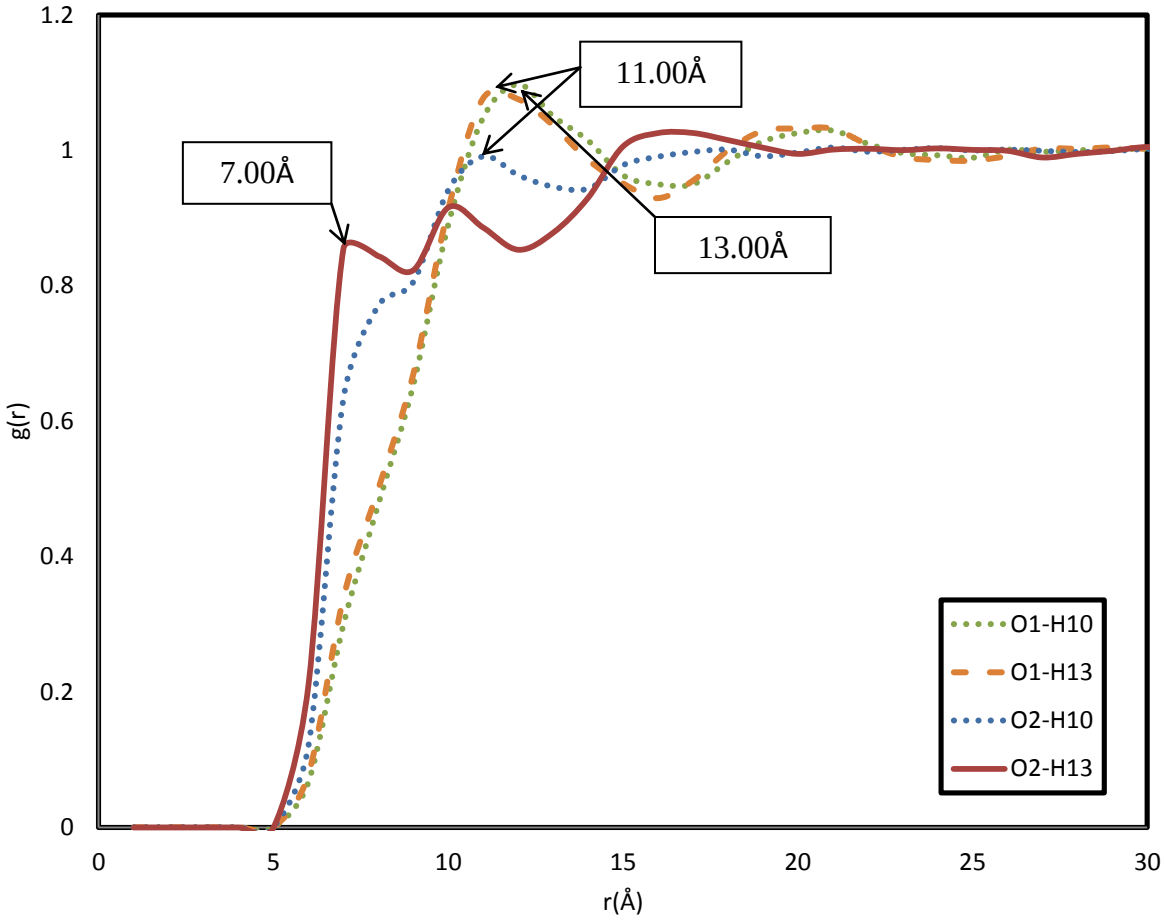


Figure 4.5 RDF graph for O1-H10, O1-H13, O2-H10 and O2-H13 interaction in pure ethyl acetate

The similar trends of radial distribution functions of the ethyl acetate atoms are shown in Figure 4.6. It seems that all this atom interaction is almost the same because there are not hydrogen bonds occur in the ethyl acetate pure system.

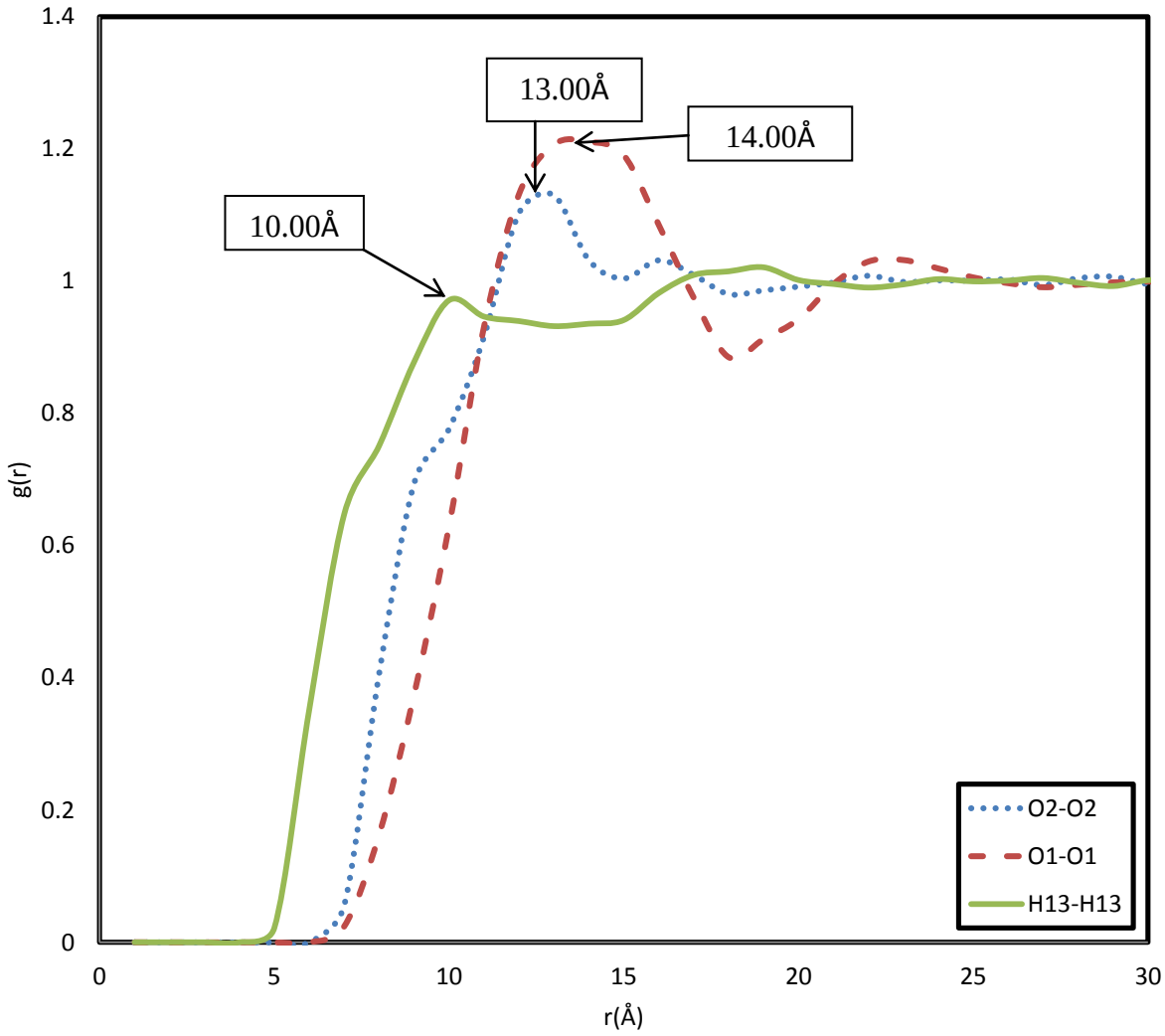


Figure 4.6 Atoms interaction for O1-O1, O2-O2 and H13-H13 in pure ethyl acetate

4.1.2 Binary System of Solute Solvent

4.1.2.1 Ethanol Mixture

Based on the Figure 4.7 (a), the graph of radial distribution function shows the radial between the O ethanol with the H33 ibuprofen, O ethanol with H6 ethanol in binary

system and O ethanol with H6 ethanol in pure system. It is shown that the strong hydrogen bond occurs between O ethanol with the H33 ibuprofen and O ethanol with H6 ethanol in binary system which at 5.00 Å. As compare between the O ethanol with H6 ethanol in binary systems and O ethanol with H6 ethanol in pure system, the radial are the same which at 5.00 Å. This is due to the ethanol oxygen that can act as hydrogen bond donors.

For the Figure 4.7 (b), the hydrogen bond is stronger between the O1 ibuprofen with H6 ethanol which at 8.00 Å if compare with the O1 ibuprofen with H33 ibuprofen. This shows that the solute oxygen atom is more attracted to attach with the solvent hydrogen atoms to form a hydrogen bond. In addition, the interaction between the solute-solute atoms in pure system shows a bigger radial value which 9.00 Å. That means, the oxygen atoms of ibuprofen are prefer to attach with the with the hydrogen atoms from the solvents.

Meanwhile, from the Figure 4.7 (c), the hydrogen bond is stronger for all the interaction which between the O2 ibuprofen with H6 ethanol and O2 ibuprofen with H33 ibuprofen for binary system which the radial is at 5.00 Å. This probably because of the O2 ibuprofen function which acts as hydrogen bond acceptor makes it available for all the interaction between the hydrogen atoms in solute molecules or solvents molecules. The peak of the radial distribution function between the O2 ibuprofen with H33 ibuprofen for binary system and O2 ibuprofen with H33 ibuprofen for pure system seems to show a little deviation where the peak for binary is 5.00 Å and 4.00 Å for pure respectively. This

situation might be because of the binary system still not archiving its equilibrium state where the hydrogen bond can attach strongly.

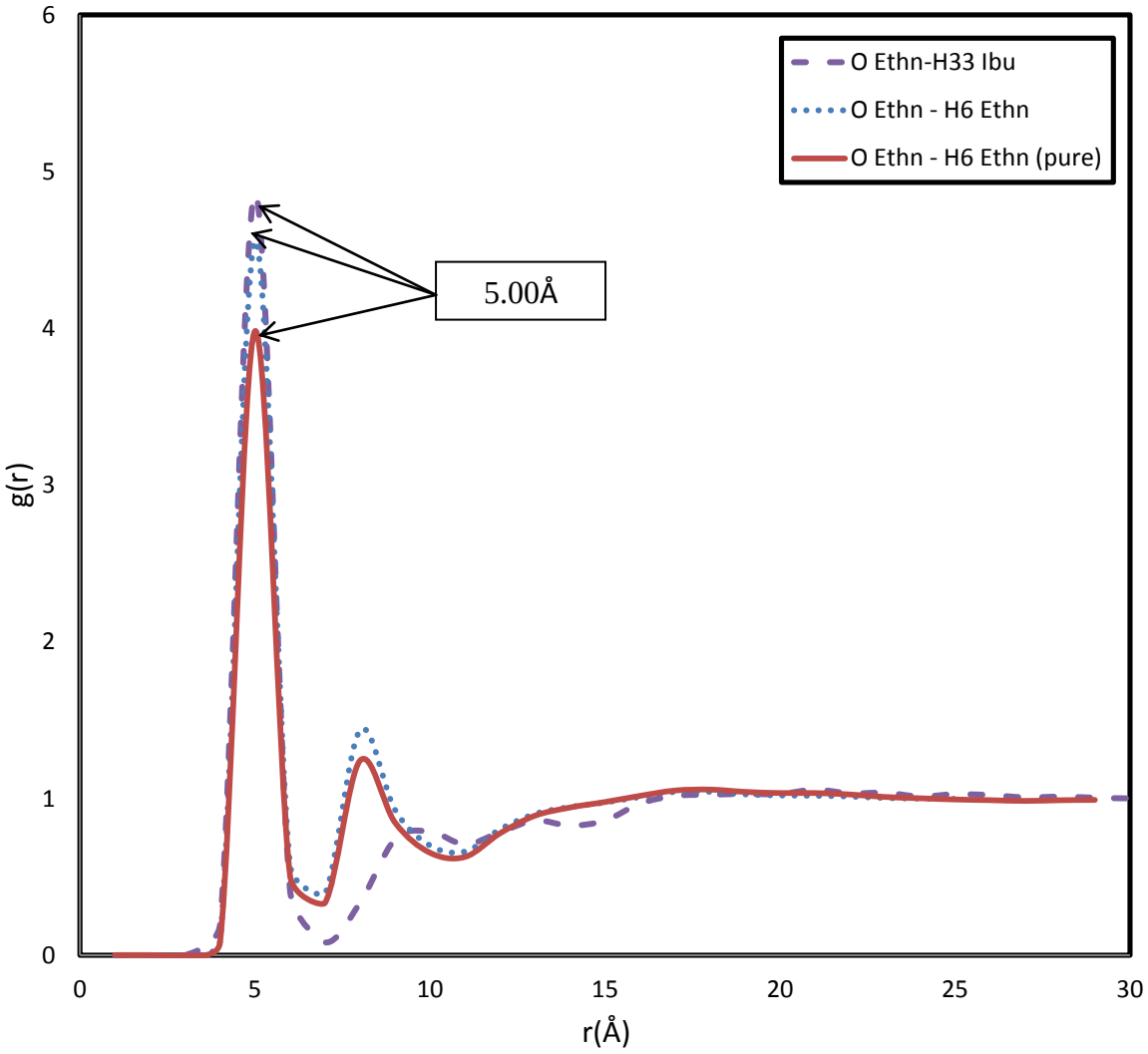


Figure 4.7 (a) RDF graph for O ethanol with H6 ethanol and H33 ibuprofen in binary system and between O ethanol and H6 ethanol in pure system

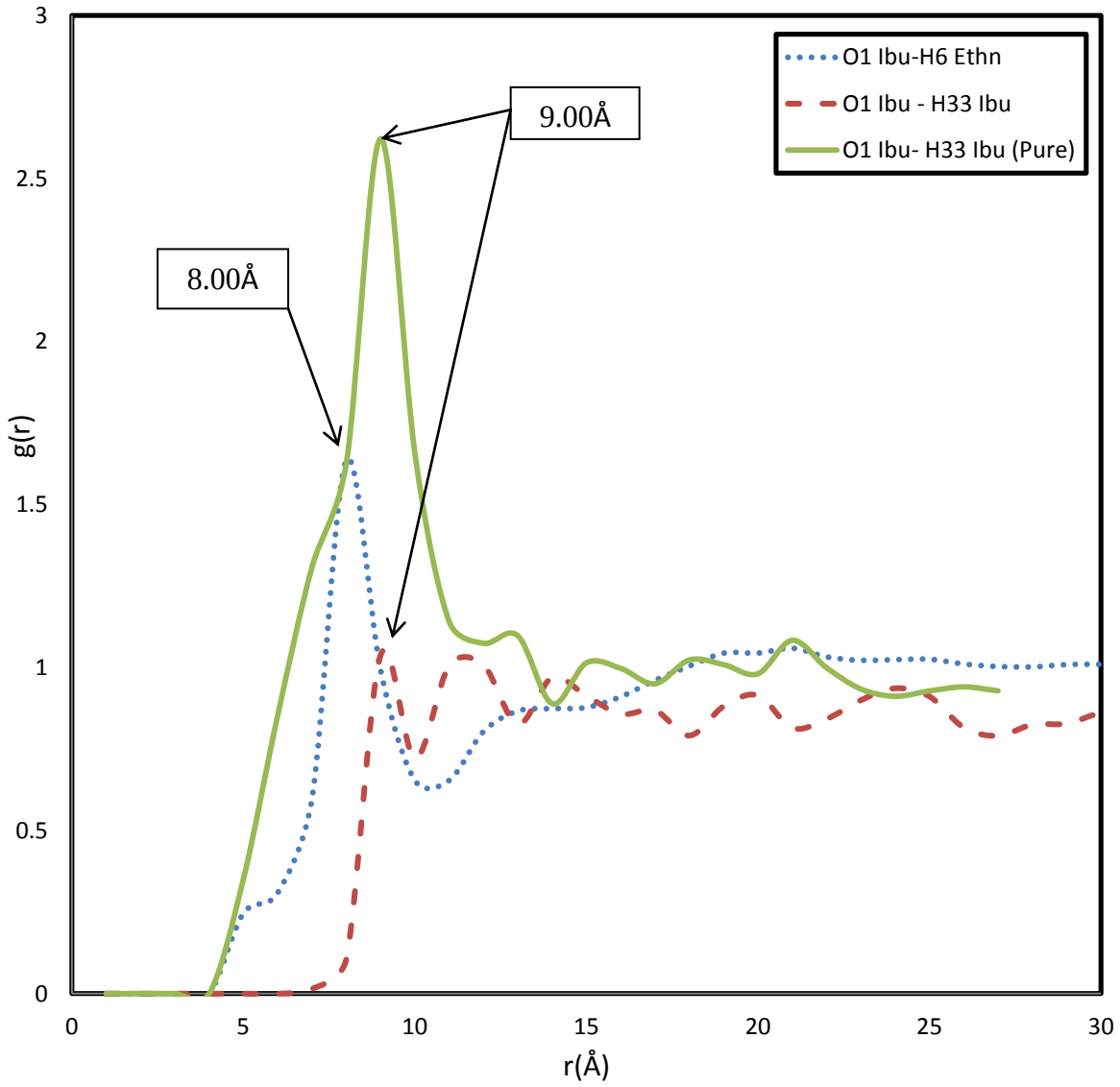


Figure 4.7 (b) RDF graph for O1 ibuprofen with H6 ethanol and H33 ibuprofen in binary systems and between O1 ibuprofen and H33 ibuprofen in pure system

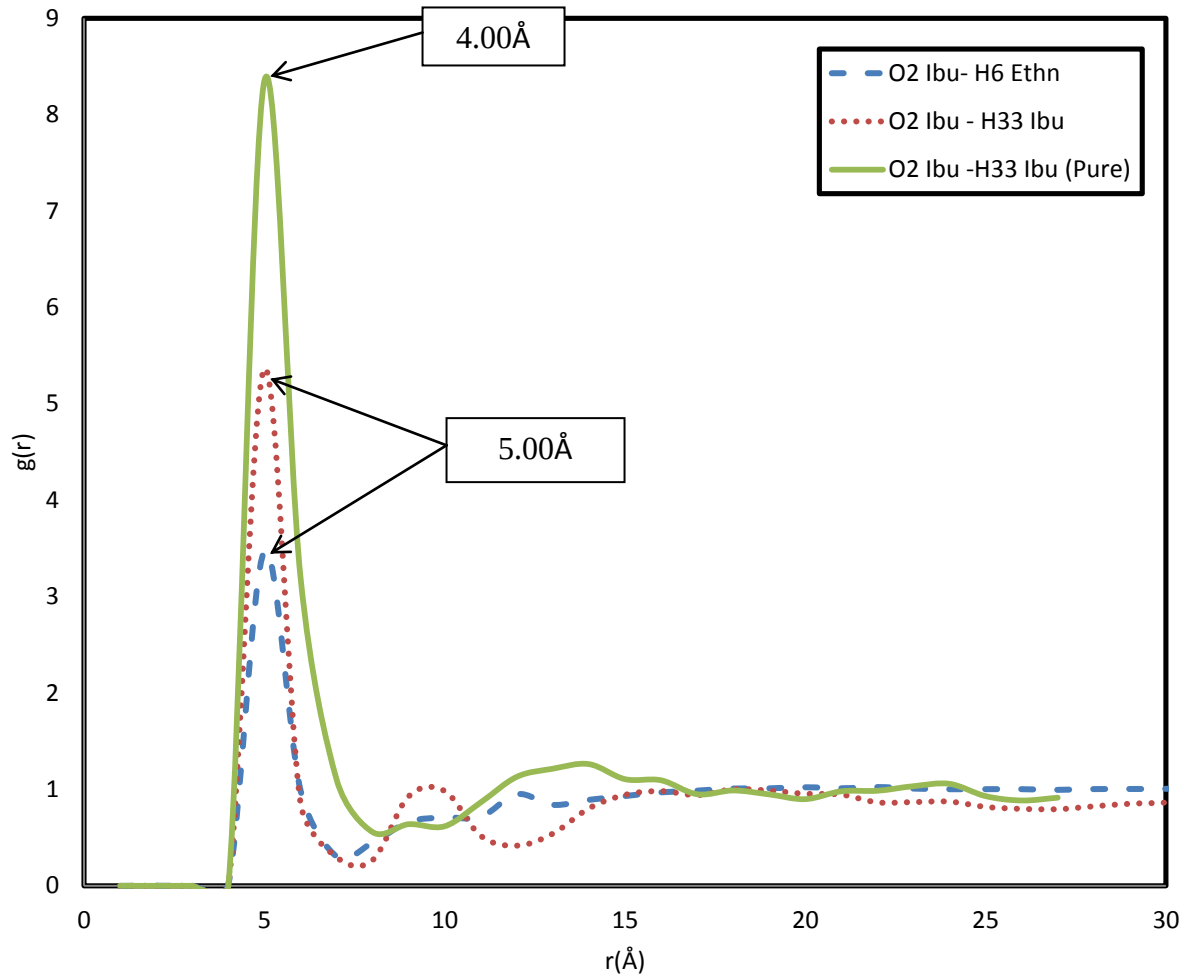


Figure 4.7 (c) RDF graph for O2 ibuprofen with H6 ethanol and H33 ibuprofen in binary systems and between O2 ibuprofen and H33 ibuprofen in pure system

The radial distribution function in Figure 4.8 shows the interaction of the ethanol oxygen atoms with the both ibuprofen oxygen atoms. The radial distance between the O1 ibuprofen with O ethanol shows a 6.00Å and for the distance between the O2 ibuprofen with O ethanol shows a value at 7.00Å respectively.

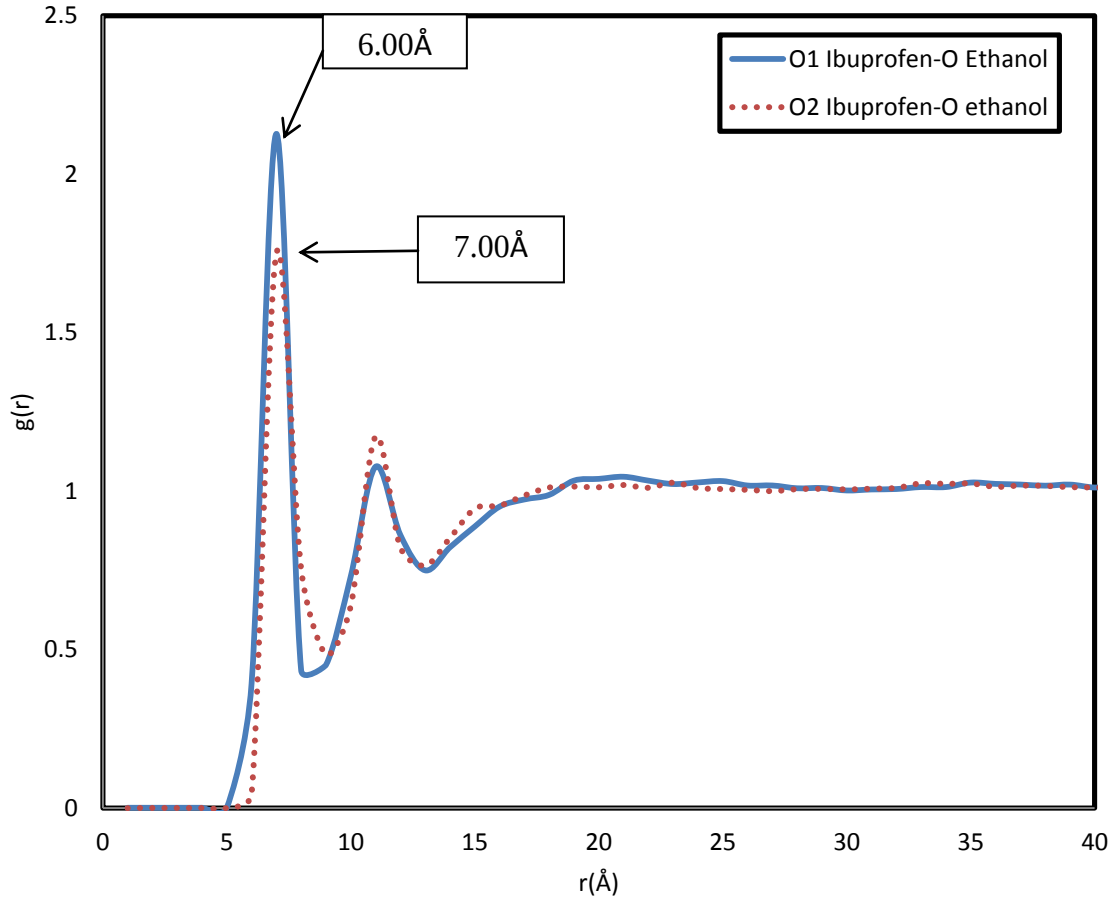


Figure 4.8 Atoms interaction between O1ibuprofen with O ethanol and O2 ibuprofen with O ethanol in ethanol mixture

4.1.2.2 Ethyl Acetate Mixture

The Figure 4.9 (a) indicates the radial distribution function for the distance between O1 ethyl acetate with H33 ibuprofen and H13 ethyl acetate in binary systems and between O1 ethyl acetate and H13 ethyl acetate in pure system. The short distances between the atoms are shown for the O1 ethyl acetate with H33 ibuprofen which at 8.00Å which describes that there are strong hydrogen bonds between these two atoms. As the

comparison between the O1 ethyl acetate with H13 ethyl acetate in binary systems and O1 ethyl acetate with H13 ethyl acetate in pure system, the atoms interaction show a bigger distance that represents there are no hydrogen bond. The atoms from the same component will repel each other's due to its same chargers.

In the Figure 4.9 (b), the hydrogen bonding between O2 ethyl acetate with H33 ibuprofen are stronger if compare with hydrogen bonding between O2 ethyl acetate and H13 ethyl acetate in binary system due to the distance of the O2 ethyl acetate with H33 ibuprofen which at 5.00Å. Meanwhile, the radial distance between the O2 ethyl acetate with H13 ethyl acetate in binary systems and pure system respectively shows a higher distance. This situation happens the atoms are not attracted to attach with the same molecular atoms.

In the Figure 4.9 (c) and (d), the radial distribution function shows the interaction between the both ibuprofen oxygen atoms with the selected ethyl acetate hydrogen atoms. In both interactions, the ibuprofen oxygen atoms show a really low radial distribution function. The ibuprofen oxygen atoms are more tendencies to attach with the ibuprofen hydrogen atoms also. The value for the radial between O1 ibuprofen with H33 ibuprofen is 9.00Å and 4.00Å for the radial between O2 ibuprofen with H33 ibuprofen respectively. This proves that the ibuprofen is not forming the hydrogen bonding with the ethyl acetate hydrogen atoms in the solute solvent system. For the comparison between the solute-solute interaction in pure system and binary system, the value shows the little deviation. That means the ibuprofen molecules prefer to attach with the same molecules even in the mixture situation.

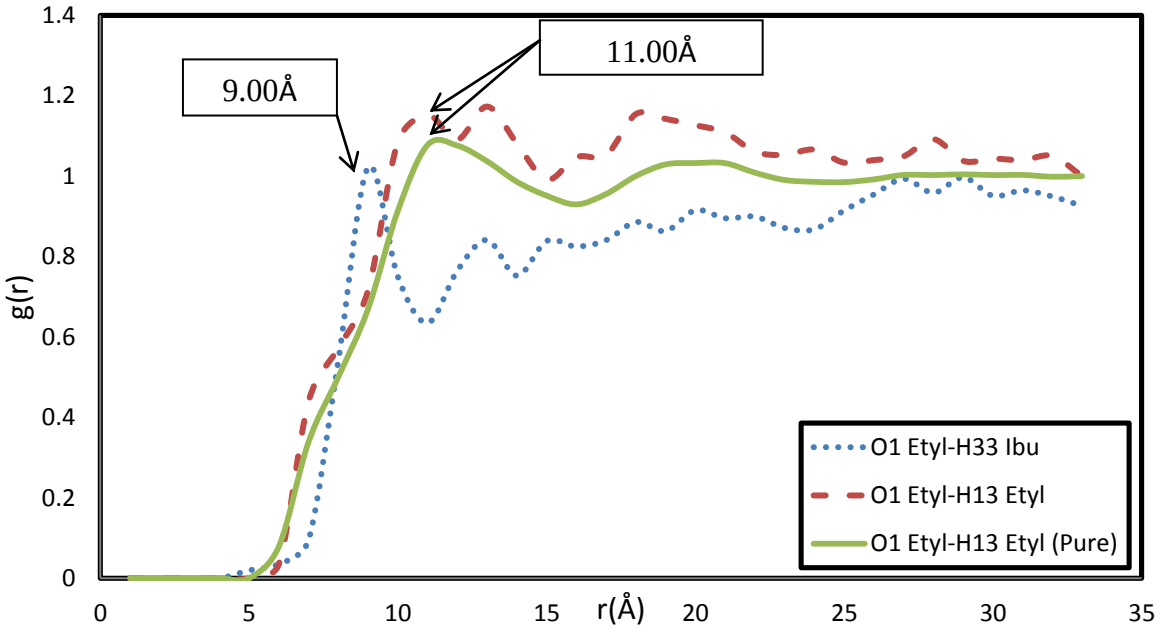


Figure 4.9 (a) RDF graph for O1 ethyl acetate with H33 ibuprofen and H13 ethyl acetate in binary system and between O1 ethyl acetate and H13 ethyl acetate in pure system

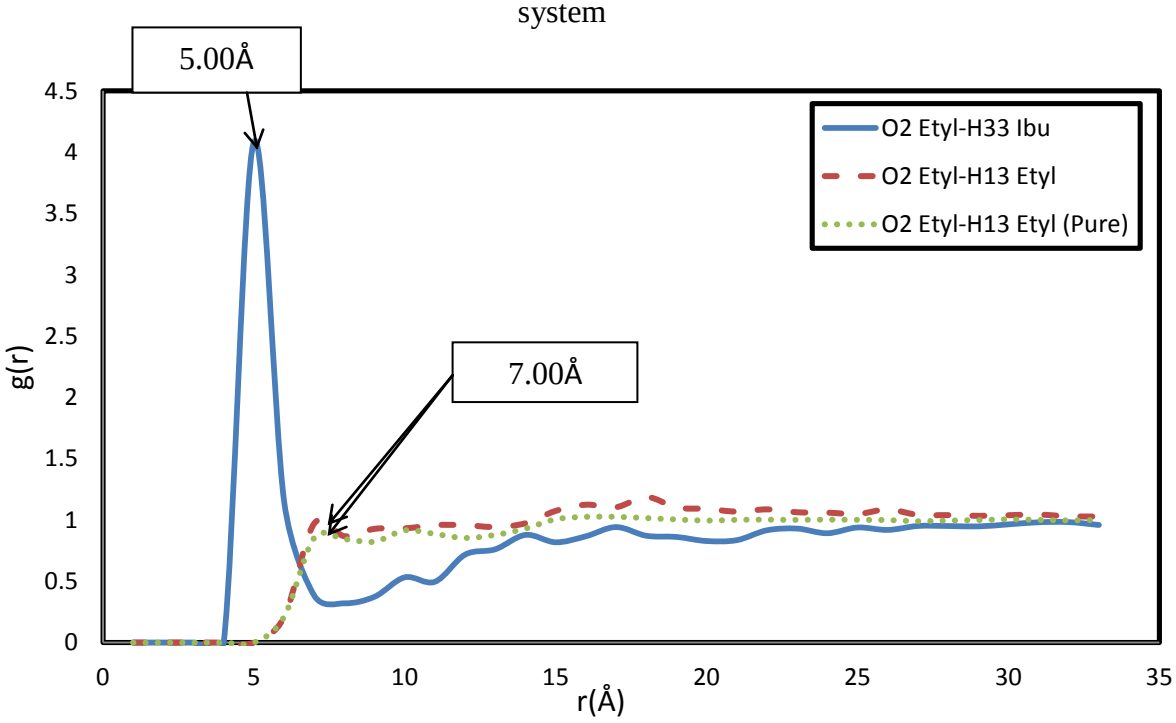


Figure 4.9 (b) RDF graph for O2 ethyl acetate with H33 ibuprofen and H13 ethyl acetate in binary system and between O2 ethyl acetate and H13 ethyl acetate in pure system

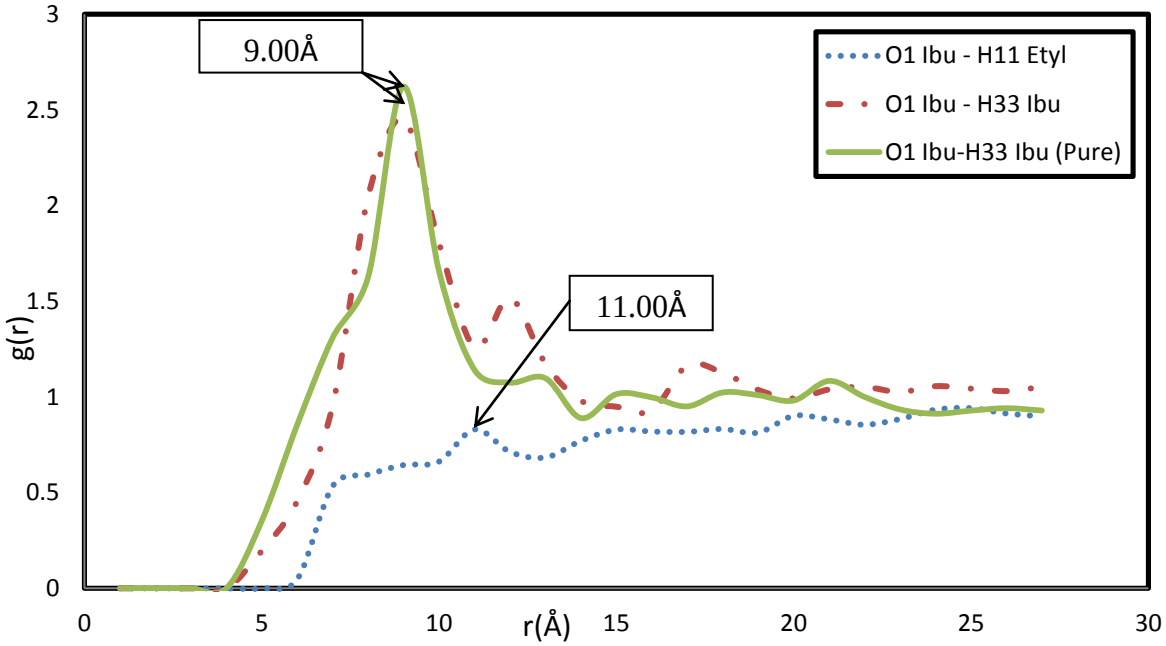


Figure 4.9 (c) RDF graph O1 ibuprofen with H11 ethyl acetate and H33 ibuprofen in binary system and between O1 ibuprofen and H33 ibuprofen in pure system

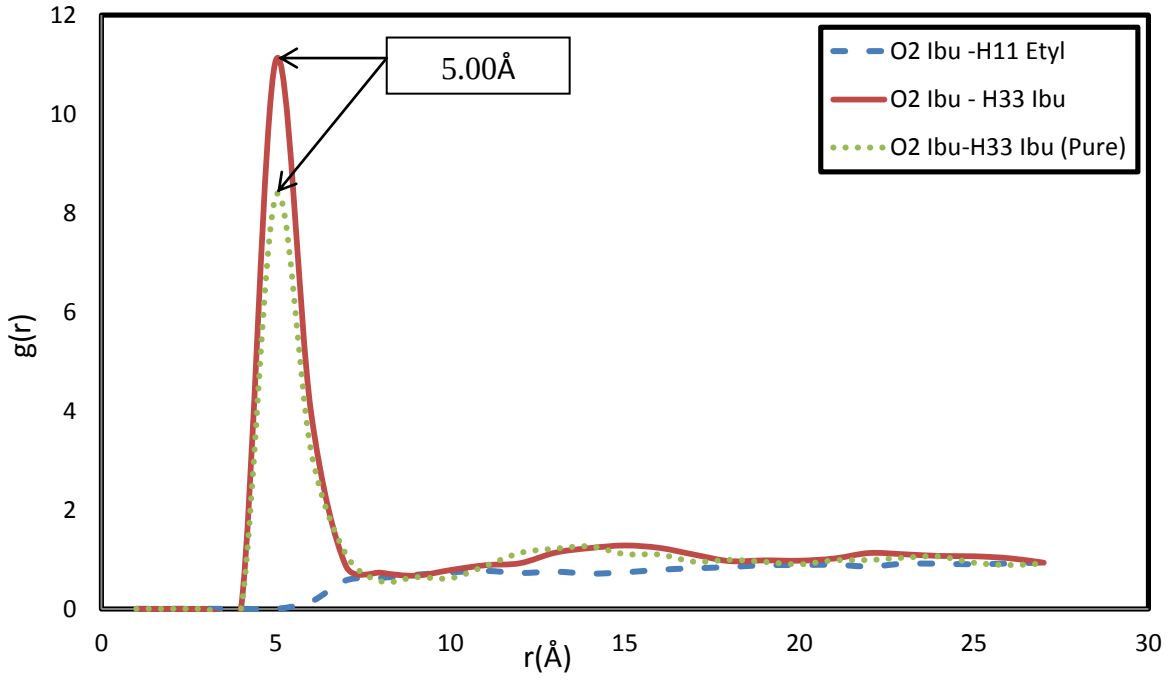


Figure 4.9 (d) RDF graph for O2 ibuprofen with H11 ethyl acetate and H33 ibuprofen in binary system and between O2 ibuprofen and H33 ibuprofen in pure system

The Figure 4.10 shows the radial distribution function for the both ethyl acetate oxygen atoms with the both ibuprofen oxygen atoms. The distance between the O1 ibuprofen are lower with O2 ethyl acetate if compare to the other interaction between the O1 ibuprofen with O1 ethyl acetate, O2 ibuprofen with O1 ethyl acetate and with O2 ibuprofen and O2 ethyl acetate.

Ibuprofen has a functional group of COOH which plays a significant role in forming the hydrogen bond. Based on the solvent selection, ibuprofen can produce a desired polymorph by choosing the suitable solvent since the crystal polymorph of ibuprofen are strong influences by the solvents. Ethanol and ethyl acetate will conduct strong intermolecular forces with the ibuprofen. So, it is clearly shown that the solvent selection use in the crystallization process of the ibuprofen may lead to polymorphism.

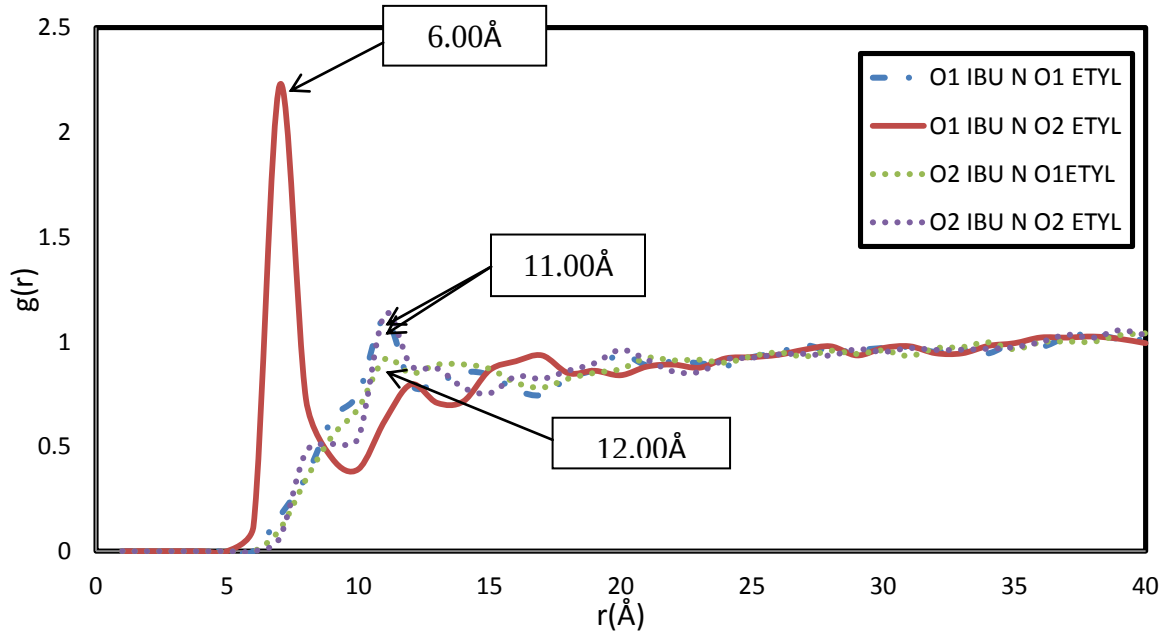


Figure 4.10 Atoms interaction between O1 ibuprofen with O1 ethyl acetate, O1 ibuprofen with O2 ethyl acetate, O2 ibuprofen with O1 ethyl acetate and O2 ibuprofen with O2 ethyl acetate in ethyl acetate mixture

4.2 Experimental Data

The experimental analysis is done by the use of Fourier transform infrared spectroscopy (FTIR). A mixture of solute (ibuprofen) and solvents (ethanol, ethyl acetate and hexane) have to undergo gravimetric method where the mixture sample will be put in the thermomixer for approximately 3 hours. Meanwhile, for the pure solvents which the ethanol, ethyl acetate and hexane, these solvents just directly run for the analysis using FTIR.

4.2.1 Discussion

Solubility is which the chemical substances called solute dissolve in the in the solvent at any state to form and homogeneous solution. The solubility of solute towards solvent can be identified by infinitely soluble or poorly soluble. Under the dynamic equilibrium the solubility can occur by means that the solubility results from the simultaneous and opposing process of dissolution. In this analysis, the solubility of the solute which the ibuprofen were studies of the balance of the intermolecular forces between the solute and the solvent selection.

4.2.1.1 Pure System

The analysis of solvent types is done by using in Fourier transform infrared spectroscopy (FTIR). Details of the analysis were explained in results obtain from the FTIR analysis in Figure 4.2,

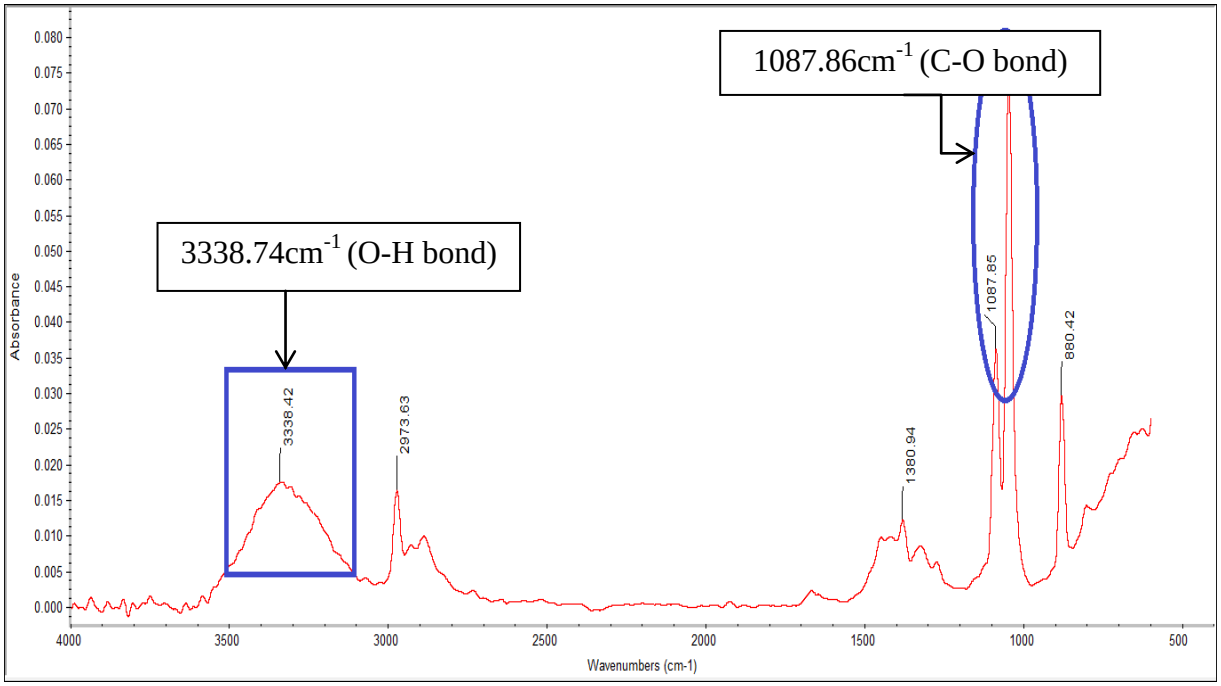


Figure 4.11 (a) Ethanol infrared FTIR analysis pattern

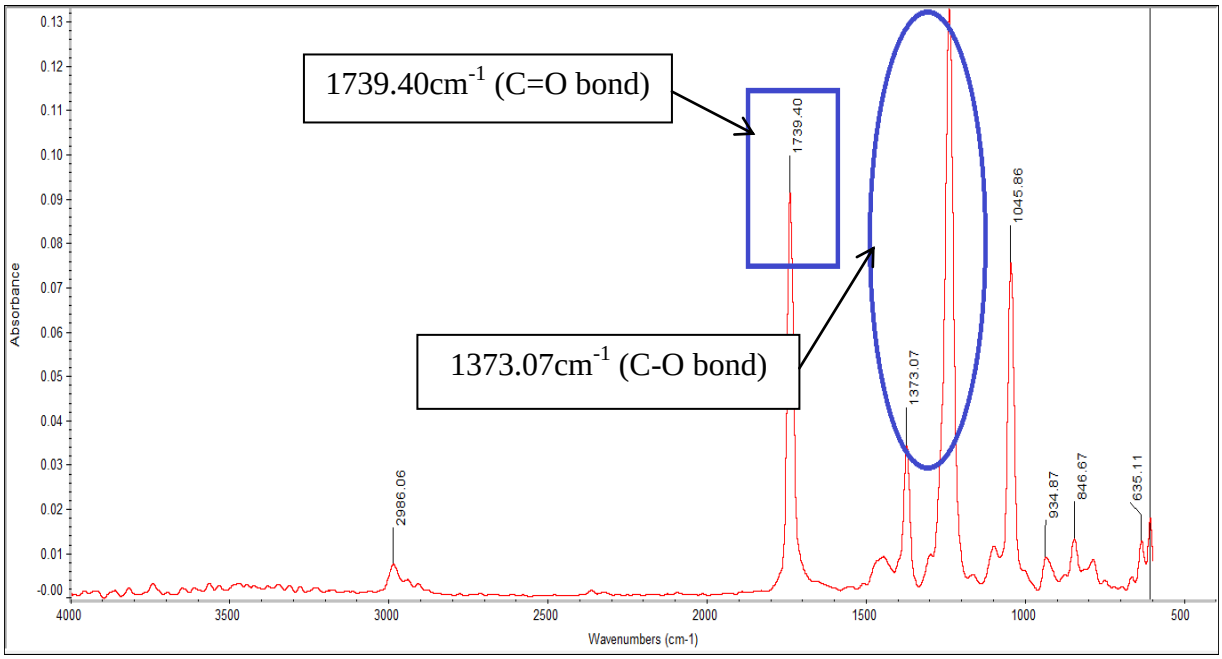


Figure 4.11 (b) Ethyl acetate infrared FTIR analysis pattern

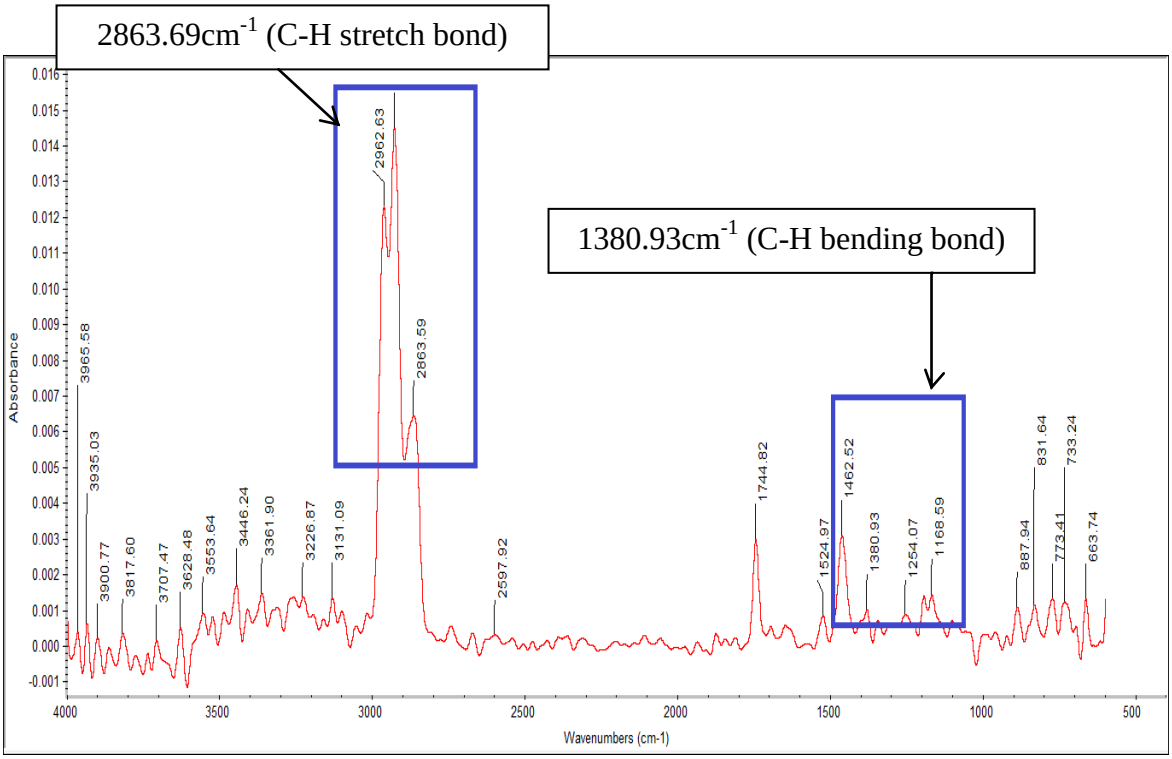


Figure 4.11 (c) Hexane infrared FTIR analysis pattern

From the results given in the FTIR analysis, then, all the three different solvents shows a difference in the terms of the peak of the graph which indicates the bonding and the functional groups exist in the solvents based on their class specification. From the Figure 4.11 (a), the peak of the ethanol analysis shows at a wavelength of 1087.85 cm^{-1} which indicates the C-O bond in the molecular structure that will help in the hydrogen bonding which acts as the hydrogen bond donors. Besides that, the wavelength also shows a peak at 3338.42 cm^{-1} which shows that this molecule has hydrogen bonding. It is proven that the ethanol is classified as the polar protic solvents that will display hydrogen bonding and has a high dielectric constant.

For the Figure 4.11 (b), the ethyl acetate FTIR analysis shows the peak of the wavelength at 1373.07 cm^{-1} which shows the C-O bond in the molecular structure and at a wavelength of 1739.40 cm^{-1} also shows a C=O bond. This is shown that, the ethyl acetate is classified as the dipolar aprotic solvents which act as hydrogen acceptor. And for the Figure 4.11 (c), the peaks for hexane analysis shows the wavelength at certain values which indicates that only the C-H bond are present in the molecular structure of hexane. Compare to the ethanol and ethyl acetate, hexane is classified non-polar solvents or well known as apolar aprotic which neither hydrogen bond acceptor nor donor (Adam, 2012).

4.2.1.2 Binary System of Solute-Solvent

The intermolecular forces between the solute and the solvents in the solution are shown in the Figure 4.12 by the FTIR analysis

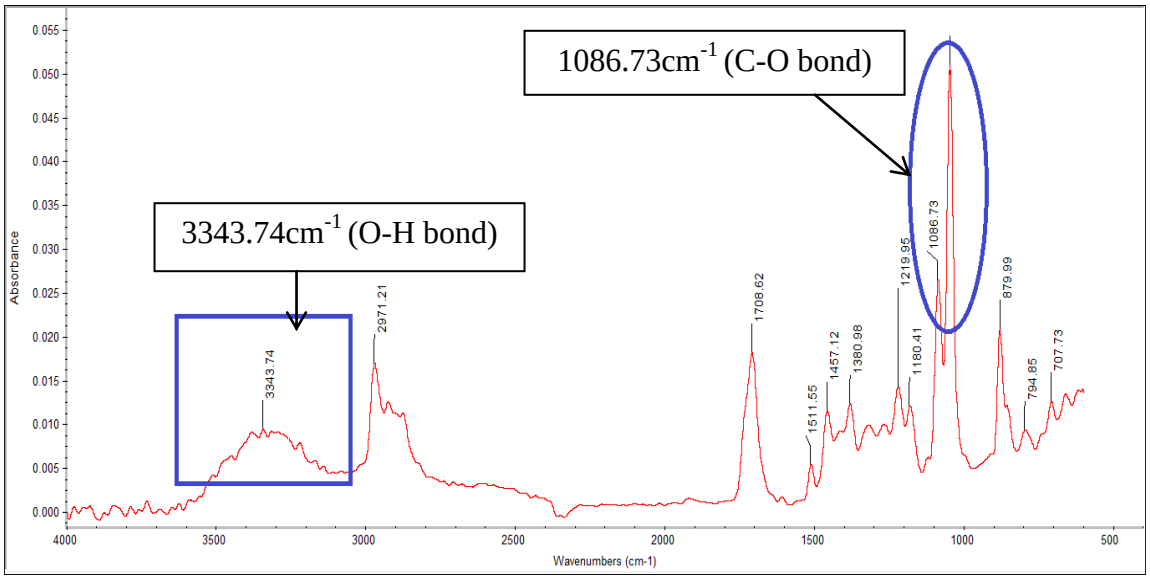


Figure 4.12 (a) Ethanol mixture infrared FTIR analysis pattern

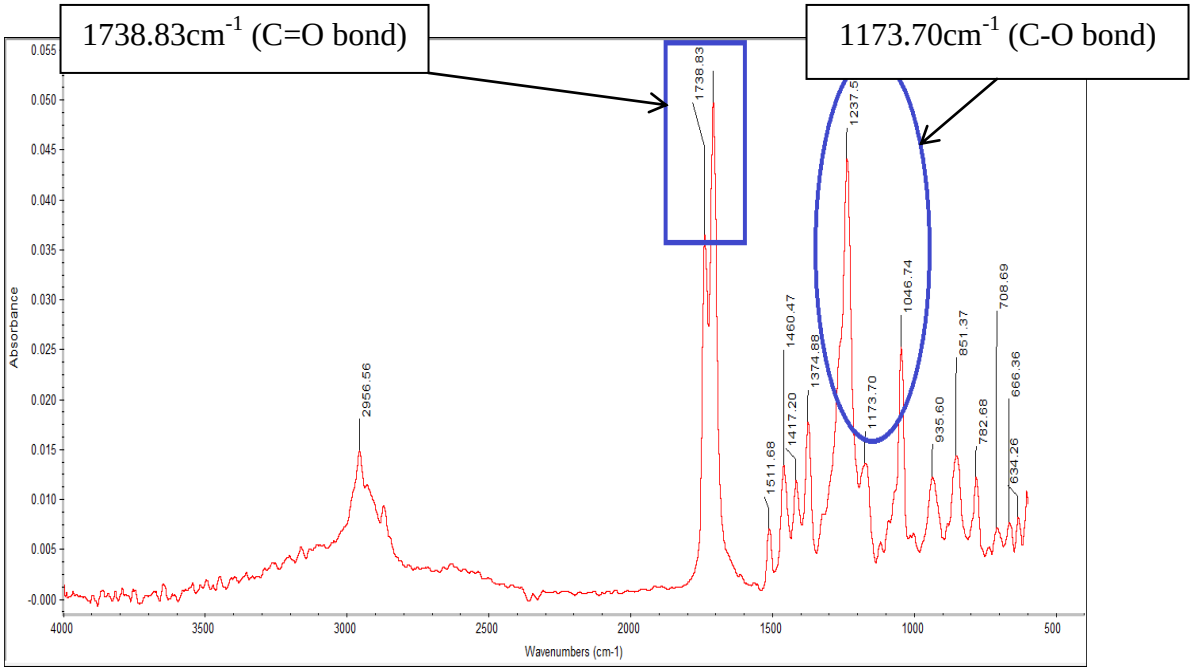


Figure 4.12 (b) Ethyl acetate mixture infrared FTIR analysis pattern

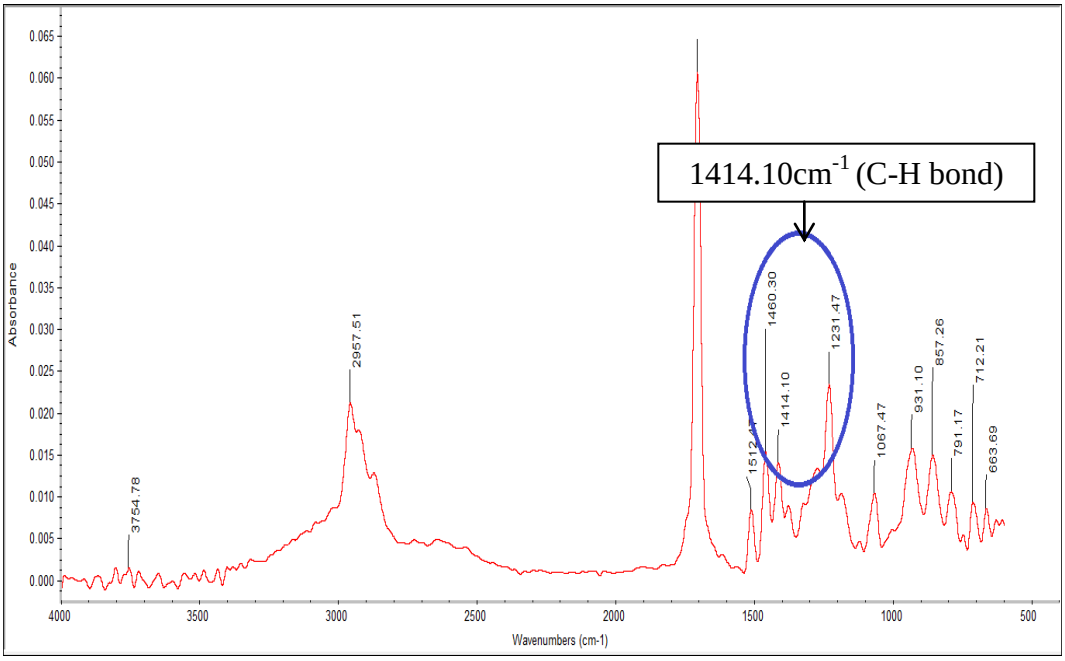


Figure 4.12 (c) Hexane infrared FTIR analysis pattern

From Figure 4.12 (a), the peak of the wavelength for binary ibuprofen and ethanol are shown in 1088.73 cm^{-1} which present of C-O bond in the system. And at the 3343.74 cm^{-1} wavelength indicates the presence of hydrogen bonds in the system. The ethanol as the polar protic solvent will act as the hydrogen bond donors with the solute which ibuprofen also can act as the hydrogen bond donors or hydrogen bond acceptor based on the molecular structure of the ibuprofen which contains the C-O and C=O in the structure. This will make the solution become more soluble for the ethanol to dissolve in the ibuprofen. As compare between experimental and simulation data analysis, the hydrogen bond for this analysis shows a same situation which indicates the strong hydrogen bond are exist in the system.

As for the Figure 4.12 (b) which the binary system for the ibuprofen and ethyl acetate, the peak of wavelength shown a peak at the 1237.59 cm^{-1} which indicates the C-O bond in the system and at 1738.83 cm^{-1} wavelength present the C=O bond in the system. The ethyl acetate will accept the hydrogen bond by the ibuprofen in the system and make the system soluble. These types of dipolar aprotic solvent will help in dissolving the ethyl acetate in the ibuprofen solution and by that the solvents can be said as soluble in the solute. The comparison data analysis between the simulation and experimental, both of the analysis shows a positive sign in the presence of strong hydrogen bond in the mixed solution. It can be said that, both experiment and analysis shows a good agreement with the previous study.

Based on the Figure 4.12 (c) which indicates the binary system for the ibuprofen and hexane. The FTIR analysis shows a peak of the wavelength at 1231.47 cm^{-1} which

indicates the presence of C-O bond in the system and the peak at the wavelength around 1670.00 to 1760.00 cm^{-1} indicates the C=O bond in the system. From the FTIR analysis, even the characteristics of hexane which classified as apolar aprotic solvent, but the ibuprofen molecular structure which allows for the hydrogen bond donor or acceptor makes the system soluble even the non-polar solvent as hexane but can be classified as the moderate soluble. It is shown that all the solvent selection of this study shown a positive sign on the solubility towards the solution by using ibuprofen as the solute.

4.2.2 Solubility

The solubility of the ibuprofen is determined at the 298.15K where the temperature of the room. From the experimental, the data of the mass of ibuprofen used in the different types of solvents are shown in the Table 4.1.

Table 4.1 Ibuprofen solubility in different types of solvents

Component	Ethanol	Ethyl acetate	hexane
Mass ibuprofen (g)	2.5001	1.9944	0.3662
Volume (ml)	3.000	3.000	3.000
Solubility	0.1909	0.2841	0.3471

Based on the Table 4.1, the calculations of the solubility of ibuprofen in the solvents are calculated using the formula given by the previous researcher in section 3.2. From this calculation, the solubility get for the ethanol mixture is 0.1909, 0.2841 for ethyl acetate and 0.3471 for hexane mixture. From these values calculated, the error of the experimental data in this study with the experimental data from the previous research shows a positive agreement where the error between the solubility is 3.55% and 3.25% respectively for ethanol and ethyl acetate (Shui et al. 2010). This shows that the solubility of this study shows a good sign with the experimental values from the previous researchers.

CHAPTER 5

CONCLUSION AND RECOMMENDATIONS

5.1 Conclusions

From the molecular dynamic simulation, there is a difference in the intermolecular interaction behavior between the solute of ibuprofen depending on the types of solvents used which polar protic (ethanol), dipolar aprotic (ethyl acetate) and apolar aprotic (hexane). Based on those differences, it shows that different polymorphs will be produced with different types of solvents such as the elongated crystal is produced from dipolar aprotic solvent. The isomeric crystal form is produced by the use of polar protic solvent and the needle like crystal is form from the apolar aprotic solvents. For the experimental study, the solubility of the ethanol mixture, ethyl acetate mixture and hexane mixture shows a great agreement with the previous study. It is shown that the solubility of different types of solvents will affect the solubility of the solvents towards its solute.

5.2 Recommendations for Future Research

From this study, there are a few problems that occur such as cannot isolate the solute and solvent molecules as their have same atom label and those problems influence our result for the rdf analysis. Therefore, as a suggestion for future research, make sure that the solute and solvent can be isolated first before running the experiment. Besides, the calculated rdf from this study is not in good agreement with the previous study. As a recommendation, the simulation should be run for a longer time for the molecules to achieve its equilibrium state. In addition, for future research, the analysis should be done based on the diffusion, mean square displacement and use different method analysis such as TGA, XRD, DSC, and morphology. Besides that, the solubility testing of the solvent solute recommend to be run in different temperature as the temperature also affect the solubility of solvents to the solute.

REFERENCES

Angel Martin, Katharine Scholle, Facundo Mattea, Darja Meterc and Maria Jose Cocero. (2009) Production of Polymorphs Of Ibuprofen Sodium By Supercritical Antisolvent (SAS) Precipitation Prepared By *American Chemical Society* 2504-2511.

Arunprakash T. Karunanithi, Charles Acquah and Luke E.K. Achenie (2008). Tuning The Morphology Of Pharmaceutical Compounds *via* Model Vased Solvent Selection Prepared By *Chinese Journal Of Chemical Engineering 16(3)*. 465-473

Arunprakash T. Karunanithi, Charles Acquah, Luke E.K. Achenie, Shanthakumar Sithambaram, Steven L. Suib, Rafiqul Gani. (2007) An Experimental Verification Of Morphology Of Ibuprofen Crystals From CAMD Design Solvent Prepared By *Chemical Engineering Science 62* .3276-3281.

Barbara Rodríguez-Spong, Christopher P Price,Adivaraha Jayasankar, Adam J Matzger And Naír Rodríguez-Hornedo (2004). General Principles Of Pharmaceuticals Solid Polymorphism: A Supramolecular Perspective Prepared By *Advanced Drug Delivery Reviews 56.* 241-274.

Charles Acquah, Arunprakash T. Karunanithi, Matthew Cangetta, Luke E.K. Achenie And Steven L. Suib (2008). Linear Models For Prediction Of Ibuprofen Crystal Morphology Based On Hydrogen Bonding Propensities Prepared By *Fluid Phase Equilibria 277*. 73-80

Chong-Hui Gu, Hua Li, Rajesh B Gandhi And Krishnaswany Raghavan (2004). Grouping Solvents by Statistical Analysis Of Solvent Property Parameters: Implication To Polymorph Screening Prepared By *International Journal Of Pharmaceutics 283*.117-125

Emelia Dudognon, Florence Danede, Amrc Descamps And Natalia T. Correia (2008). Evidence For A New Crystalline Phase Of Racemic Ibuprofen Prepared By *Pharmaceutical Research Vol 25. No.12.*

Fatima L. Mota, Aristides P. Carneiro, Antonio J. Queimada, Simao P. Pinho And Eugenia A. Macedo(2009). Temperature And Solvent Effects In The Solubility Of Some Pharmaceutical Compounds: Measurement And Modeling Prepared By *European Journal Pf Pharmaceutical Sciences 37*. 499-507

Fatmawati Adam, Robert B. Hammondt And Kevin J. Roberts (2012). Force Field Performance In Recognition Of Solvent Mediated Polymorphism Of 2,6-Dihydroxybenzoic Acid From Toluene And Choloroform Solution Prepared By *School Of Process And Material Engineering.*

Gu Shan, Koichi Igarashi, Hideo Noda, Hiroshi Ooshima. (2002) Control Of Solvent-Mediated Transformation Of Crystal Polymorphs Using A Newly Develop Batch Crystallizer (WWDJ-Crystallizer) Prepared By *Chemical Engineering Journal* 85.169-176.

H. A. Garekani, F. Sadeghi, A. Bandiee, S.A. Mostafa and A.R. Rajabi-Sianhboomi (2001). Crystal Habit Modifications of Ibuprofen and Their Physicomechanical Characteristics Prepared By *Drug Development and Industrial Pharmacy, 27(8).* 803-809

J.H. Ter Horst[a], R.M. Geerman, G.M. Van Rosmalen. (2001) The Effect Of Solvent On Crystal Morphology Prepared By *Journal Of Crystal Growth*. 277-284

Kleafah A.K. Musa And Leif A. Eriksson (2007). Theoretical Study Of Ibuprofen Phototoxicity Prepared By *Journal Of Physics Chemistry, 111*. 13345-13352.

L. Seton, M. Roberts And F. Ur-Rehman (2011). Compaction Of Recrystallised Ibuprofen Prepared By *Chemical Engineering Journal 164*. 449-452

M.Delwar Hussain, Vipin Saxena, James F. Brausch, Rahmat M. Talukder. (2011) Ibuprofen-Phospholid Solid Dispersions: Improved Dissolution and Gastric Tolerance Prepared By *International Journal Of Pharmaceutics*

Madelaine R. Whelan, James L, Ford And Mark W. Powell (2002). Simultaneous Determination Of Ibuprofen And Hydroxypropl,Ethylcellulose (Hpmc) Using Hplc And Evaporative Light Scattering Detection Prepared By *Jounal Of Pharmaceutical And Biomedical Analysis 30*. 1355-1359

Michael A. Lovette, Andrea Robben Browning, Derek W. Griffin, Jacob P. Sizemore, Ryan C. Snyder And Michael F. Doherty (2008). Crystal Shape Engineering Prepared By *Department Of Chemical Engineering University Of California.*

Norbet Rasenack, and Bernd W. Muller.(2002) Ibuprofen Crystal Optimized Properties Prepared By *International Journal Of Pharmaceutical* 245. 9-24.

P.J. Salustio, H.M. Cabral-Marques, P.C. Costa And J.F Pinto (2010). Comparison Of Ibuprofen Release From Minitablets And Capsules Containing Ibuprofen: β-Cyclodextrin Complex Prepared By *European Journal Of Pharmaceutics And Biopharmaceutics 78*. 58-66

Petr Kolar, Jun-Wei Shen, Akio Tsuboi and Takeshi Ishikawa (2002). Solvent Selection For Pharmaceuticals Prepared By *Fluid Phase Equilibria 194-197*. 771-782

S. Jacob, A.B. Nair, P.N. Patil and B.P. Panda (2011). Solid State Crystallinity, Amorphous State And Its Implications In The Pharmaceutical Process Prepared By *International Journal Of Pharmaceutical Sciences And Research, Vol 2(3).* 473-482

S. Lerdkanchanaporn and D. Dollimore (1997). A Thermal Analysis Study of Ibuprofen Prepared By *Journal of Thermal Analysis. Vol 49.* 879-886

S. Schmid, C.C. Muller-Goymann, P, C. Schmidt. (2000) Interactions During Aqueos Film Coating Of Ibuprofen With Aquacoat Ecd Prepared By *International Journal Of Pharmaceutics 197*.35-39

Sabiruddin Mirza, Inna Miroshnyk, Jyrki Heinamaki, Osmo Antikainen, Jukka Rantanen, Pia Vuorela, Heiki Vuorela And Jouko Yliruusi (2009). Crystal Morphology Engineering Of Pharmaceutical Solils: Tabletting Performance Enchancement Prepared By *AAPS PharmaSciTech Vol 10.*

Sherry L. Morissette, Orn Almarsson, Matthew L. Peterson, Julius F. Remenar, Micheal J. Read, Anthony V. Lemmo, Steve Ellis, Michael J. Cima And Colin R. Gardner (2004). High-Throughput Crystallization: Polymorphs, Salts, Co-Crystals and Solvates of Pharmaceutical Solids Prepared By *Advanced Drug Delivery Review 56*. 275-300.

Sundra R. Vippagunta, Harry G. Brittain, David J.W. Grant. (2001) Crystalline Solids Prepare By *Advance Drug Delivery Review 48* 3-26.

Xiaohui Duan, Chunxue Wei, Yonggang Liu and Chonghua Pei (2010). A Molecular Dynamic Simulations of Solvent Effects On Crystal Morphology Of HMX Prepared By *Journal Of Hazardous Materials 174*. 175-180

APPENDIX

APPENDIX A PURE SNAPSHOT

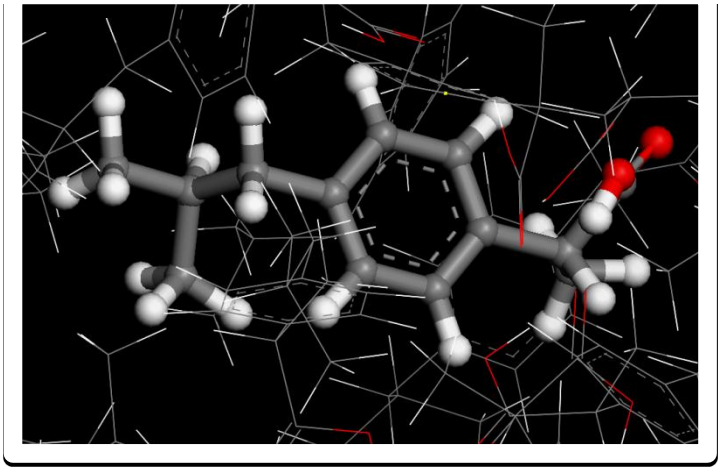


Figure A.1 Ibuprofen

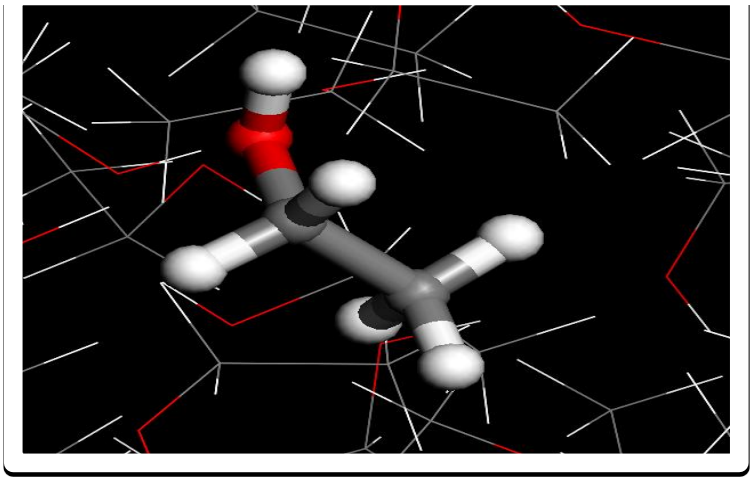


Figure A.2 Ethanol

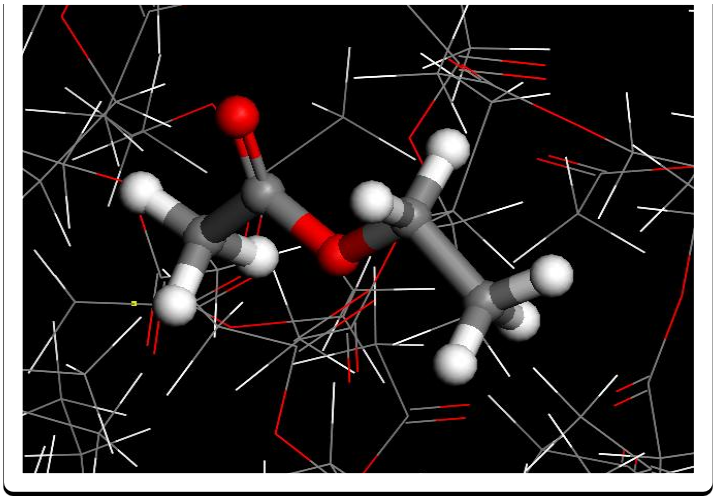


Figure A.3 Ethyl Acetate

APPENDIX B BINARY SNAPSHOT

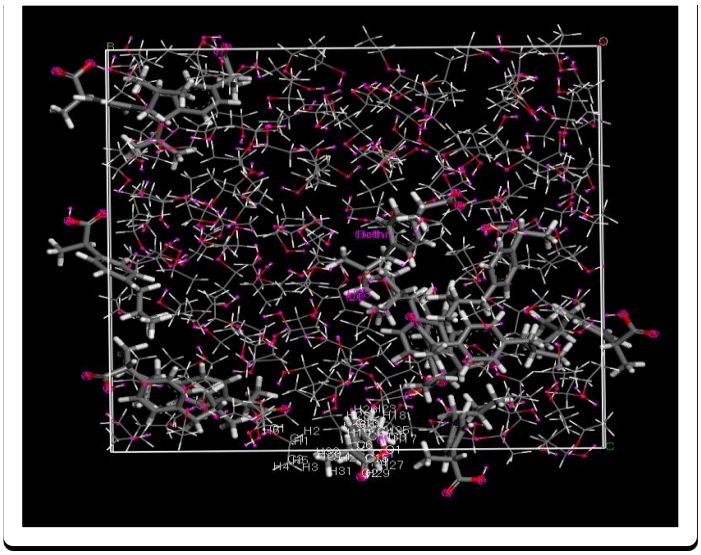


Figure B.1 Ethanol Mixture

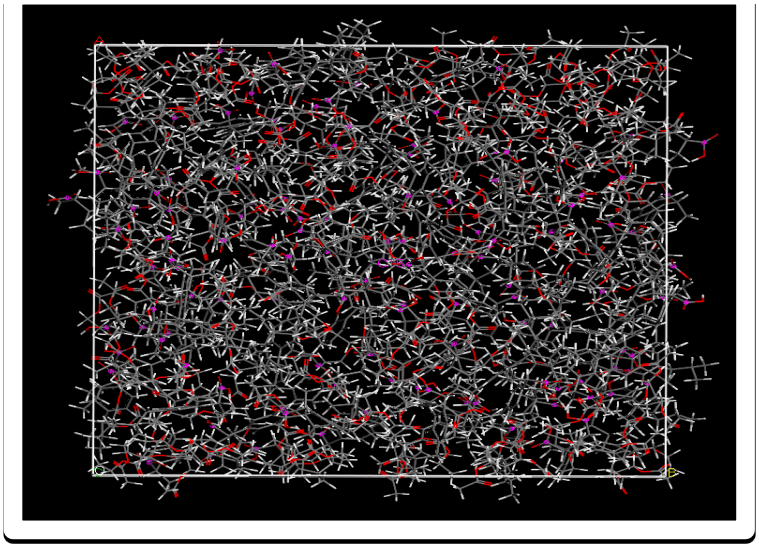


Figure B.2 Ethyl Acetate Mixture

APPENDIX C INFRARED ABSORPTION FREQUENCIES

Table C.1 Characteristic Infrared Absorption Frequencies

Bond	Compound Type	Frequency range, cm^{-1}
C-H	Alkanes	2960-2850(s) stretch
		1470-1350(v) scissoring and bending
	CH_3 Umbrella Deformation	1380(m-w) - Doublet - isopropyl, *t*-butyl
C-H	Alkenes	3080-3020(m) stretch
		1000-675(s) bend
C-H	Aromatic Rings	3100-3000(m) stretch
	Phenyl Ring Substitution Bands	870-675(s) bend
	Phenyl Ring Substitution Overtones	2000-1600(w) - fingerprint region
C-H	Alkynes	3333-3267(s) stretch
		700-610(b) bend
C=C	Alkenes	1680-1640(m,w)) stretch
C≡C	Alkynes	2260-2100(w,sh) stretch
C=C	Aromatic Rings	1600, 1500(w) stretch
C-O	Alcohols, Ethers, Carboxylic acids, Esters	1260-1000(s) stretch
C=O	Aldehydes, Ketones, Carboxylic acids, Esters	1760-1670(s) stretch
O-H	Monomeric -- Alcohols, Phenols	3640-3160(s,br) stretch
	Hydrogen-bonded -- Alcohols, Phenols	3600-3200(b) stretch
	Carboxylic acids	3000-2500(b) stretch
N-H	Amines	3500-3300(m) stretch
		1650-1580 (m) bend
C-N	Amines	1340-1020(m) stretch
C≡N	Nitriles	2260-2220(v) stretch
NO_2	Nitro Compounds	1660-1500(s) asymmetrical stretch
		1390-1260(s) symmetrical stretch

v - variable, m - medium, s - strong, br - broad, w - weak

Table C.2 Characteristic Ir Absorption Frequencies Of Organic Functional Groups

Functional Group	Type of Vibration	Characteristic Absorptions (cm^{-1})	Intensity
Alcohol			
O-H	(stretch, H-bonded)	3200-3600	strong, broad
O-H	(stretch, free)	3500-3700	strong, sharp
C-O	(stretch)	1050-1150	strong
Alkane			
C-H	stretch	2850-3000	strong
-C-H	bending	1350-1480	variable
Alkene			
=C-H	stretch	3010-3100	medium
=C-H	bending	675-1000	strong
C=C	stretch	1620-1680	variable
Alkyl Halide			
C-F	stretch	1000-1400	strong
C-Cl	stretch	600-800	strong
C-Br	stretch	500-600	strong
C-I	stretch	500	strong
Alkyne			
C-H	stretch	3300	strong,sharp
–C≡C–	stretch	2100-2260	variable, not present in symmetrical alkynes
Amine			
N-H	stretch	3300-3500	medium (primary amines have two bands; secondary have one band, often very weak)
C-N	stretch	1080-1360	medium-weak
N-H	bending	1600	medium
Aromatic			
C-H	stretch	3000-3100	medium
C=C	stretch	1400-1600	medium-weak, multiple bands
Analysis of C-H out-of-plane bending can often distinguish substitution patterns			
Carbonyl	Detailed Information on Carbonyl IR		
C=O	stretch	1670-1820	strong
(conjugation moves absorptions to lower wave numbers)			
Ether			
C-O	stretch	1000-1300 (1070-1150)	strong
Nitrile			

CN	stretch	2210-2260	medium
Nitro			
N-O	stretch	1515-1560 & 1345-1385	strong, two bands

Table C.3 Ir Absorption Frequencies Of Functional Groups Containing A Carbonyl (C=O)

Functional Group	Type of Vibration	Characteristic Absorptions (cm-1)	Intensity
Carbonyl			
C=O	stretch	1670-1820	strong
(conjugation moves absorptions to lower wave numbers)			
Acid			
C=O	stretch	1700-1725	strong
O-H	stretch	2500-3300	strong, very broad
C-O	stretch	1210-1320	strong
Aldehyde			
C=O	stretch	1740-1720	strong
=C-H	stretch	2820-2850 & 2720-2750	medium, two peaks
Amide			
C=O	stretch	1640-1690	strong
N-H	stretch	3100-3500	unsubstituted have two bands
N-H	bending	1550-1640	
Anhydride			
C=O	stretch	1800-1830 & 1740-1775	two bands
Ester			
C=O	stretch	1735-1750	strong
C-O	stretch	1000-1300	two bands or more
Ketone			
acyclic	stretch	1705-1725	strong
cyclic	stretch	3-membered - 1850 4-membered - 1780 5-membered - 1745 6-membered - 1715 7-membered - 1705	strong
α,β-unsaturated	stretch	1665-1685	strong
aryl ketone	stretch	1680-1700	strong

APPENDIX D EXPERIMENTAL INSTRUMENTS

Figure D.1 Thermomixer

Figure D.2 Vacuum Pump