NON-LINEAR PHARMACOKINETICS

- In most cases, at therapeutic doses, the change in the amount of drug in the body or the change in its plasma concentration due to absorption, distribution, binding, metabolism or excretion, is proportional to its dose, whether administered as a single dose or as multiple doses.
- In such situations, the rate processes are said to follow first-order or linear kinetics and all semi log plots of C versus t for different doses, when corrected for dose administered, are superimposable. This is called as **principle of superposition**.
- The important pharmacokinetic parameters *viz.* F, K_a, K_E, V_d, Cl_R and Cl_H which describe the time-course of a drug in the body remain unaffected by the dose i.e., the pharmacokinetics is dose-independent.
- In some instances, the rate process of a drug's ADME are dependent upon carrier or enzymes that are substrate-specific, have definite capacities, and susceptible to saturation at high drug concentration.
- In such cases, an essentially first-order kinetics transform into a mixture of first-order and zero-order rate processes and the pharmacokinetic parameters change with the size of the administered dose.
- The pharmacokinetics of such drugs are said to be **dose-dependent**. Other terms synonymous with it are **mixed-order**, **nonlinear** and **capacity-limited kinetics**. Drugs exhibiting such a kinetic profile are sources of variability in pharmacological response.

- **Difference between Linear and Non-linear Pharmacokinetics**

Linear Pharmacokinetics	Non-linear Pharmacokinetics
Pharmacokinetic parameters for drug would not change with change in dose	parameters for drug can change with change in dose
Dose Independent	Dose dependent
Follows 1st order Kinetics	Follows mixed order Kinetics, i,e combination of 1st order and zero order

Here are several tests to detect nonlinearity in pharmacokinetics but the simplest ones are –

1. *Determination of steady-state plasma concentration at different doses*. If the steady-state concentrations are directly proportional to the dose, then linearity in the kinetics exists. Such proportionality is not observable when there is nonlinearity.
2. *Determination of some of the important pharmacokinetic parameters* such as fraction bioavailable, elimination half-life or total systemic clearance at different doses of the drug. Any change in these parameters which are usually constant, is indicative of nonlinearity.

CAUSES OF NONLINEARITY

Nonlinearities can occur in drug absorption, distribution, metabolism and excretion.

Drug Absorption

Nonlinearity in drug absorption can arise from 3 important sources –

1. When absorption is solubility or dissolution rate-limited e.g., griseofulvin. At higher doses, a saturated solution of the drug is formed in the GIT or at any other extravascular site and the rate of absorption attains a constant value.

2. When absorption involves carrier-mediated transport systems e.g. absorption of riboflavin, ascorbic acid, cyanocobalamin, etc. Saturation of the transport system at higher doses of these vitamins results in nonlinearity.

3. When presystemic gut wall or hepatic metabolism attains saturation e.g. propranolol, hydralazine and verapamil. Saturation of presystemic metabolism of these drugs at high doses leads to increased bioavailability.

The parameters affected will be F, K_a, C_{max} and AUC. A decrease in these parameters is observed in the former two cases and an increase in the latter case. Other causes of nonlinearity in drug absorption are changes in gastric emptying and GI blood flow and other physiologic factors. Nonlinearity in drug absorption is of little consequence unless availability is drastically affected.

Drug Distribution

Nonlinearity in distribution of drugs administered at high doses may be due to –

1. *Saturation of binding sites on plasma proteins* e.g. phenylbutazone and naproxen. There is a finite number of binding sites for a particular drug on plasma proteins and, theoretically, as the concentration is raised, so too is the fraction unbound.
2. 2. *Saturation of tissue binding sites* e.g. thiopental and fentanyl. With large single bolus doses or multiple dosing, saturation of tissue storage sites can occur.
3. In both cases, the free plasma drug concentration increases but V_d increases only in the former case whereas it decreases in the latter. Clearance is also altered depending upon the extraction ratio of the drug. Clearance of a drug with high ER is greatly increased due to saturation of binding sites. Unbound clearance of drugs with low ER is unaffected and one can expect an increase in pharmacological response.

Drug Metabolism

1. The nonlinear kinetics of most clinical importance is capacity-limited metabolism since small changes in dose administered can produce large variations in plasma concentration at steady-state. It is a major source of large inter-subject variability in pharmacological response.
2. Two important causes of nonlinearity in metabolism are –
3. *Capacity-limited metabolism due to enzyme and/or cofactor saturation*. Typical examples include phenytoin, alcohol, theophylline, etc.
4. *Enzyme induction* e.g. carbamazepine, where a decrease in peak plasma concentration has been observed on repetitive administration over a period of time. Autoinduction characterized in this case is also dose-dependent. Thus, enzyme induction is a common cause of both dose- and time-dependent kinetics.
5. Saturation of enzyme results in decreased Cl_H and therefore increased C_{ss}. Reverse is true for enzyme induction. Other causes of nonlinearity in biotransformation include saturation of binding

sites, inhibitory effect of the metabolite on enzyme and pathologic situations such as hepatotoxicity and changes in hepatic blood flow.

Drug Excretion

1. The two active processes in renal excretion of a drug that are saturable are
2. *Active tubular secretion* e.g. penicillin G. After saturation of the carrier system, a decrease in renal clearance occurs.
3. *Active tubular reabsorption* e.g. water soluble vitamins and glucose. After saturation of the carrier system, an increase in renal clearance occurs.
4. Other sources of nonlinearity in renal excretion include forced diuresis, changes in urine pH, nephrotoxicity and saturation of binding sites.
5. Biliary secretion, which is also an active process, is also subject to saturation e.g. tetracycline and indomethacin.

MICHAELIS MENTEN EQUATION

The kinetics of capacity-limited or saturable processes is best described by Michaelis-
Menten equation:

$$-\frac{dC}{dt} = \frac{V_{max}\, C}{K_m + C} \qquad (10.1)$$

Where,

–dC/dt = rate of decline of drug concentration with time,
V_{max} = theoretical maximum rate of the process, and
K_m = Michaelis constant.

Three situations can now be considered depending upon the values of K_m and C:

1. When K_m = C

Under this situation, the equation 10.1 reduces to:

$$-\frac{dC}{dt} = \frac{V_{max}}{2} \qquad (10.2)$$

i.e. the rate of process is equal to one-half its maximum rate (Fig..1).

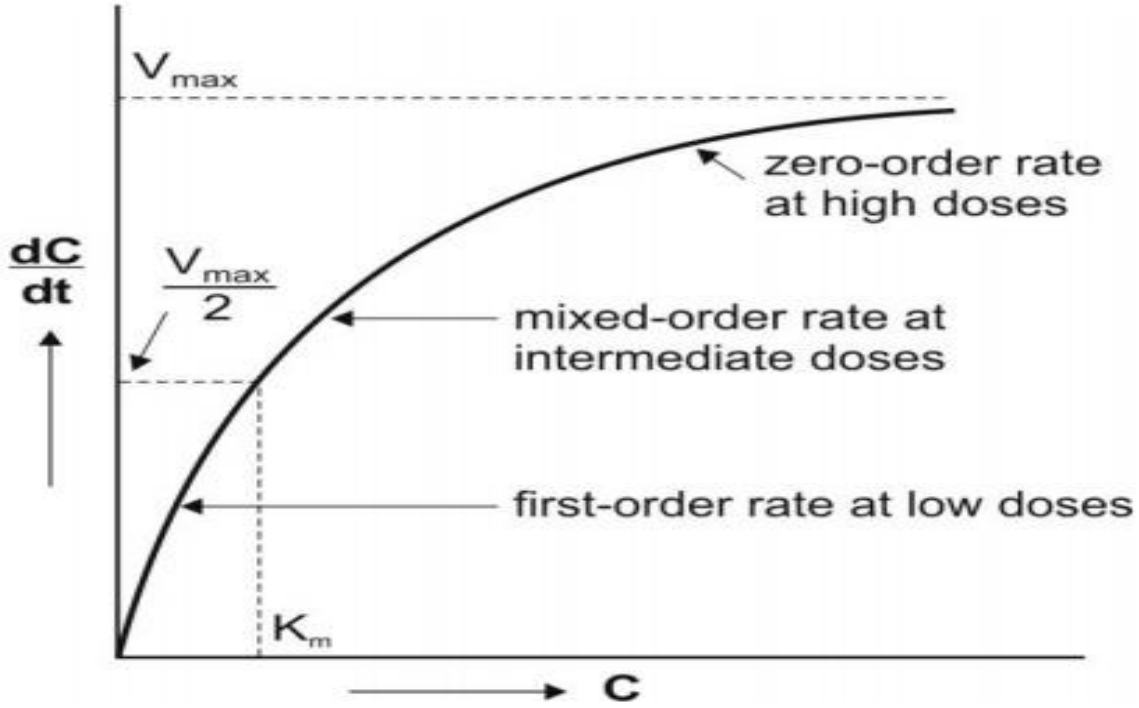

Fig. 1 *A plot of Michaelis-Menten equation (elimination rate dC/dt versus concentration C).*

- Initially, the rate increases linearly (first-order) with concentration, becomes mixed-order at higher concentration and then reaches maximum (Vmax) beyond which it proceeds at a constant rate (zero-order).

2. When $K_m >> C$

Here, $K_m + C \equiv K_m$ and the equation 10.1 reduces to:

$$-\frac{dC}{dt} = \frac{V_{max}\, C}{K_m} \qquad (10.3)$$

- The above equation is identical to the one that describes first-order elimination of a drug where $V_{max}/K_m = K_E$.
- This means that the drug concentration in the body that results from usual dosage regimens of most drugs is well below the K_m of the elimination process with certain exceptions such as **phenytoin and alcohol.**

3. When $K_m << C$

Under this condition, $K_m + C \equiv C$ and the equation 10.1 will become:

$$-\frac{dC}{dt} = V_{max} \qquad (10.4)$$

The above equation is identical to the one that describes a zero-order process i.e. the rate process occurs at a constant rate V_{max} and is independent of drug concentration e.g. metabolism of ethanol.

Estimation of Km and Vmax for iv bolus

❖ **Method:1**

The parameters of capacity-limited processes like metabolism, renal tubular secretion and biliary excretion can be easily defined by assuming one-compartment kinetics for the drug and that elimination involves only a single capacity-limited process.

The parameters Km and Vmax can be assessed from the plasma concentration-time data collected after I.V. bolus administration of a drug with nonlinear elimination characteristics. Rewriting equation 10.1.

$$-\frac{dC}{dt} = \frac{V_{max}\, C}{K_m + C} \qquad (10.1)$$

Integration of above equation followed by conversion to log base 10 yields:

$$\log C = \log C_0 + \frac{C_0 - C}{2.303 K_m} - \frac{V_{max}}{2.303 K_m} \qquad (10.5)$$

A semi log plot of C versus t yields a curve with a terminal linear portion having slope $-V_{max}/2.303K_m$ and when back extrapolated to time zero gives *Y*-intercept ($\log \bar{C}_0$) (*see* Fig. 2). The equation that describes this line is:

$$\log C = \log \bar{C}_0 - \frac{V_{max}}{2.303 K_m} \qquad (10.6)$$

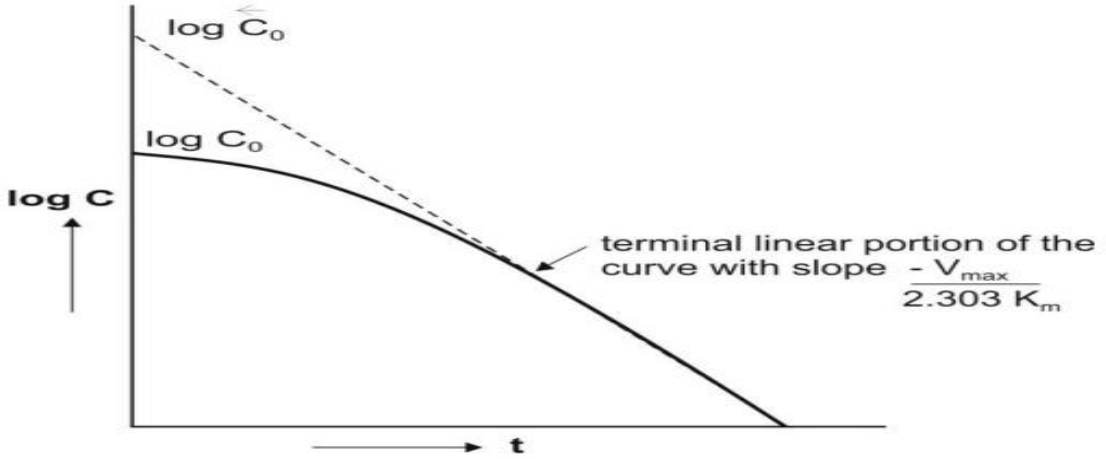

Fig. 2: *Semilog plot of a drug given as i.v. bolus with nonlinear elimination and that fits one-compartment kinetics.*

At low plasma concentrations, equations 10.5 and 10.6 are identical. Equating the two and simplifying further, we get:

$$\frac{C_0 - \bar{C}}{2.303 K_m} = \log \frac{\bar{C}_0}{C_0} \qquad (10.7)$$

K_m can thus be obtained from above equation. V_{max} can be computed by substituting the value of K_m in the slope value.

❖ **Method:2-Lineweaver-Burke plot (alternative approach)**

An alternative approach of estimating V_{max} and K_m is determining the rate of change of plasma drug concentration at different times and using the reciprocal of the equation 10.1. Thus:

$$\frac{1}{dC/dt} = \frac{K_m}{V_{max} C_m} + \frac{1}{V_{max}} \qquad (10.8)$$

where C_m = plasma concentration at midpoint of the sampling interval. A double reciprocal plot or the **Lineweaver-Burke plot** of $1/(dC/dt)$ versus $1/C_m$ of the above equation yields a straight line with slope = K_m/V_{max} and y-intercept = $1/V_{max}$.

❖ **Method 3 Hanes-Woolf plot and Woolf-Augustinsson-Hofstee plot**

A *disadvantage* of Lineweaver-Burke plot is that the points are clustered. More reliable plots in which the points are uniformly scattered are **Hanes-Woolf plot** (equation 10.9) and **Woolf-Augustinsson-Hofstee plot** (equation 10.10).

$$\frac{C_m}{dC/dt} = \frac{K_m}{V_{max}} + \frac{C_m}{V_{max}} \qquad (10.9)$$

$$\frac{dC}{dt} = V_{max} - \frac{dC/dt\ K_m}{C_m} \qquad (10.10)$$

- The above equations are rearrangements of equation 10.8.
- Equation 10.9 is used to plot $C_m/(dC/dt)$ versus C_m and
- equation 10.10 to plot dC/dt versus $(dC/dt)/C_m$.
- The parameters K_m and V_{max} can be computed from the slopes and y-intercepts of the two plots

K_m and V_{max} for IV infusion (Steady-State Concentration)

When a drug is administered as a constant rate i.v. infusion or in a multiple dose regimen, the steady-state concentration C_{ss} is given in terms of **dosing rate** DR as:

$DR = C_{ss}Cl_T$ (10.11)

where DR = R_o when the drug is administered as zero-order i.v. infusion and it is equal to FX_o/τ when administered as multiple oral dosage regimen (F is fraction bioavailable, X_o is oral dose and is dosing interval). At steady-state, the dosing rate equals rate of decline in plasma drug concentration and if the decline (elimination) is due to a single capacity-limited process (for e.g. metabolism), then;

$$DR = \frac{V_{max} C_{ss}}{K_m + C_{ss}} \qquad (10.12)$$

A plot of C_{ss} versus DR yields a typical *hockey-stick shaped curve* as shown in Fig. 10.3.

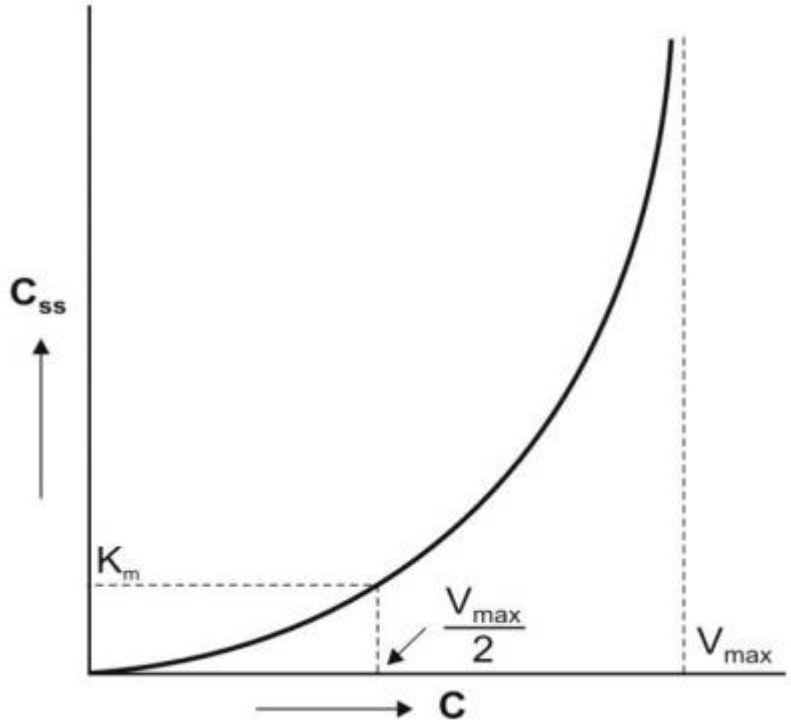

Fig. 10.3 *Curve for a drug with nonlinear kinetics obtained by plotting the steady-state concentration versus dosing rates.*

To define the characteristics of the curve with a reasonable degree of accuracy, several measurements must be made at steady-state during dosage with different doses.

Practically, one can graphically compute Km and Vmax in 3 ways:

1. Lineweaver-Burke Plot/Klotz Plot

Taking reciprocal of equation 10.12, we get:

$$\frac{1}{DR} = \frac{K_m}{V_{max}\, C_{ss}} + \frac{1}{V_{max}} \qquad (10.13)$$

Equation 10.13 is identical to equation 10.8 given earlier. A plot of 1/DR versus $1/C_{ss}$ yields a straight line with slope K_m/V_{max} and y-intercept $1/V_{max}$ (see Fig. 10.4).

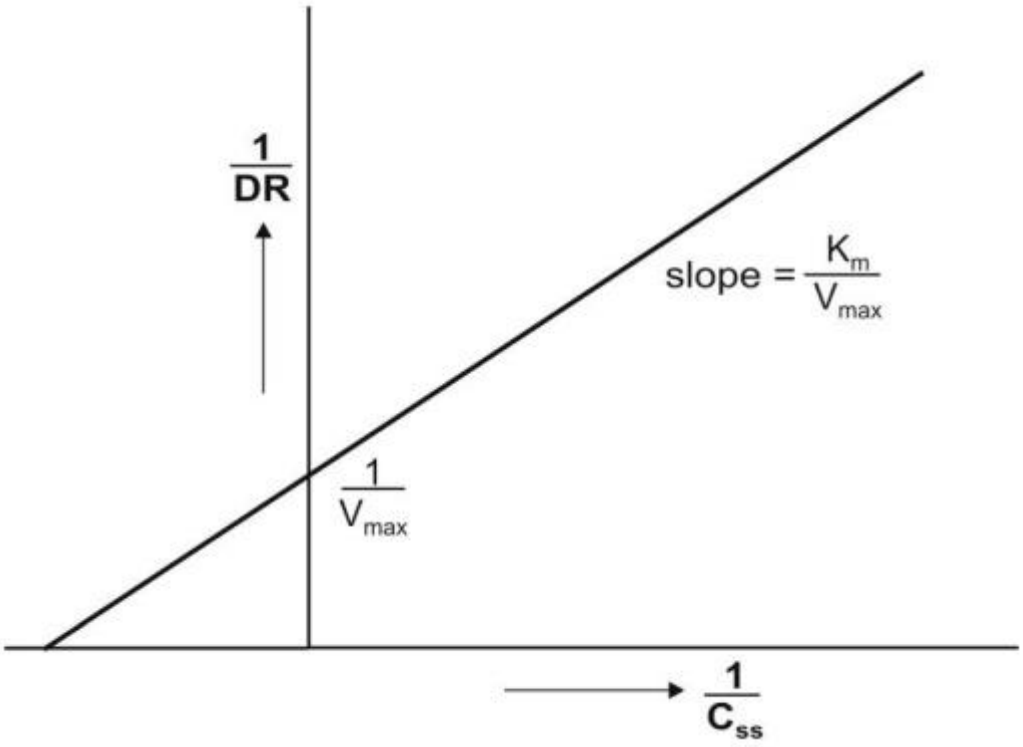

Fig. 10.4 *Lineweaver-Burke/Klotz plot for estimation of Km and Vmax at steady-state concentration of drug.*

2. Direct Linear Plot

Here, the graph is considered as shown in Fig. 10.5. A pair of C_{ss} viz. $C_{ss,1}$ and $C_{ss,2}$ obtained with two different dosing rates DR_1 and DR_2 is plotted.

The points $C_{ss,1}$ and DR_1 are joined to form a line and a second line is obtained similarly by joining $C_{ss,2}$ and DR_2. The point where these two

lines intersect each other is **extrapolated on DR axis to obtain V_{max} and on x-axis to get K_m.**

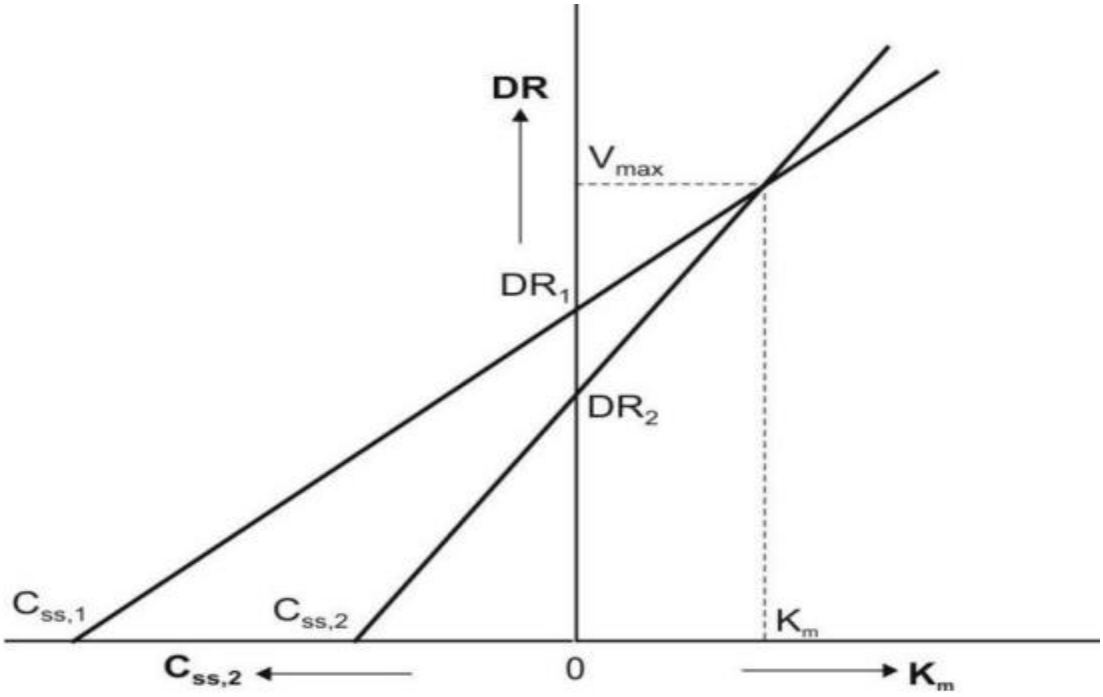

Fig. 10.5 *Direct linear plot for estimation of K_m and V_{max} at steady-state concentrations of a drug given at different dosing rates.*

3. The third graphical method of estimating K_m and V_{max} involves rearranging equation 10.12 to yield:

$$DR = V_{max} - \frac{K_m\, DR}{C_{ss}} \qquad (10.14)$$

A plot of DR versus DR/C_{ss} yields a straight line with slope $-K_m$ and *Y*-intercept V_{max}.

4. **K_m and V_{max} can also be calculated numerically by setting up simultaneous equations as shown below:**

$$DR_1 = \frac{V_{max}\, C_{ss,1}}{K_m + C_{ss,1}} \qquad (10.15)$$

$$DR_2 = \frac{V_{max}\, C_{ss,2}}{K_m + C_{ss,2}} \qquad (10.16)$$

Combination of the above two equations yields:

$$K_m = \frac{DR_2 - DR_1}{\frac{DR_1}{C_{ss,1}} - \frac{DR_2}{C_{ss,2}}} \qquad (10.17)$$

After having computed K_m, its subsequent substitution in any one of the two simultaneous equations will yield V_{max}.

- It has been observed that K_m is much less variable than V_{max}. Hence, if mean K_m for a drug is known from an earlier study, then instead of two, a single measurement of C_{ss} at any given dosing rate is sufficient to compute V_{max}.
- There are several limitations of K_m and V_{max} estimated by assuming one-compartment system and a single capacity-limited process. More complex equations will result and the computed K_m and V_{max} will usually be larger when:
    1. The drug is eliminated by more than one capacity-limited process.
    2. The drug exhibits parallel capacity-limited and first-order elimination processes.
    3. The drug follows multicompartment kinetics.

However, K_m and V_{max} obtained under such circumstances have little practical applications in dosage calculations.
Drugs that behave nonlinearly within the therapeutic range (for example, phenytoin shows saturable metabolism) yield less predictable results in drug therapy and possess greater potential in precipitating toxic effects.