Resistance is Futile

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GENERAL INTRODUCTION

1.1 INTRODUCTION

In the last few decades, the emergence of pathogens resistant to antibiotic treatment has escalated dramatically [1]. This is no different for *Mycobacterium tuberculosis*, the cause of the predominantly pulmonary disease tuberculosis (TB). Drug-resistant TB has progressed to such an extent that in some eastern European countries, up to half of the new cases of TB are of the multidrug-resistant variety [2]. Multi-drug resistant TB – defined as resistance to the two most powerful first line drugs isoniazid and rifampicin – is a daunting perspective for TB patients. Treatment is more toxic than with first-line drugs [3], treatment duration is much increased [4], and outcome is worse, if not uncertain [5]. Drug resistance is the result of genetic changes in the genome of *Mycobacterium tuberculosis*, resulting in an increase of the minimal inhibitory concentration (MIC) for that particular drug, to a level that with systemic drug exposure, such MIC is no longer attainable; in order to be effective, dosing would need to be increased to an intolerably high systemic drug exposure, as systemic toxicity would ensue.

A way to circumvent the challenge of systemic toxicity would be to target the delivery of antibiotics locally, to the site of infection [6]. This may result in higher local concentrations of a particular drug, surpassing the MIC of that drug, while limiting systemic drug exposure. If systemic exposure is limited for topically delivered drugs, the administered dose might even be further increased [7].

TB is predominantly a pulmonary disease [8], and using the pulmonary route for the targeted delivery of antibiotics would be an asset. An additional advantage is that for some antibiotics, only injectable forms are available [9]. If these drugs could be administered

via inhalation, this would likely improve the tolerability of the treatment.

So far, pulmonary administration has been used widely in asthma and COPD [10]. The drugs used in these diseases are potent, and therefore require low doses. Many formulation techniques and inhalers have been developed with these low doses in mind. For such drugs, high fractions of excipients are used to mask the physicochemical properties of the drug in question [11,12]. As antibiotics are low-potency drugs, requiring high doses, these techniques are unsuitable [7]. As a result, it is a challenge to formulate these drugs into a suitable product.

In this thesis the challenges of delivering high dose drugs via the pulmonary route are described, and new techniques are explored to meet these challenges. These steps are a prerequisite to facilitate the successful formulation of antibiotics for pulmonary administration for the treatment of TB.

1.2 OUTLINE OF THIS THESIS

In this thesis, multiple aspects of the pulmonary administration of high dose dry powders are described. This is done from a pharmaceutical technology point of view.

In **Chapter 2**, the challenges of pulmonary delivery of high doses are described. First, an explanation is given as to why dry powder inhalers are likely the most suitable for the delivery of high doses. Then, to facilitate discussion, a definition of what exactly constitutes a high dose is given in the purview of dry powder pulmonary administration. The differences between high and low doses are then discussed and the challenges of formulating high doses are described. Lastly, possible

ways to meet these challenges are discussed.

The first steps to formulate isoniazid are described in **Chapter 3**. Isoniazid is an antibiotic used in the first line treatment of TB. Isoniazid is physiochemically characterized, after which this information is used in the following formulation steps. Two formulation techniques discussed in Chapter 2 are used. Jet-milling, which has been the cornerstone in formulating dry powders for pulmonary administration for many years, and spray-drying, which enables rational particle engineering. Both techniques are tested with different conditions and with no to a limited amount of excipient. The resulting products are characterized to find the most optimum formulation, albeit without regarding longer term stability of the formulations.

The most optimum formulation of Chapter 3 is further optimized with regards to its stability in **Chapter 4**. The coating applied during spray-drying, found to be necessary in Chapter 3, is further characterized in this chapter. It was hypothesized that the poor stability previously seen is a result of a suboptimal coating. Thus, we aimed to improve the stability by improving this coating. The excipient content, the type of excipient used, and the spray-drying conditions were optimized. With the resulting products a stability study was performed. An optimal formulation was found, which could be stored at 75% RH for at least three months without deteriorating. It was furthermore determined that this formulation worked best when coupled with the Cyclops® inhaler.

Chapter 5 describes the next step in the process of developing any successful product, which is the upscaling of production. Automatic filling of low dose dry powder formulations in inhalers has

been extensively investigated. However, to the authors knowledge, no literature is available that describes the automatic filling of high dose low potent drugs which contain no to a small amount of excipient. In this chapter, two high dose formulations are automatically filled with the Omnidose powder filling machine. The formulations used are the stable isoniazid formulation developed in Chapter 4, and an amikacin formulation. Amikacin is also an antibiotic used in the treatment of TB. The precision and accuracy of automatic filling of the isoniazid and amikacin formulations is determined after which the influence of automatic filling on the dispersion behavior of these products is studied.

In **Chapter 6** the optimization of an amikacin immunoassay is described. An amikacin product was formulated and a clinical study is in preparation. As serum concentrations are likely lower after the pulmonary administration of amikacin compared to an IV injection, it was deemed necessary to optimize the used immunoassay for lower concentrations. The volumes for the sample and the two reagents were changed, after which the assay was calibrated and the lower limit of quantification was determined. The calibrated assay was then validated for accuracy and precision.

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