EFFECT OF CO-SOLVENT ON THE SOLUBILITY OF A SPARINGLY SOLUBLE CRYSTAL

HUDZAIFAH YOUSOF BIN HUMAYUN

CHEMICAL ENGINEERING
UNIVERSITI TEKNOLOGI PETRONAS
SEPTEMBER 2015

Effect of Co-solvent on the Solubility of a Sparingly Soluble Crystal

by

Hudzaifah Yousof Bin Humayun

15575

Dissertation submitted in partial fulfillment of
the requirement for the
Bachelor of Engineering (Hons)
(Chemical Engineering)

SEPTEMBER 2015

Universiti Teknologi PETRONAS
32610, Bandar Seri Iskandar
Perak Darul Ridzuan

CERTIFICATION OF APPROVAL

Effect Of Co-solvent On The Solubility Of A Sparingly Soluble Crystal

by

Hudzaifah Yousof Bin Humayun
15575

A project dissertation submitted to the

Chemical Engineering Programme

Universiti Teknologi PETRONAS

in partial fulfillment of the requirement for the

BACHELOR OF ENGINEERING (Hons)

(CHEMICAL ENGINEERING)

Approved by,

_____

(Dr. Md Abdus Salam)

UNIVERSITI TEKNOLOGI PETRONAS

BANDAR SERI ISKANDAR, PERAK

September 2015

CERTIFICATION OF ORIGINALITY

This is to certify that I am responsible for the work submitted in this project, that the original work is my own except as specified in the references and acknowledgements, and that the original work contained herein have not been undertaken or done by unspecified sources or persons.

_____

HUDZAIFAH YOUSOF BIN HUMAYUN

ABSTRACT

Solubility data plays an important role in the industry. Measuring solubility of crystal in various solvent is a key factor in compound characterizing during the whole discovery and development process where it allows engineers to design and optimize crystallization process. Benzoic acid is a simple aromatic carboxylic acid, a colorless crystalline solid that is widely used in the pharmaceutical area, plasticizers, food preservative and niche in the lab use. This chemical shows low aqueous solubility and dissolution rate and this has become the main concern in the industry that require dissolution of this chemical. This research describe an approach to improve the solubility of benzoic acid by using co-solvent. The experiment was conducted in different percentage of co-solvent and at different temperature. Co-solvent solution is prepared by using glycerol in water by volume ratio. Benzoic acid is placed in the solvent and was let to stir for three hours. Three milliliter of solution was taken out and placed in a vile to let it dry at room temperature. Result shows the relation between solubility in different co-solvent and temperature whereby as the percentage of glycerol added increase, the solubility of benzoic acid increase. Same trend was depicted in term of solubility relation with temperature, as the temperature increase, amount of benzoic acid dissolve also increase. The analyses has shown that co-solvent is an effective method in increasing the dissolution rate of a sparingly soluble chemical and temperature plays important role in increasing the solubility. The main reason of conducting this study is because of the lack of literature data on the reaction between benzoic acid and glycerol.

ACKNOWLEDGEMENT

"Cultivate the habit of being grateful for every good thing that comes to you, and to give thanks continuously. And because all things have contributed to your advancement, you should include all things in your gratitude." —Ralph Waldo Emerson. First and foremost, I would like to thank the almighty God for His blessings in giving me the opportunity to complete my Final Year Project (FYP) course.

I take this privilege and pleasure to acknowledge the contributions of many individuals who have been inspirational and supportive throughout my work undertaken and endowed with the most precious knowledge to see successful completion of the FYP with the topic "Effect of Co-solvent on the Solubility of a Sparingly Soluble Crystal". I would like to express our utmost gratitude to my supervisors, Dr. Taslima Khanam and Dr. Md Abdus Salam for Final Year Project I and II. I would like to thank them for their continuous guidance and motivation throughout the course of this research project. They had been very supportive and willing to share their knowledge, in order to ensure that I could learn and understand every single thing in this project.

I would also like to extend my gratitude to the FYP II coordinator, Dr. Nurul Ekmi Rabat for her effort in assisting us in all the possible way. Furthermore, I express my deepest gratitude to Universiti Teknologi PETRONAS (UTP) for the platform of my course. I am also grateful to Chemical Engineering Department of UTP for the support I received when undertaking the course work.

Finally, my deepest appreciation to my family and friends who has never failed in helping me through the thick and thin of time. It is the unfailing support from them that has enabled me to complete this FYP course. Not to forget those who are directly or indirectly involved in the completion of this project.

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

C : Celsius

g : Gram

K : Kelvin

kg : Kilogram

ml : Milliliter

U.S : United State

LIST OF FIGURES

LIST OF TABLES

CHAPTER 1
INTRODUCTION

This chapter discusses about the background of study for the final year project. Besides that, this chapter also defines the problem statement, the objective and the scope of the research work.

1.1 Background of Study

Crystallization is a natural or manufactured phenomena in development of solid crystals deposit from a solution, melts or precipitating directly from gas. In engineering and chemistry, crystallization is known as a technique which is used in purification of solid compounds. . Crystallization plays important role in various field of research such as pharmaceutical, physic, chemistry, food science, biological science and etc. With this knowledge, the production of a crystal can be design in the industry and the solubility of a solid which play major role in pharmaceutical area can be determined. The crystallization process consist of two events which is nucleation and crystal growth, whereby in nucleation, the solute molecules that is disperse in the solvent starts to gather into a small cluster. Crystal growth in the other hand is the growth of nuclei that successfully form stable cluster.

Solubility, in quantitative, is term as the concentration of solute in a saturated solution at certain temperature. It is also defined as the spontaneous interaction of two or more substance to form a homogeneous molecular dispersion. Although major of the solute follows the solubility principal, it was found that some solute decrease in solubility in increasing of temperature. The crystal solubility may be expressed as molality, percentage, parts, molarity, volume fraction, and mole fraction.

In determination of a compound solubility, there are a few factors that affect the solubility, such as temperature, pressure and the nature of the solute and solvent itself (Avdeef, 2007). The solubility depends on the polarity of the solute and solvent. In general, a polar solute will dissolve in a polar solvent and the solubility of a polar solute is relatively low or insoluble in a non-polar solvent. As mention previously, generally solubility will increase with the increase in temperature, but it may not be necessary in all cases. However, the solubility will follow these two behaviors: 1. In endothermic process, as the temperature increase, so does the solubility and vice versa. 2. In exothermic process, solubility decrease with the increase in temperature (Molpeceres, Bustamante, & Aberturas, 1996). In the case of pressure, the effect on solids and liquids are generally negligible and only significant in affecting the solubility of gaseous in liquid. Generally, as the pressure increase, the solubility of gases in liquid will also increase. This principal follows the combination of Henry's Law and Le Châtelier principal. Consider the Henry's Law formula:

$$p = k_h \mathrm{c} \tag{1}$$

Where:

i. $\boldsymbol{p}$ is the partial pressure of the gas above the liquid
ii. $\boldsymbol{k_h}$ is the Henry's Law constant, and
iii. $\boldsymbol{c}$ is the concentration of the gas in liquid.

It shows that at constant temperature, as the partial pressure decrease, the concentration of the gas in the liquid will also decrease, causing the solubility also to be decrease and vice versa (Zhang, & Zeng, 2014). In the effect of nature of the solute and solvent toward solubility, the characteristic of the solute plays an important rules in dissolution. As example, a gram of lead (II) chloride can only dissolve in minimum 100 grams of water at 303 kelvin while 100 grams of water can easily dissolve 200 grams of zinc chloride. This major difference in solubility is a result of their nature difference. Particle size also influence in solubility. Different shape of crystal, different surface area of the solute will have contrast effect on its solubility in the solvent. The solubility of crystal from the effect of particle size can be describe as

(2)

$$log \frac{S}{S_{\circ}} = \frac{2\gamma V}{2.303\ R\ T\ r}$$

Where:

i. $S_{\circ}$ is the solubility of infinitely large particles
ii. S is the solubility of fine particles
iii. V is molar volume
iv. r is the radius of the fine particle
v. γ is the surface tension of the solid

In term of molecular size, a substance solubility decrease when molecular weight and molecular size of a molecule increase. This tend to happen because larger molecule have difficulty in surrounding them with the solvent molecule in order to solvate the substance but when regarding the effect of molecular size in organic compound, the solubility of a compound will increase as the amount of carbon branching increase. Higher number of carbon, or carbon branching will reduce the size or volume of a molecule, thus making it easy to dissolve the molecule with the solvent.

Solubility of poorly soluble drugs or crystals is a frequently encountered challenge in screening studies of new chemical entities as well as in formulation design and development. In definition, a very soluble salt would use less volume of solvent to dissolve 1 gram of solute, while sparingly soluble salt would use more solvent in order to dissolve 1 gram of solute. The pharmacopoeia list the solubility in terms of amount of solvent in milliliter required to dissolve 1g of solute.

Table 1.1 Amount of Solvent Required to Dissolve 1g of Solute

Descriptive terms	Amounts of solvents to dissolve 1 part of solute
Very soluble	Less than 1
Freely soluble	From 1-10
Soluble	From 10-30
Sparingly soluble	From 30-100
Slightly soluble	From 100-1000
Very slightly soluble	From 1000-10,000
Insoluble or practically insoluble	More than 10,000

A number of methodologies can be adapted to improve solubility of poor water soluble crystals. A few method was establish in the study of increasing solubility of a sparingly soluble drugs, including the use of co-solvents, surfactants, organics and hydrophilic macromolecules, complexation, emulsion, liposomes, particle size reduction, solid dispersion, micronization, chemical modification, pH adjustment and others (Khadka, 2014). In many ways, the enhancement of solubility is becoming more important thus the study of the solubility is relevant.

1.2 Problem Statement

Dissolution of solute in a solvent are important in several industrial field such as chemical engineering, mineral processing, petroleum engineering, pharmaceutical and etc. From here, solubility data is an important document to have in order to produce high quality crystal. The most common problem encountered by every field is the difficulty to dissolve sparingly soluble solid in a solvent. Due to the highly demand of the pharmaceutical, food and other industry for solubility data, many research efforts have been applied in overcoming the low solubility of benzoic acid . As a matter of fact, more than one-third of the drugs listed in the U.S. Pharmacopoeia are poorly soluble (Khadka, 2014).

In the current trend, many research tends to focus on the technique for solubility enhancement such as physical modification of the crystal and chemical modification of a solution. Research done in effect of co-solvent toward solubility of a solute is generally low. For instance, literature data for solubility of benzoic acid in aqueous glycerol solution are only reported at 25^0C only. The lack of data in the effect of different solvent on the dissolution rate of a solute has leave a gap for future study (Sandilya, & Kannan, 2010). Although there are many chemicals can be used as a solvent and co-solvent, the toxicology of this chemical came into hand whereby some chemicals are corrosive and irritant and could became harmful if it is to be used in the food preservation and pharmaceutical industry. Therefore it is important to understand

the need of this study, so it would be beneficial in the pharmaceutical and food preservative industry, plus filling in the gap of research that has not been done before.

1.3 Objective

The main objective of this research is to study the effect of co-solvent on the solubility if sparingly soluble salt. To achieve the main objective, the sub-objective of this project are as follows:

i. To investigate the effect of adding co-solvent on the solubility of sparingly soluble salt.
ii. To investigate the effect of temperature on the solubility of sparingly soluble salt.
iii. To tabulate the solubility data of the sparingly soluble salt of benzoic acid.

1.4 Scope of Study

This final year project focuses on the study regarding solubility activity of benzoic acid. In this research work, glycerol will be used as the co-solvent, creating a water-glycerol solvent and will be tested at different percentage of glycerol amount in water, in a specific range of temperature. The dissolution of benzoic acid will be experimented by using continuous stirring method and the product of the experiment will be tested using gravimetric method to achieve solubility data. Since the melting point of benzoic acid is 122.41°C, the temperature will only range from room temperature up to point below its melting point.

1.5 Relevancy of Project

Benzoic acid is an important precursor in synthesizing many organic substances. In industrial scale, it is widely used as a feedstock in making large number of chemical, as example, benzoyl chloride, which is used in insect repellent and artificial flavoring. This weak acid also used in making food preservative. Benzoic

acid restrain the growth of bacteria, yeast and some mold. Benzoic acid also plays an important role in fungal disease treatment. The similarity of all this important role is that it needs pure content of benzoic acid. Since benzoic acid has a characteristic of hard to dissolve, method to expedite the dissolution rate or increase the amount of salt dissolve is important in order to save time and money. Therefore, the solubility data from this project is significant in the development of benzoic acid in every industry. The information will have positive impact in industry that depends on purity yield of benzoic acid.

1.6 Feasibility of Project

The final year project requires top to bottom understanding in Chemical Engineering and it will test the author understanding in a few engineering study field such as organic chemistry and thermodynamic. In term of research, this topic is widely covered under biochemistry which have much relation in pharmaceutical industry. Even though this topic is not thoroughly expose in the university, from the extensive researches that has been done by other researcher, it generally had help the author to understand better in solubility topic.

In term of timeframe, the time allocated for this research is reasonable. The first four month is used by the author to do an extensive study with regard of the subject. During this four month, experimental procedure is set up, the chemical and apparatus needed is determined. Another one month is spent on purchasing and collecting the chemical and equipment for the experiment. Another three month is spent on experimental work and data compilation. In overall, with the guidance of supervisor and the coordinator, the project is within capability of a final year student to be executed.

CHAPTER 2
LITERATURE REVIEW

This chapter focused on research that has been done by other researcher in regard with solubility, factors affecting solubility, and effect of co-solvent on solubility. Besides that, this chapter also summarize the basic about crystallization and solubility.

2.1 Crystallization and Solubility

Solubility is a fundamental in all chemical process. In general, the solubility can happen in any state of matter, whether it is in solid and liquid, liquid and liquid and gas and liquid (Mullin, 2001). In other word, solubility is the property of solute in solid, liquid or gaseous chemical to dissolve in solvent to form a solution. According to the International Union of Pure and Applied Chemistry (IUPAC), solubility is the analytical composition of a saturated solution expressed as a proportion of a designated solute in a designated solvent. Solubility may be stated in units of concentration, molality, mole fraction, mole ratio, and other units (IUPAC 1997). The solubility of a substance is measured as the saturation concentration in a specific solvent. The range of solubility is wide, starting from very soluble or fully miscible to poorly soluble or sparingly soluble (Clugston, & Fleming, 2000). A solution is considered saturated as the equilibrium of the solubility is achieved. In specific condition, the equilibrium of a solubility can be exceed, in result will become a supersaturated solution (Barrett, & Glennon, 2002). Solubility is important in the crystallization process whereby production of crystal with high purity is correlated with solubility (Barret, et al., 2002).

2.2 Factors Affecting Solubility

The importance of what solute dissolve in which solvent, the effect of temperature, pressure and effect of other species has been discovered since at the early stage (Delgado, & Vázquez, 2010). Some study has shown the correlation between the characteristic of a particle toward the solubility of the compound. Fine particle is mention to dissolve at faster rate compared to coarse particle due to the high surface are to volume ration. And as the point of saturation approached, the rate of dissolution will decrease. A clear transition from a distinctive octahedral structure to a rounded shape during dissolution was recorded(Barret, et al., 2002). This show the characteristic that happen towards the compound during the crystallization and dissolution process. The solubility also sometime depends on the type of solvent used. Different solvent will give different reaction due to its polarity, viscosity and other physical state. The compound solubility is determine by intermolecular force between solute and solvent. In this, altering factors such as pressure and temperature will alter the solubility of a substance. In increasing melting point of a solute will result in the decreasing soluble of the solute in the solvent (Domanska, Pobudkowska, Pelczarska, & Zukowski, 2011). As experimented in one of the thesis, solubility of genistin, a drug widely used in pharmaceutical field, increase with increase of temperature (Fan, 2015). Nowadays, many technique has been develop and under study such as micronization and nanosuspension of a particle, modification of crystal habit like polymorphs and amorphous form, cocrystallization, solid dispersion, use of buffer, supercritical fluid process, hydrotrophy and etc. to further expand knowledge in solubility which at last will give great impact on every field (Khadka, 2014).

2.2.1 Effect of Co-solvent on Solubility

As concern rise about the oral bioavailability due to low solubility, many studies are developed into enhancing the low solubility drugs as well as increasing dissolution properties. Therefore, several techniques are used including cosolvency by mean the process of adding water miscible solvents to an aqueous system is done. Many types of co-solvent can be used such as polyethylene glycol (PEG), glycerin, and ethanol. Sparingly soluble salt are known to be less soluble in water, but in many

cases, their solubility increase when react with water and its co-solvent (Long, Li, & Wan, 2010).

In recent research, solubility of drugs was experimented, and it shows that although it is low in solubility in water and alcohol, the drugs solubility recorded in alcohol is slightly higher than water. This was due to the characteristic of the solute and the solvent whereby organic compound are better soluble in alcohol with shorter chain, and the complicated structure of a compound will also give impact toward the solubility (Domanska, et al., 2011). Another study conducted shows the increment of solubility of benzoic acid with increase of co-solvent, ethylene glycol in water, which is closely related with the solubility-polarity effect (Yurquina, Manzur, Brito, Manzo, & Molina, 2003). The solubility of the Benzoic acid in the solvent can be relate to the possibility to form hydrogen bond between the solute and solvent molecules (Long, et al. 2010). The relation between Benzoic acid and polarity of a solvent plays an important role, whereby a typical non-polar solvent with its stable molecular structure determines that it has no chance to perform intermolecular hydrogen bonds with Benzoic acid molecules (Yurquina, et al., 2003).

CHAPTER 3
METHODOLOGY

This chapter discuss on the planning for the project activities and research methodology. Other than that, this chapter will also discuss on chemicals required, apparatus and material needed, technique used in dissolution of the sparingly soluble salt and calculation used in determine the solubility. Furthermore, the key milestone and the Gantt chart is also included in this chapter.

3.1 Research Methodology and Project Activities

The project activities for this research are based on extensive literature review and experimental studies. During the literature review, preliminary research on existing studies related to the topic was done in order to understand the principle of solubility and crystallization. From the extensive literature review, experimental work can be design and conducted to analyze the solubility of benzoic acid. Figure 3.1 below shows the work flow of this study.

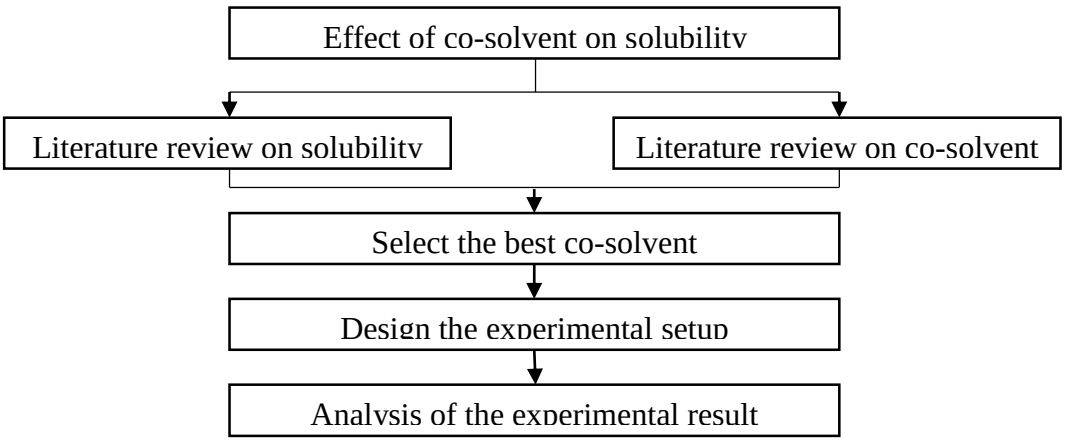

Figure 3.1 Project Flow Chart

3.2 Raw Materials and Chemicals

Several chemicals and raw materials are required in this research work to ensure the project run smoothly. The required chemicals are as listed as follows:

i. Distilled Water
ii. Benzoic Acid ($C_7H_6O_2$)
iii. Glycerol ($C_3H_8O_3$)

3.3 Apparatus and Equipment

Instrument used in this project are mostly general equipment and can be found widely in the university. Apparatus and equipment used are as follows:

a) Apparatus
   i. 1000 ml beaker
   ii. 1000 ml measuring cylinder
   iii. Syringe
   iv. Vile
   v. Thermometer
b) Equipment
   i. Magnetic stirrer and hot plate
   ii. Weighing balance
   iii. Oven

3.4 Experimental Procedure

Experimental procedure of this experiment consist of two part, preparation of solvent and dissolution of benzoic acid. Solvent that has been prepared will be used in the dissolution of benzoic acid to study its effect on co-solvent and also temperature.

3.4.1 Preparation of Solvent

Example of 10% co-solvent is used to picture the procedure. 500 ml of solvent is prepared for the experiment.

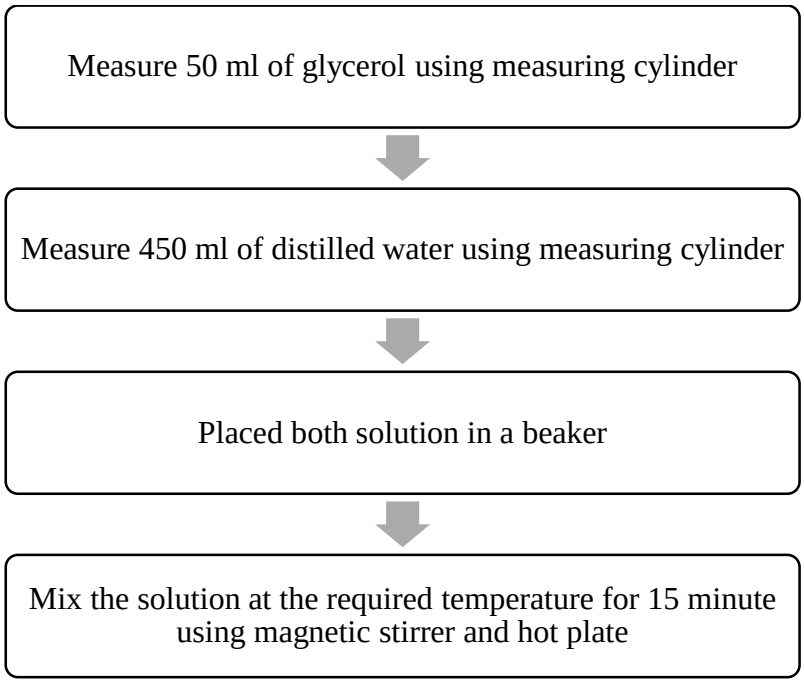

Figure 3.2 Preparation of Solvent Solution

Table 3.1 Glycerol and Water Ratio

Glycerol: Water Ratio	Glycerol, ml	Distilled Water, ml
0:100	0	500
10:90	50	450
20:80	100	400
30:70	150	350
40:60	200	300
50:50	250	250
60:40	300	200
70:30	350	150
80:20	400	100
90:10	450	50

3.4.2 Experimental Procedure

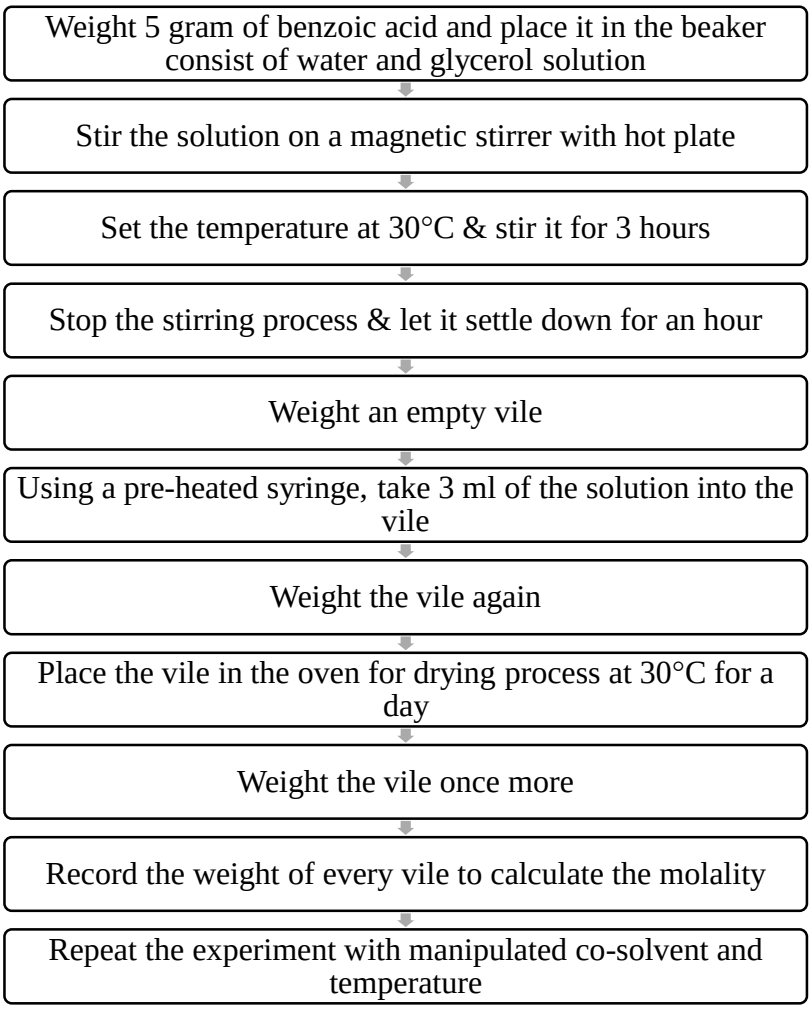

Figure 3.3 Dissolution of Benzoic Acid Procedure

3.4.3 Determination of Solubility

Gravimetric method is applied in the research study to determine the solubility of benzoic acid at different amount of glycerol and at a specific range of temperature. Gravimetric method is generally a method to determine quantitatively an analyte base on solid mass. In this research, amount of benzoic acid dissolve is determined based on benzoic acid crystal yield during the drying process. In the experiment, an empty vile is weighted first, followed by the weight of vile with 3 ml of solution and vile with the dried product. By subtracting the weight of empty vile, the mass of the solution and dried is known. From here, amount of solution vaporized can also be determined. Solubility or concentration of benzoic acid in glycerol-water solvent is denoted as

molality, which is the amount of solute dissolve in mass of solvent. It could be express in equation as:

$$Molality = \frac{mol\ of\ solute}{kg\ of\ solvent} \quad (3)$$

The unit for molality is $mol.kg^{-1}$. Mole of benzoic acid can be achieved by multiplying mass of dried product with molecular weight of benzoic acid, which is 122.12 $g.mol^{-1}$. Mass of solvent is determine from the amount of evaporated solution during drying process. As a result, solubility data is achieved and can be depicted as solubility curve.

3.5 Gantt Chart and Mile Stones

Table 3.2 FYP I Gantt Chart and Milestones

No	Detail Work	1	2	3	4	5	6	7	8	9	10	11	12	13	14
1	Selection of Project Topic	■	■												
2	Preliminary Research Work		■	■	■	■									
3	Submission of Extended Proposal							■							
4	Proposal Defense									■					
5	Project Work Continues								■	■	■	■	■		
6	Submission of Interim Draft Report												■		
7	Submission of Interim Report													■	

■ Process ■ Key Milestone

Table 3.3 FYP II Gantt Chart and Milestones

No	Detail Work	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
1	Project Work Continues															
2	Submission of Progress Report															
3	Project Work Continues															
4	Pre-SEDEX															
5	Submission of Draft Report															
6	Submission of Dissertation															
7	Submission of Technical Paper															
8	Viva Oral Presentation															
9	Submission of Project Dissertation															


Process


Key Milestone

CHAPTER 4
RESULT AND DISCUSSION

This chapter covers the result obtained from the research project. From the result, thorough analysis and discussion is done to give a clearer impact what is the effect of co-solvent on solubility is all about.

4.1 Effect of Co-solvent on Solubility of Benzoic Acid

Solubility of Benzoic acid is well known to be sparingly soluble in water. From other study, the effect of adding another solvent into the primary solvent will enhance the solvent power thus increase in solubility.

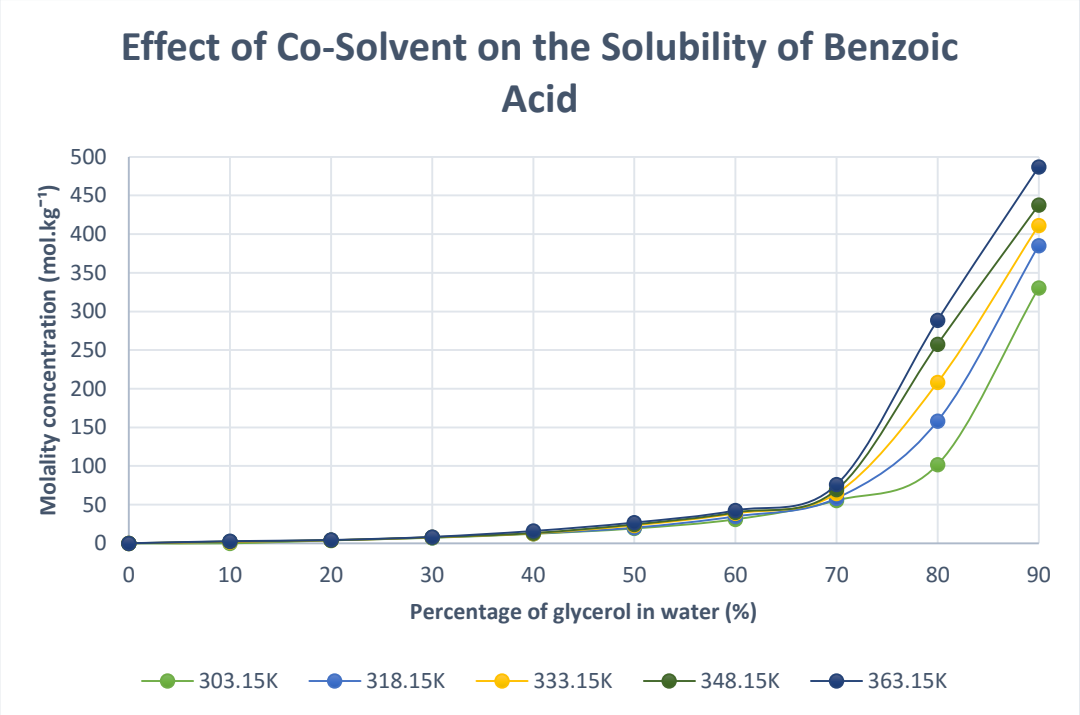

Figure 4.1 Effect of Co-Solvent on the Solubility of Benzoic Acid

Figure 4.1 shows the molality of benzoic acid dissolve in the water-glycerol solvent. The graph plotted between the molality versus the percentage of glycerol in water shows an upward trend, increase in molality as the percentage of glycerol added increase. In every set of temperature that has been test, it shows a steady increment from 0% of glycerol up until 70% of glycerol, whereby from 70% up until 90%, it shows a significant increase in molality. Thus, as the percentage of glycerol added increase, the solubility of benzoic acid also increase.

From the experiment, it can be conclude that the solubility of benzoic acid increase as the amount of glycerol added increases. To understand the phenomena, organic chemistry principal is approached. Benzoic acid is known to be partially soluble in water. This is due to the molecule structure of benzoic acid itself.

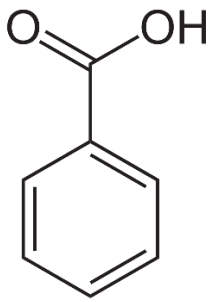

Figure 4.2 Molecular Structure of Benzoic Acid

As displayed in figure 4.2, benzoic acid is an aromatic carboxylic acid. It contain an aromatic ring or a benzene ring and one hydroxyl group attached to its carbon. The benzene ring has a hydrophobic characteristic, which tend to be non-polar and not soluble in water. The reason why benzoic acid is considered to be sparingly soluble in the first place is because of its ability to form hydrogen bonding with water. Water also consist a hydroxyl group and as the principle like dissolve like imply, meaning there is hydrogen bonding between benzoic acid and water. But due to benzene ring, it makes the benzoic acid less soluble.

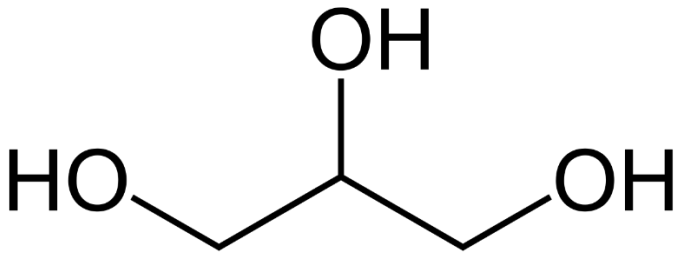

Figure 4.3 Molecular Structure of Glycerol

Glycerol is the final co-solvent used for the experiment. There are a few other chemicals that could replace glycerol as a co-solvent such as ethylene-glycol and diethylene-glycol which have similar characteristic and price is relatively cheap compare to glycerol. But in term of toxicity, glycerol is the safest chemical of all, whereby the other two example chemical are highly toxic. In term of solubility, glycerol is easily dissolve in water because of it consist three hydroxyl group attached in each carbon, making more hydrogen bonding. From the mixing of both solvent, amount of hydroxyl group increase, therefore, higher amount of benzoic acid could undergo hydrogen bonding, thus as the amount of glycerol increase, the solubility of benzoic acid also increases.

4.2 Effect of Temperature on Solubility of Benzoic Acid

One of the major factor that affect solubility is temperature. In general, the solution process will absorb energy and the solubility will increase as the temperature increase, but the solubility will decrease in increase of temperature if the solution process release energy. Some of solid solute are also known to be less soluble in higher temperature.

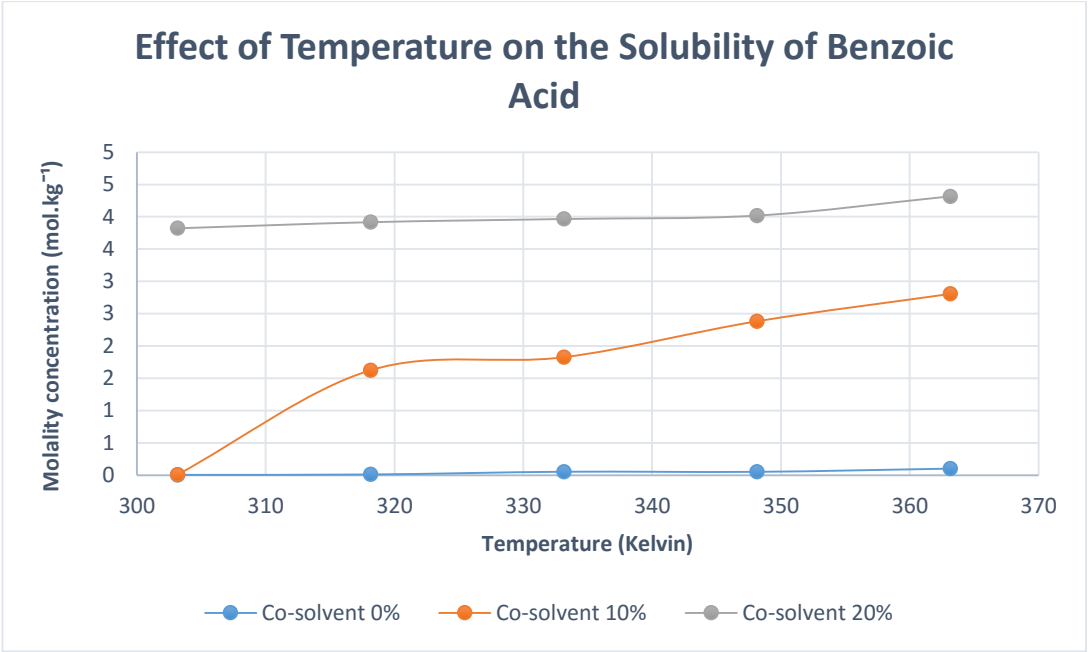

Figure 4.4 Effect of Temperature on the Solubility of Benzoic Acid (For 0% to 20% Glycerol)

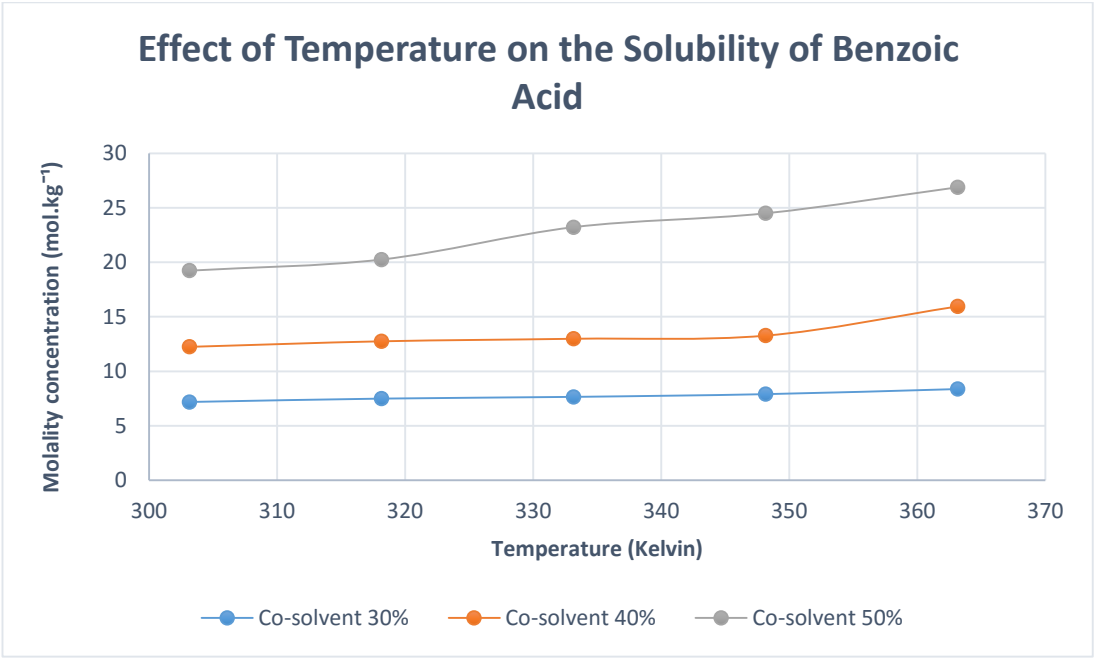

Figure 4.5 Effect of Temperature on the Solubility of Benzoic Acid (For 30% to 50% Glycerol)

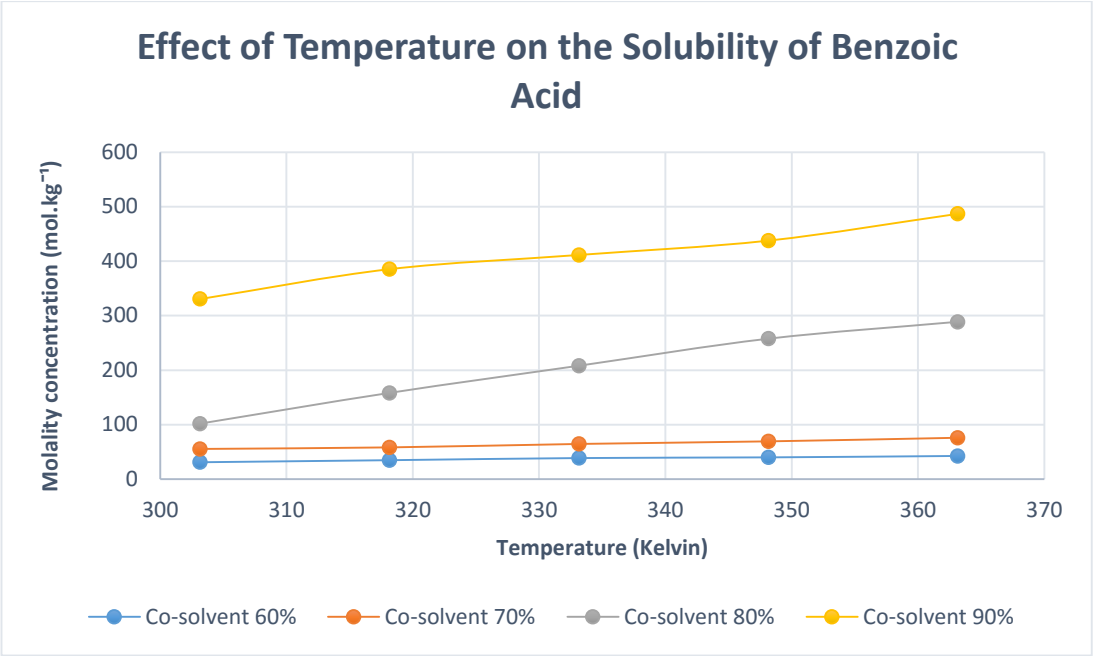

Figure 4.6 Effect of Temperature on the Solubility of Benzoic Acid (For 60% to 90% Glycerol)

Figure 4.4, figure 4.5 and figure 4.6 shows the effect of temperature on the solubility of benzoic acid. All of the figure are the same, only difference in scale due to significant difference in solubility. From the graph, it can be seen that there is an increment in solubility for every sample tested, even though the increment is not that significant. Solubility for 80% and 90% co-solvent shows very significant increment from 303 Kelvin up to 363 Kelvin, increase around 200 $mol.kg^{-1}$. Thus, the experiment indicates that the solubility of benzoic acid increase as the temperature increase.

From the result, the solubility of benzoic acid increase with the increase in temperature. The effect of temperature can be explain from the thermodynamic principle, which in general have to do with the kinetic energy of the solvent and Gibbs free energy principle. Gibbs free energy is the greatest amount of non-expansion work which could be extracted from system that is thermodynamically close. In general, Gibbs free energy could be written in form of equation:

(4)

$$\Delta G = \Delta H - T\Delta S$$

Where:

i) ΔG is the change in Gibbs free energy
ii) ΔH is the change in enthalpy
iii) T is absolute temperature
iv) ΔS is the change in entropy

Gibbs free energy is measured quantitatively, whereby Gibbs free energy will determine reaction is favorable or not. From the equation, when the calculation indicates that the change in Gibbs free energy in negative, it implies that reaction will occur and will discharge energy. Here, the energy discharge is the same as the highest amount of work that can be done from the result of chemical reaction. On the other side, if the condition demonstrate a positive change in Gibbs free energy, the energy in work form will have to be added to the reaction system in order to make the reaction occur. The change in Gibbs free energy could be demonstrate from the equation. In term of enthalpy, the dissolution process of benzoic acid is an exothermic reaction, meaning the change of enthalpy to be negative. The change of entropy is also considered to be negative since the process change the state of benzoic acid from solid to liquid. And as the temperature increase, the overall change in Gibbs free energy would be more negative, thus causing spontaneity of reaction to increase, as a result, solubility increases with temperature increase.

CHAPTER 5
CONCLUSION AND RECOMMENDATION

This chapter conclude the overall progress of this research study. In addition, few recommendation is mention to ensure this project could be further study in the future and finding for more promising result.

5.1 Conclusion

The objective of this research study were to study the effect of co-solvent of the solubility of a sparingly soluble salt, and examine the effect of temperature on solubility at the same time. The new equilibrium data for benzoic acid at different percentage of glycerol over the temperature range of (303 to 363) Kelvin was determined by using gravimetric method. The solubility of benzoic acid shows significant increase as the amount of glycerol added increase. The solubility of benzoic acid also increase as the temperature increase. Both of these result were due to the molecule properties of benzoic acid and the glycerol-water solvent, and due to Gibbs free energy respectively.

5.2 Recommendation

As the demand in finding better solution to dissolve sparingly soluble salt increases, various future work could be implemented. As mention previously, there are many factors affecting solubility, and only two factors were considered in this research, which is temperature and the nature of solute and solvent. This factors could be widen in order to achieve better understanding about solubility of benzoic acid. Plus there are various method to increase solubility of sparingly soluble crystal, and many

work are not been done yet for benzoic acid. Few recommendation could be suggested for future works:

i) Using more dynamic method rather than gravimetric method. Although gravimetric method is approved as one of the best ways in finding concentration of dissolved particle, analytical error is prone to happen, as example due to no fixed reading from weighing scale.
ii) Using imaging system such as Focused Beam Reflectance system and Particle Vision and Measurement images to observe the change in term of benzoic acid structure during the dissolution process and to record the rate of dissolution.
iii) Explore the possibility of using other method in dissolving the sparingly soluble benzoic acid.
iv) Explore the effect of other parameter such as particle size, pressure, molecular size, polarity, polymorphs and others.

REFERENCE

Avdeef, A. (2007). Solubility of Sparingly-soluble Ionizable Drugs, *Adv Drug Deliv Rev 59*(7) 568-590.

Bandry, M. B. (2006). Enhancement of the dissolution and permeation rates of meloxicam by formation of its freeze-dried solid dispersions in polyvinylpyrrolidone K-30, *Drug Dev. Ind. Pharm 32*(2) 141-150.

Barrett, P., & Glennon, B. (2002). Characterizing The Metastable Zone Width And Solubility Curve Using Lasentec FBRM And PVM, *Trans IChemE 80*(Part A) 799-805.

Betageri, G .V. (1995). Enhancement of dissolution of Glyburide by solid dispersion and lyophilization techniques, *Int. J. Pharm 126* 155-160.

Clugston, M., & Fleming, R. (2000). Advanced Chemistry, First Edition. Oxford: Oxford Publishing: 108.

Delgado, J. M. P. Q., & Vázquez, M. S. (2010). Experimental Values of Solubility of Organic Compounds in Water for a Wide Range of Temperature Values − A New Experimental Technique, *Defect and Diffusion Forum 301* 1244-1249.

Domanska, U., Pobudkowska, A., Pelczarska, A., & Zukowski, L. (2011). Modelling, solubility and pK(a) of five sparingly soluble drugs, *Int J Pharm 403*(1-2) 115-122.

Fan, J. P. (2015). Measurement and correlation of the solubility of genistin in eleven organic solvents from T=(283.2 to 323.2)K, *The Journal of Chemical Thermodynamics 89* 142-147.

Gunawan, R., Ma, D. L. & Braatz, R. D. (2002). Identification of Kinetic Parameters in Multidimensional Crystallization Processes, *International Journal of Medern Physic B: Condensed Matter Physics; Static Physics; Applied Physics 16* 367

Khadka, P. (2014). Pharmaceutical particle technologies: An approach to improve drug solubility, dissolution and bioavailability, *Asian Journal of Pharmaceutical Sciences 9*(6) 304-316.

Kougoulos, E., Jones, A. G., Jennings, K. H., & Wood-Kaczmar, M. W. (2005). Use of Focused Beam Reflectance Measurement (FBRM) and Process Video Imaging (PVI) in a Modified Mixed Suspension Mixed Product Removal (MSMPR) Cooling Crystallizer, *Cryst. Growth 273* 529–534.

Long, B., Li, J., & Wan, L. (2010). Solubility of benzoic acid in acetone, 2-propanol, acetic acid and cyclohexane: Experimental measurement and thermodynamic modeling, *Fluid Phase Equilibria 297*(1) 113-120.

Molpeceres, J., Bustamante, P., & Aberturas, M. R. (1996). Exothermic-endothermic heat of solution shift of cyclosporin. A related to poloxamer 188 behavior in aqueous solutions, *Int J Pharm 130* 75-81.

Mullin, J. W. (2001). Crystallization, *Elsevier Butterworth-Heinemann Fourth Edition.*

Nagy, Z. K. (2008). Determination of the Kinetic Parameters for Crystallization of Paracetamol from Water Using Metastable Zone Width Experiment, *Industrial & Engineering Chemistry Research 47* 1245-1252

Nagy, Z. K., Chew, J. W., Fujiwara, M., & Braatz, R. D., (2008). Comparative performance of concentration and temperature, *J. Process Control 18* 399–407.

Sandilya, D. K., & Kannan, A. (2010). Effect of ultrasound on the solubility limit of a sparingly soluble solid, *Ultrason Sonochem 17*(2) 427-434.

Seedhar, N. (2009). Various solvent systems for solubility enhancement of enrofloxacin, *Indian J Pharm 71*(1) 82-87.

Yalkowsky, S., & Roseman, T. J. (1981). Solubilization of drugs by cosolvents, in technique of solubilization of drugs, *Marcel Dekker 12* 91-134

Yurquina, A., Manzur, M. E., Brito, P., Manzo, R., & Molina, M. A. A. (2003). Solubility and dielectric properties of benzoic acid in a binary solvent: Water-ethylene glycol, *Journal of Molecular Liquids 108*(1-3) 119-133.

Zhang, X., & Zeng, Y. (2014). Calculations of Henry's law constants for organic species using relative Gibbs free energy change, *Fluid Phase Equilibria 376* 234-238.

APPENDICES

Appendix A

Temperature	0% Glycerol (g)							
K	Empty	Solution	Final	Dried BA	Evap Solv	Mole BA	Evap Solv (kg)	Molality
303	8.02510	10.80270	8.02670	0.00160	2.77600	0.00001	0.00278	0.00472
318	54.14900	56.92660	54.15270	0.00370	2.77390	0.00003	0.00277	0.01092
333	95.29760	97.93170	95.31450	0.01690	2.61720	0.00014	0.00262	0.05288
348	54.15100	57.27910	54.17060	0.01960	3.10850	0.00016	0.00311	0.05163
363	8.02470	10.83060	8.05890	0.03420	2.77170	0.00028	0.00277	0.10104
Temperature	10% Glycerol (g)							
K	Empty	Solution	Final	Dried BA	Evap Solv	Mole BA	Evap Solv (kg)	Molality
303	95.29510	98.06323	95.29750	0.00240	2.76573	0.00002	0.00277	0.00711
318	54.15107	56.90465	54.60693	0.45587	2.29772	0.00373	0.00230	1.62462
333	115.48837	118.60290	116.05620	0.56783	2.54670	0.00465	0.00255	1.82578
348	4.49223	7.52523	5.17580	0.68357	2.34943	0.00560	0.00235	2.38247
363	3.60340	6.68597	4.39013	0.78673	2.29584	0.00644	0.00230	2.80603
Temperature	20% Glycerol (g)							
K	Empty	Solution	Final	Dried BA	Evap Solv	Mole BA	Evap Solv (kg)	Molality
303	3.96740	7.34550	5.04226	1.07486	2.30324	0.00880	0.00230	3.82139
318	3.97510	7.13397	4.99710	1.02200	2.13687	0.00837	0.00214	3.91635
333	4.49407	7.74920	5.55613	1.06206	2.19307	0.00870	0.00219	3.96558
348	4.49280	7.62310	5.52330	1.03050	2.09980	0.00844	0.00210	4.01863
363	4.49326	7.48836	5.52703	1.03377	1.96133	0.00847	0.00196	4.31600

Temperature	30% Glycerol (g)							
K	Empty	Solution	Final	Dried BA	Evap Solv	Mole BA	Evap Solv (kg)	Molality
303	3.96916	7.29060	5.52120	1.55204	1.76940	0.01271	0.00177	7.18266
318	3.58786	7.09660	5.26430	1.67644	1.83230	0.01373	0.00183	7.49204
333	3.60340	6.91140	5.20120	1.59780	1.71020	0.01308	0.00171	7.65040
348	3.96740	7.16410	5.53710	1.56970	1.62700	0.01285	0.00163	7.90019
363	4.49520	7.59210	6.06036	1.56516	1.53174	0.01282	0.00153	8.36724
Temperature	40% Glycerol (g)							
K	Empty	Solution	Final	Dried BA	Evap Solv	Mole BA	Evap Solv (kg)	Molality
303	3.97510	7.20070	5.90780	1.93270	1.29290	0.01583	0.00129	12.24075
318	4.49407	7.92896	6.58550	2.09143	1.34346	0.01713	0.00134	12.74758
333	3.69700	6.85870	5.63576	1.93876	1.22294	0.01588	0.00122	12.98157
348	3.72820	6.96656	5.73066	2.00246	1.23590	0.01640	0.00124	13.26750
363	3.87690	7.10420	6.00930	2.13240	1.09490	0.01746	0.00109	15.94787
Temperature	50% Glycerol (g)							
K	Empty	Solution	Final	Dried BA	Evap Solv	Mole BA	Evap Solv (kg)	Molality
303	4.49280	7.91846	6.89540	2.40260	1.02306	0.01967	0.00102	19.23042
318	3.68850	6.83286	5.92746	2.23896	0.90540	0.01833	0.00091	20.24950
333	3.69150	7.01840	6.15100	2.45950	0.86740	0.02014	0.00087	23.21859
348	3.72836	6.57076	5.85853	2.13017	0.71223	0.01744	0.00071	24.49077
363	3.60340	7.04376	6.24040	2.63700	0.80336	0.02159	0.00080	26.87871

Temperature	60% Glycerol (g)							
K	Empty	Solution	Final	Dried BA	Evap Solv	Mole BA	Evap Solv (kg)	Molality
303	4.49250	7.70456	7.03436	2.54186	0.67020	0.02081	0.00067	31.05672
318	3.68600	6.85770	6.25376	2.56776	0.60394	0.02103	0.00060	34.81521
333	3.69076	6.91410	6.35150	2.66074	0.56260	0.02179	0.00056	38.72676
348	3.72490	6.94390	6.39706	2.67216	0.54684	0.02188	0.00055	40.01388
363	3.96740	7.52426	6.95070	2.98330	0.57356	0.02443	0.00057	42.59185
Temperature	70% Glycerol (g)							
K	Empty	Solution	Final	Dried BA	Evap Solv	Mole BA	Evap Solv (kg)	Molality
303	4.49520	7.75460	7.33540	2.84020	0.41920	0.02326	0.00042	55.47995
318	3.96916	7.48790	7.05466	3.08550	0.43324	0.02527	0.00043	58.31838
333	3.97510	7.55830	7.15540	3.18030	0.40290	0.02604	0.00040	64.63671
348	3.69700	7.58090	7.17080	3.47380	0.41010	0.02845	0.00041	69.36230
363	4.49280	8.38150	8.00310	3.51030	0.37840	0.02874	0.00038	75.96290
Temperature	80% Glycerol (g)							
K	Empty	Solution	Final	Dried BA	Evap Solv	Mole BA	Evap Solv (kg)	Molality
303	3.69700	6.77640	6.54740	2.85040	0.22900	0.02334	0.00023	101.92454
318	4.49407	7.69060	7.53336	3.03929	0.15724	0.02489	0.00016	158.27706
333	3.72820	6.99920	6.87540	3.14720	0.12380	0.02577	0.00012	208.16712
348	3.68850	6.74306	6.64900	2.96050	0.09406	0.02424	0.00009	257.73211
363	3.69150	7.18956	7.09310	3.40160	0.09646	0.02785	0.00010	288.76491

Temperature	90% Glycerol (g)							
K	Empty	Solution	Final	Dried BA	Evap Solv	Mole BA	Evap Solv (kg)	Molality
303	3.69076	7.16090	7.07700	3.38624	0.08390	0.02773	0.00008	330.49448
318	3.87690	7.12816	7.06050	3.18360	0.06766	0.02607	0.00007	385.29639
333	3.72836	7.07746	7.01210	3.28374	0.06536	0.02689	0.00007	411.40083
348	3.60340	7.13720	7.07230	3.46890	0.06490	0.02841	0.00006	437.67881
363	4.49250	8.06266	8.00360	3.51110	0.05906	0.02875	0.00006	486.80855

Appendix B

LFSU-CHE LFSU-CHE-F12

UNIVERSITI TEKNOLOGI PETRONAS

LABORATORY CLEARANCE FORM

STUDENT/STAFF DETAILS

Name : Hudzaifah Yusof Bin Humayun Matric No : 15575

Programs: Chemical Engineering

Email : hudzaifah 93@ outlook.com Contact No: 017-5729732

CLEARANCE CHECKLIST

Please fill and obtain all signature require after your had done / finish of your research work .

Description of clearance	YES	NO
1.0 Chemical / Waste Chemical & Material Benzoic Acid Glycerol		
2.0 Glassware & Apparatus Beaker Vile Measuring Cylinder Conical flask Mortar and pastle		
3.0 Equipment & spare parts		

I personally returned all items has been loaned during my work research/project in good condition : -

Student signature : _____ Date : 04 / 12 / 15

LFSU - OFFICE USE ONLY

This student has cleared up all of his/her experimental apparatus and properly disposed of chemicals, samples, gases and other lab materials and left their lab in a satisfactory condition .

I personally checked and received all item has been returned by this student : -

Representative Technologist/ : Lab Technologist

M Shaharuddin Bin A Rahman
Laboratory Technologist
Chemical Engineering Department
Universiti Teknologi PETRONAS

Signature

Date : 30 / 12 / 15

Verification By

Lab Executive :

b/p
Fadhullah Hakimi Fauzi
Laboratory Executive (LFSU)
Chemical Engineering Department
Universiti Teknologi PETRONAS

Signature

Date : 30 / 12 / 15