UNIVERSITI TEKNOLOGI MARA

INVESTIGATION ON SOLUBILISATION BEHAVIOUR OF L-ISOLEUCINE POLYMORPH AND ITS ASSOCIATED THERMODYNAMICS PROPERTIES

VANNESSA SHALLOMY ANAK DARRELL

Thesis submitted in fulfillment
of the requirements for the degree of
Master of Science
(Chemical Engineering)

College of Engineering

January 2024

ABSTRACT

The motivation to determine the relationship of thermodynamic behaviour (solubilities) and properties between L-isoleucine polymorphic forms grown in water and to understand the molecular interaction behaviour between the solute-solvent molecules at the molecular level between L-isoleucine and water has been the reasons to establish this work. To achieve these objectives, the study of physico-chemical properties of L-isoleucine was carried out, i.e., through (1) isothermal and polythermal dissolution methods, (2) solid-state properties determination, and (3) molecular modelling for solubilisation prediction. The L-isoleucine polymorphic forms were recrystallised using isothermal and polythermal crystallisation techniques. The product crystals were analysed by means of x-ray powder diffraction, differential scanning calorimetry, fourier transform infrared, and an optical microscope to evaluate the form produced. The dried L-isoleucine crystals were then used as the feed for solubility determination experiments. All solubility experiments were carried out in a 100 mL solution in a jacketed glass vessel fitted with a smart thermostatic water-circulator bath. Meanwhile, the solubilisation behaviour of L-isoleucine in water was determined by using molecular modelling and dynamic simulation approaches. The final morphology was calculated using the attachment energy method. Next, the molecular dynamics simulation was done on the solute/solvent (L-isoleucine/water) interface on the morphologically stable crystal faces and the simulation results were later analysed using the Radial Distribution Function (RDF) and Mean Square Displacement (MSD). In this work, the new polymorphic form of L-isoleucine form C was discovered. Different peaks for all the three polymorphs were observed via x-ray diffraction. The new form exhibited new peaks at 2θ = 19.5 °, 20.92 °, 24.96 °, 27.96 °, 30.66 °, 32.84 °, and 39.44 °. The DSC results also revealed the new peak of melting temperature, 216.32 ^{o}C, which indicated the new polymorphic form of L-isoleucine. The images of the crystals captured using optical microscope were then used to capture the images of the crystals prior to apex angles measurement. The solubility results showed that L-isoleucine form A has the highest solubility, followed by form C, and form B is the lowest solubility. Comparison with the ideal solubility for each polymorphic form indicated that all the polymorphic forms deviated positively from the ideal behaviour. The activity coefficient values for form A were in the range of 11 – 17, form B were between 780 – 1796, and form C were between 32 – 88. The large activity coefficient values for form B depicted poor interaction between L-isoleucine and water, consistent with its low solubility in water. The enthalpy contribution increased with increasing temperature for form A obtained by both solubility methods. The same result was also shown for form C obtained by the polythermal dissolution method. In contrast, entropy contribution decreased with increasing temperature for form C obtained by both solubility methods and form B obtained by the isothermal dissolution method. The molecular modelling study revealed that the L-isoleucine morphology obtained as a flat elongated hexagonal shape crystal, which was in good agreement with previous reports. Different facets displayed different crystal packings that affected the interaction with water. The radial distribution function analysis and the mean square displacement analysis have successfully shown that the solubilisation of L-isoleucine crystal takes place following the order of: (1 1 0) > (1 0 0) > (0 0 1). This result is consistent with the orientation of L-isoleucine molecules on the surfaces, as confirmed by the surface chemistry of the crystal.

ACKNOWLEDGEMENT

First and foremost, I would like to thank God for granting me the strength and good health to complete this research. I would like to thank and acknowledge my supervisors and my mentor, Dr Siti Nurul'ain binti Yusop, Dr Nornizar binti Anuar, Mr Muhammad Fitri bin Othman, for their invaluable support and assistance during the research and writing of this thesis.

Endless gratitude to my friends and my research collegues, including Dr. Nik Salwani Md. Azmi, Umi Rafiah Shukri, Nurshahzanani Shahrir, Mohd Zulfahmi Lukman, and Amira Nadzirah Suhaidi, for their friendship, support and words of wisdom throughout the writing process.

To Mom and Dad—thank you for your endless love, constant support, and for all the sacrifices you made to prioritize my education. Last, but not least, to all my friends, families and all those wonderful people who have contributed directly and indirectly to my personal success, no words can describe how thankful I am for them.

TABLE OF CONTENTS

CHAPTER ONE
INTRODUCTION

1.1 Research Background

Crystallisation is a separation process of vital importance, particularly in fine-chemicals and pharmaceuticals industrial and life-sciences sector (Chen & Trout, 2008; Erdemir, Lee, & Myerson, 2009). In the pharmaceutical industry, crystallisation has the paramount role starting from the intermediates separation process and the ending manufacture step of high-quality crystals in terms of size, purity, morphology, and crystal structure.

The formation of a crystalline solid from a supersaturated solid solution follows two-step nucleation mechanisms, which are the formation of a supersaturated solution and the creation of nuclei of a new crystal (Erdemir et al., 2009). There is a relationship between the presence of the pre-existing metastable dense liquid clusters and the solid-state outcome (i.e., polymorph) (Yu, Reutzel-Edens, & Mitchell, 2000).

Polymorphism phenomenon arises as a result of a difference in environmental factors (i.e., solvent, cooling and stirring rates, temperature, pressure, and seeding) leading to different arrangements in crystal lattice structures (i.e., packing patterns or conformations) (Haleblian & McCrone, 1969; Vedantam & Ranade, 2013). Polymorphic forms of the same element can have different physical properties, such as solubility, melting point, dissolution rate and bioavailability, affecting the processing of pharmaceutical and other speciality products.

Poor solubility remains the main concern for pharmaceutical industries as it results in a low dissolution rate and insufficient bioavailability of pharmaceutical products to reach their therapeutic effect. Therefore, to overcome this problem, it is mandatory to determine the specified operating conditions for a target polymorph. However, such a determination is very time-consuming and challenging to apply to many possible parameters.

In recent years, modelling methods based on computer simulation have advanced swiftly, and become valuable tools in studying the crystallisation processes. With the developments of the cost-effective molecular modelling concept, such rising oral drug delivery issues can be addressed to support direct experimentation and mimic