

MODIFYING THE THREE-DIMENSIONAL NETWORK OF POLYAMIDE 6,10 FOR DESIGNING A NOVEL DRUG DELIVERY SYSTEM

Oluwatoyin Ayotomilola Kolawole

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

of

Master of Pharmacy

Johannesburg, 2007

Supervisor:

Professor Viness Pillay, Department of Pharmacy and Pharmacology, University of
Witwatersrand, South Africa

Co-Supervisor:

Professor Michael P. Danckwerts, Department of Pharmacy and Pharmacology,
University of Witwatersrand, South Africa

DECLARATION

I, Oluwatoyin A. Kolawole declare that this dissertation is my own work. It is being submitted for the degree of Master of Pharmacy in the 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 copies of paper(s) included are part of this work.

.....

Signature

.....

Date

DEDICATION

This dissertation is dedicated to my brothers, Ayokunle, Ayoyinka and Ajibola and parents Iridayo and Ayowole Kolawole, for their love, support, encouragement and prayers that inspired me to face all the past and present challenges of my life.

PRESENTATIONS, PUBLICATION AND PATENT APPLICATION

PRESENTATIONS

1. Micromechanical Characterization of Polyamide Variants as Potential Polymeric Materials for Tissue Engineering, 26th Annual Conference of the Academy of Pharmaceutical Sciences, Port Elizabeth, South Africa, 2005.
2. Synthesis, Characterization and Preliminary Evaluation of Linear Polyamides for Controlled Drug Delivery, 26th Annual Conference of the Academy of Pharmaceutical Sciences, Port Elizabeth, South Africa, 2005.
3. Modifying the 3-D network of nylon for designing a novel drug carrier, Therapeutic Science Research Afternoons, University of the Witwatersrand, Johannesburg, South Africa, 2005.
4. Modifying the physical properties of polyhexamethylene sebacamide (PS) for the design of a novel drug delivery system, 1st Symposium on Biomaterials Sciences and Applications in South Africa, Johannesburg, South Africa, 2006.
5. Development of a novel gastroretentive mono-dispersed matrix system for rate-controlled drug delivery, 4th International Conference on Pharmaceutical and Pharmacological Sciences, Johannesburg, South Africa, 2006.
6. Design of a novel polyamide drug carrier for intracranial implantation in the treatment of depression, American Association of Pharmaceutical Scientists annual meeting and exposition, Texas, USA, 2006.

PUBLICATION

A paper titled “Novel polyamide 6,10 variants synthesized by modified interfacial polymerization for application as a rate-modulated monolithic drug delivery system” by Oluwatoyin A. Kolawole, Viness Pillay, Yahya E. Choonara and Michael P. Danckwerts accepted by the *Journal of Bioactive and Compatible Polymers*, 2006 (**In press**).

PATENT APPLICATION

South African Patent Application titled “Polyamide Rate-Modulated Monolithic Drug Delivery System” by Oluwatoyin A. Kolawole, Viness Pillay, Yahya E. Choonara and Michael P. Danckwerts, 2006.

ABSTRACT

This dissertation presents the designing of novel, optimized polyamide 6,10 monolithic matrix systems synthesized using a modified interfacial polymerization process and formulated by direct compression for rate-controlled delivery of model soluble and insoluble drugs. The modification strategy employed included varying reaction stoichiometry, volume ratio and the inclusion of solvent phase modifiers. This was guided through the statistical and mathematical principles of robust experimental designs. A general introduction to this dissertation is presented at the beginning. The initial phase of this investigation employed the Plackett-Burman screening experimental design to evaluate the effects of a partial modification strategy utilized (varying reaction stoichiometry and volume ratio) on the physicochemical and physicomechanical properties of polyamide 6,10. Subsequently, a higher performance, Box-Behnken design using the full modification strategy (varying reaction stoichiometry, volume ratio and the inclusion of solvent phase modifiers) was applied to the optimization of the physicochemical and physicomechanical properties of polyamide 6,10 to achieve the desired drug release characteristics after the competence of the statistical designs in generating effective chemical transformations were established. From this analysis, optimized, directly compressed polyamide 6,10 monolithic matrix systems were developed. The monolithic matrix systems developed in this study demonstrated slow, intermediate and controlled drug release rates. Furthermore, the influences of formulation variables on the drug release performances of the respective optimized monolithic matrices were assessed. In addition, the potentials of the slow and controlled release monolithic matrix formulations to function as implantable and gastroretentive drug delivery systems respectively were also explored. Mathematical models showed that drug release from the three optimized monolithic matrix systems were predominantly regulated by matrix relaxation and lower levels of Fickian diffusion and was observed to follow zero-order kinetics. Also, a close relationship existed between the experimental and predicted data revealing the stability of the mathematical models employed. All dissolution studies in this work employed either amitriptyline hydrochloride or theophylline as model soluble or insoluble drugs respectively. Finally, the optimized polyamide 6,10 variants were characterized based on their physicochemical and physicomechanical properties. A direct relationship was observed between the physicochemical and physicomechanical characteristics and the drug release behaviour of the optimized polyamide 6,10 variants.

ACKNOWLEDGEMENTS

I sincerely acknowledge the invaluable role my supervisor, Professor Viness Pillay, played in ensuring the successful completion of this project as well as his guidance, fatherly counsel and patience in the course of the study. I appreciate him for the priceless knowledge that he imparted in me by constructively criticizing my work. Prof, I will always remember every moment I spent with you! Thank you for being there all the way through.

I also acknowledge the great contribution of my co-supervisor, 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.

To my senior colleague, Mr. Yahya Choonara, thank you so much for your willingness to assist me always.

I am indebted to my great and wonderful brothers, Ayokunle, Ayoyinka and Ajibola, as well as my loving and caring parents; Ibiyayo and Ayowole Kolawole for their love, support, care, encouragement, understanding, patience and consistent prayers. I thank God for the gift of this precious family of mine. This is the one of the best things that has ever happened in my life. I love and appreciate you all!

To my extended family, 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. I am very grateful.

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

I would also like to thank everyone who assisted with the analysis of some of my samples and some data interpretation especially the Department of Chemistry (Polymer Laboratory), School of Chemical Engineering and Metallurgy and the Scanning Electron Microscopy Unit of the University of the Witwatersrand, Johannesburg.

I also would like to acknowledge the members of the West Campus Village Christian Fellowship and the Holy Trinity Catholic Church, Braamfontein for their persistent spiritual intercessions and encouraging words in trying times as well as making South Africa a home for me. Thank you for being there guys!

The Medical Research Council (MRC) and National Research Foundation (NRF) of South Africa are hereby acknowledged for award of research funding.

Above all, I give all Thanks, Praise and Adoration to the Almighty God who is the lover of my soul and giver of my life for grace, mercy, wisdom, strength to persevere, understanding, and immeasurable love, which He bestowed upon me. I adore you my faithful Lord and Master. Thank you so much for taking all the Glory. 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 the wonder of my being. I was only able to do everything I did because Jesus Christ strengthened me (Philippians 4:13)!!!

TABLE OF CONTENTS

DECLARATION	ii
DEDICATION	iii
PRESENTATIONS, PUBLICATIONS AND PATENT APPLICATION	iv
ABSTRACT	vi
ACKNOWLEDGMENTS	vii
TABLE OF CONTENTS	ix
LIST OF FIGURES	xiv
LIST OF TABLES	xix

CHAPTER ONE

INTRODUCTION AND MOTIVATION FOR STUDY

1.1.	Background	2
1.2.	Specific Applications and Ideal Properties of Polymeric Materials	3
1.3.	The Synthetic Aliphatic Polyamides	5
1.4.	The Role of Synthetic Aliphatic Polyamides in Drug Delivery	10
1.5.	Rationale And Motivation For This Study	13
1.6.	Technology Applied in this Study	14
1.7.	Aim and Objectives of the Study	15
1.8.	Overview of this Dissertation	17

CHAPTER TWO

INVESTIGATING THE INFLUENCE OF STOICHIOMETRIC AND VOLUMETRIC RATIO VARIATIONS (PARTIAL MODIFICATION) ON THE PHYSICOCHEMICAL AND PHYSICOMECHANICAL PROPERTIES OF POLYAMIDE 6,10 GUIDED THROUGH A SCREENING DESIGN

2.1.	Introduction	20
2.1.1.	Objectives	21
2.2.	Experimental Section	23

2.2.1. Materials	23
2.2.2. Synthesis of the Polyamide 6,10 Variants	23
2.2.3. Constructing the Experimental Design Template	25
2.2.4. Determination of the Physicomechanical Parameters	27
2.2.5. Determination of Functional Group Vibrational Frequencies	31
2.2.6. Morphological and Qualitative Characterization	31
2.2.7. Statistical Analysis of Data	31
2.3. Results and Discussion	32
2.3.1. Synthesis and Physical Appearance of the Polyamide 6,10 Variants	32
2.3.2. Elucidation of the Effects of the Varying Factor Levels	33
2.3.3. Statistical Analysis of Data	38
2.3.4. Maximization of Matrix Resilience	44
2.3.5. Fourier Transform Infrared Spectrophotometric Studies	46
2.3.6. Surface Morphology of the Polyamide 6,10 Variants	49
2.4. Concluding Statements	51

CHAPTER THREE

THE HIGHER PERFORMANCE BOX-BEHNKEN DESIGN APPLIED TO THE SYNTHESIS (FULL MODIFICATION) AND OPTIMIZATION OF NOVEL MODIFIED POLYAMIDE 6,10 MONOLITHIC MATRIX DEVICES

3.1. Introduction	53
3.2. Full Modification of the Interfacial Polymerization Process	54
3.3. Objectives	57
3.4. Experimental Section	58
3.4.1. Materials	58
3.4.2. Synthesis of the Polyamide 6,10 Variants	58
3.4.3. Constructing of the Experimental Design Template	60
3.4.4. Textural Profiling Analysis of the Polyamide 6,10 Variants	61
3.4.5. Preparation of Calibration Curves for Amitryptiline Hydrochloride	63
3.4.6. Evaluation of the <i>In vitro</i> Drug Release Characteristics	64
3.4.7. Evaluation of <i>In Vitro</i> Matrix Erosion	66
3.4.8. Electrolyte Conductivity Testing for Evaluation of Polymeric Dissolution	67
3.4.9. Fourier Transform Infra Red Spectrophotometric Analysis	68
3.4.10. Statistical Analysis of Data	68

3.5.	Results and Discussion	68
3.5.1.	Synthesis, Physical Appearance and Percentage Yield	68
3.5.2.	Evaluation of Physicomechanical Parameters	69
3.5.3.	<i>In Vitro</i> Drug Release Characteristics	73
3.5.4.	Analysis of Matrix Gravimetric Changes	75
3.5.5.	Electrolyte Conductivity Assessment	76
3.5.6.	Structural Analysis by Infrared Spectroscopy	78
3.5.7.	Constrained Optimization	80
3.6.	Concluding Statements	83

CHAPTER FOUR

DRUG RELEASE FROM THE OPTIMIZED POLYAMIDE 6,10 MONOLITHIC MATRIX SYSTEMS: INFLUENCE OF FORMULATION VARIABLES AND DETERMINATION OF RELEASE KINETICS

4.1.	Introduction	86
4.1.1.	Objectives	87
4.2.	Experimental Section	88
4.2.1.	Materials	88
4.2.2.	Formulation of Monolithic Matrix Systems	88
4.2.3.	Preparation of Calibration Curves in USP-Prescribed Buffer Solutions	89
4.2.4.	Influence of Drug Solubility on Release Characteristics	91
4.2.5.	Examining the Influence of Alternative Dissolution Approach	91
4.2.6.	Assessing the Effect of pH of Dissolution Media on Drug Release	92
4.2.7.	Examination of the Effects of Polymer and Drug Concentrations	93
4.2.8.	The Effects of Varying Compression Force	94
4.2.9.	The Effects of Polymer Particle Size	94
4.2.10.	Exploring the Effects of Different Types and Concentrations of Excipients	94
4.2.11.	Treatment of Dissolution Data	96
4.2.12.	Determination of Drug Release Kinetics	98
4.3.	Results and Discussions	98
4.3.1.	Influence of Drug Solubility on Drug Release	98
4.3.2.	Influence of an Alternative Dissolution Approach	101
4.3.3.	Effect of pH of Release Media	102
4.3.4.	Influence of Polymer and Drug Concentrations	105

4.3.5.	Effects of Varying Compression Force	107
4.3.6.	Effect of Polymer Particle Size Variation	108
4.3.7.	Elucidating the Impact of Formulation Excipients	109
4.3.8.	Analysis of Kinetic Mechanisms Associated with Drug Release	114
4.4.	Concluding Statements	119

CHAPTER FIVE

PHYSICOCHEMICAL AND PHYSICOMECHANICAL CHARACTERIZATION OF THE OPTIMIZED POLYAMIDE 6,10 MONOLITHIC MATRIX SYSTEMS

5.1.	Introduction	121
5.1.1.	Objectives	121
5.2.	Experimental Section	122
5.2.1.	Materials	122
5.2.2.	Textural Profile Analysis	122
5.2.3.	Determination of Melting Point with Differential Scanning Calorimetry	122
5.2.4.	Assessment of Semi-Crystallinity by X-ray Powder Diffractometry	123
5.2.5.	Scanning Electron Microscopy	123
5.2.6.	Fourier Transform Infrared Spectrophotometry	123
5.2.7.	Molecular Mass Determination using Mass Spectrometry	124
5.2.8.	Water Uptake and Swelling Analysis	124
5.2.9.	Conductivity Evaluation	125
5.2.10.	Dissolution and Matrix Erosion Analyses	126
5.3.	Results and Discussion	126
5.3.1.	Determination of the Physicomechanical Characteristics	126
5.3.2.	Melting Temperature Determination	127
5.3.3.	Elucidation of Semi-Crystallinity	129
5.3.4.	Assessment of Surface Morphology	131
5.3.5.	Fourier Transform Infrared Spectrophotometric Analysis	133
5.3.6.	Determination of the Molecular Masses	135
5.3.7.	Water Uptake and Swelling Analyses	136
5.3.8.	Conductivity Evaluation	139
5.3.9.	Dissolution and Matrix Erosion Analyses	139
5.4.	Concluding Statements	140

CHAPTER SIX

CONCLUSIONS AND RECOMMENDATIONS

6.1. Conclusions	143
6.2. Recommendations	144
REFERENCES	147

LIST OF FIGURES

Figure	Title	Page
1.1	Typical intramolecular hydrogen bond structure of polyamide 6,10	7
1.2	Chemical reaction between monomers of a typical aliphatic polyamide synthesized by interfacial polymerization	10
2.1	Synthesis of polyamide 6,10 by interfacial polymerization	24
2.2	Typical force-distance and force-time profiles of polyamide 6,10 for determining both unhydrated and hydrated (a) matrix hardness, (b) matrix deformation energy and (c) matrix resilience (unhydrated only) (N=10 in all cases)	30
2.3	Physicomechanical hydrational rate constants and matrix resilience values of the different polyamide 6,10 variants (N= 10 and standard deviation less than 4.04 in all cases)	36
2.4	Comparison of experimental and predicted values for the responses (a) kH_w , (b) kH_3 (c) $kH_{7.4}$, (d) kE_w , (e) kE_3 , (f) $kE_{7.4}$, and (g) MR	40
2.5	Typical (a) main effects and (b) interaction effects plots of the responses	42
2.6	Three-dimensional surface plots for the 7 responses: (a) kH_w , (b) kH_3 (c) $kH_{7.4}$, (d) kE_w , (e) kE_3 , (f) $kE_{7.4}$, and (g) MR	43

2.7	The three-dimensional surface plots showing the effects of the optimized factor levels on the matrix resilience: (a) effect of hexamethylenediamine and hexane (b) effect of sebacoyl chloride and deionized water	46
2.8	A typical FTIR spectrum of a polyamide 6,10 variant	48
2.9	SEM micrographs of the fourteen variants showing the morphological diversity (Magnification x1000, voltage 20kV)	50
3.1	A Typical force-time profile employed for the determination of matrix resilience (N=10 in all cases)	62
3.2	A typical force-displacement employed for the determination of the peak force employed in the calculation of the Brinell hardness number	63
3.3	Calibration curve of amitriptyline hydrochloride in PBS 7.4 at 240nm (N=3 and standard deviation less than 0.35 in all cases)	64
3.4	Changes in the yield of the fourteen modified polyamide 6,10 variants (N= 2 and standard deviation less than 5.03 in all cases)	69
3.5	Relationship between matrix resilience for polyamide 6,10 matrix formulations with and without drug (N= 10 and standard deviation less than 5.47 in all cases)	71
3.6	Correlation between the values of the Brinell hardness number and matrix resilience	72
3.7	Drug release profiles for the fourteen formulations in PBS	

	7.4 prior to optimization (N=3 and standard deviation less than 0.18 in all cases)	74
3.8	Percentage residual masses of eroded matrices after 24 hours (N= 3 and standard deviation less than 4.69 in all cases)	76
3.9	Proposed mechanism of ionic transfer and formation of conducting electrolytes of polyamide 6,10	77
3.10	Change in conductivity values for the fourteen polyamide 6,10 formulations (N= 3 and standard deviation less than 10.2 in all cases)	78
3.11	Dissolution profiles for the optimized monolithic matrix formulations (N= 3 and standard deviation less than 0.36 in all cases)	83
4.1	Calibration curves of: (a) Theophylline in PBS of pH 7.4 at pH 270nm (b) Amitriptyline hydrochloride and (c) Theophylline in acidic buffer of pH 1.2 at 240nm and 270nm respectively (N= 3 and standard deviation less than 0.03 in all cases)	90
4.2	The drug release profiles of amitriptyline hydrochloride and theophylline from the optimized polyamide 6,10 monolithic matrices: (a) "SR", (b) "IR" and (c) "CR" (N=3 and standard deviation less than 0.49 in all cases)	100
4.3	Graphical representations of the (a) drug release profiles and (b) percentage by weight of the matrix remaining at the end of the 30-day dissolution analysis (N=6 and standard deviation less than 3.52 in all cases)	101
4.4a	Dissolution profiles showing the influence of pH on the release of model soluble and insoluble drugs from the	

	optimized polyamide 6,10 matrix system. (N= 3 and standard deviation less than 0.04 in all cases)	103
4.4b	Profiles showing polymeric matrix gravimetric loss with amitriptyline hydrochloride and theophylline (N=3 and standard deviation less than 3.95 in all cases)	104
4.4c	Photographs of dissolution vessels showing the ability of the matrix device to remain buoyant (float) over 24 hours	104
4.5	Drug release profiles showing the effects of varying (a) polymer (polyamide 6,10) concentration and (b) drug concentration. (N=3 and standard deviation less than 0.10 in all cases)	107
4.6	Effects of changing force of compression on the release performance of an optimized polyamide 6,10 monolithic matrix system (N=3 and standard deviation less than 0.06 in all cases)	108
4.7	Diverse impact of particle size variation drug release from the optimized polyamide 6,10. (N= 3 and standard deviation less than 0.08 in all cases)	109
4.8	Profiles illustrating the effects of (a) Poly (lactides-co-glycolide) (b) Hydroxypropylmethylcellulose and on the drug release characteristics from the optimized polyamide 6,10 monolithic matrices. (N= 3 and standard deviation less than 0.05 in all cases)	111
4.9	Influence of inorganic electrolytes on the drug release performance (N= 3 and standard deviation less than 2.22 in all cases)	112
5.1	Typical DSC thermogram of an optimized polyamide 6,10	

	variant showing the melting temperature, double melting endotherm and exothermic peaks	128
5.2	X-ray diffraction patterns of the (a) slow (b) intermediate and (c) controlled release formulations	130
5.3	SEM micrographs of the (a) slow (b) intermediate and (c) controlled optimized polyamide 6,10 variants showing their surface morphological diversity (magnification $\times 1000$, voltage 20kV)	132
5.4	A Typical FTIR spectrum of an optimized polyamide 6,10 variant	135
5.5	Water uptake of the optimized polyamide 6,10 monolithic matrices (N= 2 and standard deviation less than 5.11 in all cases)	137
5.6	Volumetric swelling front movement for the optimized and selected polyamide 6,10 variants in buffer solutions of pH 7.4. (N= 2 and standard deviation less than 1.25 in all cases)	138
5.7	Change in conductivity values with time for the optimized polyamide 6,10 formulations (N= 2 and standard deviation less than 10.41 in all cases)	139
5.8	Matrix erosion analysis for the optimized polyamide 6,10 matrix formulations. (N= 2 and standard deviation less than 4.42 in all cases)	140

LIST OF TABLES

<i>Table</i>	<i>Title</i>	<i>Page</i>
2.1	Levels of the independent variables employed in the Plackett-Burman design	24
2.2	Plackett-Burman template generated for 4 factors	27
2.3	Textural settings employed for the determination of matrix hardness, deformation energy and matrix resilience	28
2.4	Symbolic representations of the physicochemical hydrational constants	29
2.5	Percentage yields of the polyamide 6,10 variants	32
2.6	Statistical descriptors for the different physicochemical response	39
2.7	Optimal factor levels maximizing matrix resilience obtained by constraints applied on the independent variables	45
2.8	Vibrational frequencies of the polyamide 6,10 variants obtained from FTIR	48
3.1	Levels of the independent variables employed in the Box-Behnken design	59
3.2	Box-Behnken template for the synthesis of the polyamide 6,10 variants	61
3.3	Matrix resilience values of the polyamide 6,10 variants	

	synthesized using the Box- Behnken design template	70
3.4	The mean dissolution time values (MDT_8) for the fourteen formulations in accordance with the Box-Behnken design template	75
3.5	Numerical targets set for the significant response parameters to generate the desired drug release performances	81
3.6	Levels of statistical significance for the response parameters	81
3.7	Experimental and fitted response values performed at optimal factor levels	82
4.1	Polymer and drug concentrations used in the different matrix formulations	93
4.2	Composition of the matrix formulations containing the hydrophobic or hydrophilic polymers	95
4.3	Constituent of the matrix formulations with the inorganic electrolytes	96
4.4a	Release kinetics obtained from the various diffusion, relaxation and erosion models for the slow release formulation ("SR")	116
4.4b	Release kinetics obtained from the various diffusion, relaxation and erosion models for the intermediate release formulation ("IR")	116
4.4c	Release kinetics obtained from the various diffusion, relaxation and erosion models for the controlled release	

	formulation (“CR”)	117
5.1	Numerical values of the physicochemical parameters that characterize the matrix strength and integrity of the optimized polyamide 6,10 matrices	126
5.2	Numerical values of the melting temperature of the optimized polyamide 6,10 variants	127
5.3	Characteristic FTIR absorption frequencies of the selected and optimized polyamide 6,10 variants	134