Nonlinear Pharmacokinetics

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Non linear pharmacokinetics:

- In some cases, the kinetics of a pharmacokinetic process change from predominantly first order to predominantly zero order with increasing dose or chronic medication.
- A mixture of both first order and zero order kinetics is called as **mixed order kinetics**. Also known as **nonlinear kinetics** or **dose dependent kinetics.**
- Eg. vitamin C, naproxen, riboflavin.
- The kinetics of such capacity limited processes can be described by the **Michaelis-Menten kinetics.**

Linear Pharmacokinetics	Non Linear Pharmacokinetics
Pharmacokinetic parameters for a drug would not change with change in dose	Pharmacokinetic parameters for a drug can change with change in dose.
Dose Independent	Dose dependent
First Order kinetics	Also called as Mixed order, Saturated kinetics, capacity limited
All semilog plots of C vs t for diff. doses are superimposable.	Not superimposable

Examples of Drugs Showing Nonlinear Kinetics

Cause	**Drug**
GI Absorption	
Absorption is carrier mediated.	Riboflavin, gebapentin, L-dopa, baclofen, ceftibuten
Drugs with low solubility in GI but relatively high dose	Chorothiazide, griseofulvin, danazol
Presystemic hepatic metabolism attains saturation	Propranolol

Distribution	
Saturable plasma protein binding	Phenylbutazone, lidocaine, salicylic acid, ceftriaxone, diazoxide, phenytoin, warfarin, disopyramide
Cellular uptake	Methicillin (rabbit)
Tissue binding	Imiprimine (rat)
Saturable transport into or out of tissues	Methotrexate

Renal Elimination	
Active secretion	Mezlocillin, para-aminohippuric acid
Tubular reabsorption	Riboflavin, ascorbic acid, cephapirin
Change in urine pH	Salicylic acid, dextroamphetamine

Metabolism	
Saturable metabolism	Phenytoin, salicyclic acid, theophylline, valproic acid
Cofactor or enzyme limitation	Acetaminophen, alcohol
Enzyme induction	Carbamazepine
Altered hepatic blood flow	Propranolol, verapamil
Metabolite inhibition	Diazepam
Biliary Excretion	
Biliary secretion	Iodipamide, sulfobromophthalein sodium
Enterohepatic recycling	Cimetidine, isotretinoin

Drugs that demonstrate saturation kinetics usually show the following characteristics:

1. Elimination of drug does not follow simple first-order kinetics—that is, elimination kinetics are nonlinear.

2. The elimination half-life changes as dose is increased. Usually,

the elimination half-life increases with increased dose due to saturation of an enzyme system.

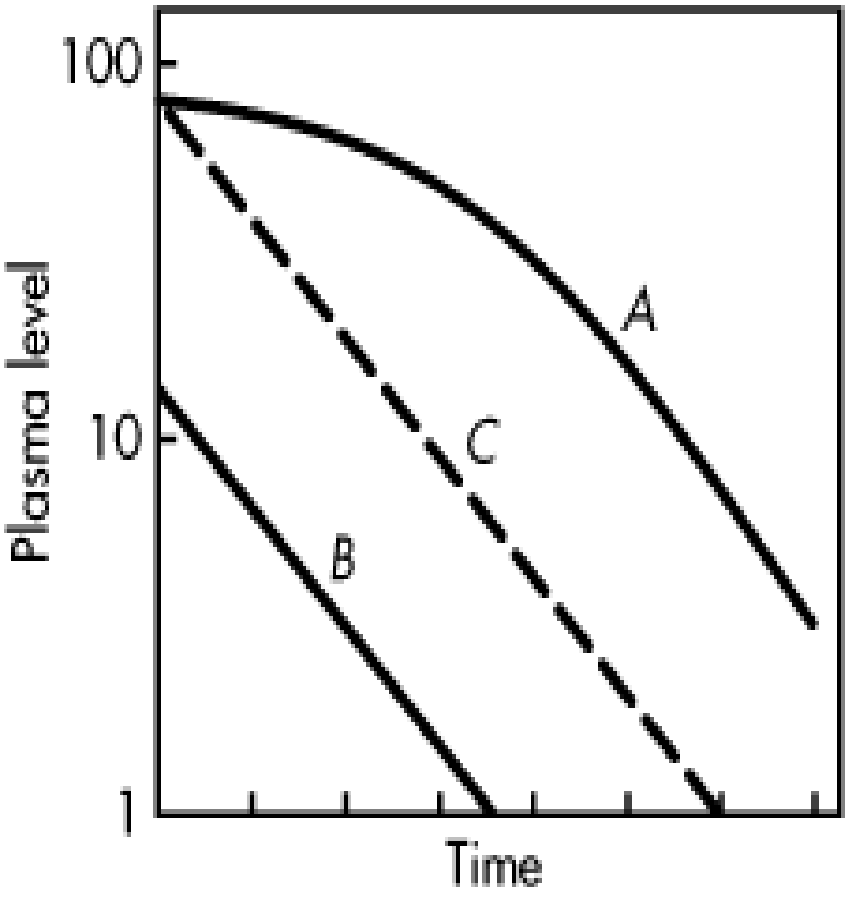
However, the elimination half-life might decrease due to "self"-induction of liver biotransformation enzymes, as is observed for carbamazepine.

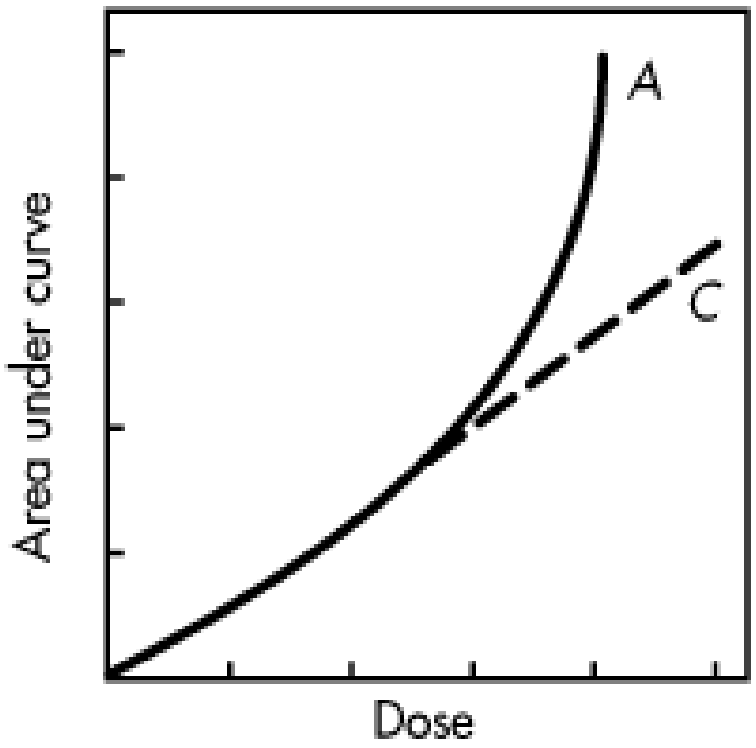
3. The area under the curve (AUC) is not proportional to the amount of bioavailable drug.

4. The saturation of capacity-limited processes may be affected by other drugs that require the same enzyme or carrier-mediated system (ie,competition effects).

5. The composition and/or ratio of the metabolites of a drug may be affected by a change in the dose.

- **large dose** ⟶ curve is obtained with an initial slow elimination phase followed by a much more rapid elimination at lower blood concentrations (curve *A*).
- **small dose** ⟶ apparent first-order kinetics are observed, because no saturation kinetics occur (curve *B*).
- If the pharmacokinetic data were estimated only from the blood levels described by curve *B*, then a twofold increase in the dose would give the blood profile presented in curve *C*, which considerably underestimates the drug concentration as well as the duration of action.





Curve A = Saturated kinetics

Curve C = Dose Independent Kinetics

A plot of the areas under the plasma level–time curves at various doses should be linear.

Saturable Enzymatic Elimination Processes

- *Michaelis–Menten kinetics:*

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

dCp/dt = rate of decline of drug concentration with time,

V_{max} = theoretical maximum rate of the process,

Km = Michaelis constant, reflects the ***capacity*** of the enzyme system , equal to the drug concentration or amount of drug in the body at $0.5\,V_{max.}$

$C_p >> K_m$	$C_p = K_m$	$C_p << K_m$
• saturation of the enzymes occurs. •The value for K_M is negligible. •The rate of elimination proceeds at a constant rate $-\frac{dC_p}{dt} = \frac{V_{max} C_p}{C_p} = V_{max}$	•Rate of process is = one half of its max. rate • $-dc/dt = V_{max}/2$	•rate of drug elimination becomes a first-order process $-\frac{dC_p}{dt} = \frac{V_{max} C_p}{C_p + K_M} = \frac{V_{max}}{K_M} C_p$ $-\frac{dC_p}{dt} = k' C_p$

Conc. (g/ml)	**Elimination rate (g/mL per hr) Calculated from equation 1**	**Elimination Rate/Concentration (hr^{-1}) equal to elimination rate comnstant**
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

Problem: from above data

Using the hypothetical drug considered in (*V* max = 0.5 g/mL per hour, *K* M = 0.1 g/mL), how long would it take for the plasma drug concentration to decrease from 20 to 12 g/mL?

- **Solution**
- Because 12 g/mL is above the saturable level, as indicated in , elimination occurs at a zero-order rate of approximately 0.5 g/mL per hour.
- 0.5 g/ml ⟶ 1 Hr
- 8 g/ml ⟶ 16Hr

Conc. (g/mL)	Elimination Rate (g/mL per hr)	Elimination Rate Constant (hr^{-1})
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

K_M = 0.8 g/mL, V_{max} = 0.9

- First order Rate constant =V max/K_M = 1.1 Hr^{-1} From this we can find out Half Life

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

- 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 integrating equation,

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

$$\frac{C_0 - C_p}{t} = V_{max} - \frac{K_M}{t} \ln \frac{C_0}{C_p}$$

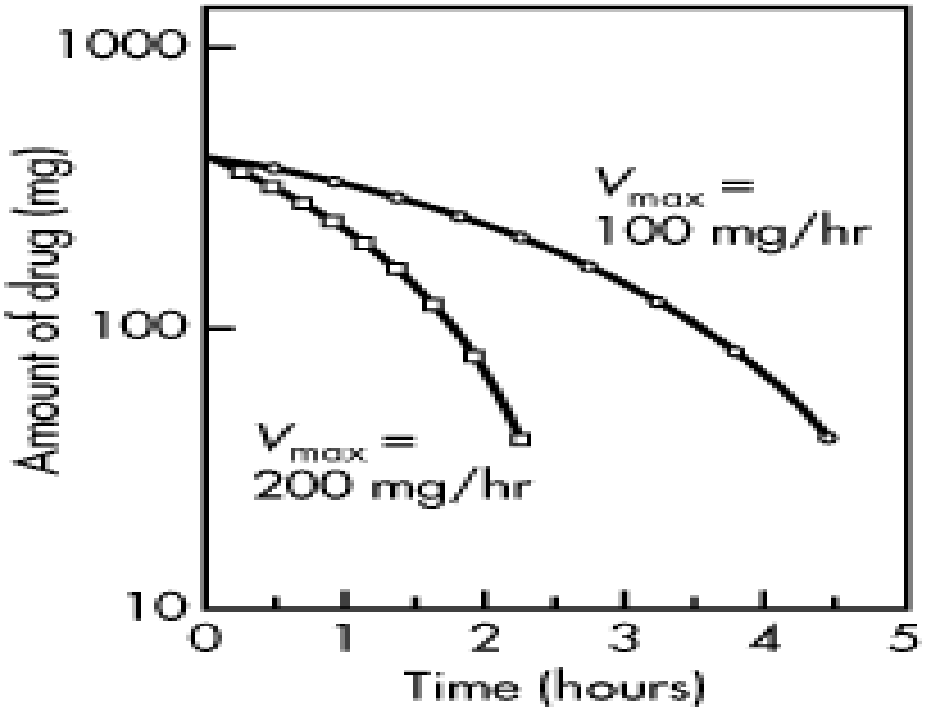
- Amount of drug in the body after IV Bolus ,

$$\frac{D_0 - D_t}{t} = V_{max} - \frac{K_M}{t} \ln \frac{D_0}{D_t}$$

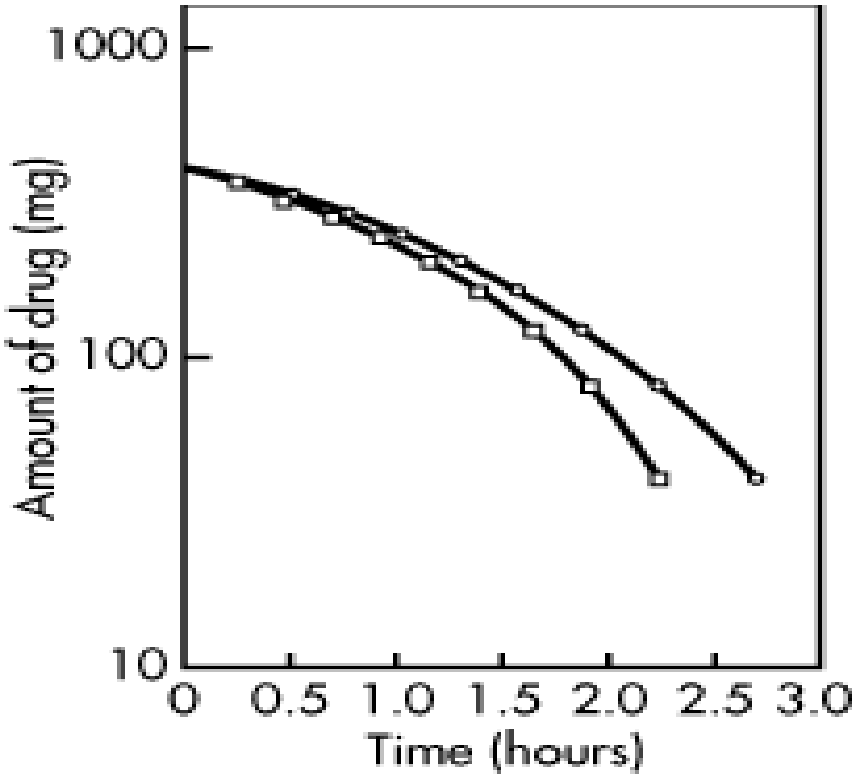
- Where, D_0 is the amount of drug in the body at $t = 0$.
- Rearranging equation:

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

The relationship of KM and V max to the time



- **Amount of drug (mg) Vs Time (hr) at diff. velocity and Constant Km**
- **Velocity Inversely Proportional to Time**



- **Amount of drug (mg) Vs Time (hr) at diff. K_M and Constant V_{max}**
- **Km is directly proportional to Time.**
- **As Km is incereases time required to decline the drug amt increases**

Practice:

A drug eliminated from the body by capacity-limited pharmacokinetics
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.

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,

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

small changes in the dose will produce large differences in the time for 50% drug elimination. Because of Saturation

If the dose is 10 mg,

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

If the dose is 5 mg,

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

- 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}

Observation Number	C (M/mL)	V (M/mL per min)	1/v	1/c
1	1	0.500	2.000	1.000
2	6	1.636	0.611	0.166
3	11	2.062	0.484	0.090
4	16	2.285	0.437	0.062
5	21	2.423	0.412	0.047
6	26	2.516	0.397	0.038
7	31	2.583	0.337	0.032
8	36	2.504	0.379	0.027
9	41	2.673	0.373	0.024
10	46	2.705	0.369	0.021

1) Lineweaver-Burke plot:

$$v = \frac{V_{max} C}{K_M + C}$$

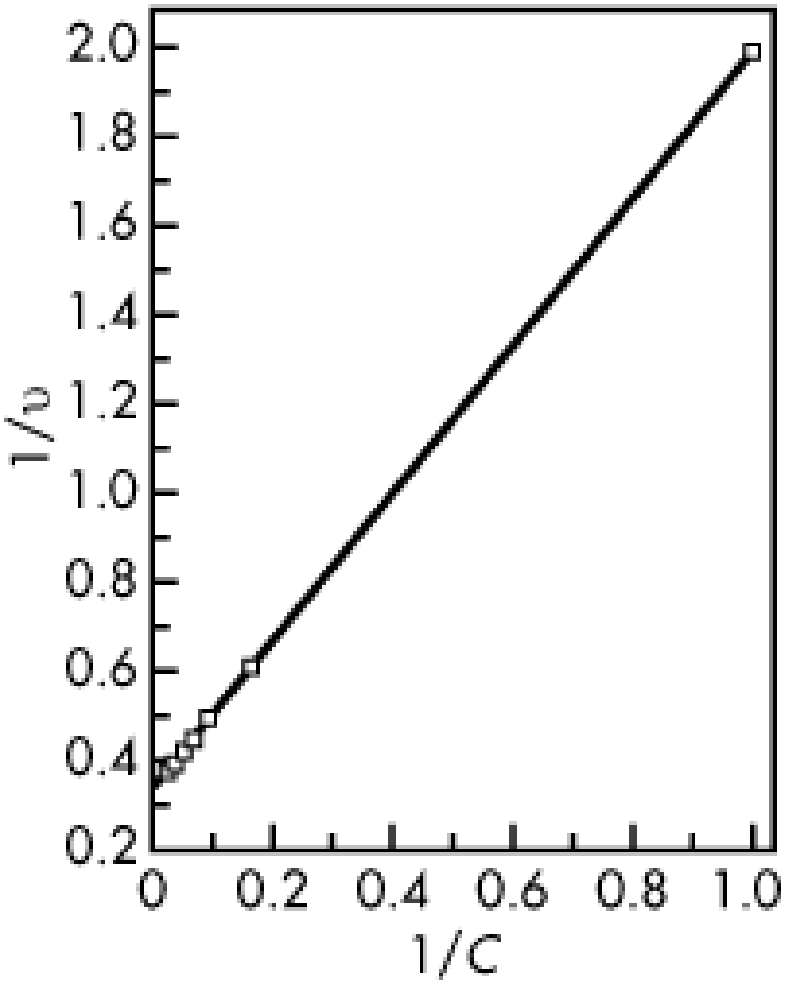
$$\frac{1}{v} = \frac{K_M}{V_{max}} \frac{1}{C} + \frac{1}{V_{max}}$$

- *y*-intercept = $1/V_{max}$

  the slope = K_M/V_{max}.

$$\frac{1}{V_{max}} = 0.33 \text{ min mL}/\mu\text{mol}$$

$$V_{max} = 3 \ \mu\text{mol}/\text{mL min}$$



- Disadvantage:

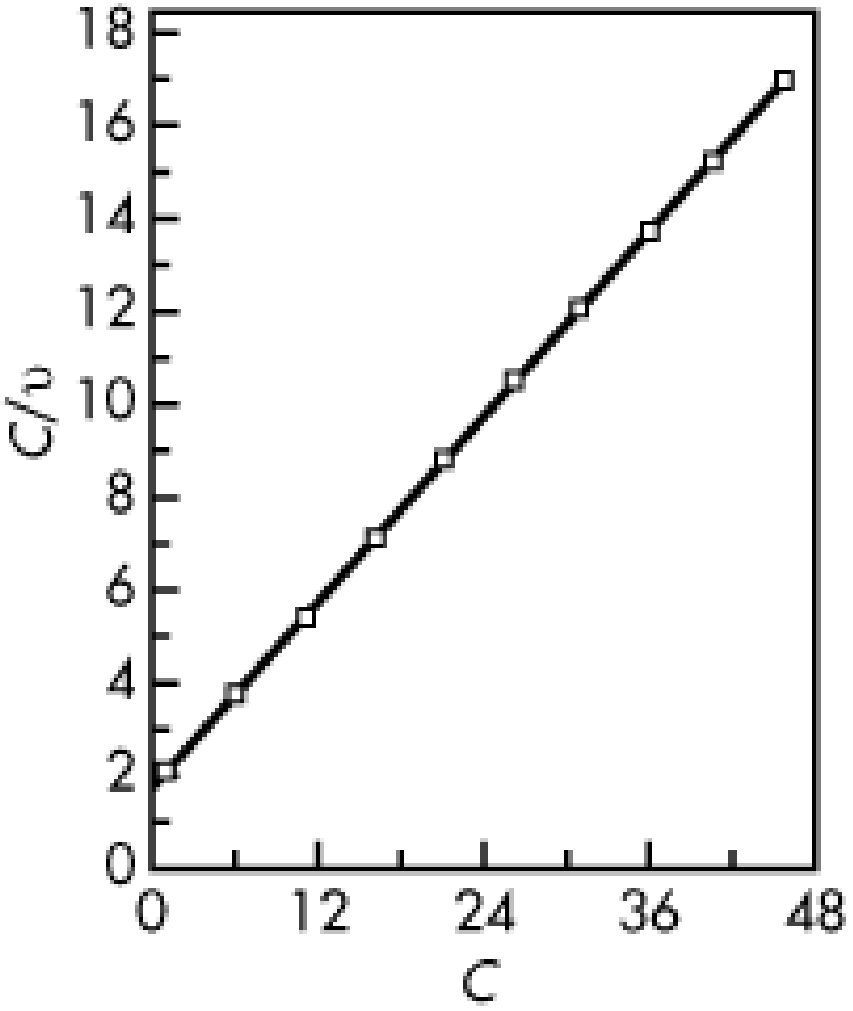
The points are clustered.

2) Plot of C/v versus C

$$v = \frac{V_{max} C}{K_M + C}$$

$$\frac{C}{v} = \frac{1}{V_{max}} C + \frac{K_M}{V_{max}}$$

- Yield a straight line
- slope = $1/V_{max}$
- Intercept = K_M/V_{max}

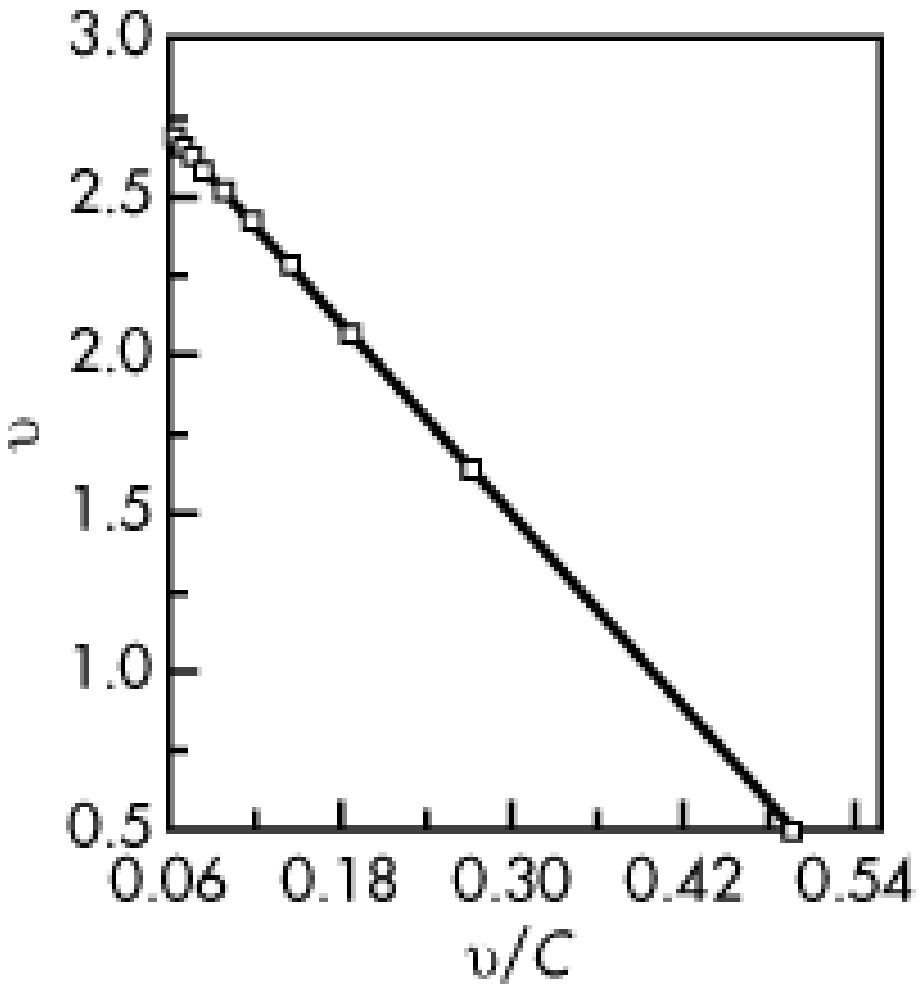


3) Plot of v Vs v/C

$$v = \frac{V_{max} C}{K_M + C}$$

$$v = -K_M \frac{v}{C} + V_{max}$$

- slope = $-K_M$
- intercept = V_{max}



4) From steady state plasm drug concentration:

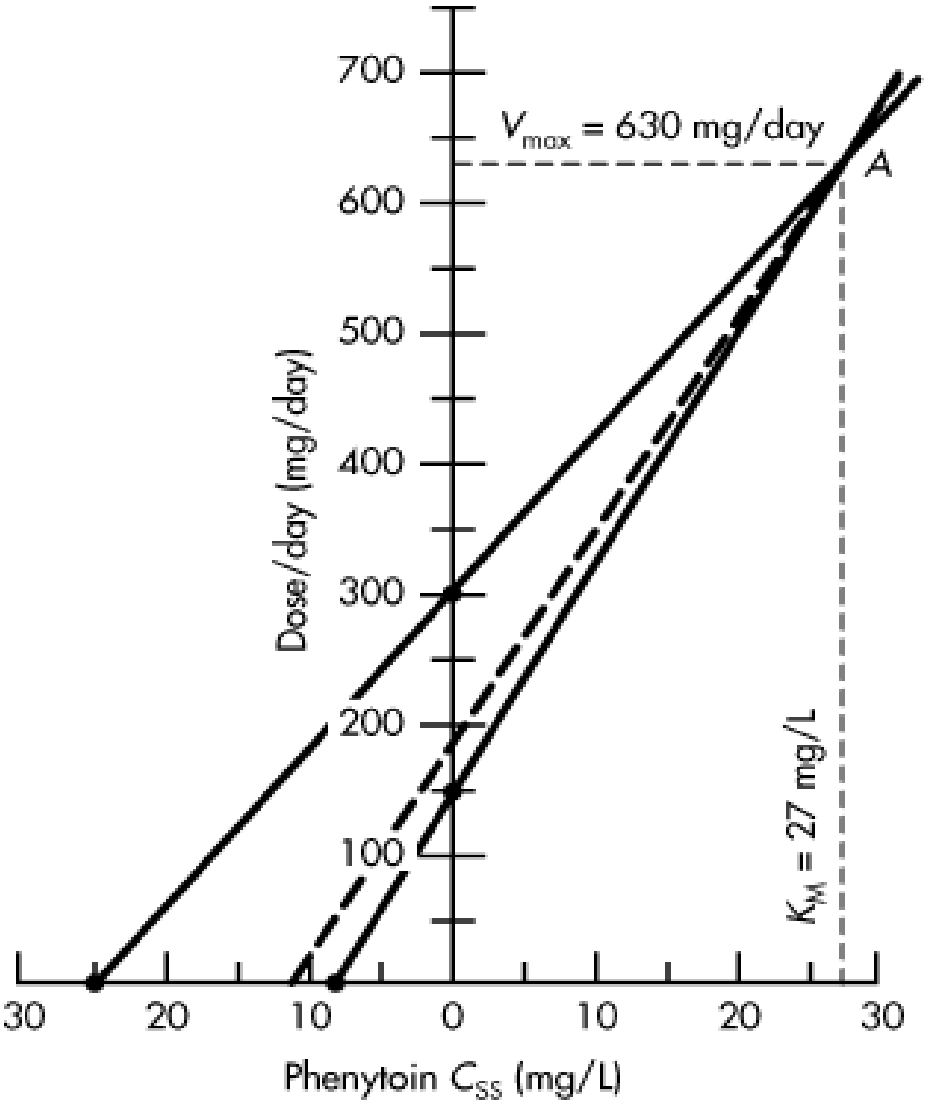
$$R = \frac{V_{max} C_{SS}}{K_M + C_{SS}}$$

- At steady state
- *the rate of drug metabolism (v) = rate of drug input $\mathcal{R}$ (dose/day).*
- *Inverting above equation:*

$$\frac{1}{R} = \frac{K_M}{V_{max}} \frac{1}{C_{SS}} + \frac{1}{V_{max}}$$

A plot of R versus C_{SS} is plotted

1. **Mark points for *R* of 300 mg/day and C_{SS} of 25.1 mg/L as shown. Connect with a straight line.**
2. **Mark points for *R* of 150 mg/day and C_{SS} of 8.6 mg/L as shown. Connect with a straight line.**
3. **Where lines from the first two steps cross is called point *A*.**
4. **From point *A*, read V_{max} on the *y* axis and K_M on the *x* axis.**



5) Direct Method

- Used when only two dose levels

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

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

- Combining Two Equations:

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

- 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,
- R_2 is the second dosing rate.

Interpretation 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.
- Eg. Conc. = 8.6mg/L

  Km =27.3 mg/L

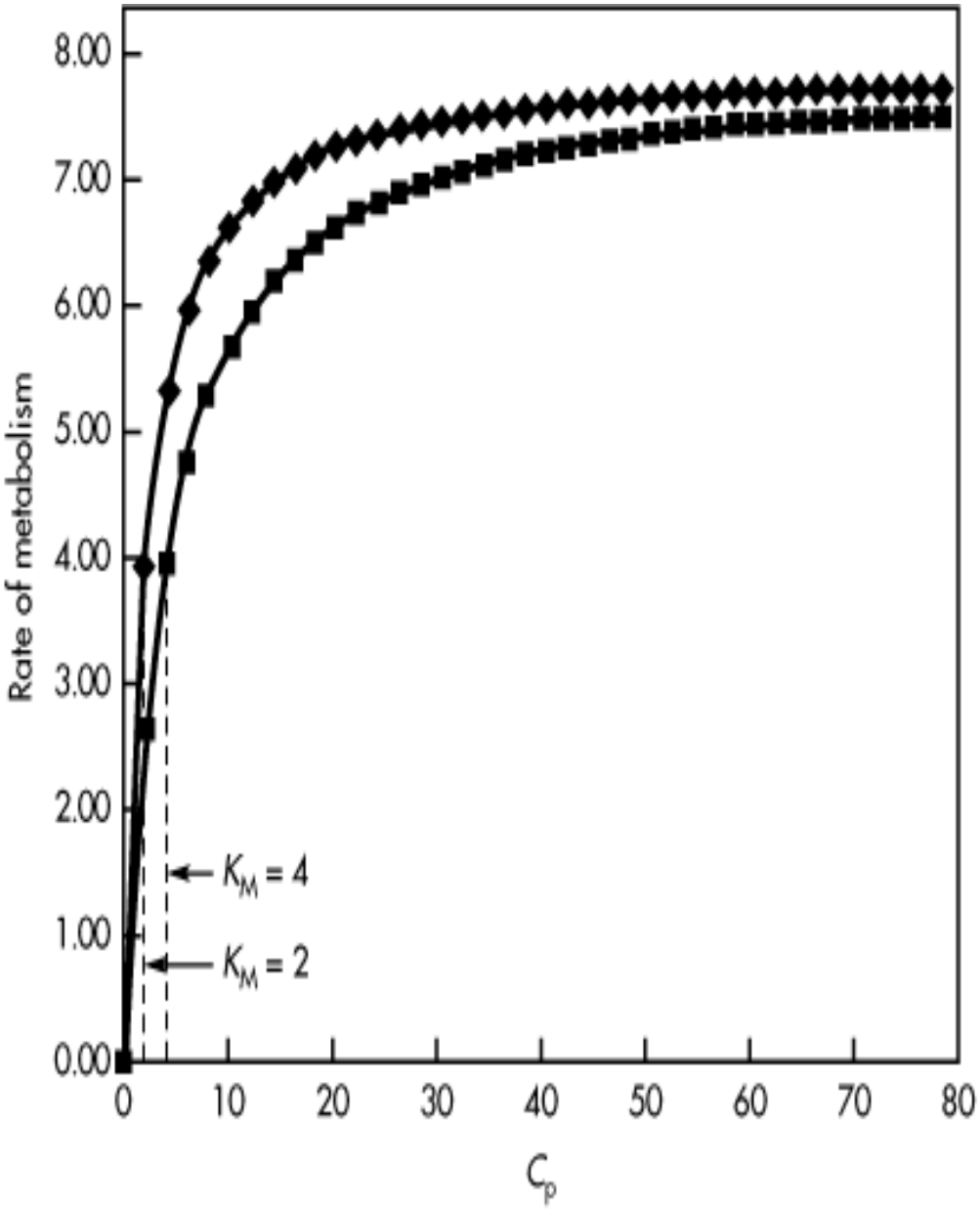
  dose = 300mg/day

  V_{max} = 626 mg/day

50% V_{max}, ie, 0.5 x 626 mg/day or 313 mg/day.

subject is receiving 300 mg of phenytoin per day, the plasma drug concentration of phenytoin is 8.6 mg/L, which is considerably below the *K* M of 27.3 mg/L

- Diagram showing the rate of metabolism
- when V_{max} is constant (8 g/mL/hr)
- K_M is changed
- K_M = 2 g/mL for top curve
- K_M = 4 g/mL for bottom curve
- Note the rate of metabolism is faster for the lower K_M, but saturation starts at lower concentration.



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:

$$\frac{dC_p}{dt} = \frac{k_0}{V_D} - \frac{V'_{max} C_p}{K_M + C_p}$$

Zero-Order Input

Non- linear Elimination

First-Order Absorption and Nonlinear Elimination

- input extravascularly (eg, orally), absorbed by first-order absorption
- Eliminated only by nonlinear pharmacokinetics :

$$\frac{dC_p}{dt} = k_a C_{GI} e^{-k_a t} - \frac{V'_{max} C_p}{K_M + C_p}$$

First-Order Absorption

Nonlinear Elimination

- k_a is the first-order absorption rate constant

- drug is eliminated by parallel pathways consisting of both linear and nonlinear pharmacokinetics:

$$\frac{dC_p}{dt} = k_a C_{GI} e^{-k_a t} - \frac{V'_{max} C_p}{K_M + C_p} - kC_p$$

- *k* is the first-order elimination rate constant.

Definition:

- ***Chronopharmacokinetics*** deals with the study of the temporal changes in absorption, distribution, metabolism and elimination and thus takes into account the influence of time of administration on these different steps.

Temporal Change

- can be cyclical over a constant period (e.g., 24-hour interval)

- Non cyclic
- in which drug absorption or elimination changes over a longer period of time.
- Dose Dependent P/K(non Linear)