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FASTtrack

Pharmaceuticals – Drug Delivery and Targeting

Yvonne Perrie
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FASTtrack

Pharmaceutics - Drug Delivery and Targeting

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Preface

The best drugs can't exert their beneficial effects if they are not reaching their target site in the body at an appropriate concentration and for a sufficient length of time. It is clear that if a tablet is still in the package it is of no benefit for the patient. Less obvious is that this may also be the case after the tablet has been swallowed.

In the stomach the tablet might not disintegrate and the drug might not be released from the dosage form. Or the drug simply has too low aqueous solubility in the gastrointestinal fluids. If the drug is not in solution it will (generally) not be able to overcome the epithelial membranes of the gastrointestinal tract and it cannot enter into the body and reach the target site of its activity. *How can we improve the solubility of poorly water-soluble drugs?*

Some drugs chemically or enzymatically degrade in the stomach. Others lead to gastric irritation. *How can these drugs still be administered via the oral route?*

In other cases the drug may dissolve very fast and is absorbed very quickly from the gastrointestinal tract. Whilst this seems a good thing (and indeed it often is), it can lead to high plasma concentration peaks of the drug followed by fast elimination of the drug, and consequently a short duration of action. So the patient has to take the drug very frequently and there will be strong fluctuations in the plasma concentration of the drug over time. *Can we formulate a dosage form to improve this situation?*

Some drugs cannot be delivered by the oral route as they are metabolised in the liver, before reaching the systemic circulation. *What can be done?*

Again other drugs may have a strong side-effect profile, which may prohibit efficient treatment. *Can we improve this situation, and direct the drug to its target site, rather than having it distributed evenly throughout the body?*

This book tries to answer these and other questions in a concise and structured way. We will systematically review important concepts and facts relating to the delivery and targeting of drugs. The emphasis of this book has not been placed on the anatomical routes of delivery, but instead on the principles of drug release and targeting, namely: immediate release, delayed release, sustained release, controlled release and targeted release. Because of its overwhelming importance in drug delivery today, we have placed some focus on oral delivery (for immediate release, delayed release, sustained release), but other routes of delivery will also be covered where appropriate (for controlled and targeted release). Relevant examples of delivery systems will be given throughout the book with a focus on delivery systems that have actually reached clinical reality.

This book aims to highlight differences and principles in a concise way (including some mind maps at the end of the book), and so we have to apologise to the experts in the field if we have drawn boundaries for clarity where a grey zone is more appropriate. In the words of Picasso, however, we feel that students should know the boundaries before they can (and should) cross them.

Yvonne Perrie
Thomas Rades
July 2009

chapter 1

Controlling drug delivery

Overview

In this chapter we will:

- differentiate drug delivery systems according to their physical state
- differentiate drug delivery systems according to their route of administration
- differentiate drug delivery systems according to their type of drug release
- discuss drug transport across epithelial barriers.

Introduction

Pharmacotherapy can be defined as the treatment and prevention of illness and disease by means of drugs of chemical or biological origin. It ranks among the most important methods of medical treatment, together with surgery, physical treatment, radiation and psychotherapy. There are many success stories concerning the use of drugs and vaccines in the treatment, prevention and in some cases even eradication of diseases (e.g. smallpox, which is currently the only human infectious disease completely eradicated). Although it is almost impossible to estimate the exact extent of the impact of pharmacotherapy on human health, there can be no doubt that pharmacotherapy, together with improved sanitation, better diet and better housing, has improved people's health, life expectancy and quality of life.

Unprecedented developments in genomics and molecular biology today offer a plethora of new drug targets. The use of modern chemical synthetic methods (such as combinatorial chemistry) enables the syntheses of a large number of new drug candidates in shorter times than ever before. At the same time, a better understanding of the immune system and rapid progress in molecular biology, cell biology and microbiology allow the development of modern vaccines against old and new challenges.

KeyPoints

- Continued developments in chemistry, molecular biology and genomics support the discovery and developments of new drugs and new drug targets.
- The drug delivery system employed can control the pharmacological action of a drug, influencing its pharmacokinetic and subsequent therapeutic profile.

Tip

Combinatorial chemistry is a way to build a variety of structurally related drug compounds rapidly and systematically. These are assembled from a range of molecular entities which are put together in different combinations. A 'library' of compounds of tens of thousands of different molecules is then screened to identify compounds that bind to therapeutic targets.

However, for all these exciting new drug and vaccine candidates, it is necessary to develop suitable dosage forms or drug delivery systems to allow the effective, safe and reliable application of these bioactive compounds to the patient. It is important to realise that the active ingredient (regardless of whether this is a small-molecular-weight 'classical' drug or a modern 'biopharmaceutical' drug like a therapeutic peptide, protein or antigen) is just one part of the medicine administered to the patient and it is the formulation of the drug into a dosage form or drug delivery system that translates drug discovery and pharmacological research into clinical practice.

Tip

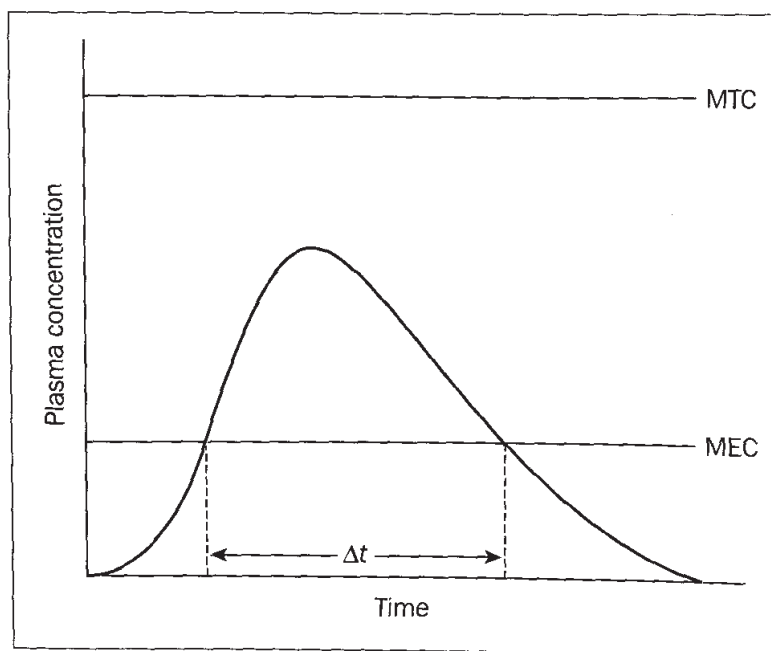
Usually the drug concentration in the body is determined in the plasma. This is done as the plasma is comparatively easy to access and drug concentrations can be reliably measured using techniques such as high-performance liquid chromatography (HPLC). However, the desired site of action for most drugs is not the plasma and in principle it would be better to determine the drug concentration at the site of action of the drug.

Indeed the drug delivery system employed plays a vital role in controlling the pharmacological effect of the drug as it can influence the pharmacokinetic profile of the drug, the rate of drug release, the site and duration of drug action and subsequently the side-effect profile. An optimal drug delivery system ensures that the active drug is available at the site of action for the correct time and duration. The drug concentration at the appropriate site should be above the minimal effective concentration (MEC) and below the minimal toxic concentration (MTC). This concentration interval is known as the therapeutic range and the concept is illustrated in Figure 1.1, showing the

drug plasma levels after oral administration of a drug from an immediate-release dosage form.

Achieving the desired concentration of a drug is dependent on the frequency of dosing, the drug clearance rates, the route of administration

Figure 1.1 Drug plasma levels after oral administration of a drug from an immediate-release dosage form. The therapeutic range is the concentration interval between the minimal effective concentration (MEC) and the minimal toxic concentration (MTC). Δt is the time interval the drug is in the therapeutic range.



and the drug delivery system employed. Within this book the terms drug delivery system, dosage form and medicine are used interchangeably. However the term dosage form is often used to refer to the physical appearance of the medicine whereas the term delivery system is often used to refer to the way the medicine releases the drug and delivers it to the body or more specifically to the target organ, tissue, cell or even cellular organelle.

Differentiating delivery systems according to their physical state

For dosage forms it is common to differentiate the various types by classifying them according to their physical state into gaseous (e.g. anaesthetics), liquid (e.g. solutions, emulsions, suspensions), semisolid (e.g. creams, ointments, gels and pastes) and solid dosage forms (e.g. powders, granules, tablets and capsules). Most dosage forms contain several phases.

Sometimes the phases of a dosage form are of the same state, for example for an emulsion which contains two liquid phases (oil and water). Whilst both phases are liquid, they differ in their physical properties, for example density and electrical conductivity, and are separated from each other by an interface. However, more often the dosage form contains phases of different states. For example, a suspension contains a liquid and a solid phase. Therefore classification into gaseous, liquid, semisolid or solid dosage forms may sometimes appear somewhat arbitrary. Finally, in these multiphase dosage forms usually one or more phases are dispersed, whilst other phases are continuous. In a suspension the solid phase is dispersed and the liquid phase is continuous, and in an oil-in-water emulsion the oil phase is dispersed and the water phase is continuous. In some dosage forms the determination of the type and number of phases is not as straightforward. For example, the phases of creams can be difficult to determine, with the presence of a dispersed water (or oil) phase in addition to several continuous phases (oil, water and surfactant phases). For liposomal dispersions, the state of the phospholipids

KeyPoints

- Dosage forms can be classified according to their physical state.
- Most dosage forms contain several phases.
- Systems containing a dispersed phase will give rise to physical instability issues.
- All systems move to a state of minimum free energy.

Tip

A phase is a volume element of a system (here the dosage form), separated from other volume elements of the system by a phase boundary (interface to another phase). The physical properties within the phase do not vary, which means that the phase is physically homogeneous. From the requirement of homogeneity within a phase it follows that the number of molecules within the phase is large compared to the number of molecules forming the interface between the phases and surrounding other phases.

Tip

To understand dosage forms from a physical perspective, try to identify the number of phases in a dosage form, their state and if they are dispersed or continuous.

Tips

Here are some examples of how dosage forms in their simplest terms can be differentiated according to the state and dispersion of their phases:

- A drug solution is a one-phase system as the dissolved drug does not fulfil the requirements for a phase. In a solution the molecularly dispersed drug will not separate out to form larger particles if the concentration of the drug is not changed (e.g. by evaporation of the solvent) and the environmental conditions (e.g. temperature) are constant.
- A suspension is a two-phase system containing a continuous liquid phase and a dispersed solid phase.
- An emulsion is a two-phase system containing two liquid phases, one dispersed and one continuous.
- Ointments are generally two-phase or multiphase gels, with at least two continuous phases (usually a crystalline or liquid crystalline surfactant phase and a lipid phase).
- Creams additionally contain a water phase which may be dispersed (water-in-oil cream) or continuous (oil-in-water cream).
- Tablets are essentially compressed powders, and might thus be classified as containing a solid and gaseous continuous phase. Of course a tablet contains several solid phases, as drug particles are usually present together with other solid phases (e.g. filler, binder, disintegrant, glidant and lubricant particles).

used to form the liposomes will determine if a liposomal dispersion is a suspension (if the lipids are in a crystalline state) or an emulsion (if the lipids are in a fluid, liquid crystalline state).

It is important to note that the presence of a dispersed phase will lead to physical instability in the system. For example, in an oil-in-water emulsion, the dispersed oil droplets have a larger interfacial area to the water than if the droplets had coalesced into one large continuous phase. This increased interfacial area leads to an increased interfacial free energy, according to the relationship:

$$G_i = A\gamma$$

where G_i is the interfacial free energy of the system, A is the interfacial area between the dispersed phase (here the oil droplets) and the continuous phase (here the water phase) and γ is the interfacial tension between the two phases. The interfacial free energy of the system (here the emulsion) can be minimised by coalescence of the droplets into larger droplets and finally into one continuous oil phase, as this maximally reduces the total interfacial area. This is of course undesirable from a formulation viewpoint. Coalescence of droplets in an emulsion is a pharmaceutical instability, but from a thermodynamic viewpoint the system has been stabilised, as the interfacial free energy has been reduced. In practical terms an emulsion is pharmaceutically stabilised by adding emulsifiers to the systems, that either lower the interfacial tension (note: if γ gets smaller, G_i will get smaller), or that act as a physical barrier against coalescence. In either case, increasing the interfacial area will still increase the surface free energy.

Differentiating delivery systems according to their route of administration

Another way of differentiating dosage forms is according to their site or route of administration. Drugs can be administered directly into the

body, though injection or infusion. This form of drug administration is termed parenteral drug delivery. Depending on the site of administration into the body one can differentiate between intravenous, intramuscular, subcutaneous, intradermal and intraperitoneal administration. Usually aqueous solutions are used for intravenous delivery, but it is also possible that the dosage form contains a dispersed phase (solid or liquid), provided the dispersed particles are small enough (e.g. smaller than 100–150 nm) to avoid embolism. For other routes of parenteral administration the delivery systems can be aqueous or oily or even solid (the latter dosage forms are termed implants).

Drugs can also be administered on to the skin to enter into the body. Mostly semisolid dosage forms are used for this, including creams, ointments, gels and pastes. However, liquid dosage forms, such as emulsions, or solid dosage forms, such as transdermal controlled drug delivery systems (patches), can also be used. These will be discussed in more depth in Chapter 6. It has to be taken into account, though, that one of the main functions of the skin as an organ is to prevent particles or compounds entering the body, rather than allowing them to be absorbed into the body. The stratum corneum of the skin forms a formidable barrier against uptake and thus transdermal delivery is difficult to achieve. Penetration enhancers often have to be added to the delivery system to improve delivery into or through the skin. In transdermal controlled drug delivery systems ideally the dosage form controls the uptake into the skin (rather than the uptake being controlled by the stratum corneum).

The most important route of drug administration into the body is through mucosal membranes. Mucosal membranes are much less of a barrier to uptake than the skin and some mucosal membranes (such as the ones in the small intestine) are indeed

KeyPoints

- The various routes of administration of a drug into the body can be generally classified into:
 - direct entry into the body
 - entry into the body by overcoming the skin
 - entry into the body by overcoming mucosal membranes.
- The oral route is often the most convenient route for drug delivery; however, drugs delivered via this route can be metabolised by the hepatic first-pass effect.

Tips

Parenteral drug delivery

Subcutaneous injection

The needle is inserted into the fatty tissue just under the skin. Volumes should be less than 2.5 ml per injection site. Insulin is commonly administered via this route.

Intramuscular injection

Injection into the muscle is preferred to the subcutaneous route if larger volumes (typically up to 5 ml in appropriate sites) have to be given.

Intravenous injection

A needle is inserted directly into a vein. This is the easiest way to give a precise dose rapidly. Small volumes can be given as a single dose whereas larger volumes can be given by infusion.

Intradermal injection

Injection is given into the skin. This form of parenteral administration is used in allergy skin testing.

Intraperitoneal injection

Injection through the peritoneum (the thin, transparent membrane that lines the walls of the abdomen).

Tips

The US Food and Drug Administration (FDA) has compiled an extensive list of different dosage forms and different routes of administration. These lists can be found on the FDA Center for Drug Research websites:

- <http://www.fda.gov/cder/dsm/DRG/drg00201.htm>
- <http://www.fda.gov/cder/dsm/DRG/drg00301.htm>

specialised sites for absorption. There are many mucosal membranes that can be used for drug administration. Of the highest importance are the mucosal membranes of the gastrointestinal tract, allowing oral drug delivery. The suitability and convenience of this route of delivery make oral dosage forms the most common of all drug delivery systems. Also the buccal, sublingual, rectal and vaginal mucosa and indeed the lung and nasal mucosal membranes can act as absorption sites. For all of these mucosal membranes dosage forms have been developed, such as buccal

and sublingual tablets, suppositories, vaginal rings, inhalers and nasal sprays, to name a few.

If drug delivery systems are designed to give a local drug effect and not systemic activity, they can be described as topical delivery systems. This is the case for many dermal dosage forms.

Oral drug delivery

As stated above, the oral route is the most popular route to administer drugs. However, some factors should be considered when looking to administer drugs via this route. In particular the transit time in the gastrointestinal tract may vary considerably:

- between patients and within the same patient, with the gastric residence time being the most variable
- with the state of the dosage form (liquid dosage forms are emptied out of the stomach faster than solid dosage forms)
- with the fasted or fed state of the patient.

The pH conditions in the gastrointestinal tract also vary considerably, from a low pH in the stomach (1.5–2 in the fasted state to around 5 in the fed state) to a higher pH in the small and large intestine. The pH in the small intestine varies from 4 to 7, with an average value of approximately 6.5. This may affect stability and will influence the degree of ionisation of ionisable drugs which in turn will influence their absorption (unionised forms of drugs are usually taken up better than ionised forms of the same drug) and solubility (unionised forms are usually less soluble than ionised forms of the same drug).

First-pass metabolism

Importantly, drugs that are taken up into the body through the gastrointestinal mucosa will be transported to the liver via the portal vein before going into general circulation. As the liver is the main metabolic organ of the body, if the drug is susceptible to metabolic degradation in the liver, this may considerably reduce the activity of

the drug. This phenomenon is known as the hepatic first-pass effect. The rectal route may also show varying degrees of the first-pass effect, while for other routes of administration (intravenous, vaginal, nasal, buccal and sublingual) the drug is distributed in the body before reaching the liver, and therefore for certain drugs these may be the preferred route of administration. However, whilst the liver is the main metabolic organ of the body, metabolism may also take place in the gastrointestinal lumen and indeed in the mucosal membranes.

Differentiating drug delivery systems according to their mechanism of drug release

Another systematic that can be used to differentiate drug delivery systems is according to the way the drug is released. Broadly, one can differentiate as follows:

- Immediate release – drug is released immediately after administration.
- Modified release – drug release only occurs some time after the administration or for a prolonged period of time or to a specific target in the body. Modified-release systems can be further classified as:
 - Delayed release: drug is released only at some point after the initial administration.
 - Extended release: prolongs the release to reduce dosing frequency.

These terms are also used by the pharmacopoeias and the FDA. Whilst immediate-release dosage forms are designed to give a fast onset of drug action, modifications in drug release are often desirable to increase the stability, safety and efficacy of the drug, to improve the therapeutic outcome of the drug treatment and/or to increase patient compliance and convenience of administration.

Tip

After oral administration first-pass metabolism may occur in the liver and the gut. For example, glyceryl trinitrate is predominantly metabolised in the liver and is therefore often formulated for sublingual delivery. In contrast, benzylpenicillin and insulin are primarily metabolised in the gut lumen while orlistat is metabolised within the gastrointestinal mucosal membrane.

KeyPoints

- Dosage forms can control the rate of release of a drug and/or the location of release.
- They can be classified into immediate-release and modified-release dosage forms.
- The modified-release systems can be further divided into delayed-, extended- and targeted-release systems.
- Extended-release systems can be further divided into sustained- and controlled-release systems.
- Modifications in drug release profiles can be used to improve the stability, safety, efficacy and therapeutic profile of a drug.

Tips

The various forms of release as defined by the FDA

Immediate release

Allows the drug to dissolve in the gastrointestinal contents, with no intention of delaying or prolonging the dissolution or absorption of the drug.

Modified release

Dosage forms whose drug release characteristics of time course and/or location are chosen to accomplish therapeutic or convenience objectives not offered by conventional dosage forms such as a solution or an immediate-release dosage form. Modified-release solid oral dosage forms include both delayed- and extended-release drug products.

Delayed release

Release of a drug (or drugs) at a time other than immediately following oral administration.

Extended release

Extended-release products are formulated to make the drug available over an extended period after ingestion. This allows a reduction in dosing frequency compared to a drug presented as a conventional dosage form (e.g. as a solution or an immediate-release dosage form).

No definition for controlled release or targeted release is provided by the FDA or pharmacopoeias.

Immediate release

Many dosage forms are designed to release the drug immediately or at least as quickly as possible after administration. This is useful if a fast onset of action is required for therapeutic reasons. For example, a tablet containing a painkiller should disintegrate quickly in the gastrointestinal tract to allow a fast uptake into the body.

The onset of action is very fast for intravenous injections and infusions and the pharmacological effect may be seen in a matter of seconds after administration. The reasons for this are twofold:

1. The drug is already in solution, so strictly speaking the drug does not have to be released from the dosage form at all.
2. The drug is directly administered into the body, so no time is lost due to drug permeation through the skin or mucosal membranes, before the target organs can be reached.

In oral solutions the drug is also already released and the solution will simply mix with the gastrointestinal fluids. However, powders and granules need to dissolve first before the drug is released by dissolution. For tablets it is initially necessary that the tablet disintegrates (if it is formed from compressed granules this will initially happen to the level of the granules, from which further disintegration into powder particles and finally drug dissolution occurs). For capsules to release their drug content it is necessary for the capsule shell material (for example, gelatin or hydroxypropylmethylcellulose (HPMC)) first to disintegrate. Thereafter the drug can either dissolve from the usually solid powders or granules in the case of hard gelatin or HPMC capsules or it can be dispersed from the usually liquid, lipophilic content of a soft gelatin capsule. These types of immediate-release dosage forms have an onset of action in the order of minutes to hours.

Immediate-release dosage forms usually release (dissolve or disperse) the drug in a single

KeyPoints

- Immediate-release delivery systems give a fast onset of action.
- For a therapeutic action the drug should be in solution, therefore disintegration of the dosage form and dissolution of the drug may have to occur first depending on the dosage form.
- Immediate-release systems usually release the drug in a single action following a first-order kinetics profile.
- The time of action of the drug is limited to the time that the concentration of the drug is above the MEC.

action following a first-order kinetics profile. This means the drug is released initially very quickly and then passes through the mucosal membrane into the body, reaching the highest plasma level (termed $C_{\max}$) in a comparatively short time (termed $t_{\max}$). Uptake through the mucosal membranes may be due to passive diffusion or by receptor-mediated active transport mechanisms (see section on modified release). Once taken up into the body the drug is distributed throughout the body and elimination of the drug by metabolism and excretion occurs. The elimination process also usually follows first-order kinetics. Therefore the plasma levels measured over time after administration of an immediate-release dosage form (the plasma concentration time curve) basically are the sum of a first-order absorption and a first-order elimination process. The resulting function is known as the Bateman function. Figure 1.2 shows an idealised plasma concentration versus time profile of an immediate-release oral dosage form.

Tips

First-order kinetics

The rate of the process is proportional to the concentration of one of the reactants, in our case the drug.

Bateman function

This function was initially used to describe the concentration of a radioactive material B that stems from a first-order decay of another radioactive material A and that in its own right further decays to another material C . If both decay processes ($A \rightarrow B$ and $B \rightarrow C$) follow first-order kinetics, exactly the same function results as for the plasma concentration time curve of a drug from an immediate-release oral dosage form. The $A \rightarrow B$ decay is equivalent to the absorption process and the $B \rightarrow C$ process is equivalent to the elimination process.

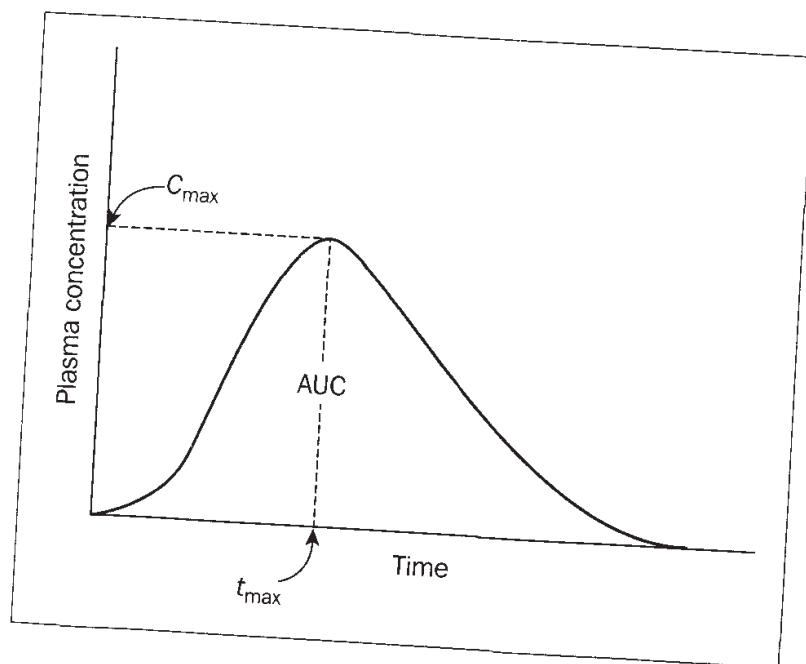


Figure 1.2 Idealised plasma concentration versus time profile of an immediate-release oral dosage form. The highest drug plasma concentration is termed $C_{\max}$. The time at which $C_{\max}$ is reached is termed $t_{\max}$. The area under the plasma concentration versus time profile is termed AUC and reflects the total amount of drug absorbed.

An important consideration for immediate-release dosage forms is that the time of action of the drug is limited to the time that the concentration of the drug is above the MEC. If the drug has a short biological half-life, this time interval may be short, requiring frequent

dosing and potentially leading to low patient compliance and suboptimal therapeutic outcome.

The biological half-life of a drug is defined as the time required to reduce the plasma concentration by 50% by metabolism or excretion. Many studies show that a large proportion of patients do not take drugs as directed (for example three times a day), especially if the disease is (at least initially) not accompanied by strong symptoms, for example in the treatment of high blood pressure or glaucoma. To reduce the frequency of drug administration it is often not possible simply to increase the dose of an immediate-release dosage form as the peak plasma concentrations may be too high and lead to unacceptable side-effects. Therefore the drug concentration within the plasma should be above the MEC and below the MTC, i.e. within the therapeutic range (Figure 1.1).

KeyPoints

- Modified-release systems are designed to influence the release profile of a drug from its delivery system.
- Oral delayed-release systems can delay release until specific regions of the gastrointestinal tract are reached.
- Extended release of a drug can be achieved using sustained- or controlled-release drug delivery systems.
- Controlled-release systems aim to control the plasma concentration of the drug after administration by various possible routes.

Modified release

Dosage forms can be designed to modify the release of the drug over a given time or after the dosage form reaches the required location.

Delayed release

Delayed-release dosage forms can be defined as systems which are formulated to release the active ingredient at a time other than immediately after administration. Delayed release from oral dosage forms can control where the drug is released, e.g. when the dosage form reaches the small intestine (enteric-coated dosage forms) or the colon (colon-specific dosage forms).

Delayed-release systems can be used to protect the drug from degradation in the low pH environment of the stomach or to protect the stomach from irritation by the drug. In these cases drug release should be delayed until the dosage form has reached the small intestine. Often polymers are used to achieve this aim. The dosage form (for example, a tablet or the granules before tableting) can be coated with a suitable polymer. The polymer dissolves as a function of pH, so when the dosage forms travel from the low-pH environment of the stomach to the higher-pH environment of the small intestine, the polymer coat dissolves and the drug can be released. Once this occurs, the release is again immediate and the resulting plasma

Tip

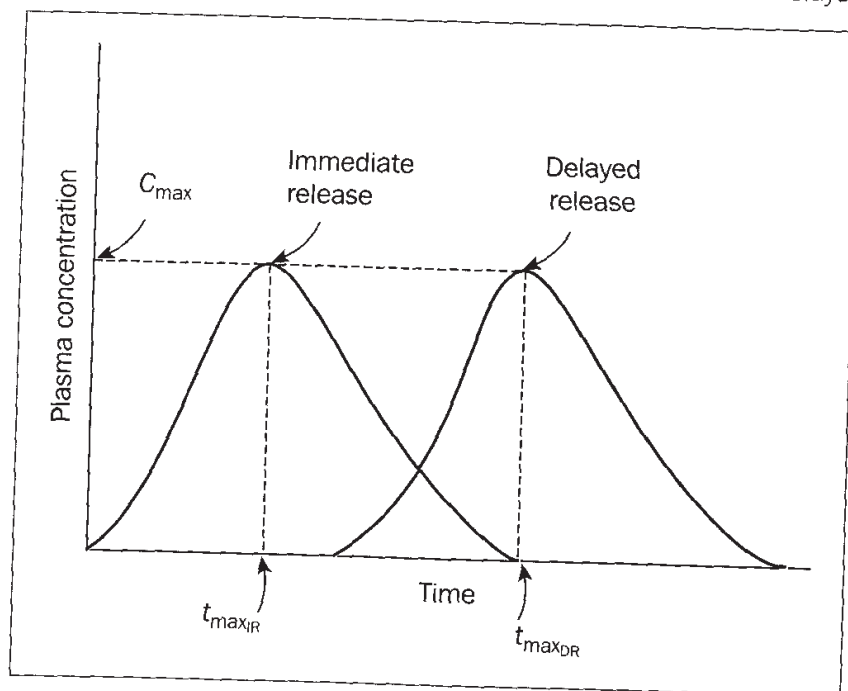
Immediate-release oral delivery systems can also have polymer coatings. In this case the polymer may be used to mask an unpleasant taste or odour, to facilitate swallowing of the drug or to improve identification of the medicine. These coats dissolve quickly in the stomach and do not delay the release of the drug.

concentration versus time curve is similar to the one for immediate-release dosage forms.

The development of colon-specific drugs and dosage forms may be advantageous for the treatment of local and systemic diseases, including colorectal cancer and Crohn's disease. Especially for peptide and protein drugs, this form of release may also be advantageous for systemic administration given the more favourable pH conditions in the colon compared to the stomach and the generally lower enzymatic activity compared to the small intestine.

Figure 1.3 shows an idealised plasma concentration versus time profile of a delayed-release oral dosage form. $T_{\max}$ (but not $C_{\max}$) is strongly dependent on the gastric emptying times which, as stated above, may be quite variable.

Figure 1.3 Idealised plasma concentration versus time profile of a delayed-release oral dosage form compared to an immediate-release dosage form. $T_{\max IR}$ is the time for maximum plasma concentration of the drug released from an immediate-release dosage form and $T_{\max DR}$ is the time for maximum plasma concentration of the drug released from a delayed-release dosage form.



Extended release

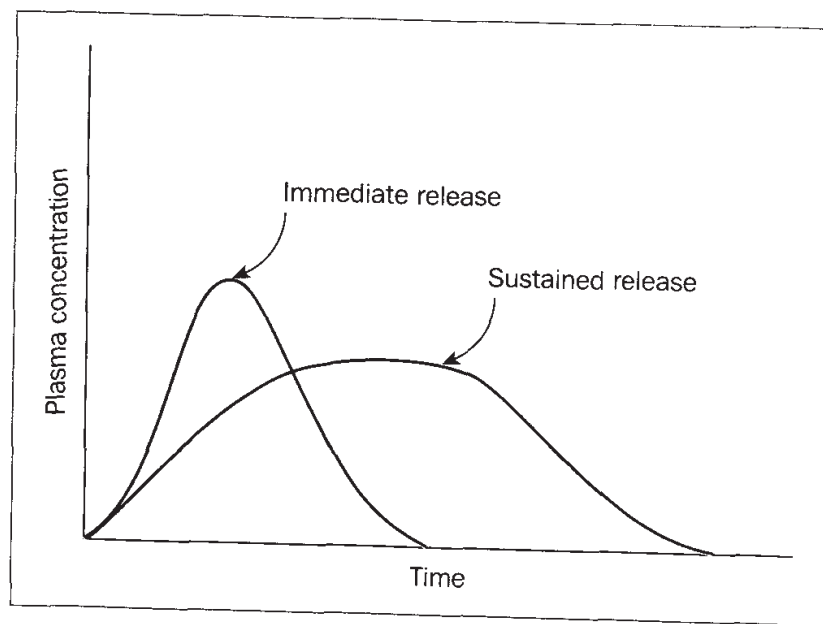
Extended-release systems allow for the drug to be released over prolonged time periods. By extending the release profile of a drug, the frequency of dosing can be reduced. For immediate-release dosage forms the time interval the plasma concentration is in the therapeutic range of the drug can be quite short. Therefore frequent dosing, with its associated compliance problems, is required. This is especially an issue in chronic diseases when patients need to take the medicine for prolonged periods of time, often for the rest of their life. Extended release can be achieved using sustained- or controlled-release dosage forms.

Sustained release

These systems maintain the rate of drug release over a sustained period (Figure 1.4). For example, if the release of the drug from the dosage form is sustained such that the release takes place throughout the entire gastrointestinal tract, one could reduce $C_{\max}$ and prolong the time interval of drug concentration in the therapeutic range. This in turn may reduce the frequency of dosing, for example from three times a day to once a day. Sustained-release dosage forms achieve this mostly by the use of suitable polymers, which are used either to coat granules or tablets (reservoir systems) or to form a matrix in which the drug is dissolved or dispersed (matrix systems). The release kinetics of the drug from these systems may differ:

- Reservoir systems often follow a zero-order kinetics (linear release as a function of time).
- Matrix systems often follow a linear release as a function of the square root of time.

Figure 1.4 Idealised plasma concentration versus time profile of a sustained-release oral dosage form compared to an immediate-release dosage form.



Controlled-release

Controlled-release systems also offer a sustained-release profile but, in contrast to sustained-release forms, controlled-release systems are designed to lead to predictably constant plasma concentrations, independently of the biological environment of the application site. This means that they are actually controlling the drug concentration in the body, not just the release of the drug from the dosage form, as is the case in a sustained-release system. Another difference between sustained- and controlled-release dosage forms is that the former are basically restricted

to oral dosage forms whilst controlled-release systems are used in a variety of administration routes, including transdermal, oral and vaginal administration.

Controlled release of drugs from a dosage form may be achieved by the use of so-called therapeutic systems. These are drug delivery systems in which the drug is released in a predetermined pattern over a fixed period of time. The release kinetics is usually zero-order. In contrast to sustained-release systems, the dose in the therapeutic systems is of less importance than the release rate from the therapeutic system. Ideally the release rate from the dosage form should be the rate-determining step for the absorption of the drug and in fact for the drug concentration in the plasma and target site. However, controlled-release systems are not necessarily target-specific, which means that they do not 'exclusively' deliver the drug to the target organ. This may be achieved by so-called targeted delivery systems which aim to exploit the characteristics of the drug carrier and the drug target to control the biodistribution of the drug. Figure 1.5 shows an idealised plasma concentration versus time profile of a controlled-release dosage form.

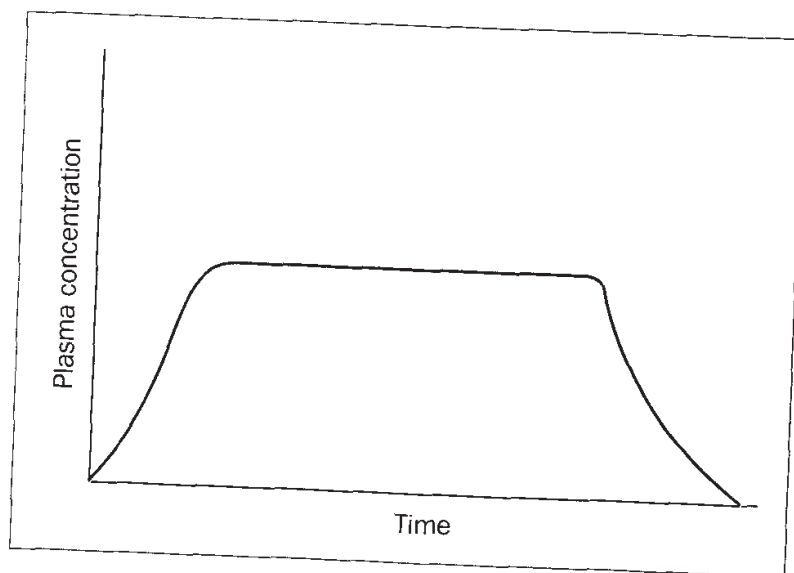


Figure 1.5 Idealised plasma concentration versus time profile of a controlled-release dosage form.

Optimum release profile

From immediate release and delayed release to sustained release and controlled release, we have seen that the resulting plasma concentration versus time curves have become increasingly flatter, prolonging the time the drug is in the therapeutic range after a single administration of the dosage form. This has led to the popular slogan: 'The flatter the better'. However, for some diseases it is advantageous to have varying release of the drug depending on the needs of the patient or circadian rhythms in the body. For example, insulin is needed in higher concentration after a meal and blood pressure has been found to be higher in the morning and

afternoon and drops off during the night. Patients with rheumatoid arthritis suffer from pain more strongly in the morning than in the night, whilst the situation is reversed for patients with osteoarthritis. It has also long been known that cortisol levels are higher in the morning and decline throughout the day. This has led to research into so-called feedback-regulated drug delivery systems in which the drug concentration (ideally at the drug target site) is measured through a sensor and, depending on the ideal drug concentration, release is either increased or slowed down. It is also possible that instead of the actual drug concentration a therapeutic effect is measured that then acts as a feedback for the drug release. These systems, however, have not yet entered the market.

KeyPoints

- Controlling the release rate of a drug does not ensure that the drug reaches the target site or is retained there.
- Passively targeted drug delivery systems can utilise the natural distribution mechanisms within the body.
- Active targeting of delivery systems uses targeting groups such as antibodies and ligands to direct the system to the appropriate target.

Targeted-release dosage forms

Whilst controlling the rate of release of a drug from its delivery system can control plasma drug concentration levels, once released there is often little control over the distribution of the drug in the body. Very few drugs bind exclusively to the desired therapeutic target and this can give rise to reduced efficacy and increased toxicity.

Drug targeting aims to control the distribution of a drug within the body such that the majority of the dose selectively interacts with the target tissue at a cellular or subcellular level. By doing so, it is possible to enhance the activity and specificity of the drug and to reduce its toxicity and side-effects. Drug targeting can be

achieved by designing systems that passively target sites by exploiting the natural conditions of the target organ or tissue to direct the drug to the target site. Alternatively drugs and certain delivery systems can be actively targeted using targeting groups such as antibodies to bind to specific receptors on cells.

The differentiation of dosage forms according to drug release places the emphasis on the delivery of the drug and will be followed in this book.

KeyPoints

- The epithelial lining presents a barrier to drug absorption.
- Epithelia are classified based on their shape, number of cells that form the epithelial barrier and their specialisation.
- Mucus secreted from goblet cells presents an additional barrier to drug absorption.

Drug absorption

By using the various drug delivery strategies outlined above, it is possible to influence the distribution of a delivery system and the release of a drug from its delivery system. However, we must also consider the process of drug absorption after the drug has been released. The absorption of drugs is dependent on the site of absorption and the nature of the drug. Nearly all internal and external body surfaces,

and hence possible drug absorption routes, are lined with epithelial tissue. For example, drugs administered orally must cross the epithelium of the gastrointestinal tract before they can enter the systemic circulation.

Barriers to drug absorption

Epithelia are tissues composed of one or more layers of cells. These layers are supported by a basement membrane which lies on top of the supporting connective tissue. The function of epithelial cells includes absorption, secretion and protection and is dependent on their location within the body. The epithelia are classified by their:

1. *Shape*
 - a. Squamous – these cells have a flat (squashed) shape.
 - b. Columnar – these are narrow, tall cells.
 - c. Cuboidal – these cells have a cubic shape, intermediate between squamous and columnar.
2. *Stratification (number of cell layers)*
 - a. Simple – single layer of cells, termed epithelium.
 - b. Stratified – multiple layers.
3. *Specialisation – some epithelia will have a specialised function*
 - a. Keratinised cells contain keratin protein to improve the strength of the barrier.
 - b. Ciliated cells have apical membrane extensions that can increase the overall absorption area and rhythmically beat to move mucus.

Mucus

Many of the epithelial linings considered as absorption sites have a mucus layer coating. Mucus is synthesised and secreted by goblet cells which are a specialised type of columnar epithelial cells. Mucus is viscous in nature and is composed of highly glycosylated peptides known as mucins and inorganic salts in water. The main role of mucus is to protect and lubricate the epithelial lining. In the respiratory tract it supports mucociliary clearance, by trapping substances and removing them through the mucociliary escalator. In the gastrointestinal tract, mucus both protects the stomach from the acidic conditions therein and helps lubricate the passage of food.

However, in terms of drug delivery, mucus serves as a physical barrier to absorption. A substance must first diffuse across the mucus barrier before it can reach the epithelia and be absorbed. Therefore the viscosity and thickness of the mucus layer and any interactions the drug and/or delivery system may have with the mucus must be considered.

Tips

Examples of epithelia include:

- Blood vessels: this epithelium lines the circulatory system and consists of a single layer of squamous cells.
- Oral: this epithelium consists of a single layer of columnar cells and lines the stomach and intestine. Cells of the small intestine have villi and microvilli to increase their surface area.
- Buccal: this epithelium consists of stratified squamous cells that may be keratinised.

KeyPoints

- Drugs can cross epithelia by transcellular and paracellular mechanisms.
- The paracellular mechanism involves passive diffusion between cells.
- Transcellular diffusion involves movement through cells and may require energy.
- The route of transport is dependent on the physicochemical nature of the drug.

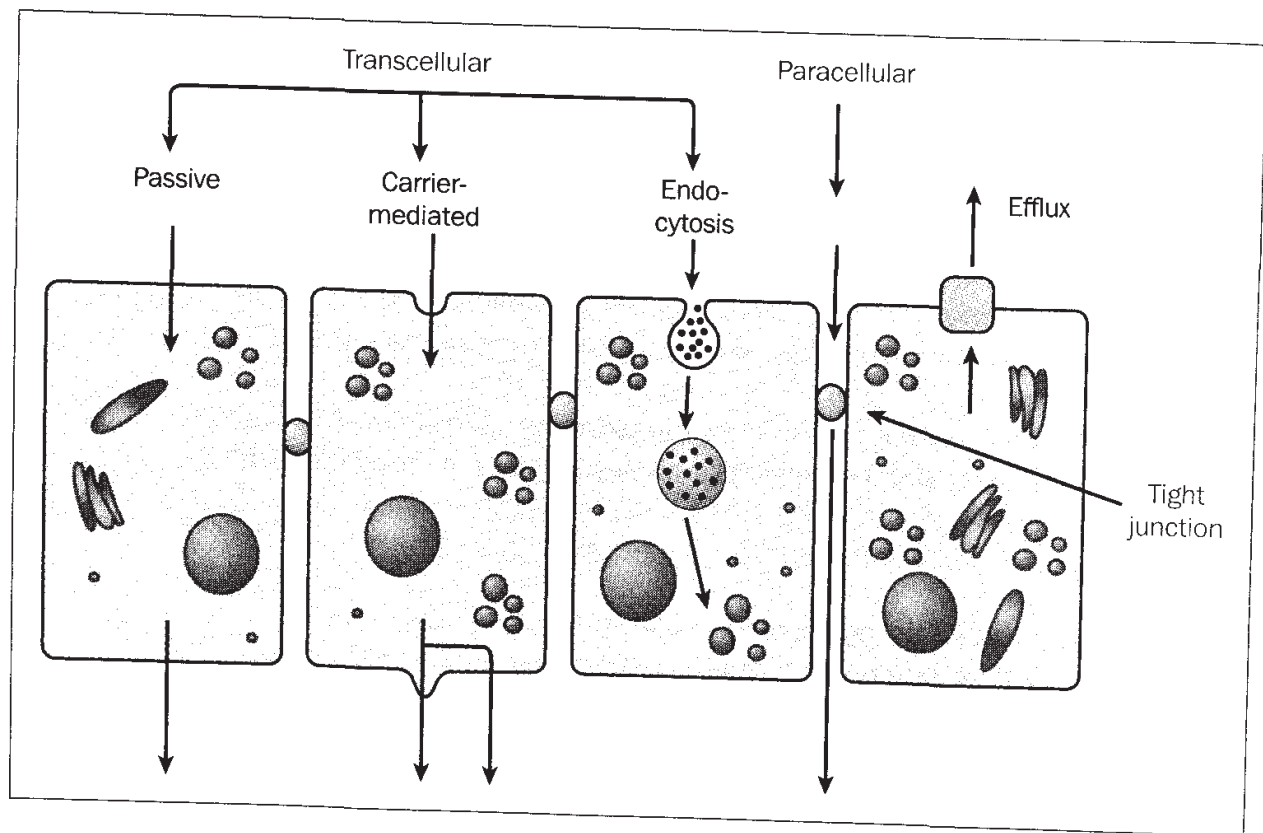
Mechanisms of drug absorption

The combination of the epithelial membranes and (where present) the mucus restricts the absorption of substances, including drugs. However there are mechanisms of absorption across the epithelial cells which involve:

- transcellular transport through cells
- paracellular transport between cells.

These mechanisms are summarised in Figure 1.6.

Figure 1.6 Transport processes across epithelial barriers.



Transcellular route

Passive diffusion

This involves the diffusion of drugs across the lipid bilayer of the cell membrane and is driven by a concentration gradient with drugs moving

from high to low concentration. The rate of diffusion is governed by Fick's law. Low-molecular-weight drugs are absorbed by passive diffusion and factors controlling the rate of diffusion include:

- drug concentration
- partition coefficient of the drug
- area of absorptive tissue.

In particular the lipophilicity of the drug is important since the drug must diffuse across the cell membrane and an optimum partition coefficient is usually observed for passive diffusion processes.

Carrier-mediated transport

This form of transport involves specific carrier proteins present in the cell membranes. Carrier-mediated transport can either act with a concentration gradient (facilitated diffusion) or against a concentration gradient (active absorption). For active absorption, as the transport is working against a concentration gradient, energy is required.

Any molecules, including drug molecules, which are similar to the natural substrate of the carrier protein are transported across the cell membrane. As this process involves a carrier protein, the mechanism is saturable at high concentrations and uptake via this route can be inhibited by competing substrates.

Endocytosis

This process involves internalisation of substances by engulfment by the cell membrane which forms membrane-based vesicles within the cell, known as endosomes. This allows larger molecules or particulates to enter the cell. There are several types of endocytosis:

- Receptor-mediated endocytosis: substances interact with specific surface receptors. As this involves receptors, the process is saturable. Drugs bind to receptors on the surface of the cell. This promotes invagination and vesicle formation in the cell. Within these vesicles, known as endosomes, the contents are subjected to low-pH conditions and digestive enzymes which can result in drug degradation/inactivation.

Tips

Fick's first law of diffusion states that the amount of a solute, for example a drug in solution, passing across a unit area, for example of the lipid bilayer of the epithelial barrier (flux, J , units: $\text{kg m}^{-2} \text{s}^{-1}$), is proportional to the concentration difference across this unit area (dC/dx , units: kg m^{-4}). The proportional constant is D (units: $\text{m}^2 \text{s}^{-1}$) and the partition coefficient of the drug is K .

$$J = -DK(dC/dx)$$

The minus sign in this equation stems from the fact that diffusion occurs along the concentration gradient, i.e. from higher concentration of the solute to lower concentration. This equation applies to steady-state conditions. Diffusion is discussed in more depth in Chapter 5.

Tips

Examples of carrier-mediated drug transport

- Facilitated diffusion: riboflavin and vitamin B₆ are absorbed by a facilitated diffusional transport.
- Active absorption: levodopa is absorbed by active absorption via amino acid transporters.

- Adsorptive endocytosis: this involves non-specific interactions with the cell surface receptors and therefore is non-saturable.
- Pinocytosis: this involves the uptake of solutes and single molecules. Large soluble macromolecules can be taken up by this process. This is a non-specific process that goes on continually in all cell types.
- Phagocytosis: with this process larger particulates may be taken up. Only specialised cells of the reticuloendothelial system (also known as the mononuclear phagocyte system) are capable of phagocytosis. This includes cells such as blood monocytes and macrophages.

Pore transport

Very small molecules may also be taken up through aqueous pores that are present in some cell membranes. These are ~ 0.4 nm in diameter so this transport mechanism is very restrictive. Only very small hydrophilic drugs can enter cells via this route.

Paracellular route

Drugs can also cross epithelia through gaps (known as gap junctions) between the cells. This route is governed by passive diffusion and small hydrophilic molecules can pass through these gap junctions. Transport across the epithelia can be enhanced using penetration enhancers which can damage the gap junctions; however possible toxicity implications should be considered with such methods.

Efflux

Substances can also be pushed back out of cells by an energy-dependent efflux system. There are various apical transmembrane proteins which can transport drugs out of the cell. Drugs that are subjected to efflux processes include cytotoxic drugs such as taxol, steroids, immunosuppressants and antibiotics.

Efflux is a major concern in the development of antimicrobial resistance. The genetic information for efflux pumps can be contained within chromosomes and/or plasmids. This allows for the efflux pump genes to be passed to various bacterial species. Expression of several efflux pumps in bacteria can lead to multidrug resistance.

KeyPoints

- The role of the drug delivery systems is to allow the effective, safe, and reliable application of the drug to the patient.
- To achieve this aim the drug must reach its target site.
- The system must be able to be produced in a technically feasible way and the quality of the formulation process must be assured.

Summary

No matter how dosage forms are classified, the role of the drug delivery systems is to

allow the effective, safe, and reliable application of the drug to the patient.

For the development of dosage forms the formulation scientist needs to optimise the bioavailability of the drug. This means the delivery systems should allow and facilitate the drug to reach its target site in the body. For example, a tablet formulation containing an antihypertensive drug must disintegrate in the gastrointestinal tract, the drug needs to dissolve and the dissolved drug needs to permeate across the mucosal membrane of the gastrointestinal tract into the body.

Whilst some drugs are meant to act locally, e.g. in the oral cavity, in the gastrointestinal tract, in the eye or on the skin, nevertheless the prime role of the drug delivery system is to allow the drug to reach its target site.

Another role of the delivery systems is to allow the safe application of the drug. This includes that the drug in the formulation must be chemically, physically and microbiologically stable. Side-effects of the drug and drug interactions should be avoided or minimised by the use of suitable drug delivery systems. The delivery systems also need to improve the patient's compliance with the pharmacotherapy by the development of convenient applications. For example, one can improve patient compliance by developing an oral dosage form where previously only parenteral application was possible.

Finally, the delivery system needs to be reliable and its formulation needs to be technically feasible. This means the pharmaceutical quality of the delivery systems needs to be assured, drug release from the system needs to be reproducible and the influence of the body on drug release should be minimised (for example, food effects after oral administration). However, for any application of a drug delivery system on the market, the dosage form needs to be produced in large quantities and at low costs to make affordable medicines available. Therefore, it is also necessary to investigate the feasibility of the developed systems to be scaled up from the laboratory to the production scale. Figure 1.7 summarises the key attributes to be optimised to develop a drug into a medicine.

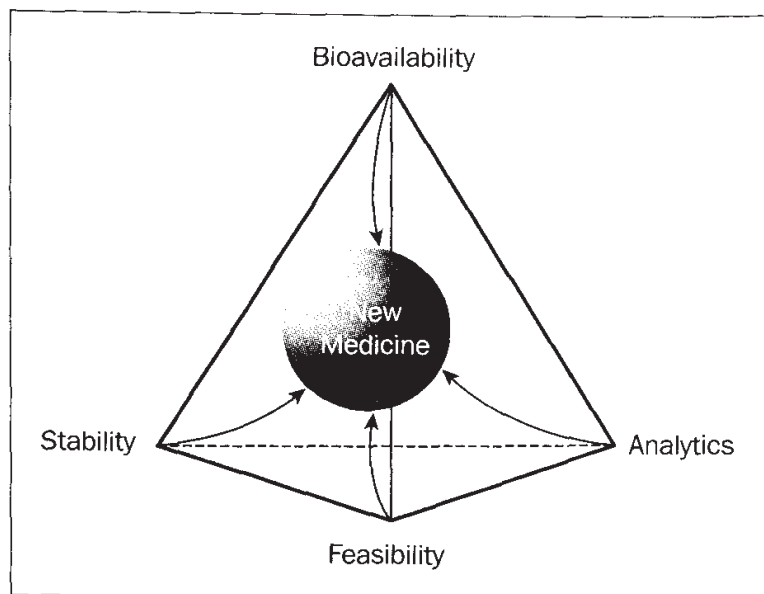
Tip

If a drug is in the gastrointestinal tract it is still outside the body.

Tip

Some confusion may arise from the use of the expression targeted drug delivery systems. In this book we define targeted delivery system as systems that allow selective targeting of the drug to a specific tissue, organ or specific cells inside the body to achieve a targeted drug action. If the release of the drug from the dosage form is targeted to a specific organ, these systems may be better called topical delivery systems (although some authors define only dermal application of dosage forms as being topical).

Figure 1.7 Key attributes that need to be optimised to develop a drug into a medicine.



Self-assessment

After having read this chapter you should be able to:

- differentiate dosage forms according to their physical state and to give examples for each category
- differentiate dosage forms according to their route of administration and to list examples for each category
- differentiate dosage forms according to their drug release and to list examples for each category
- describe and explain plasma concentration versus time profiles of immediate-release oral dosage forms
- describe and explain plasma concentration versus time profiles of delayed-release oral dosage forms
- describe and explain plasma concentration versus time profiles of sustained-release oral dosage forms
- describe and explain plasma concentration versus time profiles of controlled-release oral dosage forms
- discuss the therapeutic range of a drug and how it is linked to the plasma concentration versus time profiles of oral dosage forms
- compare and contrast targeted and non-targeted drug release
- identify the essential features of transcellular and paracellular absorption via:
 - passive diffusion
 - carrier-mediated transport
 - endocytosis
 - paracellular absorption
 - efflux
- discuss the key attributes to be optimised to develop a drug into a medicine.

Questions

1. **Indicate which one of the following statements is not correct:**
 - a. The drug delivery system can play a vital role in controlling the pharmacological effect of the drug.
 - b. The drug delivery system can influence the pharmacokinetic profile of the drug, the rate of drug release, the site and duration of drug action and subsequently the side-effect profile.
 - c. An optimal drug delivery system ensures that the active drug is available at the site of action for the correct time and duration.
 - d. The drug concentration at the appropriate site should be below the minimal effective concentration (MEC).
 - e. The concentration interval between the MEC and the minimal toxic concentration (MTC) is known as the therapeutic range.
2. **Indicate which one of the following statements is not correct:**
 - a. A simple emulsion contains two liquid phases (oil and water).
 - b. In a water-in-oil emulsion, the oil phase is dispersed and the water phase is continuous.
 - c. A simple suspension contains a liquid and a solid phase.
 - d. In a suspension the solid phase is dispersed and the liquid phase is continuous.
 - e. In most multiphase dosage forms one or more phases are dispersed, whilst other phases are continuous.
3. **Indicate which one of the following statements is not correct:**
 - a. Dispersing one phase into the other will lead to a larger interfacial area between the two phases.
 - b. A larger interfacial area between the two phases leads to an increased interfacial free energy, according to the relationship:
 $G_i = A\gamma$.
 - c. In the equation $G_i = A\gamma$, G_i is the interfacial free energy of the system.
 - d. In the equation $G_i = A\gamma$, A is the interfacial area between the dispersed phase and the continuous phase.
 - e. In the equation $G_i = A\gamma$, γ is the surface tension of the continuous phase.
4. **Indicate which one of the following statements is not correct:**
 - a. The most important route of drug administration into the body is through mucosal membranes.
 - b. Mucosal membranes are a stronger barrier to drug uptake than the skin.
 - c. The mucosal membranes of the small intestine are specialised sites for absorption.
 - d. There are many mucosal membranes that can be used for drug administration.

- e. Absorption of drugs through the mucosal membranes of the gastrointestinal tract allows for oral drug delivery.
5. **Indicate which one of the following statements is not correct:**
- a. Drugs that are taken up into the body through the gastrointestinal mucosa will be transported to the liver via the portal vein before going into general circulation.
 - b. If the drug is susceptible to metabolic degradation in the liver, this may considerably enhance the activity of the drug. This phenomenon is known as the hepatic first-pass effect.
 - c. The rectal route may also show varying degrees of the first-pass effect.
 - d. In other routes of administration (intravenous, vaginal, nasal, buccal and sublingual) the drug is distributed in the body before reaching the liver.
 - e. Whilst the liver is the main metabolic organ of the body, metabolism may also take place in the gastrointestinal lumen and indeed in the mucosal membranes.
6. **Indicate which one of the following statements is not correct:**
- a. Many dosage forms are designed to release the drug immediately after administration. This is useful if a fast onset of action is required for therapeutic reasons.
 - b. The onset of action is very fast for intravenous injections and infusions and a pharmacological effect may be seen in a matter of seconds after administration.
 - c. The onset of action is fast for oral delivery of immediate-release dosage forms, such as simple tablets, and a pharmacological effect may be seen in a matter of minutes to hours.
 - d. If the drug has a long biological half-life, the time interval between administrations may be short, requiring frequent dosing and potentially leading to low patient compliance and suboptimal therapeutic outcome.
 - e. Uptake of a drug through the mucosal membranes may be due to passive diffusion or by receptor-mediated active transport mechanisms.
7. **Indicate which one of the following statements is not correct:**
- a. Delayed-release dosage forms can be defined as systems formulated to release the active ingredient at a time other than immediately after administration.
 - b. Colon-specific dosage forms are developed for the treatment of local and systemic diseases in the colon, including colorectal cancer and Crohn's disease.
 - c. In the plasma concentration versus time profile of a delayed-release oral dosage form $C_{\max}$ (but not $T_{\max}$) is strongly dependent on the gastric emptying times.

- d. Delayed-release systems can be used to protect the drug from degradation in the low-pH environment of the stomach.
- e. Delayed-release systems can be used to protect the stomach from irritation by the drug.

8. Indicate which one of the following statements is not correct:

- a. The release kinetics of the drugs from sustained-release matrix systems often follows a first-order kinetics.
- b. The release kinetics of the drugs from sustained-release reservoir systems often follows a zero-order kinetics.
- c. If the release of the drug from the dosage form is sustained such that the release takes place throughout the entire gastrointestinal tract, one can reduce $C_{\max}$ and prolong the time interval of drug concentration in the therapeutic range.
- d. The use of sustained-release dosage forms may reduce the frequency of dosing, for example from three times a day to once a day.
- e. Sustained-release dosage forms can achieve their release characteristics by the use of suitable polymers.

9. Indicate which one of the following statements is not correct:

- a. In contrast to sustained-release forms, controlled-release systems are designed to lead to predictable and constant plasma concentrations, independently of the biological environment of the application site.
- b. Controlled-release systems are controlling the drug concentration in the body, not just the release of the drug from the dosage form.
- c. Controlled-release systems are used in a variety of administration routes, including transdermal, oral and vaginal administration.
- d. In contrast to sustained-release forms, in controlled-release systems the dose is of less importance than the release rate from the therapeutic system.
- e. Controlled-release systems are target-specific, which means they 'exclusively' deliver the drug to the target organ inside the body.

10. Indicate which one of the following statements is not correct:

- a. In drug absorption, passive diffusion involves the diffusion of drugs across the cell membrane and is driven by a concentration gradient, with drugs moving from high to low concentration.
- b. Carrier-mediated transport involves specific carrier proteins present in the cell membranes and can act either with a concentration gradient (facilitated diffusion) or against a concentration gradient (active absorption).
- c. Endocytosis involves internalisation of substances by engulfment by the cell membrane which forms membrane-based vesicles within the cell, known as liposomes.

- d. Some drugs can cross epithelia through gaps between the cells. This route is governed by passive diffusion and small hydrophilic molecules can pass through these gap junctions.
- e. Drugs that are subjected to efflux processes include cytotoxic drugs such as taxol, steroids, immunosuppressants and antibiotics.

Further reading

Pharmaceutical dosage forms

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