To produce its characteristic effects, a drug must be present in appropriate concentrations at its site of action. The concentrations attained also depend upon the extent and rate of its absorption, distribution, binding or localization in tissues, biotransformation, and excretion.

The absorption, distribution, biotransformation and excretion of a drug all involve its passage across cell membranes. It is essential, therefore, to consider the mechanisms by which drugs cross membranes and the physicochemical properties of molecules (drugs) and membranes that influence this transfer. Important characteristics of drugs are its molecular size and shape, solubility at the site of absorption, degree of ionization and relative lipid solubility of its ionized and non-ionized forms.

When a drug permeates a cell, it must obviously traverse the cellular plasma membrane. Other barriers to drug movement may be a single layer of cells (intestinal epithelium) or several layers of cells (skin). Despite these structural differences, the diffusion and transport of drugs across these various boundaries have many common characteristics, since drugs in general pass through cells rather than between them. The plasma membrane thus represents the common barrier.

The plasma membrane consists of a bilayer of amphipathic lipids, with their hydrocarbon chains oriented inward to form a continuous hydrophobic phase and their hydrophilic heads oriented outward. Individual lipid molecules in bilayer can move laterally, endowing the membrane with fluidity, flexibility, high electrical resistance and relative impermeability to high polar molecules. Membrane proteins embedded in the bilayer serve as receptors to elicit electrical or chemical signaling pathways and provide selective targets for drug action. Drug molecules move across the plasma membrane by different mechanisms like 1) Passive processes, 2) Bulk flow through intercellular pores, 3) Pinocytosis, 4) Carrier mediated active membrane transport, and 5) Facilitated diffusion.

1. Passive processes

The drug molecule usually penetrates by passive diffusion along a concentration gradient by virtue of its solubility in the lipid bilayer. Such transfer is directly proportional to the magnitude of the concentration gradient across the membrane and the lipid-water partition coefficient of the drug. The greater the partition coefficient of the drug, the greater the partition coefficient, and the higher is the concentration of drug in the membrane and the faster is its diffusion. After a steady state is attained, the concentration of the free drug is the same on both sides of membrane, if the drug is non-electrolyte. For ionic compounds, the steady state concentration will be dependent on differences in P across the membrane, which may influence the state of ionization of the molecule on each side of the membrane and on the electrochemical gradient for the ion.

Most biological membranes are relatively permeable to water, either by diffusion or by flow that results from hydrostatic or osmotic differences across the membrane. Such bulk flow of water can carry with it small water-soluble substances such as urea, and others whose molecular masses are lesser than 100 to 200 Daltons. Most of the inorganic ions would seem to be sufficiently small to penetrate the membrane; their hydrated ionic radius is relatively large. The concentration gradient of many inorganic ions is largely determined by active transport. E.g. Na+, K+. 

**Pharmacokinetics**
Weak electrolytes and influence of pH:

Most drugs are weak acids or bases that are present in solution as both the non-ionized and ionized species. The non-ionized molecules are usually lipid soluble and can diffuse across the cell membrane. In contrast, the ionized molecules are usually unable to penetrate the lipid membrane of their low lipid solubility.

Therefore, its Pka and the pH gradient across the membrane, usually determine the transmembrane distribution of a weak electrolyte. Establishment of pH gradient is, however an active process.

Passive diffusion is major one in absorption and distribution of most drugs.

2. Bulk flow through intercellular pores:

Bulk flow through intercellular pores is the major mechanism of passage of drugs across most capillary endothelial membranes with the important exception of the CNS. These intercellular gaps are sufficiently large that diffusion across most capillaries is limited by blood flow and not by the lipid solubility of drug or pH gradient. This is an important factor in filtration across glomerular membranes in the kidney. Tight junctions are characteristic of capillaries of the CNS and a variety of epithelia. Intercellular diffusion is consequently limited.

3. Pinocytosis:

Pinocytosis is the formation and movement of vesicles along substance to be transported across the cell membranes and it has been implicated in drug absorption. However, the quantitative significance of pinocytosis probably is negligible.

4. Carrier mediated membrane transport:

Active and selective mechanisms also play important roles in transport across membrane. Active transport of some drugs occurs across neuronal membranes, the choroids plexus, renal tubular cells and hepatocytes. The characteristics of active transport is selectivity, competitive inhibition of congeners, a requirement for energy, saturability and movement against an electrochemical gradient; may be important in the mechanism of action of drugs that are subject to active transport or that interfere with active transport of natural metabolites or neurotransmitters.

5. Facilitated diffusion:

Describes a carrier mediated transport process to which there is no input of energy, and movement of the substances in question thus cannot occur against an electrochemical gradient. This mechanisms are highly selective for specific conformational structures of drugs, are necessary for the transport of endogenous compounds whose rate of movement across biological membranes by simple diffusion other wise would be to slow.

Absorption of Drugs

Absorption describes rate and extent at which a drug leaves its site of administration.
Factors that modify absorption

Many variables in addition to the physicochemical factors that affect transport across membranes influence the absorption of drugs.

1. Solubility of drug: regardless of the site of administration, the drug absorption depends on the drug solubility.
2. Aqueous solutions: drugs given in aqueous solutions are more rapidly absorbed than those given in oily solution, suspension or solid form, because they mix more readily with the aqueous phase at the absorption site.
3. Dissolution rate: drugs given in solid form, the rate of dissolution may be the limiting factor in their absorption.
4. Local condition at the site of absorption alters solubility, particularly, in the gastrointestinal tract. Aspirin, which is relatively insoluble in acidic gastric contents, is a common example of such a drug.
5. The concentration of drug: concentration of drug influences its rate of absorption of drugs introduced at an administration site in solutions of high concentration are absorbed more rapidly than are drugs in solutions of low concentration.
6. The circulation to the site of absorption also effects drug absorption. Increased blood flow, brought about by massage or local application of heat, enhances the rate of drug absorption. Decreased blood flow, produced by vasoconstrictor agents, shock, or other disease factors, can slow absorption.
7. The area of absorbing surface to which a drug is exposed is one of the more important determinants of the rated of drug absorption. Drugs are absorbed very rapidly from large surface areas such as the pulmonary alveolar epithelium, the intestinal mucosa or in a few cases after extensive application on the skin. Largely the route of administration determines the absorbing surface.

Each of these factors separately or in conjunction with one another may have profound effects on the clinical efficacy and toxicity of a drug.

Enteral (oral) Vs. Parenteral administration of drugs

Oral:

1. Most common method of drug administration.
2. It also safest, most convenient and most economical.

Disadvantages:

1. Incapability to absorb some drugs because of their physical characteristics, E.g. polarity, alkaline drugs are not absorbed in gastric acidic environment.
2. Emesis as a result of irritation to the gastrointestinal mucosa, destruction of some drugs by digestive enzymes or low gastric P", irregularities in absorption or propulsion in the presence of food or other drugs.
3. Necessity for cooperation on the part of patient.
4. Drugs in the gastrointestinal tract may be metabolized by the enzymes of the mucosa, the rumenoreticular flora or intestinal flora or the liver before they gain access to the general circulation.

Parenteral:

Has certain distinct advantage over oral administration.

1. In some instances parenteral administration is essential for the drug to be absorbed in active form.
2. Availability is usually more rapid and more predictable than when a drug is given by mouth. The effective dose can therefore be more accurately selected.
3. In emergence therapy. Parenteral administration is particularly serviceable.
4. If a patient is unconscious, uncooperative or unable to retain anything given by mouth, then the parenteral therapy may be necessary.

Disadvantages:

1. Asepsis must be maintained.
2. An intravascular injection may occur when it is not intended.
3. Pain may accompany the injection and difficult to perform the injection by the owner.
4. Expense.

Oral

Most drugs absorption from the gastrointestinal tract occurs via passive processes, absorption is favored when the drug is in the non-ionized and lipophilic form. Absorption of weak acids in the acidic environment of stomach is optimal; where as absorption of bases might be favored in the relatively alkaline small intestine.

A thick, mucous cover membrane with a small surface area and high electrical resistance lines the stomach. The primary function of stomach is digestion. In contrast the epithelium of the intestine has an extremely large surface area. It is thin, it has low electrical resistance, and its primary function is to facilitate the absorption of nutrients.

Final conclusion is non ionized form of a drug will be absorbed more rapidly than the ionized form at any particular site in gastrointestinal tract. However the rate of absorption of a drug from the intestine will be greater than that from the stomach even it the drug is predominantly ionized in the intestine and largely nonionized in the stomach.

Drugs that are destroyed by gastric juice or that cause gastric irritation some times are administered in dosage forms with a coating that prevents dissolution in the acidic gastric contents.

Although some oral solutions, either elixir or aqueous and suspensions are available, most oral dosage forms are solids include tablet, bolus for large animals, pellets, capsule and a variety of specialized sustained-release products for ruminant animals. Before entering the systemic circulation a drug administered as a solid dosage form must undergo three events. 1) Release from the dosage form (dissolution), 2) transport across the gastrointestinal mucosa, 3) passage through liver. Each of these events has the potential to decrease the amount of drug reaching the circulation
intact (unchanged). The net effect is reflected in the bioavailability profile.

Dissolution is the rate-limiting step that determines release of drug from a solid dosage form, and it frequently controls the rate of drug absorption. The dissolution process can be enhanced by administering the drug in salt form or by decreasing the particle size, a technique called micronization (griseofulvin). Following its release, the drug in solution must be stable in the environment with in the stomach (reticulorumen) and small intestine and must be sufficiently lipid soluble to diffuse through mucosal barrier to enter the hepatic portal venous blood. A drug that is stable (neither chemically nor enzymatically inactivated) in gastrointestinal fluids, not completely ionized, and lipid soluble would be expected to be completely absorbed.

The rate of gastric emptying is the most important physiologic factor controlling drug absorption rate, since the small intestine is the principal site of absorption.

Despite the stratified squamous nature of its epithelial lining, the rumen has been shown to have considerable absorptive capacity. Rumen PH 5.5-6.5, high concentration of volatile fatty acids, buffers secreted in alkaline saliva (PH 8.0 to 8.4) and drug appear directly by fore stomach epithelium.

Owing to large volume of ruminal fluid, a drug can attain only a low concentration in this organ, whether it is given in solution or as a solid dosage form. Non-ionized, lipid soluble form of weak organic acids in particular should normally be well absorbed from the rumen. Indigenous micro flora may inactivate certain drugs by metabolic transformations of a hydrolytic or reductive nature. Chronic oral dosage with an antimicrobial agent can suppress micro flora activity and there by disturb carbohydrate digestion, which is essential function of fore stomach.

**Sublingual administration**

In this solid dosage form is place under the tongue, which is highly vascular and drug is absorbed slowly in the sublingual blood capillaries. E.g. Nitroglycerine. Not commonly used in veterinary practice.

**Rectal administration**

The rectal route is often is useful when oral ingestion is precluded by vomiting or patient is unconscious. 50 percent of drug absorbed from rectum by pass liver. However rectal absorption is irregular and incomplete, and many drugs cause irritation of the rectal mucosa. Rectal injections Enemata is carried out to produce evacuation of bowels either with soap and warm water or as glycerin enema.

**Parenteral injections**

Major routes of parenteral administration are intravenous (i/v), intramuscular (i/m), and subcutaneous (s/c). Absorption from s/c and i/m sites occurs by simple diffusion along the gradient from drug depot to plasma. The rate is limited by the area of the absorbing capillary membranes and by the solubility of the substance in the interstitial fluid. Relatively large aqueous channels present in the endothelial membrane are account for the indiscriminate diffusion of molecules regardless of their lipid solubility. Larger molecules, such as proteins slowly gain access to the circulation by way of lymphatic channels.
Drugs administered into the systemic circulation by any route, excluding the intra-arterial route, are subject to possible first-pass elimination into the lung prior to distribution to the rest of the body. The lungs serve as a temporary clearing site for a number of agents, especially drugs that are weak bases and are predominantly nonionized at the blood pH, apparently by their partition into lipid. The lungs also serve as a filter for particulate matter that may be given intravenously. Of course they provide a route of elimination for volatile substances.

**Intravenous**

Injection of a drug solution directly into the blood stream gives a predictable concentration of the drug in plasma and in most instances produces an immediate pharmacological response. I/v injection should be performed slowly except in special circumstances like induction of anesthesia by rapid introduction into the blood stream of small dose of thiopental as an i/v bolus. Surgical anesthesia by barbiturates, the dose of a drug is not predetermined but is adjusted to the response of the patient. Certain irritating solutions can be given only in this manner. Since blood vessel walls are relatively insensitive, and the drug if injected slowly is greatly diluted by the blood, usually required for high molecular weight protein and peptide drugs. Large volumes of drugs can be given through this route.

Once the drug is injected there is no retreat. Repeated intravenous injections are dependent upon the ability to maintain a potent vein. Through this route, should not give drugs in an oily vehicle or those that precipitate blood constituents or hemolyse erythrocytes.

Intravenous injections usually must be performed slowly and with constant monitoring of the response of patient.

**Subcutaneous**

It can be used only for drugs that are not irritating to tissue; otherwise sever pain, necrosis and slough may occur. Rate of absorption often is sufficiently constant and slow to provide a sustained effect. Moreover, it may be varied intentionally. For example the rate of absorption of a suspension of insoluble insulin is slow compared with that of soluble preparation. The incorporation of vasconstrictor agent in a solution of a drug to be injected s/c also retards absorption. Absorption of drugs Implanted under the skin in a solid pellet form occurs slowly over a period of weeks or months. Some hormones are effectively administered in this manner.

**Intramuscular**

Drugs in aqueous solution are absorbed quite rapidly, depending upon rate of blood flow to the injection site. Very slow, constant absorption from the intramuscular site results if the drug is injected in solution in oil or suspended in various other repository vehicles. Substances too irritating to s/c may some times be given intramuscularly. This route is suitable for moderate volumes of drug preparations.

**Intraarterial**

Occasionally a drug is injected directly into artery to localize its effect in a particular tissue or organ. Sometimes, diagnostic agents are administered through this route. It required great care and should be
reserved for experts. The first pass and cleansing effects of lungs are not available.

**Intrathecal**

Blood brain barrier (BBB) and blood cerebrospinal fluid barrier often preclude or slow the entrance of drugs into the CNS. Therefore, when local and rapid effects of drugs on the meninges or cerebrospinal axis are desired, as in spinal anesthesia or acute CNS infections, then the drugs are injected directly into the spinal subarachnoid space.

**Intraperitoneal**

The peritoneal cavity offers a large absorbing surface from which drugs enter the circulation rapidly, but primarily by way of portal vein, first pass hepatic losses are thus possible. It is common laboratory procedure, seldom employed clinically, because of dangers of producing infection and adhesions are too great towards the routine use of this route.

**Pulmonary**

Gaseous and volatile drug may be inhaled and absorbed through the pulmonary epithelium and mucous membranes of the respiratory tract. Access to the circulation is rapid, because the surface area is large.

In addition, solutions of drugs can be atomized and the fine droplets in air (aerosol) inhaled.

**Advantages**

1) Most instantaneous absorption of drug into the blood.
2) Avoidance of hepatic first-pass loss.
3) In the case of pulmonary disease local application of the drug at the desired site of action.
E.g. drugs can be given in this manner for the treatment of bronchial asthma.

**Disadvantages**

1) Poor ability to regulate the dose.
2) Cumberomeness of methods of administration.
3) Many gaseous and volatile drugs produce irritation of the pulmonary epithelium.

**Inoculation**

Pox vaccine is administered by superficial puncture or scaring of the epidermis. The vaccine drop is slowly absorbed by the lymphatics.

**Intradermal**

Drug is given with in the skin layers (dermis). This route is used for testing sensitivity to drugs. E.g. penicillin, antitetanus serum (ATS), tuberculin test. Highly diluted and small quantity of drug is administered even this is painful. Absorption is through lymphatics. Thus intradermal sensitivity test gives a clue as to whether drug to be injected would be safe or allergic in nature for the concerned patient.
Hypodermoclysis

It is special process of infusing large amount of drugs like glucose and saline through loose subcutaneous tissues of the body.

Intracardiac

It is given quickly and directly in to the cardiac muscle in sudden stoppage of healthy heart (adrenaline in drowning). It is the last resort of defeated physicians to revive a stand still heart.

Intramedullary

It is given in the modularly cavity of the bone when i/v is not possible. Glucose and saline solutions, plasma and blood transfusion etc can be administered especially young animals.

Serous cavity injections

To achieve local concentrations of drugs are injected in serous cavities, peritoneal, pleural, pericardial and articular cavities. Of these intra peritoneal injections are quickly effective because of the rich lymphatic supply in that region.

Intra articular injections of antibiotics and corticosteroids are administered in inflamed joint cavities (rheumatoid arthritis). Experts, with precision, should perform this type of injections.

Intracerebral, Intracisternal, Intraventricular, Intraneural

In this drugs are given in certain parts of the brain in rare conditions. These are surgical procedures.

Intravenous in young animals: Drugs are injected through umbilical vein.

Epidural injections

Drug solutions are injected on and around the duramater for inducing local or regional anesthesia without involving the CNS.

Sub conjunctival injection: Used in corneal disorders.

Intramammary infusion: Used for introduction of antiseptics in mastitis condition.

Other routes of administration

Skin

Drugs are applied to skin mainly for their local action as few drugs can penetrate the skin and get absorbed. Usually applied as ointments with a fatty basis, which adhere to skin serving as a means of applying on active substance and as they do not dry up, protect the surface from air and irritation.

Few drugs readily penetrate skin. Absorption depends on surface area over which applied and lipid solubility. Since epidermis behaves as a lipid barrier. The dermis however, is freely permeable to many solutes; consequently systemic absorption of many drugs occurs much more readily.
through abraded, burned, or denuded skin. Inflammation and other conditions that increase cutaneous blood flow and also enhance absorption. Toxic effects some times are produced by absorption through the skin of highly lipid-soluble substances e.g. lipid soluble insecticides in an organic solvents.

Suspending the drug in an oily vehicle and rubbing the resulting preparation into the skin can enhance absorption through the skin. This procedure is called inunction.

Ionizable drugs may be made to penetrate into deeper tissues by the help of galvanic current where they may be taken up by blood stream and act particularly on tissues in the neighborhood of the point of application. Such method of administration of drugs is known as Iontophorsis.

Cataplasma, plasters, collodions are other pharmacological preparations for local application. In addition drugs in solution or as powders or as solid masses (for caterisation) may be applied to skin.

Some special preparations are specifically administered into the certain body cavities. E.g. Bougies – urethra; pessaries – uterus; douches – vagina; suppository – rectum.

Ophthalmic preparations

These are the solutions for administration in to the eye. For prolonged effect Lamellae, occulenta or as powders for local action on the conjunctiva.