UNIVERSITI TEKNOLOGI MARA

SOLUBILITY ENHANCEMENT OF STATIN-BASED MOLECULES BY ARGININE: THERMODYNAMICS, SOLUTE-SOLVENT INTERACTION AND SOLID STATE CHARACTERIZATION

MEOR MOHD REDZUAN
BIN
MEOR MOHD AFFANDI

Thesis submitted in fulfilment
of the requirements for the degree of
Doctor of Philosophy

Faculty of Pharmacy

July 2016

CONFIRMATION BY PANEL OF EXAMINERS

I certify that a panel of examiners has met on 23rd June 2016 to conduct the final examination of Meor Mohd Redzuan B Meor Mohd Affandi on his Doctor of Philosophy thesis entitled "Solubility Enhancement Of Statin-Based Molecules By Arginine: Thermodynamics, Solute-Solvent Interaction And Solid State Characterization" in accordance with Universiti Teknologi MARA Act 1976 (Akta 173). The panel of Examiners recommends that the student be awarded the relevant degree. The panel of Examiners was as follows:

A'edah Bt Abu Bakar, PhD
Associate Professor
Faculty of Pharmacy
Universiti Teknologi MARA
(Chairman)

Wong Tin Wui, PhD
Associate Professor
Faculty of Pharmacy
Universiti Teknologi MARA
(Internal Examiner)

Mohd Cairul Iqbal B Mohd Amin, PhD
Professor
Faculty of Pharmacy
Universiti Kebangsaan Malaysia
(External Examiner)

Shin Aoki, PhD
Professor
Faculty of Pharmacy Sciences
University of Tokyo
(External Examiner)

MOHAMMAD NAWAWI
DATO' HJ SEROJI, PhD
Dean
Institute of Graduate Studies
Universiti Teknologi MARA
Date: 20th July, 2016

AUTHOR'S DECLARATION

I declare that the work in this thesis was carried out in accordance with the regulations of Universiti Teknologi MARA. It is original and is the result of my own work, unless otherwise indicated or acknowledged as referenced work. This thesis has not been submitted to any other academic institution or non-academic institution for any degree or qualification.

I, hereby, acknowledge that I have been supplied with the Academic Rules and Regulations for Post Graduate, Universiti Teknologi MARA, regulating the conduct of my study and research.

Name of Student	:	Meor Mohd Redzuan B Meor Mohd Affandi
Student I.D. No.	:	2013838056
Programme	:	Doctor of Philosophy (Pharmaceutics) – PH964
Faculty	:	Pharmacy
Thesis Title	:	Solubility Enhancement Of Statin-Based Molecules By Arginine: Thermodynamics, Solute-Solvent Interaction And Solid State Characterization
Signature of Student	:	.....
Date	:	July 2016

ABSTRACT

Categorized as a Biopharmaceutics Classification System (BCS) Class II drugs, statins exhibit low aqueous solubility and bioavailability thus presenting an obstacle and great challenge to formulation researchers. As a consequence, abundant studies are available in regard to the solubility enhancement of statins but very few actually describe this phenomenon in terms of thermodynamics and the solute solvent interaction. The present study aimed to elucidate the solute-solvent and solute-cosolute interactions, solid state characteristics, wetting behaviour, surface energy and thermodynamic parameters that bolstered the solubility of simvastatin (SMV) and atorvastatin (ATV) in the presence of ARG. First, the solubility of SMV and ATV in 0.01, 0.02, 0.04, 0.09, 0.18, 0.36 and 0.73 mol dm^{-3} arginine (ARG) in water solutions was determined. These solutions were subjected to conductometric, volumetric, viscometric, acoustic and refractometric measurements at temperatures (T) of 298.15, 303.15, 308.15 and 313.15 K. Results indicated that there was a massive increase of SMV and ATV solubility in the presence of ARG as a cosolute. Based on physical characteristics, a strong solute-solvent and solute-cosolute interaction has occurred in the SMV-ARG and ATV-ARG binary solution mixture. Furthermore, results of spectral analysis complemented the thermophysical findings which proved that SMV-ARG and ATV-ARG complexes were formed as a result of an interaction between the molecules. The second part of the study looked at how easy SMV and ATV formed a complex with ARG. The complexes were characterized based on their physicochemical properties and subjected to solubility and *in vitro* dissolution study. SMV-ARG and ATV-ARG complexes enhanced solubility by 12,000 and 25-fold respectively, as compared to the pure drug. Additionally, an increase in the dissolution rate for both acidic and alkaline dissolution media was also observed. Results from physicochemical properties revealed molecular interaction between SMV or ATV and ARG during the complexation formation. Finally, the study on the influence of various ratios of statin-arginine complexes on the surface wettability and energy was carried out. Results from this study indicate that a high ratio of ARG in the statin arginine complexes leads to a reduction in the contact angle and an increase in the work of adhesion and surface energy values.

ACKNOWLEDGEMENTS

Syukur Alhamdullilah to Almighty Allah swt for giving me the strength, health and patience to pursue and complete my PhD journey. It is a pleasure to thank those who made this thesis possible. First and foremost, I would like to express the deepest appreciation to my supervisor Dr Minaketan Tripathy for his supervision, guidance and advice throughout this work. His truly scientist's instinct has made him a constant oasis of thoughts and passion in science, which inspires and enriches my growth as a student, a researcher and a scientist. I am obliged to him more than he knows.

Secondly, I wish to express my heartfelt thanks to Professor Dato' Dr Abu Bakar bin Abdul Majeed for his support, guidance and precious suggestions. Without his persistent help, this thesis would not have been completed. Not to forget my lab mate and colleagues at the Faculty of Pharmacy UiTM and Fundamental of Pharmaceutics Laboratory; Anwar, Mazurra, Ashakirin & Gurmeet for the great help, support and encouragement in various ways.

Finally, to my late father and mother Meor Mohd Affandi B Mohd Ali & Nazmah Abdullah, my beloved wife Norjan Yusof, my son Meor Muhamad Nurhakim and my daughter Wan Nur Athirah; all of you are my inspiration and strength. I am very privileged to have all of you in my life.