1

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

A.J. Hickey

RTI International, RTP, NC, USA

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.

Drug Delivery Systems for Tuberculosis Prevention and Treatment, First Edition.
Edited by Anthony J. Hickey, Amit Misra and P. Bernard Fourie.

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.

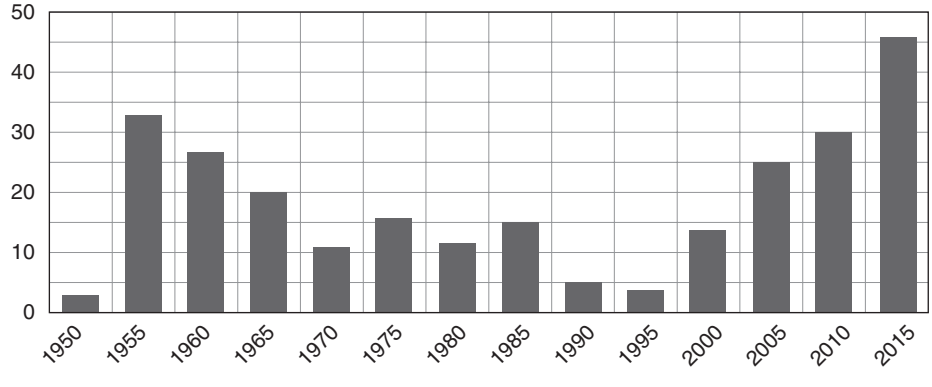

Figure 1.1 *Reports of Aerosol Delivery Extracted from PubMed from the earliest citations in the modern literature*

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

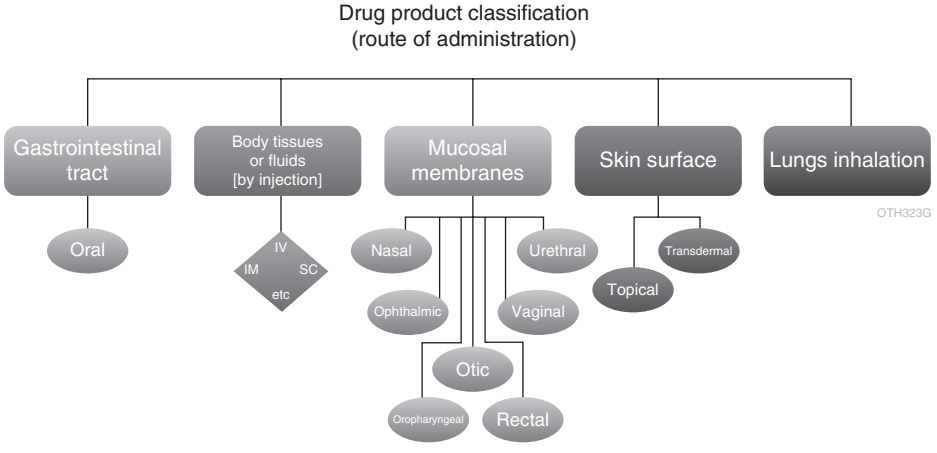

Figure 1.2 *United States Pharmacopeia Taxonomy of Dosage Forms structured from: Tier 1 – Route of Administration; through Tier 2 – Dosage Form to; Tier 3 – Performance (not shown). (Modified from ref. [4] Courtesy of Margareth Marques and the USP)*

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

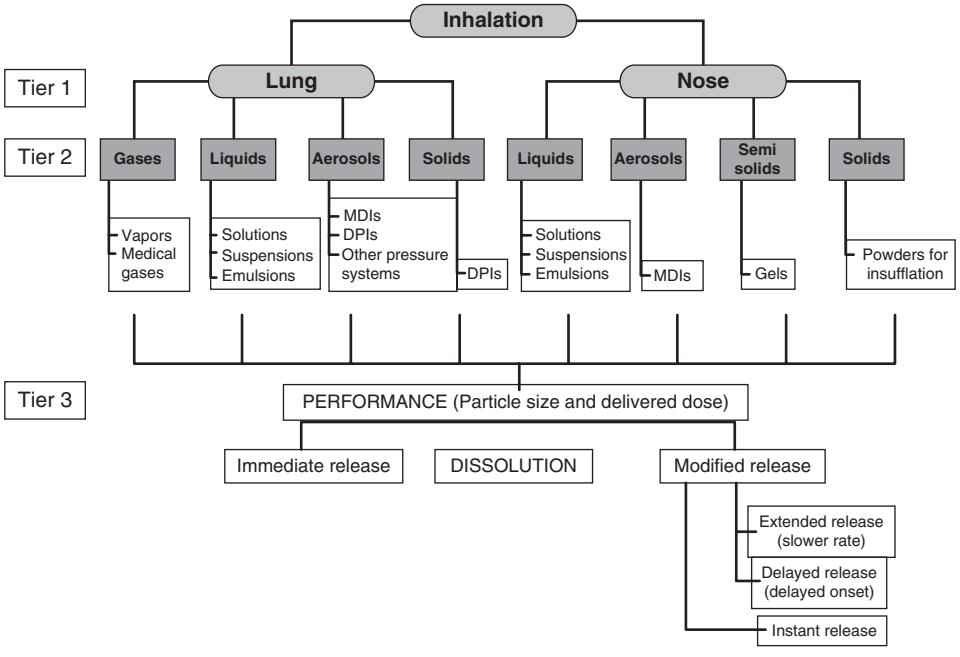

Figure 1.3 *Dosage forms intended for delivery of drugs to the respiratory tract divided according to the USP taxonomy of route of administration (tier 1), dosage form (tier 2) and performance measures (tier 3)(Modified from Ref. [4] Courtesy of Vinod Shah and the USP)*

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

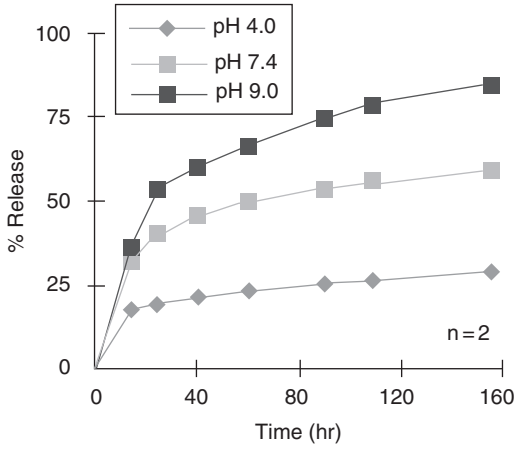

Figure 1.4 *Dissolution of 7.5% rifampicin in poly(lactide-co-glycolide) in three media of different pH values (4.0, 7.4 and 9.0) (Ref. [15])*

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.

References

[1] Sakula, A. (1983) Robert Koch: Centenary of the discovery of the tubercle bacillus (1882), *Can. Vet. J.*, **24**, 127–131.
[2] Hickey, A.J., Durham, P.G., Dharmadhikari, A. and Nardell, E.A. (2016), Inhaled drug treatment for tuberculosis: Past Progress and Future Prospects, *J. Controlled Release*, submitted.
[3] Federal Food, Drug and Cosmetics Act (1938) To prohibit the movement in interstate commerce of adulterated and misbranded food, drugs, devices, and cosmetics, and for other purposes.
[4] Marshall, K., Foster, T.S., Carlin, H.S. and Williams, R.L. (2003) Development of a compendial taxonomy and glossary for pharmaceutical dosage forms. *Pharm. Forum*, **29**, 1741–1752.
[5] Augsburger, L.L. (2002) Hard and Soft Shell capsules, in *Modern Pharmaceutics*, 4th edn (eds G. Banker and C. Rhodes), Marcel Dekker, New York, NY, pp. 335–380.
[6] Kottke, M.J. and Rudnik, E.M. (2002) Tablet dosage forms, in *Modern Pharmaceutics*, 4th edn, Marcel Dekker, New York, NY, pp. 287–333.
[7] Lipinski, C.A., Lombardo, F., Dominy, B.W. and Feeney, P.J. (2001) Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings, *Adv. Drug. Del. Rev.*, **46**, 3–26.
[8] Amidon, G.L., Lennernas, H., Shah, V.P. and Crison, J.R. (1995) A theoretical basis for a biopharmaceutical drug classification: the correlation of in vitro drug product dissolution and in vivo bioavailability, *Pharm. Res.*, **12**, 413–420.
[9] Boylan, J.J. and Nail, S.L. (2002) Parenteral Products, in *Modern Pharmaceutics*, 4th edn, Marcel Dekker, New York, NY, pp. 381–414.
[10] Martin, A. (1993) Non-electrolytes, electrolytes, ionic equilibria and buffers, in *Physical Pharmacy*, 4th edn, Lea and Febiger, Malvern, MA, pp. 101–189.
[11] Langille, S.L. (2013) Particulate matter in injectable drug products, *PDA J. Pharm. Sci. Technol.*, **67**, 186–200.

[12] Hickey, A.J. (2004) Summary of common approaches to pharmaceutical aerosol administration, in *Pharmaceutical Inhalation Aerosol Technology*, 2nd edn, (ed. A.J. Hickey), Marcel Dekker, New York, NY, pp. 385–421.
[13] Denkbas, E.B., Kaitan, X., Tuncel, A. and Piskin, E. (1995) Rifampicin-carrying poly (D,L-lactide) microspheres: Loading and release, *J. Biomater. Sci., Polym. Ed.*, **6**, 815–825.
[14] O'Hara, P., and Hickey, A.J. (2000) Respirable PLGA microspheres containing rifampicin for the treatment of tuberculosis: manufacture and characterization, *Pharm. Res.*, **17**, 955–961.
[15] Barrow, E.L., Winchester, G.A., Staas, J.K., Quenelle, D.C. and Barrow, W.W (1998) Use of microsphere technology for targeted delivery of rifampicin to Mycobacterium tuberculosis-infected macrophages, *Antimicrob. Agents Chemother.*, **42**, 2682–2689.
[16] Suarez, S., O'Hara, P., Kazantseva, M., Newcomer, C.E., Hopfer, R., McMurray, D.N. and Hickey, A.J. (2001) Airways delivery of rifampicin microparticles for the treatment of tuberculosis, *J. Antimicrob. Chemother.*, **48**, 431–434.
[17] Suarez, S., O'Hara, P., Kazantseva, M., Newcomer, C.E., Hopfer, R., McMurray, D.N. and Hickey, A.J. (2001) Respirable PLGA microspheres containing rifampicin for the treatment of tuberculosis: screening in an infectious disease model, *Pharm. Res.*, **18**, 1315–1319.
[18] Geller, D.E., Weers, J. and Heuerding, S. (2011) Development of an inhaled dry powder formulation of tobramycin using PulmoSphere™ technology. *J. Aerosol. Med. Pulm. Drug Deliv.*, **24**, 175–182.
[19] Mortensen, N.P., Durham, P. and Hickey, A.J. (2014) The role of particle physico-chemical properties in pulmonary drug delivery for tuberculosis therapy. *J Microencapsul.*, **31**, 785–795.