كلية الصيدلة
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Biopharmaceutics
Course #414:

NONLINEAR PHARMACOKINETICS

UOBCOP

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Introduction:

- Linear pharmacokinetics:
  - When the dose of a drug is increased, we expect that the concentration at steady state(Css) will increase proportionately,
  - i.e. if the dose rate is increased or decreased say two-fold, the plasma drug concentration will also increase or decrease two-fold.
- Nonlinear pharmacokinetics
  - the plasma drug concentration changes either more or less than would be expected from a change in dose rate.
  - This can cause problems when adjusting doses.
  - This is because one or more of the kinetic processes (absorption, distribution and/or elimination) of the drug may be occurring via a mechanism other than simple first-order kinetics

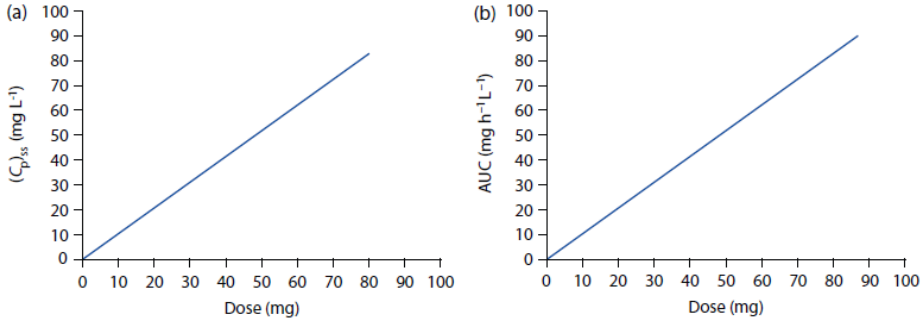
Linear pharmacokinetics

- Change in plasma concentration due to ADME process is proportional to dose of drug administered (single or multiple)
- Follow First order kinetics
- Semilog plot for concentration vs time is super imposable (Principle of superimposition).
- No change in F, Ka, Ke, Vd, Clearance etc., when different doses are administered and/or when the drug is administered via different routes as a single dose or multiple doses.

Nonlinear Pharmacokinetics

- Saturated process:
  - Rate process of ADME are dependent on carrier or enzymes having definite capacity and subjected to saturation.
- Change in concentration is no more proportional to dose administered during the total process of ADME.
- Follow First order + Zero order kinetics
- Change in different pharmacokinetic parameters depending on the administered dose

Introduction: Linear



The term linear simply means that plasma concentration at a given time at steady state and the area under the plasma concentration versus time curve (AUC) will both be directly proportional to the dose administered

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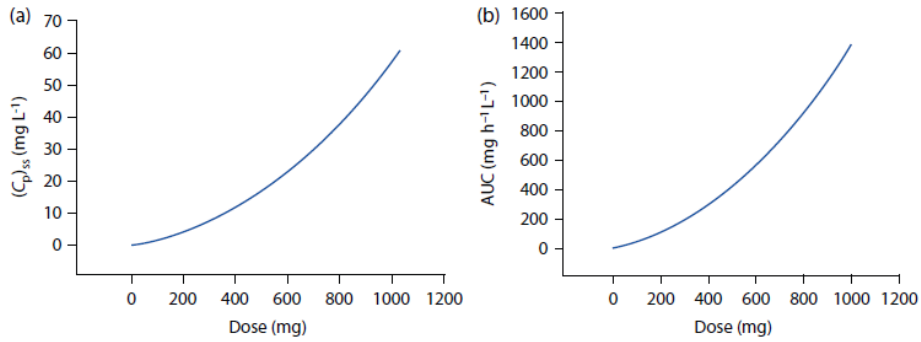
Introduction: Nonlinear



For these drugs, therefore, the relationship between the AUC or the plasma concentration at a given time **at steady state** and the administered dose **is not linear**

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- In some cases, the rates of ADME of drug are dependent upon carrier or enzymes that are substrate-specific, have definite capacities & susceptible to saturation at high drug concentration.
- Such pharmacokinetics are said to be:
  - DOSE DEPENDENT, MIXED ORDER, NONLINEAR, CAPACITY LIMITED KINETICS.

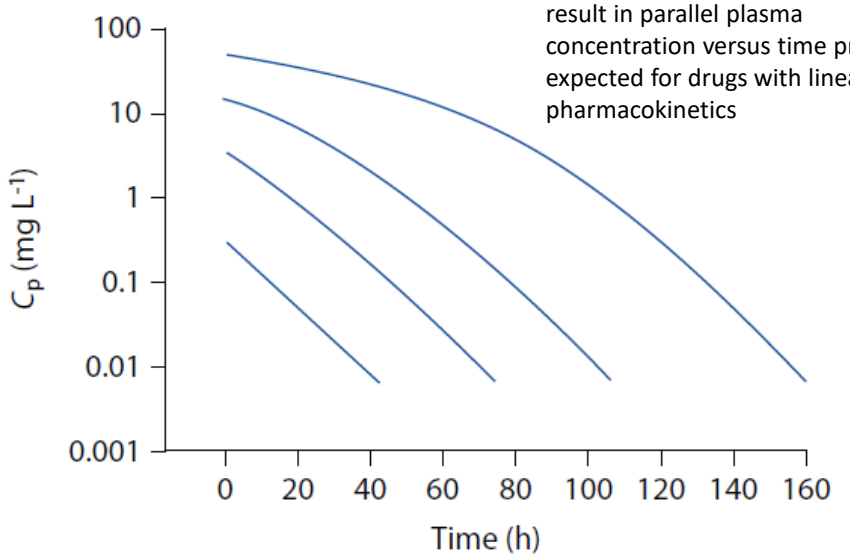
DETECTION OF NONLINEARITY

- Two simple tests for detection of nonlinearity:

1. Determination of steady state plasma conc. at different doses.
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.

Nonlinear

Administration of different doses of drugs with nonlinear kinetics may not result in parallel plasma concentration versus time profiles expected for drugs with linear pharmacokinetics



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CAUSES OF NONLINEARITY

- one or more of the below kinetic processes of the drug may be occurring via a mechanism other than simple first-order kinetics
  - Drug absorption
  - Drug distribution
  - Drug metabolism
  - Drug excretion

GIT ABSORPTION

- Sources of nonlinearity:
  - When absorption is solubility or dissolution rate limited.
    - Ex:- Griseofulvin .
  - Intestinal metabolism (1st pass metabolism).
    - Ex:- Salicylamide , propranolol
  - Drugs with low solubility in GI but relatively high dose
    - Ex:- Chorothiazide , griseofulvin , danazol
  - Saturable gastric or GI decomposition
    - Ex:- Penicillin G, omeprazole , saquinavir
  - Saturable transport in gut wall
    - Ex:- Riboflavin, gebapentin , L-dopa, baclofen , ceftibuten
  - Other causes include change in gastric emptying, GI blood flow & other physiological factors

DRUG DISTRIBUTION

- **Sources of nonlinearity in drug distribution:**

➢ Saturation of binding sites on plasma proteins.
  - ➢ Ex:- naproxen, lidocaine , ceftriaxone , warfarin .

➢ Saturation of tissue binding sites.
  - ➢ Ex:- thiopental & Fentanyl ., disopyramide

➢ Cellular uptake
  - ➢ Ex:- Methicillin

➢ Tissue binding
  - ➢ Ex:- Imiprimine

➢ CSF transport
  - ➢ Ex:- Benzylpenicillins

➢ Saturable transport into or out of tissues
  - ➢ Ex:- Methotrexate Clearance is also altered depending upon extraction ratio of drug.

DRUG METABOLISM

Causes of nonlinearity in metabolism are:

➢ Capacity limited metabolism due to enzyme & cofactor saturation.
  - ➢ Ex:- Phenytoin, alcohol, theophylline.

➢ Enzyme induction.
  - ➢ Ex:- Carbamazepine, where a decrease in peak plasma concentration has been observed on repetitive administration.

➢ Cofactor or enzyme limitation
  - ➢ Ex:- Acetaminophen,

➢ Altered hepatic blood flow
  - ➢ Ex:- Propranolol , verapamil Metabolite inhibition Diazepam.

➢ Other causes, saturation of binding sites & pathological situation such as hepatotoxicity

DRUG EXCRETION

- **saturable processes are:**

1. Active tubular secretion.
   - Ex:- Penicillin G.
2. Active tubular reabsorption .
   - Ex:- Water soluble vitamins & glucose.
3. Biliary secretion
   - Ex:- Iodipamide ,
4. Enterohepatic recycling
   - Ex:- Cimetidine , isotretinoin .
5. Other causes include:
   1. forced diuresis,
   2. change in pH, nephrotoxicity & saturation of binding sites.

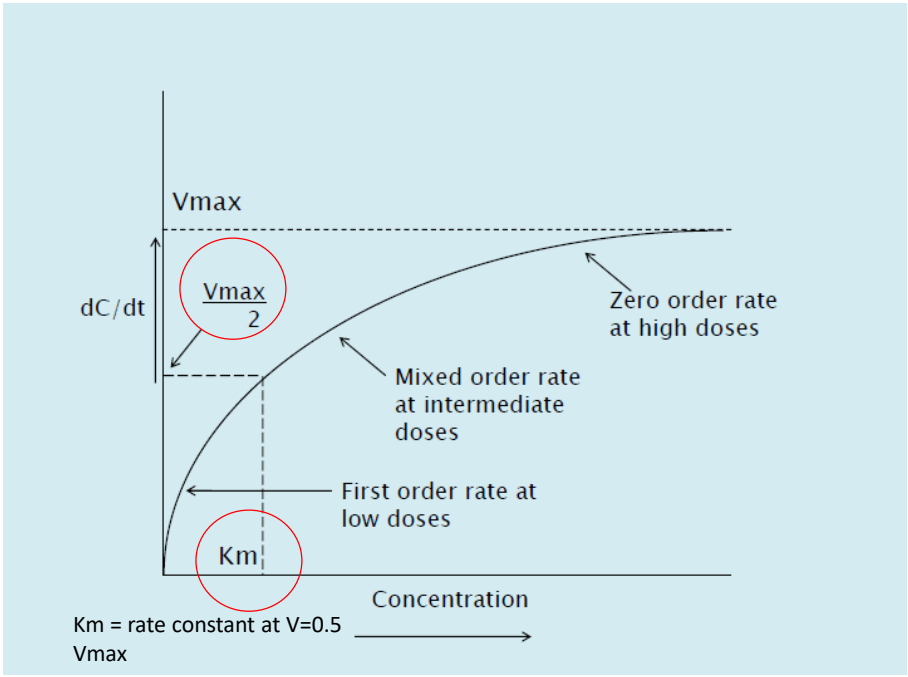
Saturable Enzymatic Elimination Processes

Kinetic of capacity-limited or saturable processes is best described by Michaelis-menten equation

$$\text{Elimination rate} = \frac{dC_p}{dt} = \frac{V_{max} C_p}{K_M + C_p} \qquad (9.1)$$

Where:
V_{max} is the maximum elimination rate
K_M is the Michaelis constant

- K_M reflects the *capacity* of the enzyme system.
- It is important to note that K_M is not an elimination constant, but is actually a hybrid rate constant in enzyme kinetics, representing both the forward and backward reaction rates and equal to the drug concentration **or amount of drug in the body at $0.5V_{max}$.**
- **The values for K_M and V_{max} are dependent on the nature of the drug and the enzymatic process involved**.



Km = rate constant at V=0.5 Vmax

Example:

The elimination rate of drug X with a K_M of 0.1 ug/mL and a V max of 0.5 ug/mL per hour is calculated by using equation :

$$\text{Elimination rate} = \frac{dC_p}{dt} = \frac{V_{max} C_p}{K_M + C_p} \qquad (9.1)$$

- Rate constant (The ratio of the elimination rate/ the concentration) is not equal at different concentrations.
- ***In contrast, a first-order elimination process would yield the same elimination rate constant at all plasma drug concentrations***.

At drug concentrations of 0.4–10 ug/mL, the enzyme system is not saturated and the rate of elimination is a mixed or nonlinear process

- At higher drug concentrations, 11.2ug/mL and above, the elimination rate approaches the maximum velocity (V max) of approximately 0.5 ug/mL per hour.
- At V max, the elimination rate is a constant and is considered a zero-order process.

Table 9.2 Effect of Drug Concentration on the Elimination Rate and Rate Constant[a]

Drug Concentration (μg/mL)	Elimination Rate (μg/mL per hr)	Elimination Rate/Concentration[b] (hr^{-1}) Elimination constant
0.4	0.400	1.000
0.8	0.444	0.556
1.2	0.462	0.385
1.6	0.472	0.294
2.0	0.476	0.238
2.4	0.480	0.200
2.8	0.483	0.172
3.2	0.485	0.152
10.0	0.495	0.0495
10.4	0.495	0.0476
10.8	0.495	0.0459
11.2	0.496	0.0442
11.6	0.496	0.0427

[a] K_M = 0.1 μg/mL, V_{max} = 0.5 μg/mL per hour.

- When the drug concentration C_p is large in relation to K_M ($C_p >> K_m$), saturation of the enzymes occurs and the value for K_M is negligible.
- The rate of elimination proceeds at a fixed or constant rate equal to V_{max}. Thus, elimination of drug becomes a zero-order process:

$$\text{Elimination rate} = \frac{dC_p}{dt} = \frac{V_{max} C_p}{K_M + C_p} \qquad (9.1)$$

$$-\frac{dC_p}{dt} = \frac{V_{max} C_p}{C_p} = V_{max} \qquad (9.2)$$

Example

- drug X (V max = 0.5 ug/mL per hour, K M = 0.1 ug/mL), how long would it take for the plasma drug concentration to decrease from 20 to 12 ug/mL?
- Solution
- Because 12ug/mL >> Km, elimination occurs at a zero-order rate of approximately 0.5 g/mL per hour.

$$-\frac{dC_p}{dt} = \frac{V_{max} C_p}{C_p} = V_{max} \qquad (9.2)$$

Time(*dt)* =dCp/Vmax➔time=20-12/0.5g/ml=16hrs

- when drug concentrations are much less than enzyme concentrations. (K_M>>Cp) rate of drug elimination becomes **a first-order process**.
- enzymatic drug elimination can change from a nonlinear to a linear process over a restricted concentration range.

Table 9.3 Effect of Drug Concentration on the Elimination Rate and Rate Constant[a]

		Elimination Rate
Drug Concentration (C_p) (μg/mL)	Elimination Rate (μg/mL per hr)	Concentration (hr^{-1})[b]
0.01	0.011	1.1
0.02	0.022	1.1
0.03	0.033	1.1
0.04	0.043	1.1
0.05	0.053	1.1
0.06	0.063	1.0
0.07	0.072	1.0
0.08	0.082	1.0
0.09	0.091	1.0

[a] K'_M = 0.8 μg/mL, V_{max} = 0.9 μg/mL per hour.

[b] The ratio of the elimination rate to the concentration is equal to the rate constant.

The first-order rate constant for a saturable process, *k'*, can be calculated from Equation 9.3:

This is evident because the rate constant (or elimination rate/drug concentration) values are constant. (Cp bellow 0.05 ug/mL, the ratio of elimination rate/drug concentration= 1.1 hr– 1.

$$-\frac{dC_P}{dt} = \frac{V_{max} C_P}{C_P + K_M} = \frac{V_{max}}{K_M} C_P$$

$$-\frac{dC_P}{dt} = k' C_P$$

If KM>>>Cp

The first-order rate constant for a saturable process, *k'*, can be calculated from Equation :

$$k' = \frac{V_{max}}{K_M}$$

- the t 1/2 due to enzymatic elimination can be calculated:
  - t1/2=0.693/k’

In summary

$$\text{Elimination rate} = \frac{dC_p}{dt} = \frac{V_{max} C_p}{K_M + C_p} \qquad (9.1)$$

- When Km = C

$$-\frac{dC}{dt} = \frac{Vmax}{2}$$

- When Km>>C

$$-\frac{dC}{dt} = \frac{Vmax.C}{Km}$$

- When Km<<C

$$-\frac{dC}{dt} = Vmax$$

- When a drug given in therapeutic doses, most drugs produce plasma drug concentrations well below K_M for all carrier-mediated enzyme systems affecting the pharmacokinetics of the drug.
- ***Therefore, most drugs at normal therapeutic concentrations follow first-order rate processes.***
- Only a few drugs, such as salicylate and phenytoin, tend to saturate the hepatic mixed-function oxidases at higher therapeutic doses.
  - With these drugs, elimination kinetics are first-order with very small doses, mixed order at higher doses, and may approach zero-order with very high therapeutic doses.

Drug Elimination by Capacity-Limited Pharmacokinetics: One-Compartment Model, IV Bolus Injection

- The rate of elimination of a drug that follows capacity-limited pharmacokinetics is governed by the V_{max} and K_M of the drug.
- If a single IV bolus injection of drug (D_0) is given at $t = 0$, the drug concentration (C_p) in the plasma at any time t may be calculated by an integrated form

$$\text{Elimination rate} = \frac{dC_p}{dt} = \frac{V_{max} C_p}{K_M + C_p} \qquad \frac{C_0 - C_p}{t} = V_{max} - \frac{K_M}{t} \ln \frac{C_0}{C_p} \qquad (9.4)$$

Alternatively, the amount of drug in the body after an IV bolus injection may be calculated by the following relationship

$$\frac{D_0 - D_t}{t} = V_{max} - \frac{K_M}{t} \ln \frac{D_0}{D_t} \qquad (9.5)$$

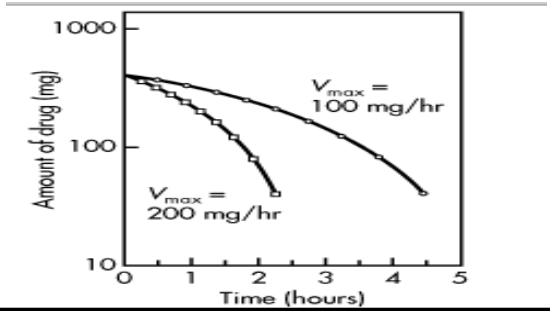
where D_0 is the amount of drug in the body at $t = 0$.

these eqs. may be used to simulate the decline of drug in the body after various size doses are given, provided the K_M and V_{max} of drug are known.

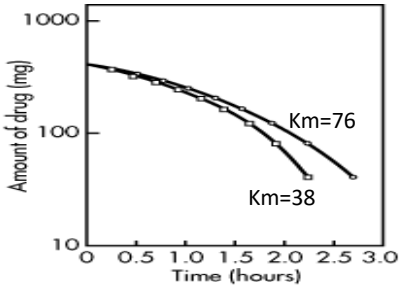
- In order to calculate the time for the dose of the drug to decline to a certain amount of drug in the body:

$$t = \frac{1}{V_{max}} \left(D_0 - D_t + K_M \ln \frac{D_0}{D_t} \right) \qquad (9.6)$$

- the time for a single 400-mg dose given by IV bolus injection to decline to 20 mg was calculated for a drug with a K_M of 38 mg/L and a V_{max} that varied from 200 to 100 mg/hr
- With a V_{max} of 200 mg/hr, the time for the 400-mg dose to decline to 20 mg in the body is 2.46 hours,
- when the V_{max} is decreased to 100 mg/hr, the time for the 400-mg dose to decrease to 20 mg is increased to 4.93 hours .
- **Thus, there is an inverse relationship between the time for the dose to decline to a certain amount of drug in the body and the V_{max}**



- If V_{max} is constant at 200 mg/hr, the time for the drug to decline from 400 to 20 mg is 2.46 hours when K_M is 38 mg/L;
- whereas when K_M is 76 mg/L, the time for the drug dose to decline to 20 mg is 3.03 hours.
- **Thus, an increase in K_M (with no change in V_{max}) will increase the time for the drug to be eliminated from the body.**



Example:

- A drug eliminated from the body by capacity-limited pharmacokinetics has a K_M of 100 mg/L and a V_{max} of 50 mg/hr. If 400 mg of the drug is given to a patient by IV bolus injection, calculate the time for the drug to be 50% eliminated. If 320 mg of the drug is to be given by IV bolus injection, calculate the time for 50% of the dose to be eliminated. Explain why there is a difference in the time for 50% elimination of a 400-mg dose compared to a 320-mg dose.

$$t = \frac{1}{V_{max}}\left(D_0 - D_t + K_M \ln \frac{D_0}{D_t}\right) \qquad (9.6)$$

Solution

Use Equation 9.6 to calculate the time for the dose to decline to a given amount of drug in the body. For this problem, D_t is equal to 50% of the dose D_0.

If the dose is 400 mg,

$$t = \frac{1}{50}\left(400 - 200 + 100 \ln \frac{400}{200}\right) = 5.39 \text{ hr}$$

If the dose is 320 mg,

$$t = \frac{1}{50}\left(320 - 160 + 100 \ln \frac{320}{160}\right) = 4.59 \text{ hr}$$

For capacity-limited elimination, the elimination half-life is dose-dependent, because the drug elimination process is partially saturated. Therefore, small changes in the dose will produce large differences in the time for 50% drug elimination. The parameters K_M and V_{max} determine when the dose is saturated.

- **2.** Using the same drug, calculate the time for 50% elimination of the dose when the doses are 10 and 5 mg. Explain why the times for 50% drug elimination are similar even though the dose is reduced by one-half.

$$t = \frac{1}{V_{max}}\left(D_0 - D_t + K_M \ln \frac{D_0}{D_t}\right) \qquad (9.6)$$

$$t = \frac{1}{50}\left(10 - 5 + 100 \ln \frac{10}{5}\right) = 1.49 \text{ hr}$$

If the dose is 5 mg,

$$t = \frac{1}{50}\left(5 - 2.5 + 100 \ln \frac{5}{2.5}\right) = 1.44 \text{ hr}$$

Whether the patient is given a 10- or a 5-mg dose by IV bolus injection, the times for the amount of drug to decline 50% are approximately the same. For 10- and 5-mg doses the amount of drug in the body is much less than the K_M of 100 mg. Therefore, the amount of drug in the body is well below saturation of the elimination process and the drug declines at a first-order rate.

Determination of K_M and V_{max} :

1-by examining the linearity of graph data

$$\text{Elimination rate} = \frac{dC_p}{dt} = \frac{V_{max} C_p}{K_M + C_p} \qquad (9.1)$$

- The eq. above relates the rate of drug biotransformation to the concentration of the drug in the body.

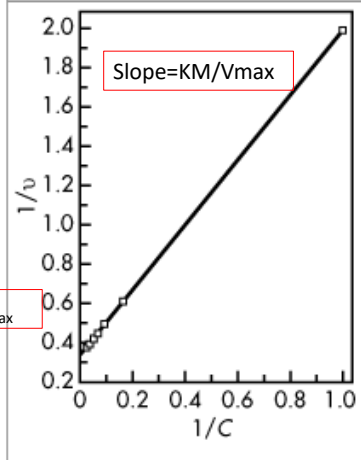
The same equation may be applied to determine the rate of enzymatic reaction of a drug *in vitro*

$$v = \frac{V_{max} C}{K_M + C} \qquad (9.7)$$

$$\frac{1}{v} = \frac{K_M}{V_{max}} \frac{1}{C} + \frac{1}{V_{max}} \qquad (9.8)$$

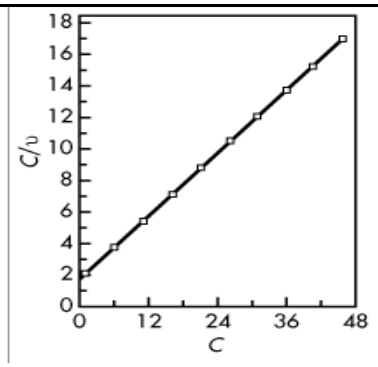
V= rate of in vitro enzymatic reaction
C= concentration of drug in vitro

Figure 9-6.



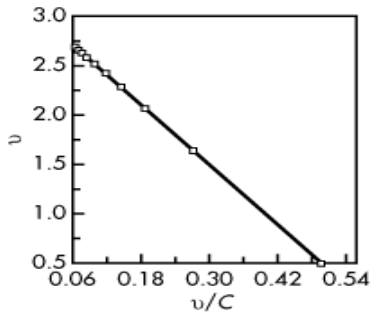
$$\frac{C}{v} = \frac{1}{V_{max}} C + \frac{K_M}{V_{max}} \qquad (9.9)$$

A plot of C/v versus C would yield a straight line with $1/V_{max}$ as slope and K_M/V_{max} as intercept



$$v = -K_M \frac{v}{C} + V_{max} \qquad (9.10)$$

A plot of v versus v/C would yield a slope of $-K_M$ and an intercept of V_{max}



Determination of K_M and V_{max} in Patients

$$v = \frac{V_{max} C}{K_M + C} \qquad (9.7)$$

- The rate of drug metabolism will vary depending on the concentration of drug C_p as well as on the metabolic rate constants K_M and V_{max} of the drug in each individual

- An example for the determination of K_M and V_{max} is given for the drug phenytoin.
- Phenytoin undergoes capacity-limited kinetics at therapeutic drug concentrations in the body.
- To determine K_M and V_{max}, two different dose regimens are given at different times, until steady state is reached.
- The steady-state drug concentrations are then measured by assay.
- At steady state, the rate of drug metabolism (v) is assumed to be the same as the rate of drug input R (dose/day).

$$R = \frac{V_{max} C_{SS}}{K_M + C_{SS}} \qquad (9.11)$$

where R = dose/day or dosing rate;
C_{ss} = steady-state plasma drug concentration,
V_{max} = maximum metabolic rate constant in the body,
and K_M = Michaelis–Menten constant of the drug in the body.

- Example
- Phenytoin was administered to a patient at dosing rates of 150 and 300 mg/day, respectively. The steady-state plasma drug concentrations were 8.6 and 25.1 mg/L, respectively. Find the K_M and V_{max} of this patient. What dose is needed to achieve a steady-state concentration of 11.3 mg/L?

$$K_M = \frac{300 - 150}{(150/8.6) - (300/25.1)} = 27.3 \text{ mg/L}$$

Substitute K_M into either of the two simultaneous equations to solve for V_{max}.

$$150 = \frac{V_{max}(8.6)}{27.3 + 8.6}$$

$$V_{max} = 626 \text{ mg/day}$$

Determination of K_M and V_{max} by Direct Method

- When steady-state concentrations of phenytoin are known at only two dose levels, there is no advantage in using the graphic method. K_M and V_{max} may be calculated by solving two simultaneous equations formed by substituting C_{SS} and R (Eq. 9.11) with C_1, R_1, C_2, and R_2. The equations contain two unknowns, K_M and V_{max}, and may be solved easily.

$$R_1 = \frac{V_{max} C_1}{K_M + C_1}$$

$$R_2 = \frac{V_{max} C_2}{K_M + C_2}$$

Combining the two equations yields Equation 9.15

$$K_M = \frac{R_2 - R_1}{(R_1/C_1) - (R_2/C_2)} \qquad (9.15)$$

where C_1 is steady-state plasma drug concentration after dose 1, C_2 is steady-state plasma drug concentration after dose 2, R_1 is the first dosing rate, and R_2 is the second dosing rate. To calculate K_M and V_{max}, use Equation 9.15 with the values C_1 = 8.6 mg/L, C_2 = 25.1 mg/L, R_1 = 150 mg/day, and R_2 = 300 mg/day. The results are

Interpretation and importance of K_M and V_{max}

- An understanding of Michaelis–Menten kinetics provides insight into the nonlinear kinetics and helps to avoid dosing a drug at a concentration near enzyme saturation.
- For example, in phenytoin dosing, since K M occurs at 0.5V max, K M = 27.3 mg/L, the implication is that at a plasma concentration of 27.3 mg/L, enzymes responsible for phenytoin metabolism are eliminating the drug at 50% V max, ie, 0.5 x 626 mg/day or 313 mg/day.
- *Patients with a low K M tend to have greater changes in plasma concentrations during dosing adjustments.*
- *Patients with a smaller K M (same V max) will show a greater change in the rate of elimination when plasma drug concentration changes compared to subjects with a higher K M.*

Dependence of Elimination Half-Life on Dose

- The relationship between elimination half-life and drug concentration is:

$$t_{1/2} = \frac{0.693}{V_{max}}(K_M + C_p) \qquad (9.16)$$

1. in Nonlinear, the elimination half-life becomes longer, clearance becomes smaller, and the area under the curve becomes disproportionately larger with increasing dose.
2. The elimination half-life is dependent on the Michaelis–Menten parameters and concentration.
3. ***It is not preferable*** to calculate the elimination half-life of a nonlinear drug because the elimination half-life is not constant.
4. ***Clinically***, if the half-life is increasing as plasma concentration increases, and there is no apparent change in metabolic or renal function, then there is a good possibility that the drug may be metabolized by nonlinear kinetics.

Dependence of Clearance on Dose

- The total body clearance that follows a one-compartment model with Michaelis–Menten elimination kinetics changes with respect ***to time and plasma drug concentration.***
- Within a certain drug concentration range, an average or mean clearance (Cl_{av}) may be determined.
- Because the drug follows Michaelis–Menten kinetics, Cl_{av} is dose-dependent.

$$Cl_{av} = \frac{V_{max}}{(D_0/2V_D) + K_M} \qquad (9.23)$$

$$Cl = \frac{V_D(dC_P/dt)}{C_P} = \frac{V_{max}}{K_M + C_P} \qquad (9.24)$$

$$Cl_T = \frac{dD_E/dt}{C_P} \qquad (9.25)$$

Mixed Drug Elimination

- The Drugs are metabolized to several different metabolites by parallel pathways.
- For example, sodium salicylate is metabolized to both a glucuronide and a glycine conjugate (hippurate).
- The rate of formation of the glycine conjugate is limited by the amount of glycine available. Thus, the rate of formation of the glucuronide continues as a first-order process; whereas the rate of conjugation with glycine is capacity limited.
- The equation that describes a drug that is eliminated by both first-order and Michaelis–Menten kinetics after IV bolus injection is given by:

$$-\frac{dC_P}{dt} = kC_P + \frac{V'_{max}C_P}{K_M + C_P} \qquad (9.26)$$

Where:

k is the first-order rate constant representing the sum of all first-order elimination processes,
V'_{max} is simply V_{max} expressed as concentration by dividing by V_D

Zero-Order Input and Nonlinear Elimination

- The usual example of zero-order input is constant IV infusion. If the drug is given by constant IV infusion and is eliminated only by nonlinear pharmacokinetics, then the following equation describes the rate of change of the plasma drug concentration:

$$\frac{dC_P}{dt} = \frac{k_0}{V_D} - \frac{V'_{max} C_P}{K_M + C_P} \qquad (9.27)$$

where k_0 is the infusion rate and V_D is the apparent volume of distribution.

First-Order Absorption and Nonlinear Elimination

The relationship that describes the rate of change in the plasma drug concentration for a drug that is given extravascularly (eg, orally), absorbed by first-order absorption, and eliminated only by nonlinear pharmacokinetics, is given by the following equation. C_{GI} is concentration in the GI tract.

$$\frac{dC_P}{dt} = k_a C_{GI} e^{-k_a t} - \frac{V'_{max} C_P}{K_M + C_P} \qquad (9.28)$$

where k_a is the first-order absorption rate constant.

If the drug is eliminated by parallel pathways consisting of both linear and nonlinear pharmacokinetics, Equation 9.28 may be extended to Equation 9.29.

$$\frac{dC_P}{dt} = k_a C_{GI} e^{-k_a t} - \frac{V'_{max} C_P}{K_M + C_P} - kC_P \qquad (9.29)$$

where k is the first-order elimination rate constant.

Bioavailability of Drugs that Follow Nonlinear Pharmacokinetics

- The bioavailability of drugs that follow nonlinear pharmacokinetics is difficult to estimate accurately. EXPLAIN WHY?
- As shown in , each process of drug absorption, distribution, and elimination is potentially saturable. Drugs that follow linear pharmacokinetics follow the principle of superposition (). The assumption in applying the rule of superposition is that each dose of drug superimposes on the previous dose. Consequently, the bioavailability of subsequent doses is predictable and not affected by the previous dose. In the presence of a saturable pathway for drug absorption, distribution, or elimination, drug bioavailability will change within a single dose or with subsequent (multiple) doses.