Definition and Processes of Pharmacokinetics

See online here

How a drug works and what happens to it upon entering the body are important factors in drug design, in order to ensure optimal action in the desired amount of time. Drugs are absorbed from the site of administration into the systemic circulation, where they may interact with the proteins; they then reach their target tissues, changed or unchanged, and act on them. The moment a drug enters the systemic circulation, it starts to be simultaneously eliminated by certain biological processes. All these together constitute pharmacokinetics of the drug.

Definition of Pharmacokinetics

Pharmacokinetics is the movement of a drug through the **body's biological systems**, these processes include absorption, distribution, bioavailability, metabolism, and elimination. It can be used to study the onset, duration, and intensity of the effect of a drug. It determines the movement of the drug into, inside and out of the body.

Absorption of Drugs

To reach its target tissue, a drug must enter the systemic circulation, this includes being introduced directly into the blood (intravenous or intra-arterial administration), absorbed

through the skin, and though the digestive system.

Blood flow, the concentration of the drug at the administered site, its formulation, its physicochemical properties and the route of administration (see the section on bioavailability in Elimination Kinetics notes) are important factors that affect the absorption of the drug. In the case of oral administration, local pH and gastrointestinal contents can affect the absorption. The absorption of solid drug also depends on its disintegration in the solution.

Important: Intravenous administration provides 100 % bioavailability.

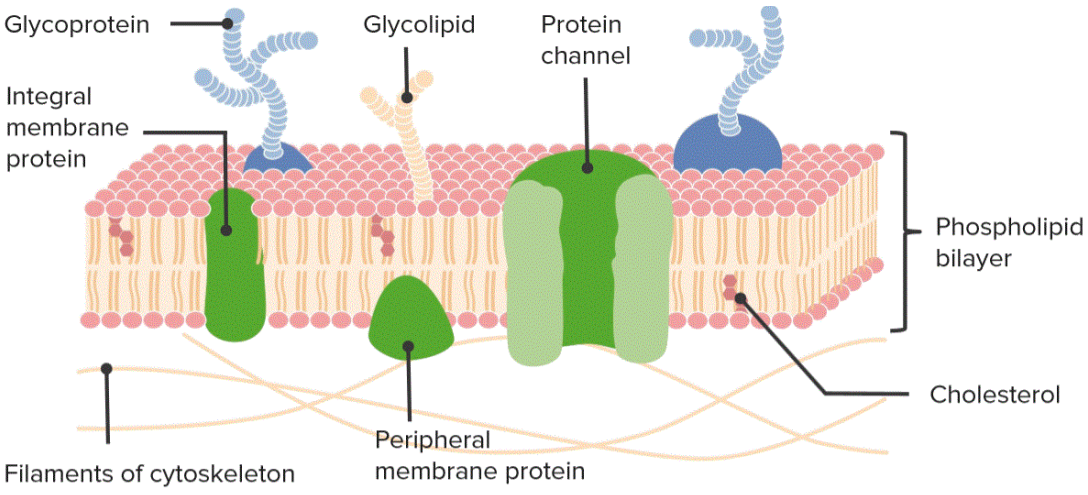
Cell Membrane

Cell membranes act as a semipermeable membrane that restricts the passage of drug molecules. Cell membranes have a **phospholipid bilayer**, with the hydrophilic heads of the each of the phospholipid layers facing outwards and the lipophilic ends facing inwards. Embedded throughout the span of this bilayer are **glycoproteins**; these glycoproteins act as ion channels, receptors, secondary messengers (G-proteins), or enzymes. Some tissues have a slightly modified cell membrane for more specialized functions. For example:

In the **capillary endothelium**, there are regions where the outer and inner membranes are fused together with no intervening cytosol—called fenestrae—which make the endothelium relatively permeable, especially to the fluid.

In the **glomerular endothelium**, there are gaps/clefts between cells; this permits larger molecules to filter through.

The **blood-brain barrier** (BBB) limits the passage of certain molecules (polar drugs) and proteins across the two fluid compartments.



"Cell Membrane" Image created by Lecturio

Transportation of drugs

A drug is absorbed from the site of administration (e.g., the gastrointestinal tract) by **passive diffusion** or **active transportation**, depending on the physicochemical properties of the drug.

For example, small lipid- or water-soluble drugs can move across the plasma membrane (through the membrane bilayers or aqueous channels/pores, respectively) from areas of high concentration to the low concentration. This is called **simple passive diffusion**. Some drugs require specialized transmembrane carrier proteins to aid their passage across the cell membrane. This is called **facilitated diffusion**. This process does not need energy and the drug molecule is not transported against the concentration gradient.

Some drugs need to be actively transported across the cell membrane by a carrier protein, a process that uses energy (usually in the form of ATP) and can be transported against a concentration gradient mostly in specific areas in the small intestine. This is called **active transport**. This usually occurs for drugs that are structurally similar to endogenous molecules, such as vitamins, sugars, and amino acids.

Drugs of very large sizes mainly protein drugs are transported by engulfment of the drug molecule by the cell membrane, which is transported inside the cell; this process is called **endocytosis**. This vesicle can either be used in the cell (e.g., iron), pushed across the cell (e.g., vitamin B12), or stored for later use (e.g., neurotransmitters).

All pharmacokinetic processes involve transport of the drug across the cell membrane.

Aqueous and lipid diffusion

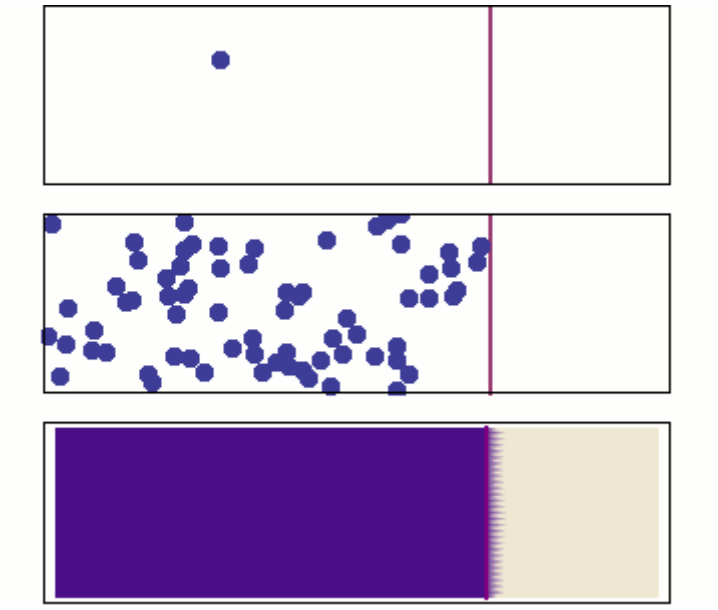


Image: “Diffusion from a microscopic and macroscopic point of view. Initially, there are solute molecules on the left side of a barrier (purple line) and none on the right. The barrier is removed, and the solute diffuses to fill the whole container. Top: A single molecule moves around randomly. Middle: With more molecules, there is a clear trend where the solute fills the container more and more evenly. Bottom: With an enormous number of solute molecules, the randomness is gone: The solute appears to move smoothly and systematically from high-concentration areas to low-concentration areas, following Fick’s laws. ”

Both aqueous diffusion and lipid diffusion are types of simple passive diffusion and are governed by **Fick’s law of diffusion**: molecules are diffused from a region of high concentration to a region of low concentration until equilibrium is achieved. It depends on the concentration gradient, size and degree of ionization, solubility in lipids and area of

the absorptive surface.

Aqueous diffusion

- Occurs through aqueous pores that are found in most cell membranes.
- Water-soluble drugs can pass along the concentration gradient.
- Permits small molecules to pass through easily
- Some tissues, e.g., the brain, testes, lack aqueous pores
- **Charged molecules pass more readily** through pores because they are attracted by water molecules in pores.
- Protein-bound drugs cannot permeate through pores.

Lipid diffusion

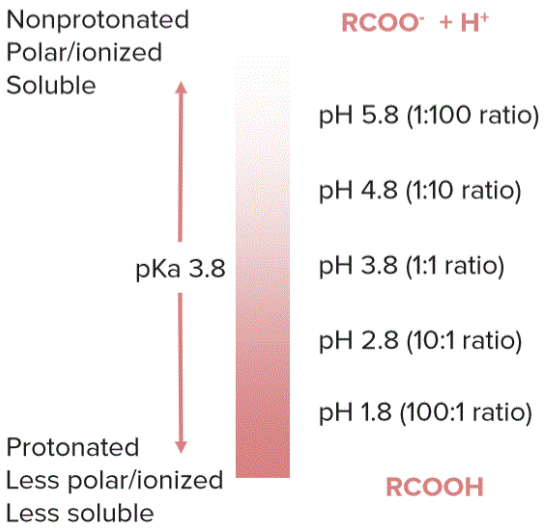
- Occurs directly across the cell membrane
- Lipid soluble drugs pass more rapidly.
- Lipid-soluble drugs pass along the concentration gradient.
- **Uncharged drugs cross membranes more easily** than charged drugs, thus, ionization of a drug will reduce its ability to cross the membrane.

Examples of acidic drugs and basic drugs

Acidic drugs	Basic drugs
• Phenytoin • Pentobarbital • Aspirin • Ibuprofen • Cloxacillin • Ethosuximide	• Caffeine • Theophylline • Codeine • Amitriptyline

Drug pKa and solubility

As mentioned, the ionization of the drug affects its transportation across the cell membrane. The amount of the ionized form present depends on the environmental pH (of the stomach, for example) and the pKa of the drug.



"Solubility of Drugs. Weak Acids (Some Drugs)" Image created by Lecturio

The **pKa of the drug is the pH at which the ionized and unionized forms of the**

drug are present in equal amounts. If the pH and the pKa are known, the fraction of the drug present in ionized state can be calculated by the **Henderson–Hasselbalch equation**. The ionized form of the drug is water-soluble and the non-ionized form of the drug is lipid-soluble. The ionization of the drug increases its renal clearance.

When the Henderson-Hasselbalch equation is more, the pH difference of drug and cell membrane is high, then trapping of ion occurs. For example, aspirin is a weak acid drug that can cause ulcers as it gets trapped due to high acidity, other drugs that can help in emptying of aspirin from the ileum.

Making urine more alkaline (i.e. by giving intravenous sodium bicarbonate) can increase the excretion of acidic drugs such as aspirin, barbiturates, and methotrexate. Alkalization also increases the ionization of drugs, which results in enhanced solubility of the acidic drug and consequently rapid elimination from the body. Thus, it helps in the treatment of drug overdose.

Important: Normal pH of urine is 6.0, through alkalization; the pH of urine can increase up to 7.5.
Acidification of urine (i.e. by giving IV ascorbic acid or ammonium chloride) increases the excretion of basic drugs such as caffeine, cocaine, and amphetamine. Similarly, acidification of urine increases the ionization of drugs which results in enhanced solubility of a basic drug and consequently rapid elimination from the body.

Important: Normal pH of urine is 6.0, through acidification; the pH of urine can decrease to 5.0.

Distribution of Drugs

After entering the systemic circulating, a drug is distributed and eliminated, often at the same time. The body has a multi-fluid compartment structure, and the drug can be distributed in any or all of those compartments:

- **Central compartment:** Organs with good blood flow (e.g., brain, heart, kidney)
- **Peripheral compartment:** Tissues with lesser blood flow (e.g., fat and muscle tissues); drugs that are stored in fat, for example, take a long time to equilibrate and the tissues can act as a reservoir, e.g., thiopental sodium.

Drugs can be bound to plasma proteins. Only the **free (unbound) drug** is available to act on the cell membranes of the target tissues. Protein binding must be taken into account when interpreting the concentration of a drug in the blood. This means a high concentration does not necessarily mean the drug is highly active, since only a small portion may be unbound while the rest is bound to protein. The unbound part of the drug is distributed to the tissues and the bound part remains in the blood. As the level of unbound drug in the blood reduces, bounded part of the drug is gradually released in the blood to meet the requirement. Thus protein-bound part remains in the blood as a storehouse of the drug.

Key points of protein binding

- Protein-bound drug is pharmacodynamically inert, neither metabolized nor excreted.
- Drugs bound to proteins through weak chemical bonds → reversible process.
- Irreversible binding of drugs can result in toxicity (e.g., irreversible binding of

paracetamol metabolites to the hepatocytes).

- Most drugs bind to human serum albumin (HSA); it's also the most abundant plasma protein.
- HSA has 4 drug binding sites.
- Competition between 2 drugs for the same binding site on HSA can result in displacement interactions; displaced drugs can cause increased toxicity (e.g., when phenylbutazone & warfarin are administered simultaneously, phenylbutazone displaces warfarin from HSA because of its higher affinity to HSA and the displaced warfarin can increase blood loss).
- Some drugs (e.g., sodium salicylate, sodium benzoate & sulfonamides) have more affinity to HSA than bilirubin → results in a displacement of bilirubin from its protein binding site; free bilirubin crosses BBB & causes brain damage (**kernicterus**).
- Decreased protein binding of a drug can result in its increased metabolism/elimination from the body.
- Increased concentration of free drug in the body can result in toxicity or increased therapeutic action.

Barriers to the distribution of drugs

- CSF barrier
- Blood-brain barrier
- Placental barrier
- Blood-testis barrier

Volume of distribution

The **apparent volume of distribution (Vd)** is defined as the volume of fluid required to contain the amount of the drug present in the body at the same concentration as measured in the plasma.

Vd = total amount of the drug administered/drug concentration of the blood

Note that Vd does not represent an actual volume (it is a **theoretical value**); it is an indicator of the amount of body fluid that would be required if the drug were distributed equally throughout the body.

Factors affecting Vd

- Higher protein binding will decrease Vd (e.g., warfarin, which has Vd of 10 liters).
- Solubility of the drug in lipids
- Binding of drug with tissues
- Storage in extravascular spaces (e.g., fat) increases Vd (e.g., chloroquine, which has Vd of 15,000 liters; these drugs show toxic effects as they eliminated from body slowly).
- Disease states can affect Vd (e.g., chronic liver disease lowers serum proteins, thereby decreasing protein binding and increasing Vd).
- Affinity for different tissues

Biotransformation

See the notes on Biotransformation of Drugs.

Elimination

See the notes on Elimination Kinetics.

Drug Development

The development of a new drug can take around 10–15 years and can cost billions of dollars. Most of the drugs fail in early clinical trials either due to toxicity or solubility/stability issues. There are several steps in the development of novel drugs.

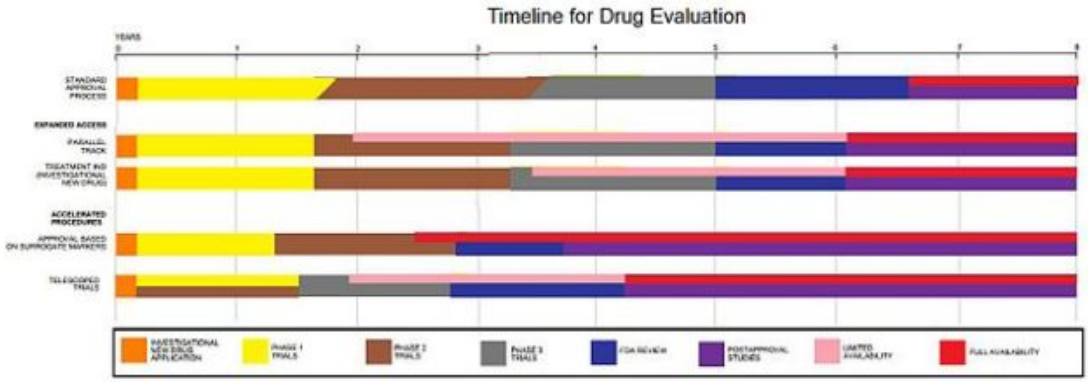


Image: "Graph showing the various approval tracks and research phases" by Kernsters. License: CC BY-SA 3.0

Step 1: Drug discovery and development

After the discovery of the drug through rigorous testing, the drug is tested for its physiochemical, pharmacokinetic, and pharmacodynamic properties. These tests aim to find out the beneficial effects of the drug against a number of diseases.

Step 2: Preclinical research

In vivo and in vitro testing to determine dosing and toxicity levels is done in animals.

Step 3: Clinical research

- **Phase I trial:** Performed in healthy volunteers (20–250) or people with the disease to determine safety and efficacy
- **Phase II trial:** Further explore safety and efficacy in a small number (100–250) of patients with the disease
- **Phase III trial:** Compare the new drug's efficacy to commonly used treatments and record adverse effects in a large group of patients (1000–6000) with the disease
- **Phase IV trial:** Long-term use in a large group of people who have the disease, often as post-marketing surveillance

Step 4: FDA review (NDA) and approval/rejection

Step 5: FDA post-marketing surveillance

The adverse effects (ADRs) not detected during clinical trials are reported to the FDA in the post-marketing surveillance phase.

Important terms

- **IND:** Investigational new drug application, an application filed to the FDA to

seek the approval to start the clinical trials of a new drug on humans

- **NDA:** New drug application, an application seeking final approval of a drug by FDA to market in the USA
- **Single and double-blind study:** A study in which a physician knows which patients are receiving active drug and placebo is called single-blind study. A study in which neither of the physician and patient knows which patients are receiving active drug and placebo is called double-blind study.
- **ANDA:** Abbreviated new drug application, an application seeking final approval of a drug whose patent has been expired (generic drug) by FDA to market in the USA. Sponsor of a drug has to prove the bioequivalence to the reference listed drug.
- **Orphan drug:** A drug that is used to treat a disease that affects only 200,000 people in the USA.
- **Blockbuster drug:** A drug that generates revenue of more than $1 billion dollars annually for a pharmaceutical company (e.g., Lipitor and Viagra).
- **FDA:** Food and drug administration, drug regulatory body of the USA

References

Harvey, R. A., Clark, M. A., Finkel, R., Rey, J. A., & Whalen, K. (2012). Lippincott's illustrated reviews: Pharmacology. Philadelphia: Wolters Kluwer.

Trevor, A. J., Katzung, B. G., Masters, S. B., & Kruidering-Hall, M. (2010). Pharmacology Examination & Board Review. New York: McGraw-Hill Medical.

Tripathi, K. D. (2013). Essentials of medical pharmacology. JP Medical Ltd.

Shaw, L. M. (Ed.). (2001). The clinical toxicology laboratory: contemporary practice of poisoning evaluation. Amer. Assoc. for Clinical Chemistry.

Biopharmaceutics and Pharmacokinetics by ByBrahmankar DM, Jaiswal SB, Publisher: VallabhPrakashan.

Drug Absorption via merckmanuals.com

The Drug Development Process via fda.gov

Notes