Drug Delivery Systems for Tuberculosis Prevention and Treatment
Drug Delivery Systems for Tuberculosis Prevention and Treatment
ADVANCES IN PHARMACEUTICAL TECHNOLOGY
A Wiley Book Series

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Contents

List of Contributors xvi
Foreword xviii
Series Preface xxi
Preface xxiii

1 Introduction: A Guide to Treatment and Prevention of Tuberculosis Based on Principles of Dosage Form Design and Delivery
A.J. Hickey 1

1.1 Background 1
1.2 Dosage Form Classification 3
  1.2.1 Dosage Forms 3
1.3 Controlled and Targeted Delivery 5
1.4 Physiological and Disease Considerations 6
1.5 Therapeutic Considerations 7
1.6 Conclusion 8
References 8

Section 1 Pathogen and Host 11

2 Host Pathogen Biology for Airborne Mycobacterium tuberculosis:
Cellular and Molecular Events in the Lung
Eusondia Arnett, Nitya Krishnan, Brian D. Robertson and Larry S. Schlesinger 13

2.1 Introduction 13
2.2 Lung 14
  2.2.1 Alveoli 16
  2.2.2 The Different Lung Macrophages 17
  2.2.3 Other Immune Cells in the Lung 17
4.4 Novel TB Vaccination Strategies 76
   4.4.1 Formulation and Stabilization Techniques 78
   4.4.2 Manufacturing of TB Vaccines 81
   4.4.3 Whole-Cell Vaccine 82
   4.4.4 Subunit Vaccines 83
   4.4.5 Regulatory Approval Process 83
   4.4.6 Vaccine Packaging 84
4.5 Future Perspective 84
4.6 Conclusions 85
References 85

5 TB Vaccine Assessment 91
André G. Loxton, Mary K. Hondalus and Samantha L. Sampson
5.1 Introduction 91
5.2 Preclinical Vaccine Assessment 92
   5.2.1 Murine Model 93
   5.2.2 Guinea Pig Model 94
   5.2.3 Cattle Model 94
   5.2.4 Non-human Primate Model 95
5.3 Clinical Assessment of Vaccines 97
   5.3.1 Human Clinical Trials and Phases of Testing 97
   5.3.2 Live Attenuated Vaccine Candidates 97
   5.3.3 Viral Vectored Subunit Vaccines 99
   5.3.4 Adjuvanted Subunit Vaccines 100
   5.3.5 Therapeutic Vaccines 101
   5.3.6 Route of Immunization 101
5.4 Laboratory Immunological Analysis and Assessment of Vaccine Trials 102
   5.4.1 Decision on Population of Interest 102
   5.4.2 Detection of Infection 102
   5.4.3 Detection of Protective Immunity 102
5.5 How well do the Available Preclinical Models Predict Vaccine Success in Humans? 103
References 105

Section 3 Drug Treatment 111

6 Testing Inhaled Drug Therapies for Treating Tuberculosis 113
Ellen F. Young, Anthony J. Hickey and Miriam Braunstein
6.1 Introduction 113
6.2 The Need for New Drug Treatments for Tuberculosis 114
6.3 Inhaled Drug Therapy for Tuberculosis 114
6.4 Published Studies of Inhalation Therapy for TB 115
6.5 The Guinea Pig Model for Testing Inhaled Therapies for TB 116
6.6 Guinea Pig Study Design 117
6.7 Purchase and Grouping Animals 118
6.8 Infecting Guinea Pigs with Virulent Mycobacterium tuberculosis 118
7 Preclinical Pharmacokinetics of Antitubercular Drugs

Mariam Ibrahim and Lucila Garcia-Contreras

7.1 Introduction 131
7.2 Factors Influencing the Pharmacokinetic Behavior of Drugs 132
  7.2.1 Physicochemical Properties of the Drug 132
  7.2.2 Formulation and Routes of Administration 137
  7.2.3 Disease State 138
7.3 Pulmonary Delivery of Anti-TB Drugs 138
7.4 Pharmacokinetic Study Design 140
  7.4.1 Animal Models 140
  7.4.2 Biological Samples 141
  7.4.3 Analytical Method 142
  7.4.4 Calculation of PK Parameters 142
7.5 Implications of PK Parameters on Efficacy 144
  7.5.1 Tissue Samples 144
  7.5.2 Pharmacokinetics of Anti-TB Drug in Granulomas 145
  7.5.3 PK/PD Correlations 146
7.6 Case Studies (Drugs Administered by Conventional and Pulmonary Routes) 146
  7.6.1 Rifampicin 146
  7.6.2 Capreomycin 151
References 152

8 Drug Particle Manufacture – Supercritical Fluid, High-Pressure Homogenization

Kimiko Makino and Hiroshi Terada

8.1 Introduction 156
8.2 Preparation of Nano- and Micro-particles 157
  8.2.1 Microparticles Prepared by a Supercritical Antisolvent–Drug Excipient Mixing (SAS–DEM) Technique 157
  8.2.2 Nanoparticles Prepared by a Supercritical Fluid (SCF) Technique 157
  8.2.3 Nanosuspension 158
  8.2.4 Liposomes 159
References 159
## 9 Spray Drying Strategies to Stop Tuberculosis
*Jennifer Wong, Maurizio Ricci and Hak-Kim Chan*

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>9.1 Introduction</td>
<td>161</td>
</tr>
<tr>
<td>9.2 Overview of Spray Drying</td>
<td>162</td>
</tr>
<tr>
<td>9.2.1 Advantages of Spray Drying</td>
<td>163</td>
</tr>
<tr>
<td>9.2.2 Hardware</td>
<td>163</td>
</tr>
<tr>
<td>9.2.3 Spray Dryer Classifications</td>
<td>168</td>
</tr>
<tr>
<td>9.2.4 Process Parameters</td>
<td>170</td>
</tr>
<tr>
<td>9.2.5 Particle Formation Mechanism</td>
<td>172</td>
</tr>
<tr>
<td>9.3 Advances in Spray Drying Technology</td>
<td>174</td>
</tr>
<tr>
<td>9.3.1 The ‘Quality by Design’ Approach</td>
<td>174</td>
</tr>
<tr>
<td>9.3.2 The Nano Spray Dryer B-90</td>
<td>175</td>
</tr>
<tr>
<td>9.3.3 Novel Multi-Channel Nozzles</td>
<td>177</td>
</tr>
<tr>
<td>9.4 Anti-Tuberculosis Therapeutics Produced by Spray Drying</td>
<td>179</td>
</tr>
<tr>
<td>9.4.1 Controlled-Release Microparticles</td>
<td>179</td>
</tr>
<tr>
<td>9.4.2 Maximal Drug-loaded Microparticles</td>
<td>184</td>
</tr>
<tr>
<td>9.4.3 Vaccines</td>
<td>186</td>
</tr>
<tr>
<td>9.5 Conclusion</td>
<td>187</td>
</tr>
<tr>
<td>9.6 Acknowledgements</td>
<td>187</td>
</tr>
<tr>
<td>References</td>
<td>187</td>
</tr>
</tbody>
</table>

## 10 Formulation Strategies for Antitubercular Drugs by Inhalation
*Francesca Buttini and Gaia Colombo*

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>10.1 Introduction</td>
<td>197</td>
</tr>
<tr>
<td>10.2 Lung Delivery of TB Drugs</td>
<td>198</td>
</tr>
<tr>
<td>10.3 Powders for Inhalation and Liquids for Nebulization</td>
<td>200</td>
</tr>
<tr>
<td>10.4 Antibacterial Powders for Inhalation: Manufacturing of Respirable Microparticles</td>
<td>202</td>
</tr>
<tr>
<td>10.5 Antibacterial Powders for Inhalation: Devices and Delivery Strategies</td>
<td>208</td>
</tr>
<tr>
<td>10.6 Conclusions and Perspectives</td>
<td>211</td>
</tr>
<tr>
<td>References</td>
<td>211</td>
</tr>
</tbody>
</table>

## 11 Inhaled Drug Combinations
*Sanketkumar Pandya, Anuradha Gupta, Rajeev Ranjan, Madhur Sachan, Atul Kumar Agrawal and Amit Misra*

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>11.1 Introduction</td>
<td>213</td>
</tr>
<tr>
<td>11.2 Standard Combinations in Oral and Parenteral Regimens</td>
<td>214</td>
</tr>
<tr>
<td>11.2.1 Combinations for the Directly Observed Treatment Short-Course (DOTS) Regimen</td>
<td>214</td>
</tr>
<tr>
<td>11.3 The Rationale for Inhaled Therapies of TB</td>
<td>216</td>
</tr>
<tr>
<td>11.3.1 Single Drug, Supplementing Other Orally Administered Drugs</td>
<td>218</td>
</tr>
<tr>
<td>11.3.2 Single Drug Replacing Injectable First- or Second-Line Agents</td>
<td>219</td>
</tr>
<tr>
<td>11.3.3 Multiple Inhaled Drugs, Adjunct or Stand-alone Therapy</td>
<td>220</td>
</tr>
<tr>
<td>11.3.4 “Stimulate the Phagocyte”</td>
<td>220</td>
</tr>
<tr>
<td>References</td>
<td>211</td>
</tr>
</tbody>
</table>
## Contents

11.4 Combinations of Anti-TB Drugs with Other Agents 222
  11.4.1 Drugs that Primarily Affect the Pathogen 222
  11.4.2 Drugs that Affect Host Responses 223
  11.4.3 Drugs that Affect both Host and Pathogen 224

11.5 Formulation of Inhaled Drug Combinations 224
  11.5.1 Excipient-free Formulations 224
  11.5.2 Applications of Excipients 225
  11.5.3 Preparing Multi-Component Particles and Vesicles 227
  11.5.4 Shelf Stability 227
  11.5.5 Drug Release and Pharmacokinetics 228
  11.5.6 Inhalation Dosimetry 229

11.6 Conclusions 230

References 230

12 Ion Pairing for Controlling Drug Delivery 239
  Stefano Giovagnoli, Aurélie Schoubben and Carlo Rossi
  12.1 Introduction 239
  12.2 Ion Pairing Definitions and Concepts 240
    12.2.1 Ion Pairing as Physicochemical Tuning Tool 241
    12.2.2 Metal Ion Complexation 242
    12.2.3 Some Considerations on Ion Pair and Metal Complex Stability 244
  12.3 Ion Pairs, Complexes and Drug Delivery 245
    12.3.1 Oral Route 245
    12.3.2 Transdermal/Dermal and Mucosal Route 246
    12.3.3 Parenteral Route 247
    12.3.4 The Pulmonary Route and Infectious Diseases 247
    12.3.5 Toxicity Considerations 248
  12.4 Remarks 252

References 254

13 Understanding the Respiratory Delivery of High Dose Anti-Tubercular Drugs 258
  Shyamal C. Das and Peter J. Stewart
  13.1 Introduction 258
  13.2 Tuberculosis 259
  13.3 Drugs Used to Treat Tuberculosis, Doses, Challenges and Requirements for Therapy in Lungs 260
    13.3.1 Current TB Treatment Regimen 260
    13.3.2 Challenges of Conventional Oral and Parenteral Therapy 261
    13.3.3 Rationale for Respiratory Delivery 261
  13.4 Approaches for Respiratory Delivery of Drugs 262
  13.5 Current DPI Formulations and Their Mechanisms of Aerosolization 262
  13.6 DPI Formulations for Tuberculosis and Requirements 264
  13.7 Issues to Consider in Respiratory Delivery of Powders for Tuberculosis 264
  13.8 Relationship between De-agglomeration and Tensile Strength 266
  13.9 Strategies to Improve De-agglomeration 268
13.10 DPI Formulations having High Aerosolization 269
13.11 Devices for High Dose Delivery 270
13.12 Future Considerations 271
References 272

Section 4 Alternative Approaches 275

14 Respirable Bacteriophage Aerosols for the Prevention and Treatment of Tuberculosis 277
Graham F. Hatfull and Reinhard Vehring
14.1 Introduction 277
14.1.1 Bacteriophages 277
14.1.2 Mycobacteriophages 280
14.1.3 Mycobacterium tuberculosis as a Host for Phage Infection in vivo 282
14.1.4 Mycobacteriophages and TB Diagnosis 282
14.2 Treatment or Prevention of Tuberculosis Using Phage-based Agents 282
14.2.1 Bacteriophages as Therapeutic Agents 282
14.2.2 Prospects for Using Mycobacteriophages for Therapy or TB Prevention 283
14.3 Selection of Mycobacteriophages 284
14.4 Respiratory Drug Delivery of Phages 285
14.5 Summary and Outlook 288
Acknowledgements 288
References 288

15 RNA Nanoparticles as Potential Vaccines 293
Robert DeLong
15.1 Introduction 293
15.2 Nanoparticles 293
15.3 RNA Nanoparticle Vaccines 294
15.4 Progression of Nanomedicines into the Clinic 295
15.5 The Stability Problem 295
15.6 The Delivery Problem 298
15.7 RNA as Targeting Agent or Adjuvant? 298
15.8 Challenges for RNA Nanoparticle Vaccine Characterization 300
15.9 On the Horizon 301
References 301

16 Local Pulmonary Host-Directed Therapies for Tuberculosis via Aerosol Delivery 307
Mercedes Gonzalez-Juarrero
16.1 Introduction 307
16.1.1 Tuberculosis Disease and Control 308
16.1.2 Chemotherapy and Host Immunity to Tuberculosis 308
16.1.3 Aerosol Delivery of Host-Directed Therapies for Tuberculosis Treatment 309
16.2 Lung Immunity to Pulmonary *M. tuberculosis* Infection 309
  16.2.1 Overview 309
  16.2.2 Influence of Lung Alveoli Environment on Bacilli Survival and its Impact on Tuberculosis Chemotherapy 310
  16.2.3 Potential Targets for Host-Directed Therapy 311
16.3 Host-Directed Therapies 313
  16.3.1 Previous Studies via Systemic Administration of Host-Directed Therapies 313
  16.3.2 Previous Studies via Aerosol Delivery of Host-Directed Therapies 315
16.4 Limitations of Preclinical Studies to Develop Inhalational Host-Directed Therapies for Tuberculosis 317
16.5 Preclinical Testing of Inhaled Small Interference RNA as Host-Directed Therapies for Tuberculosis 318
Acknowledgements 319
References 319

Section 5  Future Opportunities 325

17 Treatments for Mycobacterial Persistence and Biofilm Growth 327
  *David L. Hava and Jean C. Sung*
  17.1 Introduction 327
  17.2 Mycobacterial Persistence and Drug Tolerance 328
  17.3 Mycobacterial Multicellular Growth 329
  17.4 Mycobacterial Lipids Involved in Biofilm Formation 330
  17.5 Therapies to Treat Mycobacterial Biofilms and Persistence 332
    17.5.1 Therapies to Treat Mycobacterial Biofilms 332
    17.5.2 Therapies to Disrupt Nutrient Acquisition and Persistence 334
    17.5.3 Treatments for Biofilm Dispersion 335
    17.5.4 Treatments Derived from Host Innate Defenses 336
    17.5.5 Treatments with Inhaled Antibiotics 337
  17.6 Conclusion 339
References 339

18 Directed Intervention and Immunomodulation against Pulmonary Tuberculosis 346
  *Dominique N. Price and Pavan Muttil*
  18.1 Introduction 346
  18.2 TB Immunology 347
    18.2.1 Early Events of Infection 347
    18.2.2 Delayed Adaptive Immunity 348
    18.2.3 Humoral Immunity and Innate Lymphocytes 348
    18.2.4 Latent Infection 349
    18.2.5 Correlates of Protection and Tolerance 350
    18.2.6 Natural Immunity against TB Infection 351
## 18.3 Animal Models of Immunotherapies and Vaccines for TB

18.3.1 Mouse Model

18.3.2 Guinea Pig Model

18.3.3 Non-human Primates Model

## 18.4 The Current TB Vaccine – Bacille Calmette Guérin

18.4.1 BCG Vaccine History

18.4.2 Alternative Routes of BCG Delivery

18.4.3 Failures of BCG

## 18.5 Other Vaccines Platforms

18.5.1 Live Bacterial Vaccines

18.5.2 Inactivated Whole-cell Vaccines

18.5.3 Viral Vector-based TB Vaccines

18.5.4 Heterologous Prime-boost Vaccination Strategy in TB

## 18.6 Pulmonary Immunization

18.6.1 Biomimicry: Harnessing Natural Immunity for Protection against TB

18.6.2 Pulmonary Immunization for Global Protection

18.6.3 Safety Concerns for Pulmonary Immunization

18.6.4 Role of Adjuvants

18.6.5 Live vs Dead Vaccines

## 18.7 Immunotherapeutic Agents against TB

18.7.1 Cytokines

18.7.2 Vitamin D Therapy

18.7.3 Re-purposed Drugs

18.7.4 Stem Cell Therapy

## 18.8 Conclusion

References

### Section 6 Clinical Perspective

## 19 Clinical and Public Health Perspectives

*Ruvandhi R. Nathavitharana and Edward A. Nardell*

19.1 Introduction

19.2 Background

19.3 Clinical Considerations

19.3.1 Pill Burden and Fixed-dose Combinations

19.3.2 Non-adherence and Medication Monitoring

19.3.3 Intermittent Therapy

19.3.4 Drug Toxicity

19.3.5 Drug Absorption and Therapeutic Drug Monitoring

19.4 Public Health Considerations

19.4.1 DOTS

19.4.2 Community-based Therapy

19.4.3 Incentives and Enablers to Promote Adherence

19.5 Inhaled Drugs and Other Alternative Delivery Systems

19.5.1 Possible Advantages
Contents

19.5.2 Concerns and Limitations 388
19.5.3 Acceptance of Novel Therapies 388
19.6 Clinical Trials of Inhaled Injectable Drugs 388
  19.6.1 Capreomycin Phase 1 Clinical Study 390
  19.6.2 Inhaled Therapy to Reduce Transmission, especially of Highly
     Drug-resistant Strains – a Trial of Inhaled Colistin
     (or Polymyxin E) 391
19.7 Other Novel Delivery Strategies 393
19.8 Pediatric Delivery Systems 393
19.9 Conclusion 394
References 394

20 Concluding Remarks: Prospects and Challenges for Advancing
New Drug and Vaccine Delivery Systems into Clinical Application 400
P. Bernard Fourie and Richard Hafner
20.1 Introduction 400
20.2 Progress in the Formulation and Manufacturing of Drugs and Vaccines
   for Tuberculosis 401
   20.2.1 Inhaled Drugs and Drug Combinations 401
20.3 Considerations in the Development of TB Drug and Vaccine
   Delivery Options 404
   20.3.1 Lung Biology and Pulmonary Administration of Drugs
   and Vaccines 404
   20.3.2 Choice of Animal Model in the Evaluation of Drug
   and Vaccine Delivery Systems 405
   20.3.3 Demonstrating Bioequivalence and Clinical Efficacy of
   Inhaled Drugs to Oral/Parenteral Dosage Forms 406
   20.3.4 Inhaled Vaccines for TB – are there Potential Advantages? 408
   20.3.5 Safety of Pulmonary Vaccination 409
20.4 Concluding Remarks 410
References 411

Index 415
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“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
Alfred Fahr
Jürgen Siepmann
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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
1

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.
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](image-url)

**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

![Drug product classification (route of administration)](image)

*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 1–5μm [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