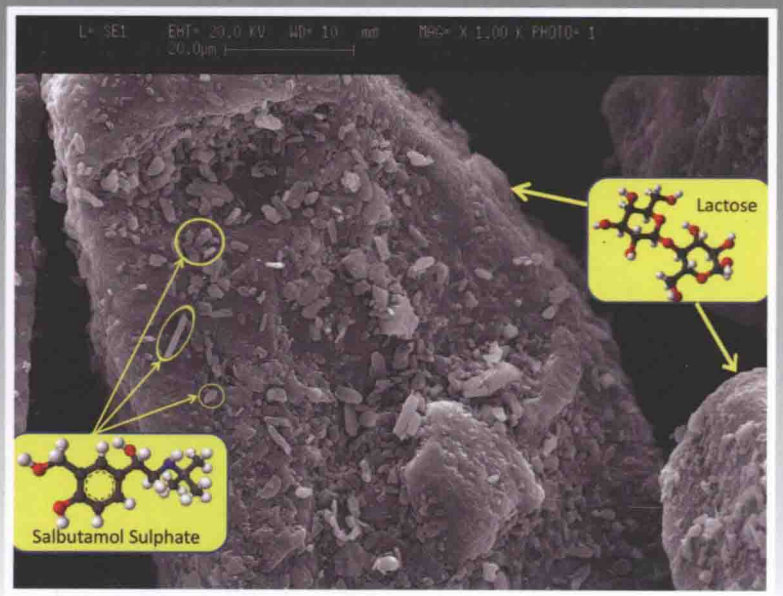
ADVANCES IN PHARMACEUTICAL TECHNOLOGY

Editors
Ali Nokhodchi
Gary P. Martin

Pulmonary Drug Delivery

Advances and Challenges



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Advances and Challenges

Edited by

ALI NOKHODCHI AND GARY P. MARTIN

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Pulmonary Drug Delivery

Advances in Pharmaceutical Technology

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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 use 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:

Formulation: The manufacture of tablets in all forms (caplets, dispersible, and 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, 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 gastro-intestinal 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; 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 (GLP), good manufacturing practice (GMP), quality by design (QbD), 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, 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, molds, 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
Juergen Siepmann
Martin Snowden
Vladimir Torchilin

Preface

One of the first axioms imparted to students interested in formulating drugs for human and animal administration is that a drug (or active pharmaceutical ingredient) itself does not comprise a medicine. The drug has first to be formulated into a medicine that can be ingested by the patient. The most popular medicinal form (both with patient and healthcare workers), easiest to take or administer, dose-reproducible, cheapest, most stable, and safest form is generally acknowledged to be the tablet. To achieve these desirable characteristics, a large number of excipients (or 'non-pharmacologically active' materials) have to be included. These could include, for example, fillers, lubricants, glidants, disintegrants, colours, coating agents, etc.

However the challenges of treating diseases, such as asthma, chronic obstructive pulmonary disease, cystic fibrosis, infections, tuberculosis, and lung cancer which involves the airways, render the tablet a less advantageous choice compared with the patient employing an inhaled formulation as a means of therapeutic management. This is because an inhaled drug can be delivered locally at a lower dose and hence with fewer side-effects compared to that taken via the gastrointestinal tract. In addition, it might appear initially that some of the formulation issues might be reduced because most inhaled formulations comprise either none or possibly only one or two excipients (in addition to the drug). However this tenet is clearly false. For example currently, over 40% of patients suffering from asthma and chronic obstructive pulmonary disease use dry powder inhaler (DPI) formulations and this number is expected to grow in the future; and despite extensive research on DPIs during the last 40 years, some of these formulations may only delivery 10–20% of the inspired drug to the lungs. A core requirement for the effective clinical management of such respiratory diseases often, therefore, depends on the efficient delivery of aerosolised drugs to the airways. For efficiency to be optimised prior to the innovation of a new medicinal aerosol, a closely integrated triumvirate of fundamental factors, namely the patient, the formulation and the device, have to be considered both individually and holistically in the development process. One of the first steps of a development process should be to define the product specifications which combine these three essential factors into a user-requirement specification. Such a specification must encompass an appreciation of the patient requirements, involving an understanding of the structure of the airways and the challenges of separate patient groups such as children and the elderly, and acknowledge the impact of disease (e.g. lung cancer) upon the delivery of the drug. To this end, the functional imaging of the airways might assist in improving pulmonary delivery. As regards the formulation of drugs for inhaled dosage forms, then the challenges are many and encompass the following: the methods by which the efficiency of delivery (and dissolution) of such medicines can be assessed *in vitro*; the strategies for formulating poorly soluble active agents; the development of novel macromolecular, micro- and nanoparticulate systems; and the techniques which are developed to assess satisfactory powder blending. The importance of understanding the physicochemistry (including surface roughness) of the so-called inactive excipients, such as lactose, in dry powder formulations and the manner in which these can be manipulated (by particle engineering) is often under-appreciated. However improvements in formulating the drug in powder or suspended form cannot be carried out without appreciating the capabilities of

the device in which it is to be both packaged and presented. The development of the aerosol medicine can then proceed according to quality by design approaches.

As editors, we have been privileged to gain the cooperation of leading expert scientists to contribute to this book, providing both an overview of their research knowledge and presenting first-hand experiences of medicine design. We believe that this proffers an accessible overview to this fast-moving and complex field, and provides the readers with a sound basis for understanding some of the key issues involved. We hope that it will inspire future scientific and technological endeavour to improve the formulation of inhaled dosage forms such that ultimately they will possess all the desirable characteristics of the tablet form (discussed earlier).

The book is written primarily for postgraduate (PhD/Masters) level for readers who require a fast-route basic understanding of the current key issues of pulmonary drug delivery formulation, including device design, powder and particle engineering, and patient considerations. This book is useful for pharmacy students at their final year, pharmaceutical sciences degree courses, postgraduate students working in the inhalation field and scientists working in the industrial sector.

Ali Nokhodchi
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