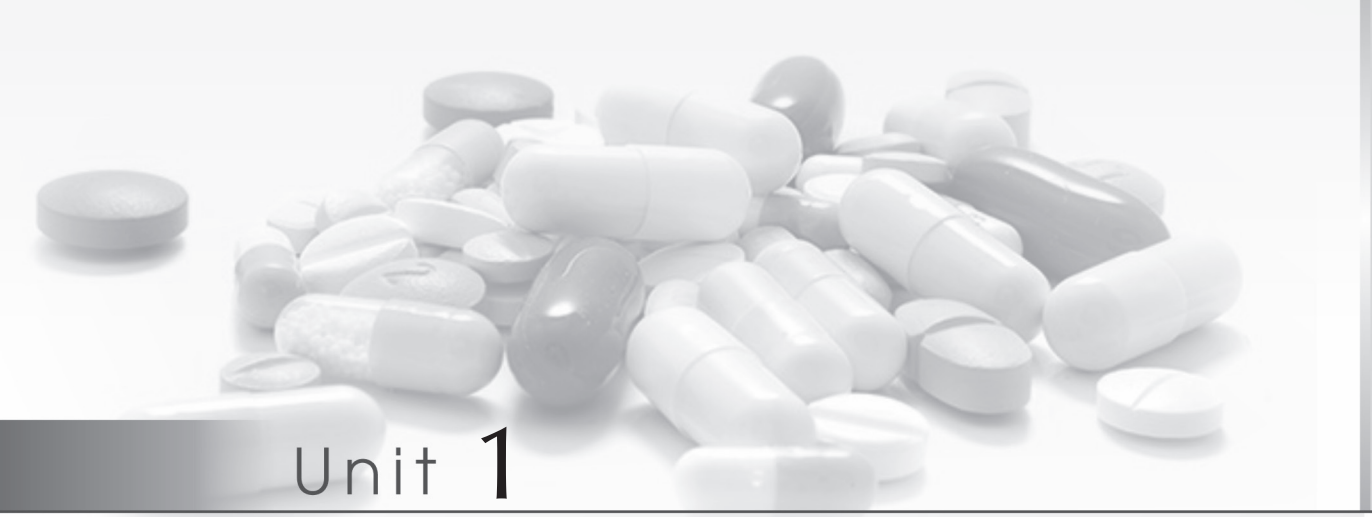

Unit 1

Absorption and Distribution

Chapter
1

Absorption

1.1 INTRODUCTION

If we go with the dictionary meaning, "Biopharmaceutics is the study of the chemical and physical properties of drugs and the biological effects they produce". Biopharmaceutics can be defined as the study of the physical and chemical properties of drugs and their proper dosage as related to the onset, duration, and intensity of drug action or as the study of the effects of physicochemical properties of the drug and the drug product, *in vitro*, on the bioavailability of the drug, *in vivo*, to produce a desired therapeutic effect. All the definitions imply the relationship between the physicochemical properties of the drug, the drug's biological fate in the body after its administration, and the resulting pharmacological action of the drug.

Biopharmaceutics is related to four processes. These are: Absorption, distribution, metabolism and excretion.

Pharmacokinetics is the study and characterization of time course of drug absorption, distribution, metabolism and excretion.

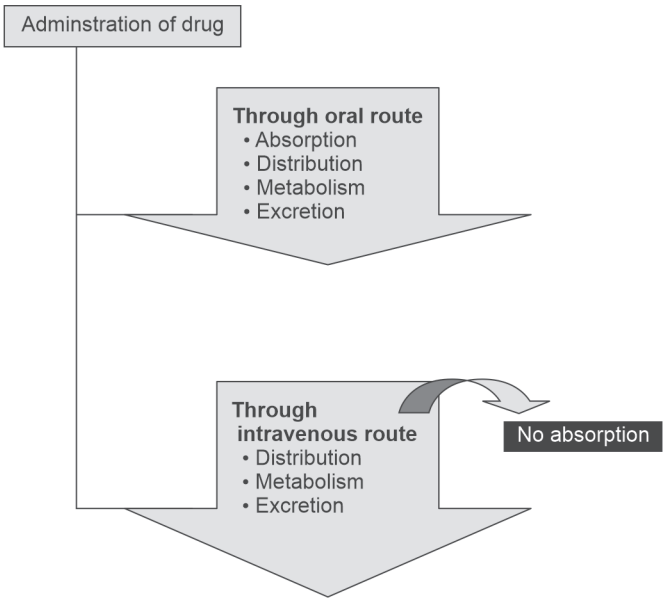

Fig. 1.1: Absorption, distribution, metabolism and excretion (ADME)

Absorption

The pharmacologic response of a drug majorly depends upon two pharmacokinetic processes. These are: Drug absorption and drug distribution. Drug absorption refers to the passage of drug molecules from the site of administration into the circulation. Drug absorption requires that drugs cross one or more layers of cells and cell membranes.

1.2 MECHANISM OF DRUG ABSORPTION

There are three mechanisms by which absorption occurs: (i) Transcellular or intracellular transport, (ii) Paracellular or intercellular transport, and (iii) Vesicular transport or endocytosis.

i. **Transcellular/Intracellular Transport:** It is defined as the passage of drugs across the GI epithelium. It is the most common pathway for drug transport.
ii. **Paracellular/Intercellular Transport:** It is defined as the transport of drugs through the junctions between the GI epithelial cells. This pathway is of minor importance in drug absorption.
iii. **Vesicular or Corpuscular Transport (Endocytosis):** It is also energy dependent processes but involves transport of substances within vesicles into a cell. Since the mechanism involves transport across the cell membrane, the process can also be classified as transcellular.

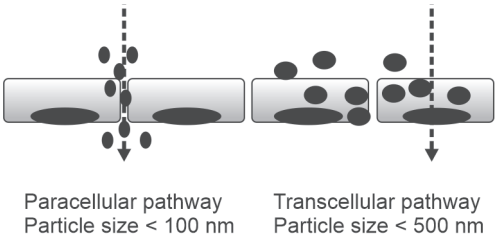

Fig. 1.2: Paracellular and transcellular pathway

Mechanism of Drug Absorption

There are several mechanisms through which drug absorption occurs. These are as follows:

1. Passive diffusion
2. Pore transport
3. Ion pair transport
4. Carrier mediated transport
5. Endocytosis

1. **PASSIVE DIFFUSION:** Drug molecule diffuse from a region of higher concentration to region of lower concentration until equilibrium is attained. It is a major and non-ionic diffusion process for absorption of more than 90% of drugs. The concentration gradient act as a driving force. Drug movement is the result of kinetic energy of molecules Fick's first law of diffusion:

$$\frac{dQ}{dt} = \frac{\mathrm{DAK}_{\frac{m}{w}}}{h}(C_{\mathrm{GIT}} - C)$$

where, dQ/dt = rate of drug diffusion (amount/time)
D = diffusion coefficient of the drug

A = surface area of the absorbing membrane for drug diffusion

$K_{m/w}$ = partition coefficient of drug between the lipoidal membrane and the aqueous GI fluids

$(C_{GIT} - C)$ = difference in the concentration of drug in the GI fluids and the plasma (concentration gradient)

h = thickness of the membrane

Passive diffusion is an energy independent process. The rate of passive diffusion is inversely proportional to the thickness of cell membrane

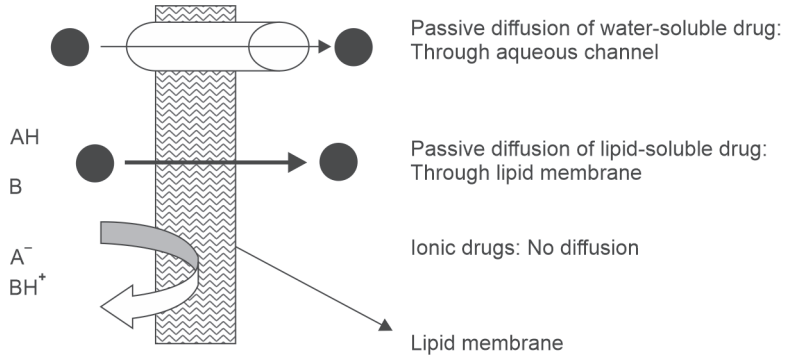

Fig. 1.3: Passive diffusion

Passive diffusion of lipid drugs: Lipid drugs are absorbed by transcellular mechanism, where the drug distributes into the lipid core of the membrane which diffuses into the other side of the membrane. The solute may also diffuse across the cell membrane and enter into the circulation.

Passive diffusion of water-soluble drugs: Another mechanism is the paracellular absorption. The aqueous-filled pores in between the cells aid absorption of the drugs. Water-soluble drugs are readily absorbed, but the molecule size of the particle plays an important role.

Passive transport has following characteristics:

- Energy independent
- No carrier involved
- Along the concentration gradient
- No saturation kinetics: As there are no carriers involved unlike active transport so, no saturation kinetics.

2. **PORE TRANSPORT:** It is also called convective transport, bulk flow or filtration and occurs through the protein channel present in the cell membrane. The hydrostatic or osmotic pressure differences across the membrane act as driving force for pore transport.

3. **ION PAIR TRANSPORT:** It is the main mechanism of drug absorption for absorption of the compounds that ionizes at all pH values, e.g. quaternary ammonium.

4. **CARRIER-MEDIATED TRANSPORT:** It involves a carrier which binds to the solute molecules and forms a solute-carrier. It is a reversible process. This molecule transverse across the membrane to the other side and dissociates, yielding the solute

molecule. The carrier then returns to the original site to accept a new molecule. There are two type of carrier mediated transport system.

- Facilitated diffusion
- Active transport

Facilitated diffusion: Facilitated diffusion is a form of carrier transport that does not require the expenditure of cellular energy. Carriers are numerous in number and are found dissolved in cell membrane. The driving force is concentration gradient, particles move from a region of high concentration to the low conc. The transport is aided by integral membrane proteins. Facilitated diffusion mediates the absorption of some simple sugars, steroids, amino acids and pyrimidines from the small intestine and their subsequent transfer across cell membranes.

Active transport: It is characterized by the transport of drug against concentration gradient with using energy. The energy is provided by hydrolysis of ATP for transportation, e.g. absorption of glucose.

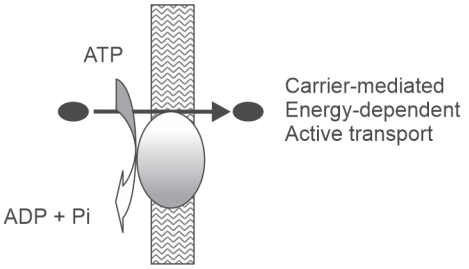

Fig. 1.4: Active transport

5. ENDOCYTOSIS: Endocytosis (Endo: Inside, Cytosis: Cell) is an energy-using process by which cells absorb molecules (such as proteins) by consuming them. It is used by large polar molecules that cannot pass through the hydrophobic plasma or cell membrane. It is a process in which cell absorbs molecules by engulfing them. It is Also termed as vesicular transport. It is a minor transport mechanism involving engulfing extracellular materials within segment of cell membrane to form a saccule or vesicle then pinched of intracellularly.

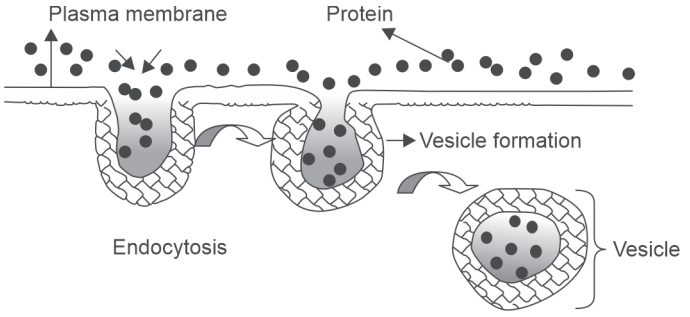

Fig. 1.5: Endocytosis

It occurs by three mechanisms:

1. Phagocytosis
2. Pinocytosis
3. Transcytosis

1. **Phagocytosis (cell eating):** It is adsorptive uptake of solid particulates
2. **Pinocytosis:** It is a form of endocytosis in which small particles are brought to the cell, forming an invagination. This process is important in the absorption of oil soluble vitamins and in the uptake of nutrients
3. **Transcytosis:** It is the process through which various macromolecules are transferred across the cell membrane. They are captured in vesicles, on one side of the cell and the endocytic vesicle is transferred from one extracellular compartment to another. Generally used for the transfer of IgA and insulin.

1.3 FACTORS INFLUENCING DRUG ABSORPTION

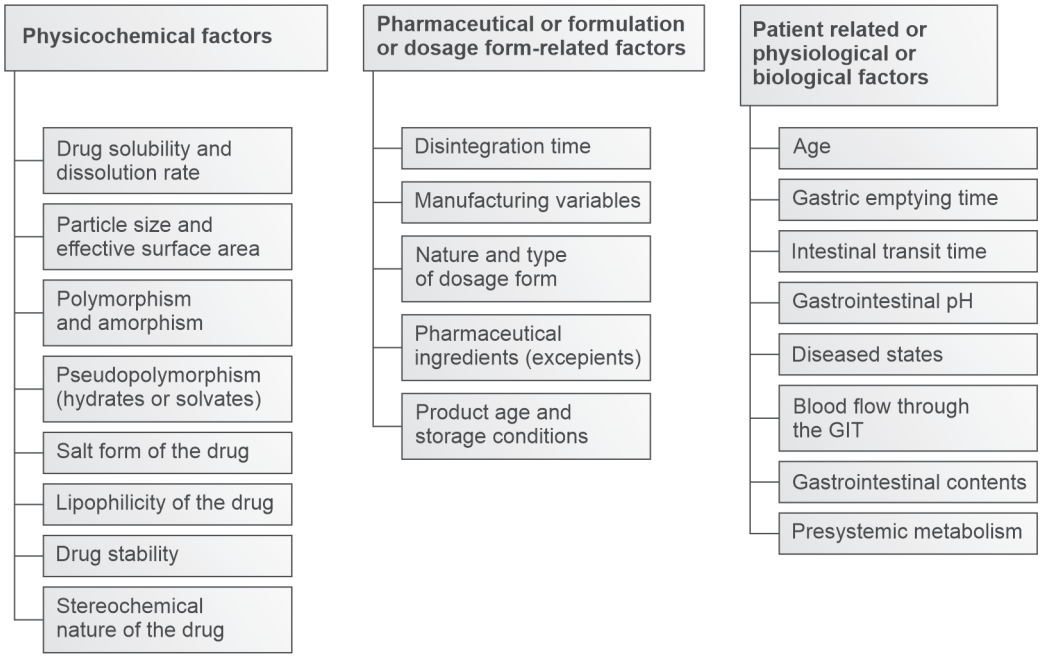

Fig. 1.6: Factors influencing the drug absorption

1. Physiochemical Properties of Drug Substances

a. **Drug solubility and dissolution rate:** The dissolution rate (e.g. in griseofulvin) and drug permeation rate (e.g. in neomycin) through the cell membrane is the rate limiting step in absorption of drugs administered through oral route. The drug will be absorbed in the form of aqueous solution. More the aqueous solubility and the dissolution rate more will be its absorption.

b. **Particle size and effective surface area:** The most effective way of increasing absorption is to reduce the particle size. Smaller the particle size greater will be the effective surface area and more contact between drug particle and aqueous solution, finally results in high dissolution rate and absorption, e.g. in case of drugs like digoxin, tolbutamide, and *bis*-hydroxycoumarin aqueous solubility can be increased by particle size reduction.

c. **Polymorphism and amorphism:** Substances may exist in different polymorphic forms. Every polymorphic form has different physical properties.

Table 1.1: Different properties of different polymorphic forms of a substance

Stable form	Metastable form	Amorphous form	Crystalline form
• High melting point • Dissolution rate limited • Less aqueous soluble	• Low melting point • Higher aqueous solubility • Better bioavailability • Better absorption	• More soluble • Good absorption • Rapidly dissolving	• Less soluble • Non-significant absorption • Slower dissolving

d. **Solvates/hydrates:** The crystals of drug may have one or more solvent molecule. This is known as solvates of the respective drug. The present of solvent (mainly water) in the drug crystal reduces its tendency to attract more water to start dissolution process. So, solvated/hydrated drug crystals are slower dissolving than anhydrous forms. For example, noticeable difference between dissolution rate of caffeine, ampicillin, theophylline, etc.

e. **Salt form of drug or prodrug:** Most drugs are either weak acid or weak base, by making salt solubility, dissolution rate and stability of the drug can be increased. For example, telmisartan sodium has much higher solubility than telmisartan. Enalapril sodium has better stability than enalapril. Similarly, by making prodrug, drug solubility, lipophilicity and stability can be altered.

f. **Lipophilicity of drug:** Absorption membrane is made up of lipids, thus if drug has higher affinity with lipid, it will have higher permeability.

g. **Drug pKa and pH:** Different drugs are either acidic or basic and are present in ionized or unionized form, which is given by their pKa values. In the body, the ratio of the ionized and unionized forms depends on the pH of the medium. Acidic drugs are unionized in the acidic medium and basic drugs are unionized in the basic medium. Acidic drugs are better absorbed from the acidic compartment. Acidic pH favours acidic drug absorption while basic pH is better for basic drugs.

h. **Stability of drug:** Stability of the tablet determines the dispersion rate of the drug, and therefore the rate of absorption.

2. Pharmaceutical Factors

a. **Disintegration time:** Frequent and rapid disintegration results in rapid absorption. So, lower the disintegration time higher will be the dissolution rate. the disintegration time of the drug can be altered as per the requirement by altering amount of binder and compression force.

b. **Manufacturing variables:** Critical manufacturing process parameters like granulation, milling, tablet compression and intensity of packing in capsule has impact on critical attributes of the product like disintegration and dissolution, which eventually has impact on absorption. For example, wet granulation method and APOC (agglomerative phase of communition) method results in formation of tablet having high dissolution rate, high compression force results in increase in hardness of tablet and hence more disintegration time but it also results in particle size reduction which increases dissolution rate and absorption.

c. **Nature and type of dosage form:** Different dosage forms have different dissolution rate.

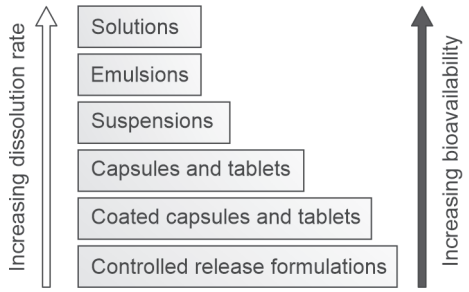

Fig. 1.7: Dissolution rate and bioavailability of different dosage forms

d. **Pharmaceutical ingredients:** Various excipients in the formulation based on their functionality, have impact on drug solubility, stability, strength of the granules and tablets, wet ability and release of the drug from the dosage form. Hence, they play a critical role in drug absorption.

Table 1.2: Impact of different excipients on absorption of drug

Few basic Excipients Category	Impact
Binder	Increase strength of granules and tablets.
Disintegrant	Increase disintegration and decrease disintegration time
Soluble diluent	Provide bulk and help to increase solubility
Solubilizing agent	Increase solubility
Sustain release polymer	Retard release of drug from dosage form
Delay release polymer	Prevent release of drug in stomach
Lubricant	If hydrophobic, can impact dissolution.
Buffers	Provide microenvironment pH, which can impact solubility and eventually bioavailability.
Colorant	Addition of water-soluble dye can have inhibitory effect on dissolution rate of crystalline drugs.
Viscosity agent	Retard GI transit of the drug by acting as a mechanical barrier to the diffusion of drug.
Bile salts	May act as absorption enhancers because of their ability to increase lipid absorption

e. **Product age and storage conditions:** There are times, when product disintegration and dissolution get impacted due to storage conditions thus, can have impact on absorption of drug.

3. Patient Related Factors Affecting Drug Absorption

In vivo drug release from oral drug formulations and absorption may be affected by a number of physiological factors including:

a. Volume and composition of gastrointestinal (GI) fluids
b. pH and buffer capacity of GI fluids and digestive enzymes
c. Contraction patterns
d. Bacterial flora in the gut
e. GI transit time and GI emptying time

f. Presence of cellular transporters
g. Metabolic enzymes
h. Blood flow through the GIT

Several of the above factors are affected by age, pathological state (disease), intake of food. The effects of food on the physiology, and consequently the *in vivo* drug release and absorption, are most pronounced in the stomach. In fact, even co-administration of water with a dosage form may influence the conditions in the stomach as a result of dilution effects. The food effects become less significant further down the GI tract but should not be disregarded.

Gastrointestinal tract

The gastrointestinal tract (GIT) has number of components. Their primary functions are secretion, digestion and absorption. The main functional components of GIT are stomach, small intestine (duodenum, jejunum and ileum) and large intestine (colon). These are differed from each other in terms of functions, anatomy, secretions and pH.

Gastric emptying can be defined as the passage from stomach to the small intestine, called gastric emptying, it can be a rate-limiting step in drug absorption because the intestine is major site of drug absorption.

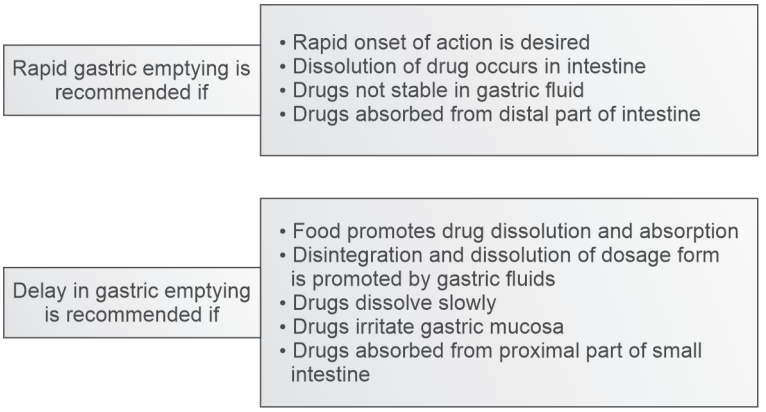

Fig. 1.8: Gastric emptying and its effect on absorption rate of drug

1.4 DRUG ABSORPTION FROM ALL NON-ORAL EXTRAVASCULAR SITES

Drug absorption from non-oral extravascular sites is governed by the similar factors that influence absorption from GIT such as the physicochemical properties of drug, anatomic, physiologic and pathologic characteristics of the patient and formulation factors. This is because of the following reasons:

a. The barrier to transport of drugs into the systemic circulation from all such sites is a lipoidal membrane similar to the GI barrier
b. The major mechanism in the absorption is passive diffusion.

Advantages

a. The greater systemic availability is attainable for drugs normally subjected to extensive presystemic elimination due to GI degradation and hepatic metabolism.
b. Peptide and protein drugs can also be delivered by such routes.

A. Buccal/Sublingual Administration

Sublingual and buccal routes are the two sites for oral mucosal delivery. In sublingual route, the drug is placed under the tongue and allowed to dissolve and in buccal route, the medicament is placed between the cheek and the gum.
Major mechanism for absorption: Passive diffusion

Advantages

1. Rapid absorption and higher blood levels due to high vascularization of the region and, therefore, particularly useful for administration of anti-anginal drugs
2. No first-pass hepatic metabolism
3. No degradation of drugs such as that encountered in the GIT
4. Presence of saliva facilitates both drug dissolution and its subsequent permeation by keeping the oral mucosa moist.

Factors affecting the oral mucosal delivery of drugs are as follows:

- Lipophilicity of drug
- Salivary secretion
- pH of the saliva
- Binding to oral mucosa
- Storage compartment
- Thickness of oral epithelium

Limited mucosal surface area that can only allow a small dose to be administered and concern for taste of the medicament and discomfort are the factors that limit drug administration by these routes. For examples: Antianginals like nitrites and nitrates, analgesics like morphine and bronchodilators like fenoterol, etc.

B. Rectal Administration

The rectal route of drug administration is an important route.

Advantages

- Good route of administration for children and old patients.
- The drugs may be administered as solutions or suppositories.
- Absorption of drugs from the lower half of rectum bypasses presystemic hepatic metabolism.

This route also has some disadvantages. Irritating suppository bases like PEG promotes defecation and drug loss. Presence of fecal matter retards drug absorption. Absorption is slower because of limited surface area. The pH of rectal fluids (around 8) also influences drug absorption according to pH-partition hypothesis.
For examples: Paracetamol, theophylline, few barbiturates, etc.

C. Topical Administration

Other than the respiratory tract's contact with the inhaled air, the skin is virtually the sole human surface directly interfacing. the body with the external environment. It is the largest organ of the body weighing approximately 2 kg and 2 meter square in area and receives about 1/3rd of total blood circulating through the body. Though tolerant to many chemicals, topically contacted xenobiotics can evoke both local and systemic effects. When topically applied drugs are meant to exert their effects systemically, the mode of administration is called percutaneous or transdermal delivery.

Anatomically, the skin has 3 distinct layers:

- The epidermis: The nonvascular, multilayered outer region of the skin
- The dermis: A highly vascular region
- The subcutaneous fat tissues

Epidermis: The dermis or true skin is, drugs permeating to this region are taken up into the systemic circulation and sink conditions are maintained.

The principal barrier to 'the entry of xenobiotics is the most superficial layer of epidermis called stratum corneum and act as the major rate limiting barrier to passive diffusion of drugs. In order to act either locally or systemically, a topically applied drug may diffuse through the skin by hair follicles, sweat glands or sebaceous glands but permeation through the multiple lipid bilayers of stratum corneum is the dominant pathway though the rate is very slow. Several factors influence passive percutaneous absorption of drugs:

1. Thickness of stratum corneum: More the thickness less will be the absorption
2. Presence of hair follicles: Absorption is rapid from the regions of hair follicles, e.g. scalp.
3. Trauma: It promote drug absorption from cuts, rashes, inflammation, mild bums, etc.
4. Hydration of skin: It increases drug absorption.
5. Environment humidity and temperature: Higher humidity and temperature increases drug absorption.
6. Age: Aged skin is more prone to allergic and irritant effects of topically contacted chemicals because of hardening of blood vessels. Infants absorb drug through skin as efficiently as adult. Their ratio of surface area to body weight is 3 times that of adults; hence, systemic toxicity of topically applied drugs is of particular concern in infants.
7. Grooming: The frequency and the products of grooming is used also contribute to variability in drug absorption.
8. Exposure to chemicals: It can accelerate shedding of epidermal cells and increases drug absorption.
9. Vehicle or base
10. Permeation enhancers: Addition of chemicals such as propylene glycol, azone, etc. in the topical formulations increases drug penetration.
11. Chronic use of certain drugs: Long term use of certain drugs like salicylic acid results in increase in drug penetration.

    Examples: Nitroglycerine, lidocaine, betamethasone, estradiol, testosterone, etc.

D. Intramuscular Administration

Absorption of drugs from IM sites is good but much slower in comparison to IV injections. Factors that determine rate of drug absorption from IM sites are:

1. Vascularity of the injection site: The decreasing order of blood flow rate to muscular tissues in which drugs are usually injected is: arm (deltoid) > thigh (vastus latera/is) > buttocks (gluteus maximus). Since blood flow rate is often the rate-limiting step in absorption of drugs from IM sites, most rapid absorption is from deltoid muscles and slowest from gluteal region. The absorption rate decreases in circulatory disorders such as hypotension.

2. Lipid solubility and ionization of drug: Highly lipophilic drugs are absorbed rapidly by passive diffusion whereas hydrophilic and ionized drugs are slowly absorbed through capillary pores.
3. Molecular size of the drug: Small molecules and ions gain direct access into capillaries through pores whereas macromolecules are taken up by the lymphatic system.
4. Volume of injection and drug concentration: A drug in concentrated injection and large volume is absorbed faster compared to its dilute form and small volume.
5. pH, composition and viscosity of injection vehicle: A solution of drug in acidic or alkaline pH (e.g. phenytoin, pH 12) or in anon-aqueous solvent when injected intramuscularly result in the precipitation of drug at the injection site followed by slow and prolonged absorption.

   Examples: Vaccines, hormonal agents, etc.

E. Subcutaneous Administration

The factors that influence IM drug absorption also influences absorption from subcutaneous site. Generally, absorption of drugs from a SC site is slower than that from IM sites. The reason for slower absorption is poor perfusion. Because of this reason SC route is used for the drugs for which a quick response is not required and also for the drugs that degrade if taken orally. The rate of absorption of a drug from SC site can be increased in two ways:

1. Enhancing blood flow to the injection site
2. Increasing the drug-tissue contact area

   Absorption can be slowed down by

   a. Causing vasoconstriction through local cooling
   b. Co-injection of a vasoconstrictor like adrenaline or by immobilization of limb

   Examples: Insulin, sodium heparin, several implants, etc.

F. Pulmonary Administration

The large surface area of the alveoli, the high permeability of the alveolar epithelium and the rich perfusion permits very rapid absorption and makes this route a very suitable candidate for systemic delivery of a drug but the drugs generally administered by inhalation are limited. Either gases or aerosol are administered through this route. The drug delivery to lungs is largely dependent upon the particle size of the aerosolized droplets. Smaller the particle size higher will be the absorption.

Examples: Bronchodilators (salbutamol), anti-inflammatory steroids (beclomethasone) and antiallergics (cromolyn), etc.

G. Intranasal Administration

The nasal route is getting popular for systemic delivery of some peptide and protein drugs. Drug absorption rate from nasal mucosa is same as observed after parenteral administration. This is because of its rich vascularity and high permeability. The route is generally used for drugs to treat nasal congestion, rhinitis, etc. Absorption through this route mainly affected by particle size and molecular weight.

Examples: Steroids, antihistaminics, etc.

H. Intraocular Administration

Topical application of drugs to the eyes is mainly for local effects such as: Mydriasis, miosis, anesthesia or treatment of infections, glaucoma, etc. The barrier to intraocular penetration of drugs is the cornea because of its both hydrophilic and lipophilic characteristics. Thus, for required intraocular permeation, drugs should have biphasic solubility.

Examples: Pilocarpine, timolol, atropine, etc.

I. Vaginal Administration

Drugs for intravaginal application are generally expected to act locally in the treatment of infections (bacterial or fungal) or to prevent conception.

Advantages:

- The route is now used for systemic delivery of contraceptives and other steroids, without going through first-pass metabolism.
- Controlled delivery and termination of drug action is possible with this route.

Factors that may influence drug absorption from intravaginal site include pH of lumen fluids (4 to 5), vaginal secretions and the microorganisms present in the vaginal lumen which may metabolize the drug.

SUMMARY

INTRODUCTION

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ABSORPTION

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FACTORS INFLUENCING DRUG ABSORPTION

- Physicochemical factors
  - Drug solubility and dissolution rate
  - Particle size and effective surface area
  - Polymorphism and amorphism
  - Pseudopolymorphism (hydrates or solvates)
  - Salt form of the drug
  - Lipophilicity of the drug
  - Drug stability
- Pharmaceutical or Formulation or Dosage form related factors
  - Disintegration time
  - Manufacturing variables
  - Nature and type of dosage form
  - Pharmaceutical ingredients (excipients)
  - Product age and storage conditions
- Patient related or physiological or biological factors
  - Age
  - Gastric emptying time
  - Intestinal transit time
  - Gastrointestinal pH
  - Diseased states
  - Blood flow through the GIT
  - Gastrointestinal contents
  - Presystemic metabolism

DRUG ABSORPTION FROM ALL NON-ORAL EXTRAVASCULAR SITES

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Advantages

A. The greater systemic availability is attainable for drugs normally subjected to extensive presystemic elimination due to GI degradation and hepatic metabolism.
B. Peptide and protein drugs can also be delivered by such routes.
   a. Buccal/sublingual administration
   b. Rectal administration
   c. Topical administration

d. Intramuscular administration
e. Subcutaneous administration
f. Pulmonary administration
g. Intranasal administration
h. Intraocular administration
i. Vaginal administration

DEFINITIONS

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Paracellular/intercellular transport: It is defined as the transport of drugs through the junctions between the GI epithelial cells. This pathway is of minor importance in drug absorption.

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Transcytosis: It is the process through which various macromolecules are transferred across the cell membrane. They are captured in vesicles, on one side of the cell and the endocytic vesicle is transferred from one extracellular compartment to another. Generally used for the transfer of IgA and insulin.

Bowel transit time: It refers to how long it takes for the food to move from the mouth to the end of the intestine.

Gastric emptying: It can be defined as the passage from stomach to the small intestine, called gastric emptying, it can be a rate-limiting step in drug absorption because the intestine is major site of drug absorption.