SECOND EDITION

Pharmaceutics

THE SCIENCE OF DOSAGE FORM DESIGN

Edited by
M. E. Aulton

CHURCHILL LIVINGSTONE

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Note
Medical knowledge is constantly changing. As new information becomes available, changes in treatment, procedures, equipment and the use of drugs become necessary. The editor, contributors and the publishers have taken care to ensure that the information given in this text is accurate and up to date. However, readers are strongly advised to confirm that the information, especially with regard to drug usage, complies with the latest legislation and standards of practice.

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Preface

This is the second edition of Pharmaceutics : the science of dosage form design and the first edition was published

In 1988. The pedigree o f the he book is actually much older than that. It was originally known as *Tutonc! Pharmacy* and edited by John Cooper and Colin Gunn, and later by Sidney Carter.

The philosophy of this second ediuon remains uncb nged, i.e. it is designed and written intentionally for newcomers to the design of dosage forms - other expert texts can take you into much more detail in each of the subject areas once you 'have mastered these basics. The subject matter of the book remains essentially the same, but the detail has been changed significantly because pharmaceutics has changed. Since the last edition there have been changes in both the concept and the content of pharmaceutics. These developments are reflected in this new edition.

The structure of the content of this edition has changed somewhat to reflect modem thinking andcurrent university curricula. More importantly, every chapter has received attention and has been updated appropriately. Some of the basic science remains· VIrtually unchanged (and will always remain so) but other areas, particularly biopharmaceutics, some areas of drug delivery and our understanding of the significance of the solid state, have changed enor- mously since the last edition. The current and future use of biotechnology products has also been reflect- ed in this new edition.

The involvernent of a wide range of authors con- tinues in this edition, each an accepted expert in the field on which they have written and, just as importantly, each has experience and the ability to impart that information to undergraduate pharma- ceurical scientists and those practitioners new to the subject. Manv authors from the first edition remain.as they are still world leaders in their field. Other (who were either unable to contribute. (Q the second edition, have retired of, sadly, died) hare been replaced by a new generation of experts: The new authorship reflects modem knowledge and thinking in pharmaceutics.

I wish you well in your studies if you a an under-graduate or with your career if you are working in industry or the hospital service. I sincerely bope thatthis book helps you with your understanding of pharmaceutics - the science of dosageform design.

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The editor wishes to take this opportunity to thank the following who have assisted with the preparation of this text:

Mr. Sidney Carter, who edited this book's predecessor, *Cooper and Gum's Tutorial Pharmacy,* for 'passing on to me the opportunity to edit the first edition of this textbook. His invaluable experience and guidance aided me throughout the preparation of that edition and those principles are carried forward to this new edition.

I am extremely indebted to the authors for the work and time that they put into their texts, often under pressure from numerous other commitments, and from me. Modern life has few spare moments and so the time that they spent in contributing so knowledgeably and professionally to this text is warmly appreciated.

The many secretaries and artists who assisted the authors in the preparation of their work,

My wife Christine, for typing and other secretarial assistance, and help in a million other wavs which enabled me to spend time on this editi on of the book.

Ellen Green and Janice Urquhart of Churchill Livingstone, for their special expertise and assistancein the preparation of this second edition. The many academic and industrial pharmaceutical scientists who helped during the cesium of the contents of this edition to ensure ran it corresponds as closely as possible with modem practice and with the curricula of current pharmacy and pharmaceutics- cal science courses.

Those publishing companies who have given their permission to reproduce material in this edition.

Michael E. Aulton

Contents

What is 'Pharmaceutics'?

One of the earliest impressions that many new pharmacy and pharmaceutical science students have of their chosen subject is the large number of long and sometimes unusual-sounding names that are used to describe the various subject areas within pharmacy. The aim of this section is to explain to the reader what is meant by the term 'pharmaceutics', how it has been interpreted for the purpose of this book, and how pharmaceutics fits into the overall scheme of pharmaceutical science. It will also lead the reader through the organization of this book and explain why an understanding of the material contained in its chapters is important in the design of modern drug delivery systems.

The word pharmaceutics is used in pharmacy and pharmaceutical science to encompass many subject areas, which are all associated with the steps to which a drug is subjected towards the end of its development – i.e. it is the stages that follow its discovery or synthesis, its isolation and purification, and testing for advantageous pharmacological effects and the absence of serious toxicological problems. Put at its most simplistic, pharmaceutics converts a drug into a medicine. Pharmaceutics, and therefore this book, is concerned with the scientific and technological aspects of the design and manufacture of dosage forms.

Pharmaceutics is arguably the most diverse of all the subject areas in pharmaceutical science and encompasses:

- an understanding of the basic physical chemistry necessary for the efficient design of dosage forms (physical pharmaceutics)
- the design and formulation of medicines (dosage form design),
- the manufacture of these medicines on both a small (compounding) and a large (pharmaceutical technology) scale;
- the cultivation, avoidance and elimination of microorganisms in medicines (microbiology).

Medicines are drug delivery systems. That is, they are a means of administering drugs to the body in a safe, efficient, reproducible and convenient manner. The first chapter in the book introduces, in a general way, the considerations that must be made so that this conversion of drug to medicine can take place. It emphasizes the fact that medicines are rarely drugs alone, but require additives to make them into dosage forms and this in turn introduces the concept of formulation. The chapter explains that there are three major considerations in the design of dosage forms:

1. The physicochemical properties of the drug itself,
2. Biopharmaceutical considerations, such as how the route of administration of a dosage form affects the rate and extent of drug absorption into the body, and
3. Therapeutic considerations of the disease state to be treated, which in turn decide the most suitable type of dosage form, possible routes of administration and the most suitable duration of action and dose frequency for the drug in question.

This first chapter is an excellent introduction to the book as a whole and the perfect justification for the need to understand the subject matter of this text. New readers are encouraged to read this chapter thoroughly and carefully so they can grasp the basics before delving into the later, more detailed information.

Part 1 of this book describes some of the more important physicochemical knowledge that it is necessary to have in order to study and understand the design and preparation of dosage forms. The chapters have been designed to give the reader an insight into those scientific and physicochemical principles that are important to the formulation scientist. They are not intended as a substitute for a thorough

understanding of physical chemistry, and many specific, more derailed, texts are available with this information.

For many reasons, which are discussed in the book. the vast majority Of dosage forms are administered. orally in the form of solid products such as tablets and capsules. This means that one of the most important stages in drug administration is the dissolution of solid particles to form a solution in the gastroinre srinal tract. This means that tho: formutation scientist must have a knowledge of both liquid and solid materials. and particularly (he properties of drugs in solution and the factors influencing drug dissolution from solid particles. Once solutions are formed, the reader must understand the properties of solutions and these are discussed next. The reader wijl see later in the book how drug release and absorption are strongly dependent on solution properties, such as solute dissociation and diffusion, and flow properties. A knowledge of these subjects is useful in solving certain problems relating to the properties of fluids and the performance of solutions and semisolids as dosage forms in their own right.

The properties of interfaces are described next. These are important to an understanding of adsorp- tion on to solid surfaces as involved in the dissolu- tion of solid particles and the study of disperse sys- tems such as colloids, suspensions and emulsions. The scientific background to such systems is also discussed.

. Before finalizing on a possible dosage form there must be a clear understanding of the stability of drug(s) and other additives in the formulation with respect to the reasons why and the rates at which they degrade. There must be an awareness of the means of inhibiting decomposition and increasing the shelf-life of a product. These pointS are discussed:

The subject known as preforrnulation is considered next. This is a consideration of the steps that need to be considered before formulation itself can begin. Preforrnnlation involves a full understanding of the physicochemical properties of drug molecules and excipients .and .how they interact in dosage forms. Thus a grasp of this knowledge early on is of great use to the formulation scientist and teaches many scientific principles on which future dosage form design is dependent. The results of tests carried out at this stage of development can give a much clearer indication of the possible dosage forms for a new drug candidate.

Pan Two of the book collects l(\get.i~ those aspects (If pharmaceutics associated „-materials. By far the majority of drugs are solid powders, and unfortunately .. most of these have numerous adverse properties that must be overcome during the design -Ofmedidnes to enable their saDs-factory manufacture and subsequent performance in dosage forms ..

The book therefore explains the concept of the solid state and how the internal and surface properties of solids are important and need to be. characterized. This is followed by an explanation of the more macroscopic properties of powders that influence rherr performance during the design and manufacrure of dosage forms - particle size and its measurement. size reduction, and size separation of powders from those of other sizes. There follows an explanation of the many problems associated with the mixing and Dow of powdersv In high-speed tablet and capsule production, fot example, pow- ders must contain a satisfactory mix of all the ingre- dients and achieve fast and uniform powder flow. For convenience, the mixing of liquids and semi- solids is also discussed here as the basic theory is the same.

Even with this fundamental knowledge it is not possible to begin to design a dosage form without having an understanding of how drugs are absorbed into the body, the various routes that can be used for this purpose, and the fate of the drugs once they enter the body and reach their site(s) of action. This book concentrates on the preparation, administra- tion, release and absorption of drugs, but stops short at the cellular level and leaves to other texts the detail of how drugs enter individual cells, how they act, how they are metabolized and how they are eliminated. These cellular considerations are not within the remit of this book.

The terms bioavailabiliry and biopharmaceutics are defined and explained in Part Three. The factors influencing the bioavailabiliry of a drug and methods of its assessment are described. This is followed by a consideration of the manner in which the frequency of administration of a drug and the rate at which it is released affect its level in the blood.at any given time. Part Three then goes on to discuss actu- al drug delivery systems which arc available to mod- ify and control the rate and extent of the release of drugs from dosage forms.

In Part Four, the book discusses the design of dosace forms and their manufacture It covers their formclauon, the rate and extent of drug release from them. their advantages and disadvantages as a dosage form. and the way in which they are manu- lacrure d on a large scale in industry.

Dosaze f6'C:ls suitable for the administration of dru~5 through almost everv possible body orifice