Drugs are introduced into the body by several routes. They may be

- Taken by mouth (orally)
- Given by injection into a vein (intravenously, IV), into a muscle (intramuscularly, IM), into the space around the spinal cord (intrathecally), or beneath the skin (subcutaneously, sc)
- Placed under the tongue (sublingually) or between the gums and cheek (buccally)
- Inserted in the rectum (rectally) or vagina (vaginally)
- Placed in the eye (by the ocular route) or the ear (by the otic route)
- Sprayed into the nose and absorbed through the nasal membranes (nasally)
- Breathed into the lungs, usually through the mouth (by inhalation) or mouth and nose (by nebulization)
- Applied to the skin (cutaneously) for a local (topical) or bodywide (systemic) effect
- Delivered through the skin by a patch (transdermally) for a systemic effect

Each route has specific purposes, advantages, and disadvantages.

Oral route is the most common route of drug administration. It is mostly used for the neutral drugs. It may be in the form of tablets, capsules, syrup, emulsions or powders.

Advantages:

1. It is convenient
2. It is the cheapest available route
3. It is easy to use
4. It is safe and acceptable.

Disadvantages:

1. Less amount of drug reaches the target tissue.
2. Some of the drug is destroyed by gastric juices e.g. adrenaline, insulin, oxytocin
3. Absorption has to take place which is slow, so is not preferred during emergency.
4. It might cause gastric irritation
5. It might be objectionable in taste.
6. It might cause discoloration of teeth e.g. iron causes staining, tetracyclines below 14 cause brown discoloration so are not advisable during pregnancy.

First Pass Effect:

First pass effect is the term used for hepatic metabolism of drug when absorbed and delivered through portal blood. Greater the first pass effect, less amounts of the drug reach the systemic circulation.

b. Sublingual Route:

Sublingual route involves tablets placed under the tongue or between cheeks or Gingiva.

The drug should be lipid soluble and small.

Advantages:

1. Rapid absorption takes place.
2. Drug is dissolved easily
3. Drug enters the blood directly
4. Less first pass effect.
5. Spitting out of the drug removes its effect

Disadvantages:

1. This method is inconvenient.
2. Irritation of the mucous membrane might occur
3. Person may swallow the drug
4. Might be unpleasant in taste.

Examples of drugs given by this route include nitroglycerin, isoprenaline and oxytocin. Nifedipine used for the treatment of hypertension in emergency is given by sublingual route.

c. Rectal Route:

Drugs in solid forms such as suppositories or in liquid forms such as enema are given by this route. This route is mostly used in old patients. Drugs may have local or systemic actions after absorption.

Advantages:

1. This route is preferred in unconscious or uncooperative patients.
2. This route avoids nausea or vomiting
3. Drug cannot be destroyed by enzymes.
4. This route is preferred if drug is irritant.

Disadvantages**:**

This route is generally not acceptable by the patients.

Locally acting drugs include glycerin and Bisacodyl suppository

Systemic acting drugs include Indomethacin (anti inflammatory) and aminophyllin (bronchodilator)

Retention enema is diagnostic and is used for finding the pathology of lower intestines.
Drugs given by rectal route have 50% first pass metabolism.

2. Parenteral Route:

Parenteral route includes:

Injections:

1. Intra muscular
2. Intra venous
3. Intra-arterial
4. Intra-cardiac
5. Intra-thecal
6. Intraosseous- into bone marrow
7. Intrapleural
8. Intraperitoneal
9. Intra-articular
10. Intradermal (Intracutaneous)
11. Subcutaneous route (Hypodermic)

Inhalation

Hypospray or jet injections

Advantages:

1. Parenteral route is rapid.
2. It is useful for uncooperative patients
3. It is useful for unconscious patients
4. Inactivation by GIT enzymes is avoided
5. First pass effect is avoided
6. Bioavailability is 100%

Disadvantages:

1. Skill is required
2. It is painful
3. This method is expensive
4. It is less safe.

Classification:

Site of Release:

Site of release may be intradermal, intraperitoneal, intrapleural, intracardiac, intra-arterial, intrathecal (into meninges of spinal cord), intra-articular (into joint cavity).

a. Subcutaneous:

Subcutaneous route might be used for the arm, forearm, thigh and subscapular space.
The volume used is 2 ml. Insoluble suspensions like insulin and solids might be applied by this route.

Advantages:

1. Absorption is slow and constant
2. It is hygienic

Disadvantages:

1. It might lead to abscess formation
2. Absorption is limited by blood flow

Examples of drugs given by subcutaneous route include insulin, adrenaline and norplant.

b. Intramuscular route:

Intramuscular route might be applied to the buttock, thigh and deltoid. The volume used is 3 ml.

Advantages:

1. Absorption is rapid than subcutaneous route.
2. Oily preparations can be used.
3. Irritative substances might be given
4. Slow releasing drugs can be given by this route.

Disadvantages

Using this route might cause nerve or vein damage.

c. Intravenous injections:

Intravenous injections might be applied to the cubital, basilic and cephalic veins.

Advantages:

1. Immediate action takes place
2. This route is preferred in emergency situations
3. This route is preferred for unconscious patients.
4. Titration of dose is possible.

5. Large volume of fluids might be injected by this route
6. Diluted irritant might be injected
7. Absorption is not required
8. No first pass effect takes place.
9. Blood plasma or fluids might be injected.

Disadvantages:

1. There is no retreat
2. This method is more risky
3. Sepsis-Infection might occur
4. Phlebitis(Inflammation of the blood vessel) might occur
5. Infiltration of surrounding tissues might result.
6. This method is not suitable for oily preparations
7. This method is not suitable for insoluble preparations

d. Intraarterial route:

This method is used for chemotherapy in cases of malignant tumors and in angiography.

e. Intradermal route:

This route is mostly used for diagnostic purposes and is involved in:
Schick test for Diphtheria
Dick test for Scarlet fever
Vaccines include DBT, BCG and polio
Sensitivity is to penicillin

f. Intracardiac route

Injection can be applied to the left ventricle in case of cardiac arrest.

g. Intrathecal route:

Intrathecal route involves the subarachnoid space. Injection may be applied for the lumbar puncture, for spinal anesthesia and for diagnostic purposes. This technique requires special precautions.

h. Intra-articular route:

Intra-articular route involves injection into the joint cavity. Corticosteroids may be injected by this route in acute arthritis.

i**. Intraperitoneal route:**

Intraperitoneal route may be used for peritoneal dialysis.

j. Intrapleural route:

Penicillin may be injected in cases of lung empyma by intrapleural route.

k. Injection into bone marrow

This route may be used for diagnostic or therapeutic purposes.

Hypospray/Jet Injection:

This method is needleless and is subcutaneous done by applying pressure over the skin. The drug solution is retained under pressure in a container called ‘gun’. It is held with nozzle against the skin. Pressure on the nozzle allows a fine jet of solution to emerge with great force. The solution can penetrate the skin and subcutaneous tissue to a variable depth as determined by the pressure. Mass inoculation is possible but the method is expensive, definite skills are required and cuts might result.

3. Inhalation:

Inhalation may be the route of choice to avoid the systemic effects. In this way drugs can pass directly to the lungs. Drugs used involve volatile drugs and gases. Examples include aerosols like salbutamol; steam inhalations include tincture and Benzoin

Advantages:

1. Rapid absorption takes place.
2. Rapid onset of action takes place.
3. This route has minimum side effects.
4. No first pass effect takes place.
5. This method is easy.
6. Fewer doses is required.

Disadvantages:

1. Special apparatus is required.
2. Irritation of the respiratory tract may take place.
3. Cooperation of the patient is required.
4. Airway must be patent.

4. Topical route:

Drugs may be applied to the external surfaces, the skin and the mucous membranes. Topical route includes:

a. Enepidermic route
When the drug is applied to the outer skin, it is called enepidermic route of drug administration. Examples include poultices, plasters, creams and ointments.
b. Epidermic route (Innunition):
When the drug is rubbed into the skin, it is known as epidermic route. Examples include different oils.
c. Insufflations:
When drug in finely powdered form is blown into the body cavities or spaces with special nebulizer, the method is known as insufflations.
d. Instillation
Liquids may be poured into the body by a dropper into the conjunctival sac, ear, nose and wounds. Solids may also be administered.
e. Irrigation or Douching
This method is used for washing a cavity e.g. urinary bladder, uterus, vagina and urethra. It is also used for application of antiseptic drugs.
f. Painting/Swabbing
Drugs are simply applied in the form of lotion on cutaneous or mucosal surfaces of buccal, nasal cavity and other internal organs.

Oral route

Many drugs can be administered orally as liquids, capsules, tablets, or chewable tablets. Because the oral route is the most convenient safe and least expensive, thus one most often used. However, it has limitations because of the way a drug typically moves through the digestive tract. For drugs administered orally, absorption may begin in the mouth and stomach. However, most drugs are usually absorbed from the small intestine. The drug passes through the intestinal wall and travels to the liver before being transported via the bloodstream to its target site. The intestinal wall and liver chemically alter (metabolize) many drugs, decreasing the amount of drug reaching the bloodstream. Consequently, these drugs are often given in smaller doses when injected intravenously to produce the same effect.

When a drug is taken orally, food and other drugs in the digestive tract may affect how much of and how fast the drug is absorbed. Thus, some drugs should be taken on an empty stomach, others should be taken with food, others should not be taken with certain other drugs, and still others cannot be taken orally at all.

Some orally administered drugs irritate the digestive tract. can harm the lining of the stomach and small intestine to potentially cause ulcers.

Other routes of administration are required when the oral route cannot be used, for example:

- When a person cannot take anything by mouth
- When a drug must be administered rapidly or in a precise or very high dose
- When a drug is poorly absorbed from the digestive tract

Injection routes

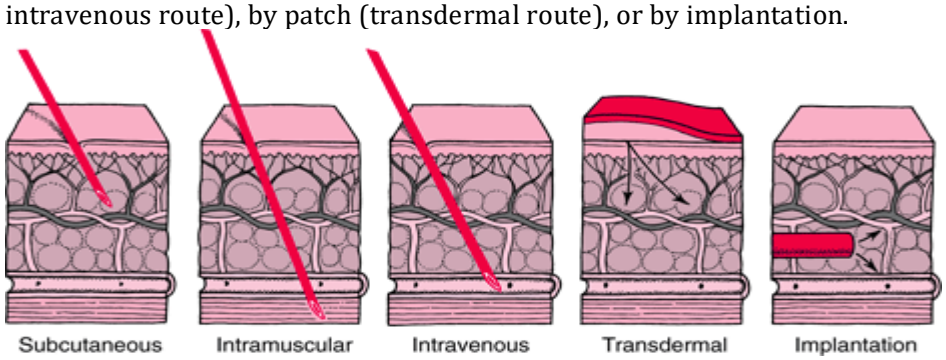
Administration by injection (parenteral administration) includes the following routes:

- Subcutaneous (under the skin)
- Intramuscular (in a muscle)
- Intravenous (in a vein)
- Intrathecal (around the spinal cord)

A drug product can be prepared or manufactured in ways that prolong drug absorption from the injection site for hours, days, or longer. Such products do not need to be administered as often as drug products with more rapid absorption.

Through the Skin

Sometimes a drug is given through the skin—by needle (subcutaneous, intramuscular, or intravenous route), by patch (transdermal route), or by implantation.



For the **subcutaneous route,** a needle is inserted into fatty tissue just beneath the skin. After a drug is injected, it then moves into small blood vessels (capillaries) and is carried away by the bloodstream. Protein drugs that are large in size, such as insulin, usually reach the bloodstream through the lymphatic vessels because these drugs move slowly from the tissues into capillaries. The subcutaneous route is used for many protein drugs because such drugs would be destroyed in the digestive tract if they were taken orally.

The **intramuscular route** is preferred to the subcutaneous route when larger volumes of a drug product are needed. Because the muscles lie below the skin and fatty tissues, a longer needle is used. Drugs are usually injected into the muscle of the upper arm, thigh, or buttock. How quickly the drug is absorbed into the bloodstream depends, in part, on the blood supply to the muscle: The sparser the blood supply, the longer it takes for the drug to be absorbed.

For the **intravenous route,** a needle is inserted directly into a vein. A solution containing the drug may be given in a single dose or by continuous infusion. For infusion, the solution is moved by gravity (from a collapsible plastic bag) or, more commonly, by an infusion pump through thin flexible tubing to a tube (catheter) inserted in a vein, usually in the forearm. Intravenous administration is the best way to deliver a precise dose quickly and in a well-controlled manner throughout the body. An intravenous injection can be more difficult to administer than a subcutaneous or intramuscular injection because inserting a needle or catheter into a vein may be difficult, especially if the person is obese.

When given intravenously, a drug is delivered immediately to the bloodstream and tends to take effect more quickly than when given by any other route.

For the **intrathecal route,** a needle is inserted between two vertebrae in the lower spine and into the space around the spinal cord. The drug is then injected into the spinal canal. A small amount of local anesthetic is often used to numb the injection site. This route is used when a drug is needed to produce rapid or local effects on the brain, spinal cord, or the layers of tissue covering them (meninges)—for example, to treat infections of these structures. Anesthetics and analgesics (such as morphine) are sometimes given this way.

Sublingual and buccal routes

A few drugs are placed under the tongue (taken sublingually) or between the gums and teeth (buccally) so that they can dissolve and be absorbed directly into the small blood vessels that lie beneath the tongue. These drugs are not swallowed. The sublingual route is especially good because absorption is rapid and the drug immediately enters the bloodstream without first passing through the intestinal wall and liver. However, most drugs cannot be taken this way because they may be absorbed incompletely or erratically.

Rectal route

Many drugs that are administered orally can also be administered rectally as a suppository. In this form, a drug is mixed with a waxy substance that dissolves or liquefies after it is inserted into the rectum.

Because the rectum's wall is thin and its blood supply rich, the drug is readily absorbed. A suppository is prescribed for people who cannot take a drug orally because they have nausea, cannot swallow, or have restrictions on eating, as is required before and after many surgical operations. Drugs that can be administered rectally include acetaminophen (for fever), diazepam (for seizures), and laxatives (for constipation). Drugs that are irritating in suppository form may have to be given by injection.

Vaginal route

Some drugs may be administered vaginally to women as a solution, tablet, cream, gel, suppository, or ring. The drug is slowly absorbed through the vaginal wall. This route is often used to give estrogen to women during menopause to relieve vaginal symptoms such as dryness, soreness, and redness.

Ocular route

Drugs used to treat eye disorders (such as glaucoma, conjunctivitis, and injuries) can be mixed with inactive substances to make a liquid, gel, or ointment so that they can be applied to the eye. Liquid eye drops are relatively easy to use but may run off the eye too quickly to be absorbed well. Gel and ointment formulations keep the drug in contact with the eye surface longer, but they may blur vision. Solid inserts, which release the drug continuously and slowly, are also available, but they may be hard to put in and keep in place.

Ocular drugs are almost always used for their local effects. For example, artificial tears are used to relieve dry eyes. Other used to dilate pupils, produce a local effect (acting directly on the eyes) Some of these drugs then enter the bloodstream and may cause unwanted side effects on other parts of the body.

Otic route

Drugs used to treat ear inflammation and infection can be applied directly to the affected ears. Ear drops containing solutions or suspensions are typically applied only to the outer ear canal. Before applying ear drops, people should thoroughly clean the ear with a moist cloth and dry it. Unless the drugs are used for a long time or used too much, little of the drugs enter the bloodstream, so bodywide side effects are absent or minimal.

Nasal route

If a drug is to be breathed in and absorbed through the thin mucous membrane that lines the nasal passages, it must be transformed into tiny droplets in air (atomized). Once absorbed, the drug enters the bloodstream. Drugs administered by this route generally work quickly. Some of them irritate the nasal passages.

Inhalation route

Drugs administered by inhalation through the mouth must be atomized into smaller droplets than those administered by the nasal route, so that the drugs can pass through the windpipe (trachea) and into the lungs. How deeply into the lungs they go depends on the size of the droplets. Smaller droplets go deeper, which increases the amount of drug absorbed. Inside the lungs, they are absorbed into the bloodstream.

Inhalers; Drug Administration by Inhalation

Relatively few drugs are administered this way because inhalation must be carefully monitored to ensure that a person receives the right amount of drug within a specified time. In addition, specialized equipment may be needed to give the drug by this route. Usually, this method is used to administer drugs that act specifically on the lungs, such as aerosolized antiasthmatic drugs in metered-dose containers (called inhalers), and to administer gases used for general anesthesia.

Nebulization route

Similar to the inhalation route, drugs given by nebulization must be aerosolized into small particles to reach the lungs. Nebulization requires the use of special devices, most commonly ultrasonic or jet nebulizer systems. Using the devices properly helps maximize the amount of drug delivered to the lungs.

Side effects can include those that occur when the drug is deposited directly in the lungs (such as cough, wheezing, shortness of breath, and lung irritation), spread of the drug into the environment (possibly affecting people other than the one taking the drug), and contamination of the device used for nebulization (particularly when the device is reused and inadequately cleaned). Using the device properly helps prevent side effects.

Cutaneous route

Drugs applied to the skin are usually used for their local effects and thus are most commonly used to treat superficial skin disorders, skin infections (viral, bacterial, and fungal), itching, and dry skin. The drug is mixed with inactive substances. Depending on the consistency of the inactive substances, the formulation may be an ointment, cream, lotion, solution, powder, or gel.

Transdermal route

Some drugs are delivered bodywide through a patch on the skin. These drugs are sometimes mixed with a chemical (such as alcohol) that enhances penetration through the skin into the bloodstream without any injection. Through a patch, the drug can be delivered slowly and continuously for many hours or days or even longer. As a result, levels of a drug in the blood can be kept relatively constant. Patches are particularly useful for drugs that are quickly eliminated from the body because such drugs, if taken in other forms, would have to be taken frequently. However, patches may irritate the skin of some people

Pharmacokinetics Pharmacokinetics can be simply described as the study of 'what the body does to the drug' and includes:

- rate and extent to which drugs are absorbed into the body and distributed to the body tissues
- the rate and pathways by which drugs are eliminated from the body by metabolism and excretion
- the relationship between time and plasma drug concentration.

Understanding these processes is extremely important for prescribers because they form the basis on which the optimal dose regimen is chosen and explain the majority of the inter-individual variation in the response to drug therapy.

Four phases of pharmacokinetics

The main processes involved in pharmacokinetics are absorption, distribution, and the two routes of drug elimination, metabolism and excretion. Together they are sometimes known by the acronym 'ADME'. Distribution, metabolism and excretion are sometimes referred to collectively as drug disposition.

Absorption is the process by which drugs enter the body. Given by any route other than intravenously, drug molecules must cross tissue membranes (e.g. skin epithelium, subcutaneous tissue, gut endothelium, capillary wall) to enter the blood.

Distribution is the process by which drugs move around the body. After entering the blood, drug molecules must cross capillary walls to enter the tissues, reach cell membranes and enter cells.

Metabolism is the process by which drugs are chemically altered to make them sufficiently water-soluble for excretion in urine or faeces (via the biliary tract). Metabolism occurs in a variety of body organs and tissues, but chiefly in the liver, gut wall, kidney and skin.

Excretion is the process by which drugs leave the body. Drugs that are sufficiently water-soluble will be excreted unchanged in the urine. Lipid-soluble drugs must be modified to water-soluble metabolites before excretion via the kidney or into the intestine via the bile.

Drug absorption

Absorption is the process by which drug molecules gain access to the bloodstream from the site of drug administration. The speed of this process (the rate of drug absorption) and its completeness (the extent of drug absorption) depend on the route of administration.

Routes of administration can be considered in two categories:

Enteral. Drugs given by mouth are normally swallowed before being absorbed in the stomach or small bowel, after which they enter the portal venous system and pass through the liver before gaining access to the systemic circulation. Some drugs introduced into the alimentary tract are absorbed directly into the systemic circulation without passing through the liver (e.g. via the buccal, sublingual or rectal routes), thereby avoiding the potential hazards of gastric acid, binding to food, and metabolism by gut wall or liver enzymes (first-pass metabolism).

Parenteral. This includes any route that avoids absorption via the gastrointestinal tract such as administration by injection, inhalation or by application to the skin.

Absorption after an oral dose is a lengthy process, during which drug molecules may be damaged (e.g. denatured by gastric acid), sequestered (e.g. bound to food preventing absorption) or modified by first-pass metabolism. As a consequence of all these hazards, it is not surprising that absorption is frequently incomplete following oral administration. The proportion of a dose that reaches the systemic circulation unscathed is known as the bioavailability of the drug.

Distribution

Distribution is the movement of drugs throughout the body. Determined by the blood flow to the tissues, it is ability of the drug to enter the vasculature system and the ability of the drug to enter the cell if required.

Drug metabolism

Metabolism is the process by which drugs are chemically changed from a lipid-soluble form suitable for absorption and distribution to a more water-soluble form that is suitable for excretion. The process effectively eliminates the parent drug.

Drug metabolism occurs in two phases:

Phase I – in which drug molecules are altered chemically (by oxidation, reduction or hydrolysis) to make them suitable for Phase II reactions or for excretion. Oxidation is much the commonest form of Phase 1 reaction and involves chiefly members of the cytochrome P450 family of membrane-bound enzymes in the smooth endoplasmic reticulum of the liver cells. Most products of Phase 1 metabolism are pharmacologically inactive, although some retain activity to a greater or lesser degree, while others have activity that the parent drug did not possess.

Phase II – in which molecules of Phase I metabolite (or in some cases, unchanged drug) combine with an endogenous substrate to form an inactive conjugate that is much more water-soluble than the Phase I metabolite. Phase II reactions include synthesis of glucuronide or sulphate products, acetylation or methylation, and conjugation with glutathione.

The rate of drug metabolism varies widely between individuals, influenced by genetic and environmental factors. This is the major reason for inter-individual differences in the plasma concentration of some drugs after a standard dose, which leads to wide variation in drug response.

Excretion

Excretion is the removal of the substance from the body. Some drugs are either excreted out unchanged or some are excreted out as metabolites in urine or bile. Drugs may also leave the body by natural routes such as tears, sweat, breath and saliva. Patients with kidney or liver problem can have elevated levels of drug in the system and it may be necessary to monitor the dose of the drug appropriately since a high dose in the blood can lead to drug toxicity.

Drug Dosage and Drug levels – Basic Definitions

Half life of a drug is the time for the drug to decrease to half of its concentration.
Minimum effective concentration: below which there will be no therapeutic effect.
Maximum safe concentration: above which there will be a toxic effect The larger the therapeutic index the more safer the drug.
Bioavailability: It describes the amount of drug that is available to the body to produce a therapeutic effect.
Onset of action : it is the time taken for the drug to reach the minimum effective concentration after a drug has been administered.
Peak Action: occurs when the drug reaches its highest blood or plasma concentration
Duration of action: is the length of time the drug has a pharmacological action.