Pharmaceutics

The science of dosage form design

Edited by M E Aulton

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Pharmaceutics: The Science of Dosage Form Design

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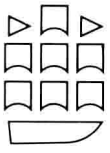

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Preface

The first edition of *Pharmaceutics* has replaced the 6th edition of *Cooper and Gunn's Tutorial Pharmacy* published by Pitman in 1972. Since then, there has been a change in editorship, a change in the title of the book, a change in some of the authors and a completely redesigned content. But all is not new and disjointed, the editorial link with Leicester School of Pharmacy continues. Sidney Carter recently retired as Deputy Head of Leicester School of Pharmacy and passed on the book to me. He in turn had inherited the book from one of its founders, the late Colin Gunn who was formerly Head of Leicester School of Pharmacy but sadly died on 25 February 1983.

There are a greater number and a wider range of authors in this edition, each an accepted expert in the field on which they have written and, just as important, each has experience and ability in imparting that information to undergraduate pharmacy students.

The philosophy of the subject matter which the book covers has changed because pharmaceutics has changed. Since the last edition of *Tutorial Pharmacy* there have been very marked changes in the concept and content of pharmaceutics. Those changes are reflected in this edition. The era of biopharmaceutics was in its infancy at the time of the previous edition. Since then we have become increasingly concerned with not merely producing elegant and accurate dosage forms but also ensuring that the optimum amount of drug reaches the required place in the body and stays there for the optimum amount of time. Now we are concerned much more with designing dosage forms and with all aspects of drug delivery. This book reflects that concern.

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My BBC micro.

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About this book

One of the earliest impressions that many new pharmacy 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 the term has been interpreted for the purpose of this book and how pharmaceutics fits into the overall scheme of pharmacy. It will also lead the reader through the organization of this book and explain the necessity of an understanding of the material contained in its chapters.

The word pharmaceutics is used in pharmacy 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. after its discovery or synthesis, isolation and purification, and testing for advantageous pharmacological effects and absence from serious toxicological properties. Pharmaceutics is arguably the most diverse of all the subject areas in pharmacy and traditionally encompasses the design and formulation of medicines (physical pharmaceutics, dosage form design), the manufacture of these medicines on both a small (compounding) and large (pharmaceutical technology) scale, the cultivation, avoidance and elimination of microorganisms (microbiology) and the distribution of medicines to patients (dispensing and pharmacy practice).

As the subtitle of this edition indicates, this book concentrates on that part of pharmaceutics which is concerned with the conversion of a drug chemical into a medicine — the design of dosage forms. Medicines are drug delivery systems; they are means of getting drugs into the body in a safe, efficient, reproducible and convenient manner. The first chapter in the book describes, 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,
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.

As a consequence of the first of these points, Part 1 of this book describes some of the more important physicochemical properties that one needs to know about 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 physicochemical principles which are important to the formulation scientist. They are not intended as a substitute for a thorough understanding of physical chemistry and specific more detailed texts are recommended throughout. For many reasons, which are discussed in the book, the vast majority of dosage forms are orally administered 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. This necessitates that the formulation scientist has a knowledge of both liquid and solid materials and particularly the properties of drugs in solution and the factors influencing drug dissolution from solid particles. However, before these subjects can be examined, the reader must first understand the way in which fluids flow and know a little about some of the resulting problems (additionally, solutions and semisolids are dosage forms in their own right). The properties of solutions are discussed next. The reader will see later in the book how drug release and absorption are strongly dependent on solution properties such as solute dissociation and diffusion. The properties of interfaces are described in the following chapter. These are important to an understanding of adsorption onto solid surfaces and as a prelude to the dissolution of solid particles and the study of disperse systems such as colloids, suspensions and emulsions. Before finalizing on a possible dosage form there must be a clear understanding of the stability of the drug(s) and other additives in the formulation with respect to the reasons why and the rates at which they degrade and there must be an awareness of means of inhibiting decomposition and increasing the shelf life of a product.

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

The terms bioavailability and biopharmaceutics are defined and explained in Part 2 of the book. The factors influencing the bioavailability of a drug and methods of assessing it are described. Finally in that section consideration is given to the manner in which the frequency of administration of a drug affects its level in the blood at any given time.

In Part 3, the book then goes on to discuss the actual drug delivery systems which are available. It covers their formulation, the release of drugs from them, and their advantages and disadvantages as a dosage form. This part starts with a consideration of the pack into which the medicine is put. This may seem odd since packaging is often the last stage in a manufacturing process but the pack and any possible interactions between it and the drug or medicine it contains are so vitally linked that it must not be considered as an afterthought; these should be uppermost in the minds of the formulators as soon as they receive the drug powder on which to work. The steps that need to be considered before formulation itself can begin — preformulation — are discussed next. Results of tests carried out at this stage can give a much clearer indication of the possible dosage forms for a new drug candidate. Part 3 then considers existing dosage forms suitable for the administration of drugs through almost every possible body orifice and external surface, as well as an intimation to novel or future drug delivery systems.

Microbiology is a very wide ranging subject that is traditionally associated with pharmaceutics in schools of pharmacy. This book, in Part 4, has concentrated 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) their presence in medicines (contamination), and preventing the growth of any microorganism which might enter the product during storage and use (preservation). Techniques for testing that these intentions have been achieved are also described.

The actual production of medicines on a large scale is dealt with in the final part of the book, pharmaceutical technology. This begins with a consideration of the reaction vessels that are used during the manufacture of the drug chemical, other additives and the dosage form itself.

There then follows an examination of those aspects of production mainly associated with liquids, i.e. heat transfer and filtration. The tech-

nological problems associated with the manufacture of solid dosage forms are then described. The reader will quickly realize that a major problem in preparing solid dosage forms is the handling of powders and thus the book explains the concept of particle size of powders and its measurement, size reduction and size separation of powders from those of other sizes and the many problems associated with the flow of powders. In tablet and capsule production, for example, it is not simply enough to achieve fast flow, but that flow must also be uniform. We then see how powders are effectively enlarged in size (granulation). This is necessary partly to overcome some powder flow and tableting problems and also because granules are themselves a dosage form. Granulation most commonly involves the wetting of dry powders and so the drying of this wet material is described next. The book then moves on to tableting, tablet coating and encapsulation.

Following this, techniques associated with the microbiological aspects of production are discussed. These are necessary in industry to eliminate microorganisms from the product both before or during manufacture. The technology of packaging and filling of products completes the book since this is the final production stage before warehousing, distribution and finally dispensing to the public.

At this point the pharmaceutical technologist passes the product on to that other aspect of pharmaceutics — the interface with the patient, i.e. dispensing and pharmacy practice. These aspects are dealt with in the companion volume Cooper and Gunn's *Dispensing for Pharmaceutical Students* later to become *Pharmaceutical Practice*.

Contents

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P York

The design of dosage forms

PRINCIPLES OF DOSAGE FORM DESIGN

Drugs are rarely administered solely as pure chemical substances but are almost always given in formulated preparations. These can vary from relatively simple solutions to complex drug delivery systems, through the use of appropriate additives or excipients in the formulations to provide varied and specialized pharmaceutical functions. It is the formulation additives that, amongst other things, solubilize, suspend, thicken, preserve, emulsify, 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, with 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 feature remains difficult to achieve. Future developments in dosage form design may well attempt to accommodate to some extent this requirement.

Reference is made in Part 2 of this book to differences in bioavailability between apparently similar formulations and possible causative reasons. In recent years increasing attention has therefore been directed towards eliminating variation in bioavailability characteristics, particularly for chemically equivalent products since 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 derivative of the drug, for example to obtain a specific solubility requirement, as well as its particle size and physical form, to combine it with appropriate additives and manufacturing aids that will not significantly alter the properties of the drug, to select the most appropriate administration route(s) and dosage form(s) and to consider aspects of manufacturing processes and suitable packaging.

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 all possible 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 which can be used to deliver drugs by the various administration routes. However, it is necessary to relate the drug substance and the disease state before the correct combination of drug and dosage form can be made since each disease or illness will require a specific type of drug therapy. In addition factors governing 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.

Table 1.1 Range of dosage forms available for different administration routes

Administration route	*Dosage forms*
Oral	Solutions, syrups, elixirs, 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
Lungs	Aerosols (solution, suspension, emulsion, powder forms), inhalations, sprays, gases
Nasal	Solutions, inhalations
Eye	Solutions, ointments
Ear	Solutions, suspensions, ointments

Versatile drugs are often formulated into several dosage forms of varying strengths, each having particular pharmaceutical characteristics which are suitable for a specific application. One such drug is the glucocorticoid prednisolone. 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, whilst the soluble sodium phosphate salt enables a soluble tablet form, and solutions for eye drops, enema and intravenous injection to be prepared. The antibacterial drug combination co-trimoxazole, consisting of a mixture of five parts of sulphamethoxazole and one part trimethoprim, is also available in a range of dosage forms and strengths to meet specific needs of the user, including tablets, dispersible tablets, double strength tablets, double strength dispersible tablets, paediatric mixture, intramuscular injection, and a strong sterile solution for the preparation of an intravenous infusion. Because of the low aqueous solubility of both drug substances, specialized solvents are used for the intramuscular injection: 52% glycofurol, and strong sterile solution, 40% propylene glycol.

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 disease to be treated and patient factors.

Appropriate and efficacious dosage forms will be prepared only when all these factors are

considered and related to each other. This is the underlying principle of dosage form design.

BIOPHARMACEUTICAL CONSIDERATIONS IN 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 of 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 absorbing membranes of the skin, gastrointestinal tract and lungs into body fluids. Drugs penetrate these membranes 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 existing across the membrane with drug molecules passing from regions of high to low concentration. The lipid solubility and 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 yet the site of action is often remote from the site of administration and has to be transported in body fluids (see Fig. 1.1).

When the drug is administered from dosage

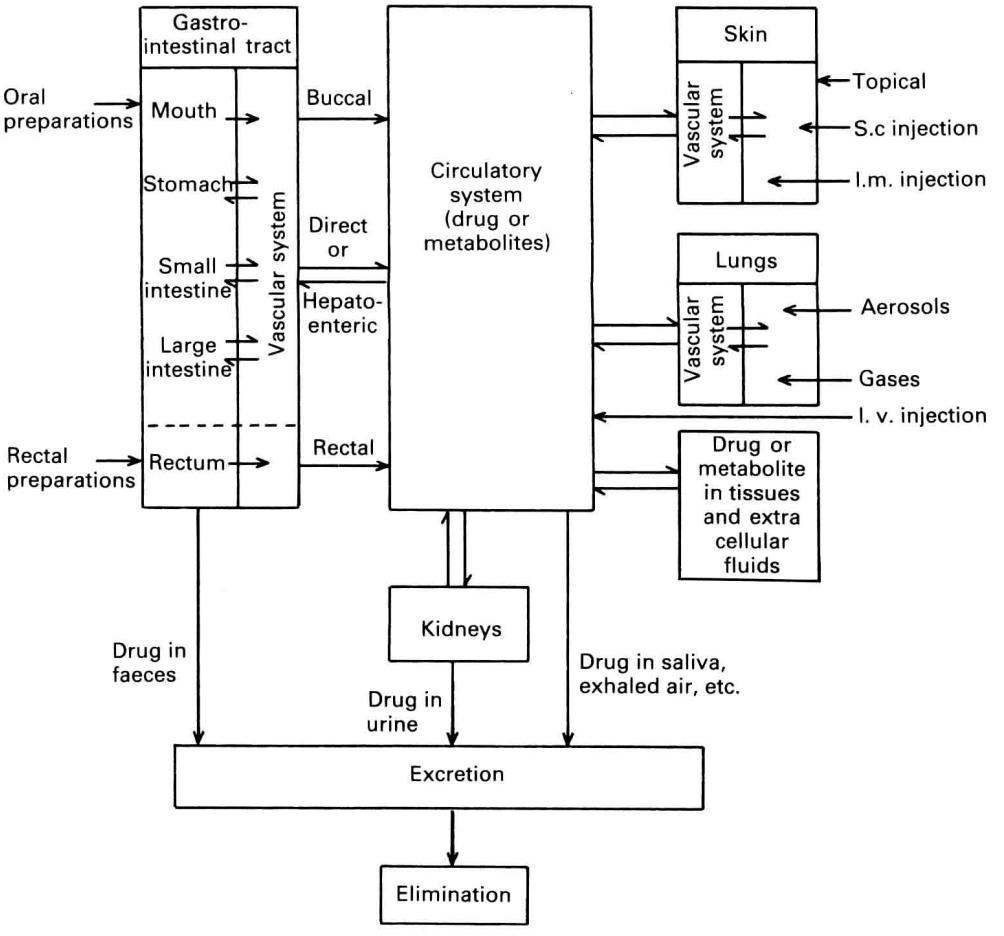

Fig. 1.1 Schematic diagram illustrating pathways a drug may take following administration of a dosage form by different routes

forms designed to deliver drugs via the buccal, rectal, intramuscular or subcutaneous routes, the drug passes directly into the circulation blood from absorbing tissues, whilst the intravenous route provides the most direct route of all. When delivered by the oral route onset of drug action will be delayed because of 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 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 speed of onset of therapeutic effect (see Table 1.2). However, all drugs irrespective of their delivery route remain foreign substances to the human body and distribution, metabolic and elimination processes commence immediately following drug absorption until the drug has been eliminated from the body via the urine, faeces, saliva, skin or lungs in unchanged or metabolized form.

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

Time of onset of action	*Dosage form*
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, sustained release tablets
Several hours	Enteric coated formulations
Days	Depot injections, implants
Varies	Topical preparations

Routes of drug administration

The absorption pattern of drugs varies considerably between one another as well as between each potential administration route. 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 in the chapters of Part 3.

Oral route

The oral route is the most frequently used route for drug administration. Oral dosage forms are usually intended for systemic effects resulting from drug absorption through the various 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 tract due to 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. Disadvantages, however, include relatively slow onset of action, 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 outlined in Chapter 9, several specific features should be emphasized. Changes in drug solubility can result from reactions with other materials present in the gastrointestinal tract, as for example the interference of 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, or slow down 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 of about 1 in the stomach to approximately 7 or 8 in the large intestine, is important to both degree and site of drug absorption. Since membranes are more permeable to unionized rather than ionized forms and since most drugs are weak acids or bases, it can be shown that weak acids being largely unionized are well absorbed from the stomach. In the small intestine (pH about 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 compression 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 coat from 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 (enteric coating). Specialized tablet formulations are also available to provide controlled drug release systems through, for example, the use of tablet core matrices or polymeric coating membranes.

Capsules are solid dosage forms containing drug and usually appropriate filler(s), enclosed in a hard or soft shell composed of gelatin. As with tablets, uniformity of dose can be readily achieved and various sizes, shapes, and colours of shell are commercially available. The gelatin shell readily ruptures and dissolves following oral administration and in most cases drugs are released from capsules faster than from tablets.[1] Recently, renewed interest has been shown in filling semi-solid formulations into hard gelatin capsules to provide rapidly dispersing dosage forms for poorly soluble drugs.

Suspensions, which contain finely divided drugs suspended in a suitable vehicle, are a useful means of administering large amounts of drugs which would be inconvenient if 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 drug is required prior to absorption following administration of a dose of drug, fine particles with a large surface area are presented to dissolving fluids which facilitates drug dissolution and thereby the onset of drug action. Not all oral suspensions, however, are formulated for systemic effects and several, for example Kaolin and Morphine Mixture B.P.C., are designed for local effects in the gastrointestinal tract. Solutions, including formulations such as elixirs, syrups and linctuses, on the other hand are absorbed more rapidly than 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 forms intended for introduction into body cavities (usually rectal, but also vaginal and urethral) where they melt, releasing the drug, and the choice of suppository base or drug carrier can greatly influence the degree and rate of drug release. This route of drug administration is indicated for drugs inactivated when given orally by the gastrointestinal fluids, when the oral route is precluded, as for example when a patient is vomiting or unconscious. Drugs administered rectally also enter the systemic circulation without passing through the liver, an advantage for drugs significantly inactivated by the liver following oral route absorption. Disadvantageously the rectal route is inconvenient and drug absorption is often irregular and difficult to predict.

Parenteral route

A drug administered parenterally is one injected via a hollow needle into the body at various sites and to varying depths. The three main parenteral routes are subcutaneous (s.c.), intramuscular (i.m.) and intravenous (i.v.), although other routes are less frequently used such as intracardiac and intrathecal. 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 or inactivated or poorly absorbed following oral administration. Absorption after parenteral drug delivery is rapid and, in general, 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 must be in solution to be absorbed and thus injection suspensions are slower acting than solution injections. In addition, since body fluids are aqueous, by using suspended drugs in oily vehicles a preparation exhibiting slower absorption characteristics can be formulated to provide a depot preparation providing a

reservoir of drug which is slowly released 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 compressed or moulded discs of drug placed in loose subcutaneous tissue under the outer layers of the skin. 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 capillary. Inclusion of vasoconstrictors or vasodilators in subcutaneous injections will clearly 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 improved drug absorption can result when vasodilators are included. Intravenous administration involves injection of sterile aqueous solutions directly into a vein at an appropriate rate. Volumes delivered can range from a few millilitres, as in emergency treatment or for hypnotics, up to litre quantities as in replacement fluid treatment or nutrient feeding.

Topical route

Drugs are applied topically, that is to the skin, mainly for local action. Whilst this route can also be used for systemic drug delivery, percutaneous absorption is generally poor and erratic. Drug absorption is via the sweat glands, hair follicles, sebaceous glands and through the stratum corneum and drugs applied to the skin for local effect include antiseptics, antifungals, anti-inflammatory agents, as well as skin emollients for protective effects.

Pharmaceutical topical formulations — ointments, creams and pastes — are composed of drug in a suitable semisolid base which is either hydrophobic or hydrophilic in character. The bases play an important role in determining the drug release character 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 in consistency. 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, suspensions and solutions are utilized. 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 or aerosol mist form. For drug particles presented as an aerosol, droplet particle size largely determines the extent to which they penetrate the alveolar region, the zone of rapid absorption. Soluble drug particles that are in the range 0.5–1 μm diameter reach the alveolar sacs. Particles outside this range are either expired or deposited upon larger bronchial airways. This delivery route has been found particularly useful for the treatment of asthmatic problems, using both powder aerosols (e.g. sodium cromoglycate) and metered aerosols containing the drug in liquefied inert propellant (e.g. isoprenaline sulphate aerosol and salbutamol aerosol).

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. By combining such data with those from pharmacological and biochemical studies, the most suitable drug form and additives can be selected for the formulation of chosen dosage forms. Whilst