Unit-3

Biopharmaceutics and Pharmacokinetics

B.Pharma 6th Sem Notes

Unit: 3

Pharmacokinetics: Definition and introduction to Pharmacokinetics, Compartment models, Non compartment models, physiological models, One compartment open model. (a). Intravenous Injection (Bolus) (b). Intravenous infusion and (c) Extra vascular administrations. Pharmacokinetics parameters- KE, t1/2, Vd, AUC, Ka, Clt and CLR- definitions methods of eliminations, understanding of their significance and application

Pharmacokinetics:

Pharmacokinetics is the study of **absorption, distribution, metabolism, and excretion (ADME)** of drugs.

Introduction:

- Pharmacokinetics helps to understand how drugs reach their **site of action**, how long they stay in the body, and how they are removed.
- It provides a scientific basis for determining the **dose, route, and frequency** of drug administration.
- By studying pharmacokinetics, we can predict:
  - Onset of drug action
  - Duration of effect
  - Possible drug accumulation or toxicity

Theatrical Aspect: Developing models to predict dung behavior and using statistical methods for interpretation.

Experimental Aspect: Developing sampling techniques and analytical methods to measure drug concentration and evaluating data.

Key terms in pharmacokinetics:

Clinical Pharmacokinetics:

- Clinical pharmacokinetics is the **application of pharmacokinetic principles to the safe and effective therapeutic management of individual patients.**
  It aims to **maximize therapeutic effects and minimize toxicity** by adjusting drug dosage according to a patient's individual needs.

Population Pharmacokinetics:

- Population pharmacokinetics studies the **variability in drug concentrations among individuals in a target population** who receive standard drug doses.
  It helps identify factors (like age, weight, disease, genetics, etc.) that cause differences in drug response.

Toxicokinetics:

- Toxicokinetics is the **study of the absorption, distribution, metabolism, and excretion (ADME) of toxic substances** (chemicals or drugs) at doses that cause harmful effects.
  It helps relate the **exposure level** of a substance to its **toxic effect**.

Pharmacokinetic models

1. Compartment Models
2. Physiological Models
3. Non-compartmental Analysis

Pharmacokinetic Model Approach:

- In this approach, models are used to describe changes in drug concentration in the body with time.
- A model is a hypothesis that employs mathematical terms to concisely describe quantitative relationships.
- Pharmacokinetic models provide concise means of expressing mathematically or quantitatively, the time course of drug throughout the body and compute meaningful pharmacokinetic parameters.

Types of Pharmacokinetic Models Pharmacokinetic models are of three different types–

1. Compartment models - are also called as empirical models, and

2. Physiological models - are realistic modells.

3. Distributed parameter models - are also realistic models.

Compartment Models:

- Compartmental analysis is the traditional and most commonly used approach to pharmacokinetic characterization of a drug.
- These models simply interpolate the experimental data and allow an empirical formula to estimate the drug concentration with time.
- A compartment is not a real physiological or anatomic region but an imaginary or hypothetical one consisting of tissue/ group of tissues with similar blood flow & affinity.
- Our body is considered as composed of several compartments connected reversibly with each other.

Advantages:

- Gives visual representation of various rate processes involved in drug disposition.
- Possible to derive equations describing drug concentration changes in each compartment.
- One can estimate the amount of drug in any compartment of the system after drug is introduced into a given compartment.

Disadvantages:

- Drug given by IV route may behave according to single compartment model but the same drug given by oral route may show 2 compartment behavior.
- The type of compartment behavior i.e. Type of compartment model may change with the route of administration.

Depending upon whether the compartments are arranged parallel or in a series, compartment models are divided into two categories –

- Mammillary model
- Catenary model

Mammillary Model:

This model is the most common compartment model used in pharmacokinetics.

It consists of one or more peripheral compartments connected to the central compartment (i.e. they are joined parallel to the central compartment).

The central compartment (or compartment 1) comprises of plasma and highly perfused tissues such as lungs, liver, kidneys, etc. which rapidly equilibrate with the drug.

The drug is directly absorbed into this compartment (i.e. blood). Elimination too occurs from this compartment since the chief organs involved in drug elimination are liver and kidneys.

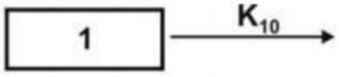
The peripheral compartments or tissue compartments (denoted by numbers 2, 3, etc.) are those with low vascularity and poor perfusion.

Distribution of drugs to these compartments is through blood. Movement of drug between compartments is defined by characteristic first-order rate constants denoted by letter K.

The subscript indicates the direction of drug movement; thus, K_{12} (K-onetwo) refers to drug movement from compartment 1 to compartment 2 and reverse for K_{21}.

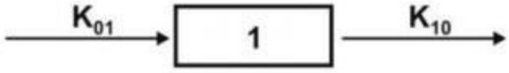
Various mammillary compartment models. The rate constant Ko1 is basically Ka, the first-order absorption rate constant and K10 is KE, the firstorder elimination rate constant.

Model 1



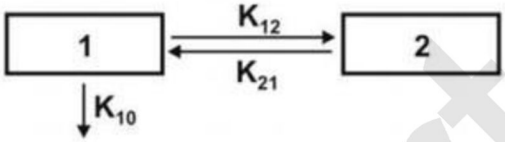
One-compartment open model, intravenous administration

Model 2



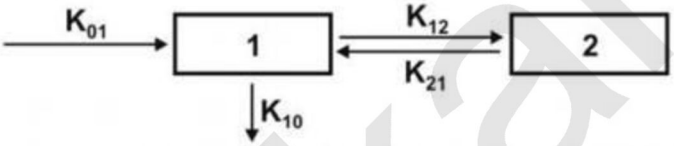
One-compartment open model, extravascular (oral, rectal, etc.) administration

Model 3



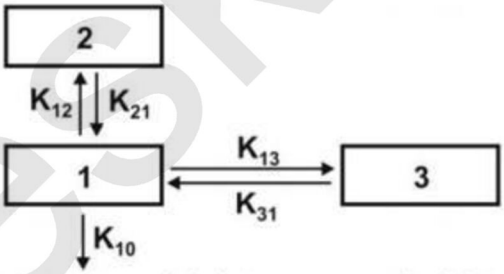
Two-compartment open model, intravenous administration

Model 4



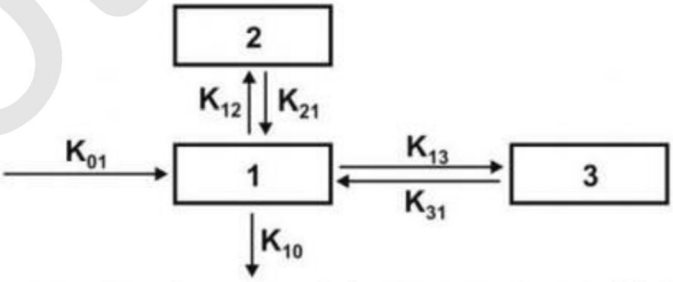
Two-compartment open model, extravascular administration

Model 5



Three-compartment open model, intravenous administration

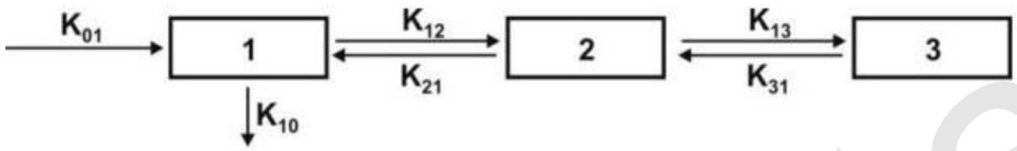
Model 6



Three-compartment open model, extravascular administration

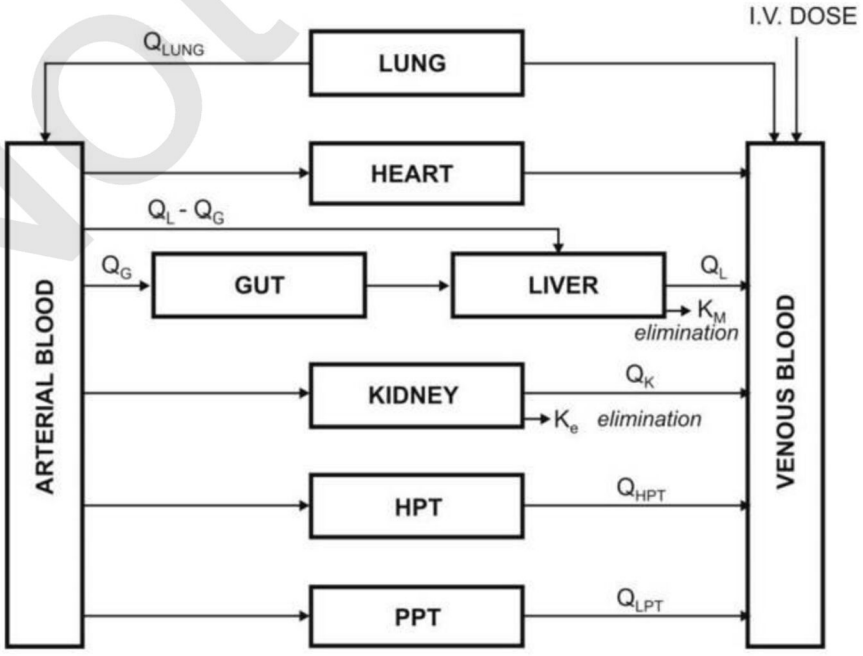
Catenary Model

In this model, the compartments are joined to one another in a series like compartments of a train. This is however not observable physiologically/anatomically as the various organs are directly linked to the blood compartment. Hence this model is rarely used.



Physiological Models:

- These models are also known as physiologically-based pharmacokinetic models (PB-PK models).
- They are drawn on the basis of known anatomic and physiological data and thus present a more realistic picture of drug disposition in various organs and tissues.
- The number of compartments to be included in the model depends upon the disposition characteristics of the drug.
- Since describing each organ/tissue with mathematic equations makes the model complex, tissues with similar perfusion properties are grouped into a single compartment.
- For example, lungs, liver, brain and kidney are grouped as rapidly equilibrating tissues (RET) while muscles and adipose as slowly equilibrating tissues (SET).
- A physiological model where the compartments are arranged in a series in a flow diagram.



Schematic representation of a physiological pharmacokinetic model. The term Q indicates blood flow rate to a body region. HPT stands for other highly perfused tissues and PPT for poorly perfused tissues. Km is rate constant for hepatic elimination and Ke is first-order rate constant for urinary excretion.

Since the rate of drug carried to a tissue organ and tissue drug uptake are dependent upon two major factors –

- Rate of blood flow to the organ, and
- Tissue/blood partition coefficient or diffusion coefficient of drug that governs its tissue permeability,

The physiological models are further categorized into two types –

1. Blood flow rate-limited models – These models are more popular and commonly used than the second type, and are based on the assumption that the drug movement within a body region is much more rapid than its rate of delivery to that region by the perfusing blood. These models are therefore also called as ***perfusion rate-limited models***. This assumption is however applicable only to the highly membrane permeable drugs i.e. low molecular weight, poorly ionised and highly lipophilic drugs, for example, thiopental, lidocaine, etc.

2. Membrane permeation rate-limited models – These models are more complex and applicable to highly polar, ionised and charged drugs, in which case the cell membrane acts as a barrier for the drug that gradually permeates by diffusion. These models are therefore also called as ***diffusion-limited models***. Owing to the time lag in equilibration between the blood and the tissue, equations for these models are very complicated.

Distributed Parameter Model

This model is analogous to physiological model but has been designed to take into account –

- Variations in blood flow to an organ, and
- Variations in drug diffusion in an organ.

Such a model is thus specifically useful for assessing regional differences in drug concentrations in tumours or necrotic tissues.

The distributed parameter model differs from physiological models in that the mathematical equations are more complex and collection of drug concentration data is more difficult.

Noncompartmental Analysis

The **noncompartmental analysis**, also called as the **model-independent method**, does not require the assumption of specific compartment model. This method is, however, based on the assumption that the drugs or metabolites follow linear kinetics, and on this basis, this technique can be applied to any compartment model.

The noncompartmental approach, based on the **statistical moments theory**, involves collection of experimental data following a single dose of drug. If one considers the time course of drug concentration in plasma as a statistical distribution curve, then:

MRT = AUMC/AUC

Where

- MRT = mean residence time
- AUMC = area under the first-moment curve
- AUC = area under the zero-moment curve

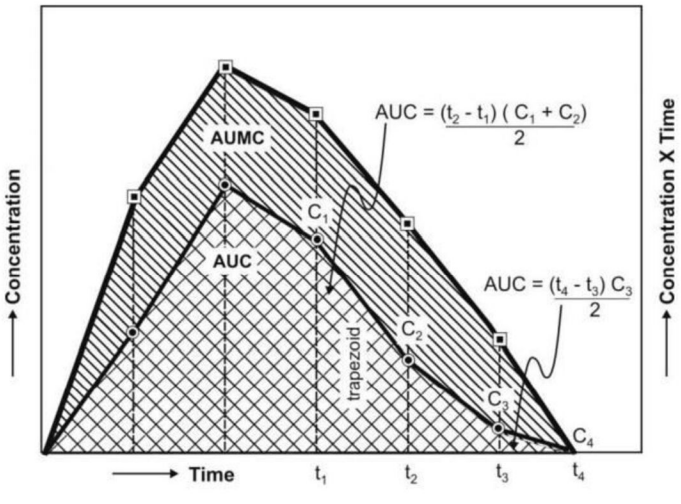
AUMC is obtained from a plot of product of plasma drug concentration and time (i.e. C.t) versus time t from zero to infinity (Fig. 8.9). Mathematically, it is expressed by equation:

$$AUMC = \int_0^\infty C\,t\,dt \qquad (9.20)$$

AUC is obtained from a plot of plasma drug concentration versus time from zero to infinity. Mathematically, it is expressed by equation:

$$AUC = \int_0^\infty C\,dt \qquad (9.21)$$

Practically, the AUMC and AUC can be calculated from the respective graphs by the **trapezoidal rule** (the method involves dividing the curve by a series of vertical lines into a number of trapezoids, calculating separately the area of each trapezoid and adding them together).



MRT *is defined as the average amount of time spent by the drug in the body before being eliminated*. In this sense, it is the statistical moment analogy of half-life, $t_{½}$. In effect, MRT represents the time for 63.2% of the intravenous bolus dose to be eliminated. The values will always be greater when the drug is administered in a fashion other than i.v. bolus.

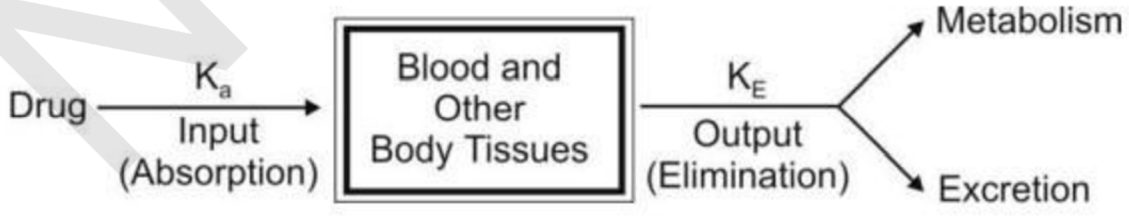
ONE-COMPARTMENT OPEN MODEL

(Instantaneous Distribution Model)

The one-compartment open model is the simplest model. Owing to its simplicity, it is based on following assumptions –

1. The body is considered as a single, kinetically homogeneous unit that has no barriers to the movement of drug.
2. Final distribution equilibrium between the drug in plasma and other body fluids (i.e. *mixing*) is attained instantaneously and maintained at all times. This model thus applies only to those drugs that distribute rapidly throughout the body.
3. Drugs move dynamically, in (absorption) and out (elimination) of this compartment.
4. Elimination is a first-order (monoexponential) process with first-order rate constant.
5. Rate of input (absorption) > rate of output (elimination).
6. The anatomical ***reference compartment*** is plasma and concentration of drug in plasma is representative of drug concentration in all body tissues i.e. any change in plasma drug concentration reflects a proportional change in drug concentration throughout the body.

However, the model does not assume that the drug concentration in plasma is equal to that in other body tissues. *The term* **open** *indicates that the input (availability) and output (elimination) are unidirectional and that the drug can be eliminated from the body*. Such a one-compartment model. One-compartment open model is generally used to describe plasma levels following administration of a single dose of a drug.



Representation of one-compartment open model showing input and output processes.

Depending upon the rate of input, several one-compartment open models can be defined:

- One-compartment open model, i.v. bolus administration.
- One-compartment open model, continuous i.v. infusion.

- One-compartment open model, e.v. administration, zero-order absorption.
- One-compartment open model, e.v. administration, first-order absorption.

Intravenous Bolus Administration:

When a drug that distributes rapidly in the body is given in the form of a rapid intravenous injection (i.e. i.v. bolus or slug), it takes about one to three minutes for complete circulation and therefore the rate of absorption is neglected in calculations. The model can be depicted as follows:

The general expression for **rate of drug presentation** to the body is:

dX/dt = Rate in (availability) - Rate out (elimination)

Since **rate in** or absorption is absent, the equation becomes:

dX / dt = - Rate out

If the **rate out** or elimination follows first-order kinetics, then:

$dX/dt = K_E X$

where, K_E = first-order elimination rate constant, and

X = amount of drug in the body at any time t remaining to be eliminated.

Negative sign indicates that the drug is being lost from the body.

Estimation of Pharmacokinetic Parameters:

For a drug that follows one-compartment kinetics and administered as rapid i.v. injection, the decline in plasma drug concentration is only due to elimination of drug from the body (and not due to distribution), the phase being called as elimination phase. **Elimination phase** can be characterized by 3 parameters—

1. Elimination rate constant
2. Elimination half-life
3. Clearance.

Elimination Rate Constant: Integration of equation 9.3 yields:

$\ln X = \ln X_o - K_E t$ (9.4)

where, X_o = amount of drug at time t = zero i.e. the initial amount of drug injected.

Equation 9.4 can also be written in the exponential form as:

$X = X_o e^{-KEt}$ (9.5)

The above equation shows that *disposition of a drug that follows one-compartment kinetics is* **monoexponential**.

Transforming equation 9.4 into common logarithms (log base 10), we get:

$$\log X = \log X_0 - \frac{K_E t}{2.303} \qquad (9.6)$$

Since it is difficult to determine directly the amount of drug in the body X, advantage is taken of the fact that a constant relationship exists between drug concentration in plasma C (easily measurable) and X; thus:

$X = V_d C$ (9.7)

where, V_d = proportionality constant popularly known as the *apparent volume of distribution*. It is a pharmacokinetic parameter that permits the use of plasma drug concentration in place of amount of drug in the body. The equation 9.6 therefore becomes:

$$\log C = \log C_0 - \frac{K_E t}{2.303} \qquad (9.8)$$

where, C_o = plasma drug concentration immediately after i.v. injection.

Equation 9.8 is that of a straight line and indicates that a semilogarithmic plot of log C versus t will be linear with *Y*-intercept log C_o. The elimination rate constant is directly obtained from the slope of the line (Fig. 9.2*b*). It has units of min^{-1}. Thus, a linear plot is easier to handle mathematically than a curve which in this case will be obtained from a plot of C versus t on regular (Cartesian) graph paper (Fig. 9.2*a*).

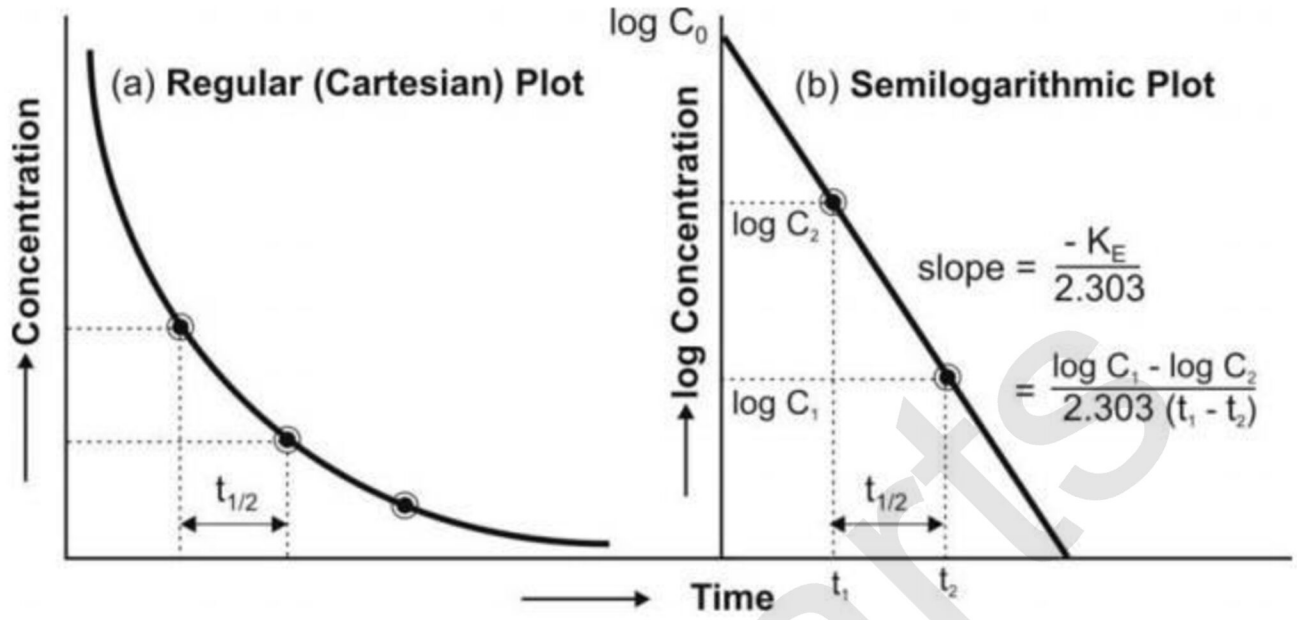


Fig. 9.2 *(a) Cartesian plot of a drug that follows one-compartment kinetics and given by rapid i.v. injection, and (b) Semilogarithmic plot for the rate of elimination in a one-compartment model.*

Thus, C_o, K_E (and $t_{½}$) can be readily obtained from log C versus t graph. The elimination or removal of the drug from the body is the sum of urinary excretion, metabolism, biliary excretion, pulmonary excretion, and other mechanisms involved therein. Thus, K_E is an additive property of rate constants for each of these processes and better called as **overall elimination rate constant**.

$$K_E = K_e + K_m + K_b + K_l + \ldots\ldots \quad (9.9)$$

The fraction of drug eliminated by a particular route can be evaluated if the number of rate constants involved and their values are known. For example, if a drug is eliminated by urinary excretion and metabolism only, then, the fraction of drug excreted unchanged in urine F_e and fraction of drug metabolized F_m can be given as:

$$F_e = \frac{K_e}{K_E} \quad (9.10a)$$

$$F_m = \frac{K_m}{K_E} \quad (9.10b)$$

Elimination Half-Life: Also called as **biological half-life**, it is the oldest and the best known of all pharmacokinetic parameters and was once considered as the most important characteristic of a drug. *It is defined as the time taken for the amount of drug in the body as well as plasma concentration to decline by one-half or 50% its initial value*. It is

expressed in hours or minutes. Half-life is related to elimination rate constant by the following equation:

$$t_{1/2} = \frac{0.693}{K_E} \qquad (9.11)$$

Elimination half-life can be readily obtained from the graph of log C versus t as shown in Fig 9.2.

Today, increased physiologic understanding of pharmacokinetics shows that *half-life is a secondary parameter that depends upon the primary parameters* clearance and apparent volume of distribution according to following equation:

$$t_{1/2} = \frac{0.693 V_d}{Cl_T} \qquad (9.12)$$

Apparent Volume of Distribution: The two separate and independent pharmacokinetic characteristics of a drug are –

1. Apparent volume of distribution, and

2. Clearance.

Since these parameters are closely related with the physiologic mechanisms in the body, they are called as **primary parameters**.

Modification of equation 9.7 defines apparent volume of distribution:

$$V_d = \frac{\text{Amount of drug in the body}}{\text{Plasma drug concentration}} = \frac{X}{C} \qquad (9.13)$$

V_d is a measure of the extent of distribution of drug and is expressed in liters. The best and the simplest way of estimating V_d of a drug is administering it by rapid i.v. injection, determining the resulting plasma concentration immediately and using the following equation:

$$V_d = \frac{X_0}{C_0} = \frac{\text{i.v. bolus dose}}{C_0} \qquad (9.14)$$

Equation 9.14 can only be used for drugs that obey one-compartment kinetics. This is because the V_d can only be estimated when distribution equilibrium is achieved between drug in plasma and that in tissues and such equilibrium is established instantaneously for a drug that follows one-compartment kinetics. A more general, more useful noncompartmental method that can be applied to many compartment models for estimating the V_d is:

For drugs given as i.v. bolus,

$$V_{d\,(area)} = \frac{X_0}{K_E\,AUC} \qquad (9.15a)$$

For drugs administered extravascularly (e.v.),

$$V_{d\,(area)} = \frac{F\,X_0}{K_E\,AUC} \qquad (9.15b)$$

where, X_o = dose administered, and F = fraction of drug absorbed into the systemic circulation. F is equal to *one* i.e. complete availability when the drug is administered intravenously.

Clearance: Difficulties arise when one applies elimination rate constant and half-life as pharmacokinetic parameters in an anatomical/physiological context and as a measure of drug elimination mechanisms. A much more valuable alternative approach for such applications is use of clearance parameters to characterize drug disposition. *Clearance is the most important parameter in clinical drug applications and is useful in evaluating the mechanism by which a drug is eliminated by the whole organism or by a particular organ.*

Just as V_d is needed to relate plasma drug concentration with amount of drug in the body, clearance is a parameter to relate plasma drug concentration with the rate of drug elimination according to following equation:

$$\text{Clearance} = \frac{\text{Rate of elimination}}{\text{Plasma drug concentration}} \qquad (9.16)$$

$$\text{or} \qquad Cl = \frac{dX/dt}{C} \qquad (9.17)$$

Clearance *is defined as the theoretical volume of body fluid containing drug* (i.e. that fraction of apparent volume of distribution) *from which the drug is completely removed in a given period of time*. It is expressed in ml/min or liters/hour. Clearance is usually further defined as **blood clearance** (Cl_b), **plasma clearance** (Cl_p) or clearance based on

unbound or free drug concentration (Cl_u) depending upon the concentration C measured for the right side of the equation 9.17.

Total Body Clearance: Elimination of a drug from the body involves processes occurring in kidney, liver, lungs and other eliminating organs. *Clearance at an individual organ level is called as* **organ clearance**. It can be estimated by dividing the rate of elimination by each organ with the concentration of drug presented to it. Thus,

Renal Clearance $$Cl_R = \frac{\text{Rate of elimination by kidney}}{C} \quad (9.18a)$$

Hepatic Clearance $$Cl_H = \frac{\text{Rate of elimination by liver}}{C} \quad (9.18b)$$

Other Organ Clearance $$Cl_{Others} = \frac{\text{Rate of elimination by other organs}}{C} \quad (9.18c)$$

The **total body clearance**, Cl_T, *also called as* **total systemic clearance**, *is an additive property of individual organ clearances*. Hence,

Total Systemic Clearance

$$Cl_T = Cl_R + Cl_H + Cl_{Others} \quad (9.18d)$$

Because of the additivity of clearance, the relative contribution by any organ in eliminating a drug can be easily calculated. *Clearance by all organs other than kidney is sometimes known as* **nonrenal clearance** Cl_{NR}. It is the difference between total clearance and renal clearance.

According to an earlier definition (equation 9.17),

$$Cl_T = \frac{dX/dt}{C} \quad (9.17)$$

Substituting $dX/dt = K_E X$ from equation 9.3 in above equation, we get:

$$Cl_T = \frac{K_E X}{C} \quad (9.19)$$

Since $X/C = V_d$ (from equation 9.13), the equation 9.19 can be written as:

$$Cl_T = K_E V_d \quad (9.20a)$$

Parallel equations can be written for renal and hepatic clearances as:

$$Cl_R = K_e V_d \quad (9.20b)$$

$$Cl_H = K_m V_{dm} \quad (9.20c)$$

Since $K_E = 0.693/t_{½}$ (from equation 9.11), clearance can be related to half-life by the following equation:

$$Cl_T = \frac{0.693\,V_d}{t_{1/2}} \qquad (9.21)$$

Identical equations can be written for Cl_R and Cl_H in which cases the $t_{½}$ will be urinary excretion half-life for unchanged drug and metabolism half-life respectively. Equation 9.21. shows that as Cl_T decreases, as in renal insufficiency, $t_{½}$ of the drug increases. As the Cl_T takes into account V_d, changes in V_d as in obesity or oedematous condition will reflect changes in Cl_T.

The noncompartmental method of computing total clearance for a drug that follows one-compartment kinetics is:

For drugs given as i.v. bolus $$Cl_T = \frac{X_0}{AUC} \qquad (9.22a)$$

For drugs given e.v. $$Cl_T = \frac{F X_0}{AUC} \qquad (9.22b)$$

For a drug given by i.v. bolus, the renal clearance Cl_R may be estimated by determining the total amount of unchanged drug excreted in urine, X_u^{∞} and AUC.

$$Cl_R = \frac{X_u^{\infty}}{t_{1/2}} \qquad (9.23)$$

Organ Clearance: The best way of understanding clearance is at individual organ level. Such a physiologic approach is advantageous in predicting and evaluating the influence of pathology, blood flow, P-D binding, enzyme activity, etc. on drug elimination. At an organ level, the rate of elimination can be written as:

Rate of elimination by an organ = **Rate of presentation to the organ** - **Rate of exit from the organ** (9.24)

Rate of presentation (input) = Organ blood flow X Entering concentration
= $Q C_{in}$ (9.25)

Rate of exit (output) = Organ blood flow X Exiting concentration
= $Q C_{out}$ (9.26)

s

Substitution of equations 9.25 and 9.26 in equation 9.24 yields:

Rate of elimination = $Q\ C_{in} - Q\ C_{out}$

(also called as **Rate of extraction**) = $Q\ (C_{in} - C_{out})$ (9.27)

Division of above equation by concentration of drug that enters the organ of elimination C_{in} yields an expression for clearance of drug by the organ under consideration. Thus:

$$\frac{\text{Rate of extraction}}{C_{in}} = Cl_{organ} = \frac{Q(C_{in} - C_{out})}{C_{in}} = Q \qquad (9.28)$$

where, ER = $(C_{in} - C_{out})/C_{in}$ is called as **extraction ratio**. It has no units and its value ranges from zero (no elimination) to one (complete elimination). Based on ER values, drugs can be classified into 3 groups:

1. Drugs with **high ER** (above 0.7),

2. Drugs with **intermediate ER** (between 0.7 to 0.3), and

3. Drugs with **low ER** (below 0.3).

ER *is an index of how efficiently the eliminating organ clears the blood flowing through it of drug*. For example, an ER of 0.6 tells that 60% of the blood flowing through the organ will be completely cleared of drug. The fraction of drug that *escapes removal* by the organ is expressed as:

$F=1-ER$ (9.29)

where, **F = systemic availability** when the eliminating organ is liver.

Hepatic Clearance: For certain drugs, the nonrenal clearance can be assumed as equal to hepatic clearance Cl_H. It is given as:

$Cl_H = Cl_T - Cl_R$ (9.30)

An equation parallel to equation 9.28 can also be written for hepatic clearance:

$Cl_H = Q_H\ ER_H$ (9.31)

where,

Q_H = hepatic blood flow (about 1.5 liters/min), and

ER_H = hepatic extraction ratio.

The hepatic clearance of drugs can be divided into two groups:

1. Drugs with hepatic blood flow rate-limited clearance, and

2. Drugs with intrinsic capacity-limited clearance.

1. Hepatic Blood Flow: When ER_H is one, Cl_H approaches its maximum value i.e. hepatic blood flow. In such a situation, hepatic clearance is said to be **perfusion rate-limited** or **flow-dependent**. Alteration in hepatic blood flow significantly affects the elimination of drugs with high ER_H e.g. propranolol, lidocaine, etc. Such drugs are removed from the blood as rapidly as they are presented to the liver (high first-pass hepatic metabolism). Indocyanine green is so rapidly eliminated by the human liver that its clearance is often used as an indicator of hepatic blood flow rate. First-pass hepatic extraction is suspected when there is lack of unchanged drug in systemic circulation after oral administration. **Maximum oral availability F** for such drugs can be computed from equation 9.29. An extension of the same equation is the noncompartmental method of estimating F:

$$F = 1 - ER_H = \frac{AUC_{oral}}{AUC_{i.v.}} \qquad (9.32)$$

TABLE 9.1

Influence of Blood Flow Rate and Protein Binding on Total Clearance of Drugs with High and with Low ER Values

Drugs with	*Changes in Total Clearance due to*			
	↑ *Blood Flow*	↓ *Blood Flow*	↑ *Binding*	↓ *Binding*
High ER (above 0.7)	↑	↓	No change	No change
Low ER (below 0.3)	No change	No change	↓	↑

where, ↑ = increase, and ↓ = decrease

On the contrary, hepatic blood flow has very little or no effect on drugs with low ER_H e.g. theophylline. For such drugs, whatever concentration of drug present in the blood perfuses liver, is more than what the liver can eliminate (low first-pass hepatic metabolism). Similar discussion can be extended to the influence of blood flow on renal clearance of drugs. This is illustrated in Table 9.1. Hepatic clearance of a drug with high ER is independent of protein binding.

2. Intrinsic Capacity Clearance: *Denoted as* **Cl_{int}**, *it is defined as the inherent ability of an organ to irreversibly remove a drug in the absence of any flow limitation*. It depends, in this case, upon the hepatic enzyme activity. Drugs with low ER_H and with elimination primarily by metabolism are greatly affected by changes in enzyme activity. Hepatic clearance of such drugs is said to be **capacity-limited**, e.g. theophylline. The $t_{½}$ of such drugs show great intersubject variability. Hepatic clearance of drugs with low ER is independent of blood flow rate but sensitive to changes in protein binding.

The hepatic and renal extraction ratios of some drugs and metabolites are given in Table 9.2.

TABLE 9.2

Hepatic and Renal Extraction Ratio of Some Drugs and Metabolites

	Extraction Ratio		
	High	*Intermediate*	*Low*
Hepatic Extraction	Propranolol Lidocaine Nitroglycerine Morphine Isoprenaline	Aspirin Codeine Nortriptyline Quinidine	Diazepam Phenobarbital Phenytoin Procainamide Theophylline
Renal Extraction	Some penicillins Hippuric acid Several sulphates Several glucuronides	Some penicillins Procainamide Cimetidine	Digoxin Furosemide Atenolol Tetracycline

Source: https://www.pharmacy180.com/article/one-compartment-open-model---intravenous-bolus-administration-2519/

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