Design And Mechanistic Evaluation Of Novel Pore-Regulated Polymer Matrices For Transmucosal Drug Delivery

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A thesis submitted to the Faculty of Health Sciences, University of the Witwatersrand, in fulfillment of the requirements for the degree of Doctor of Philosophy

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2011

DECLARATION

I, Oluwatoyin A. Adeleke (**Nee Kolawole**) declare that this thesis is my own work. It is being submitted for the degree of Doctor of Philosophy in the Department of Pharmacy and Pharmacology, Faculty of Health Sciences at the University of the Witwatersrand, Johannesburg, South Africa. It has not been submitted before for any degree or examination at this or any other University. The abstracts and copy of paper(s) included are part of this work.

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Signature

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Date

RESEARCH OUTPUTS ARISING FROM THIS WORK

CONFERENCE PROCEEDINGS

1. A pore-regulated composite matrix for prolonged transmucosal drug delivery by Oluwatoyin A. Kolawole, Viness Pillay, Yahya E. Choonara and Lisa C. du Toit at the research day and faculty postgrad expo of the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa, 2008.

2. Influence of formulation variables on the porosity, bioadhesion and drug release characteristics of a pore-regulated matrix by Oluwatoyin A. Kolawole, Viness Pillay, Yahya E. Choonara and Lisa C. du Toit at the 28th Annual conference of the Academy of Pharmaceutical Sciences, Magaleisburg, South Africa, 2008.

3. Physicochemical analysis of the formulation approach employed in constructing a porosity-controlled drug delivery system by Oluwatoyin A. Kolawole, Viness Pillay, Yahya E. Choonara and Lisa C. du Toit at the 28th Annual conference of the Academy of Pharmaceutical Sciences, Magaleisburg, South Africa, 2008.

4. A bioadhesive porous matrix for prolonged transmucosal delivery of phenytoin sodium through porcine buccal mucosa by Oluwatoyin A. Kolawole, Viness Pillay, Yahya E. Choonara and Lisa C. du Toit at the 28th Annual conference of the Academy of Pharmaceutical Sciences, Magaleisburg, South Africa, 2008.

5. Design and characterization of a pore-regulated matrix for transmucosal drug delivery by Oluwatoyin A. Kolawole, Viness Pillay, Yahya E. Choonara, Lisa C. du Toit and Valence M K. Ndesendo at the American Association of Pharmaceutical Scientists annual meeting and exposition, Atlanta World Congress Centre, Atlanta, Georgia, United States of America, 2008.

6. The influence of pore morphology on the matrix integrity, drug loading and drug release from a porous delivery platform by Oluwatoyin A. Kolawole, Viness Pillay, Yahya E. Choonara, Lisa C. du Toit and Valence M K. Ndesendo at the American Association of

Pharmaceutical Scientists annual meeting and exposition, Atlanta World Congress Centre, Atlanta, Georgia, United States of America, 2008.

7. *In vitro* and *in vivo* evaluation of a bioadhesive porous composite for the sustained transbuccal delivery of phenytoin by Oluwatoyin A. Adeleke (**Nee Kolawole**), Viness Pillay, Yahya E. Choonara and Lisa C. du Toit at the American Association of Pharmaceutical Scientists, Los Angeles Convention Centre, Los Angeles, California, United States of America, 2009.

8. Histomorphological evaluation of a mucoadhesive, porous matrix for controlled transbuccal drug delivery by Oluwatoyin A. Adeleke (**Nee Kolawole**), Viness Pillay, Yahya E. Choonara and Lisa C. du Toit at the 5th International Conference on Pharmaceutical and Pharmacological Sciences, Potchefstroom, South Africa, 2009.

PUBLICATION

Adeleke O.A. (**Nee Kolawole**), Pillay, V., du Toit, L.C. and Chonara Y.E. (2010). Construction and *in vitro* characterization of an optimized porosity-enabled amalgamated matrix for sustained transbuccal drug delivery. *International Journal of Pharmaceutics*, 391:79-89.

PATENT APPLICATION

A transmucosal delivery system by Oluwatoyin A. Adeleke, Viness Pillay and Yahya E. Choonara, South African Patents and Trade Mark Office, Patent Application Filed in 2008; *awaiting priority date.*

ABSTRACT

This thesis focuses on the fabrication, optimization and in vitro, ex vivo as well as in vivo testing/characterization of novel pore-regulated polymer matrices (P-RPM) for sustained transmucosal (transbuccal) drug delivery application employing phenytoin sodium (solubility: 100mg/mL at 25°C and log P = 2.14) and carbamazepine (solubility: 0.01mg/mL at 25°C and log P = 2.93) as model drugs. A simple and optimally efficient interphase, co-particulate-co-solvent homogenization technique coupled with pre-freezing and lyophilization were employed for the fabrication of the P-RPM formulations. The construction and optimization of these novel P-RPM formulations were guided through the statistical and mathematical principles of high performance experimental design approaches. A general introduction to the concept of this thesis is presented at the beginning. The initial phase of this investigation employed the Box-Behnken experimental design to demonstrate the effects of varying formulation variables on the physicochemical and physicomechanical performances of the P-RPMs as well as to statistically optimize these properties for the intended transbuccal drug delivery application. The impact of pore-regulation, measured as average pore diameter and cumulative surface area of pores, on the magnitude of relevant physicochemical and physicomechanical properties of the P-RPMs was also evaluated using linear/non-linear mathematical expressions. Besides, the effects of the differences in the physicochemical properties of phenytoin sodium and carbamazepine loaded unto the optimized P-RPMs revealed their versatility and robustness. In vivo studies using animal models showed the potential of the optimized P-RPM formulations to effectively initiate and sustain transbuccal permeation which regulates the systemic absorption of drug molecules as visualized by outcomes from the quantitative and qualitative assessments of collected blood plasma samples. Furthermore, comparisons of the in vitro release and in vivo absorption characteristics of phenytoin sodium (PS) and carbamazepine (CBZ) from the optimized P-RPM formulation with the comparator products namely Epanutin® and Tegretol®CR respectively showed the potential of the P-RPM formulations to attain higher and more controlled release trends at lower drug loading levels without any dose dumping. The non-compartmental PK-PD modeling process further revealed the differences in the performances of the PS or CBZ loaded P-RPM formulations in comparison with their respective comparator products. The developed point-to-point level A IVIVC model for both the PS and CBZ loaded P-RPM formulations displayed a linear trend (R^2 > 0.9) indicating the possibility of applying respective in vitro dissolution profiles as substitutes for bioequivalency testing for this set of formulations. Histological and cytological investigations confirmed that both the placebo and drug loaded P-RPM formulations had insignificant toxic and irritable effects on the buccal mucosal specimens and cell cultures evaluated indicating that the optimized P-RPMs are potentially biocompatible. Experimental and computational modeling approaches explained the mechanisms of formation of the P-RPM formulation to be based upon structurally, non-destructive physical and mechanical transitions and the mechanism of action to be due to the disruption of the ordered porous matrix structure by physical processes such as disentangling, matrix swelling, plasticization and dissolution as a result of hydration. Preliminary assessments of the impacts of scale-up processes and environmental storage conditions on the stability of the optimized P-RPM formulations suggested that scale-up processes did not significantly alter the physicochemical and physicomechanical performances of these formulations and that they are most stable at conditions with regulated humidity levels, light exposure and room temperature fluctuations.

ACKNOWLEDGEMENTS

I sincerely acknowledge the invaluable role that my supervisor, Professor Viness Pillay, played in ensuring the successful completion of this research project. I would like to thank him with a grateful heart for the consistent support, care, guidance, fatherly counsel, patience and discipline which he displayed during the course of the study. I appreciate him for the priceless knowledge that he imparted in me over the years. Prof, I truly thank you very much for being there all the way through and making me a better person/researcher. I will always remember every moment I spent with you for good.

I also acknowledge the great contribution of my Head of Department, Professor Michael P. Danckwerts to my success. Thank you so much for your encouraging words and ever-willing attitude of support and assistance towards me. I appreciate you sir.

I would like to thank Dr Yahya Choonara and Ms Lisa du Toit, for their willingness to assist me always. I am sincerely grateful for all your efforts.

To my husband, Mr. Adewale Adeleke, thank you so much my love for all that you have been to me. Words can never be used to express the magnitude of love, care, support, and patience which you have shown me. Thank you so much for those wise words of advice and encouragement as well as tireless prayers. I sincerely thank the Almighty God for the wonder of your being and I am grateful for the privilege He gave me to be united with you. Your presence has impacted my life greatly and positively and has made me a much better individual than I ever thought I could be. I genuinely appreciate your efforts.

To my precious gifts from God, Anjolaoluwa and Oluwakanyinsola Adeleke, thank you very much. Your gently, innocent smile and kind gestures gave me strength to persevere even when there seemed like there was no hope. I thank the Almighty God for giving me such wonderful gifts like you both to lighten my path when all seemed dark, discouraging and impossible.

I am indeed indebted to my great and wonderful brothers, Ajibola, Ayoyinka and Ayokunle Kolawole as well as my loving and caring parents, Ibidayo and Ayowole Kolawole, for their enduring love, care, support, understanding, patience and consistent prayers. I thank God for the gift of these precious individuals. I love and appreciate you all.

To my relatives and friends in South Africa and loved ones back home (Nigeria), thanks a great deal for your love, assistance, never-tiring support, prayers, and words of knowledge all the way through.

My special appreciation goes to all members of staff, fellow students and colleagues in the Department of Pharmacy and Pharmacology, University of the Witwatersrand, Johannesburg for their assistance, self-sacrifice and friendship. I thank you all for accepting me for who I am, building me into a better person and making my stay in the Department and South Africa worthwhile. I hold you all in high esteem and pray that the Almighty God rewards you accordingly.

To all members of the Central Animal Services (CAS) of the University of the Witwatersrand, Johannesburg, thank you so much for making the hectic and dreadful moments of performing the animal studies an interesting one for me. I am sincerely grateful.

A special thank you goes to Dr Haijera Davids of the Nelson Mandela Metropolitan University, Port Elizabeth for her assistance with the cytotoxicity assay.

The Medical Research Council (MRC), University of the Witwatersrand, TATA Africa, Biotechnology Partnerships and Development (BioPAD) of South Africa as well as the Ekiti State Scholarship Board, Nigeria are hereby acknowledged for award of scholarship and research funding.

Above all, I give all thanks, praise and adoration to the Almighty God who is the lover of my soul and the One that sustains my life. Thank you, Lord Jesus, for the grace, mercy, wisdom, strength to persevere, immeasurable love, deliverance and constant faithfulness which I experienced by walking this road with You. I adore you my Lord, Master, Author

and Finisher of my faith. Thank you so much for taking all the Glory for this research work. In my nothingness, You made me something. You are worthy to be praised my Lord and my all. My Lord Jesus Christ, you are everything to me and I thank You so much for without You I am a nobody. I was only able to complete this task because the Lord strengthened me and to Him alone I give the Glory, Honor and Adoration.

DEDICATION

This thesis is dedicated to my Lord, Saviour and best friend, Jesus Christ, for He is indeed my source of inspiration.

ANIMAL ETHICS DECLARATION

I, Oluwatoyin Ayotomilola Adeleke (**Nee Kolawole**) hereby confirm that the study entitled 'Design and mechanistic evaluation of novel pore-regulated polymer matrices for transmucosal drug delivery' received the approval from the Animal Ethics Committee of the University of the Witwatersrand with ethics clearance number AESC 2007/42/05.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES