FORMULATION OF AN ANTI-TUBERCULOSIS DRUG DELIVERY SYSTEM

LISA CLAIRE DU TOIT

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

Supervisor:

Professor Michael Paul Danckwerts
Department of Pharmacy and Pharmacology, University of the Witwatersrand, South Africa

Co-Supervisor:

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

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DECLARATION

I, Lisa Claire du Toit, declare that this dissertation is my own work. It has being submitted for the degree of Master of Pharmacy in the Faculty of Health Sciences in the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.

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This …….. day of February 2007

RESEARCH OUTPUTS

1. Research Publications

a. Lisa Claire du Toit, Viness Pillay and Michael Paul Danckwerts. Application of Synergism and Variation in Ionic Compatibilities within a Hydrophilic Polymeric Sodium Starch Glycolate-κ-Carrageenan Combination: Textural Profiling of the Suspension Behavior. *Journal of Bioactive and Compatible Polymers*. 2006, 21: 107-122.

b. Lisa Claire du Toit, Viness Pillay and Michael Paul Danckwerts. Tuberculosis Chemotherapy: Current Drug Delivery Approaches. *Respiratory Research*. 2006, 7: 118.

2. Conference Outputs

a. Lisa Claire du Toit, Michael Paul Danckwerts and Viness Pillay. Formulation of an Anti-Tuberculosis Drug Delivery System: Microencapsulation of Isoniazid. Young Scientist Competition Abstract Entrant Presented at 26th Annual Conference of the Academy of Pharmaceutical Sciences, 29 September – 2 October 2005, Port Elizabeth.

b. Lisa Claire du Toit, Michael Paul Danckwerts and Viness Pillay. A Novel Salting-Out Approach for the Formulation of Cross-linked Enterospheres Incorporating Isoniazid. Poster Presented at 33rd Annual Meeting & Exposition of the Controlled Release Society, 22-26 July 2006, Vienna, Austria.

c. Lisa Claire du Toit, Viness Pillay and Michael Paul Danckwerts. Textural Characterization of Synergism in Hydrophilic Polymeric Sodium Starch Glycolate-kappa-Carrageenan Sol and Gel Systems. Poster Presented at 33rd Annual Meeting & Exposition of the Controlled Release Society, 22-26 July 2006, Vienna, Austria.

d. Lisa Claire du Toit, Michael Paul Danckwerts and Viness Pillay. Formulation of an Anti-Tuberculosis Site-Specific Drug Delivery System: A Comparative Study of Two Methods for Enteric-Coating Isoniazid Particles. Poster Presented at 26th Annual Conference of the Academy of Pharmaceutical Sciences, 29 September – 2 October 2005, Port Elizabeth.

e. Lisa Claire du Toit, Michael Paul Danckwerts and Viness Pillay. Evaluation of Novelly-Formed Nano- and Entero-spheres for Targeted Delivery of an Anti-Tuberculosis Drug. Podium Presentation at ICPPS Conference 2006, Vanderbijlpark, South Africa.

f. Lisa Claire du Toit, Viness Pillay, Michael Paul Danckwerts, Craig Cremen, Ismail Ravat, Jayendran Subramoney and Harshen Vassan. Approaches to Fabricating Anti-TB Nanosystems Embodying a Salted-Out and Cross-linked Architecture. Poster Presented at ICPPS Conference 2006, Vanderbijlpark, South Africa.

g. Lisa Claire du Toit, Viness Pillay, Michael Paul Danckwerts, Craig Cremen, Ismail Ravat, Jayendran Subramoney and Harshen Vassan. Preliminary production of enteronanoparticles based on a salted-out and cross-linked architecture. Poster Presented at the American Association of Pharmaceutical Scientists Annual Meeting and Exposition Conference, October 2006, Texas, USA.

3. Additional Research Outputs

a. Lisa Claire du Toit, Oluwutoyin Kolawole, Viness Pillay and Michael Paul Danckwerts. The Wits Approach: A Bioactive Research Network (Article), South African Pharmacy Journal, October 2005.

b. Lisa Claire du Toit, Michael Paul Danckwerts and Viness Pillay. Formulation of an Anti-Tuberculosis Site-Specific Drug Delivery System. Podium Presentation at School

of Therapeutic Sciences Research Afternoons, University of the Witwatersrand, 10-11 August 2005.

c. Lisa Claire du Toit, Michael Paul Danckwerts and Viness Pillay. Formulation of an Anti-Tuberculosis Site-Specific Drug Delivery System: A Comparative Study of Two Methods for Enteric-Coating Isoniazid Particles. Podium Presentation at Faculty Reseach Day, University of the Witwatersrand, 23 August 2006.

d. Lisa Claire du Toit, Michael Paul Danckwerts and Viness Pillay. Formulation of an Anti-Tuberculosis Drug Delivery System. Podium Presentation at the 1st Symposium for Biomaterials Science and Applications, University of the Witwatersrand, 4 September 2006.

ABSTRACT

Tuberculosis (TB) is a leading killer of young adults worldwide and the global scourge of multi-drug resistant tuberculosis is reaching epidemic proportions. A number of novel drug delivery systems incorporating the principle anti-tuberculosis (anti-TB) agents have been fabricated that either target the site of TB infection or reduce the dosing frequency with the aim of improving patient outcomes; however, there is a requisite to manufacture an oral system, which directly addresses issues of unacceptable rifampicin (RIF) bioavailability recently reported in a number of fixed-dose combinations (FDCs). There is an urgent need to segregate the delivery of RIF and isoniazid (INH) upon co-administration, such that INH is not released in the stomach owing to the induction of accelerated hydrolysis of RIF in acidic medium to the poorly absorbed insoluble 3-formyl rifamycin SV in the presence of INH. The fabrication of a polymeric once-daily oral multiparticulate fixed-dose combination of the principal anti-TB drugs, which attains segregated delivery of RIF and INH for improved RIF bioavailability, could be a step in the right direction in addressing issues of treatment failure due to administration of poor quality FDCs and patient non-compliance.

Novel approaches were implemented for the fabrication of an oral multiparticulate system for differentiated release of RIF and INH in the gastrointesinal tract. The envisaged system comprised INH-loaded enterosoluble multiparticulate entities for targeted delivery of the INH to the small intestine and reconstitutable multiparticulate entities incorporating the poorly water-soluble RIF and appropriate gel-forming hydrophilic suspending agents, which were required to disintegrate rapidly in tepid water to form a gel network suspending RIF and the INH-loaded enterosoluble multiparticulates. The dry dispersible multiparticulate system may be reconstituted immediately prior to administration to the patient for once-daily dosing as a compliance-promoting tool.

The design of a novel anti-TB drug delivery system hinged on preformulatory investigations and preliminary experimental activities to yield a sufficient database to allow for the selection of the qualitative composition of a prototype formulation. The aforementioned activities initiated the systematic identification of an innovative method for formulating enterosoluble multiparticulates demonstrating the required enteric-release properties. The novelly-formed multiparticulates, referred to as 'enterospheres', were obtained by inducing separation ('salting-out') of a pH-sensitive poly (methacrylic acid-co-ethylacrylate) copolymer as a polymer-rich enteric film and ionotropically cross-linking the internal enterosphere matrix. Rational selection of appropriate suspending agents for design of reconstitutable multiparticulates resolved in the identification of a synergistic hydrophilic sodium starch glycolate-kappa carrageenan combination, duly characterised by physicomechanical analyses. The gel-forming composite system attained ease of dispersal and the formation of a three-dimensional supporting network possessing the essential properties for extemporaneous use.

Statistical experimental design, implementing response surface methodology, was pivotally instituted on the multiparticulate forms for the identification of critical formulation and processing variables for the development of the optimum enterosoluble and reconstitutable multiparticulate systems for delivery to the patient as the preferred multiparticulate two-drug FDC. Because there was an unequivocal relationship between the properties of a cross-linked enterospheres and their structure in such a way that both characteristics could not be considered in an isolated way, in-depth analyses on drug-free and drug-loaded enterospheres was systematically undertaken.

Of principle concern in this study was the attainment of segregated gastrointestinal delivery of RIF and INH in order to address issues of unacceptable RIF bioavailability on co-administration with INH. The proposed United States Pharmacopoeial (USP) high performance liquid chromatographic (HPLC) and colorimetric method, and a proposed regressional analysis of ultraviolet (UV) spectrophotometric absorbance data were employed to resolve RIF and INH release from the optimum multiparticulate system at simulated gastric pH for comparison with the release profiles of anti-TB FDCs commercially available in South Africa.

Ultimately, in keeping up to speed with future trends, this dissertation addressed innovations in nanotechnology, with particular reference to anti-TB nanosystems. The novelly identified method for enterosphere manufacture was adapted with a view to nanosizing the salted-out and cross-linked architecture, for controlled delivery of anti-TB drugs to the patient, in the bid to promote patient adherence.

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DEDICATION

This work is dedicated to my nephew, Liam Matthew du Toit, an unexpected, yet most wonderful gift.

This dissertation is also dedicated to my country, South Africa.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES