Drug Delivery Systems for Tuberculosis Prevention and Treatment

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Drug Delivery Systems for Tuberculosis Prevention and Treatment

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Foreword

"As a physician, I have seen how much pain TB patients experience after months of treatment by intramuscular injection (IM). It is almost impossible to inject by IM after one month. I think that aerosol delivery is the future for TB drug delivery because it is directly delivered to the target organ, and it is even more important for patients who have a hard time to take pills. I believe that aerosol delivery of TB drug(s) will be a milestone in TB treatment if successful." Li Liang, Vice Director Beijing Chest Hospital

Having plagued societies for centuries, tuberculosis (TB) is one of the oldest diseases known to man. While the first drug effective against TB was not developed until 1943, over the next three decades many additional anti-TB drugs were discovered and developed that significantly reduced morbidity and mortality. Yet today it is estimated that one-third of the world's population is infected with *Mycobacterium tuberculosis*. The most recent World Health Organization's report indicated that TB killed 1.5 million people in 2014, making it a larger cause of death than HIV/AIDS, which was responsible for 1.2 million deaths. Thus, despite the perception that tuberculosis is a disease of the past or a disease of only low-income countries, it remains a major global public health challenge that carries significant global and domestic disease burdens and risks. Because serious societal challenges remain, including extreme poverty, inequity, and disproportionate TB burdens in women and children, TB will remain a significant challenge for the foreseeable future. Furthermore, the face of TB is changing. While global numbers of new TB cases and TB deaths have decreased at an average rate of at least 2 percent per year, TB strains that are resistant to the most commonly used, inexpensive, and least-toxic TB drugs have been identified in almost every country. These *multidrug-resistant TB* (MDR-TB) strains as well as the growing numbers of the even more serious *extensively drug-resistant TB* (XDR-TB) strains have been reported from nearly all countries. MDR-TB and XDR-TB cases can be exceedingly difficult and expensive to diagnose and treat successfully.

One of the major barriers to treatment of MDR-TB today is the high cost of second-line drugs that may be 300 to 3000 times more expensive than first-line therapy. Second-line regimens which are administered for between 18 to 24 months are associated with significant adverse events that often lead to discontinuation of treatment. Despite prolonged treatment duration, these regimens are not associated with high cure rates and incomplete, sub-optimal therapy of MDR-TB likely contributes to emergence of XDR-TB. In the face of *M. tuberculosis* strains resistant to all known classes of anti-TB drugs, leaders in global public health are asking whether XDR-TB is signaling a return to a pre-antibiotic era in TB control. Thus the need for new TB drugs has never been more urgent. Importantly, the search for new regimens and alternative strategies requires a thorough understanding of the preparation and performance of dosage forms.

Recent important gains in TB discovery research, product development, and implementation science and regulatory approval of the first new TB drug in 30 years give reason for optimism. Systematic studies of the biological effects of TB infection are beginning to shed light on the complexity of the human immune response and the dynamic nature of the disease process. As the disease becomes better understood in terms of both pathogen and host molecular biology there is an opportunity for new pharmaceutical approaches based on the route and means of delivery of a range of novel therapeutic agents. New studies are identifying molecules that can be used to diagnose TB or provide the basis of new TB vaccine research strategies, as well as critical biological processes against which new drug targets can be identified. Indeed the current global TB pipeline has multiple candidates in clinical trials – but there are few novel molecular entities. Many more candidates with novel mechanisms of action and chemical diversity are needed to overcome historical drug development attrition rates and emergence of resistance.

In the past, natural products have played a pivotal role in antibiotic drug discovery with most antibacterial drugs being derived from a natural product or natural product lead. A key challenge in the development of natural products as drugs is to combine their inherent antibacterial properties with physicochemical properties that confer oral bioavailability, an attribute that is highly desirable for treatment of MDR-TB. Many drugs are lost to development due to lack of oral bioavailability. However, new approaches to TB drug delivery as described in the current volume have the potential to overcome this barrier. New developments in drug delivery systems and technologies open an exciting avenue that may potentially lead to the repurposing of old drugs and re-evaluation of potential new drugs hitherto thought undeliverable.

Finally, while BCG vaccine remains the world's most widely used vaccine and protects children against disseminated TB and meningitis, its effectiveness in preventing disease in adults varies widely. New candidate vaccines are being developed that provide protection against disease and possibly infection in animal models. Since the battle between the pathogen and immune response in TB is fought out largely in the lung, it will be essential both to understand protective immune responses in the lung and how to deliver new vaccine candidates to generate protection in the lung. This is another of the key issues in TB treated in this book.

This is a timely volume addressing the application of pharmaceutical sciences and dosage-form design to the development of novel strategies for TB therapy. This volume is arranged to consider the nature of disease, immunological responses, vaccine and drug

delivery, disposition and response. In addition to conventional treatments some novel approaches are presented that if successful would create rapid development pathways. The contributors are drawn from the relevant fields of microbiology, immunology, molecular biology, pharmaceutics, pharmacokinetics, and chemical and mechanical engineering. No doubt the knowledge shared by the authors will have a major impact upon development of urgently needed new tools to address the continuing global crisis of TB and the increasing threat of drug-resistant strains.

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Advances in Pharmaceutical Technology: Series Preface

The series *Advances in Pharmaceutical Technology* covers the principles, methods and technologies that the pharmaceutical industry uses to turn a candidate molecule or new chemical entity into a final drug form and hence a new medicine. The series will explore means of optimizing the therapeutic performance of a drug molecule by designing and manufacturing the best and most innovative of new formulations. The processes associated with the testing of new drugs, the key steps involved in the clinical trials process and the most recent approaches utilized in the manufacture of new medicinal products will all be reported. The focus of the series will very much be on new and emerging technologies and the latest methods used in the drug-development process.

The topics covered by the series include the following:

Formulation: The manufacture of tablets in all forms (caplets, dispersible, fast-melting) will be described, as will capsules, suppositories, solutions, suspensions and emulsions, aerosols and sprays, injections, powders, ointments and creams, sustained release and the latest transdermal products. The developments in engineering associated with fluid, powder and solids handling, solubility enhancement and colloidal systems, including the stability of emulsions and suspensions, will also be reported within the series. The influence of formulation design on the bioavailability of a drug will be discussed and the importance of formulation with respect to the development of an optimal final new medicinal product will be clearly illustrated.

Drug Delivery: The use of various excipients and their role in drug delivery will be reviewed. Amongst the topics to be reported and discussed will be a critical appraisal of the current range of modified-release dosage forms currently in use and also those under development. The design and mechanism(s) of controlled-release systems including macromolecular drug delivery, microparticulate-controlled drug delivery, the delivery of biopharmaceuticals, delivery vehicles created for gastrointestinal tract-targeted delivery, transdermal delivery and systems designed specifically for drug delivery to the lung will

all be reviewed and critically appraised. Further site-specific systems used for the delivery of drugs across the blood–brain barrier including dendrimers, hydrogels and new innovative biomaterials will be reported.

Manufacturing: The key elements of the manufacturing steps involved in the production of new medicines will be explored in this series. The importance of crystallization; batch and continuous processing; seeding; and mixing including a description of the key engineering principles relevant to the manufacture of new medicines will all be reviewed and reported. The fundamental processes of quality control including good laboratory practice, good manufacturing practice, Quality by Design, the Deming Cycle, Regulatory requirements and the design of appropriate robust statistical sampling procedures for the control of raw materials will all be an integral part of this book series.

An evaluation of the current analytical methods used to determine drug stability, as well as the quantitative identification of impurities, contaminants and adulterants in pharmaceutical materials will be described, as will the production of therapeutic bio-macromolecules, bacteria, viruses, yeasts, moulds, prions and toxins through chemical synthesis and emerging synthetic/molecular biology techniques. The importance of packaging including the compatibility of materials in contact with drug products and their barrier properties will also be explored.

Advances in Pharmaceutical Technology is intended as a comprehensive one-stop shop for those interested in the development and manufacture of new medicines. The series will appeal to those working in the pharmaceutical and related industries, both large and small, and will also be valuable to those who are studying and learning about the drug-development process and the translation of those drugs into new life-saving and life-enriching medicines.

Dennis Douroumis
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Vladimir Torchilin

Preface

Tuberculosis remains the world's most serious cause of disease due to a single infectious micro-organism. Despite the development of a vaccine almost a century ago and with the advent of drug treatment in the intervening period we appear to be no closer to eradicating this disease. New vaccine antigens and novel drugs have been the major focus in prevention and treatment of tuberculosis. While great effort has been expended and progress has been made in drug therapy it has occurred at a remarkably slow pace. Indeed, the challenges posed by multiple and extensively drug-resistant disease and co-infection with human immuno-deficiency virus have rendered the need for novel approaches urgent.

As the disease becomes better understood in terms of both pathogen and host molecular biology there is an opportunity for new pharmaceutical approaches based on the route and means of delivery of a range of novel therapeutic agents.

This volume is arranged to consider the nature of disease, immunological responses, vaccine and drug delivery, disposition and response. In addition to conventional treatments some novel approaches are presented that, if successful, would create rapid development pathways. The contributors are drawn from the relevant fields of microbiology, immunology, molecular biology, pharmaceutics, pharmacokinetics, and chemical and mechanical engineering.

The role of therapeutic targeting strategy, dosage-form design and route of administration in the effective treatment of tuberculosis has been a topic of personal interest that we have shared for approaching twenty years and it is our privilege to be able to bring current thinking on a range of topics into one volume. We owe a great deal to our friends and colleagues most of whom are authors of chapters in this volume who attended the meetings on 'Inhaled Tuberculosis Therapy' held in New Delhi and Tokyo in 2009 and 2013, respectively. Without their insight, enthusiasm and encouragement we would not have been able to complete this text.

It has been a great pleasure working with the staff at Wiley on the preparation of the book and we are particularly grateful for the contributions of Samanaa Srinivas, Emma Strickland and Rebecca Stubbs. Many thanks for their patience and accommodation throughout the process.

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July 2016

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Introduction: A Guide to Treatment and Prevention of Tuberculosis Based on Principles of Dosage Form Design and Delivery

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1.1 Background

Tuberculosis has been a scourge of mankind for millennia. The discovery by Koch of the causative organism *Mycobacterium tuberculosis* at the end of the nineteenth century was hailed as the discovery that would rapidly lead to its eradication [1]. Despite the speed of development of a vaccine, attenuated *Mycobacterium bovis* (bacille Calmette Guerin), and the discovery of a therapeutic drug within only a few decades, circumstances that could not have been foreseen with respect to new strains, multiple-drug resistance and co-infection with human immunodeficiency virus, have rendered the disease a more complicated challenge than originally envisaged.

As the twentieth century progressed physicians were horrified to discover that the vaccine was not universally protective and that resistance to the drug of choice, streptomycin, was increasing rapidly [2]. These observations led to further activities in both the realm of vaccine and drug development, the latter being the more clinically successful but the former yielding much need information on the pathogen, the host immunity and pathogenesis of disease.

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During this period pharmacy and pharmaceutical dosage form design were also entering a golden age. Manufacturing of drug products or compounding, which was traditionally an activity that took place in a pharmacy, was transferred to an industrial setting. Commercial products involving a variety of dosage form were being standardized to allow production on a scale previously unknown. The introduction of legislation regulating the quality of products, particularly to address adulteration and ensure safety, commenced most notably in the 1930s with the Food Drug and Cosmetics Act of the United States [3]. In the latter half of the twentieth century the underlying physical chemistry and chemical engineering required to manufacture under rigorously controlled conditions that ensured the quality, uniformity, efficacy and safety of the product were developed.

With this background it is noteworthy that the parallel developments in dosage form and tuberculosis (TB) treatment led to their convergence in the early part of the twentieth century when reproducible drug delivery could only be achieved by oral administration (tablets and capsules) or parenteral administration (injection). As a consequence, other routes and means of delivery were rarely, if ever, considered for the delivery of drugs or vaccines. This can be contrasted with the products of biotechnology developed in the late twentieth century for which both oral and parenteral administration were rarely feasible. Of course, the ease of delivery and the required dose were the leading reasons for the selection of these routes of administration.

There was a brief period in the middle of the twentieth century when the absence of new drugs and the increase in drug resistance led to studies of inhaled therapy for tuberculosis but the development of new drugs resulted in this approach being abandoned and only revisited during times when there were no apparent oral and parenteral dosage forms to meet the immediate challenge. Figure 1.1 presents the number of publications that can be found in the accessible literature for the period since the initial rise in drug-resistant tuberculosis in the 1940s. A subsequent peak appears following the rise in human immunodeficiency virus co-infected patients and multiple-drug-resistant tuberculosis requiring alternative therapeutic strategies.

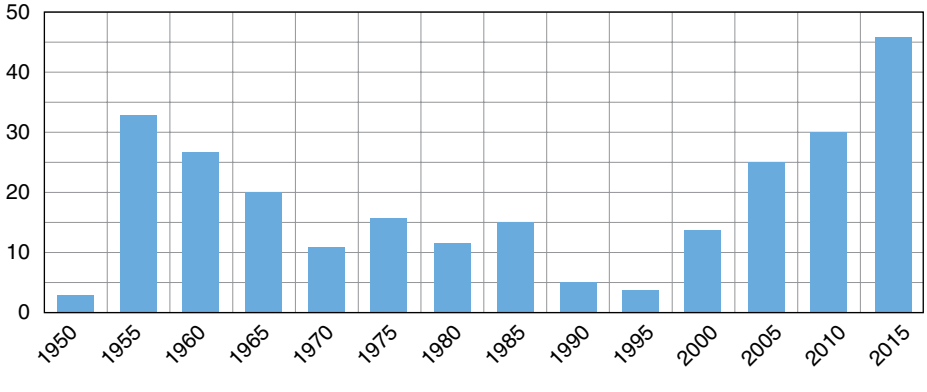

Figure 1.1 *Reports of Aerosol Delivery Extracted from PubMed from the earliest citations in the modern literature*

1.2 Dosage Form Classification

The route of administration by which drugs are delivered dictates the dosage form employed. The United States Pharmacopeia has classified therapeutic products in terms of three tiers: route of administration, dosage forms and performance test which captures all conventional and most novel strategies for disease treatment as shown in Figure 1.2 [4]. The performance measure of significance for the majority of dosage forms is the dissolution rate which, together with the biological parameter of permeability for those drugs presented at mucosal sites, dictates the appearance of the drug in the systemic circulation and ultimately its therapeutic effect.

1.2.1 Dosage Forms

It would not be possible to do justice to the science and technology underpinning the wide range of dosage forms available for drug delivery. However, to put those used in the treatment and prevention of tuberculosis in context a brief review of the key components and processes involved may be helpful to the reader.

1.2.1.1 Solid Oral Dosage Forms

These consist of a mixture of powders each of which is intended to confer a desirable property on the dosage form that leads to effective manufacture, drug delivery and therapeutic effect [5, 6].

In addition to the drug substance which must be well characterized, glidants help the powder flow which aids in filling, surfactants enhance dissolution and diluents are considered inert bulking agents that assist in metering small quantities of drug during filling and may help in compaction. Binding agents, as the name suggests, help in binding all components into a granule or tablet to preserve the integrity of the dosage form on storage and

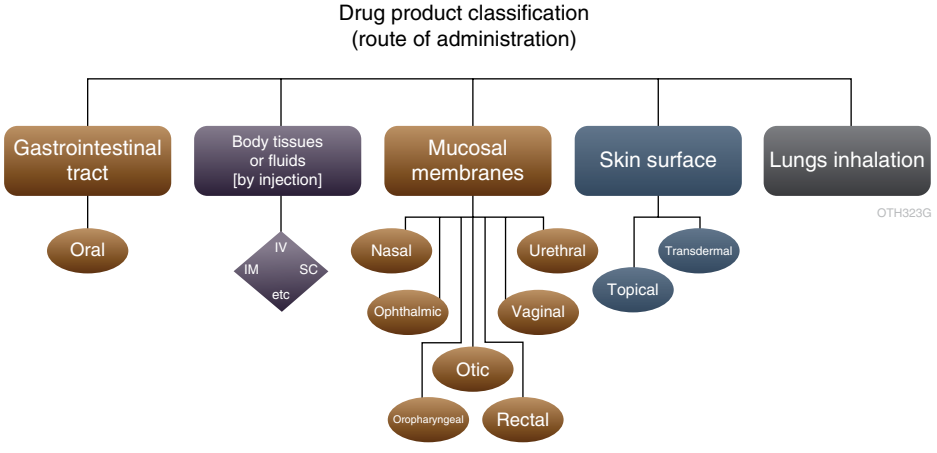

Figure 1.2 *United States Pharmacopeia Taxonomy of Dosage Forms structured from: Tier 1 – Route of Administration; through Tier 2 – Dosage Form to; Tier 3 – Performance (not shown). (Modified from ref. [4] Courtesy of Margareth Marques and the USP)*

prior to administration. The common dosage forms are capsules and tablets that differ in that the former consists of a powder or granulated loose fill while the latter requires compaction [5, 6]. The most common capsule is prepared with gelatin and filled with the optimized formulation of drug in excipients to allow for stability on storage and reproducible and efficacious dose delivery. Tablets also contain the drug and excipient compacted into a single solid dosage form that has desired performance properties in terms of stability, dissolution, dose delivery and efficacy. Biopharmaceutical considerations are of great significance to the disposition of drugs from solid oral dosage forms. Their behavior under the wide range of pH conditions (1–8) in the gastro-intestinal tract and an understanding of the influence of anatomy and physiology on local residence time and regions of absorption are significant considerations in optimization of the dosage form. Relatively recently the publication of Lipinski's rules [7] and the biopharmaceutical classification system [8] have been an enormous help in the selection of drugs and requirements of formulations that correlate with successful drug delivery by the oral route of administration.

1.2.1.2 Parenteral Dosage Forms

These are intended for injection either directly into the blood circulation [intravenous (IV)] or at a site from which the drug can readily be transported to the vasculature as would occur following subcutaneous or intramuscular administration [9]. There are other infrequently employed (intraperitoneal) or specialized (intrathecal or intratumoral) sites of injection that are not relevant to tuberculosis therapy. The key elements of a parenteral dosage form are the requirement for a formulation suitable for delivery from a syringe through a needle to the intended site. The formulation can range from simple solutions to a variety of dispersed systems (emulsions, micelles, liposomes and solid suspensions). Important physico-chemical properties must be considered to avoid local tissue damage on injection. Primarily these relate to the requirement to approximate physiological pH and ionic strength (tonicity) [10]. However, there are other safety considerations for injectable dispersed systems that relate to physical obstruction of capillaries (embolism), as well as uptake by the reticulo-endothelial system (inflammation, irritation or immune responses) [11]. The composition of any excipients, carrier systems and the nature of the injected active ingredient will dictate expectations of any of these responses.

1.2.1.3 Inhaled Dosage Forms

These deliver droplets or particles to the pulmonary mucosa that are then distributed locally and transported to the systemic circulation by absorption. The most important criteria for the efficacy of inhaled therapeutics are the aerodynamic particle size distribution and the dose delivered. The particle size range that is targeted for efficient delivery of drug to the lungs is 1–5 μm [12]. The United States Pharmacopeia has described types of inhaled drug product. Of those shown in Figure 1.3 the most important aerosol products for the treatment of pulmonary disease fall into three categories: metered dose inhalers (MDIs), dry powder inhalers (DPIs), and nebulizer systems. MDIs employ high-vapor-pressure propellant to deliver rapidly evaporating droplets containing the active ingredient; dry powder inhalers deliver particles of drug alone or by the use of a carrier particle; and nebulizers deliver aqueous solutions or suspensions of the active ingredient [12]. It is important to note that the primary performance measures for aerosol systems are aerodynamic particle size distribution and delivered dose since these are determinants of the drug reaching the

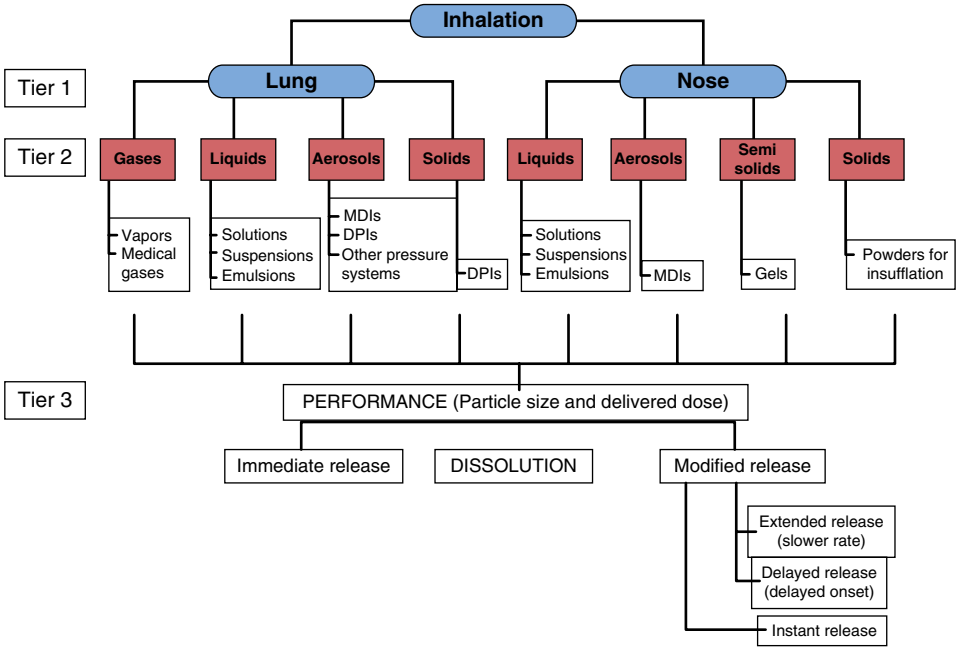

Figure 1.3 *Dosage forms intended for delivery of drugs to the respiratory tract divided according to the USP taxonomy of route of administration (tier 1), dosage form (tier 2) and performance measures (tier 3)(Modified from Ref. [4] Courtesy of Vinod Shah and the USP)*

mucosal site for action or absorption. Owing to the solubility, very small particle size and surface area of inhaled particles and droplets, dissolution is rarely the dominant factor in drug bioavailability. However, where the drug substance exhibits poor solubility or is prepared as a controlled release, dissolution is limited, and formulation dissolution rate will play an important role in location and extent of bioavailability.

Metered dose inhaler formulations are non-aqueous-based solutions or suspensions and in general are limited to delivering boluses of relatively low doses, rarely above a milligram. Dry powder inhalers in which carriers such as lactose particles are employed also deliver boluses of relatively low doses. However, the use of drug alone in engineered particles has increased the potential dose to 100 mg. Nebulizers do not deliver bolus doses, rather they deliver steady-state aerosols from a reservoir until the fixed volume has been depleted. The total dose delivered from these devices is only limited by the rate (liquid volume/time) and duration of delivery. Delivery for 15–20 minutes is commonly conducted, and precedent for the dose of antimicrobial agent has been set at several hundred milligrams.

1.3 Controlled and Targeted Delivery

In the mid-1980s the attention of some researchers turned to controlling the dissolution rate of orally administered drugs to treat tuberculosis by preparing polymeric microparticles [13, 14]. The intent was to more effectively deliver the drug and to potentially increase the duration of action by extending the period that circulating concentrations remained above

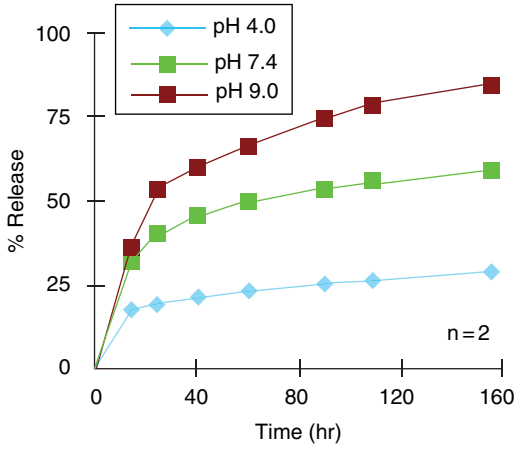

Figure 1.4 *Dissolution of 7.5% rifampicin in poly(lactide-co-glycolide) in three media of different pH values (4.0, 7.4 and 9.0) (Ref. [15])*

the minimum inhibitory concentration. Interestingly, when the dissolution profiles of rifampicin are examined as shown in Figure 1.4, the effect of pH, in the range of relevance to oral delivery, is to lower the dissolution rate and extent at lower pH. This raised the potential not only for controlled but also targeted delivery when particles of similar composition but in a respirable size range were delivered by inhalation. Aerosol particles that do not dissolve immediately when delivered to the lungs are phagocytosed by alveolar macrophages and the low pH (~5.0–5.5) in the endosome presents the opportunity for extended duration of delivery [15]. Therefore, the therapeutic effect will be enhanced in this location within the host cell for *Mycobacterium tuberculosis* [16, 17]. This observation has since launched a wide range of control and targeting strategies (nanoparticles, liposomes, micelles, etc.) for drug delivery to the lungs to treat tuberculosis [18]. The link to observations from oral delivery should not be forgotten. As more potent agents are developed and gastro-intestinal targeting strategies are informed by greater biological and biophysical understanding it is conceivable that lessons from pulmonary delivery can be translated into future options for oral dosage forms.

1.4 Physiological and Disease Considerations

Delivery of drugs by the oral route in tablets or capsules requires that the drug is absorbed and distributed from the gastro-intestinal tract to the systemic circulation where it can subsequently present to infected organs and tissues at concentrations sufficient (above the minimum inhibitory concentration) to treat the infection. The large volume of distribution for systemically circulating drugs currently in use for TB therapy usually requires large amounts of drug in order to achieve therapeutic concentrations. The need for multiple drug therapy for many months is a burden for patients and is seriously exacerbated in those with multiple or extensively drug-resistant disease where many more drugs are administered for even longer periods of time. Simply ingesting the large quantities of medicine required is

an ordeal. However, in principle oral delivery remains the simplest means of administration, the least invasive and most convenient approach for the patient, and requires no special storage or disposal requirements.

Parenteral administration by whichever route (commonly subcutaneous, intramuscular, intravenous) ensures the delivery of a controlled dose and as an invasive method circumvents the need for absorption by placing the drug either in or near the circulatory system. However, this approach is quite often painful for the patient and has additional storage and hazardous waste disposal requirements that are not required for other dosage forms.

Tuberculosis is contracted by pulmonary deposition of virulent organisms and the subsequent proliferation of disease from the lungs. The majority of individuals develop natural immunity that clearly originates at the pulmonary mucosa. Consequently, it is reasonable to propose that presentation of vaccines or drugs to this site will offer an advantage in disease prevention or therapy. Inhaled therapy has been well established through the administration of drugs to treat asthma and chronic obstructive pulmonary disease (COPD). More recently, the interest in treating other pulmonary infectious diseases has resulted in the approval of tobramycin to treat *Pseudomonas aeruginosa* in cases of cystic fibrosis [19]. Therefore, the precedent has been set for the delivery of doses of drug sufficient to treat local infection.

1.5 Therapeutic Considerations

When considering a route of administration several practical questions must be considered:

1. What is the target?
2. What dose is required for therapeutic effect?
3. What is the maximum tolerated or feasible dose?
4. Are there off-target effects?
5. Are there any drug interactions?
6. Are there any metabolic considerations?
7. Are there drug specific physico-chemical property limitations or advantages?

While there are many means and routes of administration it is generally accepted that for those drugs that are orally bioavailable following ingestion into the gastro-intestinal tract, tablets and capsules are a desirable dosage form. However, not every drug, disease and indication lends itself to oral delivery.

The diversity of geographical locations in which tuberculosis occurs does not support every route of administration equally under all circumstances. It is particularly notable that parenteral products require needles, syringes and, often, cold chain for transport and storage. These requirements add an additional level of complexity in distribution and maintenance of an adequate supply in remote or impoverished locations.

The advent of multiple and extensively drug-resistant disease and the conundrum of treatment that might be effective against latent or persistent disease has been the cause for exploring other routes and means of delivery of drugs, the most notable of which is aerosol therapy to the lungs.

In order to understand the role of the dosage form in effective disease treatment and prevention a range of considerations must be explored. The purpose of this volume is to

examine the pathogenesis of disease, animal models required to adequately assess new approaches, conventional and novel methods of preparing drugs and vaccines for delivery, testing strategies to evaluate the impact of any strategy, new considerations that might complement or disrupt the traditional approach to therapy (immunotherapeutics, biofilm busters, phage therapy) and finally anticipated clinical strategies. This will then serve the purpose of giving those involved in drug and vaccine development, dosage form design and delivery of therapeutic agents a foundation from which to consider the path to new and effective products.

1.6 Conclusion

Tuberculosis therapy and prevention has been driven by major discoveries in basic understanding of the disease, new drugs and potential new vaccines. However, the increase in multiple and extensively drug-resistant tuberculosis, HIV co-infection and absence of an approach to the treatment of latent and persistent disease still confounds our ability to control and ultimately eradicate this disease. The effectiveness of any drug or vaccine is only as good as the ability to deliver it in efficacious doses to the desired site of action which, in turn, is dictated by the nature of the dosage form, the delivery system and the disposition of the active agent following delivery. The intent of this volume is to consider the role that each of these elements plays currently, and explore future possibilities that arise from ongoing scientific and technological advances.

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Section 1

Pathogen and Host

2

Host Pathogen Biology for Airborne *Mycobacterium tuberculosis*: Cellular and Molecular Events in the Lung

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2.1 Introduction

Tuberculosis (TB), caused by the slow-growing, obligate human pathogen *Mycobacterium tuberculosis* (*M. tuberculosis*), has probably occurred in humans for a significant part of their history. Just exactly how long is a matter of debate, with differing dates suggested depending on the methodology and materials used. One study, based on whole genome sequences representing the diversity of *M. tuberculosis* across the planet [1], puts TB with humans since pre-history, some 70,000 years ago, subsequently moving with human populations out of Africa and across the globe. This would mean that TB only arrived in the Americas post-Columbus, and fits with the idea that *M. tuberculosis* first evolved to live in low-density hunter-gatherer populations where the chances of meeting a new host were low, making long-term, latent infections an evolutionary advantage. Another study [2] is based on mycobacterial DNA collected from Peruvian skeletons with evidence of TB dating from

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