

1

Introduction to dosage form design

Learning objectives

Upon completion of this chapter, you should be able to:

- Define dosage form, stability, excipient, pharmaceutical necessity, chemical stability, physical stability, microbiological stability, first pass effect, elimination and excretion.
- List the drug properties that must be considered in dosage form design.
- Describe the qualities that are built into an ideal dosage form/drug delivery system, and identify from a list of ingredients and an ingredient table, how the ingredient contributes to the manageable size of the dosage form, its palatability or comfort, its stability (chemical, microbial, or physical), the convenience of its use or the release of drug from the dosage form.
- List the properties of the routes of administration that must be considered in the design of dosage forms.
- Briefly outline the movement of an orally administered drug from its site of administration through its elimination from the body:
 - administration
 - liberation from the dosage form by (a) dissolution; (b) diffusion
 - absorption
 - distribution
 - metabolism
 - elimination.
- Distinguish between the following patterns of drug release from dosage forms:
 - immediate release
 - delayed release
 - sustained release
 - controlled release.
- Rank the different routes in terms of speed of onset of action.

Introduction

What is pharmaceuticals and why do pharmacists study this subject? Historically pharmacists provided two services in the healthcare system: they extracted drugs from their natural sources and prepared or 'compounded' the drug into a convenient form for patient use, the dosage form.

Extracted from Remington Education: Pharmaceuticals by Shelley Chambers Fox

Currently little dosage form compounding is required of most pharmacists, but the pharmacist in a compounding specialty practice has the need to design dosage forms that are both safe and effective. The pharmacist in charge of an admixture service must develop policies and procedures to ensure the products prepared remain sterile as well as physically and chemically stable. And our most pressing pharmaceutical task is to ensure that patients and caregivers are properly educated in the appropriate use of eye drops and inhalers, injections and transdermal patches such that the drugs contained in these dosage forms will provide the intended benefit. The products of biotechnology for rheumatoid arthritis and multiple sclerosis are injectable dosage forms used primarily by the patient in the home setting. New technologies to deliver drugs through the skin utilize handheld devices for iontophoresis and thermal ablation. Pharmacists serve as the dosage form experts both to other medical personnel and to our patients. The study of pharmaceutics provides the scientific foundation for the design and appropriate use of dosage forms and drug delivery systems.

Definitions

A *dosage form* is the form that we take our drug in – in other words, a tablet, a syrup, an ointment, an injection. The concept of a *drug delivery system* includes products that are designed to provide optimal control over the release of a drug to achieve enhanced safety or efficacy.

This text is about the physicochemical principles of dosage form and drug delivery system design, and the biological environment in which these systems are designed to perform to deliver a drug to its receptors.

Properties of the drug

Key Point

To design a dosage form for a drug, the following properties must be considered: water solubility; $\log P$, a measure of lipophilicity; molecular weight; stability in solution; enzymatic degradation; and location of drug receptors.

Pharmaceutics is a science that applies both drug chemistry and drug biology to the problem of delivering drugs to their target tissues. During the preformulation process, key chemical and physical properties of the drug are studied in order to rationally design a delivery system and predict the fate of the drug *in vivo* after administration. Some aspects of drug chemistry that must be considered in the development of a dosage form include:

- *Water solubility*: The drug must be dissolved in aqueous body fluids before it can cross membranes.
- *Log P*: The drug must have sufficient lipophilicity to cross membranes.
- *Molecular weight*: Large molecular weight drugs have difficulty moving across membranes.
- *Stability in solution*: Drugs may hydrolyze, oxidize, photolyze or otherwise degrade in solution.
- *Enzymatic degradation*: Some drugs may be substantially degraded by enzymes before they reach their target.
- *Location of receptors*: Intracellular drug receptors or receptors in the brain or posterior eye are challenging to target.
- *Selectivity*: Some drugs cause serious toxicity as a result of poor selectivity for their target.

Anticancer drugs are notoriously nonselective in their cytotoxic effects; however, drug delivery systems may be designed to selectively target tumor cells with known biological features. Drug delivery systems can be developed to address the challenges that drugs present: poor solubility, large molecular weight, inaccessible targets and lack of selectivity. Appendix Table A.1 provides an overview of the preferred drug properties for different routes of administration.

Pharmaceutical example

If we consider the opiate pain reliever, oxycodone, its advantages and disadvantages as a drug for administration to the gastrointestinal tract are presented in Table 1.1.

Qualities of the ideal dosage form

Key Point

Pharmaceutical excipients and manufacturing processes are used to prepare dosage forms with the following qualities:

- one dose in a manageable size unit
- palatable or comfortable
- stable chemically, microbiologically and physically
- convenient/easy to use
- release the drug to the receptors in a timely fashion with minimal side effects and for the optimal duration.

Table 1.1 Analysis of oxycodone's physicochemical properties for use by the oral route

Design issue	Drug property	Analysis
Must be dissolved before drug can cross membranes	Water solubility of 100 mg/mL, maximum dose 80 mg	Drug is soluble in the contents of the gastrointestinal tract, even better if the patient takes 250 mL water with the tablet
Must have sufficient lipophilicity to cross membranes	Log <i>P</i> of 0.3 = $\log \frac{[\text{conc}]_{\text{oil}}}{[\text{conc}]_{\text{water}}}$ Antilog(0.3) = 1.995	This drug will favor partitioning into lipid membranes over water by a 2:1 ratio
Large molecular weight drugs have difficulty moving across membranes	Formula weight of 315.37	Based on molecular weight, oxycodone should move easily through membranes
Drugs may hydrolyze, oxidize, photolyze, or otherwise degrade in solution	Stability, solid dosage form, stable to acid	Stability in the dosage form should not be an issue for this drug because it is in a solid dosage form. Stability in stomach acid is not an issue
Some drugs cannot be used by mouth because of substantial losses to enzyme degradation	Metabolized in the liver, 60–80% of the dose is delivered to the systemic circulation	Some drug is lost to enzyme deactivation but most of the drug makes it to the blood
Intracellular drug receptors or receptors in the brain or posterior eye are challenging to target	Receptors are in the brain	Oxycodone's lipophilicity is low for reaching the brain though still within the range. Its size (molecular weight) is within the optimal range
Some drugs cause serious toxicity as a result of poor selectivity of action	Not applicable	

Drugs and their delivery systems manufactured by the pharmaceutical industry or compounded by the pharmacist are prepared according to industry and compendial standards and have been carefully designed with each of the following qualities:

1. *One dose in a manageable size unit*

Dosage forms should be formulated such that the dose is contained in a unit that can be counted or measured by the patient with reasonable accuracy. For example, vehicles such as syrups or water for injection can be used to prepare solution dosage forms in measureable units.

2. *Palatable or comfortable*

Many drugs are bitter or salty, so we add sweeteners and flavors to mask their taste. Parenteral drugs (injections) and drugs for application to mucous membranes must be comfortable enough to prevent tissue damage

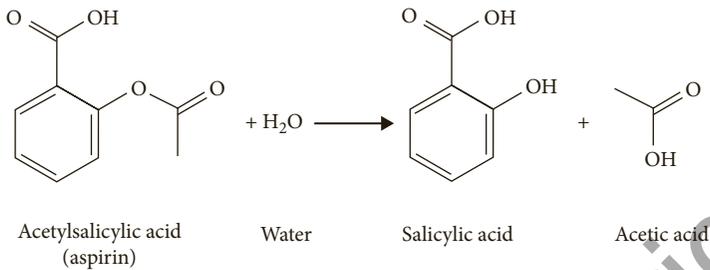


Figure 1.1 Hydrolysis of aspirin

or loss of drug from the site. We add tonicity agents and buffers to make them more comfortable and compatible with body tissues.

3. *Stable*

Stability is defined as the extent to which a product retains the same properties and characteristics that it possessed at the time of its preparation or manufacture. There are three types of stability:

- *Chemical stability*: The drug structure remains the same throughout the shelf life. Drugs in solution are particularly susceptible to chemical reactions that will change their structures (Figure 1.1).
- *Physical stability*: The product retains the original physical characteristics of the dosage form, in particular the initial appearance and uniformity. For example, precipitation may occur in a solution dosage form or a suspended drug may settle and be difficult to redisperse.
- *Microbiological stability*: Requirements will fall into one of two categories: (a) the dosage form must be sterile, or (b) the dosage form must resist microbial growth.

4. *Convenient/easy to use*

Because most drug therapy takes place in the community, the dosage form should be portable and easily carried to work or play activities. The industry has developed a variety of new inhaler products that can be carried in the purse or pocket, as well as injection devices and portable infusion pumps for administration of injections in the community setting.

Drugs that will be used for children or elderly patients should be available in liquid dosage forms that can be easily swallowed.

Protein drugs cannot be formulated as oral dosage forms because they are quickly degraded in the gastrointestinal tract. These medications can be administered as injections but will require special training and patient motivation. Recent research has shown that protein drugs can be delivered via inhalation, and a number of peptide drugs are available as nasal aerosols for systemic absorption.

5. *Release of drug*

To provide a therapeutic response, if the drug is not already in solution in the dosage form, it has to be released for absorption in a timely fashion

with minimal side effects and for the optimal duration. The design of a drug delivery system to control the dissolution or diffusion of a drug allows optimization of how fast, how much and how long the drug moves to the drug target. These designs have produced products that relieve chest pain within minutes or only need to be used once a day, once a week or once a month.

Pharmaceutical necessities

Pharmaceutical necessities are added to the drug and specific manufacturing processes are applied to build these properties into a delivery system.

Definition

Pharmaceutical necessities or *excipients* are non-drug ingredients added to the dosage form to build these properties into a delivery system (Appendix Table A.2).

Examples of pharmaceutical necessities include:

- preservatives
- buffers
- diluents
- solvents
- suspending agents.

In addition, specific manufacturing processes such as particle size reduction or sterilization are applied to provide a dosage form with these five qualities.

Pharmaceutical example

Let's consider these principles as they apply to the design of a tablet containing oxycodone and acetaminophen. This product is commercially available as a prompt release tablet that provides relatively rapid pain relief and must be taken every 4 to 6 hours. If we look at our table of excipients for oral solid dosage forms (Appendix Table A.3), we can identify the category of each of these ingredients in Endocet tablets. And if we think about each one we can see how the ingredient contributes to the qualities that we want to build into our dosage form (Table 1.2).

Table 1.2 Ingredients in immediate release oxycodone and their functions: Endocet (oxycodone and acetaminophen) tablets

Ingredient	Function	Quality
Croscarmellose sodium	Tablet disintegrant	Release: Promotes wicking of water into an oral solid so that it falls apart into particles. This causes the tablet to release drug faster because it exposes more surface to body fluids
Crospovidone	Tablet disintegrant	As above
Microcrystalline cellulose	Tablet binder	Ensures that the tablet remains intact after compression. Maintains one dose in a manageable size unit and physical stability of the tablet.
Povidone	Tablet binder	As above
Pregelatinized corn starch	Tablet binder	As above
Silicon dioxide (colloidal)	Glidant	Physical stability (uniformity of tablets). Improves flow properties and prevents caking of the powder mixture as it moves through tableting equipment so it can be accurately metered into the die and each tablet weighs the same amount and contains the same amount of drug
Stearic acid	Lubricant	Physical stability (uniformity of tablets). Prevents adhesion of the powder to tablet presses so powder can be accurately metered into the equipment and each tablet weighs the same amount and contains the same amount of drug
D&C Yellow No. 10	Dye	Makes the tablet distinctive so that pharmacists do not mistake it for a different product

Properties of the routes of administration

Key Point

Knowledge of each of the following route-related characteristics can be used to predict the rate and extent of drug travel to its target from a dosage form:

- accessibility, permeability and surface area of the absorbing membrane
- nature of the body fluids that bath the absorbing membrane
- retention of dosage form at the absorbing membrane long enough to release its drug
- location of enzymes or extremes of pH that can alter drug chemical structure before it is distributed to its target
- rate and extent of blood flow to the absorbing membrane and the distribution time from it.

To design a drug delivery system the pharmacist must apply an understanding of drug chemistry to the preparation of a product that will deliver the drug from the site of administration to the site of its activity. This requires an appreciation of drug travel in the body and the challenges and opportunities presented by the different routes of drug administration. To design dosage forms, recommend drug therapy or doses for a particular route of administration there are several key concepts to take away about each route:

- location and accessibility of the absorbing membrane – will the dosage form need to travel to reach it?
- permeability of the absorptive surface based on the number of layers and type of epithelial membrane
- the surface area of the absorbing membrane and the nature of the body fluids that bath it
- retention of the dosage form at the absorbing membrane long enough to release its drug
- enzymes or extremes of pH that can alter its chemical structure encountered by the drug before it is distributed to its target
- rate and extent of blood flow to the absorbing membrane and the distribution time from it.

Routes of administration

The routes by which we administer drugs can be divided into those that produce systemic drug effects and those that are site-specific (Tables 1.3 and 1.4).

Table 1.3 Systemic routes of administration

Route	Dosage forms – drug delivery systems	Administration	Absorbing membrane	Onset
Intravenous route	Aqueous solutions, emulsions	Places drug solution directly in a vein	Capillaries in target tissue	Within 60s
Intramuscular route	Aqueous solutions, oily solutions, suspensions	Places drug into one of the larger muscles: deltoid, vastus lateralis or gluteals	Capillaries in muscle and target tissue	15–30 minutes for aqueous solutions
Subcutaneous route	Aqueous solutions, suspensions, implants	Places drug under the layers of the skin	Capillaries in muscle and target tissue	15–60 minutes for aqueous solutions
Sublingual	Tablets, solutions, aerosols	Placed under the tongue	Sublingual mucosa	1–3 minutes
Buccal	Tablets, lozenges, chewing gum	Placed between the cheek and gum	Buccal mucosa	2–3 minutes
Oral	Tablets, solutions, suspensions	Swallowed	Mucosa of the small intestine	30–60 minutes for immediate release dosage forms
Rectal	Suppositories, ointments, creams, solutions, suspensions, foams	Placed in the rectal cavity	Rectal mucosa	30–60 minutes
Vaginal	Suppositories, creams, gels, tablets, rings	Placed in the vaginal cavity	Vaginal mucosa	Slow for systemic effects
Skin (trandermal)	Patches, ointments, gels	Applied to thinner skin surfaces (trunk, upper arm, abdomen)	Stratum corneum	1–4 hours
Nose	Aerosolized solutions or suspensions	Applied to the anterior turbinate area	Respiratory or olfactory mucosa	Within 10 minutes
Lung	Aerosolized solutions, suspensions or powders	Inhaled to bronchiolar and alveolar epithelia	Respiratory mucosa	Within 5 minutes

Table 1.4 Local routes of administration

Route	Dosage forms – drug delivery systems	Administration	Absorbing membrane	Onset
Buccal	Solutions, suspensions, lozenges	Applied to the mucosa of the oral cavity	Oral mucosa	Rapid for local effects
Rectal	Suppositories, ointments, creams, solutions, suspensions, foams	Placed in the rectal cavity	Rectal mucosa	Rapid for local effects
Vaginal	Suppositories, creams, gels, tablets, rings	Placed in the vaginal cavity	Vaginal mucosa	Rapid for local effects
Skin (local)	Ointments, creams, gels, lotions, aerosols, powders	Applied to the affected skin surface	Stratum corneum	Rapid for local effects
Eye (anterior segment)	Solutions, suspensions, ointments, gels, inserts	Applied to the conjunctival sac	Cornea, sclera	Within 10 minutes
Eye (posterior segment)	Solutions, suspensions, inserts	Injected into the vitreous humor	Retina	Varies by dosage form
Nose	Solutions, suspensions, aerosols	Applied to the anterior turbinate area	Respiratory mucosa	Rapid
Lung	Aerosolized solutions, suspensions or powders	Inhaled to bronchiolar and alveolar epithelia	Respiratory mucosa	Within 5 minutes

Definitions

- *Systemic drug administration* means that the drug is carried from the site of administration to a site of activity elsewhere and potentially exposes all body tissues to drug.
- *Site-specific drug administration* means that the drug is administered to the tissue in need of drug therapy (also known as local drug therapy) or is targeted to a particular site by specific interactions with that site, for example, by binding a cell-associated antigen or selective activation in the target cell.

Table 1.5 Onset and duration of anti-anginal effects of nitroglycerin from various dosage forms and routes

Route and dosage form	Onset	Duration
Sublingual tablet or spray	2 minutes	30 minutes
Buccal extended release tablet	2–3 minutes	3–5 hours
Oral extended release tablet	1 hour	Up to 12 hours
Intravenous solution (push)	1–2 minutes	3–5 minutes
Transdermal ointment	30 minutes	3 hours
Transdermal patch	60 minutes	12 hours

Table 1.5 illustrates how fast and how long a patient would experience the anti-anginal effects of nitroglycerin from various dosage forms and routes of administration.

Parenteral routes

Definition

- *Parenteral* means ‘other than enteral (by mouth)’ and is generally intended to mean the routes by which we inject drugs.

All drug products used by parenteral routes must be sterile and those products that will be used for multiple doses must also resist microbial growth.

The most commonly used parenteral routes are intravenous, intramuscular and subcutaneous. These routes can be used for drugs that would be destroyed by gastrointestinal acid and enzymes and to delay exposure to liver enzymes.

- The response to drug therapy by the intravenous route is generally rapid and predictable because there is no absorption step.
- Because subcutaneous injections are relatively easy to give, this route is usually chosen for drugs that require outpatient, parenteral therapy.

Enteral routes

The enteral routes include application to the oral cavity, oral dosage forms that are swallowed and administration to the rectum.

The preferred enteral route from the standpoint of ease of use is to swallow a dosage form for absorption into the blood supply of the small intestine. Although convenient and easy to explain to patients, this route

provides slower and less predictable onset than the parenteral routes or administration of drug to the oral cavity.

The loss of active drug as it encounters the extremely low pH of the stomach, the array of enzymes in the small intestine and the liver is termed the *first pass effect*.

Rectal and vaginal routes

The rectal and vaginal routes are safe and technically simple but are not often preferred. They can be used for the administration of local or systemic medications.

Drugs applied to the skin

Drugs may be applied to the skin for local or systemic absorption.

- When intended for local effects, the response to an applied drug is usually rapid and confined to the area of application.
- Drugs applied transdermally are intended to penetrate all layers of the skin and circulate from the dermal vasculature in sufficient concentration to provide systemic effects.
- The transdermal route provides safe and convenient drug therapy of long duration.

Inhalation routes: nasal and lung

Drugs administered to the lungs must be provided in finely divided aerosol dosage form in order to travel through the branches and turns of the airways to reach the lower respiratory tract.

- The lungs provide a very large surface resulting in reproducible and rapid absorption.
- If the dose is sufficiently small, the effect of the drug may be confined to the lungs.
- Drug administered to the lungs can effectively provide systemic treatment if the dose is properly titrated.

Liberation, absorption, distribution, metabolism and elimination (LADME)

The application of a drug at the site of administration is only the start of its journey to its target tissues. The drug must be liberated from the dosage form, absorbed, and distributed to the site of action. At the same time that it is distributed to its receptor, the drug is delivered to the metabolic enzymes of the liver and filtered through the kidneys into the urine. The termination of

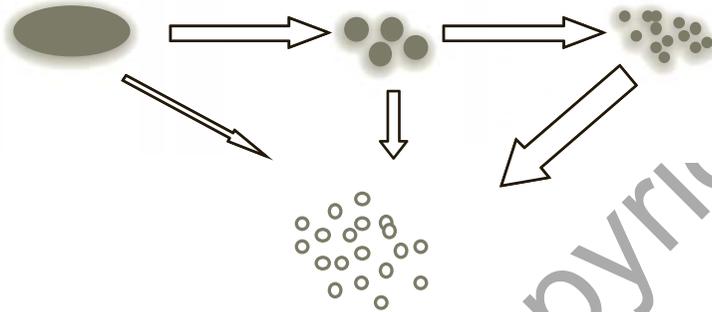


Figure 1.2 Drug dissolution from oral solid dosage form

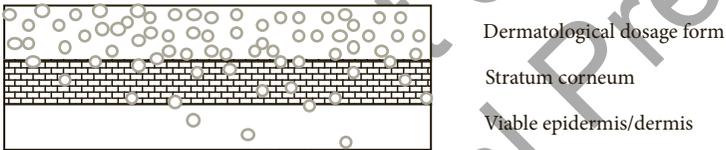


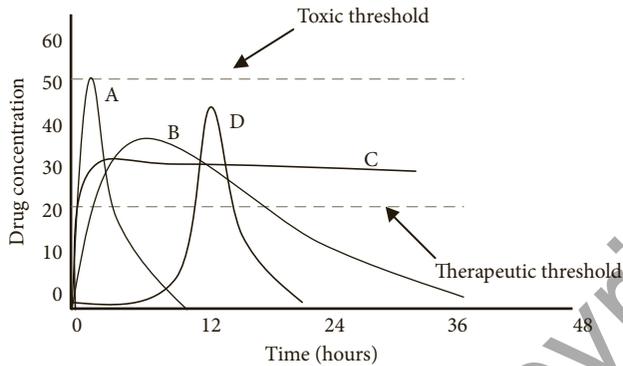
Figure 1.3 Drug diffusion from a topical dosage form

drug action through these latter two processes may be inconveniently rapid, requiring the patient to take a dose of drug frequently to sustain its effect. Advances in dosage form design based on knowledge of the biological fate of drugs have produced drug delivery systems optimized to the drug's therapeutic purpose and elimination rate.

Drug liberation

After administration, if the drug is not in an aqueous solution, it is released or liberated from the dosage form by either dissolution or diffusion or a combination of both processes.

- *Dissolution:* If the drug is administered in the form of an immediate release tablet, the tablet disintegrates into large granules in the fluids of the stomach, which in turn come apart into fine particles and finally result in the drug in solution (Figure 1.2).
- *Diffusion:* A drug administered as a transdermal patch must diffuse from an area of high concentration (the patch) to an area of low concentration (the skin) where it is dissolved in the lipid or water content of the skin (Figure 1.3).



Key:
 A Immediate release
 B Sustained release
 C Controlled release
 D Delayed release

Figure 1.4 Drug release and absorption patterns

Drug absorption and patterns of drug release

Drug absorption occurs when the dissolved drug moves across the epithelial barriers it encounters and into the blood stream.

The step that is slowest (liberation or absorption) will determine the rate of drug appearance in the blood stream.

Broadly speaking we see four different patterns of drug absorption that are a result of the release design of the dosage form and the body's handling of the drug (Figure 1.4).

- *Immediate release* is characterized by a rapid rise in blood levels of the drug followed by a decline determined by the ability of the body to eliminate the drug.
- *Delayed release*, as the name implies, delays the appearance of the drug in the blood until the dosage form reaches a certain compartment of the gastrointestinal tract, where it is able to dissolve and release medication.
- *Sustained release* is characterized by a slow rise in drug concentrations in the blood, followed by a slow decline that provides therapeutic amounts long enough to reduce the frequency of administration compared with an immediate release dosage form.
- *Controlled release* is an absorption pattern with a slow rise in drug concentrations to a level that remains constant for a predictable interval.

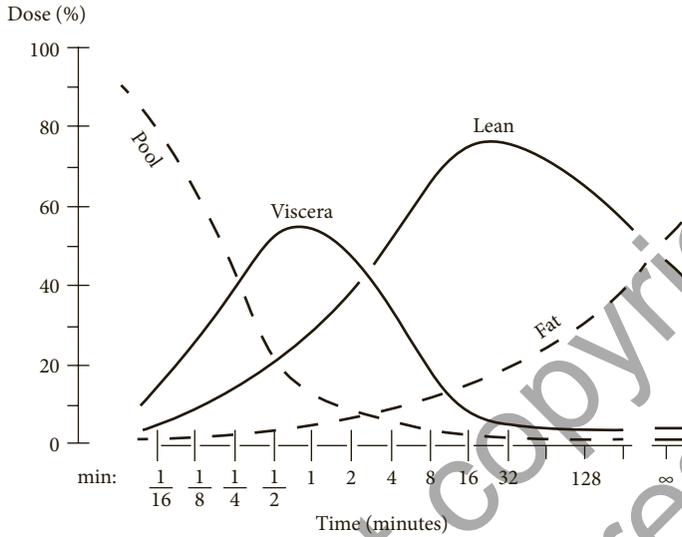


Figure 1.5 Blood flow primacy to the organs and tissues. (Reproduced with permission from selected reading 6)

Drug distribution

The drug is distributed primarily by transport with blood or lymph to the tissues, broadly speaking in order of their perfusion primacy (Figure 1.5, Table 1.6).

Some tissues are less accessible to drugs than others because of the reduced permeability of capillary endothelia in the retina, brain, spinal cord and enteric nervous system. The blood–brain barrier is one that is of great importance to drug development, in that many effects and side effects of drugs are mediated through receptors in the brain.

Drug elimination

The activity of a drug is terminated by its *elimination* either as intact drug via body wastes or by metabolic transformation to an inactive compound.

- *Excretion*, or the removal of intact drug, occurs through the kidneys into urine for water soluble drugs, the bile into feces for amphiphilic drugs and the lungs via expired air.
- Drug-metabolizing enzymes can be found in many tissues though the most significant populations are in liver, kidneys and intestine. These proteins catalyze reactions that transform fat soluble drugs into more water soluble forms or add large moieties such as amino acids to make an amphiphilic metabolite. These changes in drug structure facilitate the final elimination of the drug metabolite through urine or feces.

Extracted from Remington Education: Pharmaceutics by Shelley Chambers Fox

Table 1.6 Blood flow to body organs

Fluid compartment	Tissues	Flow rate per 100 g tissues	Time to complete drug distribution
Well perfused viscera	Brain, lungs, heart, liver, kidneys, adrenal, thyroid, gastrointestinal tract	50–400 mL/minute per 100 g tissue	<2 minutes
Intermediate perfusion: lean tissue	Muscle, skin, red marrow, non-fat subcutaneous tissue	5–12 mL/minute per 100 g tissue	60–90 minutes
Poorly perfused: fat	Adipose tissue, fatty marrow, bone cortex	1–3 mL/minute per 100 g tissue	300 minutes

Table 1.7 Characteristics of the oral (to small intestine) route

Questions	Answer	Challenge or opportunity?
What is the membrane that will absorb the drug from this route and how accessible is it?	Drug is absorbed through the small intestinal epithelium. The dosage form must be swallowed and be emptied from the stomach before absorption starts	Challenge
Is the absorbing membrane single or multiple layers and how permeable is it?	Single, excellent permeability	Opportunity
How large is its surface?	Large, 100 m ²	Opportunity
What is the nature of the body fluids that bathe the absorbing membrane?	Small intestinal fluids: pH 5.0–7.0, relatively large volume	Opportunity
Will the dosage form remain at the absorbing membrane long enough to release its drug?	Usually but not always. Some drugs are absorbed in a small window of the small intestine and are not completely released by the time they move	Neither
Will the drug encounter enzymes or extremes of pH that can alter its chemical structure before it is distributed to its target?	Yes, extremely low pH in the stomach, lots of enzymes: peptidases, esterases, cytochrome P450	Challenge
What is the blood flow primary to the absorbing membrane and the distribution time from it?	Highly perfused <2 minutes	Opportunity

Pharmaceutical example

Let's consider these characteristics of the route of administration and travel to the drug receptor as they apply to the design of our tablet containing oxycodone and acetaminophen. Think about what you know about the anatomy and physiology of the gastrointestinal tract as it applies to each of the route-related characteristics for dosage form design and whether the characteristic represents a challenge or an opportunity for drug delivery (Table 1.7).

Questions and cases

- A pharmaceutical necessity is:
 - The active ingredient
 - An ingredient required by the Food and Drug Administration
 - An ingredient that enhances the size, stability, palatability or release of a drug
 - An ingredient that prevents drug elimination
- Syrup dosage forms must be:
 - Sterile
 - Resistant to microbial growth
 - Sterile and resistant to microbial growth
 - Prepared as powders for reconstitution just prior to use
- Liberation from a dosage form refers to:
 - Movement of the drug across the epithelial barriers it encounters and into the blood stream
 - The application of a dosage form to an absorptive site
 - Movement of the drug from interaction with elements of the dosage form to interaction with molecules of biological fluid
 - Termination of drug activity
- Which of the following drugs is likely to move through membranes most rapidly?
 - Levodopa, $\log P -1.8$, molecular weight (MW) 197
 - Amphotericin, $\log P 0.8$, MW 924
 - Citalopram, $\log P 3.5$, MW 324
 - Amikacin, $\log P -7.4$, MW 585
- A patient has a prescription for ondansetron orally disintegrating tablets. The reason that the drug may be prepared in this dosage form includes:
 - Need for rapid absorption
 - Need for infrequent administration
 - Need to avoid first pass metabolism
 - Need to avoid renal excretion
 - Need to administer a small dose
- Oxytocin is a peptide drug containing nine amino acids. Because oxytocin increases trust and bonding behaviors and reduces fear, there is interest in using the drug to treat children with autism. Which of the following formulation approaches would be useful to prevent oxytocin's destruction by gastrointestinal peptidases?

- (a) Preparation as an oral suspension
 - (b) Preparation as an extended release tablet
 - (c) Preparation as a buffered solution
 - (d) Preparation as a buccal tablet
7. The lactam ring in penicillin G is hydrolyzed in solution. This is an example of:
- (a) Poor water solubility
 - (b) Formation of a precipitate
 - (c) Physical instability
 - (d) Chemical instability
 - (e) Microbial instability
8. After application to the affected area of skin, fluticasone moves out of the cream dosage form and into the skin. The mechanism of release of fluticasone from the cream can be described as:
- (a) Distribution
 - (b) Dissolution
 - (c) Diffusion
 - (d) Disintegration
9. The pattern of drug absorption characterized by a slow rise in drug levels in the blood followed by a slow decline is termed:
- (a) Immediate release
 - (b) Delayed release
 - (c) Sustained release
 - (d) Controlled release
10. The correct ranking of routes of administration in terms of fastest speed of onset to slowest speed of onset of action is:
- (a) Sublingual, oral, intravenous, transdermal
 - (b) Transdermal oral, sublingual, intravenous
 - (c) Intravenous, sublingual, oral, transdermal
 - (d) Intravenous, oral, sublingual, transdermal
11. Research the chemical and biological properties of the following drugs using Drugbank (<http://www.drugbank.ca/>) or another drug database: ibuprofen, amoxicillin, and lidocaine. Chemical stability information is available in the American Hospital Formulary Service Drug Information. What challenges do these drugs present to the formulator in terms of dissolution in body fluids, movement through membranes, stability in dosage forms, loss of drug due to metabolism, access to receptors, or selectivity of the target?

Ibuprofen

Design issue

Drug must be dissolved before it can cross membranes

Drug must have sufficient lipophilicity to cross membranes

Drug property

Analysis

Design issue	Drug property	Analysis
Large molecular weight drugs have difficulty moving across membranes		
Drugs may hydrolyze, oxidize, photolyze or otherwise degrade in solution		
Some drugs may be substantially degraded by enzymes before they reach their target		
Intracellular drug receptors or receptors in the brain or posterior eye are challenging to target		
Some drugs cause serious toxicity as a result of poor selectivity of drug action		

Amoxicillin

Design issue	Drug property	Analysis
Drug must be dissolved before it can cross membranes		
Drug must have sufficient lipophilicity to cross membranes		
Large molecular weight drugs have difficulty moving across membranes		
Drugs may hydrolyze, oxidize, photolyze or otherwise degrade in solution		
Some drugs cannot be used by mouth because of substantial losses to enzyme degradation		
Intracellular drug receptors or receptors in the brain or posterior eye are challenging to target		
Some drugs cause serious toxicity as a result of poor selectivity of drug action		

12. Research the inactive ingredients in the following dosage forms. Determine the function of the excipients using Appendix Table A.2. Categorize them as contributing to the manageable size of the dosage form, its palatability or comfort, its stability (chemical, microbial, or physical), and the convenience of its use or the release of drug from the dosage form. Note that ingredients may be included in many dosage forms for more than one purpose.

Adrenaline chloride injection multidose vial (King, other manufacturers)

Ingredient	Category	Function
Sodium bisulfate		
Chlorobutanol		
Water for injection		

Lumigan (bimatoprost) ophthalmic solution

Ingredient	Category	Purpose
Benzalkonium chloride		
Sodium chloride		
Dibasic sodium phosphate		
Citric acid		
Purified water		

Donepezil orally disintegrating tablet (Zydus)

Ingredient	Category	Purpose
Crospovidone		
Magnasweet		
Magnesium stearate		
Mannitol		
Silicon dioxide (colloidal)		
Sucralose		

Depakene (valproic acid) oral solution

Ingredient	Category	Purpose
Cherry flavor		
FD&C Red No. 40		
Glycerin		
Methyl and propyl parabens		

Ingredient	Category	Purpose
Sorbitol		
Purified water		
Sucrose		

- 13.** Discuss the following route of administration with a group of classmates. From what you know about anatomy and physiology, determine the answer to the questions below about the route. Do you think the characteristic represents a challenge or an opportunity for drug delivery? (You may conclude that it is neither or equivocal.) Appendix Table A.4 has some data that may be helpful.

Skin (local treatment) route

Questions	Answer	Challenge or opportunity?
What is the membrane that will absorb the drug from this route and how accessible is it?		
Is the absorbing membrane single or multiple layers and how permeable is it?		
How large is its surface?		
What is the nature of the body fluids that bath the absorbing membrane?		
Will the dosage form remain at the absorbing membrane long enough to release its drug?		
Will the drug encounter enzymes or extremes of pH that can alter its chemical structure before it is distributed to its target?		
What is the blood flow primacy to the absorbing membrane and the distribution time from it?		

Selected reading

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