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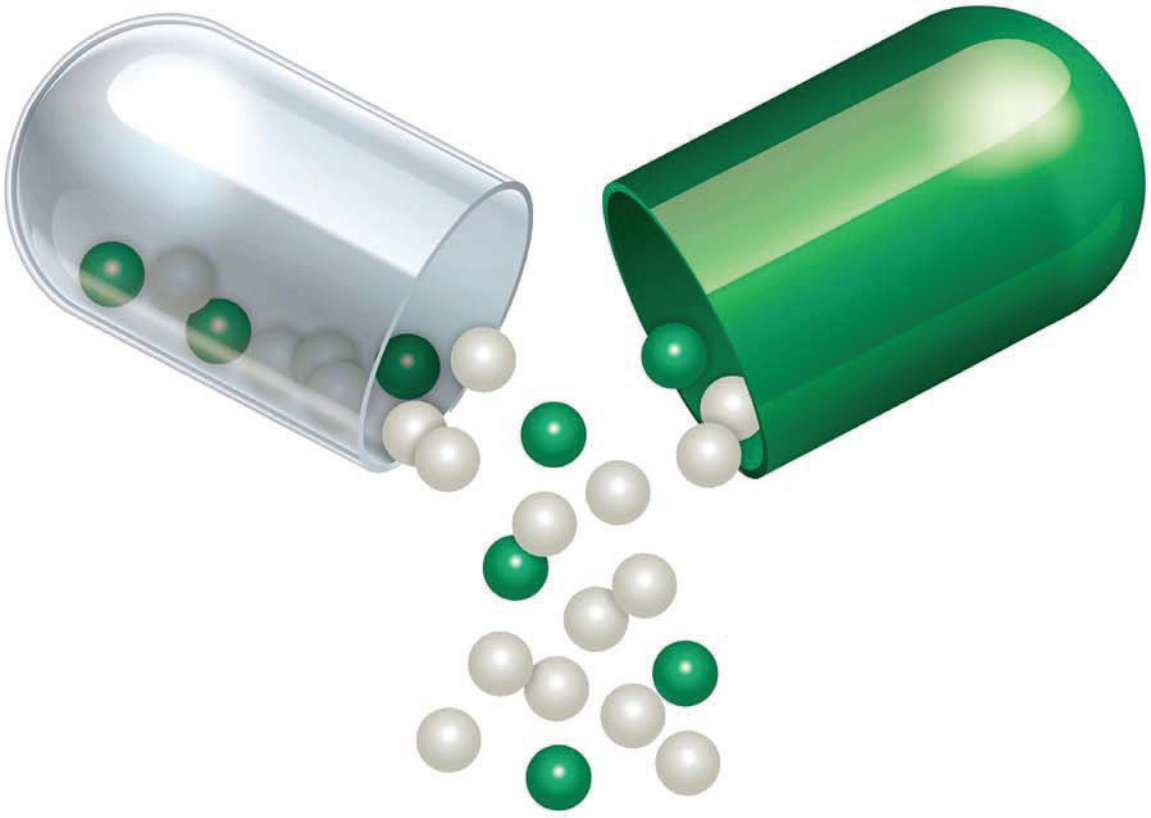
Aulton's Pharmaceutics

THE DESIGN AND MANUFACTURE OF MEDICINES



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

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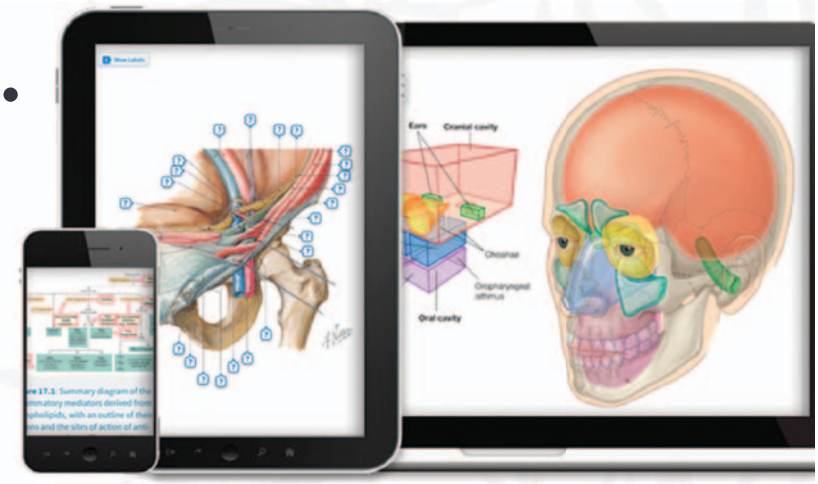

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Aulton's Pharmaceutics

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The Design and Manufacture of Medicines

Sixth Edition

Edited by

Kevin M.G. Taylor
BPharm, PhD, FRPharmS
Professor of Clinical Pharmaceutics
UCL School of Pharmacy
London, UK

Michael E. Aulton
BPharm, PhD, FAAPS, FSP, FRPharmS
Emeritus Professor
De Montfort University
Leicester, UK

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Content Development Specialist: Louise Cook
Project Manager: Andrew Riley
Design: Maggie Reid
Illustration Manager: Narayanan Ramakrishnan
Marketing Manager: Deb Watkins

Contents

Part 5: Dosage form design and manufacture

Part 6: Packaging, stability and pharmaceutical regulation

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Preface

This is the sixth edition of *Aulton's Pharmaceutics: The Design and Manufacture of Medicines*. The first edition was published in 1988 and the fifth in 2018. The pedigree of the book is, however, actually much older. It was originally known as *Tutorial Pharmacy* (which itself also went to six editions) and was initially edited by John Cooper and Colin Gunn, and later by Sidney Carter.

Professor Mike Aulton and Professor Kevin Taylor continue their editing role and have identified new authors and fresh subject matter for this new edition. The philosophy of this sixth edition remains unchanged from that of previous editions, i.e. it is intentionally designed and written for newcomers to the design of dosage forms (drug products). 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 covered by the book remains, in essence, the same but the detail has changed significantly, because pharmaceutics has changed. Since the last edition there have been changes in the way that dosage forms are designed and manufactured and drugs are delivered. These developments are reflected in this new edition.

The involvement of a wide range of authors continues in this edition, all authors being 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, to practitioners in the pharmaceutical and associated industries, and to those working in technical services within hospital pharmacy who are new to the subject. Most authors from the previous edition remain as they are still world leaders in their field. Other chapters have been written by a new generation of experts. The new authorship reflects contemporary knowledge and thinking in pharmaceutics.

Every chapter has received detailed attention and has been revised and updated appropriately to reflect modern thinking and current university curricula worldwide. Some of the basic science remains virtually unchanged — and will always do so — but other areas, such as biopharmaceutics and some areas of drug delivery, have changed significantly in recent years.

Several new authors and new subject areas have been included in this edition to ensure the comprehensive nature and currency of this text. The following new chapters have been added to the sixth edition.

- The design and preparation of dosage forms applied to the skin, including ointments, pastes, gels, cutaneous patches and topical sprays are now gathered together in a single chapter.
- Continuous manufacturing is a relatively new concept in the manufacture of pharmaceutical products. It is considered here in a new chapter with a particular focus on tablet manufacturing.
- The formulation and place in therapy of drops, semisolids, injection and implants for delivering drugs to and via the ear (otic delivery) form the subject matter of another new chapter.
- There is a new chapter on radiopharmaceuticals used for diagnostic and therapeutic purposes covering their formulation, preparation, purification, quality control and delivery.
- The book ends with a new chapter on pharmaceutical quality and the application of pharmaceutics in medicines regulation. It outlines how medicines are regulated and how their quality is assured. It shows how the application of the theories and practices described in the preceding chapters of the book enable quality to be built into a medicinal product.

Preface

All purchasers of the print version of this new edition receive the enhanced ebook, which can be used online or downloaded to their mobile device for convenient, any time access. The ebook includes more than 400 self-assessment questions, based on the content of this book, to check understanding and to help with any examination preparation.

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

K. M. G. Taylor
M. E. Aulton

Contributors

Aktham Aburub PhD
Research Fellow
Pharmaceutical Product Design
Eli Lilly and Company
Indianapolis, IN, USA

Göran Alderborn PhD
Professor in Pharmaceutical Technology
Department of Pharmaceutical Biosciences
Uppsala University
Uppsala, Sweden

Marianne Ashford BSc (Hons), PhD
Senior Principal Scientist
Pharmaceutical Sciences
AstraZeneca
Macclesfield, UK

David Attwood BPharm, PhD, DSc, CChem FRSC
Emeritus Professor
Manchester Pharmacy School
University of Manchester
Manchester, UK

Michael E. Aulton BPharm, PhD, FRPharmS, FAAPS, FSP
Emeritus Professor
Leicester School of Pharmacy
De Montfort University
Leicester, UK

Susan Barker BPharm, PhD
Head of School
Medway School of Pharmacy
Universities of Kent and Greenwich
Chatham, UK

Andrew R. Barnes BSc, PhD, FRSC
Quality Assurance Specialist
East Suffolk and North Essex NHS Foundation Trust
Ipswich Hospital
Ipswich, UK

Lara-Marie Barnes BSc, PhD
Senior Lecturer in Pharmaceutical Microbiology
School of Pharmacy and Biomolecular Sciences
University of Brighton
Brighton, UK

Abdul W. Basit PhD
Professor of Pharmaceutics
Department of Pharmaceutics
UCL School of Pharmacy
University College London
London, UK

Steve Brocchini PhD
Professor of Chemical Pharmaceutics
School of Pharmacy
University College London
London, UK

Graham Buckton BPharm, PhD, DSc
Emeritus Professor of Pharmaceutics
UCL School of Pharmacy
University College London
London, UK

Maggie Cooper BSc(Hons), MSc, PhD
Research Fellow in Translational Radiopharmacy
School of Biomedical Engineering and Imaging Sciences
King's College London
London, UK

Soraya Dhillon BPharm, (Hons) PhD, FRPharmS
Emeritus Professor
School of Life and Medical Sciences
University of Hertfordshire
Hatfield, UK

Kalliopi Dodou BSc (Hons), PhD
Associate Professor
Health Sciences and Well-being
University of Sunderland
Sunderland, UK

Gillian M. Eccleston BSc, PhD, FRPharmS, CChem, FRSC
Emeritus Professor of Pharmaceutics
Strathclyde Institute of Pharmacy and Biomedical Sciences
University of Strathclyde
Glasgow, UK

Hala M. Fadda MPharm, PhD
Associate Professor of Pharmaceutics
College of Pharmacy and Health Sciences
Butler University
Indianapolis, IN, USA;
Honorary Senior Lecturer
University College London
London, UK

Ana Cristina Freire PhD
Development Director
Aptuit
Oxford, UK

Göran Frenning
Professor in Pharmaceutical Physics
Department of Pharmaceutical Biosciences
Uppsala University
Uppsala, Sweden

Contributors

Simon Gaisford BSc, MSc, PhD
Professor of Pharmaceutics
Department of Pharmaceutics
UCL School of Pharmacy
University College London
London, UK

Francesca K.H. Gavins MPharm
PhD Researcher
Department of Pharmaceutics
UCL School of Pharmacy
University College London
London, UK

Geoffrey Hanlon BSc, PhD
Emeritus Professor of Pharmaceutical Microbiology
School of Pharmacy and Biomolecular Sciences
University of Brighton
Brighton, UK

Neil Hartman BPharm, MSc, PhD
Head of Department of Nuclear Medicine
Singleton Hospital
Swansea, UK;
Professor
Medical School
Swansea University
Swansea, UK

Norman A. Hodges MPharm, PhD
Formerly Principal Lecturer
School of Pharmacy
Brighton University
Brighton, UK

Brian E. Jones BPharm, MPharm
Honorary Senior Lecturer
Welsh School of Pharmacy
Cardiff University
Cardiff, UK

Ashkan Khalili MD, PhD, FRCOphth
Birmingham & Midland Eye Centre
Birmingham, UK

Peng Tee Khaw PhD, FRCP, FRCS, FRCOphth, FRCPath, FCOptom, Hon DSc FRSB, FARVO, FMedSci
Consultant Ophthalmic Surgeon and Professor of Glaucoma and Ocular healing
National Institute for Health Research Biomedical Research Centre at Moorfields Eye Hospital NHS Foundation Trust and UCL Institute of Ophthalmology
Moorfields Eye Hospital and UCL Institute of Ophthalmology
London, UK

Katie Laird BSc PhD
Reader/ Associate Professor in Microbiology
The School of Pharmacy
De Montfort University
Leicester, UK

Majella E. Lane BSc, PhD
Senior Lecturer
UCL School of Pharmacy
University College London
London, UK

Alison B. Lansley BSc (Hons) Pharmacy, PhD
Principal Lecturer
School of Pharmacy and Biomolecular Sciences
University of Brighton
Brighton, UK

Xu Liu PhD
Research Assistant
Department of Pharmaceutics
Molecular Pharmaceutics and Drug Delivery
College of Pharmacy
The University of Texas at Austin
Austin, TX, USA

G. Brian Lockwood BPharm, PhD, MRPharmS
Professor
Division of Pharmacy and Optometry
University of Manchester
Manchester, UK

Robert Lowe BPharm (Hons)
Director of Pharmacy Quality Assurance Specialist Services
East of England and Northamptonshire
NHS England
Norwich, UK

Christine M. Madla BSc, MSc
PhD Researcher
Department of Pharmaceutics
UCL School of Pharmacy
University College London
London, UK

Jean-Yves Maillard BSc, PhD
Professor of Pharmaceutical Microbiology
School of Pharmacy and Pharmaceutical Sciences
Cardiff University
Cardiff, UK

John Malkinson BPharm, PhD, MRPharmS, FRSC, SFHEA
Associate Professor
UCL School of Pharmacy
University College London
London, UK

Chris Marriott PhD, DSc
Emeritus Professor of Pharmaceutics
Department of Pharmacy
King's College London
London, UK

Paul Marshall BPharm, PhD
Director
Regulatory and Product Development
SMC Ltd
Brackley, UK

Gary P. Martin BPharm, PhD, FRPharmS
Professor (Emeritus) of Formulation Science
School of Cancer and Pharmaceutical Science
Institute of Pharmaceutical Science
King's College London
London, UK

Emma L. McConnell MPharm, PhD
Scientific Director
Aspire Scientific Ltd
Clarence Mill
Bollington, UK

Sudaxshina Murdan BPharm, PhD
Reader in Pharmaceutics
UCL School of Pharmacy
University College London
London, UK

Mine Orlu PhD, MSc
Associate Professor
UCL School of Pharmacy
University College London
London, UK

Yvonne Perrie PhD
Professor
Strathclyde Institute of Pharmacy and Biomedical Sciences
University of Strathclyde
Glasgow, UK

Kendal G. Pitt FRPharmS, FAPS, AFIChemE, BPharm, PhD
Senior Technical Director
Pharma Supply Chain
GlaxoSmithKline
Ware, UK

Stuart Porter PhD
President, PPT Pharma Technologies
Hatfield, PA, USA

Mark Santillo MRPharmS
Regional Quality Assurance Officer/
Honorary Financial Officer JPAG
Torbay & South Devon NHS
Foundation Trust
Torbay, UK

Andreas G. Schätzlein PhD
Professor
UCL School of Pharmacy
University College London
London, UK

Khalid A. Sheikh BPharm, MSc, PhD
Senior Teaching Fellow
UCL School of Pharmacy
University College London
London, UK

Hugh D.C. Smyth BPharm, PhD
Professor
Molecular Pharmaceutics and Drug Delivery
College of Pharmacy
The University of Texas at Austin
Austin, TX, USA

Satyanarayana Somavarapu PhD
Senior Lecturer
UCL School of Pharmacy
University College London
London, UK

Kevin M.G. Taylor BPharm, PhD, FRPharmS
Professor of Clinical Pharmaceutics
UCL School of Pharmacy
University College London
London, UK

Stephen Tindal BSc
Director, Science & Technology, Europe
Catalent Pharma Solutions
Swindon, UK

Catherine Tuleu PhD Docteur en Pharmacie
Professor
UCL School of Pharmacy
University College London
London, UK

Andrew Twitchell BSc Pharmacy, PhD
Formerly Senior Pharmaceutical Assessor
Licensing
MHRA
London, UK

Ijeoma F. Uchegbu PhD
Professor
UCL School of Pharmacy
University College London
London, UK

Nkiruka Umaru MPharm, PhD, MA
Principal Lecturer
School of Life and Medical Sciences
Clinical and Pharmaceutical Sciences
University of Hertfordshire
Hatfield, UK

Susannah E. Walsh BSc, PhD, MBA
Professor of Pharmaceutical Microbiology
School of Pharmacy
De Montfort University
Leicester, UK

Adrian C. Williams BSc, PhD
Professor of Pharmaceutics
School of Pharmacy
University of Reading
Reading, UK

Gareth Williams MChem, DPhil, FRSC, FAPS, SFHEA
Professor of Pharmaceutical Materials Science
UCL School of Pharmacy
University College London
London, UK

David J. Wright BPharm (Hons), PhD, PGCHE
Professor of Pharmacy Practice
School of Pharmacy
University of East Anglia
Norwich, UK

Peter York DSc, PhD, BSc
Emeritus Professor
School of Pharmacy
University of Bradford
Bradford, UK

Feng Zhang PhD
Associate Professor
Molecular Pharmaceutics and Drug Delivery
College of Pharmacy
The University of Texas at Austin
Austin, TX, USA

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K. M. G. Taylor
M. E. Aulton

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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'*. It 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, characterizing and manufacturing a new medicine. This section 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 and manufacture 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 its testing for beneficial 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', 'therapeutic' or 'active pharmaceutical ingredient (API)'. The book predominantly uses the simpler and still correct word, 'drug'. Phrases like 'active ingredient' to describe the drug can suggest that the other ingredients included in a medicine have no function at all. This book will teach you emphatically 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 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) and large (manufacturing) scale;
- the avoidance and elimination of microorganisms in medicines (pharmaceutical microbiology, sterilization, preservation); and
- product performance testing (physical 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, effective, 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 and formulation of a dosage form affect 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 of the book 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 (*Scientific principles of dosage form design*) introduces 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 which provide this information.

For many reasons that are discussed in the book, the large majority of dosage forms are administered via the mouth (oral route) 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 into the body across biological barriers (e.g. the epithelia of the gastrointestinal tract, airways, skin, etc.) are strongly dependent on the properties of the drug in solution, such as the degree of ionization 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) and semisolids (e.g. creams, ointments and gels) is useful in solving certain problems relating to the manufacture, performance and stability of liquid and semisolid dosage forms. This Part ends with an explanation of the kinetics of many different processes. As the chapter explains, the mathematics of these processes is important in a large number of areas of product design, manufacture, storage and drug delivery. Relevant processes include dissolution, microbiological growth and destruction, biopharmaceutics (including drug absorption, distribution, metabolism and excretion), preformulation, the rate of drug release from dosage forms, and the degradation of medicinal compounds and products.

Part 2 (*Particle science and powder technology*) collects together those aspects of pharmaceutics associated with powdered materials. The large majority of drugs are solid (mainly crystalline) powders and, unfortunately, most of these particulate solids have numerous adverse physicochemical characteristics that must be overcome or controlled 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 the separation

of powders with the desired size characteristics from those of other sizes. Knowledge and control of the particles size of a pharmaceutical material may be vitally important. Size will influence the dissolution rate of solid particles, which for drugs with dissolution-rate limited absorption may affect the safety and efficacy of the drug product. Moreover, control of size is important in the processing of powders during the manufacture of solid dosage forms, in the stability of dispersed systems such as suspensions, emulsions and creams, and in ensuring the efficacy of medicinal products, for example inhaler and nasal products, and nanomedicines amongst others.

The text then explains the many problems associated with the mixing and flow of powders. In large-scale tablet and capsule production, for example, powders must contain a satisfactory mix of all the ingredients in order to achieve uniformity of dosage in every single dosage unit manufactured. The powder must have fast and uniform powder flow in high-speed tableting and encapsulation machines. For convenience, the mixing of liquids and semisolids is also discussed here as the basic theory is the same.

Another extremely important area that must be understood before a satisfactory dosage form can be designed and manufactured is the microbiological aspects of medicines development and production. It is necessary to control or eliminate living microorganisms present in the product both before and during manufacture. Microbiology is a very wide-ranging subject. This book concentrates only on those aspects of microbiology that are directly relevant to the design, production and distribution of dosage forms. This mainly involves avoiding (asepsis) and eliminating (sterilization) the presence (contamination) of viable microorganisms in medicines, and preventing the growth of any microorganism which might enter the product during storage and use of the medicine (preservation). Techniques for testing that these intentions have been achieved are also described. The principles and practice of sterilization are also discussed. The relevant aspects of pharmaceutical microbiology and sterilization are considered in Part 3 (*Pharmaceutical microbiology and sterilization*) of this book.

It is not possible to begin to design a satisfactory dosage form without knowledge and 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. The terms *bioavailability* and *biopharmaceutics* are defined and explained in Part 4 (*Biopharmaceutical principles of drug delivery*). The factors influencing the bioavailability of a drug and methods for its assessment are described. The influence of the drug properties, the formulation and dosage form on the rate and extent of drug absorption are considered. Strategies to modify the physicochemical properties of the drug or the formulation to enhance bioavailability are outlined. This is followed by a consideration of the manner in which the frequency of drug administration and the rate at which drug is released from a dosage form affect its concentration in the blood plasma at any given time. This book concentrates on the preparation, administration, release and absorption of drugs but stops there. It leaves to other texts the detail of how drugs enter individual cells, how they act and how they are metabolized and eliminated from the body.

Having gathered this understanding of the basics of pharmaceutics, the formulation scientist should now be equipped to begin a consideration of the design and manufacture of the most suitable dosage forms for the drug in question.

Superficially, the formulation and manufacture of dosage forms containing drugs may seem relatively straightforward. The chapters in Part 5 (*Dosage form design and manufacture*) of this book will demonstrate that this is not the case. The full potential of the active pharmaceutical ingredient, whether it is a small synthetic molecule, a biotechnology product, a radioisotope or a plant extract, can only be achieved by the involvement of the formulation scientist. Good formulation can enhance therapeutic efficacy and/or limit adverse effects. A couple of examples illustrate this:

- Whilst an immediate-release capsule of nifedipine has a dosing frequency of three times a day, formulation of the drug in a modified-release capsule permits once-daily or twice-daily dosing, with an improved drug plasma profile and increased patient convenience and adherence.
- A cream formulation of a sunscreen applied to the skin restricts the active component(s) to the skin surface, whilst a gel formulation of estradiol, also applied to the skin surface, is formulated so as to ensure effective penetration of drug through the skin and into the systemic circulation.

The first stage of designing and manufacturing a dosage form is known as preformulation. This, as the name implies, is a consideration of the steps that need to be performed before formulation proper can begin. Preformulation involves a full understanding of the physicochemical properties of drugs and other ingredients (excipients) in a dosage form and how they may interact. An early grasp of this knowledge during product development is of great use to the formulation scientist as the data gathered in these early stages can influence strongly the design of the future dosage form. Results of tests carried out at this stage of development can give a much clearer indication of the possible (and indeed impossible) dosage forms for a new drug candidate.

Following consideration of preformulation, the remaining chapters of Part 5 cover the formulation, small- and large-scale manufacture, characterization and the advantages and disadvantages of the wide range of available dosage forms. The properties of these dosage forms can be modified dependent on the properties of the drug, excipients included, the route of drug administration and specific patient needs. Early chapters consider liquid dosage forms, namely solutions (drug dispersed as molecules or ions), suspensions (drug dispersed as particles) and emulsions (one liquid phase dispersed in another, with drug present in either phase). These dosage forms may be administered by a number of routes, and their formulation requirements will vary depending on the route of administration. Appropriate formulation of emulsions results in more structured semisolid creams, most frequently used for application to the skin. Other dosage forms applied to the skin include ointments, pastes, gels, cutaneous patches and topical sprays; these are all discussed.

Whilst drugs in the solid state can be administered as simple powders, they are more usually formulated as solid dosage forms, namely tablets (currently the most commonly encountered solid dosage form) and capsules. Several chapters in this Part describe the various stages in the processing of a powder required to manufacture tablets: granulation (formation of drug-excipient aggregates), drying, compaction and coating. Tablet formulation and manufacture require inclusion of several excipients, including fillers, disintegrants, binders, glidants, lubricants and antiadherents. The purposes of these are described, together with their impact on product quality and performance. The strategies to modify the release of drug from solid dosage forms primarily involve the production of monolithic matrix systems or the use of a rate-controlling membrane. These are described in a separate chapter, as are other solid dosage forms: hard and soft capsules.

Pharmaceutical manufacturing has traditionally involved a series of separate, sequential unit operations, for instance, mixing, granulation, drying, compression and coating. Continuous manufacturing is a relatively new concept, whereby materials are moved continuously between the different steps of an integrated production process. It is considered in a separate chapter here, with a particular focus on tablet manufacturing.

For all dosage forms, drug must be released at an appropriate rate at the appropriate site for drug absorption and/or drug action to occur. This is particularly pertinent for solid oral dosage forms, which must permit dissolution of drug at an appropriate rate and at an appropriate site within the gastrointestinal tract. Bioavailability (i.e. the amount of drug that is absorbed into the bloodstream) may be limited by the rate of drug dissolution, whilst the pH range in the gastrointestinal tract (pH 1−8) may adversely affect the absorption of ionizable drugs. Consequently, dissolution testing is a key development and quality control test and is considered in detail here.

Solid dosage forms are administered predominantly (though not exclusively) by the oral route. Whilst the oral route is the most common way of administering drugs, many other routes for administration exist and are necessary. Each of these is considered in detail. Such routes (and possible dosage forms) include parenteral administration (injections, infusions, implants), pulmonary (aerosols), nasal (sprays, drops, semisolids, powders), ocular (drops, semisolids, injection, implants), otic (drops, semisolids, injection, implants), topical and transdermal (semisolids, patches, liquids, powders, sprays), ungual (nail lacquers, liquids), rectal (suppositories, tablets, capsules, semisolids, liquids, foams) and vaginal (pessaries, semisolids, films, rings, tampons). For each route, consideration is given here to the nature of the administration site and the formulation requirements either to localize drug action or to control absorption, as appropriate. The dosage forms available for delivering drugs by each route are outlined and particular aspects regarding their formulation and manufacture are highlighted. The methods used to characterize and test these dosage forms, for formulation development and quality assurance purposes are also detailed.

The final chapters of Part 5 reflect special considerations in dosage form design and manufacture.

Certain biotechnology products, for instance insulin, are long established, whilst others, such as nucleic acids for gene therapy and vaccines, offer exciting therapeutic possibilities now and for the future. These are relatively large macromolecules and present particular formulation and drug delivery challenges. Recent advances in cell therapies are also considered. To meet some of the challenges associated with delivery of biotechnology products as well as small molecules, pharmaceutical nanotechnology has become established in recent years as a means of improving solubility and dissolution rate, protecting drugs from hostile environments, minimizing adverse effects and delivering drugs to specific therapeutic targets. The preparation and properties of various nanomedicines, including antibodies, polymer–drug conjugates, liposomes, nanoparticles and dendrimers are considered.

Radiopharmaceuticals emit radiation, which presents particular challenges to those preparing and using them. They differ from other pharmaceutical products in that they are usually prepared at short notice for use in a specific patient. Radiopharmaceuticals are frequently not supplied as fully manufactured medicines, but instead require a local site (a radiopharmacy) to complete the manufacturing, purification, quality control and/or dispensing. Aspects of radiation, together with the formulation, preparation and delivery of radiopharmaceuticals are outlined.

Drugs of plant origin are discussed. Unlike conventional dosage forms these comprise plant extracts that have many complex components with potentially variable composition. The challenges of formulating these materials are explained, with reference to specific examples of commercially available products.

Some specific patient groups have particular needs. There has been an emphasis in recent years on the need for age-appropriate products, as it is increasingly recognized that conventional tablets and capsules may not be suitable dosage forms for individuals who have difficulties in swallowing, particularly the very young and elderly. This may require development of liquid dosage forms, subdivision of solid dosage forms or manipulation of an existing pharmaceutical product. Certain excipients, e.g. ethanol, propylene glycol and some dyes, are deemed inappropriate for use in paediatric formulations. The practical aspects of formulating and preparing age-specific products are considered.

Before finalizing the formulation and packaging of the dosage form, there must be a clear understanding of the stability of the drug(s) and other additives in a pharmaceutical product with respect to the reasons why, and the rates at which, they may degrade during storage. Aspects of product stability, stability testing and the selection of appropriate packaging to minimize deterioration during storage are considered in Part 6 (*Packaging, stability and pharmaceutical regulation*).

The product pack (container and closure) and any possible interactions between it and the drug or medicine it contains are so vitally linked that the final pack should not be considered as an afterthought. Instead, packaging considerations should be uppermost in the minds of formulators as soon as they receive the drug substance on which to work. The technology of packaging and filling of products is discussed.

No product will be stable indefinitely, and so mechanisms (i.e. the fundamental chemistry) and kinetics of degradation must be understood so that a safe and realistic shelf-life for every product can be determined.

Possible routes of microbiological contamination of medicines and the ways in which this can be prevented or minimized are discussed. It is shown how the presence of antimicrobial preservatives in the medicine can minimize the consequences of such contamination. However, such preservatives must be nontoxic by the route of administration and should not interact with components of the drug product or its packaging.

There follows an explanation of how packaging considerations, chemical degradation and microbial contamination influence the stability of the final drug product. The methods whereby the stability of a product is assessed and a shelf-life ascribed are detailed.

The book concludes with a chapter outlining how medicines are regulated and how their quality is assured. By controlling the pharmaceutical quality of a medicinal product, manufacturers ensure that it is fit for purpose, and that it is therapeutically effective and safe. Application of the theories and practices described in the preceding chapters allows quality to be *built into* a medicinal product. This is achieved by fully characterizing and controlling the physicochemical properties of the

drug substance, understanding and optimizing the formulation, designing and controlling the manufacturing process to produce the drug product reproducibly and designing the formulation and packaging of the product to ensure stability throughout its shelf life.

Once the product is demonstrated to be of appropriate quality for patient use, and following approval by regulatory authorities, the pharmaceutical technologist passes the product on to another aspect of pharmacy — the interface with the patient, i.e. dispensing and pharmacy practice. These disciplines are dealt with in other texts.

Chapter 1

Design of dosage forms

Peter York

CHAPTER CONTENTS

Principles of dosage form design

Drugs are rarely administered as pure chemical substances alone and are almost always given as formulated preparations or medicines. These can range from relatively simple solutions to complex drug delivery systems through the use of appropriate additives or excipients in the formulations. The excipients provide varied and specialized pharmaceutical functions. It is the formulation additives that, amongst other things, solubilize, suspend, thicken, preserve, emulsify, modify dissolution, increase the compactability and improve the flavour of drug substances to form various medicines or dosage forms.

The principal objective of dosage form design is to achieve a predictable therapeutic response to a drug included in a formulation which can be manufactured on a large scale with reproducible product quality. To ensure product quality, numerous features are required: chemical and physical stability, with suitable preservation against microbial contamination if appropriate, uniformity of the dose of the drug, acceptability to users, including both prescriber and patient, and suitable packaging and labelling. Ideally, dosage forms should also be independent of patient-to-patient variation, although in practice this feature remains difficult to achieve. However, recent developments are beginning to accommodate this requirement. These include drug delivery systems that rely on the specific metabolic activity of individual patients and implants that respond, for example, to externally applied sound or magnetic fields to trigger a drug delivery function.

Consideration should be given to differences in the bioavailability of drugs (the rate and extent to which they are absorbed) and their biological fate in patients between apparently similar formulations and possible causative reasons. In recent years, increasing attention has therefore been directed towards elimination of variation in bioavailability characteristics, particularly for medicinal products containing an equivalent dose of a drug substance, as it is recognized that formulation factors can influence their therapeutic performance. To optimize the bioavailability of drug substances, it is often necessary to carefully select the most appropriate chemical form of the drug. For example, such selection should address solubility requirements, drug particle size and drug physical form and should consider appropriate additives and manufacturing aids coupled with selection of the most appropriate administration route(s) and dosage form(s). Additionally, suitable manufacturing processes, labelling and packaging are required.

There are numerous dosage forms into which a drug substance can be incorporated for the convenient and efficacious treatment of a disease. Dosage forms can be designed for

administration by a variety of delivery routes to maximize therapeutic response. Preparations can be taken orally or injected, as well as being applied to the skin or inhaled; Table 1.1 lists the range of dosage forms which can be used to deliver drugs by the various administration routes. However, it is necessary to relate the drug substance to the clinical indication being treated before the correct combination of drug and dosage form can be made, as each disease or illness often requires a specific type of drug therapy. In addition, factors governing the choice of administration route and the specific requirements of that route which affect drug absorption need to be taken into account when dosage forms are being designed.

Many drugs are formulated into several dosage forms of various strengths, each having selected pharmaceutical characteristics which are suitable for a specific application. One such drug is the glucocorticoid prednisolone used in the suppression of inflammatory and allergic disorders. Through the use of different chemical forms and formulation additives, a range of effective anti-inflammatory preparations are available, including tablets, gastro-resistant coated tablets, injections, eye drops and enemas. The extremely low aqueous solubility of the base prednisolone and its acetate salt makes these forms useful in tablet and slowly absorbed intramuscular suspension injection forms, whilst the soluble sodium phosphate salt enables preparation of a soluble tablet form and solutions for eye and ear drops, enemas and intravenous injections. The analgesic paracetamol is also available in a range of dosage forms and strengths to meet the specific needs of the user, including tablets, hard and soft capsules, dispersible tablets, effervescent tablets, paediatric soluble tablets, paediatric oral solution, sugar-free oral solution, oral suspension, double-strength oral suspension, solution for infusion and suppositories.

Table 1.1 Dosage forms available for different administration routes

Administration route	Dosage forms
Oral	Solutions, syrups, suspensions, emulsions, gels, powders, granules, capsules, tablets
Rectal	Suppositories, capsules, ointments, creams, powders, solutions, foams, tampons
Vaginal	Pessaries, creams, gels, films, rings, solutions, suspensions, emulsions, foams, tampons
Topical	Ointments, creams, pastes, lotions, gels, solutions, topical sprays, foams, topical and transdermal patches
Parenteral	Injections (solution, suspension, emulsion forms), implants, irrigation and dialysis solutions
Pulmonary	Aerosols (solution, suspension, emulsion, powder forms), inhalations, sprays, gases
Nasal	Solutions, suspensions, powders, inhalations
Ocular	Solutions, suspensions, ointments, creams
Otic	Solutions, suspensions, ointments, creams

In addition, whilst many new drugs based on low molecular weight organic compounds continue to be discovered and transformed into medicinal products, the development of drugs from biotechnology is increasing and the importance of these therapeutic agents is growing. Such active compounds are macromolecular and of relatively high molecular weight and include materials such as peptides, proteins and viral components. These drug substances present different and complex challenges in their formulation and processing into medicines because of their alternative biological, chemical and structural properties. Nevertheless, the underlying principles of dosage form design remain applicable.

At present, these therapeutic agents are principally formulated into parenteral dosage forms, although other routes of administration are being considered and researched. Delivery of biotechnologically based drug substances via these routes of administration imposes additional constraints on the selection of appropriate formulation excipients.

Another growing area of clinically important medicines is that of polymer therapeutics. These agents include designed macromolecular drugs, polymer–drug and polymer–protein conjugates as nanomedicines, generally in injection form. These agents can also provide drug-targeting features (e.g. treating specific cancers) as well as modified pharmacokinetic profiles (e.g. changed drug metabolism and elimination kinetics).

It is therefore apparent that before a drug substance can be successfully formulated into a dosage form, many factors must be considered. These can be broadly grouped into three categories:

1. biopharmaceutical considerations, including factors affecting the absorption of the drug substance from different administration routes;

2. drug factors, such as the physical and chemical properties of the drug substance; and
3. therapeutic considerations, including consideration of the clinical indication to be treated and patient factors.

High-quality and efficacious medicines will be formulated and prepared only when all these factors are considered and related to each other. This is the underlying principle of dosage form design.

Biopharmaceutical aspects of dosage form design

Biopharmaceutics can be regarded as the study of the relationship between the physical, chemical and biological sciences as applied to drugs, dosage forms and drug action. Clearly, understanding the principles of this subject is important in dosage form design, particularly with regard to drug absorption, as well as drug distribution, metabolism and excretion. In general, a drug substance must be in solution before it can be absorbed via absorbing membranes and epithelia of the skin, gastrointestinal tract and lungs into body fluids. Drugs are absorbed in two general ways: by passive diffusion and by carrier-mediated transport mechanisms. In passive diffusion, which is thought to control the absorption of many drugs, the process is driven by the concentration gradient existing across the cellular barrier, with drug molecules passing from regions of high concentration to regions of low concentration. Lipid solubility and the degree of ionization of the drug at the absorbing site influence the rate of diffusion. Recent research into carrier-mediated transport mechanisms has provided much information and knowledge, providing guidance in some cases for the design of new drug molecules. Several specialized transport mechanisms are postulated, including active and facilitated transport. Once absorbed, the drug can exert a therapeutic effect either locally or at a site of action remote from the site of administration. In the latter case the drug has to be transported in body fluids (Fig. 1.1).

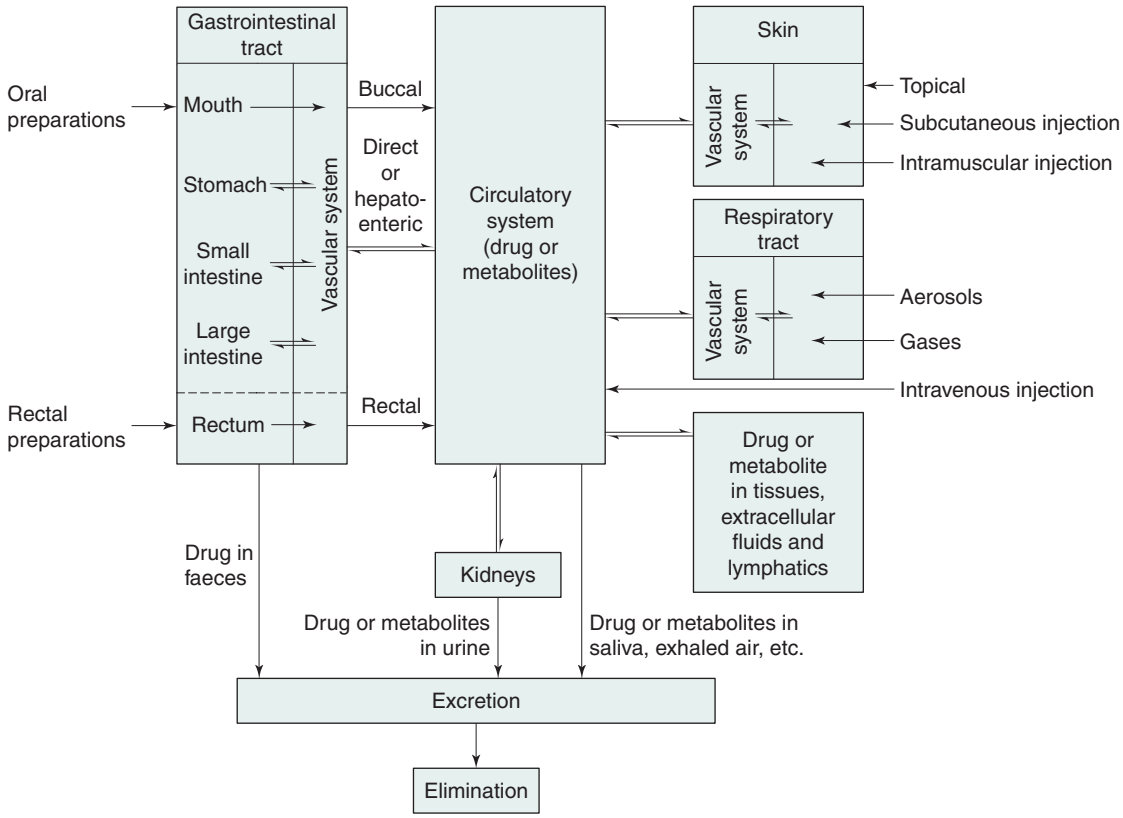

Fig. 1.1 Pathways a drug may take following the administration of a dosage form by different routes.

Table 1.2 Variation in time of onset of action for different dosage forms

Time of onset of action	Dosage forms
Seconds	Intravenous injections
Minutes	Intramuscular and subcutaneous injections, buccal tablets, aerosols, gases
Minutes to hours	Short-term depot injections, solutions, suspensions, powders, granules, capsules, tablets, modified-release tablets
Several hours	Gastro-resistant coated formulations
Days to weeks	Depot injections, implants
Varied	Topical preparations

When the dosage form is designed to deliver drugs via the buccal, respiratory, rectal, intramuscular or subcutaneous routes, the drug passes directly into the circulating blood from absorbing tissues, whilst the intravenous route provides the most direct route of all. When a drug is delivered by the oral route, the onset of drug action will be delayed because of the required transit time in the gastrointestinal tract before absorption, the absorption process and factors associated with hepatoenteric blood circulation. The physical form of the oral dosage form will also influence the absorption rate and onset of action, with solutions acting faster than suspensions, which in turn generally act faster than capsules and tablets. Dosage forms can thus be listed in order of the time of onset of the therapeutic effect (Table 1.2). However, all drugs irrespective of their delivery route remain foreign to the human body, and distribution, metabolic and elimination processes commence immediately following drug absorption until the drug is eliminated from the body via the urine, faeces, saliva, skin or lungs in unchanged or metabolized form.

Routes of drug administration

The absorption pattern of drugs differs considerably between individual drug substances, as well as between the different administration routes. Dosage forms are designed to provide the drug in a suitable form for absorption from each selected route of administration. The following discussion considers briefly the routes of drug administration and, whilst dosage forms are mentioned, this is intended only as an introduction since they will be dealt with in greater detail later in this book.

Oral route

The oral route is the most frequently used route for drug administration. Oral dosage forms are intended usually for systemic effects resulting from drug absorption through the various epithelia and mucosa of the gastrointestinal tract. A few drugs, however, are intended to dissolve in the mouth for rapid absorption or for local effect in the gastrointestinal tract because of poor absorption by this route or low aqueous solubility. Compared with other routes, the oral route is the simplest, most convenient and safest means of drug administration. However, disadvantages include the relatively slow onset of drug action and the possibilities of irregular absorption and destruction of certain drugs by the enzymes and secretions of the gastrointestinal tract. For example, insulin-containing preparations are inactivated by the action of stomach fluids.

Whilst drug absorption from the gastrointestinal tract follows the general principles described later in this book, several specific features should be emphasized. Changes in drug solubility can result from reactions with other materials present in the gastrointestinal tract, for example, interference with absorption of tetracyclines through the formation of insoluble complexes with calcium, which can be available from foodstuffs or formulation additives.

Gastric emptying time is an important factor for effective drug absorption from the intestine. Slow gastric emptying can be detrimental to drugs inactivated by the gastric juices and can delay absorption of drugs more effectively absorbed from the intestine. In addition, since environmental pH can influence the ionization and lipid solubility of drugs, the pH change occurring along the gastrointestinal tract, from a pH as low as 1 in the stomach to approximately 7 or 8 in the large intestine, is important for both the site and extent of drug absorption. Since membranes are more permeable to un-ionized forms than to ionized forms and since most drugs are weak acids or bases, it can be shown that weak acids, being largely un-ionized, are well absorbed from the stomach. In the small intestine (pH from approximately 4 to 6.5), with its extremely large absorbing surface, both weak acids and weak bases are well absorbed.

The most popular oral dosage forms are tablets, capsules, suspensions, solutions and emulsions. Tablets are prepared by compaction and contain drugs and formulation additives which are included for specific functions, such as disintegrants, which promote tablet break-up into granules and powder particles in the gastrointestinal tract, facilitating drug dissolution and absorption. Tablets are often coated, either to provide a protective barrier to environmental factors for drug stability purposes or to mask unpleasant drug taste, as well as to protect drugs from the acid conditions of the stomach (gastro-resistant coating). Increasing use is being made of modified-release

tablet products such as fast-dissolving systems and controlled-release, delayed-release or sustained-release formulations. The benefits of controlled-release tablet formulations, achieved, for example, by the use of polymeric-based tablet cores or coating membranes, include reduced frequency of drug-related side effects and maintenance of steady levels of drug in the plasma for extended periods, which are important when medications are delivered for chronic conditions or where constant levels are required to achieve optimal efficacy, as in the treatment of angina and hypertension.

Capsules are solid dosage forms containing the drug and, usually, appropriate filler(s), enclosed in a hard or soft shell composed primarily of gelatin or other suitable polymeric material. As with tablets, uniformity of dose can be readily achieved, and various sizes, shapes and colours of the shell are commercially available. The capsule shell readily ruptures and dissolves following oral administration, and in most cases drugs are released from capsules faster than from tablets. Recently, increased interest has been shown in the filling of hard capsules with semisolid and microemulsion formulations to provide rapidly dispersing dosage forms for poorly water-soluble drugs.

Suspensions, which contain finely divided drugs suspended in a suitable vehicle, are a useful means of administering large amounts of drugs that would be inconvenient if they were taken in tablet or capsule form. They are also useful for patients who experience difficulty in swallowing tablets and capsules and for paediatric use. Whilst dissolution of drugs is required before absorption, the fine solid particles in a suspension have a large surface area to present to the gastrointestinal fluids, and this facilitates drug dissolution, thus aiding absorption and thereby the onset of drug action. Not all oral suspensions, however, are formulated for systemic effects, and several are designed for local effects in the gastrointestinal tract. On the other hand, drugs presented as solutions, including formulations such as syrups and linctuses, are absorbed more rapidly than from solid dosage forms or suspensions since drug dissolution is not required.

Rectal route

Drugs given rectally in solution, suppository or emulsion form are generally administered for local rather than systemic effects. Suppositories are solid dosage forms intended for introduction into body cavities (usually rectal but also vaginal and urethral), where they melt, releasing the drug. The choice of suppository base or drug carrier can greatly influence the degree and rate of drug release. This route of drug administration is also indicated for drugs inactivated by the gastrointestinal fluids when given orally or when the oral route is precluded, for example when a patient is vomiting or unconscious. Drugs administered rectally enter the systemic circulation without passing through the liver, an advantage for drugs significantly metabolized by the liver following oral route absorption. Disadvantageously, the rectal route is inconvenient and drug absorption is often irregular and difficult to predict.

Parenteral routes

A drug administered parenterally is one injected via a hollow needle into the body at various sites and to various depths. The three main parenteral routes are subcutaneous, intramuscular and intravenous. Other routes, such as intracardiac, epidural and intrathecal, are used less frequently. The parenteral route is preferred when rapid absorption is essential, as in emergency situations or when patients are unconscious or unable to accept oral medication, and in cases when drugs are destroyed, inactivated or poorly absorbed following oral administration. In general, the blood levels attained are more predictable than those achieved by oral dosage forms.

Injectable preparations are usually sterile solutions or suspensions of drugs in water or other suitable physiologically acceptable vehicles. As referred to previously, drugs in solution are rapidly absorbed, and thus suspension injections act more slowly than solution injections. In addition, since body fluids are aqueous, by use of drugs suspended in oily vehicles, a preparation exhibiting slower absorption characteristics can be formulated to give a depot preparation, providing a reservoir of the drug, which is released slowly into the systemic circulation. Such preparations are administered by intramuscular injection deep into skeletal muscles (e.g. several penicillin-containing injections). Alternatively, depot preparations can be achieved by subcutaneous implants or pellets, which are compacted or moulded discs of drug placed in loose subcutaneous tissue under the outer layers of the skin. Such systems include solid microspheres and biodegradable polymeric microspheres (e.g. lactide and glycolic acid homopolymers and copolymers) containing proteins or peptides (e.g. human growth hormone and leuprolide). More generally, subcutaneous injections are aqueous solutions or suspensions which allow the drug to be placed in the immediate vicinity of blood capillaries. The drug then diffuses into the capillaries. Inclusion of vasoconstrictors or vasodilators in subcutaneous injections will influence blood flow through the capillaries, thereby modifying the capacity for absorption. This principle is often used in the administration of local anaesthetics with the vasoconstrictor adrenaline, which delays drug absorption. Conversely, increased drug absorption can result when vasodilators are included. Intravenous administration involves injection of sterile aqueous solutions directly into a vein at an appropriate rate. The volumes delivered can range from a few millilitres, as in emergency treatment or for hypnotics, to litre quantities, as in replacement fluid treatment or parenteral nutrition.

Given the generally negative patient acceptance of this important route of drug delivery, primarily associated with pain and inconvenience, recent developments to help with self-injection by patients have focused on 'needle-free' injection systems and devices which propel the drug in aqueous solution or powder form at high velocity directly through the external layers of the skin.

Topical route

Drugs are applied topically (i.e. to the skin) mainly for local action. Whilst this route can also be used for systemic drug delivery, percutaneous absorption is often poor and erratic, although several transdermal patches delivering drugs for systemic distribution (e.g. fentanyl patches for severe pain management and nicotine patches for cessation of smoking) are available. The drugs applied to the skin for local effect include antiseptics, antifungals and anti-inflammatory agents, as well as skin emollients for protective effects.

Pharmaceutical topical formulations — ointments, creams and pastes — are composed of the drug in a suitable semisolid base, which is either hydrophobic or hydrophilic. The bases play an important role in determining the character of drug release from the formulation. Ointments are hydrophobic, oleaginous-based dosage forms, whereas creams are semisolid emulsions. Pastes contain more solids than ointments and thus are stiffer. For topical application in liquid form other than solution, lotions, suspensions of solids in aqueous solution or emulsions are used.

Application of drugs to other topical surfaces such as the eye, ear and nose is common, and ointments, creams, suspensions and solutions are used. Ophthalmic preparations are required, amongst other features, to be sterile. Nasal dosage forms include solutions or suspensions delivered by drops or fine aerosol from a spray. Ear formulations, in general, are viscous to prolong contact with affected areas.

Respiratory route

The lungs provide an excellent surface for absorption when the drug is delivered in gaseous, aerosol mist or ultrafine solid particle form. For drug particles presented to the lungs as an aerosol, particle size largely determines the extent to which they penetrate the alveolar region, the zone of rapid absorption. Drug particles that have diameters in the region of 1 μm to 5 μm reach the deep lung. Particles smaller than 1 μm are largely exhaled, and particles larger than 5 μm are deposited on larger bronchial airways. This delivery route is particularly useful for the direct treatment of asthma, with use of both powder aerosols (e.g. salmeterol xinafoate) and pressurized metered-dose inhalers containing the drug in liquefied inert propellant (e.g. salbutamol sulfate inhaler). Importantly, this delivery route is being increasingly recognized as a useful means of administering the therapeutic agents prepared using biotechnology requiring systemic distribution and/or targeted delivery, such as peptides and proteins.

Drug factors in dosage form design

Each type of dosage form requires careful study of the physical and chemical properties of drug substances to achieve a stable, efficacious product. These properties, such as dissolution, crystal size and polymorphic form, solid-state stability and drug–additive interaction, can have profound effects on the physiological availability and physical and chemical stability of the drug. Through combination of such information and knowledge with that from pharmacological and biochemical studies, the most suitable drug form and additives can be selected for the formulation of chosen dosage forms.

Whilst comprehensive evaluation of physicochemical properties will not be required for all types of formulations, those properties which are recognized as important in dosage form design and processing are listed in Table 1.3. The stresses to which the formulation might be exposed during processing and manipulation into dosage forms, as well as the procedures involved, are also listed in Table 1.3. Variations in physicochemical properties, occurring, for example, between batches of the same material or resulting from alternative treatment procedures, can modify the formulation requirements, as well as processing and dosage form performance. For instance, the fine milling of poorly water-soluble drug substances can modify their wetting and dissolution characteristics, which are important properties during granulation and product performance respectively. Careful evaluation of these properties and understanding of the effects of these stresses on these parameters are therefore important in dosage form design and processing, as well as for product performance.

Particle size and surface area

Particle size reduction results in an increase in the specific surface area (i.e. surface area per unit weight) of powders. Drug dissolution rate, drug absorption rate, drug content uniformity in dosage forms and stability are all dependent to various degrees on particle size, particle size distribution and particle interaction with solid surfaces. In many cases, for both drugs and excipients, particle size reduction is required to achieve the desired physicochemical characteristics.