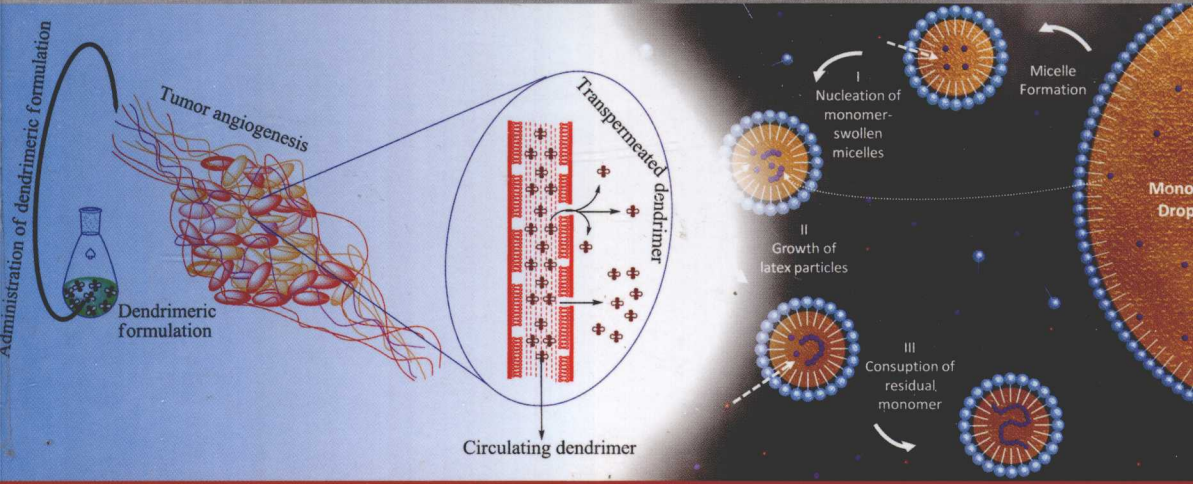


Drug Delivery Strategies for Poorly Water-Soluble Drugs

Editors

Dennis Douroumis and Alfred Fahr



Drug Delivery Strategies for Poorly Water-Soluble Drugs

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Excellence is an art won by training and habituation. We do not act rightly because we have virtue or excellence, but we rather have those because we have acted rightly. We are what we repeatedly do. Excellence, then, is not an act but a habit. (Aristotle, 384–322 BC)

This book is dedicated to my beloved mother Eugenia for her continuous support and unconditional love. It is also dedicated to my brother Bill and sister Angela for their support and patience. Thank you all.

Doubt grows with knowledge.
Johann Wolfgang von Goethe (1749–1832)

I thank my wife for her understanding for spending weekends in my home office for setting and polishing this book. I apologize to my children Fabian and Sophie that their dad was not ready on many weekends for playing and talking. I do hope, they will understand it in the near future somehow.

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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, 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. Among 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, 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
Martin Snowden

Preface

In former times, formulation specialists were not yet exposed to the many problems and subtleties that we face today in producing applicable drugs. In those ‘good old days’ the best drugs were simply generated using polar media, either by extraction from plants or by synthetic methods. Later, towards the end of the last century, an ever growing number of lipophilic drugs started to appear for oral as well as parenteral administration. Natural substances, like cyclosporine or modifications of aromatic structures that render selected drugs even more lipophilic, began to enter the vanguard of the blockbuster class. Stories about the difficulties of absorption in the gut or the bad pharmacokinetic profiles of these drugs have entered the body of canonical knowledge in many pharmaceutical companies. Desperate attempts to formulate these insoluble drugs – such as ‘encapsulating’ them in Swiss chocolate to get an oral delivery – are well remembered in the corresponding pharmacists’ clubs.

This situation has changed with the advent of the new millennium in two ways:

1. The percentage of new drug molecules that are insoluble in water has risen to about 40% in total; in various therapeutic areas this percentage has even reached 80–90%. Why is this so? Perhaps the best explanation is the invention of the so-called High ThroughPut Screening (HTPS) method. Here, a variety of substances are tested (for cases of more than 100,000 per day, the method is re-named ‘ultra-HTPS’) for their activity with regard to certain biochemical targets (alternatively a cell, organ, or organism). This often favors the selection of drugs with higher lipophilicity, as most target sites – for example, the active center of an enzyme or a membrane protein – tend to be more accessible to lipophilic drugs, which runs in parallel to non-solubility. Adding to the difficulties for a formulation specialist, oral bioavailability is not among the primary aims of the HTPS procedure.
2. Pharmaceutical scientists have responded to this challenge in the past few decades by developing a variety of formulation principles for these poorly water-soluble drugs. Insoluble drugs should be made dissolvable by physico-chemical or biological means (e.g. transfer to gut cell membranes (p.o.) or lipoproteins (i.v.)) in order to arrive at the pharmacological target in appreciable amounts.

Even though some advertisements of excipient producers do suggest this, there is no ultimate single solution for insoluble drugs (as evidenced by the variety of methods presented in this book). On the other hand, there is the old saying that if there is more than one solution for a problem, there is likely no solution at all.

Therefore, a pharmacist who has to design and develop a formulation for an insoluble drug has to be aware of all the characteristics of the drug, s/he also has to have a profound knowledge of the available and feasible formulation options. To this end, s/he is likely to end up studying the literature in depth, as there are few other resources available that provide comprehensive surveys written by the experts in the field. The present book tries to fill this gap.

The book begins with some theoretical considerations, thereby introducing and discussing basic concepts such as solubility and hydrophobicity, and also provides a modeling framework for nanocarriers and their interactions with drug and the environment (Chapter 1).

Several chapters (2, 3–6, 13, 14) show how cyclodextrins, dendrimers, micelles, liposomes, solid lipid nanoparticles, and polymeric systems can overcome the solubility problem for insoluble drugs by using carrier systems mostly intended for the parenteral route. The carrier systems may be composed of either complex single molecules as hosts (e.g. dendrimers) or an assembly of rather simple molecules (e.g. micelles), or a combination of both. The complex interplay between host and drug often plays a crucial role in the success of such formulations and is extensively discussed in the respective chapters, along with detailed production procedures.

Microemulsion technology serves both the parenteral and the oral administration route for insoluble drugs, as is demonstrated in Chapter 10. Upon the addition of water, anhydrous (micro)emulsions may spontaneously emulsify. This process is used to produce self-emulsifying drug delivery systems (SEDDS) that are mainly used for oral delivery; see the discussion in Chapter 7.

Another feasible approach to improving the solubility of orally administered drugs is the size reduction of solid-state particles, yielding a large specific surface area. In Chapters 8, 9, 16 and 17, the production of nano-sized particles is described, using several different approaches (milling techniques, nanocrystals, nanosuspensions, and spray drying). The amorphous state of, for example, spray-dried particles and nanosuspensions may increase the solubility further and this is discussed thoroughly in the respective chapters.

Hot melt extrusion (solid dispersion technology) is, like the other methods described here, already on the market and attracting ever more attention as a method to enhance the bioavailability of problematic drugs. This is thoroughly described in Chapter 11.

Mesoporous silica nanoparticles (Chapter 15) are an interesting experimental formulation for increasing the solubility of insoluble drugs – they hold promising potential for the future.

Finally, Chapter 12 demonstrates that skin delivery of highly insoluble drugs is equally as challenging as other administration routes.

The different methods described in this book share the underlying goal of improving the solubility and the dissolution rate of poorly water-soluble drugs. We wish to point out that, especially for colloidal systems, these methods can be combined with targeting approaches. Targeting constitutes a fast-growing research field in its own right; its inclusion was outside the scope of the present book.

The interested reader may notice that the chapters integrate with each other. This indeed is the intention of the book as it likely facilitates the decision on which method might be worth trying for a given formulation problem. We emphasize that despite the efforts of all authors – including their careful descriptions, practical tips, and even theoretical considerations – finding the right formulation may in the end still be a matter of educated

trial and error. Yet, even in this case, we are confident that this book will speed up the process.

The editors thank all the contributors for their time and effort in composing this compendium, for presenting the current state of the art in formulating insoluble drugs for oral, parenteral and topical administration, and for providing the reader with practical guidelines on how to start a formulation task.

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