CHAPTER 10

Conclusions and Recommendations

10.1. Conclusions

Without question, we are at the stage where the need for improved treatments for life-threatening and debilitating diseases is of fundamental societal concern. Furthermore, there is an extreme urgency to develop cheap and practical-to-use therapies for infectious and other diseases in developing countries. Emerging drug-resistant diseases such as avian influenza adds impetus to this focus. The increased understanding of the molecular basis of many diseases has culminated in the development of indispensable drug therapies; however, lack of effective drug delivery systems is often the rate-limiting step restricting their safe and effective transfer to practice.

The scourge of TB is of dire concern in South Africa, and MDR TB is increasingly reported. South Africa has one of the highest incidences of TB in the world, with 35 deaths a day according to the Kwazulu-Natal Department of Health. Breaking global reports (Green, September 7, 2006) have now established the growing emergence of the virtually untreatable extremely (or extensively) drug-resistant TB (XDR TB) strain. The WHO has classified the strain as extremely drug-resistant, defined as ineffectiveness of the drugs from two of the six agents used as a last line of defense against TB. Worldwide, about 2% of drug-resistant TB cases are classified as extremely drug-resistant. Reports from Tugela Ferry in Kwazulu Natal, South Africa confirmed the death of 52 people out of the 53 individuals infected with this strain within 25 days of diagnosis. According to Dr Karin Weyer, director of the South African Medical Research Council's unit for TB operational and policy research, a person infected with XDR TB runs the risk of infecting 10 to 15 of their close contacts in a year, with HIV-infected individuals being particularly at risk. The emergence of XDR TB in South Africa is undoubtedly frightening, added

to HIV, however, according to the national Department of Health, the solution to the problem is simply to prevent the emergence of resistant strains through reduction of treatment failure by investigating means to enhance patient compliance with existing, effective anti-TB drugs.

The ultimate goal of this research was the pragmatic investigation into the formulation of an oral multiparticulate anti-TB drug delivery system for the segregated delivery of RIF and INH in the GI tract in order to improve their oral effectiveness, all the while striving to maintain sight of clearly pertinent issues, most notably patient adherence.

With drug bioavailability concerns firmly in mind, this research sought to attain this goal from the perspective of creating a compliance-promoting drug delivery tool through presentation of the patient with a novel oral form of the RIF-INH combination. Patient adherence cannot be sufficiently stressed where TB chemotherapy is concerned.

A dry dispersible system incorporating enterosoluble multiparticulate- (enterospheres) and reconstitutable multiparticulate- entities was ultimately developed to fulfil research objectives. The enterospheres were designed and optimised to minimise INH release in the gastric environment and target drug release to the small intestine. The reconstitutable multiparticulates, incorporating appropriately selected gel-forming suspending agents, were optimally designed to disperse rapidly in tepid water to form a three-dimensional supporting network capable of suspending the poorly water-soluble RIF and INH-loaded enterospheres. The importance of critical formulation and processing factors in ensuring the desired performance of both components was emphasised.

Appropriate physicochemical and physicomechanical analyses of the respective systems underscored the mechanisms underlying the functionality of the systems, through elucidation of fundamental principles implicated in salting-out and cross-linking mechanisms, and gel-formation.

Extensive preliminary and optimising *in vitro* release studies and erosional investigations under conditions simulating gastric and intestinal pHs confirmed the gastroresistant and enterosoluble nature of the enterospheres. Subsequently, *in vitro* drug release studies of the RIF-INH combination and consequent spectrophotometric and chromatographic analyses employing established techniques confirmed segregated delivery of the designated drugs, as compared to commercially available formulations.

The novel formulatory concept employed in enterosphere manufacture was extended to anti-TB nanosystems owing to the recently recognised advantages of these sub-micrometre systems for site-specific controlled delivery. The field of nanopharmaceuticals has become fashionable, but it is important to maintain perspective such that materials and techniques are realistically employed. The described system is still in the preliminary stages but was incorporated to demonstrate the diversity of the salted-out and cross-linked MAEA polymer architecture. In order to attain an in-depth knowledge of these complex systems, further physicochemical analyses of the NS are required to enable assemblage of a mechanistic formation pathway. Knowledge of the molecular dynamics will facilitate the coordination of processes involved in NS fabrication.

Ultimately, sound application of this delivery system is achievable in conjunction with DOTS (Directly Observed Treatment-Shortcourse). Thus, together with a regular and uninterrupted supply of a high-quality anti-TB drug delivery system, the 6 months of treatment should be

supervised on an ongoing basis (including direct observation of drug-taking for, at least, the first two months). The once-daily suspension form facilitates supervision – through an improvement in the dosage form requirements of five tablets daily to a once-daily suspension and enhanced supervisory support. The suspension may be safely reconstituted at the health care facility; alternatively, for safe reconstitution of a weekly treatment supply, it is recommended that provision of 500mL bottled water should form part of the DOTS strategy for treatment control instituted at health care facilities.

10.2. Recommendations

This research provided a novel approach for the fabrication of an enterosoluble multiparticulate system in a single processing step, precluding organic solvent implementation. This system may be successfully applied to any number of incorporable acid-sensitive bioactives for which enteric-release is prescribed. These include, but are not limited to, bioactives unstable or degraded at acidic pH (e.g. enzymes, proteins, macrolide antibiotics such as erythromycin), bioactives affecting gastric performance, bioactives causing local irritation of the gastric mucosa (e.g. valproic acid, NSAIDs such as diclofenac and acetylsalicylic acid), bioactives for which intestinal targeting is required for attainment of adequate concentrations in the lower GI tract (e.g. 5-aminosalicylic acid, prodrugs of mesalazine and sulfasalazine), and bioactives which accelerate the degradation of other bioactives in acidic media (e.g. INH, pyrazinamide).

Furthermore, a versatile formulatory approach for delivering two bioactives, for which differentiated GI delivery is prescribed to address bioavailability concerns, was postulated. This technology has the potential to be used as a once-daily multi-unit drug delivery product incorporating multiple drugs that will be able to deliver these drugs simultaneously, and therefore not only eliminate potential deleterious reactions between them if any, but also improve patient

compliance, which is crucial when numerous tablets have to be taken in certain disease conditions. An extemporaneous dry dispersible multiparticulate system that rapidly forms a suspension in tepid water, and which may be reconstituted immediately prior to administration to the patient, serves as a compliance-promoting tool and a novel means of delivering modified-release multi-units to patients, bearing the benefits of such systems in mind. The provision of administration methods that will allow patients to safely treat themselves and enhance their compliance with the drug regimen is a significant health care development, particularly in developing countries where access to doctors, clean syringes, sterile needles, and sophisticated treatments are few and far between. Additionally, scale-up can be performed by the appropriate equipment currently available, or by employing a spray-drying apparatus adapted with various atomisation, drying and separation techniques.

The set-up and process staging for large-scale or industrial manufacture of enterospheres is schematically illustrated in Figure 10.1. The electrolyte solution, at the optimum concentration setting, is sprayed into the drying chamber of the spray-dryer maintained at a relatively low temperature for the aqueous dispersion feed, saturating the drying chamber with the salting-out and cross-linking electrolyte. The drug-loaded aqueous dispersion is pumped at a controlled rate into the spray-dryer where it is atomised into droplets using a rotary atomiser. The atomiser facilitates the production of near-uniform droplets that is contacted by electrolyte-saturated air-filled chamber maintained at the designated temperature setting for optimum annealing of the plasticised enterosphere matrix. This induces the formation of an unmitigated enteric film and an internal matrix exhibiting the optimally defined degree of cross-linkage. The hot air eventually evaporates the water from the formed enterosphere, leading to ultimate solidification. The solid enterospheres exit the spray-dryer in a gas stream and are separated in the product collection operation.

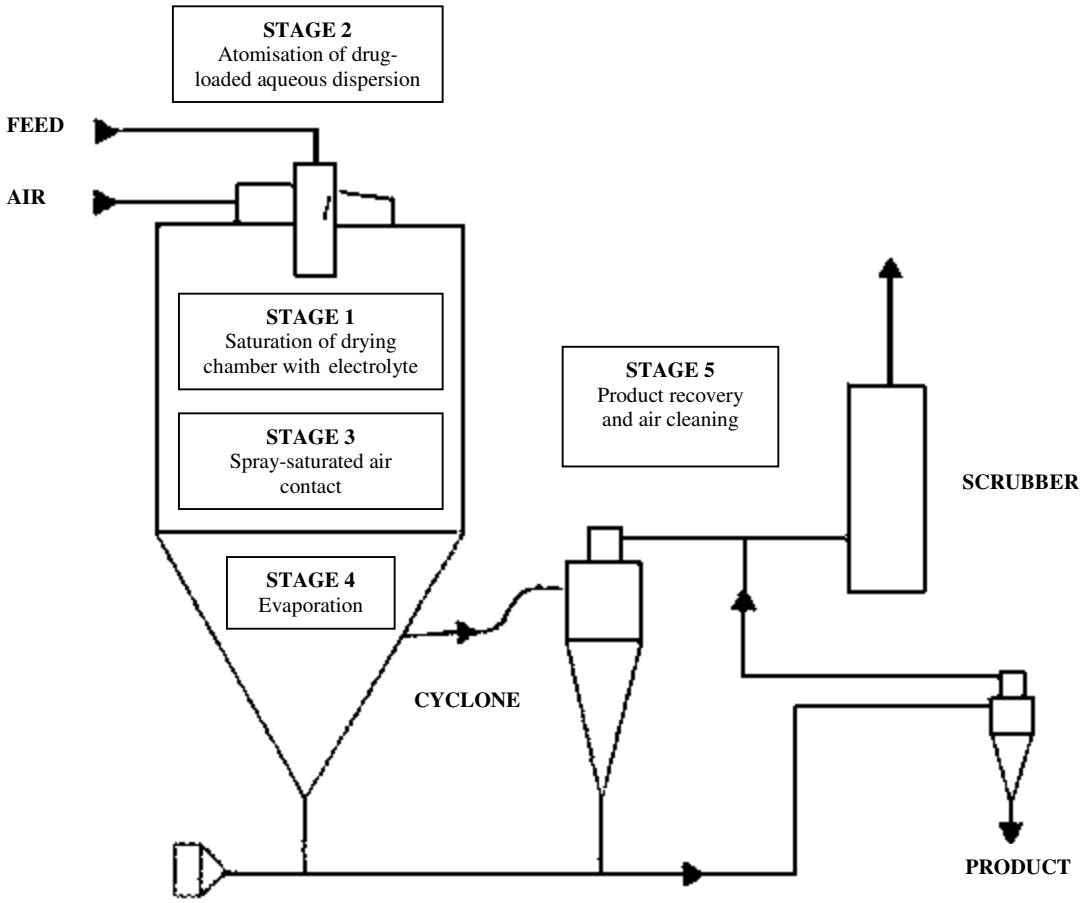

Figure 10.1: Spray-dryer configuration and process staging

The developed system technology may thus be pivotally applied to various disease therapies calling for FDC treatments of two or more drugs, where one or more drugs would benefit from small intestinal delivery, such as antiretrovirals (ARVs) for AIDS chemotherapy and concomittantly prescribed therapies for opportunistic infections. For example, certain ARVs, such as didanosine, are degraded by an acidic pH; and certain adjunctive AIDS therapies (e.g. probenicid) are implicated in gastric irritation. Segregated drug delivery may also be successfully implemented where oral coadministration of ARVs negatively impacts on bioavailability (e.g. indinavir and didanosine, and didanosine and fluoroquinolone and tetracycline antibiotics), which currently necessitates separation of doses by at least 1 hour. Development of an effective

compliance-enhancing combination of the existing cocktail of ARVs, which is easy to administer, is significant, especially in lieu of the high incidence of oral and oesophageal ulceration in these patients.

Although not a defined objective of this research, *in vivo* studies need to be performed in future. *In vitro* release testing under simulated conditions is significant in characterising drug release from the novel form, however, such tests cannot wholly simulate *in vivo* conditions with special reference to the wide intra- and inter-patient variability in GI conditions. *In vivo* release studies are imperative to define pharmacokinetic parameters and to foster an *in vitro/in vivo* correlation. *In vivo* animal studies are followed by stringently controlled human trials.

Clinical realisation of the newly developed drug delivery systems following this basic research phase for identification of a credible candidate formulation requires controlled manufacture and controlled clinical trials (to ensure safety) and ultimately dictates a minimum timeline of ~10 years.

The attainment of research objectives and the continual need for novel oral systems to promote patient adherence, especially in a disease where drug resistance is rife, makes patenting of the developed drug delivery system followed by licensing of the product to a South African pharmaceutical company a viable progressive step. The system was formulated using a limited number of widely available materials to derive maximum benefit, with minimal processing steps or harsh procedures. Growth of the South African economy resulting from the marketing of a viable delivery system is inexorable.