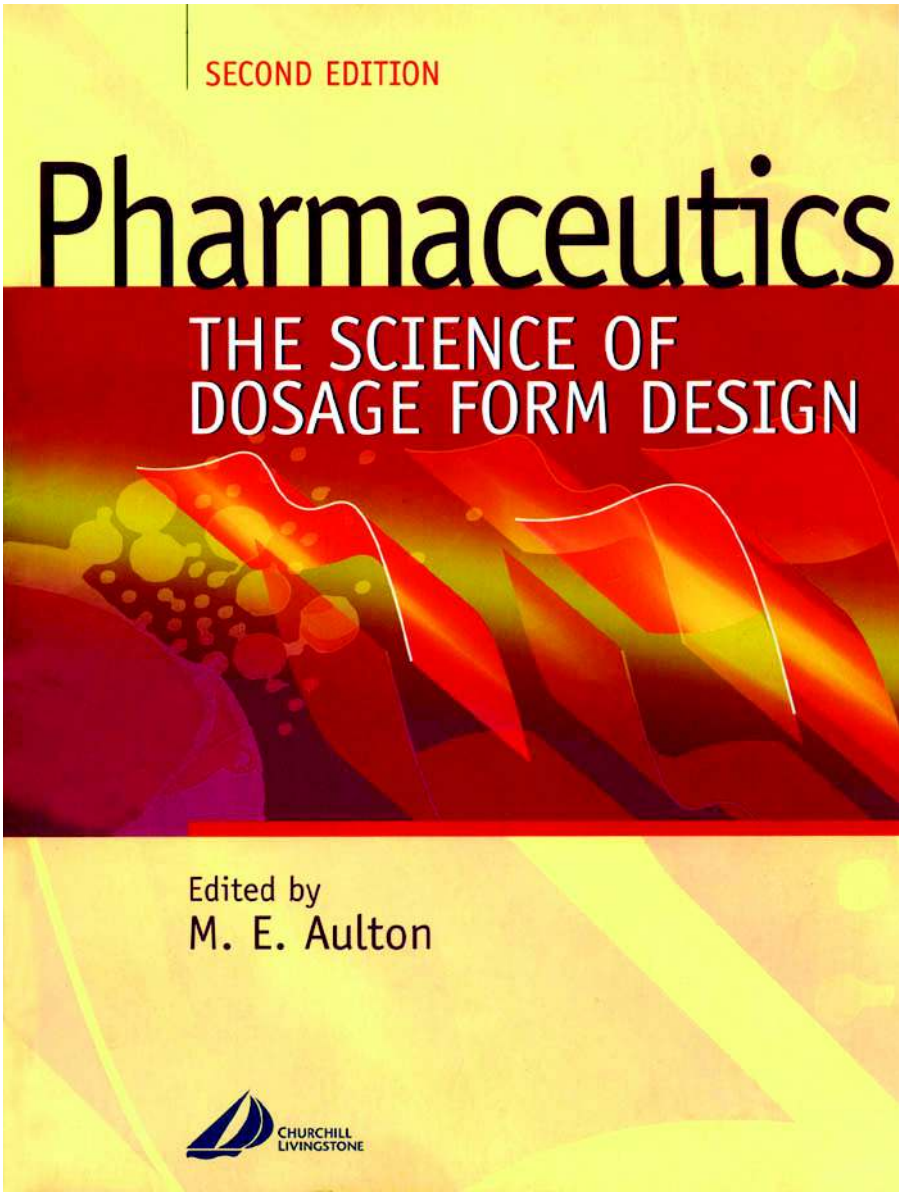

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The design of dosage forms

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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

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 physical form, and consider appropriate additives and manufacturing aids coupled to selecting the most appropriate administration route(s) and dosage form(s). Suitable manufacturing processes and packaging are also 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 alternative delivery routes to maximize therapeutic response. Preparations can be taken orally or injected, as well as being applied to the skin or inhaled, and Table 1.1 lists the range of dosage forms that 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 designing dosage forms.

Many drugs are formulated into several dosage forms of varying strengths, each having selected pharmaceutical characteristics 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 tablet, enteric-coated tablet, injections, eye drops and enema. The extremely low aqueous solubility of the base prednisolone and acetate salt makes these forms useful in tablet and slowly absorbed intramuscular suspension injection forms, whereas the soluble sodium phosphate salt enables a soluble tablet form, and solutions for eye and ear drops, enema and intravenous injection to be prepared. The analgesic paracetamol is also available in a range of dosage forms and strengths to meet specific needs of the user, including tablets, dispersible tablets, paediatric soluble tablets, paediatric oral solution, sugar-free oral solution, oral suspension, double-strength oral suspension 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, ointments, creams, powders, solutions
Topical	Ointments, creams, pastes, lotions, gels, solutions, topical aerosols
Parenteral	Injections (solution, suspension, emulsion forms), implants, irrigation and dialysis solutions
Respiratory	Aerosols (solution, suspension, emulsion, powder forms) inhalations, sprays, gases
Nasal	Solutions, inhalations
Eye	Solutions, ointments, creams
Ear	Solutions, suspensions, ointments creams

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;
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 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 form before it can be absorbed via the 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 specialized transport mechanisms. In passive diffusion, which is thought to control the absorption of most drugs, the process is driven by the concentration gradient that exists across the cellular barrier, with drug molecules passing from regions of high to those of low concentration. Lipid solubility and the degree of ionization of the drug at the absorbing site influence the rate of diffusion. 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 that of administration. In the latter case the drug has to be transported in body fluids (Fig. 1.1).

When the drug is administered from dosage forms designed to deliver via the buccal, respiratory, rectal, intramuscular or subcutaneous routes, it passes directly into the blood-stream from absorbing tissues, but the intravenous route is the most direct of all. When delivered by the oral route the onset of drug action will be delayed because of the required transit time in the gastrointestinal tract, the absorption process and hepatoenteric blood circulation features. The physical form of the oral dosage form will also influence 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 time of onset of therapeutic effect (Table 1.2). However, all drugs, irre-

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

Time of onset of action	Dosage forms
Seconds	i.v. injections
Minutes	i.m. and s.c. injections, buccal tablets, aerosols, gases
Minutes to hours	Short-term depot injections, solutions, suspensions, powders, granules, capsules, tablets, modified-release tablets
Several hours	Enteric-coated formulations
Days	Depot injections, implants
Varies	Topical preparations

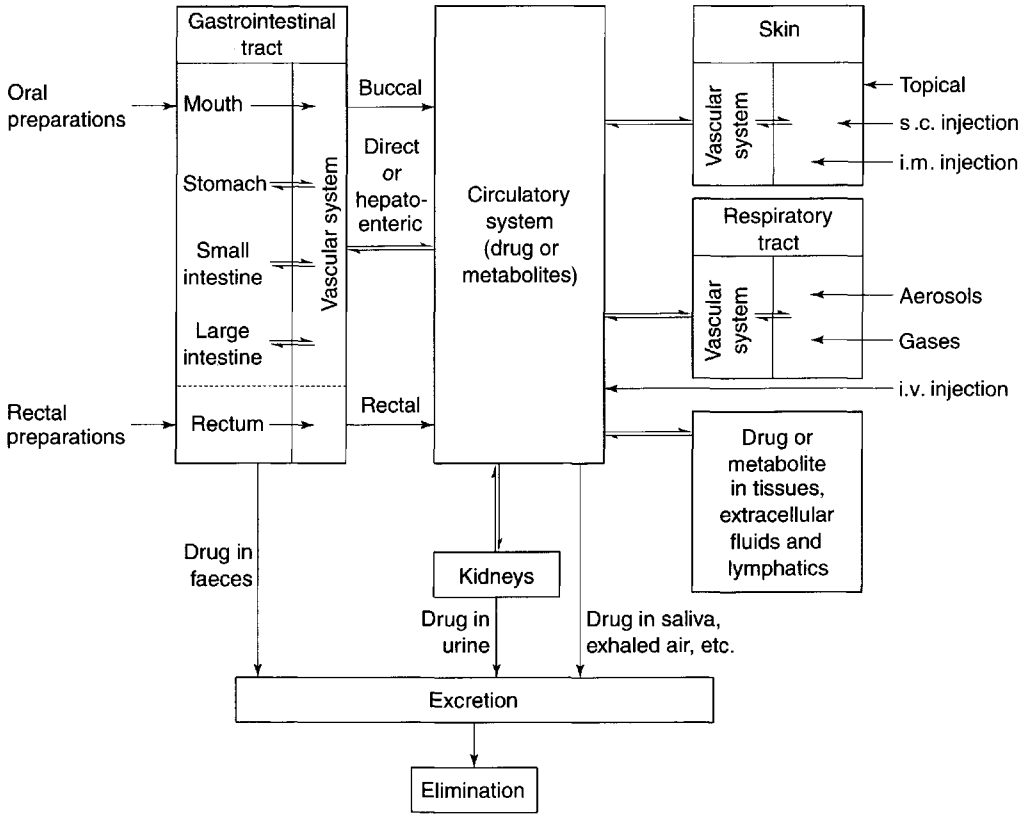

Fig. 1.1 Pathways a drug may take following the administration of a dosage form by different route.

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