CHAPTER III

THEORETICAL ANALYSIS
3.1 Theories of drug dissolution

Dissolution is a process in which a solid substance solubilizes in a given solvent i.e. mass transfer from the solid surface to the liquid phase. Several theories to explain drug dissolution have been proposed. Some of the important ones are:

1. Diffusion layer model/Film theory
2. Danckwert’s model/Penetration or Surface renewal theory, and
3. Interfacial barrier model/Double barrier or Limited solvation theory

3.1.1 Diffusion Layer Model/Film Theory

This is the simplest and the most common theory for dissolution. Here, the process of dissolution of solid particles in a liquid, in the absence of reactive or chemical forces, consists of two consecutive steps:

1. Solution of the solid to form a thin film or layer at the solid/liquid interface called as the stagnant film or diffusion layer which is saturated with the drug; this step is usually rapid, and
2. Diffusion of the soluble solute from the stagnant layer to the bulk of the solution; this step is slower and is therefore the rate-determining step in drug dissolution. The model is depicted in Fig. 3.1.

![Diffusion layer model for drug dissolution](image)

**Fig. 3.1**: Diffusion layer model for drug dissolution
The earliest equation to explain the rate of dissolution when the process is diffusion controlled and involves no chemical reaction was given by Noyes and Whitney:

\[
\frac{dC}{dt} = k(C_s - C_b)
\]

Where

\( DC/dt \) = dissolution rate of the drug

\( K \) = dissolution rate constant (first order),

\( C_s \) = concentration of drug in the stagnant layer (also called as the saturation or maximum drug solubility), and

\( C_b \) = concentration of drug in the bulk of the solution at time \( t \).

Equation 3.1 was based on Fick's second law of diffusion. Brunner incorporated Fick's first law of diffusion and modified the Noyes-Whitney's equation to:

\[
\frac{dC}{dt} = \frac{DAK_{\text{w-o}}(C_s - C_b)}{Vh}
\]

where,

\( D \) = diffusion coefficient (diffusivity) of the drug

\( A \) = surface area of the dissolving solid

\( K_{\text{w-o}} \) = water/oil partition coefficient of the drug considering the fact that dissolution body fluids are aqueous. Since the rapidity with which a drug dissolves depends on the \( K_{\text{w-o}} \), it is also called as the intrinsic dissolution rate constant. It is a characteristic of drugs.

\( V \) = volume of dissolution medium

\( H \) = thickness of the stagnant layer

\((C_s - C_b)\) = concentration gradient for diffusion of drug

The influence of various parameters in equation 3.2 on drug dissolution is depicted in Table 3.1.
Table 3.1

Influence of Some Parameters on Dissolution Rate of Drug

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Symbol</th>
<th>Influence on Drug Dissolution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diffusion Coefficient of Drug</td>
<td>D</td>
<td>Greater the value, faster the dissolution. Diffusion decreases as the viscosity of dissolution medium increases.</td>
</tr>
<tr>
<td>Surface Area of Solid Drug</td>
<td>A</td>
<td>Greater the surface area, faster the dissolution; can be increased by micronization of drug.</td>
</tr>
<tr>
<td>Water/Oil Partition Coefficient of Drug</td>
<td>K&lt;sub&gt;mo&lt;/sub&gt;</td>
<td>Higher the value, more the hydrophilicity and faster the dissolution in aqueous fluids.</td>
</tr>
<tr>
<td>Concentration Gradient</td>
<td>(C&lt;sub&gt;s&lt;/sub&gt; - C&lt;sub&gt;b&lt;/sub&gt;)</td>
<td>Greater the concentration gradient faster the diffusion and drug dissolution; can be increased by increasing drug solubility and the volume of dissolution medium.</td>
</tr>
<tr>
<td>Thickness of Stagnant Layer</td>
<td>h</td>
<td>More the thickness, lesser the diffusion and drug dissolution, can be decreased by increasing agitation.</td>
</tr>
</tbody>
</table>

Equation 3.2 represents first-order dissolution rate process, the driving force for which is the concentration gradient (C<sub>s</sub> - C<sub>b</sub>). Under such a situation, dissolution is said to be under nonsink conditions. This is true in case of in vitro dissolution in a limited dissolution medium. Dissolution in such a situation slows down after sometime due to build-up in the concentration of drug in the bulk of the solution. The in vivo dissolution is always rapid than in vivo dissolution because the moment the drug dissolves, it is absorbed into the systemic circulation. As a result, C<sub>b</sub> = 0, and dissolution is at its maximum. Thus, under in vivo conditions, there is no concentration build-up in the bulk of the solution and hence no retarding effect on the dissolution rate of the drug i.e. C<sub>s</sub> >> C<sub>b</sub> and sink conditions are maintained. Under sink conditions, if the volume and surface area of solid are kept constant, then equation 3.2 reduces to:

\[
\frac{dC}{dt} = K
\]  

3.3
where K incorporates all the constants in equation 3.2. Equation 3.3 represents that the dissolution rate is constant under sink conditions and follows zero-order kinetics i.e. yields a linear plot (Fig. 3.2)

To obtain good in vitro – in vivo dissolution rate correlation, the in vitro dissolution must always be carried under sink conditions. This can be achieved by:

1. Bathing the dissolving solid in fresh solvent from time to time.
2. Increasing the volume of dissolution fluid
3. Removing the dissolved drug by partitioning it from the aqueous phase of the dissolution fluid into an organic phase placed either above or below the dissolution fluid – for example, hexane or chloroform.
4. Adding a water miscible solvent such as alcohol to the dissolution fluid, or
5. By adding selected adsorbents to remove the dissolved drug.

Fig. 3.2 : Dissolution rate under nonsink and sink conditions

The in vitro sink conditions are so maintained that \( C_b \) is always less than 10% of \( C_a \).
The Noyes-Whitney's equation assumes that the surface area of the dissolving solid remains constant during dissolution, which is practically not possible for dissolving particles. Hence, dissolution methods that involve use of constant surface area discs are employed to determine the rate of dissolution.

To account for the particle size decrease and change in surface area accompanying dissolution, Hixson and Crowell's cubic root law of dissolution is used:

\[ W_o^{1/3} - W^{1/3} = Kt \]  \hspace{1cm} 3.4

Where

- \( W_o \) = original mass of the drug
- \( W \) = mass of the drug remaining to dissolve at time \( t \)
- \( K \) = dissolution rate constant

3.1.2 Danckwert's Model (Penetration or Surface Renewal Theory)

Danckwert did not approve of the existence of a stagnant layer and suggested that turbulence in the dissolution medium exists at the solid/liquid interface. As a result, the agitated fluid consisting of macroscopic mass of eddies or packets reach the solid/liquid interface in a random fashion due to eddy currents, absorb the solute by diffusion and carry it to the bulk of the solution. Such solute containing packets are continuously replaced with new packets of fresh solvent due to which the drug concentration at the solid/liquid interface never reaches \( C_o \) and has a lower limiting value of \( C_e \). Since the solvent packets are exposed to new solid surface each time, the theory is called as surface renewal theory.

The Danckwert's model is expressed by equation:

\[ \sqrt[3]{\frac{dC}{dt}} = \frac{dm}{dt} = A(C_o - C_b) \sqrt{\gamma D} \]  \hspace{1cm} 3.5

where,

- \( m \) = mass of solid dissolved, and
- \( \gamma \) = rate of surface renewal (or the interfacial tension)

The model is depicted in Fig. 3.3
3.1.3 Interfacial Barrier Model (Double barrier or limited solvation theory)

The diffusion layer model and the Danckwert's model were based on two assumptions:

1. The rate-determining step that controls dissolution is the mass transport.
2. Solid-solution equilibrium is achieved at the solid/liquid interface.

According to the interfacial barrier model, an intermediate concentration can exist at the interface as a result of solvation mechanism and is a function of solubility rather than diffusion. When considering the dissolution of a crystal, each face of the crystal will have a different interfacial barrier. Such a concept is given by the following equation.

\[ G = K_i (C_s - C_b) \]  

Where,

- \( G \) = dissolution rate per unit area, and
- \( K_i \) = effective interfacial transport constant

In this theory, the diffusivity \( D \) may not be independent of saturation concentration \( C_s \).

The interfacial barrier model can be extended to both diffusion layer model and the Danckwert's model.

3.2 In vitro drug dissolution testing models

For an in vitro test to be useful, it must predict the in vivo behavior to such an extent that in vivo bioavailability test need not be performed. Despite attempts to standardize the test performance,
the in vitro dissolution technique is still by no means a perfect approach. The efforts are mainly aimed at mimicking the environment offered by the biological system.

There are several factors that must be considered in the design of a dissolution test. They are:

1. **Factors relating to the dissolution apparatus** such as – the design, the size of the container (several ml, to several liters), the shape of the container (round bottomed or flat), nature of agitation (stirring, rotating or oscillating methods), speed of agitation, performance precision of the apparatus, etc.

2. **Factors relating to the dissolution fluid** such as – composition (water, 0.1N HCl, phosphate buffer, simulated gastric fluid, simulated intestinal fluid, etc.), viscosity, volume (generally larger than that needed to completely dissolve the drug under test), temperature (generally 37°C) and maintenance of sink (drug concentration in solution maintained constant at a low level) or nonsink conditions (gradual increase in the drug concentration in the dissolution medium).

3. **Process parameters** such as method of introduction of dosage form, sampling techniques, changing the dissolution fluid, etc.

The dissolution apparatus has evolved gradually and considerably from a simple beaker type to a highly versatile and fully automated instrument. The devices can be classified in a number of ways. Based on the absence or presence of sink conditions, there are two principal types of dissolution apparatus:

1. **Closed-compartment apparatus**: It is basically a limited-volume apparatus operating under nonsink conditions. The dissolution fluid is restrained to the size of the container, e.g. beaker type apparatus.

2. **Open-compartment apparatus**: It is the one in which the dosage form is contained in a column which is brought in continuous contact with fresh, flowing dissolution medium (perfect sink condition).

A third type called as **dialysis systems** are used for very poorly aqueous soluble drugs for which maintenance of sink conditions would otherwise require large volume of dissolution fluid.
3.2.1 Rotating Basket Apparatus (apparatus 1)

It is basically a closed-compartment, beaker type apparatus comprising of a cylindrical glass vessel with hemispherical bottom of one liter capacity partially immersed in a water bath to maintain the temperature at 37°C. A cylindrical basket made of 22 mesh to hold the dosage form is located centrally in the vessel at a distance of 2 cm from the bottom and rotated by a variable speed motor through a shaft. The basket should remain in motion during drawing of samples. All metal parts like basket and shaft are made of S.S. 316.

3.2.2 Rotating Paddle Apparatus (Apparatus 2)

The assembly is same as that for apparatus 1 except that the rotating basket is replaced with a paddle which acts as a stirrer. The dosage form is allowed to sink to the bottom of the vessel. A small, loose, wire helix may be attached to the dosage form that would otherwise float.

Fig. 3.4: Schematic representation of official dissolution apparatus forced convection nonsink type (a) Rotating basket apparatus, and (b) rotating paddle apparatus
3.3 Bioavailability

The therapeutic effectiveness of a drug depends upon the ability of the dosage form to deliver the medicament to its site of action at a rate and amount sufficient to elicit the desired pharmacologic response. This attribute of the dosage form is referred to as physiologic availability, biologic availability or simply bioavailability. For most drugs, the pharmacologic response can be related directly to the plasma levels. Thus, the term bioavailability is defined as the rate and extent (amount) of absorption of unchanged drug from its dosage form. It is an absolute absorption of unchanged drug from its dosage form. It is an absolute term. The rate or rapidity with which a drug is absorbed is an important consideration when a rapid onset of action is desired as in the treatment of acute conditions such as asthma attack, pain, etc. A slower absorption rate is however desired when the aim is to prolong the duration of action or to avoid the adverse effects. On the other hand, extent of absorption is of special significance in the treatment of chronic conditions like hypertension, epilepsy, etc.

If the size of the dose to be administered is same, then bioavailability of a drug from its dosage form depends upon 3 major factors:

1. Pharmacetic factors related to physicochemical properties of the drug and characteristics of the dosage form.
2. Patient related factors
3. Route of administration

The influence of route of administration on drug's bioavailability is generally in the following order: parenteral > oral > rectal > topical with few exceptions. Within the parenteral route, intravenous injection of a drug results in 100% bioavailability as the absorption process is bypassed. However, for reasons of stability and convenience, most drugs are administered orally. In such cases, the dose available to the patient called as the bioavailable dose, is often less than the administered dose. The amount of drug that reaches the systemic circulation (i.e. extent of absorption) is called a systemic availability or simply availability. The term bioavailable fraction F, refers to the fraction of administered dose that enters the systemic circulation.

\[
F = \frac{\text{Bioavailable dose}}{\text{Administered dose}}
\]
3.3.1 Objectives of Bioavailability Studies

Bioavailability studies are important in the –

1. Primary stages of development of a suitable dosage form for a new drug entity.
2. Determination of influence of excipients, patient related factors and possible interaction with other drugs on the efficiency of absorption.
3. Development of new formulations of the existing drugs.
4. Control of quality of a drug product during the early stages of marketing in order to determine the influence of processing factors, storage and stability on drug absorption.

3.3.2 Considerations in bioavailability study design

3.3.2.1 Bioavailability – Absolute versus Relative

When the systemic availability of a drug administered orally is determined in comparison to its intravenous administration, it is called as absolute bioavailability. It is denoted by symbol $F$. Its determination is used to characterize a drug’s inherent absorption properties from the e.v. site. Intravenous dose is selected as a standard because the drug is administered directly into the systemic circulation (100% bioavailability) and avoids absorption step. Intramuscular dose can also be taken as a standard if the drug is poorly water soluble. An oral solution as reference standard has also been used in certain cases. However, there are several drawbacks of using oral solution as a standard instead of an i.v. dose.

- Limits the pharmacokinetic treatment to one-compartment model only; one cannot apply the most applicable two-compartment kinetics to the data and all pharmacokinetic parameters cannot be assessed.
- Differentiation between the fraction of dose unabsorbed and that metabolized is difficult.
- If the rate of oral absorption is not sufficiently greater than the rate of elimination, the true elimination rate constant cannot be computed.
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At best, when oral solution is used in conjunction with i.v. route, one can distinguish the dissolution rate limitation in drug absorption from solid dosage forms.

When the systemic availability of a drug after oral administration is compared with that of an oral standard of the same drug (such as an aqueous or nonaqueous solution or a suspension), it is referred to as relative bioavailability. It is denoted by symbol $F_r$. In contrast to
absolute bioavailability, it is used to characterize absorption of a drug from its formulation. \( F \) and \( F_i \) are generally expressed in percentages.

3.3.2.2 Single dose versus multiple dose studies

The dose to be administered for a bioavailability study is determined from preliminary clinical experiments. Single dose bioavailability studies are very common. They are easy, offer less exposure to drugs and are less tedious. However, it is difficult to predict the steady-state characteristics of a drug and intersubject variability with such studies. On the other hand, multiple dose study is difficult to control (poor subject compliance), exposes the subject to more drug and is highly tedious and time consuming. Nevertheless, such a study has several advantages –

1. More accurately reflects the manner in which the drug should be used
2. Easy to predict the peak and valley characteristics of the drug since the bioavailability is determined at steady-state.
3. Requires collection of fewer blood samples.
4. The drug blood levels are higher due to cumulative effect which makes its determination possible even by the less sensitive analytic methods.
5. Can be ethically performed in patients because of the therapeutic benefit to the patient.
6. Small intersubject variability is observed in such a study which allows use of fewer subjects.
7. Better evaluation of the performance of a controlled release formulation is possible.
8. Nonlinearity in pharmacokinetics, if present, can be easily detected.

In multiple dose study, one must ensure that the steady-state has been reached. For this, the drug should be administered for 5 to 6 elimination half-lives before collecting the blood samples.

3.3.2.3 Human volunteers – Healthy subjects versus patients

Ideally, the bioavailability study should be carried out in patients for whom the drug is intended to be used because of the apparent advantages –

1. The patient will be benefited from the study
2. Reflects better the therapeutic efficacy of a drug
3. Drug absorption pattern in disease states can be evaluated.

4. Avoids the ethical quandary of administering drugs to healthy subjects.

Patients are generally preferred in multiple dose bioavailability studies. The drawbacks of using patients as volunteers are equally large – disease, other drugs, physiologic changes, etc. may modify the drug absorption pattern. Stringent study conditions such as fasting state required to be followed by the subject is also difficult. In short, establishing a standard set of conditions necessary for a bioavailability study is difficult with patients as volunteers. Such studies are therefore usually performed in young (20 to 40 years), healthy, male adult volunteers (body weight with a narrow range; ± 10%), under restricted dietary and fixed activity conditions. Female volunteers are used only when drugs such as oral contraceptives are to be tested. The number of subjects to be selected depends upon the extent of intersubject variability but should be kept to a minimum required to obtain a reliable data. The consent of volunteers must be obtained and they must be informed about the importance of the study, conditions to be followed during the study and possible hazards if any, prior to starting the study. Medical examination should be performed in order to exclude subjects with any kind of abnormality or disease. The volunteers must be instructed to abstain from any medication for at least a week and to fast overnight prior to and for a minimum of 4 hours after dosing. The volume and type of fluid and the standard diet to be taken must also be specified. Drug washout period for a minimum of ten biological half-lives must be allowed for between any two studies in the same subject.

3.3.3 Measurement of Bioavailability

The methods useful in quantitative evaluation of bioavailability can be broadly divided into two categories – pharmacokinetic methods and pharmacodynamic methods.

3.3.3.1. Pharmacokinetic Methods

These are very widely used and based on the assumption that the pharmacokinetic profile reflects the therapeutic effectiveness of a drug. Thus, these are indirect methods. The two major pharmacokinetic methods are:

1. Plasma level-time studies.

2. Urinary excretion studies.
3.3.3.2. **Pharmacodynamic Methods**

These methods are complementary to pharmacokinetic approaches and involve direct measurement of drug effect on a (patho)physiologic process as a function of time. The two pharmacodynamic methods involve determination of bioavailability from:

1. Acute pharmacologic response
2. Therapeutic response

3.3.3.3 **Plasma Level - Time Studies**

Unless determination of plasma drug concentration is difficult or impossible, it is the most reliable method and method of choice in comparison to urine data. The method is based on the assumption that two dosage forms that exhibit superimposable plasma level-time profiles in a group of subjects should result in identical therapeutic activity.

With single dose study, the method requires collection of serial blood samples for a period of 2 to 3 biological half-lives after drug administration, their analysis for drug concentration and making a plot of concentration versus corresponding time of sample collection to obtain the plasma level-time profile. With i.v. dose, sampling should start within 5 minutes of drug administration and subsequent samples taken at 15 minute intervals. To adequately describe the disposition phase, at least 3 sample points should be taken if the drug follows one-compartment kinetics and 5 to 6 points if it fits a two-compartment model. For oral dose, at least 3 points should be taken on the ascending part of the curve for accurate determination of $K_e$. The points for disposition or descending phase of the curve must be taken in a manner similar to that for i.v. dose.

The 3 parameters of plasma level-time studies which are considered important for determining bioavailability are:

1. $C_{\text{max}}$: The peak plasma concentration that gives an indication whether the drug is sufficiently absorbed systemically to provide a therapeutic response.
2. $t_{\text{max}}$: The peak time that gives an indication of the rate of absorption.
3. AUC: The area under the plasma level-time curve that gives a measure of the extent of absorption or the amount of drug that reaches the systemic circulation.

The extent of bioavailability can be determined by following equations:
\[ F = \frac{[\text{AUC}]_{\text{oral}}D_{\text{iv}}}{[\text{AUC}]_{\text{iv}}D_{\text{oral}}} \]  
\[ Fr = \frac{[\text{AUC}]_{\text{test}}D_{\text{std}}}{[\text{AUC}]_{\text{std}}D_{\text{test}}} \]

where \( D \) stands for dose administered and subscripts iv and oral indicates the route of administration. Subscripts test and std indicate the test and the standard doses of the same drug to determine relative availability.

Fig. 3.6: Determination of AUC and \( C_{\text{ss, max}} \) on multiple dosing upto steady-state

With multiple dose study, the method involves drug administration for at least 5 biological half-lives with a dosing interval equal to or greater than the biological half-life (i.e. administration of at least 5 doses) to reach the steady-state. A blood sample should be taken at the end of previous dosing interval and 8 to 10 samples after the administration of next dose. The extent of bioavailability is given as:
\begin{equation}
F_r = \frac{[\text{AUC}]_{\text{test}} \ D_{\text{std}} \ \tau_{\text{test}}}{[\text{AUC}]_{\text{std}} \ D_{\text{test}} \ \tau_{\text{std}}}
\end{equation}

where [AUC] values are area under the plasma level-time curve of one dosing interval in a multiple dosage regimen, after reaching the steady state (Fig. 3.11) and \( \tau \) is the dosing interval.

Bioavailability can also be determined from the peak plasma concentration at steady-state \( C_{\text{ss,max}} \) according to following equation:

\begin{equation}
F_r = \frac{(C_{\text{ss,max}})_{\text{test}} \ D_{\text{std}} \ \tau_{\text{test}}}{(C_{\text{ss,max}})_{\text{std}} \ D_{\text{test}} \ \tau_{\text{std}}}
\end{equation}

The rate of absorption is not important in the multiple dosing method.

3.4 Urinary Excretion Studies

This method of assessing bioavailability is based on the principle that the urinary excretion of unchanged drug is directly proportional to the plasma concentration of drug. Thus, even if a drug is excreted to some extent (at least 10 to 20%) in the urine, bioavailability can be determined. The study is particularly useful for drugs extensively excreted unchanged in the urine – for example, certain thiazide, diuretics and sulfonamides and for drugs that have urine as the site of action – for example, urinary antiseptics such as nitrofurantoin and hexamine. The method has several advantages and disadvantages. Concentration of metabolites excreted in urine is never taken into account in calculations since a drug may undergo presystemic metabolism at different stages before being absorbed. The method involves collection of urine at regular intervals for a time span equal to 7 biological half-lives, analysis of unchanged drug in the collected sample and determination of the amount of drug excreted in each interval and cumulative amount excreted. At each sample collection, total emptying of the bladder is necessary to avoid errors resulting from addition of residual amount to the next urine sample. Frequent sampling is also essential in the beginning in order to compute correctly the rate of absorption.
The three major parameters examined in urinary excretion data obtained with a single dose study are:

3.4.1. \((dX/dt)_{\text{max}}\)

The maximum urinary excretion rate, it is obtained from the peak of plot between rate of excretion versus midpoint time of urine collection period. It is analogous to the \(C_{\text{max}}\) derived from plasma level studies since the rate of appearance of drug in the urine is proportional to its concentration in systemic circulation. Its value increases as the rate of and/or extent of absorption increases.

3.4.2. \((t_{\text{max}})\)

The time for maximum excretion rate, it is analogous to the \(t_{\text{max}}\) of plasma level data. Its value decreases as the absorption rate increases.

3.4.3. \(X_{\text{c}}\)

The cumulative amount of drug excreted in the urine, it is related to the AUC of plasma level data and increases as the extent of absorption increases.

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**Fig. 3.6**: Plot of excretion rate Vs. time. Note that the curve is analogous to a typical plasma level - time profile obtained after oral administration of a single dose of drug.

The extent of bioavailability is calculated from the equations given below:
$F = \frac{(X_u^\infty)_{oral}}{(X_u^\infty)_{IV}} \frac{D_{IV}}{D_{oral}}$

$F_r = \frac{(X_u^\infty)_{test}}{(X_u^\infty)_{std}} \frac{D_{std}}{D_{test}}$

With multiple dose study to steady-state, the equation for computing bioavailability is:

$F_r = \frac{(X_{u,ss})_{test}}{(X_{u,ss})_{std}} \frac{D_{std} \tau_{test}}{D_{test} \tau_{std}}$

where $(X_{u,ss})$ is the amount of drug excreted unchanged during a single dosing interval at steady-state.

Bioavailability can also be determined for a few drugs by assay of biologic fluids other than plasma and urine. In case of theophylline, salivary excretion can be used whereas for cephalosporin antibiotics, appearance of drug in CSF and bile can be determined. Caution must however be exercised to account for salivary and enterohepatic cycling of the drugs.

3.5 Acute Pharmacologic Response

When bioavailability measurement by pharmacokinetic methods is difficult, inaccurate or nonreproducible, an acute pharmacologic effect such as change in ECG or EEG readings, pupil diameter, etc. is related to the time course of a given drug. Bioavailability can then be determined by construction of pharmacologic effect-time curve as well as dose-response graphs. The method requires measurement of responses for at least 3 biological half-lives of the drug in order to obtain a good estimate of AUC.

A disadvantage of this method is that the pharmacologic response tends to be more variable and accurate correlation between measured response and drug available from the formulation is difficult. Moreover, the observed response may be due to an active metabolite whose concentration is not proportional to the concentration of parent drug responsible for the pharmacologic effect.
3.6 Therapeutic Response

Theoretically the most definite, this method is based on observing the clinical response to a drug formulation given to patients suffering from disease for which it is intended to be used. A major drawback of this method is that quantitation of observed response is too improper to allow for reasonable assessment of relative bioavailability between two dosage forms of the same drug.

3.7 Drug dissolution rate and bioavailability

The physiochemical property of most drugs that has greater influence on their absorption characteristics from the GIT is dissolution rate. The best way of assessing therapeutic efficacy of drugs with a slow dissolution rate is in vivo determination of bioavailability which is usually done whenever a new formulation is to be introduced into the market. However, monitoring batch-to-batch consistency through use of such in vivo tests is extremely costly, tedious and time consuming besides exposing the healthy subjects to hazards of drugs. It would therefore be always desirable to substitute the in vivo bioavailability tests with inexpensive in vitro methods.

The simple in vitro disintegration test is unreliable. The best available tool today which can at least quantitatively assure about the biologic availability of a drug from its formulation is its in vitro dissolution test.

3.8 Pharmacokinetics

Pharmacokinetics is defined as the kinetics of drug absorption, distribution, metabolism and excretion (KADME) and their relationship with the pharmacologic, therapeutic or toxicologic response in man and animals. The applications of pharmacokinetic principles in the safe and effective management of individual patient is called as clinical pharmacokinetics.

3.9 Plasma Drug Concentration – Time profile

A direct relationship exists between the concentration of drug at the biophase (site of action) and the concentration of drug in plasma. A typical plasma drug concentration-time curve obtained after a single oral dose of a drug and showing various pharmacokinetic and pharmacodynamic parameters is depicted in Fig. 3.7. Such a profile can be obtained by measuring the concentration of drug in plasma samples taken at various intervals of time after administration of a dosage form and plotting the concentration of drug in plasma (Y-axis) versus the corresponding time at which the plasma sample was collected (X-axis).
3.9.1. Peak Plasma Concentration ($C_{\text{max}}$)

The point of maximum concentration of drug in plasma is called as the peak and the concentration of drug at peak is known as peak plasma concentration. It is also called as peak height concentration and maximum drug concentration. $C_{\text{max}}$ is expressed in mcg/ml. The peak level depends upon the administered dose and rate of absorption and elimination. The peak represents the point of time when absorption rate equals elimination rate of drug. The portion of curve to the left of peak represents absorption phase i.e. when the rate of absorption is greater than the rate of elimination. The section of curve to the right of peak generally represents elimination phase i.e. when the rate of elimination exceeds rate of absorption. Peak concentration is often related to the intensity of pharmacologic response and should ideally be above minimum effective concentration (MEC) but less than the maximum safe concentration (MSC).
3.9.2. **Time of Peak Concentration (t\(_{\text{max}}\))**

The time for drug to reach peak concentration in plasma after extravascular administration) is called as the time of peak concentration. It is expressed in hours and is useful in estimating the rate of absorption. Onset time and onset of action are dependent upon \(t_{\text{max}}\). The parameter is of particular importance in assessing the efficacy of drugs used to treat acute conditions like pain and insomnia which can be treated by a single dose.

3.9.3. **Area Under the Curve (AUC)**

It represents the total integrated area under the plasma level-time profile and expresses the total amount of drug that comes into the systemic circulation after its administration. AUC is expressed in mcg/ml X hours. It is the most important parameter in evaluating the bioavailability of a drug from its dosage form as it represents the extent of absorption. AUC is also important for drugs that are administered repetitively for the treatment of chronic conditions like asthma or epilepsy.

3.9.4. **The various pharmacodynamic parameters are:**

3.9.4.1. **Minimum Effective Concentration (MEC)**

It is defined as the minimum concentration of drug in plasma required to produce the therapeutic effect. It reflects the minimum concentration of drug at the receptor site to elicit the desired pharmacologic response. The concentration of drug below MEC is said to be in the subtherapeutic level.

In case of antibiotics, the term minimum inhibitory concentration (MIC) is used. It describes the minimum concentration of antibiotic in plasma required to kill or inhibit the growth of microorganisms.

3.9.4.2. **Maximum Safe Concentration (MSC)**

Also called as minimum toxic concentration (MTC), it is the concentration of drug in plasma above which adverse or unwanted effects are precipitated. Concentration of drug above MSC is said to be in the toxic level.

3.9.4.3. **Onset of Action**
The beginning of pharmacologic response is called as onset of action. It occurs when the plasma drug concentration just exceeds the required MEC.

3.9.4.4. **Onset Time**

It is the time required for the drug to start producing pharmacologic response. It corresponds to the time for the plasma concentration to reach MEC after administration of drug.

3.9.4.5. **Duration of Action**

The time period for which the plasma concentration of drug remains above the MEC level is called as duration of drug action.

3.9.4.6. **Intensity of Action**

It is the maximum pharmacologic response produced by the peak plasma concentration of drug. It is also called as peak response.

3.9.4.7. **Therapeutic Range**

The drug concentration between MEC and MSC represents the therapeutic range.

3.10 **Elimination Rate Constant**

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 – elimination rate constant, elimination half-life and clearance.

The rate out or elimination follows first order kinetics; then:

$$\frac{dX}{dt} = K_e \cdot X \quad 3.15$$

Integration of equation 3.15 yields

$$\ln X = \ln X_0 - K_e \cdot t \quad 3.16$$

Where, $X_0 = \text{amount of drug at time } t = \text{zero i.e. the initial amount of drug injected.}$

Equation 3.5 can also be written in the exponential form as:

$$X = X_0 \cdot e^{K_e t} \quad 3.17$$

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

Transforming equation 3.16 into common logarithms (log base 10), we get:
Log $X = \log X_0 - \frac{K_E t}{2.303}$ \hspace{1cm} 3.18

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:

$$X = V_d C$$ \hspace{1cm} 3.19

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 3.18 therefore becomes:

$$\log C = \log C_0 - \frac{K_E t}{2.303}$$ \hspace{1cm} 3.20

where, $C_0$ = plasma drug concentration immediately after i.v. injection.

Equation 3.20 is that of a straight line and indicates that a semi-logarithmic plot of $\log C$ versus $t$ will be linear with $Y$-intercept $\log C_0$. The elimination rate constant is directly obtained from the slope of the line (Fig. 3.8b). 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. 3.8a).

Thus, $C_0$, $K_E$ (and $t\%$) 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.

$$K_E = K_o + K_m + K_b + K_l + \ldots$$ \hspace{1cm} 3.21
Fig. 3.8: (a) Cartesian plot of a drug that follows one-compartment kinetics and given by rapid i.v. injection and (b) semi-logarithmic plot for the rate of elimination in a one-compartment model.

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:

$$F_e = \frac{K_e}{K_E} \quad 3.22a$$
$$F_m = \frac{K_m}{K_E} \quad 3.23$$

3.11 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:

$$t_{1/2} = \frac{0.693}{K_E}$$  \hspace{1cm} (3.23a)

Elimination half-life can be readily obtained from the graph of log C versus t as shown in Fig. 3.8.

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:

$$t_{1/2} = \frac{0.63 \cdot V_d}{CIT}$$  \hspace{1cm} (3.24)

### 3.12 Apparent Volume of Distribution

Clearance and apparent volume of distribution are two separate and independent pharmacokinetic characteristics of a drug. Since they are closely related with the physiologic mechanisms in the body, they are called as primary parameters.

Modification of equation 3.19 defines apparent volume of distribution.

$$V_d = \frac{\text{Amount of drug in the body}}{\text{Plasma drug concentration}} = \frac{X}{C}$$  \hspace{1cm} (3.25)

$V_d$ 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 and using the following equation:

$$V_d = \frac{X_o}{C_o} = \frac{\text{i.v. bolus dose}}{C_o}$$  \hspace{1cm} (3.26)

Equation 3.26 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 an 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
For drugs administered extravascularly (e.v.),

$$V_{d(\text{area})} = \frac{X_0}{K_E \cdot \text{AUC}}$$  \hspace{1cm} 3.27

where $X_0 = \text{dose administered}$ and $F = \text{fraction of drug absorbed into the systemic circulation}$. $F$ is equal to one i.e. complete availability when the drug is administered intravenously.

3.13 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.

$$\text{Clearance} = \frac{\text{Rate of elimination}}{\text{Plasma drug concentration}}$$  \hspace{1cm} 3.29

or

$$\text{Cl} = \frac{dX/dt}{C}$$  \hspace{1cm} 3.30

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 3.30.

3.14 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,

\[
\text{Renal Clearance } Cl_R = \frac{\text{Rate of elimination by kidney}}{C} \tag{3.30a}
\]

\[
\text{Hepatic Clearance } Cl_H = \frac{\text{Rate of elimination by liver}}{C} \tag{3.30b}
\]

Other Organ Clearance

\[
Cl_{\text{others}} = \frac{\text{Rate of elimination by other organs}}{C} \tag{3.30c}
\]

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

\[
\text{Total Systemic Clearance, } Cl_T = Cl_R + Cl_H + Cl_{\text{others}} \tag{3.30d}
\]

Because of the 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 \( Cl_{\text{nonrenal}} \). It is the difference between total clearance and renal clearance.

According to an earlier definition (equation 3.31)

\[
Cl_T = \frac{dX/dt}{C} \tag{3.31}
\]

Substituting \( dX/dt = KE \text{X} \) from equation 3.15 in above equation, we get:

\[
Cl_T = \frac{KE \text{X}}{C} \tag{3.32}
\]

Since \( X/C = V_d \) (from equation 3.25), the equation 3.32 can be written as:

\[
Cl_T = KE \text{V}_d \tag{3.33a}
\]
Parallel equations can be written for renal and hepatic clearances as:

\[ \text{Cl}_r = K_e V_d \]  \hspace{1cm} \text{(3.33b)}

\[ \text{Cl}_h = K_m V_d \]  \hspace{1cm} \text{(3.34)}

Since \( K_e = 0.693/t_{1/2} \) (from equation 3.25), clearance can be related to half-life by the following equation:

\[ \text{Cl}_T = \frac{0.693 \times V_d}{t_{1/2}} \]  \hspace{1cm} \text{(3.35)}

Identical equations can be written for \( \text{Cl}_h \) and \( \text{Cl}_r \) in which cases the \( t_{1/2} \) will be urinary excretion half-life for unchanged drug and metabolism half-life respectively. Equation 3.35 shows that as \( \text{Cl}_T \) decreases, as in renal insufficiency, \( t_{1/2} \) of the drug increases. As the \( \text{Cl}_T \) takes into account \( V_d \) changes in \( V_d \) as in obesity or eliminations condition will reflect changes in \( \text{Cl}_T \).

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

\[ \text{Cl}_T = \frac{X_o}{AUC} \]  \hspace{1cm} \text{(3.35a)}

For drugs administered e.v.

\[ \text{Cl}_T = \frac{F \times X_o}{AUC} \]  \hspace{1cm} \text{(3.35b)}

For a drug given by i.v. bolus, the renal clearance \( \text{Cl}_r \) may be estimated by determining the total amount of unchanged drug excreted in urine, \( X_u^\infty \) and AUC.

\[ \text{Cl}_r = \frac{X_u^\infty}{AUC} \]  \hspace{1cm} \text{(3.36)}
3.16 Assessment of Pharmacokinetic Parameters following extravascular administration

3.16.1 $C_{\text{max}}$ and $t_{\text{max}}$

At peak plasma concentration, the rate of absorption equals rate of elimination i.e. $K_e X_a = K_e X$ and the rate of change in plasma drug concentration $dC/dt = 0$. This rate can be obtained by differentiating equation 3.37.

\[ C = \frac{K_a F X_0}{V_d (K_a - K_E)} [e^{-K_E t} - e^{-K_a t}] \]  \hspace{1cm} (3.37)

\[ \frac{dC}{dt} = \frac{K_a F X_0}{V_d (K_a - K_E)} [-K_E e^{-K_E t} + K_a e^{-K_a t}] = 0 \]  \hspace{1cm} (3.38)

On simplifying, the above equation becomes

\[ K_E e^{-K_E t} = K_a e^{-K_a t} \]  \hspace{1cm} (3.39)

Converting to logarithmic form,

\[ \log K_E - \frac{K_E t}{2.303} = \log K_a - \frac{K_a t}{2.303} \]  \hspace{1cm} (3.40)

where $t$ is $t_{\text{max}}$. Rearrangement of above equation yields:

\[ t_{\text{max}} = \frac{2.303 \log (K_a/K_E)}{K_a - K_E} \]  \hspace{1cm} (3.41)

The above equation shows that as $K_a$ becomes larger than $K_E$, $t_{\text{max}}$ becomes smaller since $(K_a - K_E)$ increases much faster than $\log K_a/K_E$. $C_{\text{max}}$ can be obtained by substituting equation 3.41 in equation 3.37. However, a simpler expression for the same is:

\[ C_{\text{max}} = \frac{F X_0}{V_d} e^{-K_E t_{\text{max}}} \]  \hspace{1cm} (3.42)

It has been shown that at $C_{\text{max}}$, when $K_a = K_E$, $t_{\text{max}} = 1/K_E$. Hence, the above equation further reduces to:

\[ C_{\text{max}} = \frac{F X_0}{V_d} e^{-1} = \frac{0.37 F X_0}{V_d} \]  \hspace{1cm} (3.43)

Since $FX_0/V_d$ represents $C_0$ following i.v. bolus, the maximum plasma concentration that can be attained after e.v. administration is just 37% of the maximum level attainable with i.v.
bolus in the same dose. If bioavailability is less than 100%, still lower concentration will be attained.

3.16.2 Elimination Rate Constant:

This parameter can be computed from the elimination phase of the plasma level time profile. For most drugs administered e.v., absorption rate is significantly greater than the elimination rate i.e. $K_a \gg K_E$. Hence, one can say that $e^{K_a t}$ approaches zero much faster than does $e^{-K_E t}$. At such a stage, when absorption is complete, the change in plasma concentration is dependent only on elimination rate and equation 3.37 reduces to:

$$C = \frac{K_a F X_0}{V_d(K_a - K_E)} e^{-K_E t}$$

Transforming into log form, the equation becomes:

$$\log C = \log \left( \frac{K_a F X_0}{V_d(K_a - K_E)} \right) - \frac{K_E t}{2.303}$$

A plot of $\log C$ versus $t$ yields a straight line with slope $-K_E/2.303$ (half-life can then be computed from $K_E$). $K_E$ can also be estimated from urinary excretion data.

3.15.3 Absorption Rate Constant

It can be calculated by the method of residuals. The technique is also known as feathering, peeling and stripping. It is commonly used in pharmacokinetics to resolve a multiexponential curve into its individual components. For a drug that follows one-compartment kinetics and administered e.v., the concentration of drug in plasma is expressed by a biexponential equation 3.37:

$$C = \frac{K_a F X_0}{V_d(K_a - K_E)} \left[ e^{-K_E t} - e^{-K_a t} \right]$$

If $K_a F X_0 / V_d(K_a - K_E) = A$, a hybrid constant, then:

$$C = A e^{-K_E t} - A e^{-K_a t}$$
During the elimination phase, when absorption is almost over, $K_a >> K_e$ and the value of second exponential $e^{-K_e t}$ approaches zero whereas the first exponential $e^{-K_a t}$ retains some finite value. At this time, the equation 3.46 reduces to:

$$ C = A e^{-K_e t} $$

In log form, the above equation is:

$$ \log C = \log A - \frac{K_e t}{2.303} $$

where $C$ represents the back extrapolated plasma concentration values. A plot of $\log C$ versus $t$ yields a biexponential curve with a terminal linear phase having slope $-K_e/2.303$. Back extrapolation of this straight line to time zero yields y-intercept equal to $\log A$.

Fig. 3.9: Plasma concentration - time profile after oral administration of a single dose of a drug. The biexponential curve has been resolved into its two components - absorption and elimination.

Subtraction of true plasma concentration values i.e. equation 3.46 from the extrapolated plasma concentration values i.e. equation 3.47 yields a series of residual concentration values $C_r$. 

![Graph showing plasma concentration-time profile after oral administration of a single dose of a drug. The biexponential curve has been resolved into its two components - absorption and elimination. Subtraction of true plasma concentration values from the extrapolated plasma concentration values yields a series of residual concentration values $C_r$.](image-url)
\[
(C - C) = C_r = Ae^{-K_at}
\]

In log form, the equation is:

\[
\log C_r = \log A - \frac{K_a t}{2.303}
\]

A plot of log \(C_r\) versus \(t\) yields a straight line with slope \(-K_a/2.303\) and y-intercept \(\log A\). Absorption half-life can then be computed from \(K_a\) using the relation \(0.693/K_a\). Thus, the method of residuals enables resolution of the biexponential plasma level-time curve into its two exponential components. The technique works best when the difference between \(K_e\) and \(K_l\) is large (\(K_e/K_l \geq 3\)). In some instances, the \(K_e\) obtained after i.v. bolus of the same drug is very large, much larger than the \(K_e\) obtained by the method of residuals (e.g. isoprenaline) and if \(K_e/K_a \geq 3\), the terminal slope estimates \(K_a\) and not \(K_e\) whereas the slope of residual line gives \(K_e\) and not \(K_a\). This is called as flip-flop phenomenon since the slopes of the two lines have exchanged their meanings.

Ideally, the extrapolated and the residual lines intersect each other on y-axis i.e. at time \(t = 0\) and there is no lag in absorption. However, if such an intersection occurs at a time greater than zero, it indicates time lag. It is defined as the time difference between drug administration and start of absorption. It is denoted by symbol \(t_{lag}\) and represents the beginning of absorption process. Lag time should not be confused with onset time.

The above method for the estimation of \(K_a\) is a curve-fitting method. The method is best suited for drugs which are rapidly and completely absorbed and follow one-compartment kinetics even when given i.v. However, if the absorption of the drug is affected in some way such as GI motility or enzymatic degradation and if the drug shows multicompartent characteristics after i.v. administration (which is true for virtually all drugs), then \(K_a\) computed by curve-fitting method is incorrect even if the drug were truly absorbed by first-order kinetics. The \(K_a\) so obtained is at best, estimate of first-order disappearance of drug from the GIT rather than of first-order appearance in the systemic circulation.
3.15.4 Wagner-Nelson Method for Estimation of $K_e$

One of the better alternatives to curve-fitting method in the estimation of $K_e$ is Wagner-Nelson method. The method involves determination of $K_e$ from percent unabsorbed-time plots and does not require the assumption of zero- or first-order absorption.

After oral administration of a single dose of a drug, at any given time, the amount of drug absorbed into the systemic circulation $X_A$, is the sum of amount of drug in the body $X$ and the amount of drug eliminated from the body $X_E$. Thus:

$$X_A = X + X_E \quad 3.51$$

The amount of drug in the body is $X = V_d C$. The amount of drug eliminated at any time $t$ can be calculated as follows:

$$X_E = K_e V_d [AUC]_t \quad 3.52$$

Substitution of values of $X$ and $X_E$ in equation 3.51 yields:

$$X_A = V_d C + K_e V_d [AUC]_t \quad 3.53$$

The total amount of drug absorbed into the systemic circulation from time zero to infinity $X_A^\infty$ can be given as:

$$X_A^\infty = V_d C^\infty + K_e V_d [AUC]_t^\infty \quad 3.54$$

Since at $t = \infty$, $C^\infty = 0$, the above equation reduces to:

$$X_A^\infty = K_e V_d [AUC]_t^\infty \quad 3.55$$

The fraction of drug absorbed at any time $t$ is given as:

$$\frac{X_A}{X_A^\infty} = \frac{V_d C + K_E V_d [AUC]_t}{K_E V_d [AUC]_t^\infty} \quad 3.56$$

$$= \frac{C + K_E [AUC]_t}{K_E [AUC]_t^\infty} \quad 3.56$$

Percent drug unabsorbed at any time is therefore:

$$% \text{ARA} = \left[ 1 - \frac{X_A}{X_A^\infty} \right] \times 100 = \left[ 1 - \frac{C + K_E [AUC]_t}{K_E [AUC]_t^\infty} \right] \times 100 \quad 3.57$$
Fig. 3.10: Semi log plot of percent ARA versus time according to Wagner–Nelson method

The method requires collection of blood samples after a single oral dose at regular intervals of time till the entire amount of drug is eliminated from the body. $K_e$ is obtained from log $C$ versus $t$ plot and $[AUC]_0^\infty$ and $[AUC]_0^\infty$ are obtained from plots of $C$ versus $t$. A semilog plot of percent unabsorbed (i.e. percent ARA) versus $t$. A semilog plot of percent unabsorbed (i.e. percent ARA) versus $t$ yields a straight line whose slope is $-K_e/2.303$. If a regular plot of the same is a straight line, then absorption is zero-order.

$K_e$ can similarly be estimated from urinary excretion data. The biggest disadvantage of Wagner-Nelson method is that it applies only to drugs with one-compartment characteristics. Problem arises when a drug that obeys one-compartment model after e.v. administration shows multicompartment characteristics on i.v. injection.

3.15.5 Effect of $K_e$ and $K_e$ on $C_{max}$, $t_{max}$ and AUC

A summary of the influence of changes in $K_e$ at constant $K_e$ and of $K_e$ at constant $K_e$ on $C_{max}$, $t_{max}$ and AUC of a drug administered e.v. is shown Table 3.2.
<table>
<thead>
<tr>
<th>Parameters affected</th>
<th>Influence when ( K_e ) is Constant</th>
<th>Influence when ( K_e ) is Constant</th>
</tr>
</thead>
<tbody>
<tr>
<td>( C_{\text{max}} )</td>
<td>( \downarrow )</td>
<td>( \uparrow )</td>
</tr>
<tr>
<td>( T_{\text{max}} )</td>
<td>Long</td>
<td>Short</td>
</tr>
<tr>
<td>( AUC )</td>
<td>No change</td>
<td>No change</td>
</tr>
</tbody>
</table>

Where, \( \uparrow \) = increase and \( \downarrow \) = decrease

### 3.15.6 Apparent volume of distribution and clearance

For a drug that follows one-compartment kinetics after e.v. administration, \( V_d \) and \( \text{Cl}_{\text{T}} \) can be computed from equations 3.28 where \( F \) is the fraction absorbed into the systemic circulation.

\[
V_d = \frac{FX_0}{KE \text{ AUC}} \tag{3.28}
\]

\[
\text{Cl}_{\text{T}} = \frac{FX_0}{\text{AUC}} \tag{3.35b}
\]