SECOND EDITION

Pharmaceutics

THE SCIENCE OF DOSAGE FORM DESIGN

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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

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The 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 vary 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, among other things, solubilize, suspend, thicken, preserve, emulsify, modify dissolution, improve the compressibility and flavour drug substances to form various preparations 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 is capable of large-scale manufacture with reproducible product quality. To ensure product quality, numerous features are required: chemical and physical stability, suitable preservation against microbial contamination if appropriate, uniformity of dose of drug, acceptability to users including both prescriber and patient, as well as suitable packaging and labelling. Ideally, dosage forms should also be independent of patient to patient variation, although in practice this is difficult to achieve. However, recent developments that rely on the specific metabolic activity of individual patients, or implants that respond, for example, to externally applied sound or magnetic fields to trigger a drug delivery function, are beginning to accommodate this requirement.

Consideration should be given to differences in bioavailability between apparently similar formulations, and the possible causes for this. In recent years increasing attention has therefore been directed towards eliminating variation in bioavailability characteristics, particularly for chemically equivalent products, as it is now recognized that formulation

sensitive drugs antioxidants can be included in the formulation and, as with light-sensitive materials, suitable packaging can reduce or eliminate the problem. For drugs administered in liquid form, the stability in solution as well as the effects of pH over the gastrointestinal pH range of 1–8 should be understood. Buffers may be required to control the pH of the preparation to improve stability, or where liquid dosage forms are sensitive to microbial attack, preservatives are required. In these formulations, and indeed in all dosage forms incorporating additives, it is also important to ensure that the components, which may include additional drug substances as in multivitamin preparations, do not produce chemical interactions themselves. Interactions between drug(s) and added excipients, such as antioxidants, preservatives, suspending agents, colourants, tablet lubricants and packaging materials, do occur and must be checked for during formulation. Over recent years data from thermal analysis techniques, particularly differential scanning calorimetry (DSC), when critically examined have been found useful in rapid screening for possible drug-additive and drug–drug interactions. For example, using DSC it has been demonstrated that the widely used tableting lubricant magnesium stearate interacts with aspirin and should be avoided in formulations containing this drug.

Organoleptic properties

Modern medicines require that pharmaceutical dosage forms are acceptable to the patient. Unfortunately, many drug substances in use today are unpalatable and unattractive in their natural state and dosage forms containing such drugs, particularly oral preparations, may require the addition of approved flavours and/or colours.

The use of flavours applies primarily to liquid dosage forms intended for oral administration. Available as concentrated extracts, solutions, adsorbed on to powders or microencapsulated, flavours are usually composed of mixtures of natural and synthetic materials. The taste buds of the tongue respond quickly to bitter, sweet, salt or acid elements of a flavour. In addition, unpleasant taste can be overcome by using water-insoluble derivatives of drugs which have little or no taste. An example is the use of amitriptyline pamoate. In such approaches other factors, such as bioavailability, must remain unchanged. If an insoluble derivative is unavailable or cannot be used, a flavour or perfume can be used. Alternatively, unpleasant drugs can be administered in capsules or prepared as coated particles, or tablets may be easily swallowed avoiding the taste buds.

The selection of flavour depends upon several factors, but particularly on the taste of the drug substance. Certain flavours are more effective at masking various taste elements: for example, citrus flavours are frequently used to combat sour or acid-tasting drugs. The solubility and stability of the flavour in the vehicle are also important. The age of the intended patient should also be considered, as children, for example, prefer sweet tastes, as well as the psychological links between colours and flavours (e.g. yellow is associated with lemon flavour). Sweetening agents may also be required to mask bitter tastes. Sucrose continues to be used, but alternatives such as sodium saccharin, which is 200–700 times sweeter depending on concentration, are available. Sorbitol is recommended for diabetic preparations.

Colours are employed to standardize or improve an existing drug colour, to mask a colour change or complement a flavour. Although colours are obtained both from natural sources (e.g. carotenoids) and synthesized (e.g. amaranth), the majority used are synthetically produced. Dyes may be aqueous (e.g. amaranth) or oil soluble (e.g. Sudan IV) or insoluble in both (e.g. aluminium lakes). Insoluble colours are known as pigments. Lakes (which are generally water-insoluble calcium or aluminium complexes of water-soluble dyes) are particularly useful in tablets and tablet coatings because of their greater stability to light than corresponding dyes, which also vary in their stability to pH and reducing agents. However, in recent years the inclusion of colours in formulations has become extremely complex because of the banning of many traditionally used colours in many countries. (A useful summary on colours is given in Martindale, *The Extra Pharmacopoeia*).

Other drug properties

At the same time as ensuring that dosage forms are chemically and physically stable and are therapeutically efficacious, it is also relevant to establish that the selected formulation is capable of efficient and, in most cases, large-scale manufacture. In addition to those properties previously discussed, such as particle size and crystal form, other characteristics, such as hygroscopicity, flowability and compressibility, are particularly valuable when preparing solid dosage forms where the drugs constitute a large percentage of the formulation. Hygroscopic drugs can require low-moisture manufacturing environments and need to avoid water during preparation. Poorly flowing

Application of aerosols in pharmacy The use of aerosols as a dosage form is particularly important in the administration of drugs via the respiratory system. In addition to local effects, systemic effects may be obtained if the drug is absorbed into the bloodstream from the lungs. Topical preparations are also well suited for presentation as aerosols. Therapeutic aerosols are discussed in more detail in Chapter 31.

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formulations may require the addition of flow agents (e.g. fumed silica). Studies of the compressibility of drug substances are frequently undertaken using instrumented tablet machines in formulation laboratories to examine the tableting potential of the material, in order to foresee any potential problems during compaction, such as lamination or sticking which may require modification to the formulation or processing conditions.

THERAPEUTIC CONSIDERATIONS IN DOSAGE FORM DESIGN

The nature of the clinical indication, disease or illness against which the drug is intended is an important factor when selecting the range of dosage forms to be prepared. Factors such as the need for systemic or local therapy, the duration of action required and whether the drug will be used in emergency situations, need to be considered. In the vast majority of cases a single drug substance is prepared into a number of dosage forms to satisfy both the particular preferences of the patient or physician and the specific needs of a certain clinical situation. For example, many asthmatic patients use inhalation aerosols from which the drug is rapidly absorbed into the systematic circulation following deep inhalation for rapid emergency relief, and oral products for chronic therapy.

Patients requiring urgent relief from angina pectoris, a coronary circulatory problem, place tablets of nitroglycerin sublingually for rapid drug absorption from the buccal cavity. Thus, although systemic effects are generally obtained following oral and parenteral drug administration, other routes can be employed as the drug and the situation demand. Local effects are generally restricted to dosage forms applied directly, such as those applied to the skin, ear, eye and throat. Some drugs may be well absorbed by one route and not another, and must therefore be considered individually.

The age of the patient also plays a role in defining the types of dosage forms made available. Infants generally prefer liquid dosage forms, usually solutions and mixtures, given orally. Also, with a liquid preparation the amount of drug administered can be readily adjusted by dilution to give the required dose for the particular patient, taking weight, age and patient's condition into account. Children can have difficulty in swallowing solid dosage forms, and for this reason many oral preparations are prepared as pleasantly flavoured syrups or mixtures. Adults generally prefer solid dosage forms, primarily because of their convenience. However, alternative liquid preparations are usually available for those unable to take tablets and capsules.

Interest has grown recently in the design of formulations that deliver drugs to specific 'targets' in the body, for example the use of liposomes and nanoparticles, as well as providing drugs over longer periods of time at controlled rates. Alternative technologies for preparing particles with required properties – crystal engineering – provide new opportunities. Supercritical fluid processing using carbon dioxide as a solvent or antisolvent is one such method, allowing fine-tuning of crystal properties and particle design and fabrication. Undoubtedly these new technologies and others, as well as sophisticated formulations, will be required to deal with peptide and protein drugs, the advent of gene therapy and the need to deliver such labile macromolecules to specific cells in the body. Interest is also likely to be directed to individual patient requirements, such as age, weight and physiological and metabolic factors, features that can influence drug absorption and bioavailability.

SUMMARY

This chapter has demonstrated that the formulation of drugs into dosage forms requires the interpretation and application of a wide range of information from several study areas. Although the physical and chemical properties of drugs and additives need to be understood, the factors influencing drug absorption and the requirements of the disease to be treated also have to be taken into account when identifying potential delivery routes. The formulation and associated preparation of dosage forms demand the highest standards, with careful examination, analysis and evaluation of wide-ranging information by pharmaceutical scientists to achieve the objective of creating high-quality and efficacious dosage forms.

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PART ONE

SCIENTIFIC PRINCIPLES OF DOSAGE FORM DESIGN

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