# UNIT

# V

# DRUG DISTRIBUTION

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## INTRODUCTION

**Disposition** refers to the procedures that tend to reduce the drug's plasma concentration. The two most popular drug disposal procedures are-

- Drug distribution including the reversible transfer of a drug across compartments (Figure 5.1).
- Elimination, which results in the permanent removal of the drug from the body. Elimination is further subdivided into two steps–
    1. Biotransformation (metabolism)
    2. Excretion

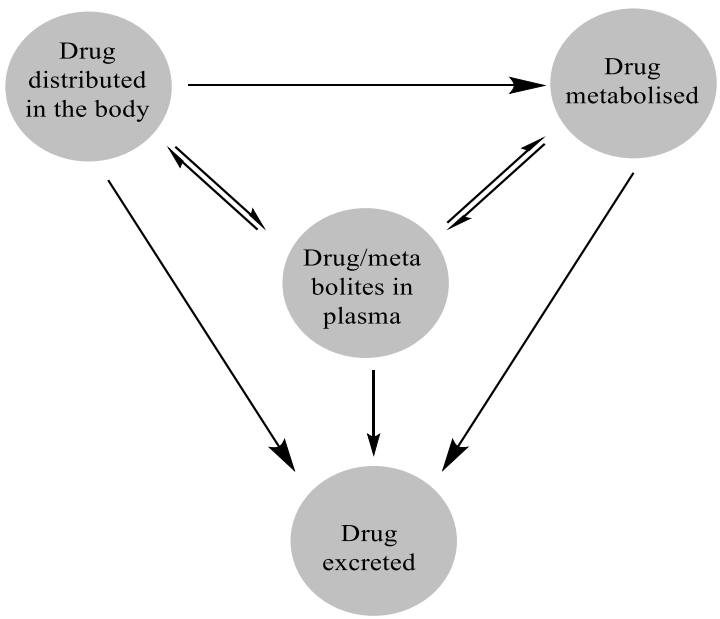


**Figure 5.1: Drug distribution.**

**Distribution** refers to the reversible movement of a drug between the blood and extravascular fluids and tissues. Distribution, which is a passive process, influences the commencement, strength, and occasionally duration of pharmaceutical action.

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## PROCESS OF DRUG DISTRIBUTION

The following are the steps required in transferring a medicine from the systemic circulation to extravascular tissues:

1. Free or unbound drugs in the blood pass through the capillary wall and reach the interstitial/extracellular fluid (this happens fast) (ECF).
2. Drug penetration from the ECF into the intracellular fluid through tissue cell membranes. This is a rate-limiting stage that is impacted by two major factors: The rate of extracellular tissue perfusion, as well as the drug's membrane permeability (Figure 5.2).

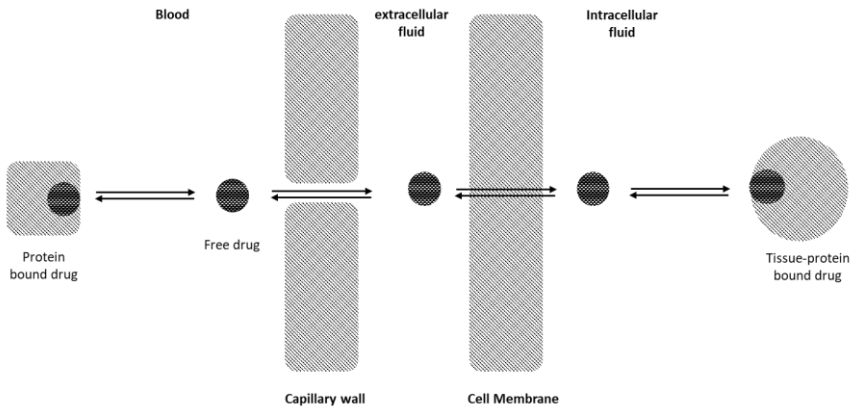


**Figure 5.2: Process of Drug Distribution**

## FACTORS AFFECTING DRUG DISTRIBUTION

Distribution of drugs is affected by various factors such as Tissue permeability, organ size, perfusion rate, drug binding to tissue, age, pregnancy, obesity, diet, etc. as given in Figure 5.3.

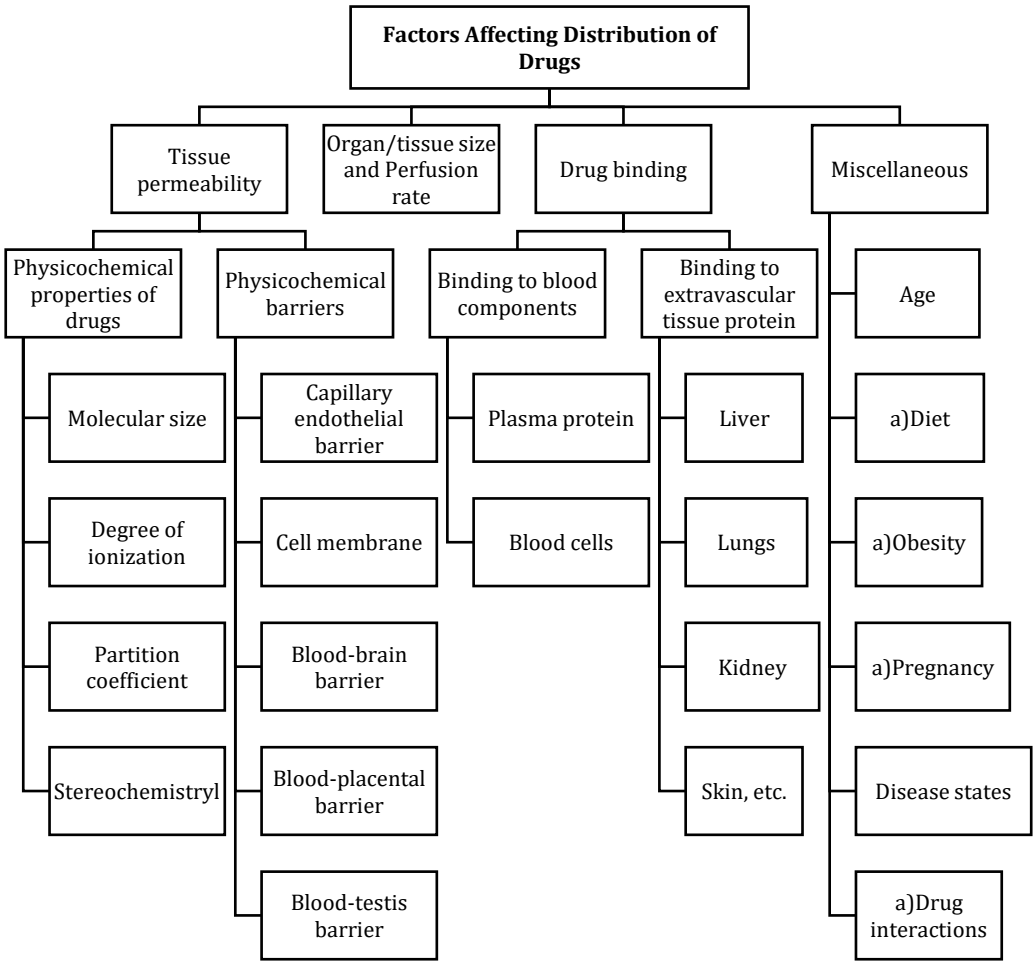


**Figure 5.3: Factor affecting drug distribution.**

## TISSUE PERMEABILITY OF THE DRUG

The distribution of a medicine is regarded to be permeability rate-limited under the following conditions:

1. If the medication in question is either ionic or polar in nature, or if it is water-soluble.
2. Situations in which very specific physiological barriers prohibit some drugs from entering the inside of the cell.

Tissue permeability is determined not only by the physicochemical properties of a medicine but also by the physiological barriers that inhibit drug diffusion into tissues.

## PHYSICOCHEMICAL PROPERTIES OF THE DRUG

The molecule size, degree of ionisation, partition coefficient, and stereochemical nature of the medication are important physicochemical parameters that determine its distribution.

**1. Molecular size of drug molecule**

A specialised transport mechanism is required for bigger molecules and ions, which can only enter the cell if they are water-soluble and have a mass that is greater than 50 Daltons. Aqueous-filled channels are only accessible to smaller, water-soluble molecules and ions.

**2. Degree of ionization of drug**

A medication that is able to remain unionised at blood/extravascular pH levels of 7.4 has a greater chance of rapidly penetrating cells. Medications that undergo ionisation at plasma pH, also known as polar and hydrophilic medicines, are unable to pass through the lipoidal cell membrane. The tissue permeability stage is the rate-limiting stage in the distribution of these medications.

**3. Partition coefficient**

A drug's partition coefficient should be between 1 to 2 for it to have acceptable tissue permeability. When two drugs have the same o/w partition coefficient but differ in the extent to which they ionise at blood pH, the drug that ionises to a lesser extent has greater penetrability than the drug that ionises to a greater extent; for instance, pentobarbital and salicylic acid have nearly the same $K_{o/w}$, but the former is more unionised at blood pH and therefore distributes more rapidly than the latter.

**4. Stereo-chemical composition**

Stereo-chemical property of the medicine will also impact its distribution properties, particularly if it has a tendency for interacting with macromolecules like proteins. This will be the case if the drug has a propensity for interacting with macromolecules.

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## PHYSIOLOGICAL BARRIERS TO DISTRIBUTION OF DRUGS

It's possible that a membrane (or a barrier) with certain structural features might act as a permeability limitation for the delivery of medicine to certain tissues.

- **Endothelial Barrier**

Whether they are ionised or unionised, the molecules of any drug with a molecular size of less than 600 Daltons are able to pass past the endothelium of the capillary and into the interstitial fluid. Because of the huge size of the complex's molecules, only drugs that are attached to blood components may be brought within.

- **The Barrier of a Simple Cell Membrane**

The figure that follows provides a concise summary of the physical characteristics that govern the amount of medicine that can pass through such a barrier (Figure 5.4).

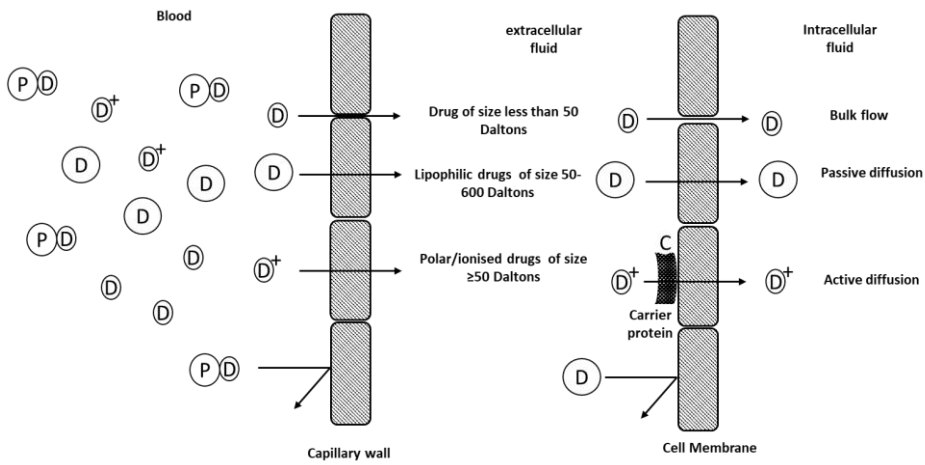


**Figure 5.4: The Barrier of a simple cell membrane.**

- **Blood-Brain Barrier (BBB)**

Endothelial cells, which are joined to one another by continuous tight intercellular junctions, are what make up the blood-brain barrier. Because of this, the channel between the cells, known as the intercellular passage, is closed, and in order for a drug to enter the brain via the

capillary circulation, it must go through the cells, known as the transcellular passage, rather than between the cells (Figure 5.5).

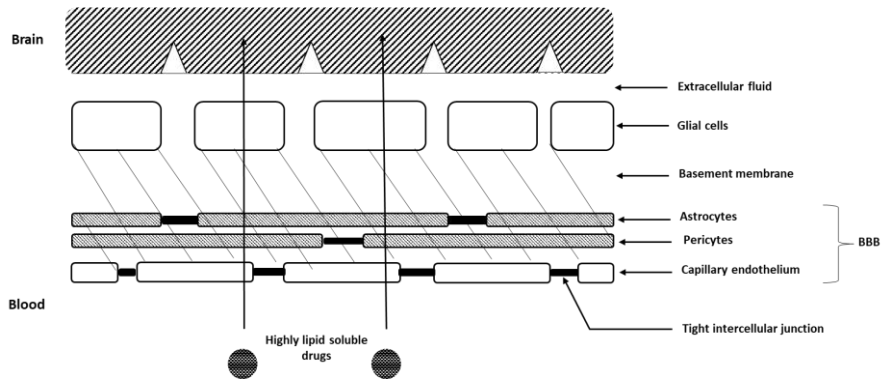


**Figure 5.5: Blood-Brain Barrier (BBB).**

**Therefore, there is only one of two routes by which a solute can enter the brain:**

1. **Passive diffusion through the lipoidal barrier** – This is limited to molecules that are very tiny (having a molecular weight that is lower than a threshold of around 700 Daltons) and have a high o/w partition coefficient.
2. **Active transport** including vital nutrients like carbohydrates and amino acids, for example. Therefore, foreign molecules with a comparable structural make-up can likewise get across the BBB via the same process.

- **Blood-Placental Barrier**

Numerous pharmaceuticals, such as ethanol, sulphonamides, barbiturates, gaseous anaesthetics, steroids, narcotic analgesics, anticonvulsants, and some antibiotics, have molecular weights that are lower than 1000 daltons and are moderately to highly soluble in lipids. These pharmaceuticals are able to easily cross the barrier through the process of simple diffusion. A chemical that has the potential to cause abnormal development in a foetus is known as a teratogen. The term "teratogenecity" refers to abnormalities in the developing foetus that are

produced by the use of a medicine when the mother is pregnant (Figure 5.6).

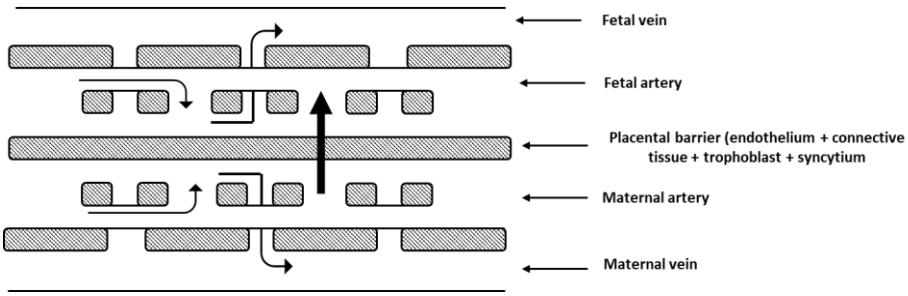


**Figure 5.6: Blood-Placental Barrier.**

- **Blood-Testis Barrier**

This barrier can be present at the intersection between two sertoli cells, rather than at the endothelium of the capillary. Due to the presence of this barrier, drugs are unable to access spermatocytes and spermatids.

### Organ/Tissue Size and Perfusion Rate

The perfusion rate will limit the distribution of a medication when the following conditions are met:

1. The drug has a very high degree of lipophilicity.
2. The membrane that the medicine is intended to diffuse through is one that is extremely permeable, such as the membranes that are found in capillaries and muscles.

The term "perfusion rate" refers to the amount of blood that flows through a tissue in a given area in a given amount of time. The rate is calculated in millilitres per minute for each millilitre of tissue. The lungs, kidneys, adrenal glands, liver, heart, and brain are all examples of highly perfused tissues. Moderately perfused tissues, such as muscle and skin, are examples of moderately perfused tissues. Finally, poorly perfused tissues are examples of poorly perfused tissues (adipose tissue and bone).

The extent to which a medicine is distributed throughout a particular organ or tissue is determined by two factors: the size of the tissue, measured in terms of its volume, and the tissue/blood partition coefficient of the drug. For instance, a rapid distribution of thiopental into

the brain following an intravenous administration of the drug was made possible by the fast perfusion rate in the brain. However, once equilibrium is reached, the medication quickly diffuses out of the brain and begins to accumulate in adipose tissue. Adipose tissue has a greater affinity for the drug as well as a volume that is more than five times that of the brain.

### Drug Binding to Body Protein

A drug can bind to many different components in the body, such as blood components (plasma proteins, blood cells, and haemoglobin) and extravascular tissue protein, and then be distributed throughout the body as required. Protein binding of drugs is the term used to describe the process in which a drug forms a complex with a protein. Due to the fact that a drug that is bound to protein is neither metabolised nor eliminated, pharmacologically speaking, it is inactive because of its inertness in both pharmacokinetics and pharmacodynamics.

**Protein + Drug ⇌ Protein-Drug complex**

The phenomenon of protein binding can be divided into the two groups. One of these is called **intracellular binding**, and it refers to the process by which a pharmacological response is brought about when a drug binds to a cell protein that may or may not be the drug receptor. **Extracellular binding** is another mechanism. When a drug binds to an extracellular protein, it does not often produce any pharmacological effects. There are two different classes for extracellular binding (Figure 5.7).

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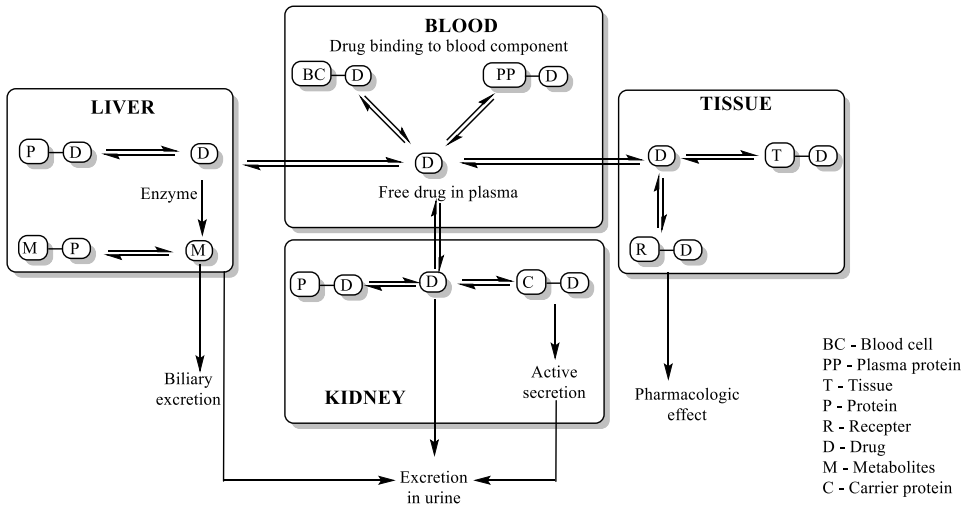


**Figure 5.7: Protein-Drug Binding.**

1. Binding of drugs to blood components such as plasma protein and blood cells, and
2. Binding of drugs to extravascular tissue proteins such as fats, bones, and so on.

The plasma protein-drug binding is the most significant type of binding and the one that has received the most attention from researchers.

### Miscellaneous Factors Affecting Drug Distribution

**1. Age**

The primary reasons for variations in the way a medicine is distributed between age groups are related to changes in the following:

- The amount of total body water that is both intracellular and extracellular in newborns is significantly higher than it is in adults.
- Compared to adults, newborns have a much higher total body water content (including both intracellular and extracellular water).
- In babies, the blood-brain barrier (BBB) is not fully established, myelin content is low, and cerebral blood flow is high; all of these factors contribute to increased drug penetration in the brain.

- Protein concentration in the plasma; babies and the elderly have a relatively low albumin concentration.
- Organ composition - In babies, the blood-brain barrier (BBB) is not fully established; myelin content is low; and cerebral blood flow is high; all of these factors contribute to increased drug penetration in the brain.

**2. Pregnancy**

As a result of the enlargement of the uterus, placenta, and foetus that occurs during pregnancy, there is a greater volume available for the distribution of drugs. Even though there is a decrease in albumin concentration, there is an increase in the volume of plasma and ECF.

**3. Obesity**

In people who are obese, the high adipose tissue content can take up a considerable percentage of lipophilic medications despite the fact that perfusion through it is poor. This is because fat has a high surface area to volume ratio.

4. **Diet**

A diet that is high in fat will cause an increase in the amounts of free fatty acids in circulation, which will have an effect on the binding of acidic medicines to albumin, such as NSAIDs.

**5. Disease States**

In meningitis and encephalitis, the blood-brain barrier (BBB) becomes more porous, allowing polar medicines such as penicillin G and ampicillin, which ordinarily cannot enter the brain, to enter.

## Apparent Volume of Distribution

It is the volume of hypothetical bodily fluid into which a medicine is dissolved or disseminated, and its definition may be found here. It is referred to as apparent volume due to the fact that not all regions of the body that have been equilibrated with the medication have the same concentration.

$$Apparent\ Volume\ of\ Distribution = \frac{Amount\ of\ Drug\ in\ the\ Body}{Plasma\ Drug\ Concentration}$$

$$V_d = \frac{X}{C}$$

Unit = Litres

There is a wide variety of $V_d$ values for different medications, ranging from as little as 3 litres (plasma volume) to as much as 40,000 litres (much above the total body size).

Distribution volume is sometimes represented as Distribution Coefficient, which may be defined as apparent volume of distribution per Kg of body weight. Sometimes, distribution volume is written as Distribution Coefficient.

$$Distribution\ Coefficient = \frac{Apparent\ Volume\ of\ Distribution}{Body\ wieght}$$

Unit = Litres/Kg

There is no correlation between the perceived volume of dispersion and the actual volume of dissemination. The true volume of distribution has an immediate bearing on physiology and is connected to the water content of the body. There are three main regions of water that make up the body water as present in Table 5.1.

**Table 5.1: Fluid Compartments of a 70 Kg Adults.**

| **Body Fluid** | **Volume (Litres)** | **% of Body Wight** | **% of TBW** |
|---|---|---|---|
| Vascular fluid/blood (Plasma) | 6 (3) | 9 (4.5) | 15 (7.5) |
| Extracellular fluid (excluding plasma) | 12 | 17 | 28 |
| Intracellular fluid (excluding blood cells | 24 | 34 | 57 |
| **Total Body Water (TBW)** | **42** | **60** | **100** |