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

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

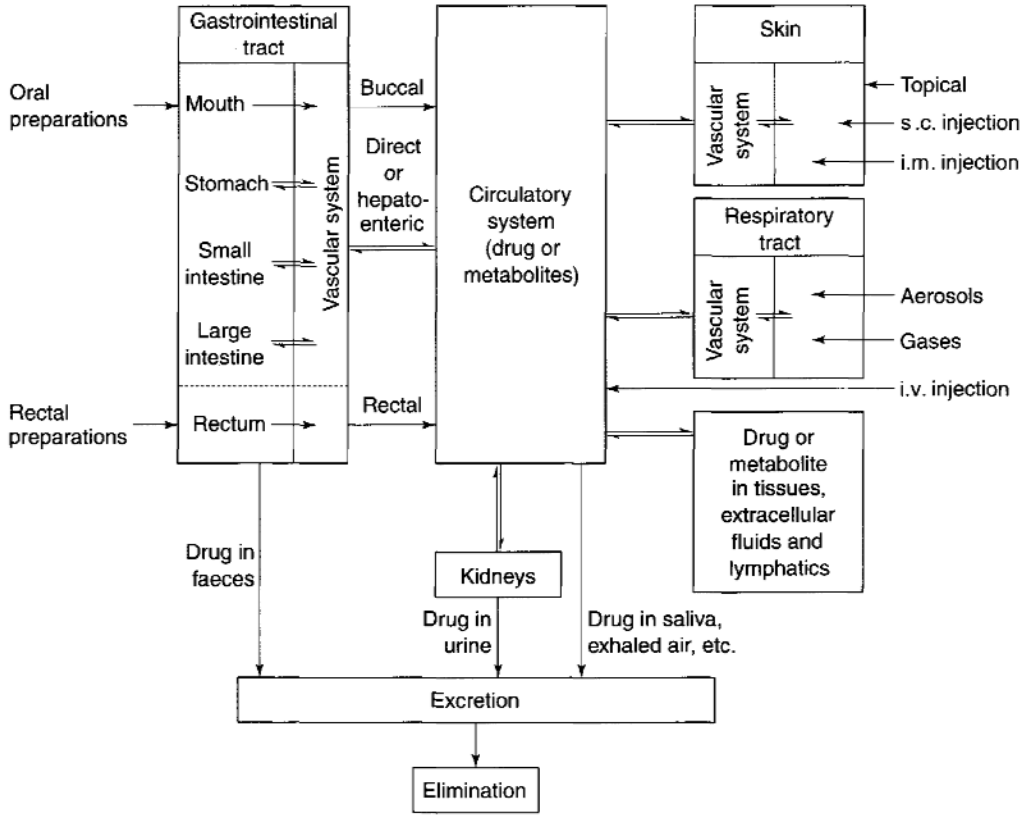

Fig. 1.1 Pathways a drug may take following the administration of a dosage form by different route.

spective of their delivery route, remain foreign substances to the human body, and distribution, metabolic and elimination processes commence immediately following absorption until the drug is eliminated from the body via the urine, faeces, saliva, skin or lungs in either unchanged or metabolized form.

Routes of drug administration

The absorption pattern of drugs varies considerably between individual 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 although dosage forms are mentioned this is intended only as an introduction, as they will be dealt with in greater detail in other parts of this book.

Oral route

The oral route is the one most frequently used for drug administration. Oral dosage forms are usually intended 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 tract, either because of the poor absorption by this route or because of their low aqueous solubility. Compared with other routes, the oral route is the simplest, most convenient and safest means of drug administration. Disadvantages, however, include the relatively slow onset of action, the possibilities of irregular absorption and the 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.

Several specific features relating to drug absorption from the gastrointestinal tract can be emphasized in the context of routes of administration. 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 the absorption of drugs that are more effectively absorbed from the intestine. In addition, because environmental pH can influence the ionization and lipid solubility of drugs, the pH change that occurs along the gastrointestinal tract, from about 1 in the stomach to approximately 7 or 8 in the large intestine, is important to both degree and site of drug absorption. As membranes are more permeable to unionized rather than ionized forms, and as 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, thereby facilitating drug dissolution and absorption. Tablets are often coated, either to provide a protection against 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). Increasing use is being made of modified-release tablet products, such as fast-dissolving systems and controlled, delayed 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 the maintenance of steady drug-plasma levels for extended periods. These factors are important when medications are delivered for chronic conditions, or where constant levels are required to achieve optimal efficacy, as in treating angina and hypertension.

Capsules are solid dosage forms containing drug and usually appropriate filler(s), enclosed in a hard or soft gelatin shell. 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 the drug is released from a capsule faster than from a tablet. Recently, renewed interest has been shown in filling semisolid and microemulsion 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 that 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. Whereas dissolution of drugs is required prior to absorption following administration, fine particles with a large surface area are presented to dissolving fluids, which facilitate dissolution in the gastrointestinal tract, absorption, and hence the onset of drug action. Not all oral suspensions are formulated for systemic effects however, and several, for example kaolin and morphine mixture, are designed for local effects in the gastrointestinal tract. On the other hand, solutions, including formulations such as syrups and linctuses, are absorbed more rapidly than solid dosage forms or suspensions, as 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 administration is indicated for drugs that are inactivated by the gastrointestinal fluids when given orally, or 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 that are significantly inactivated by the liver following oral absorption. However, 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.). Other routes, such as intracardiac 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 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 previously mentioned, drugs in solution are rapidly absorbed and so injection suspensions are slower acting than solutions. In addition, because body fluids are aqueous, by using drugs suspended 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. Such systems include solid microspheres, polymeric biodegradable polymeric microspheres (e.g. polylactide co-glycollic acid homo- and copolymers) containing proteins or peptides (e.g. human growth hormone and leuprolide). More generally, subcutaneous injections are aqueous solutions or suspensions that allow the drug to be placed in the immediate vicinity of blood capillaries. The drug then diffuses into the capillaries. The 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 the 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.

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

Topical route

Drugs are applied topically, that is to the skin, mainly for local action. Although this route can also be used for systemic drug delivery, percutaneous absorption is often poor and erratic, although several transdermal patches delivering drug for systemic distribution are available (e.g. glyceryl trinitrate patches for the prophylaxis and treatment of angina). 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 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 in consistency. For topical application in liquid form other than solution, lotions – suspensions of solids in aqueous solution – or emulsions are used. More recently, interest in transdermal electrotransport systems has grown. Here a low electrical potential maintained across the skin can improve drug transport.

The application of drugs to other topical surfaces, such as the eye, ear and nose, is common and ointments, creams, suspensions and solutions are utilized. Ophthalmic preparations are required, among 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 presented in an aerosol or solid form, particle size largely determines the extent to which they penetrate the alveolar region, the zone of rapid absorption. Particles in the region 0.5–1 μm diameter reach the alveolar sacs. Particles outside this range are either exhaled 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. salbutamol sulphate aerosol). Importantly, this delivery route is being increasingly recognized as a means of administering the therapeutic agents emerging from biotechnology, 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, effective product. These properties, such as dissolution, crystal size and polymorphic form, solid-state stability and drug – additive interactions, 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. Although comprehensive property evaluation will not be required for all types of formulations, those properties that are recognized as important in dosage form design and processing are listed in Table 1.3, together with the stresses to which the formulation might be exposed during processing and manipulation into dosage forms, as well as the procedures involved. Variations in physicochemical properties, occurring for example between batches of the same material or resulting from alternative treatment procedures, can modify formulation requirements as well as processing and dosage form performance. For instance, the fine milling of poorly soluble drug substances can modify their wetting and dissolution characteristics, properties that are important during granulation and product performance, respectively. Careful evaluation of these properties and understanding of the effects of these stresses upon these parameters is therefore important in dosage form design and processing, as well as in product performance.

Particle size and surface area

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

It is now generally recognized that poorly aqueous-soluble drugs showing a dissolution rate-limiting step in the absorption process will be more readily bioavailable when administered in a finely subdivided form with larger surface than as a coarse material. Examples include griseofulvin, tolbutamide, indomethacin, spironolactone and nifedipine. The fine material, often in micrometre or submicrometre (nanometre) form with large specific surface, dissolves at a faster rate, which can lead to improved drug absorption by passive diffusion. On the other hand, with formulated nitrofurantoin preparations an

Table 1.3 Properties of drug substances important in dosage form design and potential stresses occurring during processes, with range of manufacturing procedures

Properties	Processing stresses	Manufacturing procedures
Particle size, surface area	Pressure	Precipitation
Solubility	Mechanical	Filtration
Dissolution	Radiation	Emulsification
Partition coefficient	Exposure to liquids	Milling
Ionization constant	Exposure to gases and liquid vapours	Mixing
Crystal properties, polymorphism	Temperature	Granulation
Stability		Drying
Organoleptic		Compression
(Other properties)		Autoclaving
		Crystallization
		Handling
		Storage
		Transport

optimal particle size of 150 μm reduces gastrointestinal distress while still permitting sufficient urinary excretion of this urinary antibacterial agent.

Rates of drug dissolution can be adversely affected, however, by unsuitable choice of formulation additives, even though solids of appropriate particle size are used. Tableting lubricant powders, for example, can impart hydrophobicity to a formulation and inhibit drug dissolution. Fine powders can also increase air adsorption or static charge, leading to wetting or agglomeration problems. Micronizing drug powders can lead to polymorphic and surface energy changes which cause reduced chemical stability. Drug particle size also influences content uniformity in solid dosage forms, particularly for low-dose formulations. It is important in such cases to have as many particles as possible per dose to minimize potency variation between dosage units. Other dosage forms are also affected by particle size, including suspensions (for controlling flow properties and particle interactions), inhalation aerosols (for optimal penetration of drug particles to absorbing mucosa) and topical formulations (for freedom from grittiness).

Solubility

All drugs, by whatever route they are administered, must exhibit at least limited aqueous solubility for therapeutic efficiency. Thus relatively insoluble compounds can exhibit erratic or incomplete absorption, and it might be appropriate to use more soluble salt or other chemical derivatives. Alternatively, micronizing, complexation or solid dispersion techniques might be employed. Solubility, and especially degree of saturation in the vehicle, can also be important in the absorption of drugs already in solution in liquid dosage forms, as precipitation in the gastrointestinal tract can occur and bioavailability be modified.

The solubilities of acidic or basic compounds are pH dependent and can be altered by forming salt forms with different salts exhibiting different equilibrium solubilities. However, the solubility of a salt of a strong acid is less affected by changes in pH than is the solubility of a salt of a weak acid. In the latter case, when pH is lower the salt hydrolyses to an extent dependent on pH and pK_a, resulting in decreased solubility. Reduced solubility can also occur for slightly soluble salts of drugs through the common ion effect. If one of the ions involved is added as a different, more water-soluble salt, the solubility product can be exceeded and a portion of the drug precipitates.

Dissolution

As mentioned above, for a drug to be absorbed it must first be dissolved in the fluid at the site of absorption. For example, an orally administered drug in tablet form is not absorbed until drug particles are