

UNIVERSITI TEKNOLOGI MARA

**A STUDY ON SOLUTION CHEMISTRY AND
CRYSTALLIZATION BEHAVIOR OF L-ALANINE
IN THE PRESENCE OF ADDITIVES**

MUHAMAD FITRI BIN OTHMAN

Thesis submitted in fulfillment
of the requirements for the degree of
Master of Sciences

Faculty of Chemical Engineering

July 2013

ABSTRACT

Crystallization is one of important purification process especially in pharmaceutical industries. However, the presence of impurities in the solution is known to cause a profound effect on the final crystal product. Increasing the level of understanding on the effect of additives to the solution crystallization is important. It is the objective of this thesis to investigate the effect of additives on the solution chemistry and the produced crystals. The ability of incorporation of additive on the surface morphology was also assessed through computational technique. The solubility experiment of L-alanine, with L-leucine and glycine as additives to the L-alanine solution were carried out by using isothermal method. Prediction of L-alanine crystal morphology and the likelihood of additives incorporation on selective site of the crystal surface via molecular modelling are also presented. The binary system and ternary systems were found to deviate from the ideal system by negative deviations representing a high solute-solvent interaction. Meanwhile, the results from PXRD and DSC analyses indicate that there is an interaction between additives molecules and host crystal surface through adsorption mechanism and thus promotes the formation of a solid solution. The simulated morphology and the calculated lattice energy reveal small deviation from the experimental data. Thus, Dreiding potential function and Mulliken atomic charge are the most suitable set to be used to predict the morphology of L-alanine. Modelling studies of additives incorporation on the L-alanine crystal reveal that both additives have different propensity to incorporate on the selective facet of L-alanine.

ACKNOWLEDGEMENT

Firstly, Alhamdulillah, I am most grateful to Allah S.W.T for giving me enough strength, time, and help me to complete this study in order to fulfill the requirement for the Master Degree of Science (Chemical Engineering), Faculty of Chemical Engineering at Universiti Teknologi MARA.

I would like to thanks my academic supervisors Miss Nornizar Anuar and Dr. Noor Fitrah Abu Bakar for their advice, support, and encouragement for this project and for providing an amiable working environment.

My thanks go to all members of the Particle Engineering Technology Group: Mohd Zulfahmi Bin Lukman, Umi Rafiah Bt Syukri, Nik Salwani Bt Mohd Azmi and Bashariah Bt Basaruddin for their friendly and continuous support. I would like to express my special gratitude to my dearest family especially lovely parents; Othman Bin Mat Taib and , my brothers Fadhil and Firdaus and my lovely sisters, Faridah and Fauziah for their unconditional love, understanding, never ending encouragement and financial support to proceed and complete my studies in Universiti Teknologi MARA.

Finally, thanks directly or indirectly to persons that contributed to this project for their helps and supports. I will always remember and appreciate everything that you had done for me.

TABLE OF CONTENTS

	Page
AUTHOR'S DECLARATION	ii
ABSTRACT	iii
ACKNOWLEDGEMENT	iv
TABLE OF CONTENTS	v
LIST OF TABLES	ix
LIST OF FIGURES	xi
LIST OF ABBREVIATIONS	xvi
LIST OF PLATES	xviii
LIST OF SYMBOLS	xix
CHAPTER ONE: INTRODUCTION	
1.1 Research Background	1
1.2 L-Alanine – Important Crystalline Material	3
1.3 Problem Statement	5
1.4 Significance of Research	6
1.5 Objectives	6
1.6 Scope of Work	7
1.7 Outline of the Thesis	8
CHAPTER TWO: LITERATURE REVIEW	
2.1 Introduction	10
2.2 Properties of Amino Acids	10
2.2.1 Basic Structure of Amino Acid	10
2.2.2 Production and Classification of Amino Acids	11
2.2.3 Properties of Amino Acids in Solution	15
2.2.4 Solubility of Amino Acids in Aqueous Solutions	15
2.2.5 Solubility of Amino Acids Mixtures	17
2.2.6 Polarity of Amino Acids	19
2.3 Crystallization of Amino Acids	21
2.3.1 Crystallization of L-alanine	23
2.4 Crystals and Basic Crystallography	26

CHAPTER ONE

INTRODUCTION

1.1 RESEARCH BACKGROUND

In current years, the world has seen much progress in the chemical product market moving from capital-intensive bulk chemical to the manufacture of the high additives substances materials such as pharmaceuticals, food, surfactants, dyes and pigments (Robert, 1996). Crystallization process is an important separation and purification technique employed to produce these high value-added substance materials especially in the pharmaceutical industry (Chen, Sarma, Evans & Myerson, 2011). Crystallization is defined as the process of solid crystal formation from a uniform solution and this process also involves mass transfer of solute from liquid solution to a pure solid crystalline phase.

Crystallization is the most important key component of all processes in the production of small molecule pharmaceuticals. Over 80% of the crystallization was used in pharmaceuticals, fine chemicals, agrochemicals, foods and cosmetics industries (Novasep, 2010). In the pharmaceutical manufacturing, crystallization is always the key process used for purification of intermediates and as the ultimate stage in the manufacture of active pharmaceutical ingredients (APIs) (Chen et al. 2011).

Pharmaceutical industries have high potential growth in both domestic and export markets which are very important component for the healthcare sector in Malaysia (MATRADE, 2008). It has been recorded that in 2006, the global pharmaceutical markets stood at RM1842.0 billion and it is estimated by 2013 can be reaching RM2482 billion as shown in Figure 1.1. The pharmaceutical market in Malaysia is one of the fastest growing in Asia Pacific region with a compound annual growth rate (CAGR) of 10.5%. According to Frost & Sullivan estimates, the Malaysian pharmaceutical industry was valued at RM3.12 billion in 2007 and is expected to reach RM5.46 billion by 2013 (Tham & Yahya, 2008).

In addition, Malaysia ranks fifth in the healthcare spending in comparison to Asian countries such as India, Indonesia, China, and Thailand in spite of relatively small population. It also reported that Malaysians' spending on healthcare has increased at about 13% per year. This shows that the trend towards healthier lifestyle or an increase to the need of medical care, due to unhealthy lifestyle. Thus in turn