Pharmacokinetic and Numerical Analysis

What is Pharmacokinetic (PK) modeling?

Pharmacokinetic (PK) modeling relates to the prediction of concentration–time profiles of a drug in the body after drug administration. It is the study of the absorption, distribution, metabolism, and elimination (ADME) processes of the drug. There are multiple modeling and simulation techniques used to predict the way a drug responds to the body. Pharmacodynamic (PD) modeling relates to the relationship of the drug concentration to the pharmacological response. One of the ways that a response can be achieved is by binding to a receptor. Once the drug is bound to a receptor, the drug-induced activation or inhibition can lead to the observed pharmacological response. This relationship between drug concentration and positive/negative response can be further studied via simulation and modeling techniques. The relationship between pharmacokinetics and pharmacodynamics is to determine the appropriate dosing regimen of a drug to achieve the required pharmacological response in the body.

Examples of Pharmacokinetic (PK) modeling:

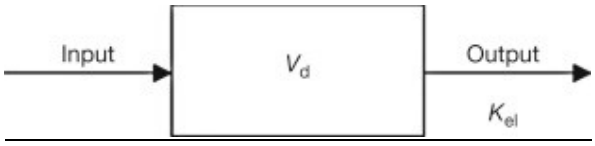
1- The one-compartment open model assumes that the body can be described as a single, uniform compartment (ie, one compartment), and that drugs can enter and leave the body (ie, open model). The simplest drug administration is when the entire drug is given in a rapid IV injection, also known as an IV bolus.

2- The two-compartment pharmacokinetic model describes the evolution of drug levels in the organism by depicting the body as two pharmacokinetic compartments

Reasons why first order elimination is valid for many drugs:

One-Compartment Model—Instantaneous Intravenous Input

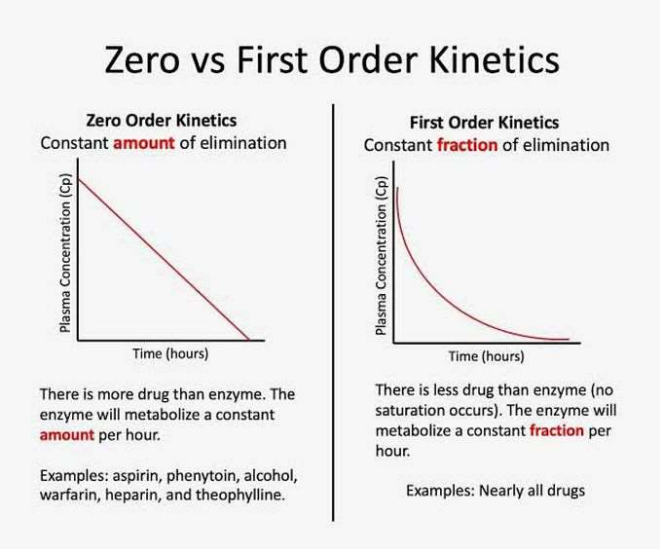
The one-compartment model represents the body as a single kinetically homogeneous entity with a defined volume into which the drug is administered and from which drug elimination occurs. This model assumes that the drug achieves instantaneous distribution and equilibration throughout the body following drug administration. In the case on the one-compartment model (instantaneous intravenous input), a single bolus dose of a drug is administered directly into the systemic circulation thereby bypassing the process of absorption. The administered drug is then rapidly distributed throughout the body, and is removed from the body by a single first-order elimination pathway. In this case, the equation that describes the rate of change of drug concentrations in plasma (dC_p/dt) after intravenous bolus administration of a drug that follows first-order elimination is shown in Eq. (3). The integrated form of Eq. (3) that describes the concentration of the drug in plasma (C_p) at any time (t) following drug administration is depicted in Eq. (4). The elimination rate constant (k_{el}) is a first order rate constant that controls the amount of the drug eliminated per unit time. The pharmacokinetic parameters such as k_{el}, elimination half-life ($t_{1/2}$), volume of distribution (V_d), and clearance (CL) that are determined from the blood concentration–time profile of a drug are useful in drug discovery and development, and for the design of suitable dosage regimens in the clinical setting.



This figure shows schematic representation of the one-compartment model showing drug input, a single first-order elimination step, and associated pharmacokinetic parameters.

$$\frac{dC_p}{dt} = -K_{el}C_p$$

$$C_p = C_0 e^{-k_{el}t}$$



Application on first order elimination: Ibuprofen:

Ibuprofen is a nonsteroidal anti-inflammatory drug that is used to relieve pain, fever, and inflammation. This includes painful menstrual periods, migraines, and rheumatoid arthritis. It may also be used to close a patent ductus arteriosus in a premature baby. It can be taken orally or intravenously.

Ibuprofen is rapidly metabolized and eliminated in the urine thus, this via accounts for more than 90% of the administered dose. It is completely eliminated in 24 hours after the last dose and almost all the administered dose goes through metabolism, representing about 99% of the eliminated dose.

The elimination rate constant from the effect compartment was 0.564 hour -1 , corresponding to a half-life of ibuprofen concentration in the effect compartment of 1.1 hours.

Table 1. The change of concentration of ibuprofen in plasma

Time [h]	Concentration [mg/L]
0.25	17.8
0.5	26.6
0.75	33.2
1	34.0
2	30.4
3	19.7
4	13. 5
6	6.5
9	2.2
12	0.6

Table 2. The change of concentration of ibuprofen in urine

Time [h]	Concentration [mg/L]	Urine volume [mL]
2	25.4	290
4	132.0	70
6	29.1	210
8	20.7	170
10	4.9	170
12	8.2	120
24	0.4	200