

Pharmaceutics

The science of dosage form design

Edited by M E Aulton

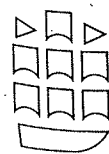
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Pharm Dosag

EDITED BY
Michael
Reader in Pharmacy

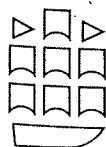


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Pharmaceutics: The Science of Dosage Form Design

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Preface

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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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The Editor wishes to take this opportunity to thank the following who have assisted with the preparation of this text:

Mr Sidney Carter, who edited this book's predecessor, *Cooper and Gunn's Tutorial Pharmacy*, for passing on to me the opportunity to edit the first edition of this new textbook. His invaluable experience and guidance aided me throughout the preparation of this edition and are greatly appreciated.

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My BBC micro.

Katharine Watts and Alison Walsh of Churchill Livingstone, and Howard Bailey of Pitman, for their special expertise and assistance in introducing me to the world of publishing.

The many academic and industrial pharmacists who helped during the design of the contents of this edition to ensure that it corresponds as closely as possible with modern practice and with the syllabuses of most schools of pharmacy.

Those publishing companies who have given their permission to reproduce material here.

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 micro-organisms (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 pharmaceuticals 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-

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nological problems associated with the manufac-
ture 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 phar-
maceutics — 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*.

The design of dosage forms

PRINCIPLES OF DOSAGE FORM DESIGN

BIOPHARMACEUTICAL CONSIDERATIONS IN DOSAGE FORM DESIGN

Routes of drug administration

Oral route
Rectal route
Parenteral route
Topical route
Respiratory route

DRUG FACTORS IN DOSAGE FORM DESIGN

Organoleptic properties

Particle size and surface area

Solubility

Dissolution

Partition coefficient and pK_a

Crystal properties; polymorphism

Stability

Other drug properties

THERAPEUTIC CONSIDERATIONS IN DOSAGE FORM DESIGN

SUMMARY

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 require-

ments of that route which affect drug absorption need to be taken into account when designing dosage forms.

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

Table 1.1 Range of dosage forms available for different administration routes

<i>Administration route</i>	<i>Dosage forms</i>
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

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

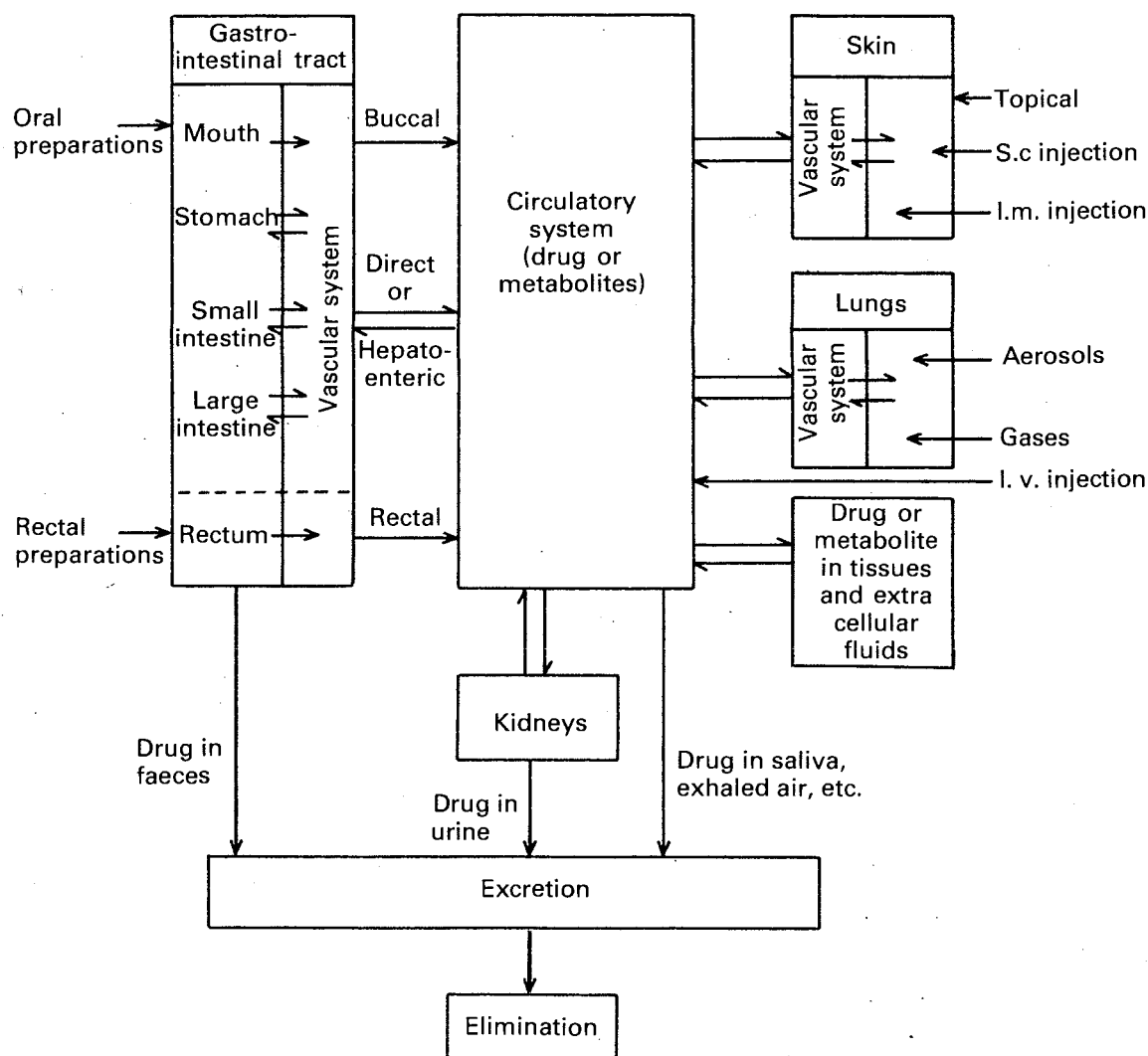


Fig. 1.1 Schematic diagram illustrating pathways a drug may take following administration of a dosage form by different routes

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

<i>Time of onset of action</i>	<i>Dosage form</i>
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 table

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. 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

comprehensive property evaluation 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. Also listed in Table 1.3 are the stresses to which the formulation might be exposed during processing or 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, important properties 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 product performance.

Table 1.3 Physical and chemical properties of drug substances important in dosage form design and potential stresses with range of manufacturing procedures used in processing

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

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, particularly oral preparations, containing such drugs may require the addition of approved flavours, perfumes and/or colours.

The use of flavours and perfumes applies primarily to liquid dosage forms intended for oral administration. Available as concentrated extracts, solutions, adsorbed onto powders or microencapsulated, flavours and perfumes 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. All other elements are recognized by smell, which can be altered more readily than taste using perfumes. Unpleasant taste can be overcome by using water-insoluble derivatives of drugs which have little or no taste. Examples are the use of chloramphenicol palmitate and amitriptyline pamoate, although 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. However, unpleasant drugs in capsules or prepared as coated tablets may be easily swallowed avoiding the taste buds.

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. Solubility and stability of the flavour in the vehicle are also important. In addition the age of the intended patient should also be considered, since children for example prefer sweet tastes, as well as the psychological links between colours and flavours (e.g. yellow colour is associated with lemon flavour). Sweetening agents may also be required to mask bitter tastes. Sucrose remains widely 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 or perfume. Whilst colours are obtained both from natural sources (e.g. carotenoids) or synthesized (e.g. amaranth), the majority used are synthetically produced. Dyes may be aqueous (e.g. amaranth) or oil

soluble (e.g. Sudan III) or insoluble in both (e.g. aluminium lakes). Lakes which are generally calcium or aluminium complexes of water-soluble dyes are particularly useful in tablets and tablet coatings because of 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 some countries and not others. (A useful summary on colours is given in Martindale, *The Extra Pharmacopoeia*).

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 physicochemical characteristics.

It is now generally recognized that poorly 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, phenothiazine, diphenylhydantoin, chloramphenicol, tolbutamide, indomethacin and spironolactone. The fine material often in micronized form with larger specific surface dissolves at faster rates which can lead to improved drug absorption by passive diffusion. On the other hand, with formulated nitrofurantoin preparations an optimal particle size of 150 μm reduced gastrointestinal distress whilst 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 which inhibits 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, whatever route they are administered by, 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 ester derivatives. Alternatively, micronizing, complexation or solid dispersion techniques might be employed. Solubility can also be important in the absorption of drugs already in solution in liquid dosage forms since precipitation in the gastrointestinal tract can occur and bioavailability modified.

Solubilities of acidic or basic compounds are pH dependent and can be altered by forming salts, 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 the solubility of a salt of a weak acid. In the latter case, when pH is low, the salt hydrolyses to an extent dependent of 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 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 dissolved or solubilized by the fluids at some point along the gastrointestinal tract, depending on the pH-solubility profile of the drug substance. Dissolution describes the process by which the drug particles dissolve.

During dissolution, the drug molecules in the surface layer dissolve to form a saturated solution around the particles to form the diffusion layer. Dissolved drug molecules then pass throughout the dissolving fluid to contact absorbing mucosa and are absorbed. Replenishment of diffusing drug molecules in the diffusion layer is achieved by further drug dissolution and the absorption process continues. If dissolution is fast or the drug is delivered and remains in solution form, the rate of absorption is primarily dependent upon its ability to transverse the absorbing membrane. If, however, drug dissolution is slow due to its physicochemical properties or formulation factors, then dissolution may be the rate-limiting step in absorption and influence drug bioavailability. The dissolution of a drug is described by the general Noyes-Whitney equation:

$$\frac{dm}{dt} = kA (C_s - C)$$

where $\frac{dm}{dt}$ is the dissolution rate, k is the dissolution rate constant, A is the surface area of dissolving solid, C_s is the concentration of drug in the saturated diffusing layer and C is the concentration of drug in the dissolution medium at time t . The equation reveals that dissolution rate can be raised by increasing the surface area (reducing particle size) of the drug, by increasing the solubility of the drug in the diffusing layer and by increasing k which incorporates the drug diffusion coefficient and diffusion layer thickness. During the early phases of dissolution, $C_s \geq C$ and if the surface area, A , and experimental conditions are kept constant then k can be determined for compacts containing drug alone. The constant k is now termed the intrinsic dissolution rate constant and is a characteristic of each solid drug compound in a given solvent under fixed hydrodynamic condition. (See Chapter 5 for description of a suitable apparatus and technique.)

Drugs with values of k below $0.1 \text{ mg}^{-1} \text{ cm}^{-2}$ usually exhibit dissolution rate-limiting absorption. Particulate dissolution can also be examined where an effort is made to control A , and formulation effects can be studied.

Dissolution rate data when combined with solubility, partition coefficient and pK_a results provide an insight to the formulator into the potential *in vivo* absorption characteristics of a drug. However, *in vitro* tests only have significance if they can be related to *in vivo* results. Once such a relationship has been established, *in vitro* dissolution tests can be used as a quality control test. Nevertheless the importance of dissolution testing has been recognized recently by official compendia with the inclusion in recent editions of dissolution specification using standardized testing procedures for a range of official preparations.

Partition coefficient and pK_a

As pointed out earlier, for relatively insoluble compounds the dissolution rate is often the rate-determining step in the overall absorption process. Alternatively, for soluble compounds the rate of permeation across biological membranes is the rate-determining step. Whilst dissolution rate can be changed by modifying the physicochemical properties of the drug and/or by altering the formulation composition, the permeation rate is dependent upon the size, relative aqueous and lipid solubility and ionic charge of drug molecules, factors which can be altered through molecular modifications. The absorbing membrane acts as a lipophilic barrier to the passage of drugs which is related to the lipophilic nature of the drug molecule. The partition coefficient, for example between oil and water, is a measure of lipophilic character.

The majority of drugs are weak acids or bases and depending on the pH exist in an ionized or unionized form. Membranes of absorbing mucosa are more permeable to unionized forms of drugs than to ionized species because of the greater lipid solubility of the unionized forms and to the highly charged nature of the cell membrane which results in the binding or repelling of the ionized drug, thereby decreasing penetration.

The factors therefore that influence the absorp-

tion of weak acids and bases are the pH at the site of absorption and the lipid solubility of the unionized species. These factors, together with the Henderson-Hasselbalch equations for calculating the proportions of ionized and unionized species at a particular pH, constitute the widely accepted pH-partition theory for drug absorption (see Chapter 9). However, these factors do not describe completely the process of absorption since certain compounds with low partition coefficients and/or which are highly ionized over the entire physiological pH range show good bioavailability and therefore other factors are involved.

Crystal properties; polymorphism

Practically all drug substances are handled in powder form at some stage during manufacture into dosage forms. However, for those substances composed of, or containing, powders or compressed powders in the finished product the crystal properties and solid state form of the drug must be carefully considered. It is well recognized that drug substances can be amorphous (i.e. without regular molecular lattice arrangements), crystalline, anhydrous, at various degrees of hydration or solvated with other entrapped solvent molecules, as well as varying in crystal hardness, shape and size. In addition many drug substances can exist in more than one crystalline form with different lattice arrangements. This property is termed polymorphism and different polymorphs may be prepared by manipulation of conditions of crystallization such as solvent, temperature and rate of cooling. It is known that only one form of a pure drug substance is stable at a given temperature and pressure with the other forms, termed metastable, converting at different rates to the stable crystalline form. The different polymorphs vary in physical properties such as solubility, dissolution, solid state stability as well as processing behaviour in terms of powder flow and compaction during tableting.

These different crystalline forms can be of considerable importance in relation to ease or difficulty of formulation and as regards stability and biological activity. As might be expected, higher dissolution rates and solubilities are obtained for metastable polymorphic forms; for

example the metastable forms of chloramphenicol palmitate and chlortetracycline hydrochloride exhibit improved rate and extent of bioavailability. In some cases such as novobiocin, amorphous forms are more active than crystalline forms.

The widely used hormonal substance insulin also demonstrates how differing degrees of activity can result from the use of different crystalline forms of the same agent. In the presence of acetate buffer, zinc combines with insulin to form an extremely insoluble complex of the proteinaceous hormone. This complex is an amorphous precipitate (termed semi-lente) or crystalline product depending on environmental pH. The semi-lente form is rapidly absorbed following i.m. or s.c. injection and has a short duration of action, whilst the large crystalline product called ultra-lente, is more slowly absorbed and is of longer duration of action. A physical mixture of 7 parts ultra-lente and 3 parts semi-lente provides lente insulin which is intermediate in duration of action.

Polymorphic transitions can also occur during milling, granulating, drying and compressing operations (e.g. transitions during milling for digoxin, spironolactone; transitions during compression for phenylbutazone and some sulphonamides). Granulation can result in solvate formation or, during drying a solvated or hydrated molecule may be lost to form an anhydrous material. Consequently, the formulator must be aware of these potential transformations which can result in undesirable modified product performance, even though routine chemical analyses may not reveal any changes. Reversion from metastable forms, if used, to the stable form may also occur during the lifetime of the product. In suspensions, this may be accompanied by changes in the consistency of the preparation which affects its shelf life and stability. Such changes can often be prevented by additives, such as hydrocolloids and surface-active agents which appear to poison the crystal lattice.

Stability

The chemical aspects of formulation generally centre around the chemical stability of the drug and its compatibility with the other formulation ingredients. In addition it should be stressed that

the packaging of the dosage form is an important contributing factor to product stability and must be an integral part of stability testing programmes. Chapter 7 examines these aspects and only a brief summary is given at this point. It has been mentioned previously that one of the principles of dosage form design is to ensure that the chemical integrity of drug substances is maintained during the usable life of the product. At the same time chemical changes involving additive and any physical modifications to the product must be carefully monitored to optimize formulation stability.

In general drug substances decompose as a result of the effects of heat, oxygen, light and moisture. For example, esters such as aspirin and procaine are susceptible to solvolytic breakdown, whilst oxidative decomposition occurs for substances such as ascorbic acid. Drugs can be classified according to their sensitivity to breakdown:

- 1 stable at all conditions (e.g. kaolin),
- 2 stable if handled correctly (e.g. aspirin),
- 3 moderately unstable even with special handling (e.g. vitamins),
- 4 very unstable (e.g. certain antibiotics in solution form).

Whilst the mechanisms of solid-state degradation are complex and difficult to analyse, a full understanding is not a prerequisite in the design of a suitable formulation containing solids. For example, in cases where drug substances are sensitive to hydrolysis, steps such as minimum exposure to moisture during preparation, low moisture content specifications in the final product and moisture resistant packaging can be used. For oxygen-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 physiological 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, packaging materials, do occur and must be checked for during formulation. Over recent years thermal analysis techniques, particularly differential scanning calorimetry (DSC), have been found to be particularly useful in 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 sodium dicloxacillin and should be avoided in formulations containing these drug substances.

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 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 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, 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 situation. For example many asthmatic patients use inhalation aerosols from which the drug is rapidly absorbed into the systematic circulation following deep inhalation.

Patients requiring relief from angina pectoris, a coronary circulatory problem, place tablets of nitroglycerin sublingually for rapid drug absorption from the buccal cavity. Thus, whilst systemic effects are generally obtained following oral and parenteral drug administration, other routes can be employed as the drug and situation demands. Local effects are generally restricted to those 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.

Recently interest has been growing in the design of drug-containing formulations which 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 and several products such as the topical adhesive patches containing nitroglycerin have been marketed. Undoubtedly more of these sophisticated formulations will be developed and interest is likely to be directed to individual patient requirements such as age, weight, and physiological and metabolic factors, features

which can influence drug absorption and bioavailability.

The age of the patient does play an important role in the types of dosage form prepared. Infants generally prefer liquid dosage forms, usually solutions and mixtures, given orally. Also, by having liquid preparations 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.

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. Whilst 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 demands careful examination, analysis and evaluation of wide ranging information by pharmaceutical scientists to achieve the objective of creating high quality and efficacious dosage forms.

BIBLIOGRAPHY

- Ansel, H. C. (1976) General considerations in dosage form design. In: *Introduction to Pharmaceutical Dosage Forms*, 2nd edn, Chap. 3, pp. 61–106, Lea and Febiger, Philadelphia.
- Carstensen, J. T. (1974) Stability of solids and solid dosage forms. *J. pharm. Sci.*, **63**, 1–14.
- Florence, A. T. and Attwood, D. (1981) Principles of drug absorption and routes of administration. In *Physicochemical Principles of Pharmacy*, Chap. 9, pp. 325–400, The Macmillan Press, London.
- Habelain, J. (1975) Characterisation of habits and crystalline modifications of solids and their pharmaceutical applications. *J. pharm. Sci.*, **64**, 1269–1288.
- Lowenthal, W. (1976) Bioavailability. In: *Dispensing of Medication* (Ed. J. E. Hoover), Chap. 2, pp. 39–83.
- Martindale, *The Extra Pharmacopoeia* (1982) (Ed. J. E. F. Reynolds), Pharmaceutical Press, London, pp. 423–433.
- Macek, T. J. (1975) Formulation. In: *Remington's Pharmaceutical Sciences*, 15th edn (Eds A. Osol, et al.), Chap. 75, pp. 1355–1367, Mack Publishing Co.,

- Easton, Pennsylvania.
- Polderman, J. (Ed.) (1977) *Formulation and Preparation of Dosage Forms*, Elsevier, Netherlands.
- Shami, E.G., Dubzinski, J. R. and Lantz, R. J. (1976) Preformulation. In: *Theory and Practice of Industrial Pharmacy*, 2nd edn (Eds L. Lachman, H. A. Lieberman and J. L. Kanig), Chap. 1, pp. 1-31, Lea and Febiger, Philadelphia.
- Talman, F. A. J. (1977) Formulation. In: *Bentley's Textbook of Pharmaceutics*, 8th edn (Ed. E. A. Rawlins), Chap. 37, pp. 641-668.
- Wadke, D. A. and Jacobson, H. (1981) Preformulation. In: *Pharmaceutical Dosage Forms — Tablets* (Eds H. A. Lieberman and L. Lachman), Vol. 1, Chap. 1, pp. 1-59 Marcel Dekker, New York, 1-59.
- York, P. (1983) Solid state properties of powders in the formulation and processing of solid dosage forms. *Int. J. Pharm.*, **14**, 1-28.

Introduction to biopharmaceutics

The concept of bioavailability The concept of biopharmaceutics

Before the reader can appreciate the meaning and clinical significance of *biopharmaceutics*, it is necessary to introduce the concept of drug bioavailability.

The concept of bioavailability

The therapeutic response of a drug is normally dependent on an adequate concentration of the drug being achieved and then maintained at the site or sites of action of the drug. In the case of systemically acting drugs (i.e. drugs that reach these sites via the systemic circulation) it is generally accepted for clinical purposes that a dynamic equilibrium exists between the concentration of drug at its site(s) of action and the concentration of drug in blood plasma. An important consequence of this dynamic equilibrium is that it permits a therapeutically effective concentration of drug to be achieved at its site(s) of action by adjustment of the concentration of drug in blood plasma. Strictly speaking, the concentration of drug in plasma water (i.e. protein-free plasma) is a more accurate index of drug concentration at the site(s) of action than is the concentration of drug in whole plasma since a drug may often bind in a reversible manner to plasma protein. Only drug which is unbound (i.e. dissolved in plasma water) can pass out of the plasma through the capillary endothelium and reach other body fluids and tissues and hence its site(s) of action. Drug concentration in whole blood is also not considered to be an accurate indirect index of the concentration of drug at its site(s) of action since drug can bind to and enter blood cells. However, to measure the concentration of an unbound drug in plasma water

requires more complex and sensitive assay methods than to measure the total concentration of both unbound and bound drug in total plasma. Thus, for clinical purposes, drug concentration in blood plasma is usually measured and is regarded as an index of drug concentration at the site(s) of action of the drug and of the clinical effects of the drug. However, it should be realized that this is a simplification and may not always be valid. Indeed one should not draw inferences about the clinical effects of a drug from its plasma concentration until it has been established that the two are consistently correlated. For simplicity, in the remainder of this chapter, it has been assumed that the plasma drug concentration is directly proportional to the clinical effect of that drug.

The concentration of drug in blood plasma depends on numerous factors. These include the relative amount of an administered dose that enters the systemic circulation, the rate at which this occurs, the rate and extent of distribution of the drug between the systemic circulation and other tissues and fluids and the rate of elimination of the drug from the body.

A schematic representation of some of the factors which can influence the concentration of

a drug in the blood plasma and also at its site(s) of action is shown in Fig. 8.1.

Apart from the intravenous route of drug administration, where a drug is introduced directly into the blood circulation, all other routes of administering systemically acting drugs involve the absorption of drug from the place of administration into the blood. Drug must be absorbed in a sufficient quantity and at a sufficient rate in order to achieve a certain blood plasma concentration which, in turn, will produce an appropriate concentration of drug at its site(s) of action to elicit the desired therapeutic response.

It follows that there are two aspects of drug absorption which are important in clinical practice, namely, the rate and the extent to which the administered dose is absorbed. Simply because a certain dose of a drug is administered to a patient, there is no guarantee (except for intravenous administration) that all of that dose will reach the systemic circulation. The fraction of an administered dose of drug that reaches the systemic circulation in unchanged form is known as the *bioavailable dose*. The relative amount of an administered dose of a particular drug which reaches the systemic circulation intact and the rate

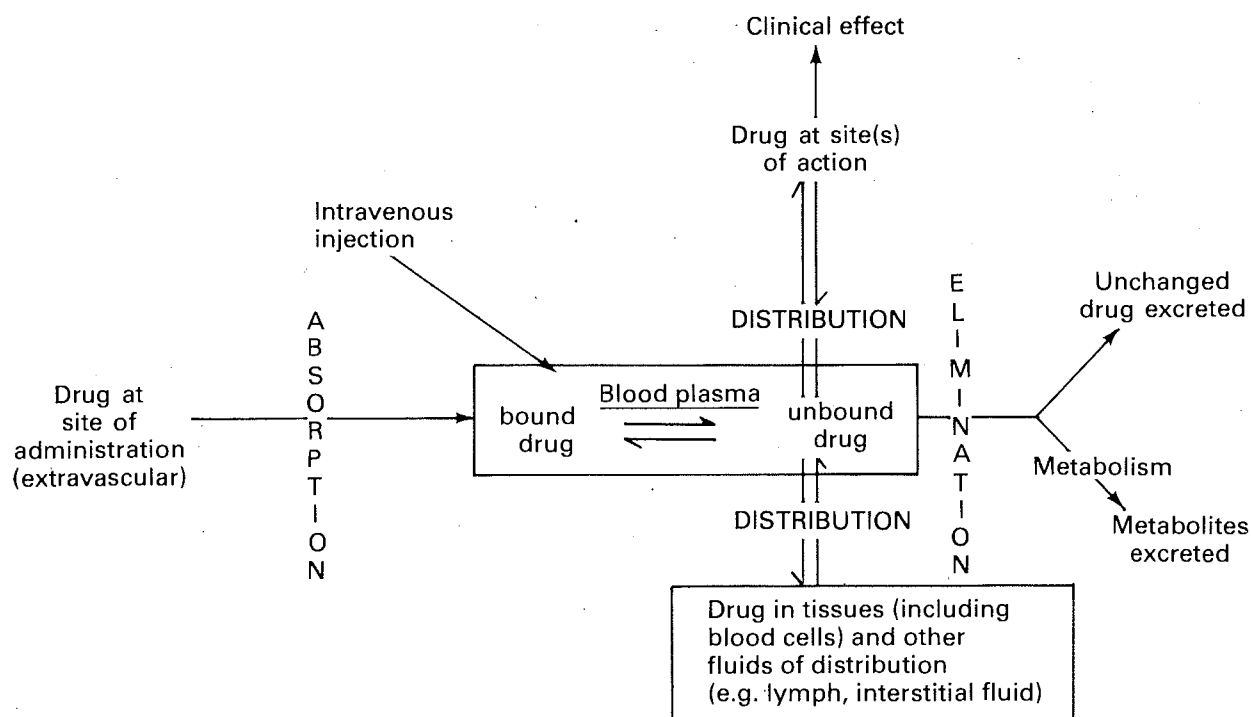


Fig. 8.1 Schematic representation of drug absorption, distribution and elimination.

at which this occurs is known as the *bioavailability* of that drug. Bioavailability is thus concerned with the quantity and rate at which the *intact* form of a particular drug appears in the systemic circulation following administration of that drug. The bioavailability exhibited by a drug is thus very important in determining whether a therapeutically effective concentration is achieved at the site(s) of action of the drug.

In defining bioavailability in these terms it is assumed that intact drug is the therapeutically active form of the drug. This definition of bioavailability would not be valid in the case of a pro-drug, whose therapeutic action normally depends on it being converted into its therapeutically active form prior to or on reaching the systemic circulation. It should also be noted that in the context of bioavailability, the term systemic circulation refers primarily to venous blood (excluding the hepatic portal blood during the absorption phase) and arterial blood which carries the intact drug to the tissues.

Hence according to the definition of bioavailability an administered dose of a particular drug in an oral dosage form will be 100% bioavailable only if the drug is completely released from the dosage form into solution in the gastrointestinal fluids. The released drug must also be completely stable in solution in the gastrointestinal fluids and all of the drug must pass through the gastrointestinal barrier into the mesenteric circulation without being metabolized. Finally, all of the absorbed drug must pass into the systemic circulation without being metabolized on passing through the liver. Thus any factor which adversely affects either the release of the drug from the dosage form, its dissolution in the gastrointestinal fluids, its stability in the gastrointestinal fluids, its permeation through and stability in the gastrointestinal barrier or its stability in the hepatic portal circulation will influence the bioavailability exhibited by that drug from the dosage form in which it was administered.

The concept of biopharmaceutics

Many factors have been found to influence the time course of a drug in the plasma and hence at

its site(s) of action. These include the foods eaten by the patient, the effect of the disease state on drug absorption, the age of the patient, the site(s) of absorption of the administered drug, the co-administration of other drugs, the physical and chemical properties of the administered drug, the type of dosage form, the composition and method of manufacture of the dosage form and the size of dose and frequency of administration of the dosage form. Thus, a given drug may exhibit differences in its bioavailability if it is administered in the same type of dosage form by different routes of administration, e.g. an aqueous solution of a given drug administered by the oral and intramuscular routes of administration. A given drug may also show differences in its bioavailability from one type of dosage form to another when given by the same route, e.g. a tablet, a hard gelatin capsule and an aqueous suspension administered by the peroral route. A given drug might show different bioavailabilities from different formulations of the same type of dosage form given by the same route of administration, e.g. different formulations of an aqueous suspension of a given drug administered by the peroral route. Variability in the bioavailability exhibited by a given drug from different formulations of the same type of dosage form or from different types of dosage forms etc., can cause patients to be under- or overmedicated. The result may be therapeutic failure or serious adverse effects particularly in the case of drugs which have a narrow therapeutic range (see Chapter 10).

The entry of a drug into the systemic circulation following the administration of a drug product usually involves

- 1 the release of the drug from its dosage form into solution in the biological fluids at the absorption site, and
- 2 the movement of the dissolved drug across biological membranes into the systemic circulation.

The study of the various factors which can affect these processes and the application of this knowledge to obtain the expected therapeutic effect from a drug product when it is used by a patient is known as *biopharmaceutics*.

BIBLIOGRAPHY

- Cadwallader, D. E. (1973) *Biopharmaceutics and Drug Interactions*, F. Hoffman-La Roche, Basel.
- Eadie, M. J., Tyrer, J. H. and Bochner, F. (1981) *Introduction to Clinical Pharmacology*, MTP Press Ltd, Lancaster.
- Gibaldi, M. (1984) *Biopharmaceutics and Clinical Pharmacokinetics*, 3rd edn, Lea and Febiger, Philadelphia.
- Notari, R. E. (1980) *Biopharmaceutics and Clinical Pharmacokinetics. An Introduction*, 3rd edn, Marcel Dekker Inc., New York.
- Wagner, J. G. (1971) *Biopharmaceutics and Relevant Pharmacokinetics*, 1st edn, Drug Intelligence Publications, Hamilton, Illinois.
- World Health Organisation (1974) *Bioavailability of Drugs: Principles and Problems*. Report of a WHO Scientific Group. Wld. Hlth. Org. Techn. Rep. Ser., 1974, No. 536. HMSO, London

Factors influencing bioavailability: factors influencing drug absorption from the gastrointestinal tract

DRUG ABSORPTION FROM THE GASTROINTESTINAL TRACT

Structure of the gastrointestinal tract

Mechanisms of drug transport across the gastrointestinal/blood barrier

Passive diffusion

Carrier-mediated transport

Active transport

Facilitated diffusion or transport

Ion-pair absorption

Convective absorption (pore transport)

Pinocytosis

PHYSIOLOGICAL FACTORS INFLUENCING DRUG ABSORPTION FROM THE GASTROINTESTINAL TRACT

Surface area of the gastrointestinal absorption sites

pH of gastrointestinal fluids

Gastric emptying rate

Intestinal motility

Drug stability in the gastrointestinal tract

Hepatic metabolism

Influence of food and diet

Alteration in the rate of gastric emptying

Stimulation of gastrointestinal secretions

*Competition between food components and drugs
for specialized absorption mechanisms*

*Complexation of drugs with components in the
diet*

Increased viscosity of gastrointestinal contents

Food-induced changes in blood flow to the liver

Miscellaneous physiological factors influencing gastrointestinal absorption

PHYSICOCHEMICAL FACTORS INFLUENCING DRUG ABSORPTION FROM THE GASTROINTESTINAL TRACT

Drug dissociation constant and lipid solubility

pH-partition hypothesis of drug absorption

Absorption of a weak acidic drug

Absorption of a weak basic drug

Limitations of the pH-partition hypothesis

Dissolution rate of drugs

*Absorption from solution or following rapid
dissolution of solid drug particles*

*Absorption following the slow dissolution of solid
drug particles*

*Factors influencing the dissolution rates of drugs
in the gastrointestinal tract*

Physiological conditions

Particle size

Crystal form

**Solubility of drug in the diffusion layer
(salt forms)**

Complexation

Adsorption

Chemical stability of drugs in the gastrointestinal fluids

DOSAGE FORM FACTORS INFLUENCING DRUG ABSORPTION FROM THE GASTROINTESTINAL TRACT

Influence of excipients

Diluents

Surfactants

Viscosity-enhancing agents

Influence of the type of dosage form

Aqueous solutions

Aqueous suspensions

Soft gelatin capsules

Hard gelatin capsules

Tablets

Uncoated tablets

Coated tablets

Enteric coated tablets

DRUG ABSORPTION FROM THE GASTROINTESTINAL TRACT

The various factors which can influence drug release from dosage forms and absorption into the systemic circulation will be considered in this chapter by reference to the peroral (i.e. gastrointestinal) route of administration. This route is chosen as the example, since the majority of drugs are administered orally and the vast majority of orally administered drugs are intended to be absorbed from the gastrointestinal tract. Thus, a

detailed consideration of the factors which can influence the absorption of drugs from this region is warranted.

In order that the reader may gain an insight into the numerous factors which can potentially influence the rate and extent of appearance of intact drug into the systemic circulation, a schematic illustration of the steps involved in the release and gastrointestinal absorption of a drug from a tablet is presented in Fig. 9.1. It is evident from this diagram that the rate and extent of appearance of intact drug into the systemic circulation depends

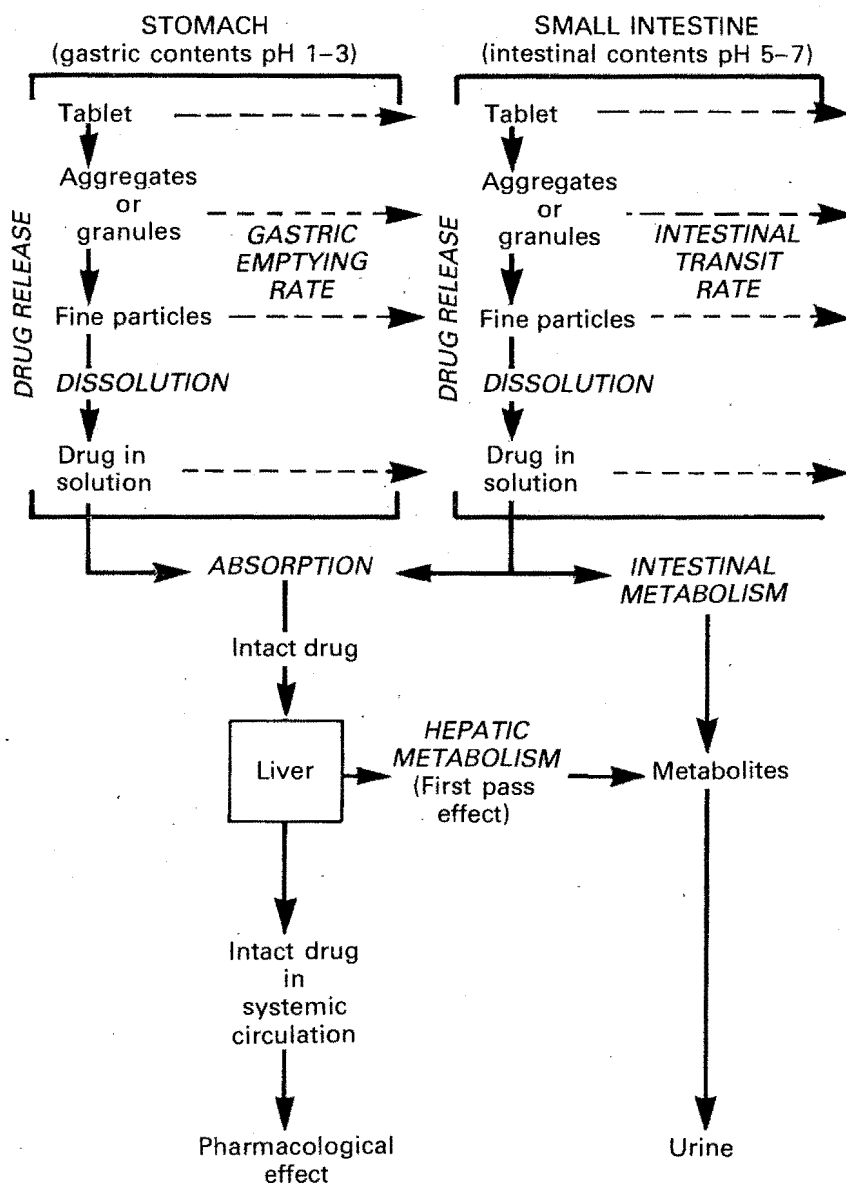


Fig. 9.1 Schematic illustration of steps involved in the appearance of intact drug in the systemic circulation following peroral administration of a tablet. Potential rate-limiting steps with respect to drug bioavailability are shown in italic capitals. (After Barr, 1972)

on a succession of rate (kinetic) processes. The slowest step in this series of rate processes, which is known as the rate-limiting step, will control the overall rate and extent of appearance of intact drug in the systemic circulation. The particular rate-limiting step may vary from drug to drug. Thus for a drug which exhibits a very poor aqueous solubility, the rate at which the drug dissolves in the gastrointestinal fluids is often the slowest step and therefore exhibits a rate-limiting effect on a drug bioavailability. In contrast, for a drug which has a high aqueous solubility, its dissolution rate will be rapid and the rate at which the drug crosses the gastrointestinal membrane may be the rate-limiting step. Other potential rate-limiting steps include the rate of release of the drug from the dosage form (especially important in the case of controlled released dosage forms), the rate at which the stomach empties the drug into the small intestine, the rate at which drug is metabolized by enzymes in the intestinal mucosal cells during its passage into the mesenteric blood vessels and the rate of metabolism of drug during

its initial passage through the liver, i.e. the 'first pass' effect.

Structure of the gastrointestinal tract

The gastrointestinal tract consists of three major anatomical regions: the stomach, the small intestine and the large intestine (colon). The small intestine includes the duodenum, jejunum and ileum. As a drug descends through these regions of the gastrointestinal tract, it encounters different environments with respect to pH, enzymes, electrolytes, fluidity and surface features, all of which can influence drug absorption (see later in this chapter).

The gastrointestinal tract is basically a hollow muscular tube composed of four concentric layers of tissue named from the innermost to the outermost as the mucosa (or mucous membrane), the submucosa, the muscularis externa and the serosa. These are shown diagrammatically in Fig. 9.2. Of these four layers, the mucosa is the most important with respect to the absorption of drugs

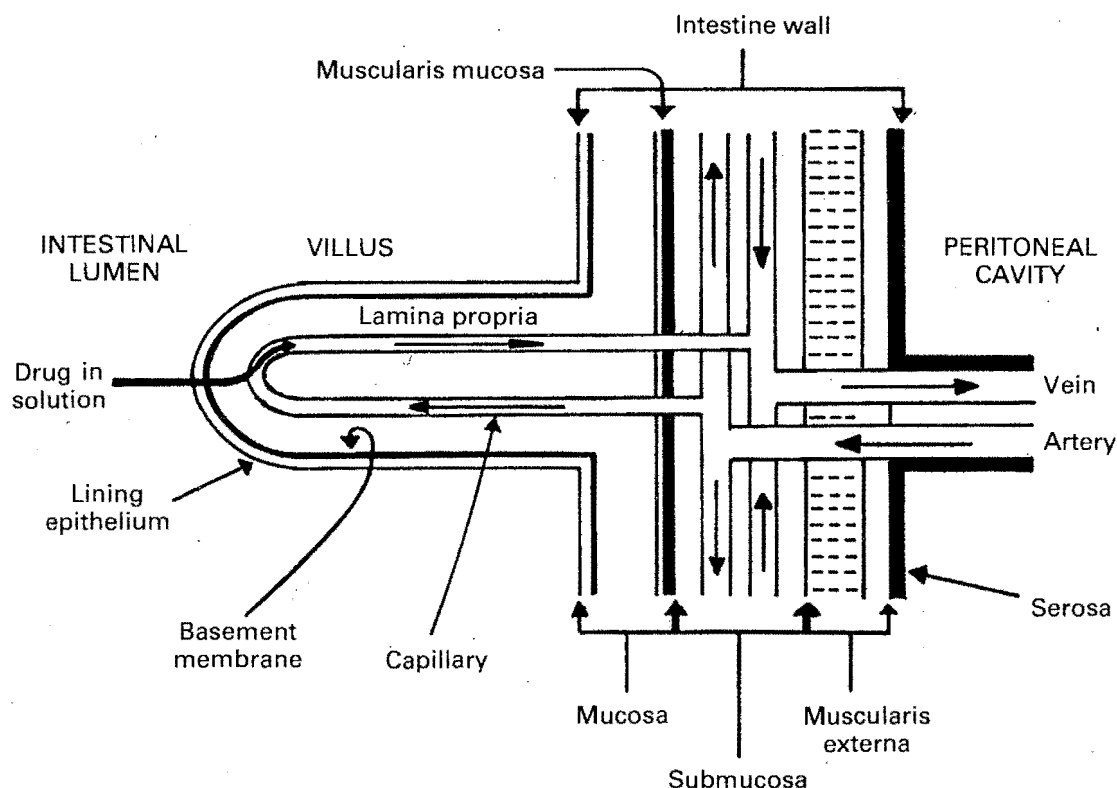


Fig. 9.2 Diagrammatic representation of the small intestine showing the absorption of a drug from the intestinal lumen into a blood capillary. (After Smith 1964)

from the lumen of the gastrointestinal tract. The mucosa contains the cellular membranes and regions through which a drug must pass in order to reach the blood (or lymph). Figure 9.2 shows that the mucosa, itself, consists of three layers: the lining epithelium, the lamina propria and the muscularis mucosa. The epithelium lining the lumen of the gastrointestinal tract comprises a single layer of columnar and some specialized secretory cells (e.g. mucus secreting goblet cells). Of these cells only the columnar cells are concerned with absorption. The layer underlying the epithelium is the lamina propria which contains connective tissue, blood and lymph vessels. The final layer comprising the mucosa is the muscularis mucosa which is a relatively thin layer of muscle fibres.

In the stomach the mucosa contains many folds which increase the total surface area over that afforded by a flat smooth lining. Although the stomach does not function primarily as an absorption organ, its excellent blood supply and the fact that a drug can potentially reside in the stomach for 30 minutes up to several hours in contact with a reasonably large epithelial surface, provide conditions which are conducive to the absorption of certain drugs, e.g. weak acidic drugs.

The small intestine is the most important site for drug absorption in the gastrointestinal tract. The outstanding anatomical feature of the small intestine is the tremendously large epithelial surface area through which drug absorption can take place. This large epithelial surface area results from the existence of (a) folds in the intestinal mucosa known as the folds of Kerckring, (b) villi and (c) microvilli. Villi are finger-like projections which arise from the entire mucosal surface (including the folds of Kerckring) of the small intestine. Villi range in length from 0.5 to 1.5 mm and there are estimated to be 10–40 villi per mm² of intestinal mucosa. Figure 9.2 shows that each villus is covered by a single continuous layer of epithelium (i.e. the epithelial lining of the intestinal mucosa) which is made up primarily of the columnar absorption cells and the mucus-secreting goblet cells. In terms of drug absorption from the small intestine the columnar cells are extremely important since it is the anatomical structure of the apical surface of each columnar cell (i.e. the

cell surface facing the intestinal lumen) which further increases the epithelial surface area of the small intestine that is available for drug absorption. Figure 9.3 shows that the apical surface of each cell consists of numerous minute slender projections, approximately 1 μm long, known as microvilli. Microvilli appear to be microtubular projections of the apical cell membrane of each columnar cell. The microvilli (between 700 and 1000 per columnar cell), together with the villi and folds of Kerckring, are estimated to increase the surface area available for absorption by 600 times that which would be available if the inner surface of the small intestine was flat.

Intimately associated with the microvilli is a coating of fine filamentous material composed of mucopolysaccharides. This coating is known as the glycocalyx. In addition to the glycocalyx there are two further layers of material between the microvilli and the luminal contents of the small intestine, i.e. a layer of protective mucus secreted by the goblet cells and the so-called 'unstirred aqueous layer'. Figures 9.2 and 9.3 show that the absorption of a drug from the lumen of the intestine into the blood draining the villi involves the passage of drug through several barriers and regions. Thus drug molecules in the lumen of the small intestine must first diffuse through the unstirred aqueous layer, the mucous layer and the glycocalyx in order to reach the microvilli, i.e. the apical cell membrane of the columnar cell. The apical cell membrane of each epithelial cell lining the gastrointestinal tract appears to be tightly bound to that of adjacent epithelial cells. This so-called 'tight junction' between the cell membranes of adjacent epithelial cells (see Fig. 9.3) is thought to act as a barrier to the intercellular passage of drug molecules from the intestinal lumen to the lamina propria. Thus a drug molecule must cross the apical cell membrane into the interior of a columnar cell. After diffusing through the fluids within this cell, a drug molecule must cross the basal cell membrane of the columnar cell. On emerging from the columnar cell the molecule must cross the underlying basement membrane into the lamina propria. Finally, after diffusing through the tissue region of the lamina propria, drug molecules must cross the endothelium of one of the blood capillaries present in this region.

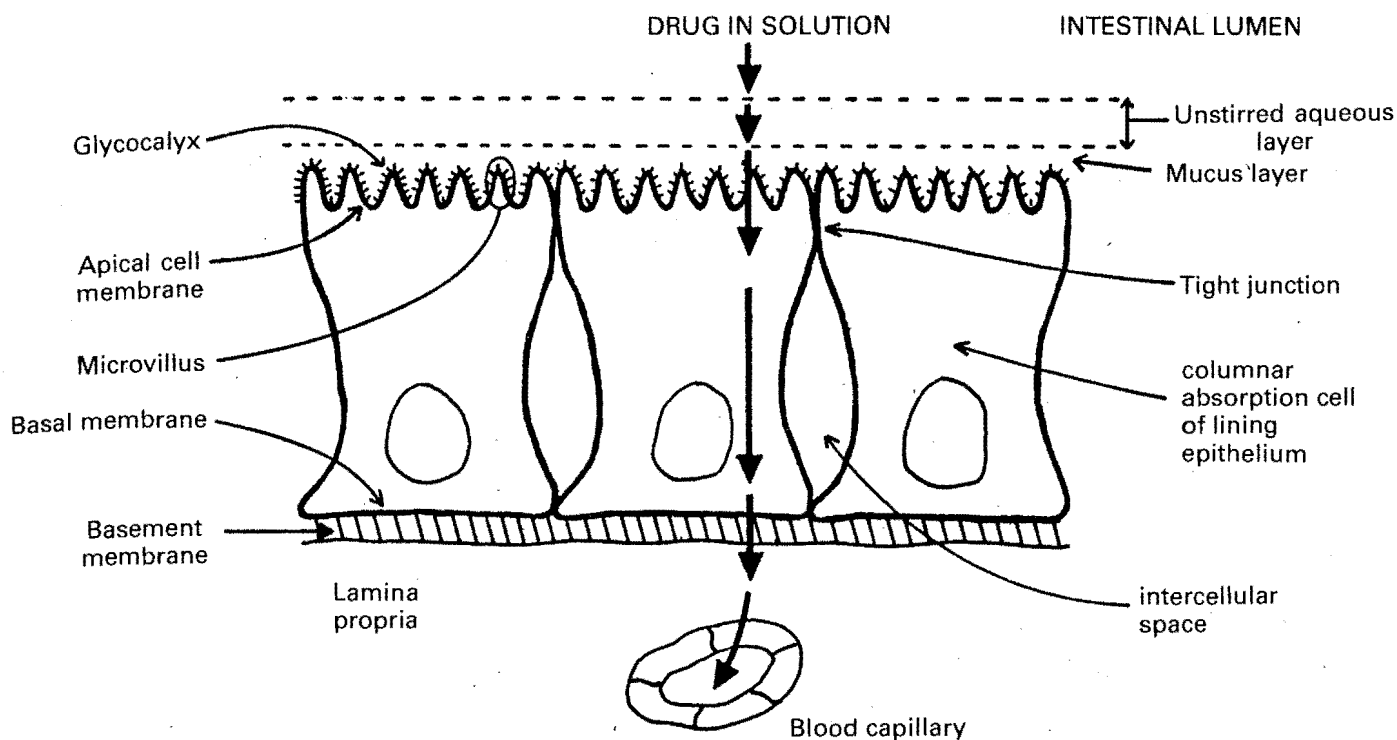


Fig. 9.3 Diagrammatic representation of intestinal columnar absorption cells in the lining epithelium showing a pathway of drug absorption from the intestinal lumen to a blood capillary lying in the lamina propria

Drug molecules would then be carried away in the blood to the systemic circulation via the liver. Most drugs reach the systemic circulation via the blood stream of the capillary network in the villi. However, it is possible that the absorption of highly lipid-soluble drugs, particularly if administered in an oily vehicle, may occur via fat absorption pathways. In such cases, drug removal from the villi would involve the central lacteals and the lymphatic circulation.

Although the above description of drug absorption refers specifically to the small intestine, absorption from other areas of the gastrointestinal tract would also involve the passage of drug through similar barriers and regions. Thus the term gastrointestinal absorption will be used in this chapter to encompass the separate processes by which drug passes from the lumen of the gastrointestinal tract into columnar absorption cells and its movement through and out of these cells into the blood vessels via the lamina propria.

The *large intestine* like the stomach lacks villi (and microvilli). However, the large intestine serves as a site for the absorption of drug which has not been completely absorbed in the more proximal regions of the gastrointestinal tract, i.e.

the stomach and small intestine. Incomplete drug absorption in the more proximal regions may be due to the physicochemical properties of the drug itself (e.g. very low aqueous solubility and dissolution rate) or as a result of the intended slow release of drug from a prolonged/sustained/controlled release dosage form. In general if a large proportion of an orally administered dose of drug reaches the large intestine, it is likely that the drug will exhibit poor bioavailability (Gibaldi, 1984).

Mechanisms of drug transport across the gastrointestinal/blood barrier

It is apparent from the previous section that absorption of a drug from the lumen of the gastrointestinal tract into the blood involves the passage of drug molecules across several cellular membranes and fluid regions within the mucosa, i.e. the gastrointestinal/blood barrier. The epithelium lining the gastrointestinal tract is considered to constitute the main cellular barrier to the absorption of drugs from the gastrointestinal tract (Blanchard, 1975). The permeability characteristics of this epithelial layer appear to be directly

related to the properties of the apical cell membrane of the columnar absorption cell and thus gastrointestinal absorption becomes a special case of the general biological phenomenon of membrane transport (Levine, 1971). The apical cell membrane exhibits the characteristic trilaminar membrane structure upon electron microscopic examination and is composed largely of protein and lipid. Although the precise molecular structure of a cell membrane is not known, the apical cell membrane of the columnar absorption cell appears to behave, with respect to the absorption of drugs and nutrients, as a 'lipoidal' membrane penetrated periodically by submicroscopic aqueous filled channels or pores. Water-soluble substances of small molecular size (radius less than 0.4 nm), such as urea, are absorbed by simple diffusion through the water filled channels. Most drug molecules, however, are too large to pass through these channels and the apical cell membrane (and hence the gastrointestinal/blood barrier) behaves like a 'lipoidal sieve' with respect to the absorption of drugs. Thus the barrier allows the passage of lipid-soluble drugs in preference to lipid-insoluble drugs. The majority of drugs appear to cross the apical cell membrane of the lining epithelium (and other cell membranes within the gastrointestinal/blood barrier) by the mechanism known as passive diffusion. This and other mechanisms by which some drugs are absorbed will be considered.

Passive diffusion

In this process the apical cell membrane of a columnar absorption cell plays a passive role and does not participate actively in the transport process. The rate of drug transport is determined by the physicochemical properties of the drug, the nature of the membrane and the concentration gradient of drug across the membrane. The process of passive diffusion, shown in Fig. 9.4, initially involves partition of a drug between the aqueous fluid in the gastrointestinal tract and the lipoidal-like cell membrane of the lining epithelium. The drug in solution in the membrane then diffuses across the membrane followed by a second partition of drug between the membrane and the aqueous fluids within the columnar absorption cells. The drug would cross the other cell membranes in the gastrointestinal/blood barrier by this sequence of steps and thus would eventually enter the blood of the capillary network in the lamina propria. If we considered that the cell membranes and fluid regions making up the gastrointestinal/blood barrier could be represented by a single 'membrane', the gastrointestinal membrane, separating the aqueous gastrointestinal fluid from the capillary blood supply in the lamina propria, then the stages involved in the gastrointestinal absorption of a drug by passive diffusion could be represented by the model shown in Fig. 9.4.

Passive diffusion of drugs across the gastro-

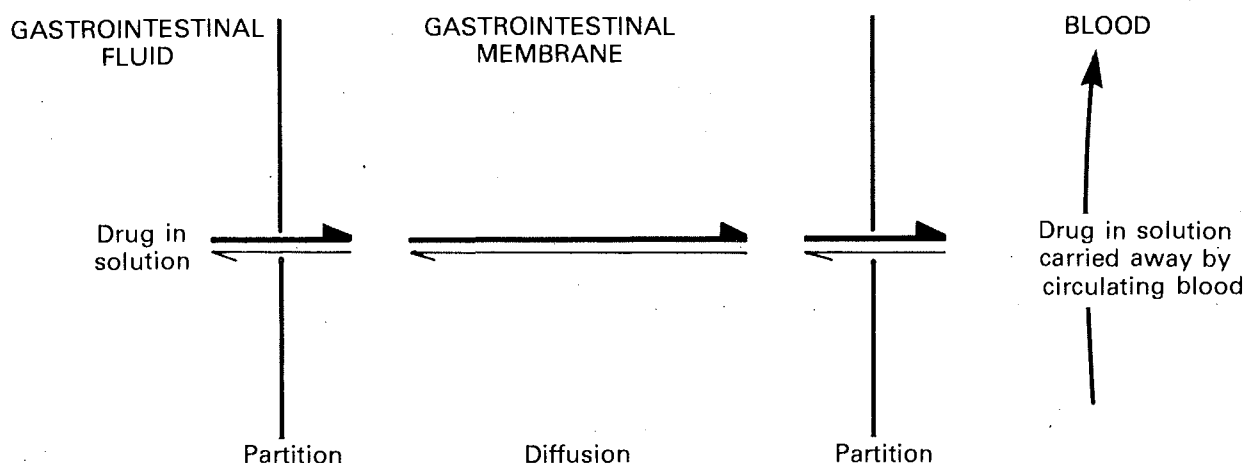


Fig. 9.4 Diagrammatic representation of gastrointestinal absorption via passive diffusion (bold arrows indicate direction of net movement of drug)

intestinal/blood barrier can often be described mathematically by Fick's first law of diffusion. Accordingly the rate of appearance of drug in the blood at the site of absorption is given by

$$\frac{dm}{dt} = \frac{D A (K_1 C_g - K_2 C_b)}{h} \quad (9.1)$$

where dm/dt is the rate of appearance of drug in the blood at the site of absorption, D is the effective diffusion coefficient of the drug in the gastrointestinal (g.i.) 'membrane', A is the surface area of the gastrointestinal 'membrane' available for absorption by passive diffusion, K_1 is the apparent partition coefficient of the drug between the gastrointestinal 'membrane' and the gastrointestinal fluid i.e.

$$K_1 = \frac{\text{concentration of drug inside 'membrane' at g.i. fluid/membrane interface}}{\text{concentration of drug in g.i. fluid}}$$

C_g is the concentration of drug in solution in the gastrointestinal fluid at the site of absorption, K_2 is the apparent partition coefficient of the drug between the gastrointestinal 'membrane' and the blood, C_b is the concentration of drug in the blood at the site of absorption, and h is the thickness of the gastrointestinal 'membrane'.

Hence $K_1 C_g$ and $K_2 C_b$ represent the concentrations of drug inside the gastrointestinal membrane at the g.i. fluid/membrane interface and g.i. membrane/blood interface respectively. The expression

$$\frac{(K_1 C_g - K_2 C_b)}{h}$$

represents the concentration gradient of drug across the 'membrane'.

Eqn 9.1 indicates that the rate of gastrointestinal absorption of a drug by passive diffusion depends on the surface area of the 'membrane' that is available for drug absorption. This is compatible with the observation that the small intestine, particularly the duodenum, is the major site for drug absorption due principally to the presence of villi and microvilli which provide an enormous surface area for absorption. Eqn 9.1 also indicates that the rate of drug absorption

depends on a large concentration gradient of drug existing across the gastrointestinal 'membrane'. It is of interest to note that the concentration gradient of drug across the membrane is influenced by the apparent partition coefficients exhibited by the drug with respect to the g.i. 'membrane'/g.i. fluid interface and the g.i. 'membrane'/blood interface. It is important that the drug has sufficient affinity (solubility) for the 'membrane' phase that it can partition readily into the gastrointestinal 'membrane', i.e. K_1 should exceed unity. In addition, after diffusing across the 'membrane' the drug should exhibit sufficient solubility for the blood such that it can partition readily out of the 'membrane' phase into the blood, i.e. K_2 should be less than 1. Drug on entering the blood in the capillary network in the lamina propria will be carried away from the site of absorption by the rapidly circulating gastrointestinal blood supply and will become diluted by

- 1 distribution in a large volume of blood, i.e. the systemic circulation,
- 2 distribution into body tissue and other fluids of distribution, and
- 3 by metabolism and excretion.

In addition, proteins in the blood may bind drug molecules and thereby further lower the concentration of 'free' (diffusible) drug in the blood. Consequently the blood acts as a 'sink' for absorbed drug and ensures that the concentration of drug in the blood at the site of absorption is low in relation to the concentration of drug in solution in the gastrointestinal fluids at the site of absorption, i.e. $C_g \gg C_b$. The 'sink' conditions provided by the systemic circulation ensures that a large concentration gradient is maintained across the gastrointestinal 'membrane' during the absorption process. The passive absorption process is driven solely by the concentration gradient of the diffusible species of the drug which exists across the gastrointestinal/blood barrier. Under such conditions that $K_1 C_g \gg K_2 C_b$ and thus $(K_1 C_g - K_2 C_b)$ approximates to $K_1 C_g$, Eqn 9.1 may be rewritten in the form

$$\frac{dm}{dt} = \frac{D A K_1 C_g}{h} \quad (9.2)$$

For a given drug and 'membrane' under specified conditions, D , A , K_1 and h may be regarded as constants which can be incorporated into a combined constant known as the permeability constant, P . Hence Eqn 9.2 becomes

$$\frac{dm}{dt} = P C_g \quad (9.3)$$

where

$$P = \frac{D A K_1}{h}$$

Eqn 9.3 is an expression for a first order kinetic process and indicates that the rate of passive drug absorption will be proportional to the concentration of absorbable drug in solution in the gastrointestinal fluids at the site of absorption. In practice, the gastrointestinal absorption of most drugs by passive diffusion follows first order kinetics.

It has been assumed that the drug in aqueous solution on each side of the gastrointestinal/blood barrier (see Fig. 9.4) existed entirely in the form of a single absorbable (via passive diffusion) species which exhibited definite partition coefficients for distribution between

- 1 the aqueous gastrointestinal fluids and the lipoidal 'membrane', and
- 2 the blood and the lipoidal 'membrane'.

However, many drugs are weak electrolytes which exist in aqueous solution as two species, namely the unionized and ionized species. Since it is the unionized form of a weak electrolyte drug which exhibits greater lipid solubility compared to the corresponding ionized form, the gastrointestinal 'membrane' (like other membranes) is permeable preferentially to the unionized species. Thus the rate of passive absorption of weak electrolyte drugs is related to the fraction of total drug that exists in the unionized form in solution in the gastrointestinal fluids at the site of absorption. This fraction is determined by the dissociation constant of the drug (i.e. its pK_a value) and by the pH of its aqueous environment in accordance with the Henderson-Hasselbalch equations for weak acids and bases. The gastrointestinal absorption of a weak electrolyte drug is enhanced when the pH

at the site of absorption favours the formation of a large fraction of the drug in aqueous solution that is unionized. These observations form the basis of the pH-partition hypothesis (see later in this chapter).

Carrier-mediated transport

Active transport Most drugs are absorbed from the gastrointestinal tract by passive diffusion. However, a few lipid-insoluble drugs (such as 5-fluorouracil) and many substances of nutritional interest are absorbed by active transport mechanisms. In contrast to passive diffusion, active transport involves active participation by the apical cell membrane of the columnar absorption cell (and presumably also by the other cell membranes constituting the gastrointestinal/blood barrier) in the gastrointestinal absorption of a drug. A 'carrier' which may be an enzyme or some other component of the cell membrane is responsible for effecting the transfer of drug by a process which is represented in Fig. 9.5.

Figure 9.5 shows that the drug molecule or ion forms a complex with the 'carrier' in the surface of the apical cell membrane of a columnar absorption cell involved in the active transport of the particular drug. The 'drug-carrier' complex then moves across the membrane and liberates the drug on the other side of the membrane. The carrier (now free) returns to its initial position in the surface of the cell membrane adjacent to the lumen of the gastrointestinal tract to await the arrival of another drug molecule or ion.

Active transport is a process whereby materials can be transported against a concentration gradient across a cell membrane, i.e. transport can occur from a region of lower concentration to one of higher concentration. Therefore active transport is an energy consuming absorption process. In the case of the gastrointestinal absorption of drugs by active transport, transfer of drug occurs in the direction of the gastrointestinal lumen to the blood and not normally in the reverse direction, i.e. drug absorption by active transport across the gastrointestinal/blood barrier does not normally occur against a concentration gradient of the drug. The carrier system is generally a 'one-way' transport system.

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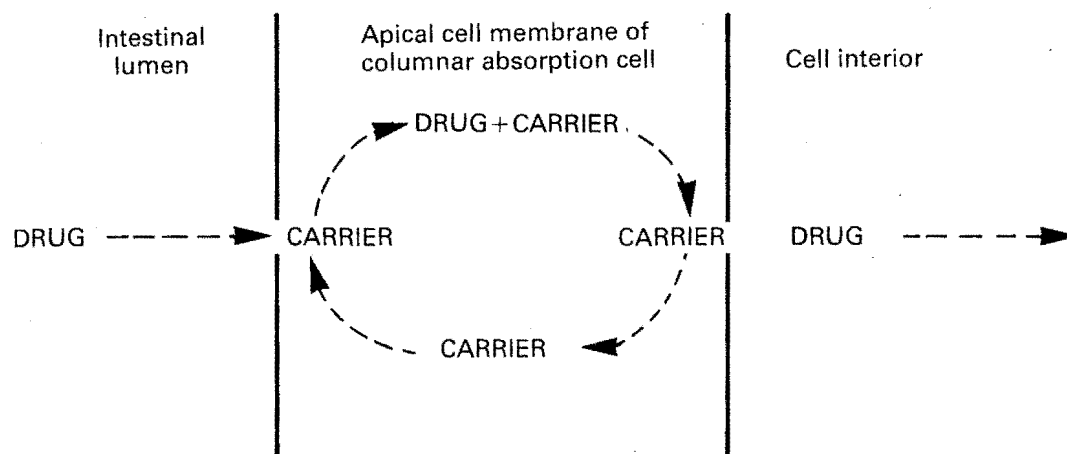


Fig. 9.5 Diagrammatic representation of active transport of a drug across a cell membrane

There appear to be several carrier-mediated active transport systems in the small intestine. Each carrier appears to be highly selective with respect to the chemical structure of the substance which it will transport. Thus if a drug structurally resembles a natural substance which is actively transported then that drug is also likely to be transported by the same carrier mechanism. For instance the drug levodopa, which is structurally related to the amino acids tyrosine and phenylalanine, is absorbed by the same active transport system that is used to transport these amino acids from the lumen of the small intestine into the blood. Each carrier system is generally concentrated in a specific segment of the gastrointestinal tract. The substance which is transported by that carrier will thus be absorbed preferentially in the location of highest carrier density. For instance, more riboflavin is absorbed from the proximal portion of the small intestine than from the large or upper intestine.

Unlike passive absorption, where the rate of absorption is directly proportional to the concentration of the absorbable species of the drug at the absorption site, active transport proceeds at a rate which is proportional to the drug concentration only at low concentrations. At higher concentrations the carrier mechanism becomes saturated and further increases in drug concentration will not increase the rate of absorption, i.e. the rate of absorption remains constant.

Many body nutrients such as sugars and L-amino acids are transported across the gastrointestinal 'membrane' by active transport processes.

Vitamins such as thiamine, nicotinic acid, riboflavin and B₆ require an active transport system. The anticancer drug 5-fluorouracil, methyldopa and nicotinamide are absorbed by active transport. Active transport also plays an important role in the renal and biliary excretion of many drugs and metabolites.

Facilitated diffusion or transport This is also a carrier-mediated transport system which differs from active transport in that it cannot transport a substance against a concentration gradient of that substance. Therefore facilitated diffusion does not require an energy input but it does require a concentration gradient for its driving force (as does passive diffusion). In terms of drug absorption, facilitated diffusion seems to play a very minor role.

Ion-pair absorption

This mechanism of absorption has been proposed to explain how certain drugs such as quaternary ammonium compounds and tetracyclines, which are ionized over the entire gastrointestinal pH range, are absorbed from the gastrointestinal tract. Such drug ions are considered to be too lipid insoluble to partition directly into the lipoidal apical cell membrane of the columnar absorption cells lining the gastrointestinal tract. In addition, these water-soluble drug ions are too large to pass through the aqueous filled pores or channels which are considered to exist in the cell membrane lining the gastrointestinal tract. However, the interaction of such drug ions with endogenous

organic ions of opposite charge to form an absorbable neutral species (i.e. an ion-pair) is a possible explanation of their mechanism of absorption. Since the charges are 'buried' in the ion-pair, the latter can now partition into the lipoidal cell membrane lining the gastrointestinal tract and be absorbed by passive diffusion.

Convective absorption (pore transport)

Very small molecules such as water, urea and low molecular weight sugars and organic electrolytes are able to cross cell membranes as if the membrane contained aqueous filled channels or pores. The effective radius of these channels has been estimated to be of the order of 0.4 nm. As a result of molecular size limitations, this mechanism of absorption appears to be of minor importance with respect to the gastrointestinal absorption of large water-soluble drug molecules or ions. However, convective absorption is involved in the renal excretion of drugs and the uptake of drugs into the liver.

Pinocytosis

Pinocytosis is the only mechanism of absorption in which the material does not have to be in aqueous solution in order to be absorbed. The mechanism is comparable to phagocytosis and involves invagination of the material by the apical cell membrane of the columnar absorption cells lining the gastrointestinal tract to form vacuoles containing the material. These vacuoles then cross the columnar absorption cells. This mechanism of absorption appears to be of little importance for drugs but is important for the absorption of macromolecules such as proteins.

PHYSIOLOGICAL FACTORS INFLUENCING DRUG ABSORPTION FROM THE GASTROINTESTINAL TRACT

In discussing how various physiological properties of the gastrointestinal tract may influence drug absorption, it should be noted that it is assumed (unless otherwise stated) that the drug is in solution in the appropriate gastrointestinal fluid.

Where appropriate, consideration will be given also to the influence that physiological factors can have on the release and dissolution of a drug from a dosage form. A drug must be in solution before it can be absorbed and the rate of drug release/dissolution can under certain conditions be the rate-controlling step in the appearance of a drug in the systemic circulation (see later in this chapter).

Surface area of the gastrointestinal absorption sites

The biological environments and the areas of membrane available for absorption in the stomach, the small intestine and the large intestine are quite different and these differences give rise to variations in the rate and extent of absorption of a drug from these anatomical regions.

As previously discussed, the presence of (a) folds in the mucosa, (b) villi and (c) microvilli is responsible for the small intestine having the largest effective surface area available for absorption. Consequently the small intestine is the region of maximum absorption for the majority of drugs even though the pH of the intestinal fluid does not provide optimum conditions for the absorption of all drugs, e.g. weak acidic drugs. In addition to its large absorptive surface area the small intestine is the most important region for carrier-mediated drug absorption, i.e. the small intestine is the location of highest 'carrier' density.

In contrast to the small intestine, the absorptive surface areas of the stomach and the large intestine are relatively small since neither of these regions possess villi or microvilli. Despite the relatively small absorptive surface area available in the stomach, certain drugs (e.g. weak acidic drugs in solution which are unionized) are absorbed in this region. It should be noted that following oral ingestion of a drug in solution a major part of the stomach's absorptive area will be immediately in contact with dissolved drug and, providing that the intrinsic physicochemical properties of the drug permit permeation of the gastrointestinal/blood barrier, good absorption may occur. However, because the absorptive surface area in the stomach is so small compared to that in the small intestine, the rate and extent of absorption of a given drug

from the stomach will, in most cases, be less than from the small intestine. The large intestine functions as an absorptive site for drugs that are so slowly absorbed that a significant portion of the administered dose passes through the stomach and small intestine. In addition, the large intestine is important for the absorption of some drugs such as sulphasalazine which must be degraded by the bacterial flora in this region before absorption can occur.

pH of gastrointestinal fluids

The pH of the fluids varies considerably along the length of the gastrointestinal tract. Gastric fluid is highly acidic, exhibiting a pH within the range 1–3.5. The fluid in the small intestine is generally considered to have a pH in the range 5–8, generally from a pH range of 5–6 in the duodenum to about pH 8 in the lower ileum. The fluid in the large intestine is generally considered to have a pH of about 8. Considerable variations within the above pH ranges may occur in an individual. For instance, there appears to be a diurnal cycle of gastric acidity, the fluids becoming more acidic at night and fluctuating during the day primarily in response to food ingestion. Gastric fluid pH generally increases when food is ingested and then slowly decreases over the following few hours. There is also considerable intersubject variation in gastrointestinal pH depending on such factors as:

- 1 the general health of the individual,
- 2 the presence of localized disease conditions (e.g. gastric and duodenal ulcers) along the gastrointestinal tract,
- 3 the types and amounts of food ingested, and
- 4 drug therapy.

In the case of drug therapy, anticholinergic drugs inhibit or reduce gastric secretion and the oral administration of antacids usually elevates gastric pH for a short period of time.

Gastrointestinal pH may influence drug absorption in a variety of ways. The degree to which a given weak electrolyte drug ionizes in solution in the gastrointestinal fluids is a function of pH (and pK_a of the drug). In general the unionized form of a drug in solution will be absorbed faster than the ionized form of the same drug at any

particular site along the gastrointestinal tract. Thus any change in pH of the gastric fluid (caused by any of the above variables), to a value which increases the extent to which a weak electrolyte drug in solution exists in its unionized form, will result in faster absorption from the stomach than was observed from this site at the original pH. However, most drugs in solution are absorbed more rapidly from the small intestine regardless of differences in pH between the stomach, small intestine and large intestine. This is a reflection of the over-riding influence of the available absorptive surface area on the rate of absorption of drugs in solution from these sites.

Since the aqueous solubility of a weak electrolyte drug is influenced by pH, the rate of dissolution of such a drug from a solid dosage form will be pH dependent. In the case of a poorly soluble weak electrolyte drug administered in a solid dosage form, the rate of drug dissolution in the gastrointestinal fluids may be the rate-limiting step for the absorption of such a drug. Hence gastrointestinal pH would be expected to exert a major influence on the dissolution rate and hence the overall absorption rate of such a drug administered in a solid dosage form such as a tablet or a hard gelatin capsule. Consequently a poorly soluble weak acidic drug, which only exhibits a high dissolution rate in an alkaline aqueous environment, will only be expected to be rapidly absorbed from a solid dosage form when the drug passes through the acid environment of the stomach and reaches the more alkaline intestinal fluids where rapid drug dissolution can occur. In contrast, a poorly aqueous-soluble weak basic drug, which only exhibits a high dissolution rate in an acidic aqueous environment, must first dissolve in the acidic gastric fluid before it reaches the small intestine in order to be rapidly absorbed from the small intestine. Any undissolved weak basic drug which reaches the small intestine would be expected to exhibit a relatively low absorption rate since its dissolution rate in the relatively alkaline intestinal fluids would be low (Mayersohn, 1979).

A further way by which gastrointestinal pH can influence drug absorption is in the case of drugs which exhibit limited chemical stability in either acidic or alkaline environments. The influence

that the chemical stability exhibited by a drug in the gastrointestinal fluids can have on the absorption of such a drug from the gastrointestinal tract is discussed later in this chapter.

Gastric emptying rate

Most drugs are optimally absorbed from the small intestine following peroral administration. Hence any reduction in the rate at which a drug in solution leaves the stomach and enters the duodenum (i.e. the gastric emptying rate) is likely to reduce the overall rate of drug absorption and therefore delay the onset of the therapeutic response of the drug. In addition the intensity of the therapeutic response may be reduced. The rate of gastric emptying is also important for drugs which are prone to chemical degradation in the stomach by virtue of the low pH or enzyme activity associated with the gastric fluid. The longer the time that a susceptible drug spends in the stomach, the more likely the drug is to be degraded with an accompanying reduction in its effective concentration and hence bioavailability. Drugs contained in enteric-coated dosage forms, which are formulated so as to prevent drug release into gastric fluid but to allow release into the fluid in the duodenum, will show a delayed onset of therapeutic activity if the gastric emptying rate is suppressed.

The gastric emptying of fluids and small particles appears to be an exponential process (Bechgaard and Christensen, 1982). Standard low bulk meals and liquids are transferred from the stomach into the duodenum in an apparent first order rate process, i.e. the rate of gastric emptying is proportional to the volume of the material remaining in the stomach. Gastric emptying rate is influenced by a large number of factors. Factors promoting gastric emptying rate include hunger, anxiety, the patient's body position (i.e. lying on the right side), the intake of liquids and the antiemetic drug, metoclopramide (Gibaldi, 1984). Gastric emptying rate is retarded by factors such as fatty foods, a high bulk (viscous) diet, mental depression, gastric ulcers, pyloric stenosis, hypothyroidism, the patient's body position (lying on the left side) and drugs such as anticholinergics, tricyclic antidepressants, aluminium hydroxide

and alcohol (Mayersohn, 1979). In view of these numerous factors which can influence gastric emptying rate, it is not surprising that this is a highly variable parameter both among different individuals and within any one individual at different times. It is likely that such variation in gastric emptying rate contributes to the inter-subject and intrasubject variation observed in the bioavailability of a given drug.

The gastric emptying of solution-type dosage forms and suspensions of fine drug particles is generally much faster and less variable than that of solid, non-disintegrating unit dosage forms and lumpy masses of aggregated particles. For instance the gastric emptying times of single non-disintegrating tablets (diameter 10–16 mm) range from 0.5 to 4.5 hours whereas dosage forms which disintegrate into small subunits (e.g. granules, pellets) are emptied gradually from the stomach with a mean time of 1.5 hours (Bechgaard and Christensen, 1982). It is thus not surprising to find that the gastric emptying times of enteric-coated tablets, which are designed to remain intact in the stomach, are very erratic and this contributes to the unusually large intersubject variability found in the absorption of drugs from this type of dosage form (Gibaldi, 1984).

In general, the presence of food in the stomach reduces the gastric emptying rate and thus can delay the absorption of drugs which are normally absorbed from the small intestine. Hence, unless a drug is irritating to the gastric mucosa, a drug should not be administered with or immediately after a bulky meal. In general a drug will reach the small intestine most rapidly if it is administered with water to a patient whose stomach is empty of food. However, effects of food on drug absorption from the gastrointestinal tract are quite variable and are considered in greater detail later in this chapter.

Whilst the above discussion suggests that a decrease in gastric emptying rate will be disadvantageous with respect to the overall rate of absorption of many drugs, the opposite may also be true. An example is the case of a solid dosage form containing a poorly soluble drug which must first dissolve in gastric fluid prior to being absorbed rapidly from the small intestine. Such would be the case for a poorly soluble weak basic drug since

any of this drug which reached the small intestine in the undissolved state would be expected to dissolve (and hence be absorbed) slowly. This is a consequence of the reduced solubility exhibited by such drugs at intestinal pH conditions. Hence a decrease in gastric emptying rate would permit a longer time in which dissolution of such a drug could occur in the more favourable acidic pH conditions of the stomach. A greater proportion of the administered dose of drug would dissolve and thus be in an absorbable form when it passed into the duodenum. The enhanced bioavailability exhibited by the poorly soluble drug nitrofurantoin in the presence of food was considered to be a result of the accompanying decreased gastric emptying rate which permitted a greater proportion of the drug to dissolve in the gastric fluids before passing into the duodenum from where it is optimally absorbed (Rosenberg and Bates, 1976).

Intestinal motility

Once a drug empties from the stomach and enters the small intestine it will be exposed to an environment which is totally different from that of the stomach. Since the small intestine is the primary site of drug absorption, the longer the residence time in this region the greater is the potential for efficient drug absorption assuming that the drug is stable in the intestinal fluids and does not react with endogenous materials to form poorly absorbable 'complexes' (Mayersohn, 1979).

There are two types of intestinal movements, propulsive and mixing. The propulsive movements primarily determine the intestinal transit rate and thus the residence time of a drug or a dosage form in the small intestine. The greater the intestinal motility, the shorter the residence time and the less time there is for dissolution and absorption of drugs to occur. Under normal circumstances, peristaltic waves propel the intestinal contents relatively slowly, i.e. it takes 3–10 hours to move a meal in the form of chyme along the entire length of the small intestine (Mayer-sohn, 1979). The residence time in the small intestine, as determined by intestinal motility, may be an important factor with respect to drug bioavailability. The longer a drug is in contact with the

absorption site(s) the greater the amount of drug absorbed (Bates and Gibaldi, 1970). Intestinal residence time will thus be important for

- 1 dosage forms which release drug slowly (e.g. controlled/sustained/prolonged release dosage forms) as they pass along the entire length of the gastrointestinal tract,
- 2 enteric-coated dosage forms which release drug only when they reach the small intestine,
- 3 drugs which dissolve slowly in the intestinal fluids and
- 4 drugs which are absorbed by intestinal carrier-mediated transport systems.

Mixing movements of the small intestine bring drug which is in solution in the intestinal contents into intimate contact with the large epithelial absorptive surface area of the small intestine. The mixing movements thus increase the area of contact between drug in solution and the gastrointestinal 'membrane'. In addition, the mixing movements will also increase the dissolution rate of drugs from solid dosage forms and this will be particularly significant in the case of poorly soluble drugs which exhibit dissolution rate-limited absorption.

Drug stability in the gastrointestinal tract

Absorption is not the only process that can occur as a drug in solution passes along the gastrointestinal tract. A drug may be chemically degraded and/or metabolized in the gastrointestinal tract. The consequence of this is usually incomplete bioavailability since only a fraction of the administered dose reaches the systemic circulation in the form of intact drug. Chemical degradation, particularly pH-dependent reactions such as hydrolysis, can occur in the fluids of the gastrointestinal tract. For instance, erythromycin undergoes acid-catalysed hydrolysis in gastric fluid. Drugs which resemble nutrients such as polypeptides, nucleotides or fatty acids may be especially susceptible to enzymic hydrolysis in the gastrointestinal tract. In addition to enzymic metabolism in the gastrointestinal fluids, drugs may be metabolized by enzymes located in the intestinal mucosa. For instance, intestinal metabolism accounts for orally administered isoproter-

enol being 1000 times less active than intravenously administered isoproterenol (Gibaldi, 1984). Other drugs which appear to be metabolized in the gastrointestinal mucosa include chlorpromazine, L-dopa, stilboestrol, progesterone and testosterone. The metabolic potential of the gastrointestinal microflora is also now recognized (Mayersohn, 1979).

It would seem that metabolism and degradation of a drug in the gastrointestinal tract would serve primarily to reduce the extent of its bioavailability. However, in some instances these processes may be essential for drug absorption to occur. Many pro-drugs such as erythromycin stearate and chloramphenicol palmitate depend on degradation in the gastrointestinal tract in order to release the therapeutically active parent molecule.

Hepatic metabolism

All drugs that are absorbed from the stomach, small intestine and colon pass into the hepatic portal system and are presented to the liver before reaching the systemic circulation. The liver is the primary site of drug metabolism. Hence this first pass of absorbed drug through the liver may result in extensive metabolism of the drug and a significant proportion of the absorbed dose of intact drug may never reach the systemic circulation. This phenomenon is known as the *first pass effect* and results in a decrease in bioavailability of those drugs which are rapidly metabolised by the liver. The bioavailability of a susceptible drug may be reduced to such an extent so as to render the gastrointestinal route of administration ineffective (as in the case of lignocaine where 70% of the oral dose is metabolized by the intestinal wall and liver) or to necessitate an oral dose which is many times larger than the intravenous dose (e.g. propranolol). Other drugs which are subject to the first pass effect include alprenolol, pethidine, organic nitrates and propoxyphene.

Influence of food and diet

There is considerable evidence that the rate and/or extent of drug absorption can be influenced by the

presence of food in the gastrointestinal tract (Welling, 1980). Food may influence drug bioavailability by means of the following mechanisms.

Alteration in the rate of gastric emptying

For instance, solid meals (particularly those which are hot and contain a high proportion of fat) tend to decrease gastric emptying rate and can thus delay the onset of therapeutic action of some drugs. Further information on the potential consequences of reduced gastric emptying rate on drug bioavailability has been given earlier in this chapter.

Stimulation of gastrointestinal secretions

Gastrointestinal secretions (e.g. gastric hydrochloric acid, pepsin) secreted in response to the presence of food may result in the degradation of drugs which are susceptible to chemical hydrolysis or enzymic metabolism. This would lead to a reduction in drug bioavailability. In the case of stable drugs, the stimulation of gastrointestinal secretions may increase bioavailability by assisting drug dissolution. The ingestion of food, especially fat, stimulates the secretion of bile. Bile salts are surface-active agents and can increase the dissolution of some poorly soluble drugs thereby enhancing their absorption. For instance the enhanced absorption exhibited by griseofulvin when fatty meals are ingested may be due to the solubilizing effect of bile salts secreted in response to the fatty components of the meal. However bile salts have been shown to form insoluble, non-absorbable complexes with such drugs as neomycin, kanamycin and nystatin.

Competition between food components and drugs for specialized absorption mechanisms

In the case of those drugs which have a chemical structure similar to nutrients required by the body for which specialized absorption mechanisms exist, there is the possibility of competitive inhibition of drug absorption. One example appears to be L-dopa whose absorption may be inhibited

by certain amino acids resulting from the breakdown of ingested proteins.

Complexation of drugs with components in the diet

The gastrointestinal absorption of tetracycline is reduced by virtue of the formation of a non-absorbable complex with calcium present in dairy foods. Foods containing a high iron content also reduce the bioavailability of tetracycline due to complex formation. In general, complexation is only important (with respect to bioavailability) when an irreversible or an insoluble complex is formed. In such cases the fraction of the administered dose of drug which becomes complexed is unavailable for absorption. Consequently the effective concentration of drug in solution in the gastrointestinal fluids is reduced and both the rate and/or extent of drug absorption is reduced. If the complex formed is water soluble and readily dissociates to liberate the 'free' (absorbable) drug, then little or no effect of complexation on drug absorption is noted. The rate at which the complex dissociates determines whether drug absorption is as rapid and/or complete as in the absence of complex formation. Further information on the effects of complexation on drug absorption is given later in this chapter.

Increased viscosity of gastrointestinal contents

The presence of food in the gastrointestinal tract will provide a viscous environment which may result in a reduction in the rate of drug dissolution in the gastrointestinal contents. In addition, the rate of diffusion of a drug in solution from the lumen to the absorbing membrane lining the gastrointestinal tract may be reduced by an increase in viscosity. Both of these effects will tend to decrease the bioavailability of drug.

Food-induced changes in blood flow to the liver

Blood flow to the gastrointestinal tract and liver increases shortly after a meal. This increased blood flow to the liver will increase the rate at which drugs are presented to the liver. The metabolism of some drugs (e.g. propranolol,

hydralazine, dextropropoxyphene) is sensitive to their rate of presentation to the liver. The greater the rate of presentation of such drugs to the liver, the larger the fraction of drug that escapes first pass metabolism. This is because the enzyme systems responsible for their metabolism become 'swamped' (i.e. saturated) by the increased rate of presentation of drug to the site of biotransformation. Under these circumstances food, by virtue of causing a transient increase in hepatic blood flow, can increase the amounts of such drugs that reach the systemic circulation intact.

It is thus evident that food can influence the absorption of drugs from the gastrointestinal tract by a variety of mechanisms. A summary of the influences that food may have on the absorption of a number of drugs is given in Table 9.1. Whilst food has been reported to increase or decrease the rate and/or extent of absorption of numerous drugs, it should be noted that the absorption of some drugs does not appear to be influenced by food ingestion. Drugs whose absorption is reported to be unaffected by food include chlorpropamide, oxazepam and prednisolone (Welling, 1980).

Miscellaneous physiological factors influencing gastrointestinal absorption

Disease states and physiological disorders associated with the gastrointestinal tract are likely to influence the absorption and hence bioavailabilities of drugs administered via this route. Local disease states can cause alterations in gastric pH. For instance, the pH of gastric fluid is elevated (up to pH 6.9) in patients with gastric cancer. The various ways by which alterations in gastric pH can influence drug bioavailability have been discussed earlier in this chapter. Gastric surgery can cause drugs to exhibit different bioavailabilities in such patients compared to normal individuals. Partial or total gastrectomy results in drugs reaching the duodenum more rapidly than in the case of normal individuals. This increased rate of presentation of drug to the small intestine may result in an increased overall rate of absorption of drugs which are best absorbed from this segment of the gastrointestinal tract. However, drugs

Table 9.1 The influence of food on the gastrointestinal absorption of some drugs (Mayersohn, 1979)

<i>Drug</i>	<i>Influence of food on absorption</i>	<i>Comments</i>
Aspirin	Reduction in rate but not in extent of absorption	Reduced rate of gastric emptying gives delayed onset of analgesia
Barbiturates	Reduction in rate but not in extent of absorption	Reduced rate of gastric emptying gives delayed hypnotic response
Cephalosporins	Reduction in rate but not in extent of absorption	Reduced rate of gastric emptying gives lower peak plasma concentrations
Griseofulvin	Absorption increased when fatty meal ingested	Solubilizing effect of bile salts secreted in response to fatty meal
Nitrofurantoin	Reduced rate but increased extent of absorption gives higher urinary concentrations	Prolonged residence in stomach gives improved dissolution in gastric fluids
Penicillins (benzylpenicillin, methicillin, oxacillin)	Rate and extent of absorption reduced	Prolonged residence in stomach causes increased loss of those penicillins which are sensitive to acid hydrolysis
Hydralazine	Extent of absorption increased	Reduction in first pass degradation
Tetracyclines (tetracycline, oxytetracycline)	Extent of absorption decreased	Formation of non-absorbable complex with calcium ions present in dairy products

which require a period of time in the stomach in order to facilitate their dissolution may show reduced bioavailabilities in such patients. Diarrhoeal conditions may reduce drug bioavailability by virtue of reducing the drug's residence time in the small intestine.

Other factors which may influence the bioavailabilities of drugs from the gastrointestinal tract include age (i.e. children, adults and elderly patients), stress (e.g. stress induced through illness) and whether a patient is bedridden or not.

PHYSICOCHEMICAL FACTORS INFLUENCING DRUG ABSORPTION FROM THE GASTROINTESTINAL TRACT

In the previous section, drug absorption has been shown to be influenced by many physiological factors. The absorption and hence the bioavailability of a drug is also influenced by many of its physicochemical properties, notably pK_a , lipid solubility, dissolution rate, chemical stability and complexation.

Drug dissociation constant and lipid solubility

The dissociation constant and lipid solubility of a drug and the pH at the absorption site often

dictate the absorption characteristics of a drug throughout the gastrointestinal tract. The inter-relationship between the degree of ionization of a weak electrolyte drug (which is determined by its dissociation constant and the pH at the absorption site) and the extent of drug absorption is embodied in the pH-partition hypothesis of drug absorption.

pH-partition hypothesis of drug absorption

According to this hypothesis, the gastrointestinal/blood barrier acts as a lipid barrier towards weak electrolyte drugs which are absorbed by passive diffusion. The gastrointestinal/blood barrier is thus impermeable to the ionized (i.e. poorly lipid-soluble) form of a weak acidic or basic drug but relatively permeable to the non-ionized (i.e. more lipid-soluble) form of such a drug. Consequently, according to the pH-partition hypothesis, the absorption of a weak electrolyte drug will be determined chiefly by the extent to which the drug exists in its unionized form at the site of absorption.

In order to illustrate the concept of the pH-partition hypothesis, let us consider the distribution of weak acidic and basic drugs across the gastrointestinal barrier between the gastric fluid and the blood. The extent to which a weak acidic

or basic drug ionizes in solution in gastric fluid or blood may be calculated using the appropriate form of the Henderson-Hasselbalch equation (see Chapter 3). For a weak acidic drug having a single ionizable group (e.g. aspirin, phenylbutazone, salicylic acid) the equation takes the form of . . .

$$\log \frac{[A^-]}{[HA]} = \text{pH} - \text{p}K_a \quad (9.4)$$

where $\text{p}K_a$ is the negative logarithm of the acid dissociation constant of the drug, $[HA]$ and $[A^-]$ are the respective concentrations (mol dm^{-3}) of the unionized and ionized forms of the weak acidic drug, which are in equilibrium and in solution either the gastric fluid or the blood. pH refers to the pH of the environment of the ionized and unionized species of the weak acidic drug, i.e. gastric fluid or blood.

For a weak basic drug possessing a single ionizable group (e.g. chlorpromazine) the analogous equation is

$$\log \frac{[BH^+]}{[B]} = \text{p}K_a - \text{pH} \quad (9.5)$$

where $[BH^+]$ and $[B]$ are the respective concentrations (mol dm^{-3}) of the ionized and unionized forms of the weak basic drug which are in equilibrium and in solution in either the blood or gastric fluid.

Absorption of a weak acidic drug Consider the distribution of a weak acidic drug having a $\text{p}K_a$ of 3.0 between the blood and gastric fluid. For the purposes of this calculation, assume that the pH of gastric fluid is 1.2 and the pH of blood is 7.4. Equation 9.4 may be used to calculate the ratios of the concentrations of the ionized form (A^-) and unionized form (HA^-) of the weak acidic drug which exist in equilibrium in solution in gastric fluid and blood, respectively. In gastric fluid, pH 1.2

$$\begin{aligned} \log \frac{[A^-]}{[HA]} &= \text{pH} - \text{p}K_a \\ &= 1.2 - 3.0 = -1.8 \end{aligned}$$

Therefore,

$$\frac{[A^-]}{[HA]} = \text{antilog}(-1.8) = 0.016$$

Thus the ratio of the concentrations of the ionized and unionized forms of the weak acidic drug ($\text{p}K_a = 3.0$) in solution in gastric fluid (pH 1.2) is 0.016 : 1, respectively. The vast majority (98.4%) of the drug in solution in gastric fluid exists therefore in the ionized (absorbable) form. Thus the vast majority of the drug in solution in gastric fluid will be absorbed passively through the gastrointestinal barrier and enter the blood. On partitioning into the blood, the drug will experience a pH of 7.4. The extent of ionization of the weak acidic drug ($\text{p}K_a = 3.0$) in the blood (pH 7.4) may be calculated using Eqn 9.4 as follows:

$$\begin{aligned} \log \frac{[A^-]}{[HA]} &= \text{pH} - \text{p}K_a \\ &= 7.4 - 3.0 = 4.4 \end{aligned}$$

Therefore,

$$\begin{aligned} \frac{[A^-]}{[HA]} &= \text{antilog}(4.4) \\ &= 25\,119 \end{aligned}$$

Thus the ratio of the concentrations of the ionized and unionized forms of the weak acidic drug in solution in the blood is 25 119 : 1, respectively. It is evident that the weak acidic drug, once present in the blood, will exist almost entirely (99.996%) in its ionized form, A^- . Thus irrespective of the sink conditions provided by the systemic circulation to absorbed drug, there will be virtually no tendency for the weak acidic drug in the blood to be absorbed back into the stomach since only 0.004% of the drug in the blood exists in the absorbable, unionized form.

If the stomach and blood are considered to be two enclosed compartments separated by the gastrointestinal barrier, which is freely permeable to the unionized form of the weak acidic drug but impermeable to the ionized form of the drug, then the unionized form of the drug (HA) will distribute between the gastric fluid and the blood until equilibrium is reached, i.e. the concentrations of unionized drug on each side of the gastrointestinal barrier are equal. However, because the pH on each side of the gastrointestinal barrier is different and the barrier is assumed to

be impermeable to the ionized form of the drug, the concentration of the ionized form on each side of the membrane when this equilibrium is attained, may not be equal. The equilibrium distribution of the weak acidic drug ($pK_a = 3.0$) between gastric fluid (pH 1.2) and blood (pH 7.4) may be represented as shown in Fig 9.6.

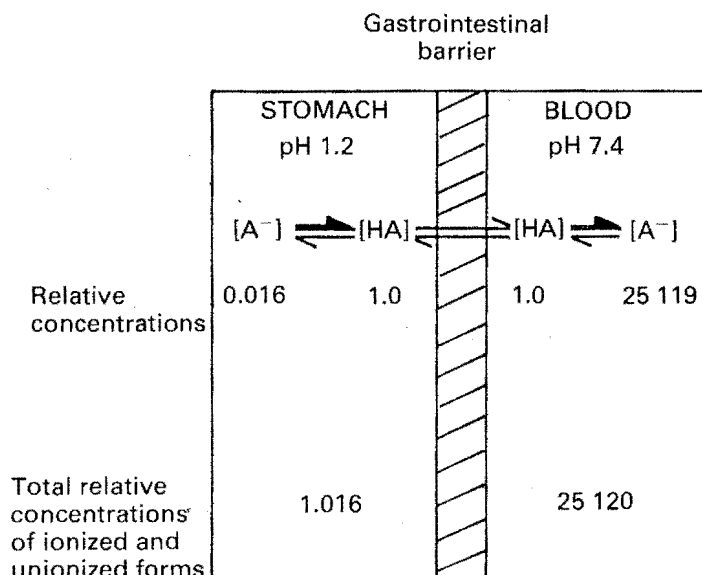


Fig. 9.6 Diagrammatic representation of the equilibrium distribution of a weak acidic drug ($pK_a = 3.0$) between the stomach and the blood

For this particular example the total relative equilibrium concentrations of weak acidic drug in the stomach and the blood are in the ratio of 1.016 : 25 120 respectively. The total equilibrium concentration of weak acidic drug is thus approximately 25 000 times greater in the blood than in the stomach. Hence according to the pH-partition hypothesis drugs such as weak acidic drugs which exist predominantly in the unionized form at gastric pHs will be well absorbed from the stomach.

Absorption of a weak basic drug Let us now consider how a weak basic drug having a pK_a of 5.0 becomes distributed between the gastric fluid (pH = 1.2) and the blood (pH = 7.4). Eqn 9.5 may be used to calculate the ratios of the unionized (B) and ionized (BH^+) forms of the drug which exist in equilibrium in solution in the gastric fluid and in the blood, respectively.

In gastric fluid, pH 1.2,

$$\log \frac{[BH^+]}{[B]} = pK_a - pH$$

$$= 5.0 - 1.2 = 3.8$$

Therefore,

$$\frac{[BH^+]}{[B]} = \text{antilog}(3.8)$$

$$= 6309.6$$

Hence, in gastric fluid (pH 1.2) the ratio of the equilibrium concentrations of the ionized and unionized forms of the weak basic drug ($pK_a = 5.0$) is 6309.6 : 1, respectively. The vast majority of the drug (i.e. 99.98%) in solution exists in the ionized, unabsorbable form.

In blood, pH 7.4,

$$\log \frac{[BH^+]}{[B]} = pK_a - pH$$

$$= 5.0 - 7.4 = -2.4$$

Therefore,

$$\frac{[BH^+]}{[B]} = \text{antilog}(-2.4)$$

$$= 0.004$$

Hence in blood (pH 7.4) the ratio of the equilibrium concentrations of the ionized and unionized forms of the weak basic drug ($pK_a = 5.0$) is 0.004 : 1, respectively. It is thus evident that any of the weak basic drug which is absorbed from the stomach into the blood will exist predominantly (i.e. 99.6%) in the unionized form. If we consider that the blood and stomach are enclosed compartments separated by the gastrointestinal barrier which is freely permeable to the unionized species (B) but impermeable to the ionized species (BH^+) of the weak basic drug, then the unionized species will distribute between these two compartments until its concentration on each side of the barrier is equal. The equilibrium distribution of the weak basic drug ($pK_a = 5.0$) between the stomach and blood may be represented as shown in Fig. 9.7.

For this particular example, Fig. 9.7 shows that the total relative equilibrium concentrations of weak basic drug in solution in the gastric fluid and

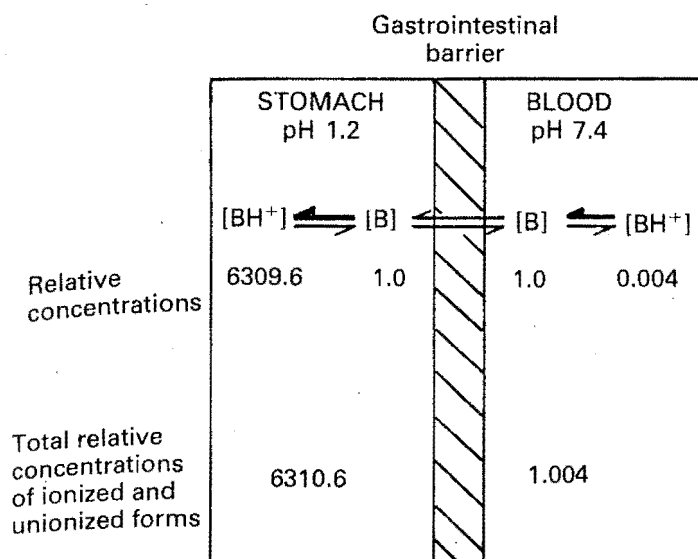


Fig. 9.7 Diagrammatic representation of the equilibrium distribution of a weak basic drug ($pK_a = 5.0$) between the stomach and the blood

the blood are in the ratio of 6310.6 : 1.004, respectively. At equilibrium the total concentration of the weak basic drug in the stomach is approximately 6300 times greater than that in the blood. Thus according to the pH-partition hypothesis, drugs such as weak basic drugs which are predominantly ionized at gastric pHs will be poorly absorbed from the stomach.

Limitations of the pH-partition hypothesis In calculating the distribution of a typical weak acidic drug and a typical weak basic drug between the stomach and blood, it has been assumed that an equilibrium distribution is attained. In practice such an equilibrium will rarely (if ever) be achieved since the stomach and the blood are not closed, static compartments. Drug is removed from the stomach into the intestine by the normal contractions of the stomach. Drug which enters the blood is removed from the site of absorption by circulation of the blood and is removed from the blood by distribution into tissues, by glomerular filtration and by metabolism. However, despite the above criticism, absorption from the stomach, as determined by direct measurements, generally conforms qualitatively to the pH-partition hypothesis. Weak organic acids are relatively well absorbed since they are all almost completely unionized at gastric pHs. Strong organic acids ($pK_a < 1$) which are ionized even in

the acid conditions of the stomach are not well absorbed. Weak bases, which are ionized at gastric pHs tend to be only absorbed negligibly but their absorption can be increased, as expected, by raising the pH of the gastric fluid. For more detailed information concerning the influence of pK_a and pH on the gastric absorption of weak basic and acidic drugs the reader should refer to the work of Hogben *et al.* (1957), Schanker *et al.* (1957), Shore *et al.* (1957) and Brodie (1964).

The pH range of the small intestinal fluids is less acid than that of the stomach. Thus, in accordance with the pH-partition hypothesis, the absorption of weak bases generally tends to be favoured over weak acids since a larger fraction of a weak basic drug in solution will be in the unionized form. However, the extent to which a drug exists in the unionized form is not the sole criterion determining the extent of absorption of a drug from the small intestine. For instance, it is found that despite their high degree of ionization, weak acids are still quite well absorbed from the small intestine. In fact, the rate of intestinal absorption of a weak acid drug is often higher than its rate of absorption from the stomach even though the drug will be unionized in the stomach. The existence of an effective pH at the surface of the intestinal mucosa (the so-called 'virtual membrane pH' of about pH 5.3), which is lower than the bulk pH in the lumen of the small intestine, has been proposed to account for the unexpectedly high rate of absorption of weak acids from this segment of the gastrointestinal tract. However, it is likely that the larger mucosal surface area available for absorption in the small intestine more than compensates for the low degree of unionization of weak acidic drugs at intestinal pHs.

A further illustration that the absorption of a drug from the gastrointestinal tract is not solely dependent on the drug being unionized, is provided by the observation that a number of drugs are poorly absorbed from certain areas of the gastrointestinal tract despite the fact that their unionized forms predominate in such areas. For instance barbitone ($pK_a 7.8$), which is almost totally unionized at gastric pHs, is only poorly absorbed from the stomach. However thiopen-

tone, which has a similar pK_a value (i.e. pK_a 7.6) is much better absorbed from the stomach than barbitone. The reason for this difference is that the absorption of drugs is also affected by the lipid solubility exhibited by the unionized form. Thus the unionized form of thiopentone, being more lipid soluble than the unionized form of barbitone, exhibits a greater affinity for the gastrointestinal 'membrane' and is thus better absorbed than barbitone from the stomach. The importance of lipid solubility to the gastrointestinal absorption of barbiturates has been demonstrated by Schanker (1960).

A further observation which cannot be explained by the pH-partition hypothesis is that certain drugs (e.g. quaternary ammonium compounds and tetracyclines) are absorbed readily despite being ionized over the enter pH range of the gastrointestinal tract. For more detailed discussions on the limitations of the pH-partition hypothesis of drug absorption, the reader is referred to articles by Benet (1973), Wagner and Sedman (1973) and Florence and Attwood (1981a).

To summarize, the gastrointestinal absorption characteristics of drugs which are weak electrolytes cannot be explained completely on the basis of their degree of ionization at any particular site of absorption. However, in general, the unionized form of drug in aqueous solution will be absorbed faster than the ionized form of the same drug at any particular site in the gastrointestinal tract. Since the absorptive surface area of the small intestine is so large in comparison to the stomach, this region is accepted as the major site of absorption for both weak acids and bases. Hence the rate of absorption of a given weak electrolyte drug from the small intestine will be greater than from the stomach even if the drug is ionized in the intestine and unionized in the stomach. Despite its limitations, the pH-partition hypothesis remains a useful guide in predicting general trends in drug absorption as a function of pH and pK_a within a specific region of the gastrointestinal tract.

Dissolution rate of drugs

Most drugs are absorbed and reach the systemic circulation by one of the following processes.

Absorption from solution or following rapid dissolution of solid drug particles

The drug is usually administered orally in the form of either a solution (e.g. an elixir) or a suspension, tablet or hard gelatin capsule from which rapid drug release/dissolution occurs. In such cases the bioavailability of a drug is influenced chiefly by:

- 1 how rapidly and how much of the drug in solution reaches the site(s) of absorption in an absorbable form,
- 2 the rate and extent of absorption across the gastrointestinal barrier, and
- 3 the extent to which the drug is metabolized during passage through the gastrointestinal barrier and/or the liver.

Absorption following the slow dissolution of solid drug particles

In those cases where a sparingly soluble drug* is administered in the form of a suspension, a tablet or a hard gelatin capsule, the rate at which the solid drug particles dissolve in the gastrointestinal fluids may be the slowest step in the sequence of events leading to the appearance of intact drug in the systemic circulation (refer back to Fig. 9.1). In such cases, drug absorption and hence bioavailability is dependent on how fast the drug dissolves in the gastrointestinal fluids, i.e. drug bioavailability is dissolution rate limited. Hence factors which influence the rate of dissolution of the drug in the gastrointestinal fluids will also influence the bioavailability of the drug.

Factors influencing the dissolution rates of drugs in the gastrointestinal tract

A schematic outline of the dissolution of a spherical drug particle in the gastrointestinal fluids is shown in Fig. 9.8.

* The term sparingly soluble refers to the solubility exhibited by a drug in the gastric and/or intestinal contents. A drug which was administered as an aqueous solution could still exhibit dissolution rate-limited absorption if the drug was precipitated by the conditions in the gastrointestinal tract and the dissolution rate exhibited by the precipitated drug was sufficiently low.

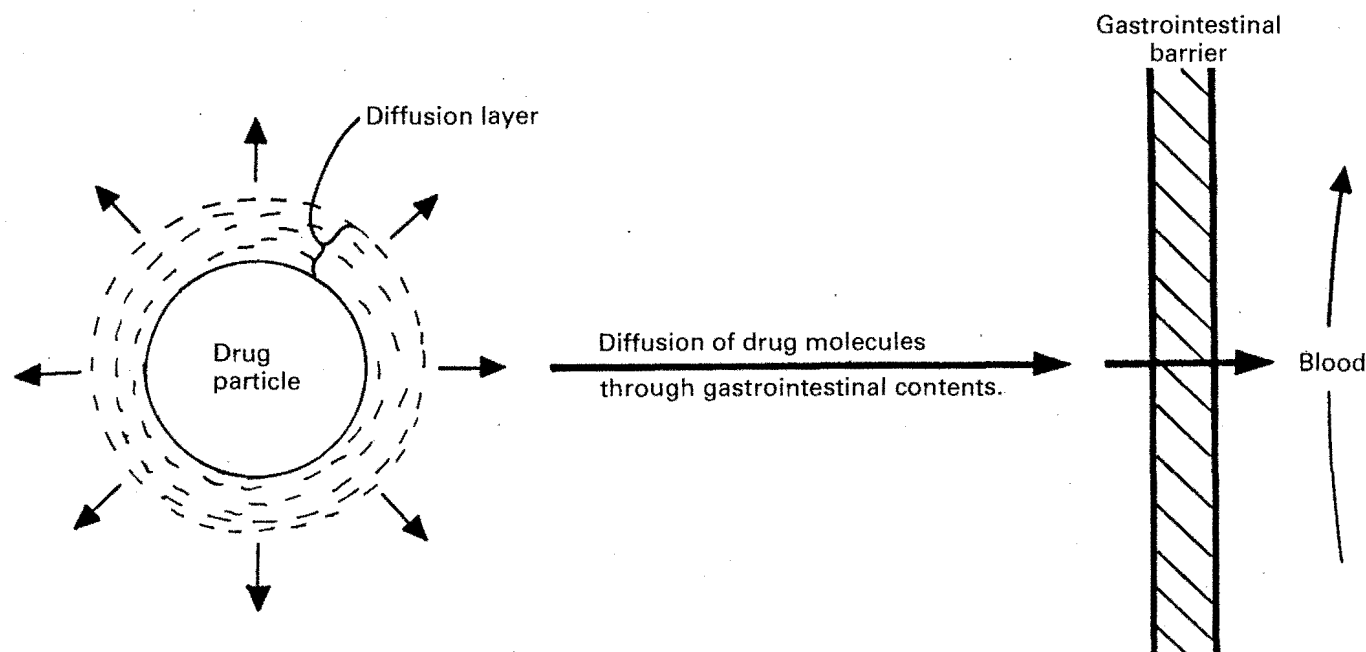


Fig. 9.8 Schematic representation of the dissolution of a drug particle in the gastrointestinal fluids

An equation which describes this process of dissolution is the Noyes–Whitney equation. This equation, which describes the rate of dissolution of spherical drug particles when the dissolution process is diffusion controlled and involves no chemical reaction, may be written

$$\frac{dm}{dt} = \frac{D A}{h} (C_s - C) \quad (9.6)$$

where dm/dt is the rate of dissolution of the drug particles, D is the diffusion coefficient of the drug in solution in the gastrointestinal fluids, A is the effective surface area of the drug particles in contact with the gastrointestinal fluids, h is the thickness of the diffusion layer around each drug particle, C_s is the saturation solubility of the drug in the diffusion layer, and C is the concentration of drug in solution in the bulk of the gastrointestinal fluids.

The limitations of the Noyes–Whitney equation in describing the dissolution of drug particles are discussed in Chapter 5. Despite its limitations, the Noyes–Whitney equation serves to illustrate and explain how various physicochemical and physiological factors can influence the rate of dissolution of drugs in the gastrointestinal tract.

Physiological conditions In this context, it is of interest to consider how certain parameters in the Noyes–Whitney equation (and hence the

dissolution rate of a drug) may be influenced by the physiological conditions in the gastrointestinal tract. For instance, the diffusion coefficient, D , of the drug in the gastrointestinal fluids may be decreased by the presence of substances which increase the viscosity of the fluids. Hence the presence of food in the gastrointestinal tract may cause a decrease in the dissolution rate of a drug by virtue of reducing the rate of diffusion of drug molecules away from the diffusion layer surrounding each undissolved drug particle. The thickness of the diffusion layer, h , will be influenced by the degree of agitation experienced by each drug particle in the gastrointestinal tract. Hence, an increase in gastric and/or intestinal motility may increase the dissolution rate of a sparingly soluble drug by virtue of decreasing the thickness of the diffusion layer around each drug particle. The concentration, C , of drug in solution in the bulk of the gastrointestinal fluids will be influenced by such factors as the rate of removal of dissolved drug by absorption through the gastrointestinal/blood barrier and by the volume of fluid available for dissolution. In the stomach, the volume of fluid will be influenced by the intake of fluid in the diet. According to the Noyes–Whitney equation, a low value of C will favour rapid dissolution of the drug by virtue of increasing the value of the term $(C_s - C)$. In the case of drugs whose absorp-

tion is dissolution rate limited, the value of C is normally maintained at a very low value by virtue of absorption of the drug. Hence dissolution occurs under so-called 'sink' conditions, (see Chapter 5) i.e., under conditions such that the value of $(C_s - C)$ approximates to C_s . Thus for dissolution of a drug in the gastrointestinal fluids under sink conditions, the Noyes-Whitney equation may be expressed as

$$\frac{dm}{dt} = \frac{D A C_s}{h} \quad (9.7)$$

Let us now consider how various physico-chemical properties exhibited by a drug can influence its rate of dissolution in the gastrointestinal fluids.

Particle size According to the Noyes-Whitney equation, an increase in the total effective surface area of drug in contact with the gastrointestinal fluids will cause an increase in dissolution rate. Provided that each particle of drug is intimately wetted by the gastrointestinal fluids, the effective surface area exhibited by the drug will be directly proportional to the particle size of the drug. Hence the smaller the particle size, the greater the effective surface area exhibited by a given mass of drug and the higher will be the dissolution rate. Particle size reduction is thus likely to result in increased bioavailability provided that absorption of the drug is dissolution rate limited.

A striking example of this effect is provided by griseofulvin. A reduction in particle size from about $10 \mu\text{m}$ (specific surface area = $0.4 \text{ m}^2 \text{ g}^{-1}$) to $2.7 \mu\text{m}$ (specific surface area = $1.5 \text{ m}^2 \text{ g}^{-1}$) was shown by Atkinson *et al.* (1962) to produce an approximate doubling in the amount of griseofulvin absorbed in humans. Duncan *et al.* (1962) also demonstrated that particle size reduction of griseofulvin permitted similar blood levels of this drug to be obtained in humans with half the original dose, i.e. a dose of 0.25 g instead of 0.5 g of griseofulvin.

Other drugs whose bioavailabilities have been enhanced by particle size reduction include sulphadiazine, phenothiazine, tolbutamide, spironolactone, aspirin, nitrofurantoin, digoxin and bishydroxycoumarin (Fincher, 1968; Shaw *et al.*, 1973; Florence *et al.*, 1974; Nash *et al.*, 1974/75). It is interesting to note that in the case

of nitrofurantoin, the inclusion of small-sized particles of this drug in tablets gave an increased incidence of undesirable side effects. The enhanced bioavailability resulting from particle size reduction was believed to be responsible for these undesirable side effects. This is an example where improved bioavailability resulted in patients becoming overmedicated.

It is possible that particle size reduction may fail to increase the bioavailability exhibited by a drug. This would be the case for a drug whose absorption was not dissolution rate limited. In the case of a poorly soluble, hydrophobic drug, whose absorption is dissolution rate limited, extensive particle size reduction can increase the tendency of the particles to aggregate in the aqueous gastrointestinal fluids with a consequent reduction in effective surface area, dissolution rate and hence bioavailability. Certain drugs such as penicillin G and erythromycin are unstable in gastric fluids. Thus chemical degradation will be minimized if such a drug does not dissolve readily in gastric fluids. Hence particle size reduction would not only produce an increased rate of drug dissolution in gastric fluid but also an increase in the extent of drug degradation. This would result in a decrease in the amount of intact drug available for absorption from the small intestine.

Solid dispersions A unique approach to presenting a poorly soluble drug in an extremely fine state of subdivision to the gastrointestinal fluids, is the administration of the drug in the form of a solid eutectic mixture. Such a mixture consists of a microcrystalline dispersion of the poorly soluble drug (e.g. sulphathiazole) in a matrix consisting of a physiologically inert, readily water-soluble solid such as urea. The water-soluble solid is often referred to as the 'carrier'. Exposure of this type of solid dispersion system to the gastrointestinal fluids results in dissolution of the water-soluble matrix (carrier). As the matrix dissolves it exposes the dispersed poorly soluble drug, which is in an extremely fine state of subdivision, to the aqueous gastrointestinal fluids. Hence the poorly soluble drug is presented to the aqueous fluids in a form which facilitates its dissolution rate and bioavailability. It is interesting to note that the bioavailability of sulphathiazole was found to be increased when this drug was presented in the form of a

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solid eutectic mixture with urea (Sekiguchi and Obi, 1961). The formation of a solid solution of a poorly soluble drug in a water-soluble physiologically inert solid should offer a greater improvement in dissolution rate and bioavailability of the poorly soluble drug than would a eutectic mixture. In the case of a solid solution the poorly soluble drug would be dispersed as single molecules throughout the water-soluble solid (carrier), i.e. the dispersed drug is in the ultimate form of subdivision.

The advantages of the solid solution over the eutectic mixture has been discussed by Goldberg *et al.* (1965, 1966a, b, c). The increased dissolution rates and bioavailabilities exhibited by solid dispersions of griseofulvin in polyethylene glycols of high molecular weight were originally attributed to solid solution formation (Chiou and Riegelman, 1971). However, later work by Chiou (1977) and Kaur *et al.* (1980) suggested that griseofulvin had negligible or very limited solubility in polyethylene glycol dispersion systems. The marked enhancement of dissolution and absorption rate of griseofulvin dispersed in such systems seemed to be primarily the result of the reduced size of the griseofulvin crystals, i.e. griseofulvin was in the form of microcrystals. In addition to this reduction in crystal size, other factors may also contribute to the improved dissolution rate and bioavailability exhibited by a drug presented in the form of a solid dispersion system. These factors are:

- 1 an increase in aqueous solubility of the drug because of its extremely small particle size,
- 2 a possible solubilization effect on the drug by the 'carrier' in the diffusion layer surrounding each dissolving drug particle in the gastrointestinal fluids,
- 3 a reduction or absence of aggregation and agglomeration of the drug particles exposed to the gastrointestinal fluids,
- 4 excellent wettability and dispersibility of the exposed drug particles in the gastrointestinal fluids (factors 3 and 4 will ensure that the effective surface area of the drug in contact with the gastrointestinal fluids is very large), and
- 5 possible formation of metastable polymorphic forms (which are more soluble and rapidly

dissolving in the gastrointestinal fluids) of the drug during formation of the solid dispersion system (Chiou and Riegelman, 1971).

Crystal form

Polymorphism Many drugs can exist in more than one crystalline form, e.g. chloramphenicol palmitate, cortisone acetate, tetracyclines and sulphathiazole. This property is referred to as polymorphism and each crystalline form is known as a polymorph. As discussed in Chapter 5, a metastable polymorph usually exhibits a greater aqueous solubility and dissolution rate than the corresponding stable polymorph. Consequently the metastable polymorphic form of a poorly soluble drug may exhibit an increased bioavailability in comparison to the stable polymorphic form of that drug.

A classic example of the influence of polymorphism on drug bioavailability is provided by chloramphenicol palmitate. This drug exists in three crystalline forms designated A, B and C. At normal temperature and pressure, A is the stable polymorph, B is the metastable polymorph and C is the unstable polymorph. The unstable polymorphic form of chloramphenicol palmitate is too unstable to be included in a dosage form. However, the metastable form is sufficiently stable to permit its incorporation in a dosage form. The mean blood serum levels and urinary excretion rates of chloramphenicol from orally administered suspensions containing varying proportions of the polymorphic forms A and B of chloramphenicol palmitate were studied by Augiar *et al.* (1967). The extent of absorption of chloramphenicol increased as the proportion of polymorphic form B of chloramphenicol palmitate increased in each suspension. This was attributed to the more rapid *in vivo* rate of dissolution of the metastable polymorphic form, B, of chloramphenicol palmitate. Following dissolution, chloramphenicol palmitate is hydrolysed to give free chloramphenicol in solution which is then absorbed. The stable polymorphic form A of chloramphenicol palmitate dissolves so slowly and consequently is hydrolysed so slowly to chloramphenicol *in vivo* that this polymorph is virtually without biological activity. The importance of polymorphism to the gastrointestinal bioavailability of chloramphenicol palmitate

tate is reflected by a limit being placed on the content of the inactive polymorphic form, A, in Chloramphenicol Palmitate Mixture BP.

Amorphous solids In addition to different polymorphic crystalline forms, a drug may exist in an amorphous form. Since the amorphous form is usually more soluble and rapidly dissolving than the corresponding crystalline form(s), the possibility exists that there will be significant differences in the bioavailabilities exhibited by the amorphous and crystalline form(s) of a given poorly soluble drug. A classic example of the influence of amorphous versus crystalline form of a drug on its gastrointestinal bioavailability is provided by the work of Mullins and Macek (1960) on the antibiotic drug, novobiocin. The more soluble and more rapidly dissolving amorphous form of novobiocin was readily absorbed following oral administration of an aqueous suspension to humans and dogs. However, the less soluble and slower dissolving crystalline form of novobiocin did not appear to be absorbed to any significant extent. The crystalline form was thus therapeutically ineffective. A further important observation was made in the case of aqueous suspensions of novobiocin. The amorphous form of novobiocin slowly converts to the more thermodynamically stable crystalline form with an accompanying loss of therapeutic effectiveness. Thus unless adequate precautions are taken to ensure the stability of the less stable, more therapeutically effective amorphous form of a drug in a dosage form, then unacceptable variations in therapeutic effectiveness may occur.

Solvates Another variation in the crystalline form of a drug can occur if the drug is able to associate with solvent molecules to produce crystalline forms known as solvates. When water is the solvent, the solvate formed is called a hydrate. Generally the greater the solvation in the crystal, the lower is the solubility and dissolution rate in a solvent identical to the solvation molecules. Since the solvated and non-solvated forms of a drug usually exhibit differences in solubility and dissolution rates, it is reasonable to expect that such forms may also exhibit differences in bioavailability particularly in the case of a poorly soluble drug which exhibits dissolution rate-limited bioavailability.

Poole *et al.* (1968) showed that the more aqueous soluble and rapidly dissolving anhydrous form of ampicillin was absorbed to a greater extent from hard gelatin capsule or aqueous suspension dosage forms administered to humans or dogs than was the less soluble, slower dissolving trihydrate form of ampicillin. However, it is possible that the observed difference may not have been due entirely to the state of solvation of ampicillin but also due to formulation differences within each type of dosage form tested.

Solubility of the drug in the diffusion layer (salt forms) According to the Noyes-Whitney equation (referred to earlier in this chapter) the dissolution rate of a drug in the gastrointestinal fluids is influenced by the solubility (C_s) that the drug exhibits in the diffusion layer surrounding each dissolving drug particle. In the case of drugs which are weak electrolytes, their overall aqueous solubilities are dependent on pH (see Chapter 5). Hence in the case of an orally administered solid dosage form containing a weak electrolyte drug, the dissolution rate of the drug will be influenced by its solubility and hence the pH in the diffusion layer surrounding each dissolving drug particle. It should be noted that the pH in the diffusion layer is not necessarily equal to the pH in the bulk of the gastrointestinal fluids. The dissolution rate of a weak acidic drug in gastric fluid (pH 1–3) will be relatively low. This is a consequence of the low solubility (C_s) exhibited by the drug in the diffusion layer because of the low pH in this layer. If the pH in the diffusion layer could be increased, then the solubility (C_s) exhibited by the weak acidic drug in this layer and hence the dissolution rate of the drug in the gastric fluids would be increased even though the bulk pH of the gastric fluids remained at the same low value. The pH of the diffusion layer would be increased if the chemical nature of the weak acidic drug was changed from that of the free acid to a strong alkali salt form of the free acid, e.g. the sodium or potassium salt form of the free acid. The pH in the diffusion layer surrounding each particle of the salt form would be higher (e.g. pH 5–6) than the low bulk pH (pH 1–3) of the gastric fluids because of the neutralizing action of the strong alkali cations (e.g. K^+ or Na^+ ions) present in the diffusion layer (see Fig. 9.9).

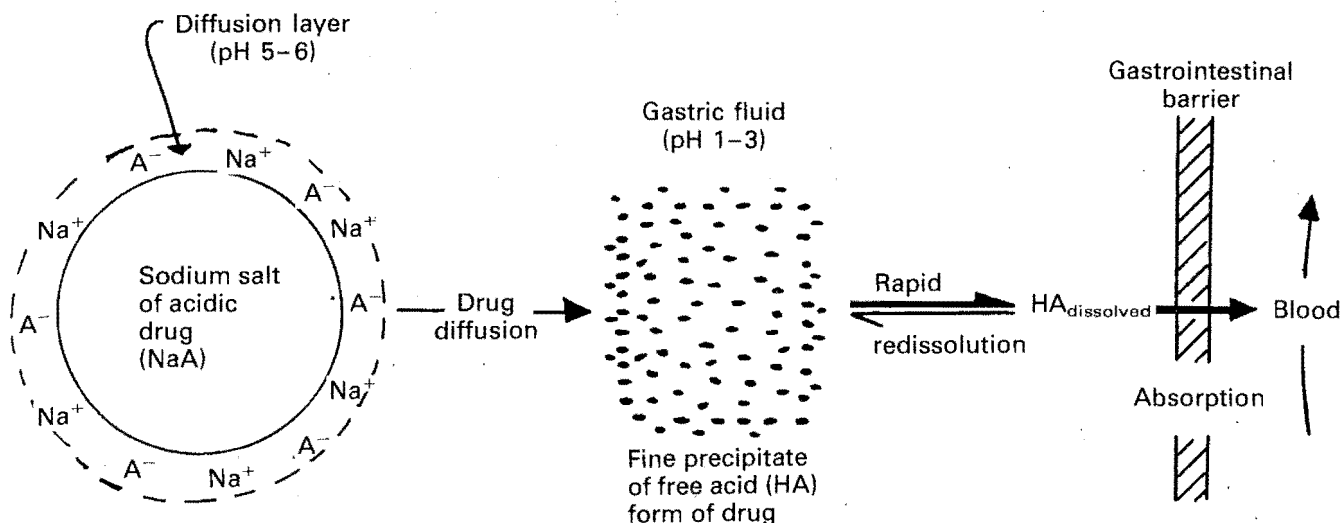


Fig. 9.9 Schematic representation of the dissolution process of a salt form of a weak acidic drug in gastric fluid. (After Cadwallader, 1973)

Since the salt form of the weak acidic drug has a relatively high solubility at the elevated pH in the diffusion layer, dissolution of the drug particles will take place at a faster rate. When dissolved drug diffuses out of the diffusion layer into the bulk of the gastric fluid where the pH is lower than that in the diffusion layer, precipitation of the free acid form of the drug is likely to occur. This will be a result of the lower overall solubility exhibited by the drug at the lower bulk pH. Thus the free acid form of the drug in solution, which is in excess of its solubility at the bulk pH of the gastric fluid, will precipitate out leaving a saturated (or near saturated) solution of free acid in the gastric fluid. It is considered that the precipitated free acid will be in the form of very fine, non-ionized, wetted drug particles which exhibit a very large total effective surface area in contact with the gastric fluids (much larger than would have been obtained if the free acid form of the drug had been administered). This large total effective surface area will facilitate rapid redissolution of the precipitated particles of free acid when additional gastric fluid becomes available as a consequence of either

- 1 dissolved drug being absorbed,
- 2 additional fluid accumulating in the stomach, or
- 3 the fine precipitated particles being emptied from the stomach into the intestine.

This rapid redissolution will ensure that the concentration of free acid in solution in the bulk

of the gastric fluids will be at or near to saturation (at the bulk pH conditions prevailing in the stomach).

Thus the oral administration of a solid dosage form containing a strong alkali salt of a weak acidic drug would be expected to give a more rapid rate of drug dissolution and (in the case of drugs exhibiting dissolution rate-limited absorption) a more rapid rate of drug absorption than if the free acid form of the drug itself had been included in the dosage form. This is well illustrated by the work of Nelson *et al* (1962) who showed that oral administration of a non-disintegrating disc of the more rapidly dissolving sodium salt of tolbutamide produced a very rapid decrease in blood sugar level (a consequence of the rapid rate of drug absorption) followed by a rapid recovery. In contrast, a non-disintegrating disc of the more slowly dissolving tolbutamide base produced a much slower rate of decrease of blood sugar level (a consequence of the slower rate of drug absorption) but the lower sugar level was maintained for a longer period of time. It is interesting to note that the gradual but prolonged decrease in blood sugar levels, and not the sharp dip and recovery is the preferred clinical response to oral hypoglycaemic drugs (Cadwallader, 1973).

An alternative method of increasing the dissolution rate of a weak acidic drug in gastric fluid is the inclusion of non-toxic basic substances in a solid dosage form containing the free acid form of the drug. The presence of the basic ingre-

dients ensures that a relatively alkaline diffusion layer is formed around each dissolving drug particle. The inclusion of the basic ingredients aluminium dihydroxyaminoacetate and magnesium carbonate in acetylsalicylic acid tablets was found to increase the gastric dissolution rate and the bioavailability of this drug following oral administration (Cadwallader, 1973).

A similar scheme to that described and shown in Fig. 9.9 can also be used to explain why strongly acidic salt forms of weak basic drugs (e.g. chlorpromazine hydrochloride) dissolve more rapidly in gastric or intestinal fluids than do the corresponding free bases (e.g. chlorpromazine). The presence of strongly acidic cations (e.g. Cl^- ions) in the diffusion layer formed around each dissolving acidic salt particle of drug ensures that the pH in that layer is lower than the bulk pH in either gastric or intestinal fluid. This lower pH will increase the solubility of the drug (C_s) in the diffusion layer. The oral administration of a salt form of a weak basic drug in a solid dosage form generally ensures that dissolution of the drug occurs in the gastric fluid before the drug passes into the small intestine where the pH conditions are less favourable to the dissolution of weak bases. Hence the use of strong acidic salt forms of weak basic drugs generally ensures that stomach emptying (and not dissolution rate) is the rate-determining step for the absorption of such drugs from the small intestine (Notari, 1980).

For further information concerning the usefulness and limitations of salt forms of drugs, the reader is referred to the review by Berge *et al.* (1977).

Complexation The rate and extent of absorption of a drug depends on the effective concentration of that drug, i.e. the concentration of drug in solution in the gastrointestinal fluids which is in an absorbable form. Complexation is one of the principal types of physicochemical interactions which can influence the effective drug concentration in the gastrointestinal fluids. The other types of interaction are adsorption and micellar solubilization. Complexation of a drug may occur within the dosage form and/or in the gastrointestinal fluids.

An example of complexation between a drug and a normal component of the gastrointestinal

tract is that between mucin and certain drugs. Mucin is a viscous mucopolysaccharide which lines the mucosal surfaces of the stomach and intestines. Streptomycin, dihydrostreptomycin, anticholinergic and hypotensive quaternary ammonium compounds bind strongly to mucin forming unabsorbable complexes. Thus complexation with mucin reduces the effective concentration and bioavailability of each of these drugs.

Another example of complexation occurring in the gastrointestinal fluids is that between certain drugs and dietary components. Tetracyclines form insoluble complexes with calcium ions and other polyvalent metal ions present in food (Remmers *et al.*, 1965). Since the complex formed is insoluble in the gastrointestinal fluids, that fraction of the antibiotic which has become complexed is unavailable for absorption. Consequently tetracyclines tend to show reduced absorption if taken with milk or dairy products which contain calcium ions. In addition antacids containing Ca^{2+} , Mg^{2+} or Al^{3+} ions and iron preparations (particularly those containing ferrous sulphate) also reduce the bioavailabilities exhibited by tetracyclines via the formation of insoluble complexes.

Tetracyclines also provide an example of drugs whose bioavailabilities are reduced by the formation of poorly soluble complexes with excipients present in dosage forms. The extent of absorption of tetracycline is reduced if dicalcium phosphate is included as a diluent in a tablet or hard gelatin capsule containing this antibiotic. Other examples of complexes which give reduced drug bioavailability are those between amphetamine and sodium carboxymethylcellulose and between phenobarbitone and polyethylene glycol 4000. Complexation between drugs and excipients such as cellulose derivatives, polyols, gums and surfactants probably occurs quite often in liquid dosage forms; complexation is sometimes used to increase drug stability or solubility.

In many cases the drug-excipient complexes are soluble in the gastrointestinal fluids and rapidly dissociate to liberate the 'free' drug. In such cases, little or no effect of complexation on drug absorption is noted. Hence the rate at which a complex dissociates will determine whether absorption of the drug is as rapid and/or complete as in the absence of complex formation.

It is also interesting to note that in a limited number of cases, complex formation has been found to improve drug absorption possibly as a consequence of increased drug solubility/dissolution rate and/or formation of well absorbed lipid-soluble complexes. The gastrointestinal absorption of ergotamine tartrate is increased by the simultaneous intake of caffeine (Schmidt and Fonchamps, 1974).

For additional information on complex formation, the reader is referred to Florence and Attwood (1981b).

Adsorption The concurrent administration of drugs and medicinal products containing solid adsorbents (e.g. antidiarrhoeal mixtures) may result in the adsorbents interfering with the absorption of such drugs from the gastrointestinal tract. The adsorption of a drug onto solid adsorbents such as kaolin, attapulgit or charcoal may reduce the rate and/or extent of drug absorption from the gastrointestinal tract. A decrease in the effective concentration of drug in solution which is available for absorption will occur if a significant proportion of the administered dose of drug is adsorbed to the solid adsorbent at the site(s) of absorption of that drug. A consequence of the reduced concentration of 'free' (i.e. absorbable) drug in solution at the site(s) of absorption will be a reduction in the rate of drug absorption. Whether or not there will also be a reduction in the extent of drug absorption will depend on whether or not the drug-adsorbent interaction is readily reversible. If the adsorbed drug is not readily released from the solid adsorbent in order to replace that 'free' drug which has been absorbed from the gastrointestinal tract, then there will be a reduction in the extent of absorption of that drug.

Examples of drug-adsorbent interactions which give reduced extents of drug absorption are promazine/charcoal and lincomycin/kapectate. In contrast the adsorption of promazine by the solid adsorbent, attapulgit, only produces a reduction in the rate but not extent of absorption of promazine in humans. This is because the adsorbed promazine is readily released from attapulgit in order to replace that 'free' promazine which has been absorbed from the gastrointestinal tract (Sorby, 1965).

Based on the above discussion, insoluble excipients included in dosage forms should exhibit little tendency to adsorb drugs present in the dosage form otherwise these so-called inert excipients could interfere with the absorption of drugs. Talc, which may be included in tablets as a glident is claimed to interfere with the absorption of cyanocobalamin by virtue of its ability to adsorb this vitamin. For further details of the biopharmaceutical implications of adsorption, the reader is referred to Florence and Attwood (1981c).

Chemical stability of drugs in the gastrointestinal fluids

Poor bioavailability usually results if a drug undergoes extensive acid or enzyme hydrolysis in the gastrointestinal tract. For instance, both penicillin G and erythromycin are susceptible to acid-catalysed hydrolysis and the extent of absorption of these drugs is thus influenced by the time that they reside in the stomach and on the gastric pH. When a drug is unstable in gastric fluid, its extent of degradation would be minimized (and hence its bioavailability would be improved) if it exhibited minimal dissolution in gastric fluid and rapid dissolution in intestinal fluid. The concept of delaying the dissolution of a drug until it reaches the small intestine has been employed to improve the bioavailability exhibited by erythromycin from the gastrointestinal tract. Enteric coating of tablets containing the free base, erythromycin, is one method which has been used to protect this drug from gastric fluid. The enteric coating resists gastric fluid but disrupts or dissolves at the less acid pH range of the small intestine. Hence the drug is not liberated until the coated tablet reaches the small intestine (further details concerning enteric coating may be found later in this chapter and in Chapters 18 and 40). However, despite the protection offered to susceptible drugs from gastric fluid by enteric coating, the bioavailability exhibited by drugs from enteric-coated tablets is potentially more variable than from any other type of dosage form (see later in this chapter).

Pro-drugs An alternative method of protecting a susceptible drug from gastric fluid, which has been employed in the case of erythromycin, is the administration of chemical derivations of the

parent drugs. These derivatives (called pro-drugs) exhibit limited solubility (and hence minimal dissolution) in gastric fluid but, once in the small intestine, liberate the parent drug to be absorbed. For instance, erythromycin stearate after passing through the stomach undissolved, dissolves and dissociates in the intestinal fluid yielding the free base, erythromycin, which is absorbed. In the case of erythromycin estolate, which is the lauryl sulphate salt of the ester erythromycin propionate, the improved bioavailability exhibited by this pro-drug is achieved in two ways. First, the poorly soluble lauryl sulphate salt remains undissolved and is thus not degraded during its passage through the stomach. Once in the small intestine, the lauryl sulphate salt dissolves and dissociates to give the ester, erythromycin propionate. Second, erythromycin propionate by virtue of its increased lipid solubility is better absorbed than the free base erythromycin. Once present in the blood, erythromycin propionate hydrolyses to liberate erythromycin, the active form of the antibiotic.

DOSAGE FORM FACTORS INFLUENCING DRUG ABSORPTION FROM THE GASTROINTESTINAL TRACT

The rate and/or extent of absorption of a drug from the gastrointestinal tract has been shown to be influenced by many physiological factors associated with this route of drug administration and by many physicochemical properties associated with the drug itself. The bioavailability of a drug administered in a dosage form can also be influenced by factors associated with the formulation and production of the dosage form. This aspect of biopharmaceutics will now be considered.

Influence of excipients

Drugs are almost never administered alone to patients but in the form of dosage forms. A dosage form generally consists of a drug (or drugs) together with a varying number of other substances (called excipients) that have been added to the formulation in order to facilitate the preparation, patient acceptability and functioning

of the dosage form as a drug delivery system. Excipients include disintegrating agents, diluents, lubricants, suspending agents, emulsifying agents, flavouring agents, colouring agents, chemical stabilizers etc. Excipients are also referred to as adjuvants, additives or inert ingredients. Although excipients were considered to be inert in that they, themselves, should not exert any therapeutic or biological action or modify the biological action of the drug present in the dosage form, it is now recognized that excipients can potentially influence the rate and/or extent of absorption of the drug. For instance, the potential influence of excipients on drug bioavailability has already been implicated by virtue of the formation of poorly soluble, non-absorbable drug-excipients complexes between tetracyclines and dicalcium phosphate, amphetamine and sodium carboxymethylcellulose and phenobarbitone and polyethylene glycol 4000.

Diluents

A dramatic example of the influence that excipients employed as diluents can have on drug bioavailability is provided by the Australian outbreak of phenytoin intoxication which occurred in epileptic patients as a consequence of the diluent being changed in sodium phenytoin capsules (Tyler *et al.*, 1970). Many epileptic patients who had been previously stabilized with sodium phenytoin capsules containing calcium sulphate dihydrate as the diluent, developed clinical features of phenytoin overdose when given sodium phenytoin capsules containing lactose as the diluent even though the quantity of drug in each capsule formulation was identical. It was later shown that the excipient calcium sulphate dihydrate had been responsible for decreasing the gastrointestinal absorption of phenytoin, possibly because part of the administered dose of drug formed a poorly absorbable calcium-phenytoin complex. Hence, although the size of dose and frequency of administration of the sodium phenytoin capsules containing calcium sulphate dihydrate gave therapeutic blood levels of phenytoin in epileptic patients, the efficiency of absorption of phenytoin has been lowered by the incorporation of this excipient in the hard gelatin capsules. Hence when the calcium sulphate

dihydrate was replaced by lactose, without any alteration in the quantity of drug in each capsule or in the frequency of administration of such capsules, the accompanying improved bioavailability resulted in higher plasma levels of phenytoin. In many patients, the higher plasma levels exceeded the maximum safe concentration for phenytoin and produced toxic side effects. This case is also discussed in Chapter 19.

Surfactants

Surfactants are often employed as emulsifying agents, solubilizing agents, suspension stabilizers or as wetting agents in dosage forms. However, surfactants in general cannot be assumed to be 'inert' excipients since they have been shown to be capable of either increasing, decreasing or exerting no effect on the transfer of drugs across biological membranes. In addition, surfactants might also be able to produce significant changes in the biological activity of drugs by perhaps exerting an influence on drug metabolizing enzymes or on the binding of drugs to receptor proteins (Florence, 1981).

Many studies aimed at elucidating the mechanisms by which surfactants can influence drug absorption have involved simple animal models of drug absorption such as the gill membrane of the goldfish, the isolated rabbit gastric mucosa and the ligated gastric fundic pouch of the dog. Although it is not clear to what extent such animal studies can be extrapolated to humans, some potential ways in which surfactants might influence drug absorption from the gastrointestinal tract in humans are as follows. Surfactant monomers can potentially disrupt the integrity and function of a membrane. Hence, such a membrane-disrupting effect would tend to enhance drug penetration and hence absorption across the gastrointestinal barrier. Inhibition of drug absorption may occur as a consequence of a drug being incorporated into surfactant micelles. If such surfactant micelles are not absorbed, which appears to be usually the case, then solubilization of a drug may result in a reduction of the concentration of 'free' drug in solution in the gastrointestinal fluids which is available for absorption. Inhibition of drug absorption in the presence of micellar concen-

trations of surfactant would be expected to occur in the case of drugs which are normally soluble in the gastrointestinal fluids, i.e. in the absence of surfactant. However, in the case of poorly soluble drugs whose absorption is dissolution rate limited, the increase in saturation solubility of the drug by solubilization in surfactant micelles could result in more rapid rates of drug dissolution and hence absorption. Very high concentrations of surfactant in excess of that required to solubilize the drug could decrease drug absorption by decreasing the chemical potential of the drug.

Release of poorly soluble drugs from tablets and hard gelatin capsules may be increased by the inclusion of surfactants in their formulations. The ability of a surfactant to reduce the solid/liquid interfacial tension will permit the gastrointestinal fluids to wet more effectively and to come into more intimate contact with the solid dosage forms. This wetting effect may thus aid the penetration of gastrointestinal fluids into the mass of capsule contents which often remains when the hard gelatin shell has dissolved and/or reduce the tendency of poorly soluble drug particles to aggregate in the gastrointestinal fluids. In each case, the resulting increase in the total effective surface area of drug in contact with the gastrointestinal fluids would tend to increase the dissolution and absorption rates of the drugs.

It is interesting to note that the enhanced gastrointestinal absorption of phenacetin in humans resulting from the addition of polysorbate 80 to an aqueous suspension of this drug was attributed to the surfactant preventing aggregation and thus increasing the effective surface area and dissolution rate of the drug particles in the gastrointestinal fluids (Prescott *et al.*, 1970).

It is also possible that surfactants could influence drug absorption by exerting a physiological action of their own on the gastrointestinal tract, for instance by altering the gastric residence time of a drug.

The possible mechanisms by which surfactants can influence drug absorption are varied and it is likely that only rarely will a single mechanism operate in isolation. In most cases, the overall effect on drug absorption will probably involve a number of different actions of the surfactant (some of which will produce opposing effects on

drug absorption) and the observed effect on drug absorption will depend on which of the different actions is the over-riding one. The ability of a surfactant to influence drug absorption will also depend on the physicochemical characteristics and concentration of the surfactant, the nature of the drug and on the type of biological membrane involved. Reviews on the effects of surfactants on drug absorption are provided by Gibaldi (1970), Gibaldi and Feldman (1970) and Florence (1981).

Viscosity-enhancing agents

Viscosity-enhancing agents are often employed in the formulation of liquid dosage forms for oral use in order to control such properties as palatability, ease of pouring and, in the case of suspensions, the rate of sedimentation of the dispersed particles. The viscosity-enhancing agent is often a hydrophilic polymer but many sugars serve the dual function of sweetening and viscosity-enhancing agents.

There are a number of mechanisms by which a viscosity-enhancing agent may produce a change in the gastrointestinal absorption of a drug. Complex formation between a drug and a hydrophilic polymer could reduce the concentration of drug in solution which is available for drug absorption (see earlier in this chapter). The administration of viscous solutions or suspensions may produce an increase in viscosity of the gastrointestinal contents. Such an increase in viscosity could lead to the following general effects:

- 1 a decrease in gastric emptying rate, i.e. an increase in gastric residence time,
- 2 a decrease in intestinal motility,
- 3 a decrease in dissolution rate of the drug, and
- 4 a decrease in the rate of movement of drug molecules to the absorbing membrane.

Normally, effect 3 would not be applicable to solution dosage forms unless dilution of the administered solution in the gastrointestinal fluids caused precipitation of the drug. Levy and Jusko (1965) suggested that effects 1, 2 and 4 would lead to a decrease in the rates of absorption of drugs from viscous solutions. Studies in which increased viscosity was found to produce reduc-

tions in the rates of absorption of drugs from solutions include the effects of sucrose solutions on the induction time of phenobarbitone sodium (Malone *et al.*, 1960), methylcellulose on the absorption of solutions of sodium salicylate (Davison *et al.*, 1961) and salicylic acid (Levy and Jusko, 1965), different gums on the urinary excretion rate of sodium salicylate solution (Bachynsky *et al.*, 1976) and sodium alginate on the bioavailability of phenolsulphonphthalein (Ashley and Levy, 1973).

In the case of suspensions containing drugs with bioavailabilities that are dissolution rate dependent, an increase in viscosity could also lead to a decrease in the rate of dissolution of the drug in the gastrointestinal tract. Thus the observation by Seager (1968) that methylcellulose reduced the rate and extent of absorption of nitrofurantoin from aqueous suspensions of this drug could have been due to effects 1, 2, 3 and 4. In addition, nitrofurantoin may form complexes with methylcellulose which could also tend to reduce the absorption of this drug (Shah and Sheth, 1976).

The potential absorption-enhancing effects of increased viscosity have been considered by Barzegar-Jalali and Richards (1979). An extended gastric residence time, or a slower intestinal transit time produced by an increase in viscosity, would allow a longer period in which drug dissolution could occur in the gastrointestinal tract and this could lead to an increase in the extent of absorption of a drug from a suspension. In addition, the increase in gastric residence time caused by an increase in viscosity could also enhance the amount of absorption of drugs with pK_a values that permit absorption of those drugs from the stomach. Similarly an increase in intestinal transit time would favour an increase in the amount of absorption of the majority of drugs since the intestine is the optimal site of absorption of most drugs. The net effect of increased viscosity on the absorption of a particular drug from the gastrointestinal tract will thus depend on whether or not the absorption-enhancing effects outweigh the absorption-reducing effects of increased viscosity. It is interesting to note that the absorption-enhancing effects of increased viscosity appeared to outweigh the absorption-reducing effects in studies on the effects of various macromolecular

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suspending agents on the bioavailabilities of aspirin and salicylic acid in the rabbit (Barzegar-Jalali and Richards, 1979).

The above examples serve to illustrate that so-called 'inert' excipients can often markedly influence the bioavailabilities of drugs administered in dosage forms via the gastrointestinal route.

Influence of the type of dosage form

In addition to the amount and physicochemical nature of each so-called 'inert' excipient included in a formulation, the type of dosage form and its method of preparation or manufacture can influence bioavailability. Thus, whether a particular drug is incorporated and administered in the form of a suspension, a hard gelatin capsule or a tablet can influence the rate and/or extent of absorption of that drug from the gastrointestinal tract. The type of oral dosage form will influence the number of possible intervening steps between administration of the dosage form and the appearance of dissolved drug in the gastrointestinal fluids, i.e. the type of dosage form will influence the release of drug into solution in the gastrointestinal fluids. A simplified scheme depicting this is shown in Fig. 9.10.

In general, drugs must be in solution in the gastrointestinal fluids before absorption can occur. Thus the greater the number of intervening steps, the greater will be the number of potential obstacles to drug absorption and the greater will be the likelihood of that type of dosage form reducing the bioavailability exhibited by the drug. Hence the bioavailability of a given drug tends to decrease in the following order of types of dosage form: aqueous solutions > aqueous suspensions > hard gelatin capsules > uncoated tablets > coated tablets. Whilst the number of intervening steps between administration and the appearance of a drug in solution in the gastrointestinal fluids may be equal in the case of the hard gelatin capsule and tablet dosage forms (see Fig. 9.10), the fine particles of drug in a hard gelatin capsule are not normally subjected to high compression forces and the subsequent reduction in effective drug surface area as a consequence of the tablet manufacturing process and to the difficulty in regenerating well dispersed drug particles after administration. Hence, particularly in the case of a poorly soluble drug, the rate of appearance of a given drug in solution in the gastrointestinal fluids is likely to be slower from a tablet than from a hard gelatin capsule. Although the above

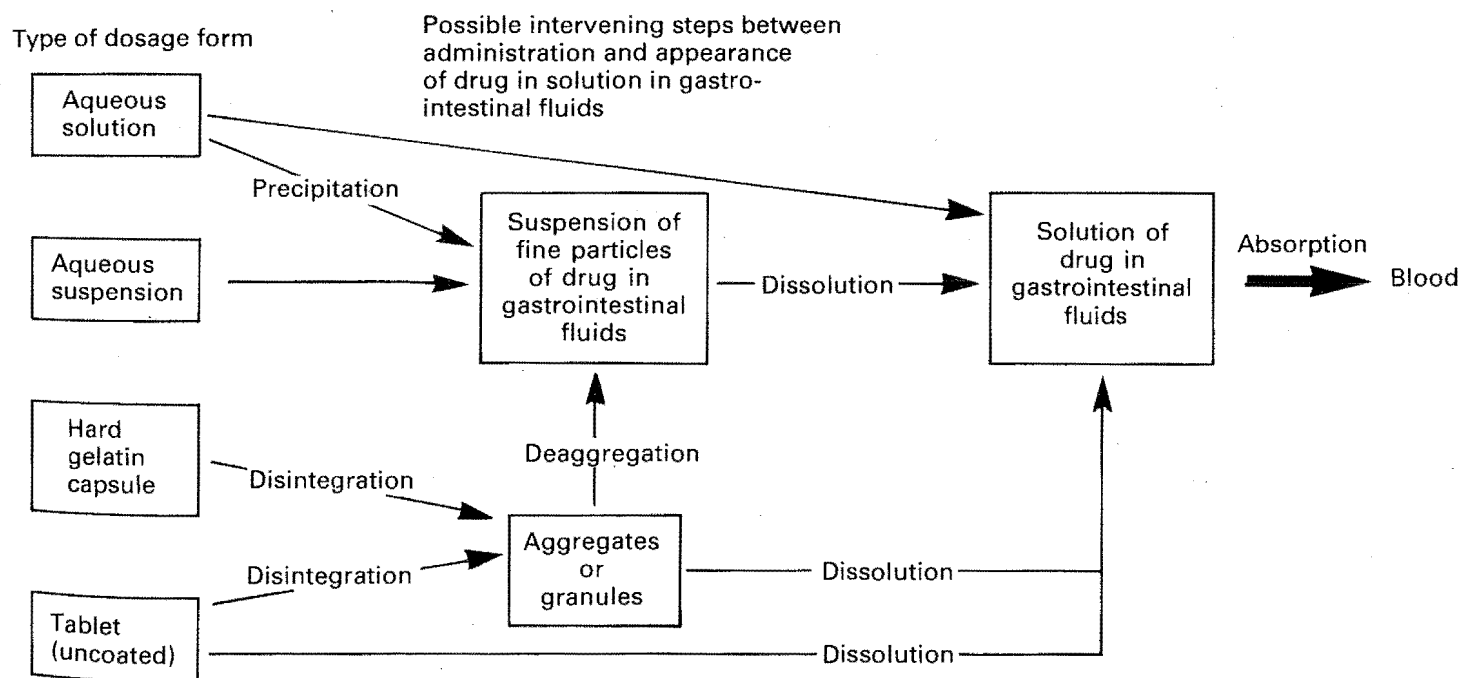


Fig. 9.10 Schematic outline of the influence of the dosage form on the appearance of a drug in solution in the gastrointestinal fluids

ranking of the types of oral dosage form is not universal, it does provide a useful guideline. In general solution and suspension dosage forms are most suitable for administering drugs intended to be rapidly absorbed. However, it should be noted that other factors (e.g. stability, patient acceptability etc.) can also influence the type of dosage form in which a drug is administered via the gastrointestinal route.

Aqueous solutions

For drugs which are water soluble and chemically stable in aqueous solution, formulation as a solution normally eliminates the *in vivo* dissolution step and presents the drug in the most readily available form for absorption (Rees, 1974). However, dilution of an aqueous solution of a poorly soluble drug (whose aqueous solubility has been increased by means of formulation techniques such as cosolvency, complex formation or solubilization) in the gastric fluids can result in precipitation of the drug. Similarly exposure of an aqueous solution of a salt of a weak acidic compound to gastric pH can also result in precipitation of the free acid form of the drug. However, in most cases, the extremely fine nature of the precipitate permits a more rapid rate of dissolution than if the drug had been administered in other types of oral dosage forms such as an aqueous suspension, a hard gelatin capsule or a tablet.

Factors associated with the formulation of aqueous solution dosage forms which can influence drug bioavailability include

- 1 the chemical stability exhibited by the drug in aqueous solution and the gastrointestinal fluids,
- 2 complexation, i.e. formation of a complex between the drug and an excipient included to increase the aqueous solubility, the chemical stability of the drug or the viscosity of the dosage form,
- 3 solubilization, i.e. the incorporation of the drug into micelles in order to increase the aqueous solubility of the drug and
- 4 the viscosity of solution dosage form, particularly if a viscosity-enhancing agent has been included.

Information concerning the potential influence of

each of the above factors on drug bioavailability from the gastrointestinal tract is given in earlier sections of this chapter. Further details concerning the formulation of oral solution dosage forms are given in Chapter 14.

Aqueous suspensions

An aqueous suspension is a useful dosage form for administering an insoluble or poorly aqueous soluble drug. Usually the absorption of a drug from this type of dosage form is dissolution rate limited. Oral administration of a dose of an aqueous suspension results in a large total surface area of dispersed drug being immediately presented to the gastrointestinal fluids. This large surface area facilitates dissolution and hence absorption of the drug. In contrast to hard gelatin capsule and tablet dosage forms, dissolution of all drug particles commences immediately on dilution of the dose of suspension in the gastrointestinal fluids. A drug contained in a tablet or hard gelatin capsule may ultimately achieve the same state of dispersion in the gastrointestinal fluids but only after a time lag. Thus a well formulated, finely subdivided aqueous suspension is regarded as being an efficient oral drug delivery system, second in efficiency only to the solution-type dosage form (Gibaldi, 1984).

Factors associated with the formulation of aqueous suspension dosage forms which can influence the bioavailabilities of drugs from the gastrointestinal tract include:

- 1 the particle size and effective surface area of the dispersed drug,
- 2 the crystal form of the drug,
- 3 complexation, i.e. the formation of a non-absorbable complex between the drug and an excipient such as the suspending agent,
- 4 the inclusion of a surfactant as a wetting, flocculating or deflocculating agent and
- 5 the viscosity of the suspension.

Information concerning the potential influence of the above factors on drug bioavailability is given in earlier sections of this chapter. Further information concerning the formulation and uses of suspensions as dosage forms is given in Chapter 15.

Soft gelatin capsules

Soft gelatin capsules combine the convenience of a unit dosage form with the potentially rapid drug absorption associated with aqueous solution and suspension types of dosage forms (Rees, 1974). Drugs encapsulated in soft gelatin capsules for peroral administration are dissolved or dispersed in a non-toxic, non-aqueous vehicle. Such vehicles may be water immiscible (i.e. lipophilic) or water miscible (i.e. hydrophilic). Vegetable oils are popular water-immiscible vehicles whilst polyethylene glycols and certain non-ionic surfactants (e.g. polysorbate 80) are employed as water-miscible vehicles.

Release of the contents of a soft gelatin capsule is effected by dissolution and splitting of the flexible shell. Following release, a water-miscible vehicle disperses and/or dissolves readily in the gastrointestinal fluids liberating the drug, depending on its aqueous solubility, as a solution or a fine suspension in the gastrointestinal fluids. The drug is thus liberated in a form which is conducive to rapid absorption. Many poorly water-soluble drugs have been found to exhibit greater bioavailabilities from soft gelatin capsules containing water-miscible vehicles than from aqueous suspensions, hard gelatin capsules or tablets (Armstrong and James, 1980). In the case of soft gelatin capsules containing drugs in solution or suspension in water-immiscible vehicles, release of the contents will almost certainly be followed by dispersion in the gastrointestinal fluids. Dispersion will be facilitated by emulsifiers included in the vehicle and also by bile. If the lipophilic vehicle is a digestible oil and the drug is highly soluble in the oil, it is possible that the drug will remain in solution in the dispersed oil phase and be absorbed (along with the oil) by fat absorption processes (Armstrong and James, 1980). For a drug which is less lipophilic or is dissolved in a non-digestible oil, absorption probably occurs following partitioning of the drug from the oily vehicle into the aqueous gastrointestinal fluids. In this case, the rate of drug absorption appears to depend on the rate at which drug partitions from the dispersed oil phase. The increase in interfacial area of contact resulting from dispersion of the oily vehicle in the gastroin-

testinal fluids will facilitate partition of the drug across the oil/aqueous interface. For a drug which is suspended in an oily vehicle, drug release may involve dissolution in the vehicle, diffusion to the oil/aqueous interface, and partition across the interface. It is also possible that release could involve the passage of solid drug particles across the oil/aqueous interface followed by dissolution in the gastrointestinal fluids. This latter mechanism has been proposed by de Blaey and Polderman (1980) as a model for drug release from lipophilic suppository vehicles containing suspended drug.

Factors associated with the formulation of soft gelatin capsules which can influence the bioavailabilities of drugs from this type of dosage form include:

- 1 solubility of the drug in the vehicle (and gastrointestinal fluids),
- 2 particle size of the drug (if suspended in the vehicle),
- 3 nature of the vehicle, i.e. hydrophilic or lipophilic (and whether a lipophilic vehicle is a digestible or non-digestible oil),
- 4 inclusion of a surfactant as a wetting agent/emulsifying agent in a lipophilic vehicle or as the vehicle itself,
- 5 inclusion of a suspending agent (viscosity-enhancing agent) in the vehicle, and
- 6 complexation, i.e. formation of a non-absorbable complex between the drug and any excipient.

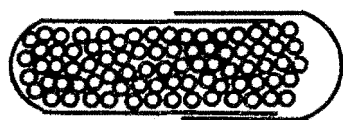
Additional information concerning soft gelatin capsules is given in Chapter 19.

Hard gelatin capsules

Generally the bioavailability of a drug from a well formulated hard gelatin capsule dosage form will be better than or at least equal to the bioavailability of the same drug from a compressed tablet. The small particles of drug in a capsule are not subjected to the same degree of compression and possible fusion which would reduce the effective surface area of the drug. Provided that the hard gelatin shell dissolves rapidly in the gastrointestinal fluids and the encapsulated mass disperses rapidly and efficiently, a relatively large effective

surface area of drug will be exposed to the gastrointestinal fluids thereby facilitating drug dissolution. However, it is incorrect to assume that because a drug formulated as a hard gelatin capsule is in a finely divided form surrounded by a water-soluble shell, no bioavailability problems can occur (Rees, 1974). The overall rate of dissolution of drugs from capsules appears to be a complex function of the rates of different processes such as:

- 1 the dissolution rate of the gelatin shell,
- 2 the rate of penetration of the gastrointestinal fluids into the encapsulated mass,

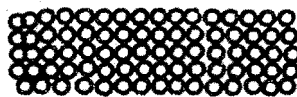


Hard gelatin capsule containing only hydrophobic drug particles



Hard gelatin capsule containing hydrophobic drug particles (o) and hydrophilic diluent particles (•)

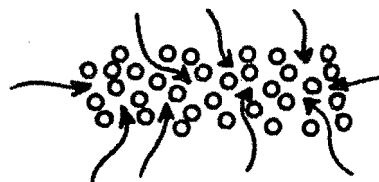
In gastrointestinal fluids, hard gelatin capsule shell dissolves, thereby exposing contents to fluids



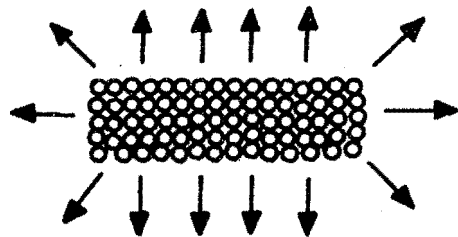
Contents remain as a capsule-shaped plug. Hydrophobic nature of contents impedes penetration of gastrointestinal fluids



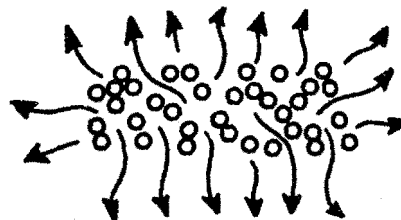
Particles of hydrophilic diluent dissolve in gastrointestinal fluids leaving a porous mass of drug



Gastrointestinal fluids can penetrate porous mass



Dissolution of drug occurs only from surface of plug-shaped mass. Relatively low rate of dissolution



Effective surface area of drug and hence dissolution rate is increased

Fig. 9.11 Diagrammatic representation of how a hydrophilic diluent can increase the rate of dissolution of a poorly soluble, hydrophobic drug from a hard gelatin capsule

sion and subsequent dissolution of the drug in these fluids. However, the diluent should exhibit no tendency to adsorb or complex with the drug since either can impair absorption from the gastrointestinal tract. For instance, the bioavailability of tetracycline is reduced if dicalcium phosphate is included as the diluent in capsules of this antibiotic. A poorly soluble, non-absorbable calcium-tetracycline complex is formed as the contents of the capsule dissolve in the gastrointestinal fluids.

Magnesium stearate is commonly included as a lubricant for the capsule-filling operation. Its hydrophobic nature often retards liquid penetration so that a capsule-shaped plug often remains after the shell has dissolved in the gastrointestinal fluids, especially when the contents have been machine-filled as a consolidated plug (Rees, 1974). However, this effect can usually be overcome by the simultaneous addition of a wetting agent (i.e. a water-soluble surfactant) and a hydrophilic diluent to the contents.

Both the formulation and the type and conditions of the capsule-filling process can affect the packing density and liquid permeability of the capsule contents (Newton, 1972). In general, an increase in packing density (i.e. a decrease in porosity) of the encapsulated mass will probably result in a decrease in liquid permeability and dissolution rate particularly if the drug is hydrophobic or if a hydrophilic drug is mixed with a hydrophobic lubricant such as magnesium stearate. If the encapsulated mass is tightly packed and the drug is hydrophobic in nature, then a decrease in dissolution rate with a concomitant reduction in particle size would be expected unless a surfactant had been included to facilitate liquid penetration. Granulation can increase the dissolution rate of a micronized hydrophobic drug by increasing the liquid permeability of the encapsulated mass (Newton, 1972).

In summary, formulation factors which can influence the bioavailabilities of drugs from hard gelatin capsules include:

- 1 surface area and particle size of drug (particularly the effective surface area exhibited by the drug in the gastrointestinal fluids),
- 2 use of the salt form of a drug in preference to the parent weak acid or base,

- 3 crystal form of the drug,
- 4 the chemical stability of the drug (in the dosage form and gastrointestinal fluids),
- 5 the natures and quantities of the diluent, lubricant and wetting agent,
- 6 drug-excipient interactions (e.g. adsorption, complexation),
- 7 the type and conditions of the filling process,
- 8 the packing density of the capsule contents,
- 9 the composition and properties of the capsule shell (including enteric capsules), and
- 10 interactions between the capsule shell and contents.

Further information concerning the hard gelatin capsule as a dosage form is given in Chapter 19.

Tablets

Uncoated tablets When a drug is formulated as a compressed tablet, there is an enormous reduction in the effective surface area of the drug due to the granulation and compression processes involved in tablet making (see Chapters 37 and 39). These processes also necessitate the addition of excipients which themselves may alter the release of a drug from a tablet. Many bioavailability problems are associated with this reduction in effective surface area of drug and with the problems of generating a fine, well dispersed suspension of drug particles in the gastrointestinal fluids following administration of a tablet. Since the effective surface area of a poorly soluble drug is an important factor influencing its dissolution rate, it is especially important that tablets containing such drugs should disintegrate rapidly and completely in the gastrointestinal fluids if rapid drug release, dissolution and absorption is required. The overall rate of tablet disintegration is influenced by several interdependent factors which include the concentration and type of drug, diluent, binder, disintegrant, lubricant and wetting agent as well as the compaction pressure (see Chapter 18).

A diagrammatic representation of the disintegration and dissolution steps that normally occur with a tablet prior to drug absorption are shown in Fig. 18.1. The dissolution of a poorly soluble drug from an intact tablet is usually extremely limited because of the relatively small effective

surface area of drug exposed to the gastrointestinal fluids. Disintegration of the tablet into granules causes a relatively large increase in effective surface area of drug and the drug dissolution rate may be likened to that of a coarse, aggregated suspension. Further disintegration into small, primary drug particles produces a further large increase in effective surface area and dissolution rate of the drug. The dissolution rate is probably comparable to that of a fine, well dispersed suspension of drug (Gibaldi 1984). Disintegration of a tablet into primary drug particles is thus important since it ensures that a large effective surface area of poorly soluble drug is generated in order to facilitate dissolution and subsequent absorption of the drug (Wells and Rubinstein, 1976).

However, simply because a tablet disintegrates rapidly does not necessarily guarantee that the liberated primary drug particles will dissolve rapidly in the gastrointestinal fluids and that the rate and extent of drug absorption will be adequate. In the case of poorly soluble drugs, the rate-controlling step for drug absorption is usually the overall rate of dissolution of the liberated drug particles in the gastrointestinal fluids. The overall dissolution rate and bioavailability of a poorly soluble drug from an uncoated conventional tablet is influenced by many factors associated with the formulation and manufacture of this type of dosage form (Finholt, 1974). These factors include:

- 1 the physicochemical properties of the liberated drug particles in the gastrointestinal fluids, e.g. wettability, effective surface area, crystal form, chemical stability,
- 2 the nature and quantity of the diluent, binder, disintegrant, lubricant and any wetting agent,
- 3 drug-exciipient interactions (e.g. complexation) the size of the granules and their method of manufacture,
- 4 the compaction pressure and speed of compression used in tableting, and
- 5 the conditions of storage and age of the tablet.

Since drug absorption and hence bioavailability are dependent upon the drug being in the dissolved state, suitable dissolution characteristics

can be an important property of a satisfactory tablet, particularly if it contains a poorly soluble drug. On this basis, specific *in vitro* dissolution test conditions and dissolution limits are included in the *British Pharmacopoeia* for tablets (and hard gelatin capsules) containing certain drugs, e.g. digoxin. That a particular drug product meets the requirements of a compendial dissolution standard provides a greater assurance that the drug will be released satisfactorily from the formulated dosage form *in vivo* and be absorbed adequately.

Further information on formulation and release of drugs from tablets is given in Chapter 18.

Coated tablets The most common of the various types of coated tablets are sugar-coated and film-coated tablets. The presence of a coating around a tablet presents a physical barrier between the tablet core and the gastrointestinal fluids. Hence coated tablets not only possess all the potential bioavailability problems associated with uncoated conventional tablets but are subject to the additional potential problem of being surrounded by a physical barrier. In the case of a coated tablet which is intended to disintegrate and release drug rapidly into solution in the gastrointestinal fluids, the coating must dissolve or disrupt before these processes can occur. The physicochemical nature and thickness of the coating can thus influence how quickly a drug is released from a tablet.

In the process of sugar coating, the tablet core is usually sealed with a thin continuous film of a poorly water-soluble polymer such as shellac or cellulose acetate phthalate (see Chapter 40). This sealing coat serves to protect the tablet core and its contents from the aqueous coating fluids used in the subsequent steps of the sugar-coating process. Hence the presence of this water-impermeable sealing coat can potentially retard drug release from sugar-coated tablets. In view of this potential problem, annealing agents such as polyethylene glycols or calcium carbonate which do not substantially reduce the water impermeability of the sealing coat during sugar coating but dissolve readily in gastric fluid, may be added to the sealer coat in order to reduce the 'barrier' effect of this coat to rapid drug release.

The coating of a tablet core by a thin film coat of a water-soluble polymer such as hydroxy-

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propyl methylcellulose should have no significant effect on the rate of disintegration of the tablet core and subsequent drug dissolution provided that the film coat dissolves rapidly and independently of the pH of the gastrointestinal fluids. However, if hydrophobic water-insoluble film coating materials such as cellulose acetate phthalate, ethylcellulose or acrylic resins are used to coat tablet cores, the resulting film coat acts as a barrier which delays and/or reduces the rate of release of drugs from tablet cores. Thus these types of film coating materials form 'barriers' which can have a significant influence on the absorption of drugs from film-coated tablets. Whilst the formation of such 'barrier' coatings would be disadvantageous in the case of film-coated tablets intended to provide rapid rates of drug absorption, the concept of 'barrier' coating has been used (along with other techniques) to obtain more precise control over drug release than is possible with conventional uncoated tablets. In this context, film coating has been used to provide

- 1 limited control over the site at which a drug is released from a tablet into the gastrointestinal tract, and
- 2 a controlled continuous rate of drug release from a non-disintegrating (intact) tablet as it passes along the gastrointestinal tract.

In this latter case, 'barrier' coating is one of many formulation techniques which have been used to increase the duration of therapeutic action of a drug contained within a peroral dosage form. For information concerning controlled/sustained/prolonged release peroral dosage forms, the reader should refer to the reviews by Ritschel (1973) and Hon-Leung Lee and Robinson (1978).

Enteric coated tablets The use of barrier coating in order to control the site of release of an orally administered drug is well illustrated by enteric-coated tablets. An enteric coat is designed to resist gastric fluids but to disrupt or dissolve when the coated tablet enters the duodenum. Polymers such as cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate and polyvinyl acetate phthalate are used as enteric coatings. These materials dissolve slowly over the gastric pH range (i.e. pH 1–3) but dissolve rapidly at the less acid pH values associated with the small intestine.

Enteric coatings should preferably begin to dissolve at about pH 5 in order to ensure the availability of drugs which are absorbed primarily in the proximal region of the small intestine (Rees, 1974). Enteric coating thus provides a means of delaying the release of a drug until the dosage form reaches the small intestine. Such delayed release provides a means of protecting drugs which would otherwise be destroyed if released into gastric fluid (see earlier in this chapter). Hence enteric coating serves to improve the peroral bioavailability exhibited by such drugs from uncoated conventional tablets. Enteric coating also protects the stomach against drugs which can produce nausea or mucosal irritation if released at this site, e.g. phenylbutazone, aspirin.

In addition to the protection offered by enteric coating, the delayed release of drug also results in a significant delay in the onset of the therapeutic response of a drug. The onset of the therapeutic response is largely dependent on the residence time of the enteric-coated tablet in the stomach. Gastric emptying of such tablets is an all-or-nothing process, i.e. the tablet is either in the stomach or in the duodenum. Consequently drug is either not being released or being released. The residence time of an intact enteric-coated tablet in the stomach can vary within and between subjects from about 30 minutes to several hours (Bechgaard and Christensen, 1982). Hence there is considerable intrasubject and intersubject variation in the onset of therapeutic action exhibited by drugs administered as enteric-coated tablets.

The formulation of an enteric-coated product in the form of small individually enteric-coated granules or pellets contained in a rapidly dissolving hard gelatin capsule or a rapidly disintegrating tablet, would largely eliminate the dependency of this type of dosage form on the all-or-nothing gastric emptying process associated with the intact enteric-coated tablet. Provided that the coated granules or pellets were sufficiently small (less than 1 mm diameter), they would be able to pass the pylorus even when the sphincter was closed (Bechgaard and Christensen, 1982). Hence enteric-coated granules and pellets would exhibit a gradual but continual release from the stomach into the duodenum. This type of release would also avoid the complete dose of drug being released

into the duodenum as occurs from an enteric-coated tablet. The intestinal mucosa would thus not be exposed locally to a potentially toxic

concentration of drug (Taylor, 1982).

Further information on coated tablets is given in Chapters 18 and 40.

REFERENCES AND BIBLIOGRAPHY

- Armstrong, N. A. and James, K. C. (1980) *Int. J. Pharm.*, **6**, 195–204.
- Ashley, J. J. and Levy, G. (1973) *J. pharm. Sci.*, **62**, 688–690.
- Atkinson, R. M., Bedford, C., Child, K. J. and Tomich, E. G. (1962) *Nature*, **193**, 588–589.
- Augiar, A. J., Krc, J. Jnr., Krinkel, A. W. and Samyn, J. C. (1967) *J. pharm. Sci.*, **56**, 847–853.
- Bachynsky, M. O., Bartilucci, A. J., Eisen, H. and Jarowski, C. I. (1976) *Drug Dev. Commun.*, **2**, 63–76.
- Barr, W. H. (1972) *Pharmacology*, **8**, 55–101.
- Barzegar-Jalali, M. and Richards, J. H. (1979) *Int. J. Pharm.*, **3**, 133–141.
- Bates, T. R. and Gibaldi, M. (1970) In: *Current Concepts in the Pharmaceutical Sciences: Biopharmaceutics* (Ed. J. J. Swarbrick), pp. 57–99, Lea and Febiger, Philadelphia.
- Bechgaard, H. and Christensen, F. N. (1982) *Pharm. J.*, **229**, 373–376.
- Benet, L. Z. (1973) In: *Drug Design* (Ed. E. J. Ariens), Vol. IV, pp. 1–35, Academic Press, New York.
- Berge, S. M., Bighley, L. D. and Monkhouse, D. C. (1977) *J. pharm. Sci.*, **66**, 1–19.
- Blanchard, J. (1975) *Am. J. Pharm.*, **147**, 135–146.
- Brodie, B. B. (1964) In: *Absorption and Distribution of Drugs* (Ed. T. B. Binns), pp. 16–48, E. and S. Livingstone Ltd, London.
- Cadwallader, D. E. (1973) *Biopharmaceutics and Drug Interactions*, p. 58, F. Hoffman-La Roche and Co. Ltd, Basel.
- Chiou, W. L. (1977) *J. pharm. Sci.*, **66**, 989–991.
- Chiou, W. L. and Riegelman, S. (1971) *J. pharm. Sci.*, **60**, 1281–1302.
- Davison, C., Guy, J. L., Levitt, M. and Smith, P. K. (1961) *J. Pharm. exp. Ther.*, **134**, 176–183.
- de Blaeys, C. J. and Polderman, J. (1980) In: *Drug Design* (Ed. E. J. Ariens), Vol. IX, pp. 237–266, Academic Press, London.
- Duncan, W. A. M., Macdonald, G. and Thornton, M. J. (1962) *J. Pharm. Pharmacol.*, **14**, 217–224.
- Fincher, J. H. (1968) *J. pharm. Sci.*, **57**, 1825–1835.
- Finholt, P. (1974) In: *Dissolution Technology* (Eds L. J. Leeson and J. T. Carstensen), pp. 106–146, Academy of Pharmaceutical Science, Washington.
- Florence, A. T. (1981) *Pure appl. Chem.*, **53**, 2057–2068.
- Florence, A. T. and Attwood, D. (1981a) *Physico-chemical Principles of Pharmacy*, pp. 337–342, The Macmillan Press Ltd, London.
- Florence, A. T. and Attwood, D. (1981b) *Ibid.*, pp. 406–413.
- Florence, A. T. and Attwood, D. (1981c) *Ibid.*, pp. 415–419.
- Florence, A. T., Salole, E. G. and Stenlake, J. B. (1974) *J. Pharm. Pharmacol.*, **26**, 479–480.
- Gibaldi, M. (1970) *Fedn. Proc.*, **29**, 1343–1349.
- Gibaldi, M. (1984) *Biopharmaceutics and Clinical Pharmacokinetics*, 3rd edn, Lea and Febiger, Philadelphia.
- Gibaldi, M. and Feldman, S. (1970) *J. pharm. Sci.*, **59**, 579–589.
- Goldberg, A. H., Gibaldi, M. and Kanig, J. L. (1965) *J. pharm. Sci.*, **54**, 1145–1148.
- Goldberg, A. H., Gibaldi, M. and Kanig, J. L. (1966a) *Ibid.*, **55**, 482–487.
- Goldberg, A. H., Gibaldi, M. and Kanig, J. L. (1966b) *Ibid.*, **55**, 487–492.
- Goldberg, A. H., Gibaldi, M. and Kanig, J. L. (1966c) *Ibid.*, **55**, 581–583.
- Hogben, C. A. M., Schanker, L. A., Tocco, D. J. and Brodie, B. B. (1957) *J. Pharm. exp. Ther.*, **120**, 540–545.
- Hon-Leung Lee, V. and Robinson, J. R. (1978) In: *Drugs and the Pharmaceutical Sciences. Vol. I. Sustained and Controlled Release Drug Delivery Systems* (Ed. J. R. Robinson), pp. 123–209, Marcel Dekker, Inc., New York.
- Kaur, R., Grant, D. J. W. and Eaves, T. (1980) *J. pharm. Sci.*, **69**, 1317–1321.
- Levine, R. R. (1971) In: *Topics in Medicinal Chemistry, Vol. 4, Absorption Phenomena* (Eds J. L. Rabinowitz and R. M. Myerson), pp. 27–95, Wiley-Interscience, London.
- Levy, G. and Jusko, W. (1965) *J. pharm. Sci.*, **54**, 219–225.
- Malone, M. H., Gibson, R. D. and Miya, T. S. (1960) *J. pharm. Sci.*, **49**, 529–534.
- Mayersohn, M. (1979) In: *Modern Pharmaceutics* (Eds G. S. Banker and C. T. Rhodes), pp. 23–85, Marcel Dekker Inc., New York.
- Mullins, J. D. and Macek, T. J. (1960) *J. Am. Pharm.*, **49**, 245–248.
- Nash, J. F., Childers, R. F., Lowary, L. R. and Rose, H. A. (1974/75) *Drug Dev. Commun.*, **1**, 459–470.
- Nelson, E., Knoechel, E. L., Hamlin, W. E. and Wagner, J. G. (1962) *J. pharm. Sci.*, **51**, 509–514.
- Newton, J. M. (1972) *Pharm. Weekblad.*, **107**, 485–498.
- Notari, R. E. (1980) *Biopharmaceutics and Clinical Pharmacokinetics. An Introduction*, 3rd edn, pp. 107–172, Marcel Dekker Inc., New York.
- Poole, J. W., Owen, G., Silverio, J., Freyhof, J. H. and Roseman, S. B. (1968) *Curr. ther. R.*, **10**, 292–303.
- Prescott, L. F., Steel, R. F. and Ferrier, W. R. (1970) *Clin. Pharmac. Ther.*, **11**, 496–504.
- Rees, J. E. (1974) *Pharm. J.*, **213**, 266–270.
- Remmers, R. G., Barringer, W. C., Sieger, G. M., Anagnostakos, N., Corbett, J. C. and Doerschuk, A. P. (1965) *J. Pharm. Sci.*, **54**, 49–52.
- Ritschel, W. A. (1973) In: *Drug Design* (Ed. E. J. Ariens), Vol. IV, pp. 37–73, Academic Press, New York.
- Rosenberg, H. A. and Bates, T. R. (1976) *Clin. Pharmac. Ther.*, **20**, 227–231.
- Schmidt, R. and Fonchamps, A. (1974) *Eur. J. clin. Pharmacol.*, **7**, 213–216.
- Seager, H. (1968) *J. Pharm. Pharmacol.*, **20**, 968–969.
- Sekiguchi, K. and Obi, N. (1961) *Chem. Pharm. Bull.*, **9**, 866–872.
- Shah, N. B. and Sheth, B. B. (1976) *J. Pharm. Sci.*, **65**, 1618–1623.

- Schanker, L. S. (1960) *J. mednl Chem.*, **2**, 343-359.
- Schanker, L. S., Shore, P. A., Brodie, B. B. and Hogben, C. A. M. (1957) *J. Pharm. exp. Ther.*, **120**, 528-539.
- Shaw, T. R. D., Carless, J. E., Howard, M. R. and Raymond, K. (1973) *Lancet*, **ii**, 209-210.
- Shore, P. A., Brodie, B. B. and Hogben, C. A. M. (1957) *J. Pharm. exp. Ther.*, **119**, 361-369.
- Smith, D. H. (1964) In: *Absorption and Distribution of Drugs* (Ed. T. B. Binns), pp. 1-15, E. and S. Livingstone Ltd, London.
- Sorby, D. L. (1965) *J. pharm. Sci.*, **54**, 677-683.
- Taylor, D. C. (1982) *Pharm. J.*, **229**, 371-373.
- Tyler, J. H., Eadie, M. J., Sutherland, J. M. and Hooper, W. D. (1970) *Br. med. J.*, **4**, 271-273.
- Wagner, J. G. and Sedman, A. J. (1973) *J. Pharmacokin. Biopharm.*, **1**, 23-50.
- Welling, P. G. (1980) *Pharm. Int.*, **1**, 14-18.
- Wells, J. I. and Rubinstein, M. H. (1976) *Pharm. J.*, **217**, 629-631.

Parenteral products

THE BIOPHARMACY OF INJECTIONS

Routes of administration

- Intracutaneous or intradermal route*
- Subcutaneous or hypodermic route*
- Intramuscular route*
- Intravascular routes*
- Intracardiac route*
- Intraspinal routes*
- Intra-articular and intrabursal routes*
- Ophthalmic routes*

Bioavailability of drugs from injections

FORMULATION OF INJECTIONS

Volume of the injection

The vehicle

- Water and pyrogens*
- Water-miscible vehicles*
- Water-immiscible vehicles*

Osmotic pressure

- Intravascular injections*
- Intrathecal injections*
- Intramuscular injections*
- Intracutaneous injections*
- Subcutaneous injections*

Hydrogen ion concentration (pH)

- To increase the stability of the injection*
- To minimize pain, irritation and necrosis on injection*
- To provide unsatisfactory conditions for growth of micro-organisms*
- To enhance physiological activity*
- Buffers*

Specific gravity of injections

Suspensions for injection

- Wettability*
- Sedimentation rate*
- Claying*

Size and shape of particles

Thixotropy

Preparation of aqueous suspension injections

Suspensions in oily vehicles

Addition of a gelling agent

Particle size

Emulsions for injection

Intravenous therapy and emulsions

Colloidal dispersions and solubilized products

QUALITY ASSURANCE OF INJECTIONS

Microbiological preservation

- The use of bactericides in single-dose injections*
- The use of bactericides in multiple-dose injections*
- Bactericides suitable for aqueous injections*
- Bactericides suitable for oily injections*
- Limitations in the use of bactericides*
- Incompatibilities of common bactericides*

Chemical stability of the medicament

- Adjustment of pH*
- Addition of a reducing agent or antioxidant*
- Replacement of air by an inert gas*
- Use of a sequestering agents*
- Inclusion of specific stabilizers*

Calcium Gluconate Injection BP

Sodium Bicarbonate Injection BP

Mersalyl Injection BP

Limitations in the use of additives

Particulate contamination

PACKAGING OF INJECTIONS

Containers for injections

- Ideal properties*
- Types of container*
- Single-dose versus multiple-dose containers*

Materials for injection containers

Glass

Types of glass

Associated problems for parenterals***Plastics******Types of plastics******Associated problems for parenterals******Closures******Types and properties of closure materials******Associated problems for parenterals*****STERILIZATION OF INJECTIONS**

Injections are sterile products intended for administration into the bodily tissues. Their formulation involves careful consideration of all the following inter-relating factors:

- 1 the proposed route of administration,
- 2 the volume of the injection,
- 3 the vehicle in which the medicament is to be dissolved or suspended,
- 4 the osmotic pressure of the solution,
- 5 the use of preservative,
- 6 the pH of the solution,
- 7 the stability of the medicament and methods of sterilization,
- 8 the specific gravity of the injection,
- 9 the properties of suspensions for injection,
- 10 the properties of emulsions for injection,
- 11 containers or closures for injections,
- 12 particulate contamination,
- 13 biopharmacy of injections.

THE BIOPHARMACY OF INJECTIONS

Injections are administered into the body by many routes. The route of administration affects the formulation and biopharmaceutics of the preparation. There now follows a description of routes of administration to clarify nomenclature used throughout the rest of the chapter. Fig. 21.1 shows the sites of injection.

Routes of administration

The most important routes are as follows.

Intracutaneous or intradermal route

Injections are made into the skin between the

inner layer (dermis) and the outer layer (epidermis). The volume that can be injected intradermally is small, usually 0.1–0.2 ml, due to the poor vascularity of the site which gives poor dispersion of the drug, and leaves blisters or weals at the site of the injection. The route is used mainly for diagnostic tests.

Subcutaneous or hypodermic route

Injections are made under the skin into the subcutaneous tissue. The volume injected is usually 1 ml or less. This route is not used for aqueous suspensions or oily suspensions and fluids since these would cause pain and irritation at the injection site.

Intramuscular route

Injections are made by passing the needle into the muscle tissue via the skin, subcutaneous tissue and membrane enclosing the muscle. The volume is usually no greater than 2 ml and should not exceed 4 ml. This route is used for aqueous and oily suspensions and oily solutions, since if they were injected intravenously blockage of small blood vessels might occur leading to poor vascular supply of local tissues possibly resulting in gangrene.

Intravascular routes

These are either intra-arterial (into arteries) or intravenous (into veins). The intra-arterial route is used for an immediate effect in a peripheral organ, e.g. to improve circulation to the extremities when arterial flow is restricted by arterial spasm or early gangrene. Tolazoline hydrochloride, a peripheral vasodilator, is sometimes administered by this route.

Substances are introduced directly into the blood stream by the intravenous route. The most common site is the median basilic vein at the anterior surface of the elbow. The volume can vary from less than 1 ml to in excess of 500 ml. Small volumes may be administered for a rapid effect (e.g. anaesthetics) and large volumes (perfusion or infusion fluids) to replace body fluid loss in shock, severe burns, vomiting and diar-

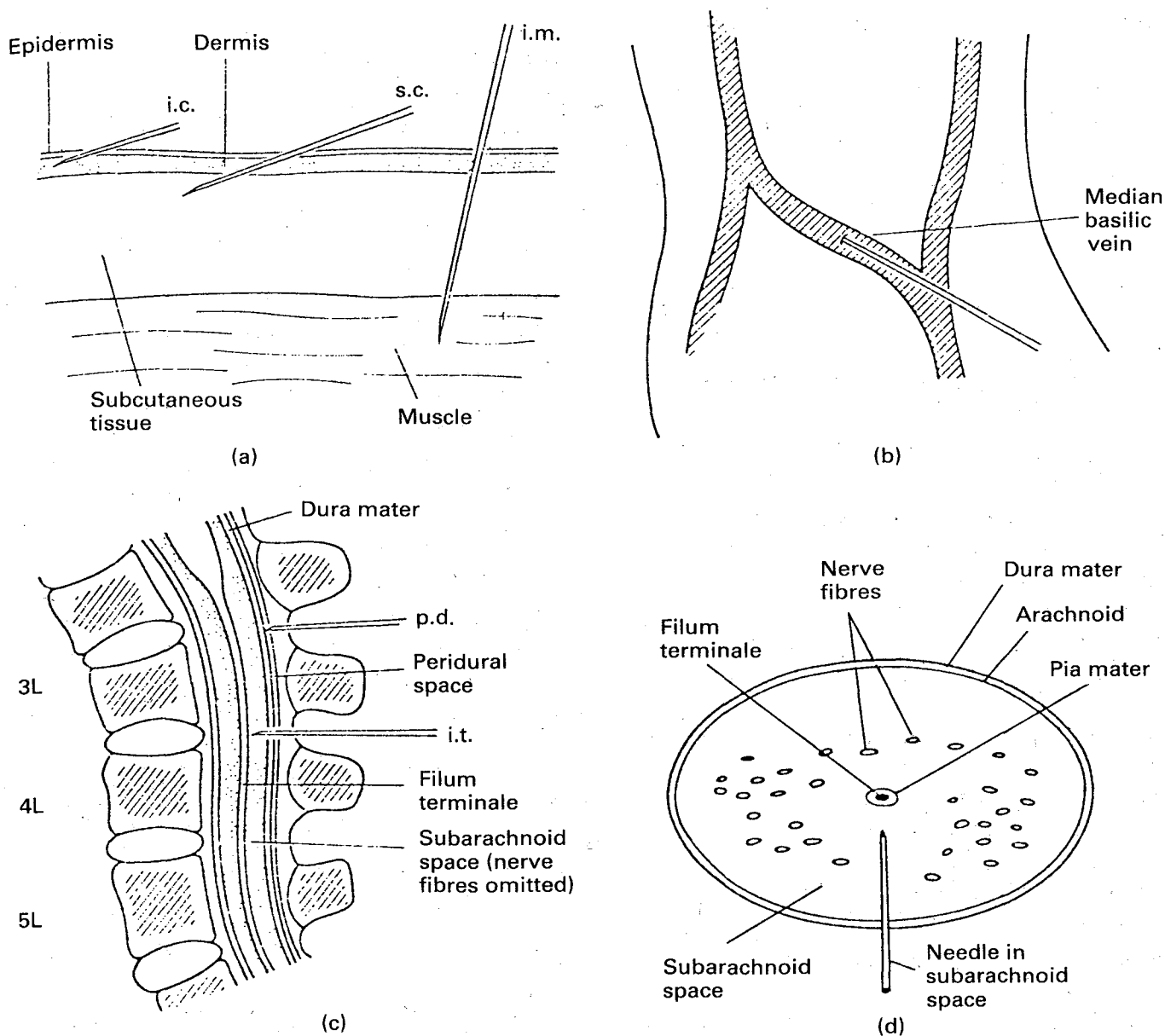


Fig. 21.1 Routes for injection. Key: (a) i.c., intracutaneous route; s.c., subcutaneous route; i.m., intramuscular route; (b) i.v., intravenous route into the median basilic vein at the anterior surface of the elbow; (c) p.d., peridural route; i.t., intrathecal route; (d) subarachnoid route.

rhoea. The route ensures rapid body dispersion and generally administration of volumes in excess of 10 ml is termed intravenous infusion. Oil-in-water emulsions may be administered by this route if the globule size is controlled but the route cannot be used for w/o emulsions.

Intracardiac route

This is used for emergencies only when stimulants, e.g. adrenaline or isoprenaline sulphate, are given directly into the heart muscles or ventricles.

Intraspinal routes

These routes involve access into or around the spinal cord. Single dose injections, no greater than 20 ml, are used. Intrathecal or subarachnoid injections are made into the subarachnoid space that surrounds the spinal cord which is enclosed in three coats. The outer one is known as the dura mater, the middle one as the arachnoid and the inner one as the pia mater. The subarachnoid space lies between the arachnoid and pia mater and contains the cerebrospinal fluid (c.s.f.). The

route is used for spinal anaesthetics (e.g. bupivacaine) and antibiotics (e.g. streptomycin in the treatment of tubercular meningitis).

Intracisternal injections are made into the cisterna magna which lies directly below the medulla. Although the route is primarily used to remove c.s.f., it is occasionally used for antibiotic treatment or for the investigation of the c.s.f. circulation by dye injection.

Peridural injections are made into the peridural space which is located between the dura mater and the inner aspect of the vertebrae. This space extends throughout the full length of the spinal column and injections may be made at different regions, e.g. thoracic, lumbar or sacral. The route is used for spinal anaesthesia although careful consideration of the specific gravity of the injection has to be made to allow exact positioning of the injection.

Great care should be taken to ensure that any chosen buffering agent does not damage the delicate nervous tissue or its coats.

Intra-articular and intrabursal routes

Intra-articular injections are made into the synovial fluid which lubricates the articulating ends of bones in a joint. Intrabursal injections are similar, being given into the bursae which are small sacs of fluids between movable parts such as tendons and bones. The common sites are the subacromial bursa in the shoulder and the olecranon bursa in the elbow. Both solutions and suspensions may be administered by these routes.

Ophthalmic routes

Because of the restricted target areas the dose-volume is never greater than 1 ml. Four routes are used; the subconjunctival route (beneath Tenon's capsule, close to the eye but not into it), the intravitreous route (into the vitreous chamber), the intracameral route (into the anterior chamber) and the intraocular route (into the posterior segment of the globe). Great care should be given to the choice of any prospective buffering agent.

Other routes which may be used include the intra-ossicular route, the intracerebral route, the intraperitoneal route (for dialysis solutions), the

intrapleural route and, in cattle, the intramammary route.

Bioavailability of drugs from injections

Injections are often used for either rapid or localized activity. An injection directly into the blood stream ensures that the drug is spread rapidly throughout the body before other factors, like plasma bonding, binding to selective sites and metabolism will reduce the achieved concentration. Intrathecal, intracisternal, intracardiac and the intravenous routes can be used for rapid onset of drug action. Unlike tablets, where there are disintegration and dissolution stages prior to absorption, injections achieve a rapid high blood level. However, formulation, coupled with variation in the site of administration may affect markedly the biopharmacy of drugs. The pH of an injection may effect the degree of ionization of a drug, rendering it more or less likely to pass through biological membranes. Increasing the viscosity of an injection will slow the absorption, especially from intramuscular injections, and drug solubility, dependent on polymorphism, will affect the activity of drugs. Thus the polymorphism of novobiocin and chloramphenicol can alter their biological properties. For suspensions, the particle size of the drug influences absorption rate and increasing the particle size of a drug, e.g. insulin, will decrease the available surface area and decrease its absorption from an injection site, giving a sustained release effect. Similarly, the blood levels of procaine penicillin G increase as the particle size of the suspension decreases.

The routes of administration markedly affect the disposition and biopharmacy of drugs. The intravenous route gives immediate and total access of the drug molecules to the body. Maximum plasma concentrations may be achieved after 4 minutes. The duration of action may be affected by dose, distribution, metabolism and excretion of the drug but the elimination usually follows first order kinetics. Constant blood levels may be obtained by intravenous drips. Intramuscular and subcutaneous routes can act as sustained release routes but this depends on the dosage form. Aqueous solutions are most rapidly absorbed into the blood stream and aqueous suspensions show

retarded release due to the dissolution step introduced into the absorption process. The use of oleaginous vehicles may further delay absorption due to a partitioning of the drug from the oil to the aqueous body fluids and oleaginous suspensions provide a retarding dissolution process prior to partitioning. For these routes, viscosity, drug concentration and the patient's movement may further alter absorption rates. Even differences in the choice of muscle may influence absorption. Generally the subcutaneous route provides slower absorption due to the low vascular supply to the skin (for further information see Gibaldi, 1977).

FORMULATION OF INJECTIONS

Throughout this section, reference is made to injections of the *British Pharmacopoeia*. These are included as illustrative examples for which the full formula can be obtained. The reader can extrapolate the principles discussed to other, non-official or novel formulations.

Volume of the injection

The volume of an injection primarily depends on the solubility of the medicament, but may be influenced by preference for a particular route. Intracutaneous injections have to be small to prevent the formation of blisters. Only the intravenous route is suitable for large volumes which must be made isotonic. Intravenous injections with doses greater than 15 ml must not contain a bactericide and therefore cannot be sterilized by heating with a bactericide. When the volume is in excess of 15 ml the injection should be free from pyrogens.

The volume should be convenient to administer. Volumes greater than 20 ml are unsuitable for injections by a syringe and infusions are not worth setting up for less than 250 ml. The volume can often be reduced by dispensing a hypertonic solution and administering by slow intravenous infusion.

The vehicle

Any vehicle used should be pharmacologically inert, non-toxic (i.e. compatible with blood, non-

sensitizing, non-irritating), maintain the solubility of the drug, be chemically and physically stable and be unaffected by pH changes. Vehicles should not interfere with the therapeutic activity of the injection. They must be exhaustively tested for freedom from toxicity, they must be pure and have no pharmacological activity of their own.

Water is the ideal vehicle for most injections since aqueous preparations are well tolerated by the body and are the safest and easiest to administer. However, a change from water may be required for a variety of reasons. Hydrolysis of certain drugs may result in the formation of inert or toxic byproducts. Some poorly water-soluble drugs may be so insoluble that they cannot be administered in water. Consequently, the use of cosolvents, e.g. propylene glycol for Dimenhydrinate Injection BP or oily vehicles such as benzylbenzoate and arachis oil for Dimercaprol Injection BP, is permitted. Oily vehicles often give a depot effect over their aqueous counterparts and steroid drugs, e.g. progesterone, which are poorly water soluble are formulated in ethyl oleate or fixed oils to enable depot release to continuously replace deficient secretions. Oily media may indeed be preferable to aqueous vehicles. Propylidone, although present in the *British Pharmacopoeia* as both an aqueous suspension and an oily suspension in arachis oil, is often preferred in oily suspension as a contrast medium of X-ray examination of the respiratory tract because this is less irritating than the aqueous suspension.

Oily injections suffer from many disadvantages including the following.

- 1 They may be too viscous in cold weather to administer without warming.
- 2 They often cause pain at the site of the injection.
- 3 They will contaminate the syringe and needle making them difficult to clean.
- 4 They must be used only by the intramuscular route, since their accidental intravenous injection may lead to thrombosis.

However, contrast media, e.g. Iodised Oil Fluid Injection BP or Propylidone Oily Injection BP, may be given by other routes because they are not injected into tissues but into the internal cavities that are under investigation, e.g. the lungs. Very

occasionally alcohol is used to dissolve the medicament but the solution must be diluted with an aqueous vehicle shortly before administration to avoid pain and tissue damage.

Water and pyrogens

Before potable water can be rendered suitable for use in injections it has to be specially purified. The injection of distilled water may cause a rise of body temperature; water producing this reaction is said to be pyrogenic (fever producing) and water free from this effect is described as apyrogenic. Substances which are pyrogenic may be produced by many micro-organisms including moulds, yeasts and bacteria. The most potent are those associated with Gram-negative bacteria and are endotoxins originating from the cell wall. The main causative substance is lipid in nature but its potency is enhanced by protein and especially polysaccharide fractions which appear to increase the solubility of the lipid fraction. Pyrogenic molecules have a high molecular weight often in excess of 1 000 000.

The sources of pyrogens may be the solvent, the medicament, any added buffering or stabilizing substance, the apparatus used in manufacture, the final containers and the method of storage between preparation and sterilization. Undoubtedly, the major source is the solvent and especially Water for Injections BP.

Injection of pyrogens into the body produces various physiological responses including erythema at the injection site, pain in the legs and trunk with general discomfort and high temperature. It is this last response that the *British Pharmacopoeia* uses as the basis to estimate pyrogens by studying temperatures in specially treated rabbits, although other methods especially the limulus amoebocyte lysate test have been developed (Thomas *et al.*, 1980).

Pyrogen tests are applied to all injections claimed to be apyrogenic, i.e. to Water for Injections BP, to single dose injections of volume greater than 15 ml and powders which require making up to a solution with vehicle prior to administration, when the reconstituted injection is tested. However, it is vital that intravenous

infusions should be free from pyrogens since a large volume injection will contain a correspondingly large amount of pyrogen. As large volume injections (perfusion fluids) are usually given intravenously the pyrogen will have a more rapid effect. Patients receiving infusion fluids are often dangerously ill and the effect of rise of temperature could be fatal.

Water for Injections BP is sterilized distilled water free from pyrogens and is prepared from potable water. Since tap water may be pyrogenic, the first aim in the preparation of Water for Injections BP must be to remove or destroy pyrogens. This is complicated as pyrogens are thermostable, water soluble and are unaffected by common bactericides and, therefore, none of the methods used to sterilize injections can be relied upon to eliminate pyrogens.

However, pyrogens are also non-volatile and they can be removed from water by distillation. Ordinary distillation is not satisfactory since pyrogens may be carried over in the receiver, dissolved in the spray which is entrained in the steam. Therefore, a trap is fitted to the distilling flask to stop this entrainment. Certain bacteria are able to multiply in distilled water. Inadequate protection from air and storage at a temperature that favours bacterial growth may cause a rapid increase in the bacterial count. Ideally distilled water for parenteral solutions should be sterilized immediately after collection from the still. The exception is when the water is used at once for making an injection that requires sterilization. Then, provided the injection is sterilized immediately after preparation (i.e. within 4 hours), freshly distilled non-sterilized water may be used. Distilled water may be used after a much longer storage provided it is maintained at a high temperature, e.g. 80 °C, when bacterial growth and hence pyrogen production will be prevented. Because of the great danger from pyrogens in large volume infusion fluids, the *British Pharmacopoeia* gives a special warning of the need for their immediate sterilization, e.g., Laevulose Intravenous Infusion BP.

For further information on the preparation of Water for Injections BP see Perkins, 1969; Ridgway, 1973; or Groves, 1973a. Another

method of preparing water for injections is reverse osmosis which is accepted by the USP (see Frith *et al.*, 1976).

Water for Injections BP is suitable as a vehicle for many official preparations. However, it may sometimes be necessary to further improve its quality by removing dissolved gases. Some medicaments, e.g. the barbiturates and sulphonamides, are weakly acidic and only slightly soluble in water and they are therefore administered as the more soluble sodium salts. For instance, amylobarbitone sodium (solubility 1 in less than 1) when dissolved in water containing carbon dioxide will rapidly precipitate the free base amylobarbitone (solubility 1 in 1500) rendering it dangerous and unsuitable for injection. Examples of other injections requiring water free from carbon dioxide are Aminophylline Injection BP, Methohexitone Injection BP and Sodium Bicarbonate Intravenous Infusion BP. However, Water for Injections BP free from carbon dioxide is unnecessary for thiopentone injection BP because the official substance is a mixture of thiopentone and sodium carbonate and the latter will keep the salt in solution. Carbon dioxide may be removed from water for injections by boiling the water for 10 minutes.

Water for injections free from dissolved air is produced in a similar manner and the residual air space at the top of the ampoules is replaced by nitrogen or another inert gas after packing, before sealing. This product replaces normal water for injections in products containing medicaments which are sensitive to low levels of oxygen and hence can be protected from oxidation. Examples include Chlorpheniramine Injection BP, Chlorpromazine Injection BP, Phenylephrine Injection BP, Sulphadimidine Injection BP and Promazine Injection BP.

Water-miscible vehicles

It is often not possible to dissolve the medicament in water for injections. To increase the solubility, non-toxic solvents can be used and these include ethyl alcohol, glycerol, propylene glycol, liquid macrogols and benzyl alcohol.

Ethyl alcohol is used only when other methods of presentation are impracticable. Its own physio-

logical activity and the pain and tissue damage it causes unless administered with special care, are serious disadvantages. It is not the main solvent in any official injection but a few (e.g. Digoxin Injection BP, Ergotamine Injection BP and Phenytoin Injection BP) contain a low concentration to facilitate solution of the active ingredient. Melphalan Injection BP is a solution in a vehicle containing 95% ethyl alcohol but is diluted before use.

Propylene glycol is included in several preparations including Cotrimoxazole, Digoxin, Dimenhydrinate, Melarsoprol, Phenobarbitone and Phenytoin injections BP. In the *British Pharmacopoeia* (1958), Digoxin Injection BP contained 70% ethyl alcohol which had to be diluted with Sodium Chloride Injection BP 1958 and given intravenously by slow injection to ensure rapid dilution with blood. The official preparation is now a stable solution in a solvent containing 40% propylene glycol, 10% ethyl alcohol and water buffered to about pH 7 and does not require dilution before use.

Until 1968, Phenobarbitone Injection BP was prepared by aseptically dissolving sterile phenobarbitone sodium in Water for Injections BP free from carbon dioxide immediately before use. The current injection is a solution in 90% propylene glycol which is stable enough to be sterilized at 98–100 °C and has a satisfactory storage life.

Although propylene glycol is relatively non-toxic (possibly because it is rapidly metabolized and excreted), it causes severe irritation on subcutaneous and intramuscular injection and preferably should not be given by these routes, unless an anaesthetic such as benzyl alcohol is included, e.g. Dimenhydrinate Injection BP. Although the liquid macrogols have been recommended as prospective vehicles (Carpenter and Shaffer, 1952) care must be taken during their sterilization as formaldehyde can be generated.

Water-immiscible vehicles

Eight of the oily injections of the *British Pharmacopoeia* are simple solutions (e.g., deoxycortone Acetate Injection BP, Hydroxyprogesterone Injection BP and Oestradiol Benzoate Injection BP).

Their prescribed solvents are a suitable fixed oil, a suitable ester (e.g. ethyl oleate) or a mixture of both. Suitable alcohols may be included in the solvents for Deoxycortone Acetate, Oestradiol Benzoate and Progesterone Injections BP.

Fixed oils must not contain mineral oils or solid paraffins as these cannot be metabolized by the body and might eventually cause tissue reaction and even tumours. They must be free from rancidity (since rancid oils contain free fatty acids) and from any material that might cause irritation.

Arachis oil is specified for Dimercaprol Injection BP and Propyl iodone Oily Injection BP but has the disadvantages of thickening slowly on exposure to air and becoming rancid. Alternatives include sesame oil (probably the most stable because it contains natural substances that prevent rancidification), cotton seed and maize oils. Sensitivity to these oils may cause problems.

Esters give less viscous preparations that are easier to inject, particularly in cold weather. However, a reduction in the length of action of depot preparations has been found when ethyl oleate has been used instead of oil. The maximum prolongation effect is obtained from the depot if it is spherical and, therefore, absorption is probably more rapid from the less viscous ester preparations because of their greater tendency to spread and offer a larger surface to the tissue fluid.

Peroxide-free ethyl oleate is the solvent for Calciferol Injection BP. Peroxides are the intermediates in the auto-oxidative rancidification of oils and fatty acids, and they are undesirable in injections, particularly when the medicament is susceptible to oxidation. Calciferol injection also requires storage in ampoules from which the air has been displaced by an inert gas.

Alcohols may be used in three official preparations because occasionally the medicament concentration may be greater than its solubility in fixed oils, ethyl oleate or a mixture of both. Either benzyl alcohol or ethyl alcohol can improve the solvent properties of these vehicles in concentrations that are harmless and non-irritant by the intramuscular route.

Table 21.1 indicates the advantage of using a

Table 21.1 Solubility of steroids in different vehicles

	Water	Arachis oil	Ethyl oleate	Alcohol 95%
Deoxycortone acetate	Almost insoluble	1 in 140	1 in 150	1 in 50
Oestradiol benzoate	Insoluble	1 in 500	1 in 200	1 in 150
Progesterone	Insoluble	1 in 60	1 in 60	1 in 8
Testosterone	Insoluble	1 in 35	1 in 20	1 in 6

solvent containing an alcohol for deoxycortone acetate, progesterone and to a less extent oestradiol benzoate. Conversely the high solubility of testosterone propionate in arachis oil and ethyl oleate makes the use of alcohols unnecessary.

Other oily bases include almond oil (for Oily Phenol Injection BP), poppyseed oil, isopropyl myristate and polyoxyethylene oleic triglycerides (Labrafils). Another solvent, benzyl benzoate is used for Dimercaprol Injection BP. Dimercaprol is a liquid formulated in oil because aqueous solutions are unstable. For strong preparations, the required amount of dimercaprol would not completely dissolve in arachis oil but was miscible with benzyl benzoate. The resulting mixture can be diluted with arachis oil to give an injection that is stable, even to dry heat sterilization, if protected from air. Although the official strength is below that which gives solubility problems, the *British Pharmacopoeia* uses benzyl benzoate because of its stabilizing effect.

Osmotic pressure

Great care has to be taken to make certain injections isotonic with plasma. Husa and his colleagues (Husa and Adams, 1944; Hartman and Husa, 1957; Thomasson and Husa, 1958) have reported that certain medicaments in solutions iso-osmotic with plasma can pass through the red blood cell membrane, i.e. these solutions are not isotonic and may be harmful in use. Although normal practice is to adjust solutions to iso-osmoticity with plasma, iso-osmotic solutions of new drugs should be checked for isotonicity and haemolytic activity on red cells before using them by the intravenous route.

Intravascular injections

Solutions with a lower osmotic pressure than blood are said to be hypotonic and those with higher pressure are hypertonic. Both may be termed paratonic, i.e. not isotonic. Blood cells swell rapidly and burst (haemolysis) in hypotonic solutions. This damage is irreversible and dangerous if a large number of cells is involved. A very hypotonic solution or a large volume of less hypotonicity can cause this damage on intravascular injection. When placed in hypertonic solutions, water passes outwards from blood cells and they shrink, becoming crenate in outline. When the osmotic pressure returns to normal the blood cells assume their normal shape. Therefore, grossly hypertonic solutions may be administered without damage to blood cells. Consequently, although isotonicity is preferred, hypertonic solutions are normally used since to produce isotonic solutions of many medicaments would require large volumes of water which would be difficult to administer. Thus injections which are hypertonic are slowly injected intravenously to ensure rapid dilution in the blood stream and minimal crenulation of red blood cells.

Certain injections may irritate and damage the walls of veins. This may be used intentionally, e.g. in the treatment of varicose veins where the circulation is sluggish and an injection may remain undiluted for a considerable time. Hypertonic solutions are used for sclerosing varicose veins, e.g. Morrhuate Sodium Injection USP and Ethanolamine Oleate Injection BP which is preferred as it is more stable and less toxic. For Quinine Dihydrochloride Injection BP a 30% solution is standard strength but is very hypertonic (5% is isotonic) and has an acid pH (1.5–3.0). Sclerosis may occur if this injection is used undiluted, so it must be diluted at least 10 times with Water for Injections BP before use and injected slowly.

Intrathecal injections

These must be isotonic. The c.s.f. has a slow circulation and even the injection of a small volume of paratonic solution would cause a local

disturbance of osmotic pressure. Also the volume of the c.s.f. is low (100–160 ml) and a comparatively small injection will affect the osmotic pressure throughout, causing headache and vomiting.

Intramuscular injections

The osmotic pressure will vary according to the type of injection and its desired therapeutic use. Aqueous solutions of medicaments intended to be absorbed quickly should be slightly hypertonic. This encourages a mild local effusion (exosmosis) of tissue fluids which will promote rapid absorption. Medicaments intended to be absorbed slowly and produce a depot effect are formulated as either an aqueous suspension (containing an insoluble form of the drug) or as a solution or suspension in a hydrophobic vehicle.

Intracutaneous injections

The intracutaneous route is used for diagnostic preparations. As the diagnosis is dependent on the subsequent development of an immune response involving inflammation, it is essential that the active principle should be the only cause of this reaction. Since paratonic solutions can irritate the skin, diagnostic intradermal injections are usually made isotonic.

Subcutaneous injections

The injection volume is very small, and since injection is made directly into fatty tissue, a wide range of paratonicity is possible without untoward effects. Isotonic solutions are preferable to reduce pain.

Comparison of the official injections shows that these principles have been followed. Thus the intracutaneously administered diagnostic preparation Schick test toxin is made isotonic. Small volume injections given subcutaneously, intramuscularly or intravenously are not adjusted, e.g. Atropine Sulphate and Methadone Injections BP. In other cases where small volumes are injected, particularly by the intramuscular or intravenous routes, the solutions are hypertonic. However,

large volume infusion fluids are usually formulated to be isotonic, or nearly isotonic with blood plasma, e.g. Sodium Chloride Injection USP, Compound Sodium Lactate Injection BP and Dextrose Injection USP.

Hydrogen ion concentration (pH)

The pH of many official preparations is adjusted to a definite pH or to within a pH range. The use of buffers to stabilize the pH is often permitted. Some of the reasons for pH adjustment are as follows.

To increase the stability of the injection

An unfavourable pH is one of the major causes of instability in pharmaceuticals. It is imperative that unstable medicaments have their pH adjusted to the optimum for maximum stability. This is especially important for injections which have to withstand a heat sterilization process or have a long shelf life. The utilization of an optimum pH is used to stabilize injections of antibiotics (e.g. benzylpenicillin, tetracycline), alkaloids (e.g. ergometrine injection to a pH of 2.7–3.5), vitamins (e.g. cyanocobalamin to a pH of 4.0–5.5) and polypeptides (e.g., oxytocin to a pH of 3.0–4.5).

To minimize pain, irritation and necrosis on injection

The optimum for stability may not, however, prove a suitable formulation. Very acid or alkaline solutions are painful on injection and may cause irritation or even necrosis of the tissues, especially with the subcutaneous or intramuscular routes. Intravenous injections, if given slowly, are rapidly diluted and the pH is further neutralized by the buffering power of the blood plasma. Consequently, injections should not be more acid or alkaline than stability dictates. Intrathecal, peridural and intracisternal injections should be adjusted to between pH 7.0 and 7.6 and ideally pH 7.4, since non-neutral solutions can cause aseptic meningitis.

When acidic or basic substance are used in the preparation of injections e.g., ethylenediamine (Aminophylline Injection BP) or sodium hydroxide

(Compound Sodium Lactate Injection BP), the pharmacopoeia ensures that no significant excess of these substances is present.

To provide unsatisfactory conditions for growth of micro-organisms

Use can be made of low and high pHs to prevent the growth of micro-organisms. Solutions of pH below 4 are bactericidal to many micro-organisms and may not require additional protection against bacteria. However, this effect is less marked with moulds because these can tolerate acid pHs. The antibacterial activities of Ethanolamine Injection BP, which does not require a bactericide in multiple-dose containers, is partly due to its high pH of 8–9.

To enhance physiological activity

For some preparations the free bases are more active than the salts themselves. However, as these substances are generally more stable at acid pHs it is often difficult to produce satisfactory preparations without using the salts. For instance, solutions of procaine and adrenaline produce the greatest anaesthetic effect when buffered to slight alkalinity yet are only stable for a few hours. Solutions of pH less than 4, although less potent, can be autoclaved with little loss of activity and the injection therefore has a pH of 3.0–4.5.

Therefore, where maximum physiological activity is shown by neutral or alkaline solutions while maximum stability is found in acid media, the pH should be kept as high as physiologically possible with an acceptance level of stability.

Buffers

Buffer systems suitable for injections should have no toxicity, be compatible with the medicament and other added substances and should have a high buffer capacity. The pH of a completed injection can be altered by the decomposition of the medicament but leaching of alkali from the glass of the container or extraction of acid or alkaline impurities from the rubber closure can be avoided by careful selection and preparation of containers and closures.

Suitable buffers include citric acid/sodium phos-

phate (Digoxin Injection BP), sodium acetate (Insulin Zinc Suspension Injection BP), sodium phosphate (Isophane Insulin Injection BP) and dipotassium hydrogen phosphate (Melfalan Injection BP). Borates are too toxic for use in injections.

Examples illustrating the use of buffers include Benzylpenicillin Injection BP and depot injections of insulin. The optimum pH range for the stability of penicillin solutions is 6.0–7.0. Hydrolysis readily occurs in aqueous solutions with the formation of inactive benzylpenicilloic acid. This is accompanied by a fall in pH which further catalyses hydrolysis leading to progressively greater acidity and more rapid hydrolysis until the antibiotic has been destroyed. Decomposition can be retarded by buffering the pH of the solution to 6.0–7.0 with 4.5% w/v sodium citrate. The life of the injection is, therefore, increased from 7 days (without buffer) to 14 days, if stored at 2–10 °C.

The use of insoluble forms of medicaments to prolong drug action has been mentioned earlier. The effect of protamine zinc insulin lasts longer (24–36 hours) than that of plain insulin (6–8 hours) because in the former insulin is in a very insoluble complex from which it is only slowly made available to the body. Because this complex is most insoluble over the very narrow pH range 6.9–7.4, a phosphate buffer is used to prevent variations.

Specific gravity of injections

This is of importance in spinal anaesthesia. If the upper part of the patient's body is raised by sloping the operating table, solutions of lower specific gravity than the spinal fluid will tend to rise on injection and those of higher specific gravity will tend to sink. On the other hand, the opposite effects will occur if, as is sometimes necessary for operations on the lower part of the body, the patient is tilted head downwards. Careful choice must be made of the specific gravity of the solution and the position of the patient so that the movement of the injection will be in the right direction. Although the specific gravity of the c.s.f. is not constant an average figure is 1.0059 at 37 °C. The terms used to

describe the specific gravity of solutions in relation to that of the c.s.f. are isobaric, hypobaric and hyperbaric, i.e. of equal, lower and higher specific gravity respectively.

For example, cinchocaine hydrochloride, 1 in 1500 in 0.5% saline is hypobaric and has a weight per ml of 1.0036 at 37 °C. Alternatively cinchocaine hydrochloride, 1 in 200 in 6% dextrose, is a hyperbaric solution and has a weight per ml of 1.02.

Suspensions for injection

It is sometimes necessary to formulate the drug to be injected as a suspension. For example, formulation of a drug of low solubility in an aqueous vehicle requires a suspension, increased stability of a drug can be attained by formulation as a suspension and suspensions provide an effective depot release (Nash, 1972).

However, the use of suspensions as injections leads to further problems. The drug must remain suspended for a time sufficient to enable withdrawal of a uniform dose, especially if packed in a multiple-dose container. Therefore, the following processes must be understood.

Wettability

Some substances, e.g. cortisone acetate and procaine penicillin, are not only poorly soluble in water but are also poorly wetted by it. This problem may also be linked to particle size since very fine particles are difficult to wet. It would be difficult, therefore, to break up the clumps in any simple aqueous suspensions prepared from them and the foam produced by shaking would take a long time to disperse because it is stabilized by the film of unwettable powder at the liquid/air interfaces. To ensure satisfactory wetting of the solid it is necessary to reduce the interfacial energy between it and the liquid. This may be achieved by adding a suitable wetting agent and non-ionic types are widely employed, e.g. the polysorbates and sorbitan trioleate.

Sedimentation rate

Despite the presence of wetting agents, a suspension will be difficult to use if the particles sedi-

ment quickly. To counteract this a hypophilic colloid may be added to increase the viscosity of the vehicle, which then holds the particles in suspension long enough for an accurate dose to be removed and at the same time helps to prevent the reformation of clumps. A desirable property of a suitable colloid is rapid solution because suspensions have to be reconstituted just before use. Choices of colloids include sodium carboxymethylcellulose, polyvinylpyrrolidone, gelatin and methylcellulose.

Claying

A deflocculated suspension is often unsatisfactory because when small particles settle they produce a very tightly packed sediment that is hard to disperse and is said to have clayed. This can be avoided by reducing the amount of wetting agent; sufficient is added to take the powder into suspension but the quantity added is not enough to break down the smaller aggregates. Such a suspension (partially deflocculated) will settle more quickly but the sediment is loose and easy to disperse.

Macek (1963) illustrated these problems with procaine penicillin suspensions. Very small quantities of aluminium trichloride produced flocculated suspensions which were unsightly. Partial flocculation was achieved using monosodium citrate, together with a small quantity of a protective colloid or sorbitol.

Size and shape of particles

The depot effect of a suspension is influenced by both the size and shape of the suspended particles. Larger particles produce a greater depot effect because they take longer to be absorbed, e.g. larger crystals in crystalline insulin-zinc suspensions cause a protracted hypoglycaemic effect. However, large crystals sediment quickly, cause more pain on injection and tend to block syringe needles. Similarly, crystals which are approximately isodiametric (cubic, e.g. insulin or platelet, e.g. procaine penicillin) are better than long acicular crystals since the latter are more likely to cause needle blockage. In certain cases, e.g. cortisone acetate, care must be taken to

prepare crystals by a method that will produce a stable structure. Some are unstable and on storage in suspension may either change into a more stable polymorphic form or show crystal growth, becoming too large and leading to the difficulties mentioned above.

Thixotropy

Although claying can be prevented by flocculation, it is possible to overdo this and produce a preparation in which the particles are so highly flocculated that the preparation becomes an unpourable paste. By careful choice of the particle size and percentage of powder, these pastes can become thixotropic, i.e. they are solid in the absence of a shearing force but become fluid if tapped or shaken, the original structure being resumed after a few minutes at rest. Thixotropic preparations have the advantage that the particles remain in more or less permanent suspension during storage and yet when required for use, the pastes are readily made fluid by tapping or shaking. The shearing force on the injection as it is pushed through the needle ensures that it is fluid when injected but the rapid resumption of the gel structure prevents excessive spreading in the tissues and, consequently, a more compact depot is produced than with non-thixotropic suspensions.

Preparation of aqueous suspension injections

Nash (1972) summarized the preparation of aqueous suspensions for injection. The sequence of manufacturing processes is:

- 1 recrystallization of the drug followed by particle size reduction,
- 2 sterilization of the drug,
- 3 sterilization of the vehicle,
- 4 aseptic wetting of the powdered drug by the vehicle,
- 5 aseptic dispersion and milling of the bulk suspensions, followed by
- 6 aseptic filling into the final sterile containers which can be sealed.

Suspensions in oily vehicles

As depot preparations, oily suspensions have the

potential advantage of combining the retarding effect of a hydrophobic vehicle and an insoluble medicament. However, because of the disadvantages of oily vehicles, aqueous formulations are preferred even though they do not have as powerful a depot effect.

Addition of a gelling agent In Sterile Penicillin G Procaine with Aluminium Stearate Suspension USP (an oily procaine penicillin injection) the medicament is suspended in peanut or sesame oil that has been gelled with 2% of aluminium stearate. The latter produces a molecular lattice structure that gives rigidity to the preparation and renders it thixotropic. Procaine penicillin tends to clay if allowed to sediment; the rigid gel prevents this.

Particle size Crystalline zinc insulin has been used to illustrate that in an aqueous suspension large particles give a greater depot effect. However, for preparations of procaine penicillin in oil containing aluminium stearate reduction of particle size gives increased prolongation. Particles of procaine penicillin are coated with the water-repellent aluminium stearate and are, therefore, less easily reached by aqueous tissue fluids and absorption will be further delayed. The greater the subdivision of the powder, the greater its surface area and consequently the greater the area of protective coating. Fine particles, majority under $5\text{ }\mu\text{m}$, are required for this type of suspension.

Emulsions for injection

Emulsions are thermodynamically unstable systems which require stabilizers in the form of either surface-active agents or finely divided particles, the latter are unsuitable for parenteral use. Ideally, emulsions should be formulated so that the dispersed droplets are $0.5\text{--}1.0\text{ }\mu\text{m}$ in diameter. This corresponds to the size of the chylomicra, which are the natural transport systems for fat through the blood stream. Few of the globules should be greater than $3\text{ }\mu\text{m}$ in diameter. Unstable emulsions are dangerous since their storage may result in increased globule size due to coalescence which would result in thrombosis if injected.

Sterile emulsions are used to make feasible the

safe injection of oily substances by the intravenous route. The emulsifiers and stabilizers used should be non-toxic e.g. lecithin, polysorbate 80, gelatin, methylcellulose and serum albumin. An example is Phytomenadione Injection BP (vitamin K) where lecithin is used as an emulsifying agent.

Intravenous therapy and emulsions

Intravenous therapy is used to correct deficiencies in the electrolyte and fluid balance of the body but may also be used to provide parenteral hyperalimentation when the patient is unable to use his gastrointestinal tract, e.g. following abdominal surgery. Solutions for intravenous infusions are clear and may contain ethanol, amino acids, carbohydrates, electrolytes and vitamins. However, glucose metabolism will provide only 14.3 kJ g^{-1} of energy whereas fat metabolism can provide up to 37.7 kJ g^{-1} .

Consequently for parenteral nutrition it is desirable to use intravenous fat emulsions as a concentrated source of energy. The aqueous phase of such emulsions will by necessity contain surface-active agents and since these can cause haemolysis of erythrocytes, the aqueous phase is made isotonic to plasma by the addition of, for example, glucose, sorbitol or glycerol. The oily phase can consist of sesame, cod-liver, linseed, peanut, olive or more commonly cotton seed or soya bean oils. Gelatin and/or cellulose derivatives may be included to increase the viscosity of the emulsion thereby preventing coalescence. Emulsifiers, like synthetic lecithins or fractionated egg yolk phospholipids together with surface-active agents like Pluronic F68 or the polysorbates are used to stabilize the emulsion. Sterilization of the emulsion is a problem since heat would coalesce the emulsion and filtration is impossible. Rapid growth of micro-organisms is possible in such emulsions since there is no preservative present.

A typical simple composition is 15% cotton seed oil, 4% dextrose, the oil being emulsified by 1.2% lecithin or soya bean phosphatide, 1% of a polyoxalkol, e.g. Poloxamer 188, and water to 100%. To further illustrate this KabiVitrum Ltd produce an oil-in-water emulsion (Intralipid 20%) to the following formula (see KabiVitrum Ltd,

1984/85):

Fractionated soya bean oil	100 g
Fractionated egg phospholipids	6 g
Glycerol	11 g
Water for injections	to 500 ml

The emulsion is formulated to pH 7 and the estimated energy provided by one litre of this preparation is 8.4 MJ compared with 4.7 MJ for one litre of Sorbitol Intravenous Infusion BP. For further details of parenteral products and their formulation see Irvine (1978).

Colloidal dispersions and solubilized products

Colloids can be prepared and used for injections. Albumin, proteins, dextrans and carbohydrate polymers dissolve in water to form hydrophilic solutions. Certain injections are colloidal solutions, e.g. Iron Dextran Injection BP and Iron Sorbitol Injection BP, the latter being a complex of ferric ions, sorbitol and citric acid stabilized with dextran and sorbitol. Solubilized products also can potentially be used as injections. Above their critical micelle concentration, surfactants in solution form micelles whose centre will act as a solvent for lipid-soluble materials. By selective use of 1 or 2 surfactants and a cosolvent it is possible to solubilize many drugs.

QUALITY ASSURANCE OF INJECTIONS

Microbiological preservation

The use of bactericides in aqueous single-dose injections

Bactericides may be found in injections which are prepared either by heating with a bactericide or by aseptic techniques. They are allowable in aseptically produced products to suppress the growth of micro-organisms inadvertently added during preparation. Thus chlorocresol (0.2% w/v), phenylmercuric nitrate (0.002% w/v) and phenylmercuric acetate (0.002% w/v) are recommended by the *British Pharmacopoeia* as being suitable for heating with a bactericide. The bactericide is included in the preparation at the concentration recommended and the contents are maintained at 98–100 °C for 30 minutes to effect sterilization.

Aseptic preparation of injections involving sterilization by membrane filtration (i.e. they are not sterilized in their final containers) requires a high degree of manipulative skill to prevent accidental contamination. The *British Pharmacopoeia*, therefore, allows (it is *not* obligatory) the addition of a suitable bactericide to the solution before filtration. If the injection solution contains a bactericide it is important to remember that single-dose injections will also contain the bactericide and cannot be used for the intra-ocular or intracardiac routes or others giving access to the cerebrospinal fluid.

The use of bactericides in multiple-dose injections

Injections are frequently dispensed in containers holding several doses. These are known as multiple-dose injections and are supplied in bottles usually closed with a rubber cap which should allow the withdrawal of single doses of the injections with minimal risk of contaminating the remainder.

Contamination may arise from many causes including failure to sterilize the cap before withdrawing a dose, failure in sterilization of the needle or syringe, injection of unsterile air or inrush of unsterile air as the needle is withdrawn. The danger in introducing bacteria into an injection is the rapidity with which they can multiply. The last dose from a bottle may contain millions of organisms. Consequently, the *British Pharmacopoeia* states:

'Aqueous preparations supplied in containers for use on more than one occasion contain a suitable antimicrobial preservative in appropriate concentration except when the preparation has adequate antimicrobial properties.'

A multiple-dose injection sterilized by the process of heating with a bactericide should not require additional bactericide.

The bactericides used in multiple-dose containers destroy vegetative bacteria in a few hours at room temperature but they are not usually capable of killing bacterial spores (i.e. sporicidal). However, spores are unlikely to germinate in their presence and, therefore, the number of contaminations will remain small. Some bacteria and moulds have a destructive action on medicaments.

Bactericides suitable for aqueous injections

The desirable features of a suitable preservative for multiple-dose injections were summarized by Sykes (1958):

- 1 ability to prevent the growth of, and preferably to kill, contaminating organisms,
- 2 compatibility with the medicament, even on long storage and should not interfere with the therapeutic efficacy of the product,
- 3 low absorption rate into rubber,
- 4 absence of toxicity to the patient.

In addition Allwood (1978) considered further properties to be desirable including:

- 5 a broad spectrum of activity to include fungi as well as vegetative bacteria,
- 6 activity over a wide pH range,
- 7 the preservative should be uninfluenced by the container, and
- 8 stability in aqueous solution at high temperatures if the injection is to be sterilized by moist heat processes.

The *British Pharmacopoeia* suggests *o*-cresol (0.3%), chlorocresol (0.1%), benzyl alcohol (1%) and phenylmercuric salts (0.002%). In addition the *Pharmaceutical Codex* includes phenol (0.5%), chlorbutol (0.5%), and phenylmercuric acetate or nitrate (but at 0.001%). This list provides a choice that allows for incompatibilities with medicaments but only phenol is not appreciably absorbed by rubber and may not always prove suitable. However, pH may affect activity (Allwood, 1978). Phenol, *o*-cresol and chlorocresol are active up to a pH of about 9, but chlorbutol is less active above a pH of 5.0 and unstable above pH 6.0. Phenylmercuric acetate is active only above pH 6.0. Care has to be taken with solubility, for instance at room temperature the saturated solubility of phenylmercuric nitrate and phenylmercuric borate are respectively 0.08% and 0.33%. Interactions of preservatives with containers may include the leaching of hydroxyl ions, reducing the activity of phenol by increasing the pH. Toxicity may involve hypersensitivity.

However, the substances listed are only suggestions and others may be substituted if they are more satisfactory in particular cases. The *Pharmaceutical Codex* requires that such alternatives should have a bactericidal activity at least

equivalent to that of 0.5% phenol. The *British Pharmacopoeia* recommends that the number of bacteria recovered per ml is reduced by a factor of not less than 10^3 within 6 hours of challenge and no organism is recovered from 1 ml at 24 hours and thereafter. In addition the number of moulds or yeasts recovered per ml is reduced by a factor of not less than 10^2 within 7 days of challenge and there is no increase thereafter. Thiomersal 0.01–0.02% is used in certain immunological preparations while Procainamide Injection BP and some commercial cortisone injections contain 0.9% benzyl alcohol.

An additional preservative is unnecessary in multiple-dose injections prepared by heating with a bactericide since they already contain one; nor is one necessary when the medicament has bactericidal activity, e.g. Ethanolamine Oleate Injection BP. This contains 2.0% benzyl alcohol as a local anaesthetic and, therefore, even if the active ingredient had no antibacterial activity there would be no need for an additional bactericide.

Bactericides suitable for oily injections

The bactericides mentioned previously are more soluble in fats and oils than in water and, therefore, when present in an aqueous liquid containing bacteria, will tend to leave the water and concentrate in the lipoid constituents of the bacteria. Oily solutions of these substances have lower antibacterial activity because the bactericides will not leave the oil as readily as they will leave an aqueous solution, i.e. the partition coefficient is not in favour of the bactericide concentrating in the bacteria.

The *Pharmaceutical Codex* recommends as bactericides for oily preparations in multiple-dose containers phenol (0.5%), cresol (0.3%) and chlorocresol (0.1%). These are exactly the same concentrations as for the aqueous products. It is not a failure to take their reduced activity into account but a reflection of the difficulty of investigating the efficiency of bactericides in oily media. The *Codex* acknowledges their probable poor effectiveness since it includes the statement:

'these bactericides may afford some protection from contamination with vegetative micro-organisms but are ineffective against sporing organisms.'

Evidence suggests that micro-organisms are

unlikely to multiply in an anhydrous environment. Eisman *et al.* (1953) studied the sporicidal activities in sesame oil of a number of substances including commonly used preservatives. Since a phenylmercuric salt, even at 0.01%, was one of the least active compounds tested it is understandable that phenylmercuric nitrate is not in the list recommended in the *Codex*.

Limitations in the use of bactericides

If bactericides were included in large volume intravenous injections, there would be a risk of administering a toxic dose. They must not be included if the dose exceeds 15 ml. Bactericidal agents cannot be used in infusion fluids which cannot be packed in multiple-dose containers nor sterilized by heating with a bactericide. There is no objection to the inclusion of a bactericide when the dose of an intravenous injection is less than 15 ml.

Bactericides should not be used in intracardiac and intra-arterial injections in case they further damage the affected tissues or organs. Similarly bactericides should never be used in intrathecal, intracisternal and peridural injections. The meninges are very easily irritated and serious inflammation (aseptic meningitis) may be set up by bactericides. As the c.s.f. is a favourable medium for bacterial growth it would be dangerous to inject even a few organisms from a contaminated multiple-dose injection. Therefore, injections for intrathecal, intracisternal and peridural use should be packed in single-dose containers, sealed by fusion of glass. Injections for ophthalmic routes should also not contain bactericides.

Parenteral solutions of radionuclides are often supplied in multiple-dose containers because decay constantly changes the dose volume and opened, partly used ampoules are less easy to store safely until the contents have decayed sufficiently for disposal. The choice of bactericide is limited by the instability of many under the influence of radiation.

Incompatibilities of common bactericides

A bactericide must be compatible with the medicaments and with the auxiliary substances present

in a solution that it is required to preserve. Incompatibility with the four common bactericides is not uncommon. Phenol is incompatible with procaine penicillin, quinine hydrochloride and thiamine hydrochloride, cresol with carbachol, ergometrine and quinine hydrochloride and phenylmercuric acetate with ascorbic acid, ergometrine, hyoscine hydrobromide, pethidine hydrochloride and thiamine hydrochloride. Chlorocresol is less satisfactory and incompatible with many substances, including benzylpenicillin, calcium chloride, carbachol, chlorpheniramine maleate, diamorphine hydrochloride, ergometrine, heparin, mersalyl, methadone, papaveretum and quinine hydrochloride. Some of these incompatibilities are due to salting out of the bactericide by strong solutions of the medicaments, others may have been caused by the use of chlorocresol of insufficient purity. Phenol and cresol do not have many incompatibilities and are particularly valuable for the majority of protein preparations, e.g. immunological products.

Chemical stability of the medicament

Adjustment of pH

Adjustment of the pH is a major method of stabilizing injections since decomposition is often catalysed by hydrogen or hydroxyl ions. Often a pH can be found at which the loss of activity is negligible, provided the preparation is packed and stored correctly, but in some cases breakdown still occurs, although at a reduced rate. Four methods can be used to increase the stability of injections.

Addition of a reducing agent or antioxidant

The most popular reducing agents for injections are sulphurous acid salts (Smith and Stevens, 1972) which include sodium sulphite, sodium metabisulphite and sodium bisulphate. They are used principally to retard the oxidation of drugs that are readily oxidized in aqueous solution to form coloured decomposition products. Sodium metabisulphite is used to prevent the decomposition of adrenaline injections and prevent the green colour due to the oxidation of apomorphine and the darkening of morphine sulphate in morphine sulphate injection (Yeh and Lach,

1961). However, the same researchers (1971) have shown that morphine reacts with sodium metabisulphite to form a product which is insoluble in water and dilute hydrochloric acid. Sodium metabisulphite is most suitable for injections of low pH but when the stability range of the medicament extends to the alkaline side of neutral (e.g. Gallamine Injection BP) sodium sulphate is more appropriate. Sodium thiosulphate is included in Sodium Iodide (^{131}I) Injection BP and Sulphadiazine Injection BP.

The reducing action of dextrose may be used, e.g. Carbachol Injection BP and Phentolamine Injection BP. Ascorbic acid has been examined but it is not as effective as sodium metabisulphite. Thiourea has been recommended as an antioxidant for ascorbic acid injections and an antioxidant, e.g. propylgallate, is usually included in injectable oils and ethyl oleate to prevent rancidification. Lachman (1968) comprehensively reviewed antioxidants and their uses.

Intrathecal injections must not contain antioxidants and, therefore, careful consideration of the formulation must be made. For instance, morphine injection may be formulated for intrathecal use without an antioxidant but will degrade to pseudomorphine and morphine IV oxide (Deeks *et al.*, 1983). Their presence must be balanced off against the risk which the presence of an antioxidant would cause.

Replacement of air by an inert gas

In injections where oxygen is a serious cause of decomposition, improved stability may be obtained by replacement of the air in the final containers with an inert gas. Nitrogen satisfactory fulfils the requirement of inertness and availability. The method may be used alone as in injections containing ergot alkaloids (e.g. ergotamine) and in Tubocurarine Injection BP, or together with one or more reducing agents, as in Apomorphine Injection BP (sodium metabisulphite) and Chlorpromazine Injection BP (sodium metabisulphite and ascorbic acid).

Use of sequestering agents

Trace quantities of many heavy metal ions often catalyse destructive changes in medicaments, e.g.

the breakdown of the sulphur-containing ring of benzylpenicillin (copper, lead, mercury and zinc), the oxidation of adrenaline (copper, iron and chromium), the degradation of thiomersal (copper) and the decomposition of oxytetracycline (copper). These effects can often be prevented by adding a substance, termed a sequestering agent, that will form a soluble coordination compound with the metal in which the latter is held in a non-ionizable form. Then the catalytic property of the ion is often, but not always, suppressed.

The agent that has been most widely used for this purpose is ethylenediamine tetra-acetic acid (EDTA), usually as its di- or tri- sodium or calcium disodium salts. Sodium polymetaphosphate and dimercaprol have been investigated as sequestering agents. Other examples include the use of disodium edetate in Sodium Bicarbonate Injection BP and citric acid in Digoxin Injection BP, Propranolol Injection BP and Urea Injection BP. When sequestering agents are used to prevent metal-catalysed oxidation, they are usually more effective if a reducing agent is present.

Inclusion of specific stabilizers

Calcium Gluconate Injection BP Calcium gluconate is sparingly soluble in cold water (1 in 30) but readily forms a supersaturated solution. A 10% injection (BP strength) can be prepared by dissolving the salt in hot water. This solution tends to deposit crystals, particularly if it has not been carefully filtered to remove foreign particles that can act as nuclei for crystal formation. To reduce this tendency to crystallize, not more than 5% of the gluconate may be replaced by calcium *D*-saccharate or another suitable harmless calcium salt (e.g. the lactobionate, glucoheptonate or laevulinate salts).

Sodium Bicarbonate Injection BP Solutions of sodium bicarbonate, when heated, form sodium carbonate and liberate carbon dioxide. Unfortunately, the carbonate may cause harmful effects, e.g. haemolysis and calcium precipitation. Therefore, to prevent decomposition, the container should be thoroughly sealed to prevent gas loss during sterilization and the injection should be saturated with carbon dioxide before sterilization. Precipitation of calcium or magnesium carbonate

may occur due to impurities in the bicarbonate or to the extraction of calcium or magnesium ions from the glass container. To minimize this problem it is permissible to add 0.01% disodium edetate to sequester the troublesome ions.

Mersalyl Injection BP Mersalyl, the sodium salt of a complex organic acid containing mercury, decomposes in solution liberating toxic mercuric ions. Sodium chloride, in plasma, would induce this breakdown if mersalyl alone was injected. However mersalyl combines with compounds containing an acidic nitrogen atom, e.g. theophylline, and makes its liberation more difficult. The acid and the stabilizer, theophylline, are suspended in water and sodium hydroxide is added until solution has been effected. The pH is adjusted to 7.6–8.2 which is the optimum for stability.

Limitations in the use of additives

No matter what the formulation or type of injection, any added substance(s) should not interfere with the activity of the drug. They should be safe, effective at low concentrations and be stable to both heat and storage. Additives should not be used unless their value is unquestionable. Ideally a patient should receive only the drug prescribed.

Particulate contamination

The origins, nature and hazards of particulate contamination have been covered extensively elsewhere (Chapter 27 and Groves *et al.*, 1973b) but need mention.

Particulate contamination may arise from four main sources:

- 1 materials arising from the drug, vehicle or added substances not filtered out at clarification prior to filling the final container,
- 2 materials present in the final container which were not removed by rinsing prior to filling,
- 3 materials falling by chance into the final container during the filling process.

Such materials from 1, 2, and 3 above may include cellulose fibres, dust, cotton fibres, hair, dandruff and loose skin from human origin as well as

microbial contamination. Some filters may shed particles during use.

- 4 The container or closures may be sources of particles either during storage or removal of doses prior to administration. Thus constituents of closures may deposit into the injection during sterilization, e.g. carbon black, whiting, zinc oxide and clay. To prevent this problem the closure may be coated with a lacquer but this may also subsequently flake into the medication. On withdrawal of a dose the penetration of the needle through the closure may result in coring or forcing rubber particles into the injection. Even glass containers are sources of contamination since the injection may react with the glass causing flaking and the physical force required to open ampoules may cause glass spicules to be deposited into the injection.

The physiological damage caused by particles following injection has been discussed (Dempsey and Webber, 1983). It has been suggested that such particles can cause inflammatory responses, tissue growths possibly leading to neoplasms, antigenic reactions and occlusion of blood vessels leading to damage especially to the brain, kidney, liver and eyes.

PACKAGING OF INJECTIONS

Containers for injections

Ideal properties

The ideal properties for containers of injections are as follows.

- 1 The container should not affect its contents.
- 2 There should be no surface changes of the container at the temperatures and pressures associated with sterilization.
- 3 They should protect from light when the contents are photosensitive.
- 4 The containers should either be cheap enough to dispose of after one use or be easy to clean and reuse.
- 5 The contents should be easy to examine through the container to detect particles, contamination and decomposition.

Types of container

Several types of container have been developed for injections. *Ampoules* are single-dose glass containers with capacity of 0.5–50 ml. They are usually made from neutral or soda (lime-soda) glass and tend to liberate glass particles on opening into the product. Ampoules are sealed by heat fusion to exclude micro-organisms and may be used either for solutions or for powders. *Cartridges* are cylindrical glass tubes sealed by rubber at each end, holding slightly more than 1 ml. For use they are inserted into a metal syringe barrel and are used for one occasion only. *Prepacked syringes* were first introduced in the 1960s and contain one dose of medicament; there is no danger of particulate contamination due to the glass. *Antibiotic vials* and *multiple-dose containers* are rubber capped and allow withdrawal of a dose via a needle once it has penetrated the rubber cap. Antibiotic vials allow easy addition of a vehicle through the rubber closure (via a needle) and facilitate dissolving of the powder immediately prior to administration. Multiple-dose containers provide flexibility in the dose to be withdrawn. However, there is a greater risk of contamination (and hence the inclusion of a bactericide in multiple-dose injections) than in ampoules.

Containers for large volume fluids (greater than 50 ml) may be constructed from either glass or plastics. Glass bottles tend to be thick walled and are sealed with materials other than glass, e.g. plastic or rubber discs with an aluminium screw cap. Plastic containers are unbreakable, light and disposable. They are less transparent than glass containers, are easily punctured and there is difficulty in estimating unused volumes.

Single-dose versus multiple-dose containers

Single-dose ampoules are difficult to manipulate during use. However, their closures are completely airtight and their use is essential for drugs which need to be packed in an atmosphere of nitrogen. There is no possibility of solvent loss. In comparison, multiple-dose containers allow variation in the dose that can be withdrawn. The presence of the rubber seal may cause problems like preservative loss and particulate contamination

from rubber coring during removal of the dose. Indrawing of air may lead to contamination of unused product.

Materials for injection containers

Glass

Glass produced by fusion of silica alone is resistant to chemical attack, thermal shock and the risks of handling but is expensive and difficult to manufacture. Other substances are added to give glasses of lower melting points, e.g., alkaline oxides, oxides of divalent elements and boric or aluminium oxides.

Types of glass Soda glass is unsuitable as a container material for injections because it yields appreciable quantities of alkali to aqueous solutions, flakes comparatively easily, loses brilliance on repeated use and is liable to fracture with sudden changes of temperature. Soda glass is, however, specified for thiopentone sodium since alkali stabilizes this medicament. Borosilicate glass was developed to avoid alkali extraction but is expensive and difficult to mould. It has been superseded by neutral glass which is soft and easier to manipulate, having good resistance to autoclaving and to solutions of pH up to 8. Neutral glass is used for alkali-sensitive injections and to produce ampoules, small vials and large transfusion bottles. Lead-free glass is required for ampoules intended for Sodium Calciumedetate Injection BP and Trisodium Edetate Injection BP. These medicines are sequestering agents which would take up lead ions from the glass.

Leaching of alkali can be further reduced by pretreatment of the glass surface. Sulphuring is used to give lime-soda glass a neutral surface through which the extraction of alkali ions is small. However, none of the glasses used for pharmaceutical containers is completely free from extractable alkali and, therefore, limit tests are given in the pharmacopoeias for extractable alkali. (For further information on glass composition, see Chapter 44 and Sanga, 1979.)

Associated problems for parenterals Glass may cause the following pharmaceutical problems.

Alkalinity Glass containers easily yield alkali ions to aqueous preparations. Alkaloidal salts in

injection (e.g. apomorphine hydrochloride, ergotamine tartrate) may precipitate the free alkaloid if the pH rises. Similarly insulin injections (pH 3.0–3.5) may precipitate the free insulin if the pH rises to the isoelectric point of insulin (pH 5.5–5.6). Rises in pH can also increase the chemical instability of formulated drugs. Although methods of stabilization may be used, e.g. pH adjustment, replacement of air by nitrogen and the inclusion of antioxidants, trace quantities of alkali will decompose apomorphine hydrochloride, atropine (hydrolysis) and morphine sulphate. Vitamins are similarly sensitive. All these injections need low-alkali content glasses. Injections prepared as the powder and dissolved immediately prior to use need not be packed in low alkalinity glasses.

Loss of brilliance and flaking Extraction of weakly bonded alkali ions from the glass under damp conditions may result in dissolution of some of the surface silica due to the high alkalinity of the deposit resulting in a loss of surface brilliance. This makes visualization of contents difficult and may be the first stage of cracking of the glass surface leading to flaking into the contents of the injection. Flakes rapidly form by alkaline solutions etching away into the silica structure, e.g. injections containing sodium citrate or phosphate. They develop more slowly in solutions of chlorides of sodium, potassium or calcium. The *British Pharmacopoeia* warns that in certain injections (e.g. Sodium Chloride, Sodium Lactate and Compound Sodium Lactate) small particles may separate from a glass container.

Plastics

Types of plastics The plastics used to pack injections are thermoplastic in nature. These soften on heating to a viscous fluid and harden on cooling. Those used include high density polyethylene, polyvinylchloride (PVC) and polypropylene. PVC is poorly flexible and, therefore, plasticizers are added to produce the flexible material required for bags for infusion fluids. Polypropylene is similar to high density polyethylene but with a higher heat resistance. All three types may be sterilized by autoclaving.

Associated problems for parenterals The *British Pharmacopoeia* stresses the importance of knowledge of the plastic composition. Injections packed in plastic should be examined under 'in use' simulations for sensory, chemical and physical changes, changes in quantity of the contents due to permeability of the plastic, change in pH, the effects of light and changes in assay results. Attention should be given to extractable substances (which, if released, should be innocuous and compatible with contents), to permeability of gases and solvent vapours and to absorption of active ingredients, bactericides and other adjuncts.

Examples of these problems include the liberation of cyclohexanone (a solvent for PVC) from PVC bags into intravenous solutions (Ulsaker and Korsnes, 1977) and the presence of liquid particles of di-2-ethylhexylphthalate (a plasticizer) in intravenous fluids (Horioka *et al.*, 1977). Many drugs, e.g. diazepam, hydralazine hydrochloride and thiopentone sodium, are adsorbed on to PVC. Such problems vary to factors including pH, concentration, octanol–water partition coefficients, lipid solubility and the extent of ionization of molecules in solution. Plastic containers should not yield more than a minimum of soluble matter. In addition plastic containers must comply with texts for toxicity, ether-soluble extractives and metal additives (heavy metals, tin and barium).

Closures

Types and properties of closure materials Closures are made from rubbers and the ideal rubber should show good ageing properties with no deterioration with age or oxidation. The hardness and elasticity should be sufficient to allow a needle to pass through without blunting yet on withdrawal of the needle the puncture should close immediately. The properties of the rubber should not be altered by the selected sterilization process and the rubber should not be permeable to air and moisture, the latter of which might degrade water-sensitive drugs, e.g. penicillin. However, injections which are sensitive to oxygen should be packed in glass-fused containers (ampoules).

Two types of rubber may be used for closures, natural or synthetic. Natural or raw rubber is unsuitable for use before additives are used to give it better physical and chemical properties. Added substances include vulcanizing agents (e.g. sulphur), accelerators to reduce this amount of sulphur (e.g. thiazoles and thiurans) and activators (e.g. stearic acid or stearates) to increase the activity of accelerators. Fillers (e.g. carbon black or magnesium carbonate) reinforce the physical properties and extending agents (e.g. talc) reduce the cost. Antioxidants are added (e.g. phenols) to reduce oxidation of rubber which is catalysed by light, copper and manganese. Rubbers may be coloured by pigments (e.g. iron oxides, sulphides and coal tar dyes) and softening agents and lubricants may be added.

In comparison with natural rubber, synthetic rubbers are more resistant to high temperature, more resistant to ageing and more expensive. However, as they are harder than natural rubbers a substantially higher level of softening agents, e.g. dibutylphthalate, is used to improve resilience. Often carbon black or fine clay is used as filler. Four types are used for closures. Butyl rubbers are resistant to chemical attack and ageing but their oil and solvent resistance is low. Nitrile rubbers are oil and heat resistant but absorption of bactericides and leaching of extractive are considerable. Chloroprene rubbers are resistant to oxygen and oils and zinc oxide rather than sulphur is used for vulcanization. Water permeability is low. Silicone rubbers are heat resistant and show low permeability to water. The advantages and disadvantages of rubbers have been reviewed by Stafford (1981).

Associated problems for parenterals The various added substances used in the preparation of the rubber should not be released into the medicament, and care should be taken that no toxic materials are released nor should inactivation of the medicament by pH changes occur. Similarly there should be no extraction of injection ingredients by the rubber. This is the biggest problem with rubber closures. Loss of bactericides from injections may occur by two processes which may similarly effect the medicament or other substances present in the injection.

Absorption by the rubber The bactericide is partitioned between the injection and the rubber according to its partition coefficient. Phenol and benzyl alcohol are attracted to the water and are not absorbed. However, others like chlorocresol and phenylmercuric nitrate are strongly attracted to the rubber and are strongly absorbed. To minimize these problems the *British Pharmacopoeia* prescribes a method of treating the rubber where closures are treated with solutions containing bactericides in concentrations twice that found in the injection. The solution should contain other ingredients that may similarly be absorbed from the injection.

Loss through volatilization from the outer surface of the rubber cap Once equilibrium has been reached the bactericide volatilizes into the atmosphere from the surface of the closure. Loss can be limited by sealing the closure with a less permeable material (e.g. paraffin wax). The choice of such a material is limited because it should not fragment. Loss can be reduced by reduction in the upper surface area of the closure exposed and by increasing its thickness.

Some rubber caps have been reported to reduce the antioxidant activity of sodium metabisulphite or sulphur dioxide by adsorption from solution.

Care should also be taken that the closure intended for oily injections should be constructed from oil-resistant materials.

STERILIZATION OF INJECTIONS

Wherever possible, injections should be sterilized in their final container to reduce to a minimum the possibility of contamination. The principles of sterilization are discussed in Chapter 26 and industrial sterilization procedures are described in Chapter 43.

Dry heat sterilization is used for oily injections, e.g. Progesterone Injection BP. However propyl-iodone is thermolabile and hence, to prepare the injection, the sterile powder is added by aseptic technique to arachis oil, previously sterilized by dry heat.

Moist heat sterilization, i.e. autoclaving, is used for most thermostable aqueous preparations.

Closures may be sterilized by autoclaving them in solutions containing preservatives (and medicaments) at concentrations twice those found in the injection.

Heating with a bactericide may be used for injections that are thermolabile to autoclaving. However, the use of this method of sterilization is forbidden when the injections are intended for certain routes, e.g. intrathecal.

Sterilization by filtration may be used as an alternative to dry heat for oils and may avoid slight changes in heat sterilized products. No heat is used and therefore the method is suitable for aqueous preparations which are thermolabile and stable in solution. Examples include Betamethasone Sodium Phosphate Injection BP, Diazepam Injection BP and Ergotamine Injection BP. Care

should be taken, however, as certain drugs may adsorb to the filter.

Certain injections may not, however, be sufficiently stable to enable sterilization by filtration. Therefore, the powders are packed, sterile in ampoules, to be reconstituted at the time of injection by *aseptic processes*. Examples include Amylobarbitone Sodium Injection BP, Pentamidine Injection BP, Tetracycline Injection BP and Thiopentone Injection BP. The powders may be sterilized by dry heat (if thermostable in dry state) or by bacterial filtration prior to aseptic precipitation or crystallization. Terminal sterilization with gaseous disinfectants (e.g. ethylene oxide) may be used provided no chemical changes occur in the drug. Erythromycin, tetracycline and penicillins are unharmed by this process.

REFERENCES

- Allwood, M. C. (1978) Antimicrobial agents in single and multi-dose injections. *J. appl. Bact.*, **44**, SVII-SXVII.
- Carpenter, C. P. and Shaffer, C. B. (1952) Polyethylene glycols as injection vehicles. *J. Am. Pharm. Ass. (Sci. Ed.)*, **41**, 27-29.
- Deeks, T., Davis, S. and Nash, S. (1983) Stability of an intrathecal morphine injection formulation. *Pharm. J.*, **230**, 495-497.
- Dempsey, G. and Webber, G. S. (1983) Hazards of particle injection. *Pharm. J.*, **231**, 63-64.
- Eisman, P. C., Jaconia, D. and Mayer, R. L. (1953) The preservation of parenteral vegetable oils by chemical agents. *J. Am. Pharm. Ass. (Sci. Ed.)*, **42**, 659-662.
- Frith, C. F., Dawson, F. W., Sampson, R. L. (1976) Water for Injection U.S.P. XIX by reverse osmosis. *Bull. Parent Drug Assoc.*, **30**, 118-127.
- Gibaldi, M. (1977) *Biopharmaceutics and Clinical Pharmacokinetics*, 2nd edn, Lea and Febiger, Philadelphia.
- Groves, M. J. (1973a) *Parenteral Products*, William Heinemann, London.
- Groves, M. J. (1973b). Particulate contamination in intravenous fluids. 1. Nature, origin and hazard. *Pharm. J.*, **210**, 185-187; 2. The detection of particulate contamination. *Pharm. J.*, **211**, 163-166; 3. Standards for control of cleanliness. *Pharm. J.*, **211**, 166-168.
- Hartman, C. W. and Husa, W. J. (1957) Isotonic solutions, V. The permeability of red corpuscles to various salts. *J. Am. Pharm. Ass. (Sci. Ed.)*, **46**, 430-433.
- Horioka, M., Aoyama, T. and Karasawa, H. (1977) Particles of di-2-ethylhexyl phthalate in intravenous infusion fluids migrating from polyvinyl chloride bags. *Chem. Pharm. Bull.*, **25**, 1791-1796.
- Husa, W. J. and Adams, J. R. (1944) Isotonic Solutions, II. The permeability of red corpuscles to various substances. *J. Am. Pharm. Ass. (Sci. Ed.)*, **33**, 329.
- KabiVitrum Ltd. (1984/85) Data in A.B.P.I. *Data sheet Compendium* (1984/85), DataPharm. Publications Ltd, London.
- Irvine, M. K. A. (1978) Products for parenteral nutrition. *Pharm. J.*, **221**, 216-219.
- Lachman, L. (1968) Antioxidants and chelating agents as stabilisers in liquid dosage forms. *Drug. Cosmet. Ind.*, **102**(1), 36-40, 146-148; **102**(2), 43-45, 146-149.
- Macek, T. J. (1963) Preparation of parenteral dispersions. *J. pharm. Sci.*, **52**, 694-699.
- Nash, R. A. (1972) Parenteral Suspensions. *Bull. Parent Drug Assoc.*, **26**, 91-95.
- Perkins, J. J. (1969) *Principles and Methods of Sterilisation*, 2nd edn, Charles C Thomas, Springfield, Illinois.
- Ridgway, K. (1973) Pyrogens and pyrogen free water. *Proc. Biochem.*, **8**(7), 9-12.
- Sanga, S. V. (1979) Review of glass types available for packaging parenteral solutions. *J. Parent Drug. Assoc.*, **33**, 61-67.
- Smith, G. and Stevens, M. F. G. (1972) Sulphur dioxide — preservative and potential mutagen. *Pharm. J.*, **209**, 570-572.
- Stafford, P. (1981) Rubber and its pharmaceutical applications. *Manufacturing Chemist and Aerosol News*, **52**(6), 25, 27.
- Sykes, G. (1958) The basis for sufficient of a suitable bacteriostatic in injections. *J. Pharm. Pharmacol.*, **10**, 40T-46T.
- Thomas, W. H., Thomson, R. and Hui, L. K. (1980) Evaluation of non-official methods of pyrogen testing of injectables. *Pharm. J.*, **224**, 259-261, 270.
- Thomasson, C. L. and Husa, W. J. (1958) Isotonic solutions, VII. The permeability of red corpuscles to various alkaloidal salts. *J. Am. Pharm. Ass. (Sci. Ed.)*, **47**, 711-714.
- Ulsaker, G. A. and Korsnes, R. M. (1977) Determination of cyclohexanone in intravenous solutions stored in PVC bags by gas chromatography. *Analyst*, **102**, 882-883.
- Yeh, S. Y. and Lach, J. L. (1961) Stability of morphine in aqueous solutions, III. *J. pharm. Sci.*, **50**, 35-42.
- Yeh, S. Y. and Lach, J. L. (1971) Stability of morphine in aqueous solution IV. *J. pharm. Sci.*, **60**, 793-794.