Elimination Kinetics: Types, Half-Life and Bioavailability

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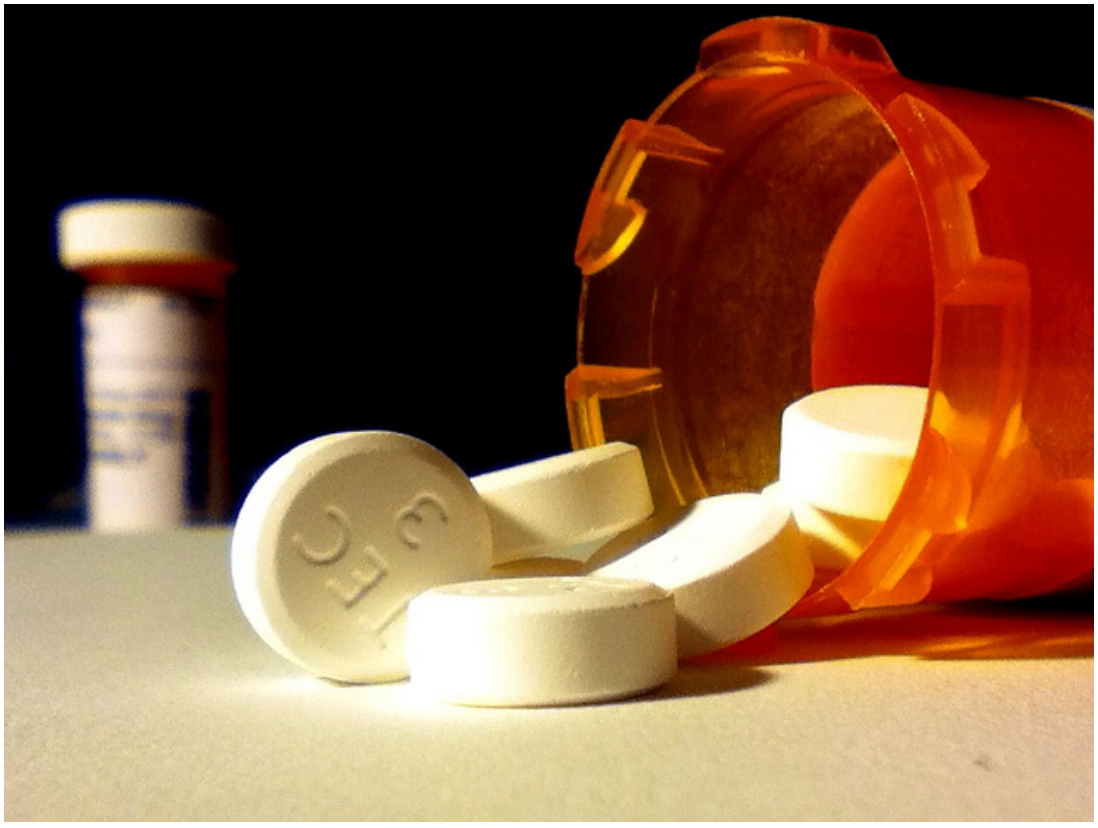
Pharmacokinetics, in simpler terms, is what a body does to a drug. Elimination or excretion of a drug is a part of the pharmacokinetic process. In this article, we will study the elimination kinetics of a drug. Various factors which affect the elimination of a drug are half-life, bioavailability, volume of distribution and first pass metabolism. To understand the pharmacokinetics or elimination kinetics of a drug effectively, these factors need to be understood first.



Background

Once a drug enters the body, it starts getting **eliminated irreversibly** (by the liver, bile, kidneys, lungs, etc.). This process reduces the plasma concentration of the drug per unit time.

When drugs dissolved in body fluids they exist in the both ionized form (water soluble and lipid insoluble and not diffuse across the body) and nonionized form (usually less water soluble and lipid soluble, it diffuses throughout lipid membranes).

Important points

- Water-soluble, non-volatile, small molecular size (less than 500 daltons) drugs are mostly eliminated through the renal route.
- Drugs having the size greater than **500 daltons** are majorly excreted in bile.
- Drugs having the size between **300–500 daltons** are excreted both in urine, as well as bile.

Routes of drug excretion

- Renal excretion – drugs are filtered, secreted and reabsorbed by the kidneys (Nonsteroidal Anti-inflammatory Drugs)
- Biliary excretion (cardiac glycosides, rifampicin, chlorpromazine)
- Pulmonary excretion (halothane)
- Salivary (caffeine, theophylline, phenytoin, carbamazepine)
- Dermal (salicylic acid)
- Swat (heavy metals)
- Mammary (diazepam, nicotine, tetracycline, morphine, barbiturates)
- Gastrointestinal (quinine)
- Genital (ciprofloxacin)

Types of Elimination Kinetics

First-order kinetics: Elimination of a constant percentage (or fraction) of the drug per unit time.
For most drugs, the elimination occurs at a **rate directly proportional to the concentration of the drug**—i.e., the higher the drug concentration, the higher its elimination rate (e.g., 50% per unit time, as shown in the figure). First-order kinetics is also referred to as non-saturable or linear kinetics.

Zero-order kinetics: Elimination of a constant quantity of the drug per unit time **independent of the concentration of the drug**.
With a few drugs, such as **aspirin**, **ethanol**, and **phenytoin**, the doses are very large. Therefore, the plasma drug concentration is much greater than the Michaelis constant Km, and drug metabolism is constant and independent of the dose. Zero-order kinetics is also known as saturable, dose- or concentration independent or nonlinear kinetics.

Half-Life

Half-life ($t1/2$) is the **time required for the plasma concentration to reduce the amount of drug in the body by 50%.** Half-life is expressed in minutes or hours**.** Thus, after two half-lifes, 25% of the drug is left; after three, 12.5%; and after 4 half-lives, 6.25%.
The half-life determines the length of the drug's effect. However, it is not the only factor, as simply calculating half-life assumes the body to be a single compartment. In reality, drugs exhibit multi compartment pharmacokinetics (i.e., distribution in different tissue and fluid spaces), which affects the "true" half-life (see the volume of distribution below).

Bioavailability

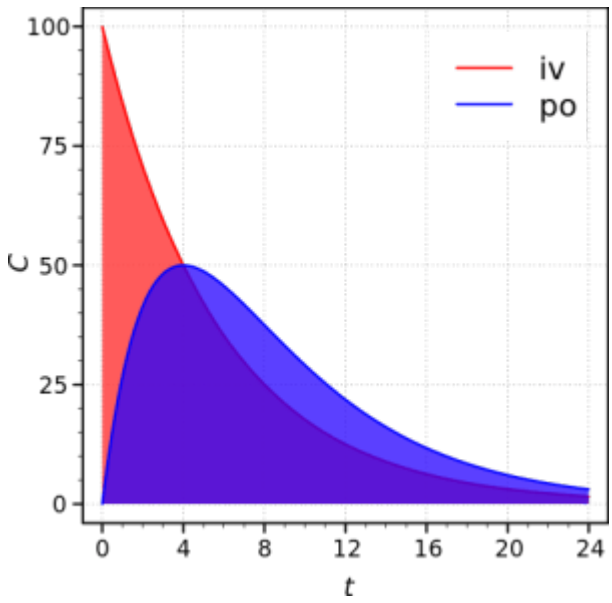


Image: “Absolute bioavailability is a ratio of areas under the curves. IV, intravenous; PO, oral route.” by Alfie. License: Public Domain

Refers to the amount of the **drug** that is absorbed from its site of administration and reaches the systemic circulation.

Bioavailability = Bioavailable dose/Administered dose

When administered intravenously, the bioavailability of the drug is assumed to be **100%.** When administered **orally**, the bioavailability of the drug is usually **less than 100% –** this is because of the following main factors:

- Extent of absorption
- First-pass metabolism (see later)
- Volume of distribution (see later)

Extent of absorption of the drug can depend on several factors, such as the physical and chemical properties of the drug **(particle size, salt form, solubility, etc.)**, its disintegration and dissolution in the lumen, pH and perfusion and poor absorption of the intestine, competing reactions (e.g., food), amount of surface available, transit time, etc.

If plasma concentration of a drug administered is plotted against time on a graph, the **area under the curve (AUC) will reflect the extent of absorption of the drug**. For a drug that follows first-order kinetics, the AUC will be proportional to its bioavailability.

Bioavailability differs not only among drugs and routes of administration, but also between different formulations of the same drug. When two drug formulations have similar bioavailability, they called **bioequivalent**.

Relative bioavailability: Whenever the bioavailability of an oral drug (for example tablet) is compared with other oral formulation (for example suspension) of same drug.

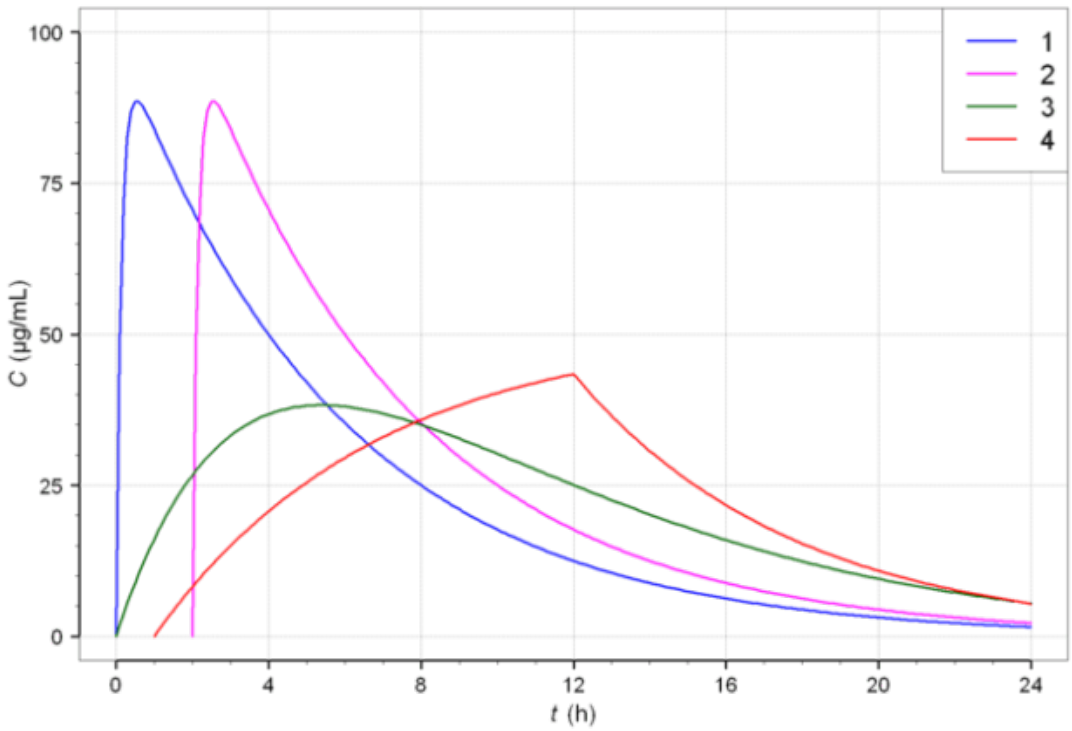


Image: “Time course of drug plasma concentrations following the administration of different extravasal formulations; t1/2 four hours: 1) IR: Immediate release oral 2) DR: Delayed release (gastric resistant; lag-time 2 hours) 3) CR: Controlled release (flip-flop PK; absorption slower than elimination) 4) TDS: Transdermal system (zero-order input rate, lag-time 1 hour; patch removed after 12 hours). Note that AUC∞ after all administrations are identical.” by Alfie. License: CC BY 3.0

First-Pass Metabolism

First-pass metabolism (or **first-pass effect**) is the phenomenon in which the **concentration of the drug is reduced after absorption** but before it reaches the systemic circulation, thereby **lowering bioavailability.**

After absorption, the portal blood carries the drug to the liver. The **drug may undergo metabolism in the liver** (or even in the portal blood or gut wall itself); in addition, the drug can be excreted into the bile.

Although preferring intravenous over oral administration may seem to be the solution for **bypassing the first-pass** effect, the oral route has numerous advantages in the form of being non-invasive, cheaper, easy to administer, etc. Alternative routes such as **transdermal and sublingual can also considerably reduce the first-pass effect**, while avoiding the risks of intravenous administration, as the drug reaches the systemic (and not portal) veins. Suppositories and the inhalational route also avoid the first-pass effect (**rectal route of administration**).

Some drugs, such as **glyceryl trinitrate** and **lignocaine**, are almost completely metabolized by the first-pass effect, and therefore cannot be administered orally. These drugs are given by **sublingual** (drug placed under the tongue) or **buccal route** (drug placed between the cheek and gum).

Other drugs that undergo considerable first-pass metabolism include the following: **alprenolol, amitriptyline, dihydroergotamine, 5-fluorouracil, hydralazine, metoprolol, nifedipine**, etc. For some of these drugs, the poor bioavailability can be overcome by administering large oral doses.

Volume of Distribution

The apparent volume of distribution (Vd) is defined that 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 is useful to compare the distribution of the drug in different compartments of the body, and thus **can be used to estimate the loading dose**.

If a drug is highly protein-bound, it remains mainly within the plasma compartment. Therefore, it said to have a low Vd. E.g., **heparin**.

If a drug has a low molecular weight, it can move through the capillaries to the interstitium, which increases its Vd. Hydrophilic drugs (e.g., **aminoglycosides**) cannot cross the interstitium through the cell membranes into the intracellular fluid, whereas lipophilic drugs can (e.g., **ethanol**).

As mentioned earlier, Vd affects half-life. If a drug has a large Vd, it means that it is spread in many extraplasmic spaces (interstitium and intracellular fluid); thus, the availability to the liver and/or kidneys for elimination is lowered, thereby extending the drug's half-life.

Clearance

Clearance (CL) of a drug is the **rate of elimination of the drug from the body in relation to its plasma concentration**. Elimination of a drug can occur at the kidneys, the liver, the lung, and/or other organs. Therefore, total systemic clearance (CL_{total}) will be a sum of clearances at all the relevant organs.

$$\mathbf{CL_{total} = CL_{hepatic} + CL_{renal} + CL_{pulmonary} + CL_{other}}$$

- Clearance is affected when there is an impairment in the function of the organ, e.g., some hepatic disease (hepatic cirrhosis, hepatitis, etc) can affect the hepatic function and decrease the metabolism and clearance of drugs in the liver (thereby prolonging the half-life).
- Drug kinetics and metabolism will affect its clearance.
- Total systemic clearance and drug half-life are important pharmacological parameters that are used for adjusting drug dosage, thereby enhancing therapeutic efficacy and minimizing toxicity.

Optimization of Dose

A drug should be administered in such a dose that maximizes the therapeutic efficacy and minimizes toxicity. The range of dose between low efficacy and high toxicity is called the **therapeutic window**. Thus, the target concentration of a drug (within the therapeutic window) can be calculated by knowing the pharmacokinetics of the drug. If the drug has a narrow therapeutic window (e.g., **warfarin** and **digoxin**), extra care is needed in the administration and drug levels may need to be monitored.

Maintenance dose: Drugs are usually administered at a frequency that maintains the concentration of the drug at a steady state within the therapeutic window. If the pharmacokinetic properties are known, the maintenance dose (or dosing rate) can be calculated as follows:

$$\mathbf{Dosing\ rate = (Target\ plasma\ concentration \times CL) / F}$$

(Where F is the bioavailability; for drugs administered via the intravenous route, F is 1.)

The maintenance dose of the same drug can also differ depending on the condition being treated. For instance, in the case of aspirin, a 300 mg dose is required to reduce pain, fever and inflammation; however, a 75 – 160 mg dose is enough if used for the prevention of cardiovascular events such as myocardial infarction and stroke in those patients with less than 160 pounds.

Loading dose: When the time taken by a drug to reach the target steady state concentration is high (for example, in drugs with long half-lifes), a loading dose should be administered to raise the plasma concentration of the drug within the target range in a shorter time. This loading dose, which is higher than the maintenance dose, can be given as one (usual) or multiple (less common) doses, and it is followed by a maintenance dose to maintain the steady state concentration.

Steady State

When a drug is administered everyday its concentration in the body increase and over time reaches a steady concentration. In that point, the concentration of drugs being absorbed is equal to the concentration of drugs being eliminated.

Dose Adjustment (for Renal Disease)

The dose that is usually prescribed is based on an average patient. However, many individual factors can affect the target plasma concentration of the drug, which has to be tailored for the individual patient if optimal therapeutic efficacy is desired.

This **adjustment is required if an organ that metabolizes (and eliminates) the drug has impairment of function**. Drugs excreted by the renal route frequently require dose adjustment based on the renal function. Renal clearance is affected by acute and chronic renal disease (in diabetes, chronic hypertension). This function of the kidneys in elimination drugs can be estimated by measuring the creatinine clearance.

Renal clearance is measuring using the **Cockcroft-Gault equation** as follows:

(140 −age) x (weight in kg) /
72 x (creatinine concentration in mg/dl)

then x (0.85 if female)

The factor of 0.85 is applied for females because women have lesser muscle mass than men, and therefore the creatinine production in women is 85% of that in men.

Limitations of this Formula

This formula is again **a more general approach**, and if very precise results are required, a 12- or 24-hour estimate should be calculated.

Hydration can affect renal clearance indirectly. Patients with stroke, for example, often have dehydration, which reduces renal clearance. However, this can be easily reversed by rehydration measures such as intravenous fluids.

Extrarenal factors can also affect renal clearance. For example, in heart failure with renal impairment, reduced clearance is seen not only because of the renal impairment, but also because of hepatic congestion and hypoxia. Thus, adjusting of the dose should

take all relevant factors into account.

Review Questions

The correct answers can be found below the references.

1. A new drug, which is to be administered orally, is being tested for its pharmacokinetic properties. Experiments show that it is almost completely absorbed through the gut. However, on measuring its systemic bioavailability, it comes to only about 33%. What is the possible mechanism behind this?

A. Saturable kinetics
B. First-pass effect
C. Long half-life
D. High volume of distribution
E. Elimination by both liver and kidney

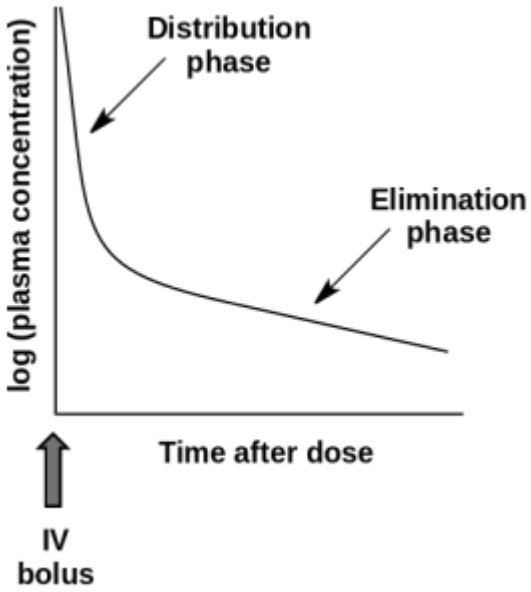


Image: "Plasma concentration (in log-scale) of drug after an IV administration" by Boghog. License: CC BY-SA 3.0

2. A drug when administered as an IV bolus shows the following multiphasic elimination, when its plasma concentration is plotted against time. Which of the following conclusions drawn from the graph is incorrect?

A. The drug follows zero-order elimination
B. The drug is rapidly distributed immediately after administration
C. The drug undergoes a substantial first-pass effect in the initial moments after administration
D. This graph can be used to calculate the t1/2 of the drug
E. The elimination phase of the drug is due to its metabolism and excretion

3. A drug with a 4-hour half-life is administered at a dose of 6mg/mL. Assuming the drug follows first-order kinetics, what amount of the drug will be left at 12 hours?

A. 0.75 mg/mL
B. 6 mg/mL
C. 3 mg/mL

D. 12 mg/mL
E. 1.5 mg/mL

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Correct answers: 1B, 2C, 3A

Notes