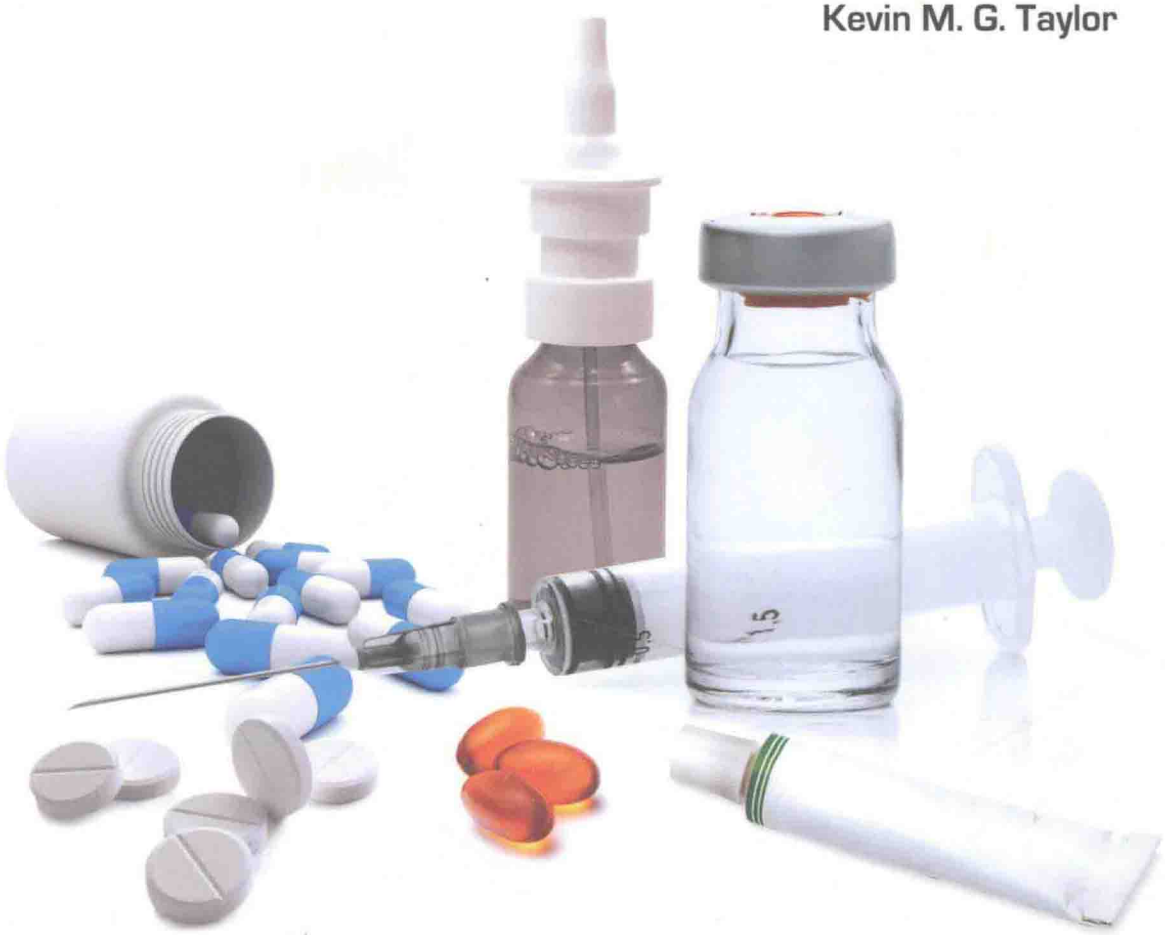
Fourth Edition

Aulton's Pharmaceutics

THE DESIGN AND MANUFACTURE OF MEDICINES

Edited by
Michael E. Aulton
Kevin M. G. Taylor



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The Design and Manufacture of Medicines

FOURTH EDITION

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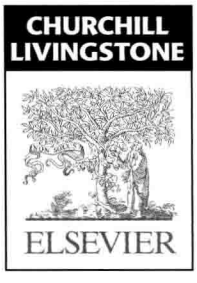

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Aulton's Pharmaceutics

The Design and Manufacture of Medicines

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Preface

This is the fourth edition of ***Pharmaceutics: The Design and Manufacture of Medicines***; the first edition was published in 1988, the second in 2002 and the third in 2007. The pedigree of the book is, however, actually much older. It was originally known as ***Tutorial Pharmacy*** and was initially edited by John Cooper and Colin Gunn, and later by Sidney Carter. For this edition, Professor Aulton has been joined by Professor Kevin Taylor of UCL School of Pharmacy, London. Professor Taylor has been instrumental in identifying new authors and contemporary subject matter for this new edition.

The philosophy of this fourth edition remains unchanged, i.e. it is intentionally designed and written for newcomers to the design of dosage forms. Other expert texts can take you into much greater detail for each of the subject areas considered here, once you have mastered these basics. The subject matter of the book remains, in essence, the same but the detail has changed significantly, because pharmaceutics itself has changed. Since the last edition there have been changes in the way that dosage forms are designed and drugs are delivered. These developments are reflected in this new edition.

The involvement of a wide range of authors continues in this edition, each a recognized expert in the field on which they have written. Just as importantly, each author has experience of imparting that information to undergraduate pharmacy and pharmaceutical science students, and to practitioners in the pharmaceutical and associated industries and those working in technical services within hospital pharmacy who are new to the subject. Many authors from the previous edition remain as they are still world leaders in their field. Others chapters have been written by a new generation of experts. The new authorship reflects modern knowledge and thinking in pharmaceutics.

The structure and the content of this edition have been altered to reflect modern thinking and current university curricula worldwide. More importantly, every chapter has received detailed attention and has been revised and updated appropriately. Some of the basic science remains virtually unchanged – and will always do so – but other areas, particularly biopharmaceutics and some areas of drug delivery, have changed enormously in recent years.

Several completely new chapters have been included in this edition to ensure the comprehensive nature and currency of this text. Part 5 of the book outlines the wide range of dosage forms available for administration by several routes. In previous editions, suspensions and emulsions as dosage forms were considered together, as disperse systems, in one chapter. In this edition, these are now considered in separate chapters, each written by a new author. This has allowed each system to be described more fully. The emulsions chapter now includes comprehensive consideration of the formulation, manufacture and properties of semisolid emulsions, namely creams. This Part is augmented by the inclusion of new chapters that describe the particular requirements for medicines administered parenterally, i.e. by injection, and for those administered to the eye.

When designing and manufacturing dosage forms, it is essential that formulation scientists consider the properties of the drug, the medicine and the needs of patients. Patients with specific pharmaceutical needs include the elderly and young children; both, in particular, have difficulties swallowing solid dosage forms. A chapter has been included outlining how medicines may be formulated specifically for these patient groups, and also how existing dosage forms can be modified to improve their properties, thus making them more suitable for the old and very young.

While most drugs comprise small synthetic molecules, there is resurgence of interest in, and tighter regulatory control of, medicines of plant origin. Also, biopharmaceutical products, including proteins, peptides, antibodies, vaccines and gene therapies are the subject of intensive research, and are becoming increasingly commercially available as medicines. Both these categories of therapeutic agent present particular formulation and drug delivery challenges. New chapters on plant medicines and biopharmaceuticals have thus been added. Nanotechnology is increasingly employed to improve drug solubility and dissolution rates and to enhance bioavailability, particularly of biopharmaceuticals

and cytotoxic drugs, and this forms the subject of another new chapter. Additionally, the section on product stability and the stability testing of medicinal products has been completely rewritten to include current protocols.

We wish you well in your studies if you are an undergraduate, or with your career if you are working in industry or the hospital service. We sincerely hope that this book helps you with your understanding of pharmaceutics – the science of the design and manufacture of medicines.

Mike Aulton
Kevin Taylor

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The many academic and industrial pharmaceutical scientists – who helped during the design of the contents and organisation of this edition to ensure that it corresponds as closely as possible with modern practice and with the curricula of current pharmacy and pharmaceutical science courses internationally.

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Contents

What is 'pharmaceutics'?

'Welcome to 'Ceutics'!'

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 and the pharmaceutical sciences. The aim of this section is to explain to the reader what is meant by just one of them – *'pharmaceutics'*. This note describes how the term has been interpreted for the purpose of this book and how pharmaceutics fits into the overall scheme of pharmaceutical science and the process of designing and manufacturing a new medicine. This note also leads the reader through the organization of this book and explains the reasons 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 the pharmaceutical sciences to encompass a wide range of subject areas that are all associated with the steps to which a drug is subjected towards the end of its development. It encompasses the stages that follow on from the discovery or synthesis of the drug, its isolation and purification, and testing for advantageous pharmacological effects and absence of serious toxicological problems. Put at its simplest – *pharmaceutics converts a drug into a medicine*.

Just a comment here about the word 'drug'. This is the pharmacologically active ingredient in a medicine. 'Drug' is the correct word, but because the word has been somewhat hijacked as the common term for a substance of misuse, alternatives are frequently used, such as 'medicinal agent', 'pharmacological agent', 'active principle', 'active ingredient', or increasingly 'active pharmaceutical ingredient (API)', etc. The book uses the simpler and still correct word, 'drug'. Phrases like 'active ingredient' can suggest that the other ingredients of a medicine have no function at all. This book will teach you loud and clear that this is not the case.

Pharmaceutics, and therefore this book, is concerned with the scientific and technological aspects of the design and manufacture of dosage forms. Arguably, it is the most diverse of all the subject areas in the pharmaceutical sciences and it encompasses:

- an understanding of the basic physical chemistry necessary for the effective design of dosage forms (physical pharmaceutics)
- an understanding of relevant body systems and how drugs arrive there following administration (biopharmaceutics)
- the design and formulation of medicines (dosage form design)
- the manufacture of these medicines on a small (compounding), intermediate (pilot-scale) and large (pharmaceutical technology, manufacturing) scale
- the avoidance and elimination of microorganisms in medicines (pharmaceutical microbiology, sterilization), and
- product performance testing (dissolution testing, drug release, stability testing).

Medicines are drug-delivery systems. That is, they are a means of administering drugs to the body in a safe, efficient, accurate, reproducible and convenient manner. The book discusses the overall

considerations that must be made so that the conversion of a drug to a medicine can take place. It emphasizes the fact that medicines are very rarely drugs alone but require additives (termed excipients) to make them into dosage forms, and this in turn introduces the concept of formulation. The book 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 administration route of a dosage form affects the rate and extent of drug absorption into the body, and
3. therapeutic considerations of the disease state and patient to be treated, which in turn determine 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.

The first chapter provides an excellent introduction to the subject matter of the book as a whole and clearly justifies the need for the pharmacist and formulation scientist to understand the science contained in this text. New readers are encouraged to read this chapter first, thoroughly and carefully, so that they can grasp the basics of the subject before proceeding onto the more detailed information that follows.

The book is then divided into various Parts that group together chapters into related subject areas. Part 1 collects some of the more important physicochemical knowledge that is required to design and prepare 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. These chapters are not intended as a substitute for a thorough understanding of physical chemistry and many specific, more detailed, texts are available containing this information.

For many reasons, which are discussed in the book, the vast majority of dosage forms are administered via the mouth 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 gastrointestinal tract. The formulation scientist therefore needs knowledge of both liquid and solid materials, in particular the properties of drugs in solution and the factors influencing their dissolution from solid particles. Once solutions are formed, the formulation scientist must understand the properties of these solutions. The reader will see later in the book how drug release from the dosage form and absorption of the drug by the body are strongly dependent on the properties of the drug in solution, such as the degree of dissociation and speed of diffusion of the drug molecules.

The properties of surfaces and interfaces are described next. These are important to an understanding of adsorption onto solid surfaces, and are involved in the dissolution of solid particles and the study of disperse systems, such as colloids, suspensions and emulsions. The scientific background to the systems mentioned is also discussed. Knowledge of the flow properties of liquids (whether solutions, suspensions or emulsions) is useful in solving certain problems relating to the manufacture and performance of solutions and semi-solids as dosage forms in their own right. This Part ends with an explanation of the kinetics of many different processes. As the chapter explains, the mathematics of these processes has importance in a large number of areas of product design, manufacture, storage and drug delivery. Relevant processes include: dissolution processes, microbiological growth and destruction, biopharmaceutics (including drug absorption, distribution, metabolism and excretion), preformulation, the rate of drug release from dosage forms, and the decomposition of medicinal compounds and products.

Part 2 collects together those aspects of pharmaceutics associated with powdered materials. By far the majority of drugs are solid (mainly crystalline) powders and, unfortunately, most of these have numerous adverse characteristics that must be overcome during the design of medicines to enable their satisfactory 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 their performance during the design and manufacture of dosage forms – particle size and its measurement, size reduction and separation of powders with the desired size characteristics from those of other sizes. There follows an explanation of the many problems associated with the mixing and flow of powders. In large-scale tablet and capsule production, for example, powders must contain a