UNIVERSITI TEKNOLOGI MARA

ELUCIDATION OF THE ROLE OF SOLVENTS ON THE GROWTH OF UREA

NURSHAHZANANI BINTI SHAHRIR

Thesis submitted in fulfilment
of the requirements for the degree of
Doctor of Philosophy
(Chemical Engineering)

College of Engineering

February 2024

ABSTRACT

The shape of drug crystals plays a crucial role in the downstream processing in pharmaceutical manufacturing. Difficulties may arise when dealing with unwanted crystal shapes, leading to challenges in manufacturing processes such as during filtration, granulation, and tabletting. Consequently, this affects the overall quality of the final products. In this work, the crystal growth and morphology of urea, its associated solubility in various solvents, and growth kinetics were investigated using experimental and molecular modelling approaches. The solubility of urea crystals was found to be most soluble in water and less soluble in alcoholic solvents. The urea crystals grown in polar protic solvents by cooling crystallisation were found to be of α-form, as confirmed by powder X-ray diffraction, differential scanning calorimetry, and Fourier transform infrared spectroscopy analyses. The crystals grown in water were flat and elongated, while those grown in other alcoholic solvents had a wedge-shaped or prismoidal morphology. The aspect ratios of the crystals ranged from 14.77 to 1.44, with isopropanol showing the smallest aspect ratio. The mean growth rates of {110} and {111} of urea in isopropanol showed both facets growing with the birth and spread (B&S) mechanism. The stable α-form can be produced using a polythermal crystallisation technique at high cooling rates (0.75 °C/min) and at high concentrations (52 g/L), which yields more crystals, making them ideal for industrial applications. In molecular modelling, urea was predicted as an elongated cuboid along the c-axis in a vacuum. This prediction lattice energy showed good agreement with the experimental lattice energies (-22.20 kcal/mol). The assessment of solute-solvent interactions using the surface docking method revealed that the non-bonded interactions computed at the stable orientation of solute-solvent were the highest for interactions between solvents and the {111} facet, followed by {001} and {110} facet. The calculated binding energy for the solvent-surfaces interactions showed that the highest strength was observed for the polar {111} and {001} capping facets, while the binding energy of the {110} facet was the lowest. The capping facets are the determining factors of the growth of urea crystals along the c-axis. The inhibition of the solvent molecules on the polar capping {111} and {001} facets was identified as capable of stopping the growth of the urea crystals along the c-axis by stopping the formation of synthon A and synthon B. In contrast, the growth along the a-axis was halted by stopping the growth of synthon B. This had an impact on the aspect ratios of the crystals. The urea crystal produced had a wedge-shaped morphology with a missing {110} facet. It could transform into a prismoid-shaped crystal through a longer crystallisation time of urea in the solvent for the {110} facet to grow. The molecular interactions between each polarity group, i.e., polar protic, polar aprotic, and non-polar solvents, with urea crystal facets were found that the polar protic solvents had the strongest interactions, i.e., non-bonded and binding energies, with the urea crystal facets, followed by polar aprotic solvents and non-polar solvents. Overall, the research highlights a crucial relationship between functional groups in both the solute and solvent, and their influence on crystal growth and morphology through specific solute-solvent interactions. Understanding this interconnectedness is vital for the development of Active Pharmaceutical Ingredients (APIs) with desired properties and to avoid downstream manufacturing failure issues.

ACKNOWLEDGEMENT

Firstly, I wish to thank Allah swt. for giving me the opportunity to embark on my PhD and for completing this long and challenging journey successfully. My gratitude and thanks go to my supervisors, Dr. Siti Nurul'ain Yusop, Prof. Madya. Dr. Nornizar Anuar, and Prof. Madya. ChM. Dr. Hamizah Mohd Zaki, for their invaluable support and assistance during the research and writing of this thesis.

My appreciation goes to my friends and my research colleagues, including Umi Rafiah Shukri, Vanessa Shallomy anak Darrell, and Muhammad Fitri bin Othman, for their friendship, support, and words of wisdom throughout the research journey.

Finally, this thesis is dedicated to the loving memory of my very dear late father Shahrir bin Shuib, and my mother [redacted] for the vision and determination to educate me. This piece of victory is dedicated to both of you. Alhamdulillah.

TABLE OF CONTENTS

CHAPTER 1

INTRODUCTION

1.1 Research Background

Crystallisation is a separation process of solid crystals formed in solution. The quality of crystals is very dependent on parameters such as solvents, supersaturation, temperature, cooling rates and, pH. In manufacturing processes, crystal morphology needs to be modified and controlled to ensure its performance. The modification of crystal properties is used intensively over the world in designing particles with desired properties. These properties have a significant influence on product performance. For example, paracetamol's poor compressibility and capping issues were tackled by engineering its particle size through additive-assisted crystal growth, leading to significantly improved powder compaction during tableting (Keshavarz et al., 2021). Similarly, equant (isometric) morphologies are hypothesised to enhance the flowability and compressibility of Active Pharmaceutical Ingredients (APIs), making them ideal for tablet formulations (Ramos Ojeda & Kind, 2024). Therefore, crystal morphology modification can be one of the promising ways to obtain a material with desired properties to ensure the efficiency of the manufacturing processes (Firaha et al., 2023; Munk et al., 2012; Ramos Ojeda & Kind, 2024). Figure 1.1 illustrates this holistic process workflow, highlighting the interconnectivity of process, from molecular and solid-form properties to manufacturing and, eventually, product performance (Leane et al., 2015; Peeling et al., 2018).

In solution crystallisation, the effect of solvents is one of the primary factors affecting final crystal morphologies (Zhu et al., 2020). Crystal growth in the presence of a solvent produces different morphology as it could hinder or promote the growth of specific crystal surfaces based on the molecular interactions between host molecules and solvent molecules (Anuar et al., 2022; Lahav & Leiserowitz, 2001). This causes a change in the physicochemical behaviour of the crystals, i.e., nucleation and crystal growth processes. The overall morphology of the crystals prepared in crystallisation processes is important, as an inadequately defined crystal morphology may have a detrimental impact on particulate properties, such as filtration and drying, as well the product qualities like flowability, compressibility, and bulk density (Anuar et al., 2022;