NONLINEAR PHARMACOKINETICS

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LINEAR PHARMACOKINETICS

» 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 situation the rate processes are said to follw first order or linear kinetics and all semilog plots of C Vs t for different doses when collected for dose administered, are superimposable.

» The important pharmacokinetic parameters viz. F, K_a, K_E, Vd, Cl_R, Cl_H which describes the time course of a drug in the body remain unaffected by the dose.

» Pharmacokinetics is dose independent.

NON-LINEAR PHARMACOKINETICS

» The rate process of drug's ADME are depend upon carrier or enzymes that are substrate specific, have definite capacities and are susceptible to saturation at a 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 are changed with the size of the administered dose.

» Pharmacokinetics of such drugs are said to be dose-dependent. Terms synonymous with it are mixed-order, nonlinear and capacity-limited kinetics.

DETECTION OF NON-LINEARITY IN PHARMACOKINETICS

- There are several tests to detect non –linearity in pharmacokinetics but the simplest ones are:

1) First test:- Determination of steady state plasma concentration at different doses.

2) Second test:- Determination of some important pharmacokinetic parameters such as fraction bioavailability, elimination half life or total systemic clearance at different doses of drug. Any change in these parameters is indicative to non-linearity which are usually constant.

CAUSES OF NON-LINEARITY

Drug absorption

- Three causes:- I) Solubility / dissolution of drug is rate-limited; Griseofulvin - at high concentration in intestine.

  II) Carrier - mediated transport system; Ascorbic acid - saturation of transport system.

  III) Presystemic gut wall / hepatic metabolism attains saturation; Propranolol.

- These parameters affected F, K_a, C_{max} and AUC.

- A decrease in these parameters is observed in former two causes and an increase in latter cause.

Drug distribution

At high doses non-linearity due to

- Two causes:- I) Binding sites on plasma proteins get saturated; Phenylbutazone.

  II) Tissue binding sites get saturated.

- In both cases there is increase in plasma drug concentration.
- Increase in V_d only in (I)
- Clearance with high ER get increased due to saturation of binding sites.

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Drug metabolism

- Non-linearity occurs due to capacity limited metabolism, small changes in dose administration - large variations in plasma concentration at steady state - large intersubject variability.

- Two imp causes:- I) Capacity - limited metabolism - enzyme &/ cofactor saturation; Phenytoin, Alcohol.

  II) Enzyme induction - decrease in plasma concentration; Carbamazepine.

- Autoinduction in dose dependent concentration.
- Saturation of enzymes - decrease in Cl_H - increase in C_{ss}.
- In case of enzyme induction reverse condition.
- Other reasons includes saturation of binding sites, inhibitory effects of the metabolites on the action of enzymes.

Drug excretion

- Two active processes which are saturable,
  - I) Active tubular secretion - Penicillin G
  - II) Active tubular reabsorption - Water soluble vitamins & Glucose.

- Saturation of carrier systems - decrease in renal clearance in case of I & increase in II. Half life also increases.
- Other reasons like forced diuresis, change in urine pH, nephrotoxicity & saturation of binding sites.
- In case of biliary excretion non - linearity due to saturation - Tetracycline & Indomethacin.

Examples of drugs showing nonlinear pharmacokinetics

Causes	Drugs
GI absorption:-	
Saturable transport in gut wall	Riboflavin, Gabapentin
Saturable GI decomposition	Penicillin G, Omeprazole
Intestinal metabolism	Propranolol, Salicylamide
Distribution:-	
Saturable plasma protein binding	Phenylbutazone, Lidocaine
Tissue binding	Imipramine
Metabolism:-	
Saturable metabolism	Phenytion, Salicylic acid
Enzyme induction	Carbamazepine
Metabolite inhibition	Diazepam
Renal elimination:-	
Active secretion	Para- aminohippuric acid
Tubular reabsorption	Ascorbic acid, Riboflavin
Change in urine pH	Salicylic acid, Dextroamphetamine

MICHAELIS MENTEN ENZYME KINETICS

- ✓ It is also called as Capacity-limited metabolism or Mixed order kinetics.

$$E + D \longleftrightarrow ED \longrightarrow E + M$$

- ✓ Enzymes usually react with the substrate to form enzyme substrate complexes; then the product is formed. The enzyme can go back to react with another substrate to form another molecule of the product.

MICHAELIS MENTEN EQUATION

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

$$-\frac{dC}{dt} = \frac{V_{max} \cdot C}{K_M + C} \quad \ldots\ldots\ldots\ldots\ldots\ldots \text{I}$$

Where ,

-dC/dt = rate of decline of drug conc. with time

V_{max}= theoretical maximum rate of the process

K_M= Michaelis constant

- Three situation can now be considered depending upon the value of $K_m$and C.

1) when K_M= C:

- under this situation , eq I reduces to,
- $-dC/dt = V_{max}/2$.....II
- The rate of process is equal to half of its maximum rate.
- This process is represented in the plot of dc/dt vs. C, shown in fig. 1

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2) If a drug at low conc. undergoes a saturable biotransformation then $K_M >> C$:

- here , $K_M + C = K_M$ and eq. I reduces to,

$$-dC/dt = V_{max} C / K_M \quad \ldots\ldots\ldots\ldots\ldots\ldots III$$

- above eq. is identical to the one that describe first order elimination of drug, where $V_{max}/K_M = K_E$.

3) When $K_M << C$:

- Under this condition ,$K_M + C = C$ and eq. I will become,

$$-dC/dt = V_{max} \quad \ldots\ldots\ldots\ldots\ldots\ldots IV$$

above eq. is identical to the one that describe a zero order process i.e. the rate process occurs at constant rate V_{max} and is independent of drug conc.

E.g. metabolism of ethanol

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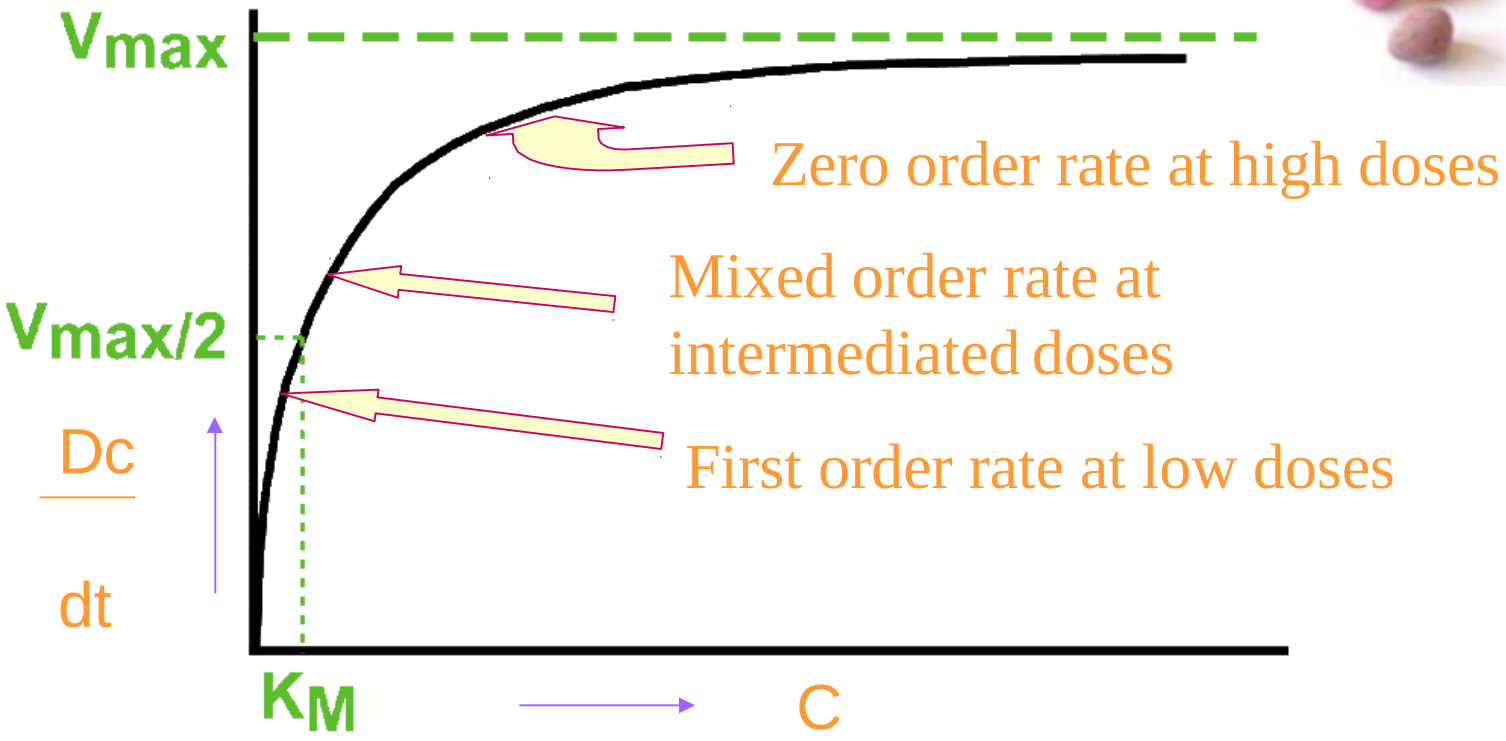

Figure 1

A plot of MME

ESTIMATION OF V_{max} & K_m

In enzymatic kinetic work, the classic Michaelis-Menten equation:

$$V = \frac{Vmax \,.\, C}{K_M + C} \quad \text{.....(1)}$$

where, V= reaction rate,
C= substrate conc. both are used to determine Vmax & Km.

The velocity of the reaction(V) at various concentration levels of drug(C) are determined either by *in-vitro* experiments or *in-vivo* experiments at constant enzyme levels.

Method 1

By reciprocating equation (1), we get :

$$\frac{1}{V} = \frac{Km \cdot 1}{Vmax \cdot C} + \frac{1}{Vmax} \quad \ldots\ldots..(2)$$

When 1/V is plotted against 1/C, a straight line is obtained with a *slope* of Km/Vmax and an *Intercept* of 1/Vmax.

E.g. : A plot of 1/ V vs 1/ C (shown in the fig. 2) gave an intercept of 0.33µmol and a slope of 1.65, Now, calculate Vmax and K_M.

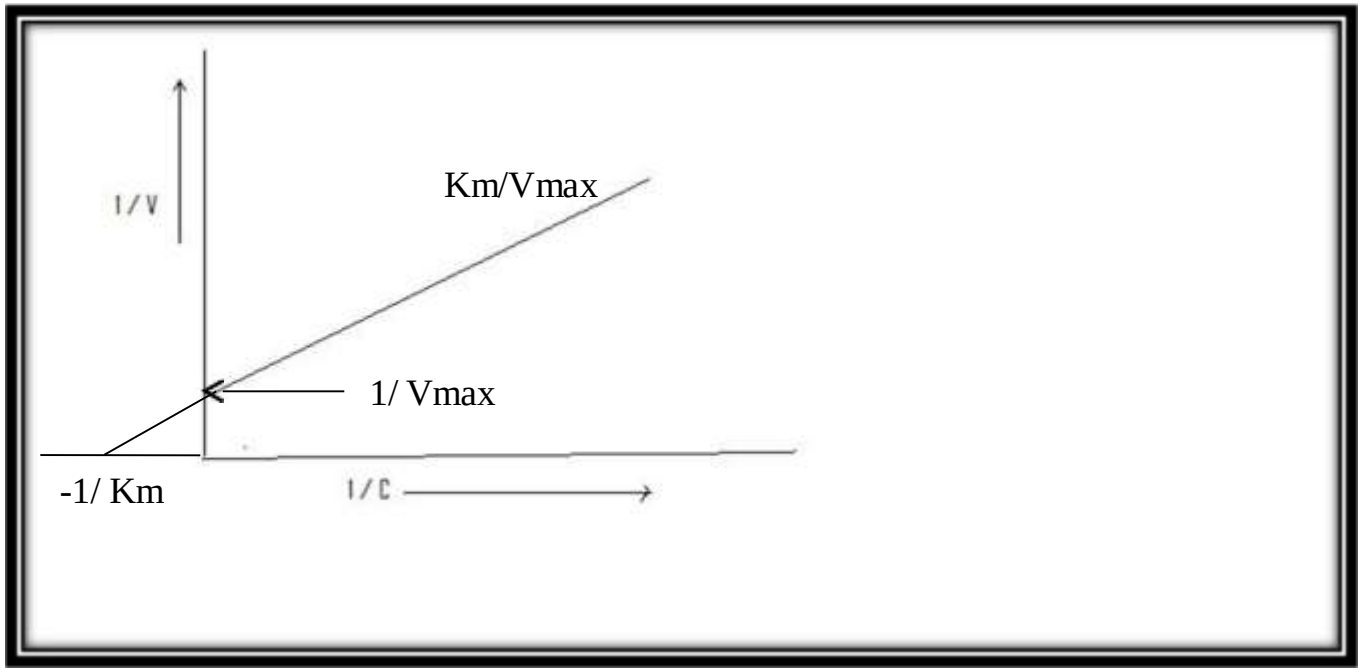

Figure 2

Plot of 1/V vs 1/C for determining Km & Vmax

Now, Intercept= 1/ Vmax = 0.33 µ mol.

Vmax = 3 µ mol/ml min

Slope = Km/ Vmax So, 1.65 = Km/ Vmax

Km = 1.65 X 3 = 4.95µmol/ ml

X-axis intercept= -1/ Km

Method 2

Multiplying eq. 2 by C, we get :

$$\frac{C}{V} = \frac{Km}{Vmax} + \frac{C}{Vmax} \quad \ldots\ldots\ldots\ldots (3)$$

A plot of C /V vs C gives a straight line with 1 / Vmax as the slope and Km / Vmax as the intercept (shown in the fig. 3).

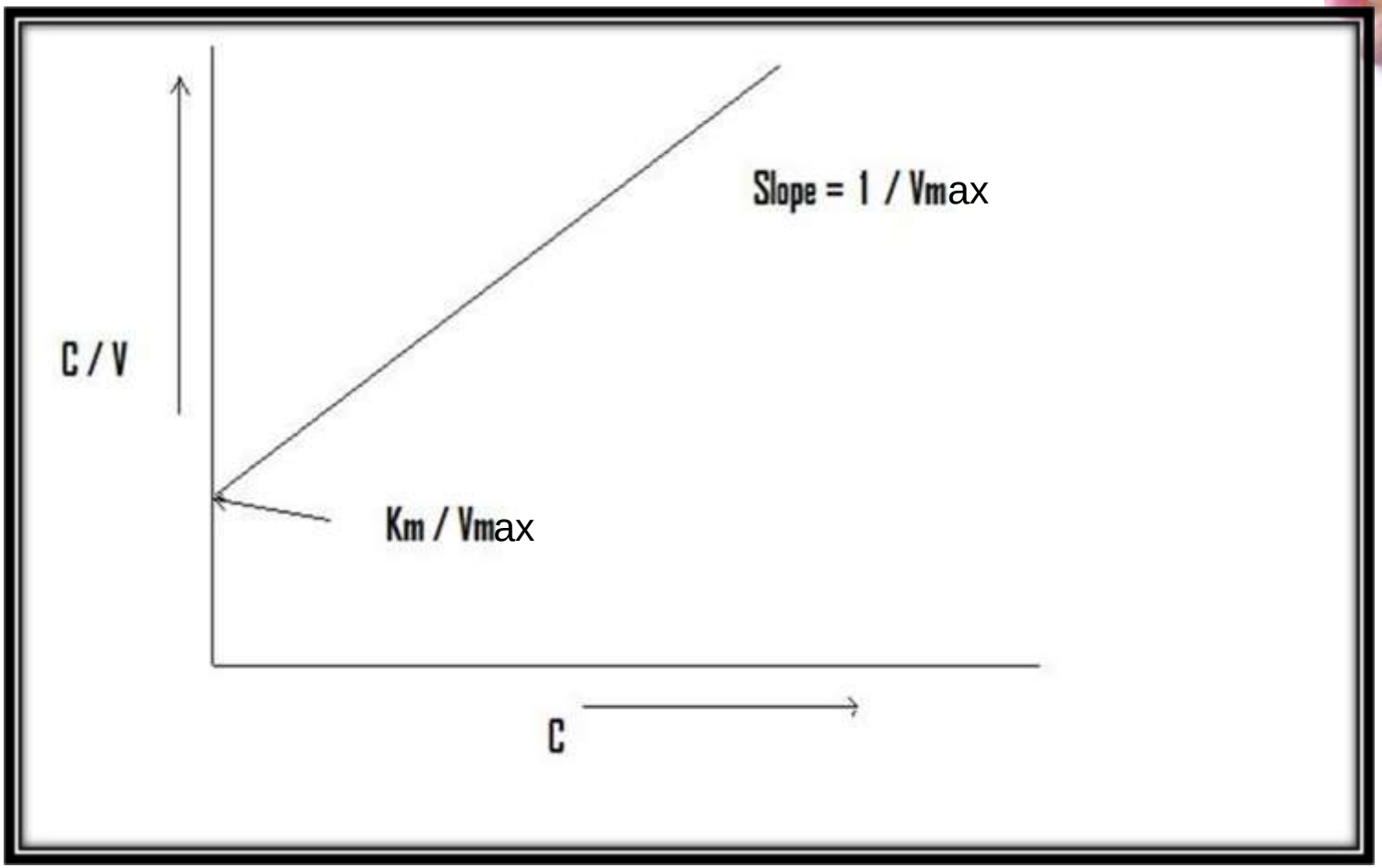

Figure 3.

Plot of C/V vs C for determining Km & Vmax

Method 3

The equation can also be written as :

$$V = -Km\frac{V}{C} + Vmax \qquad \ldots\ldots\ldots\ldots(4)$$

A plot of V vs V / C gives a straight line with a slope of –Km & an Intercept of Vmax. (shown in the fig. 4)

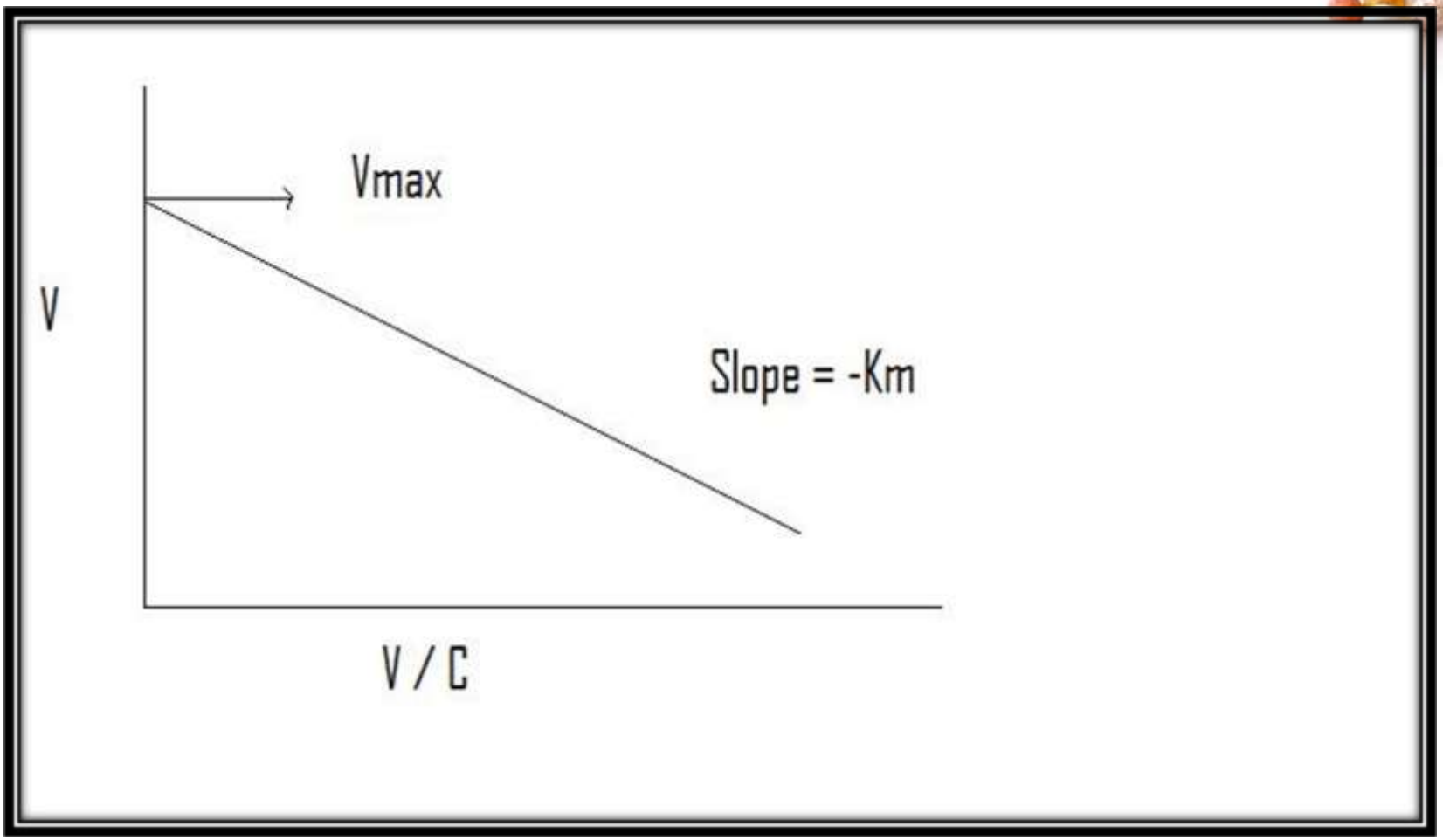

Figure 4

Plot of V vs V / C for determining Km & Vmax

CALCULATION OF K_M & V_{MAX} STEADY- STATE CONCENTRATION

- If drug is administered for constant rate IV infusion/ in a multiple dosage regimen, the steady-state conc. is given in terms of dosing rate (DR):

$$DR = C_{ss}Cl_T \qquad \text{..... (1)}$$

- If the steady-state is reached, then the dosing rate = the rate of decline in plasma drug conc. & if the decline occurs due to a single capacity-limited process then eq. I become as:

$$DR = \frac{V_{max}\, C_{ss}}{K_M + C_{ss}} \qquad \text{..... (2)}$$

- From a plot of C_{ss} vs. DR, a typical curve having a shape of hocky-stick is obtained which is shown in fig. 5.

Curve for a drug following nonlinear kinetics
By plotting the steady-state concentration against dosing rates

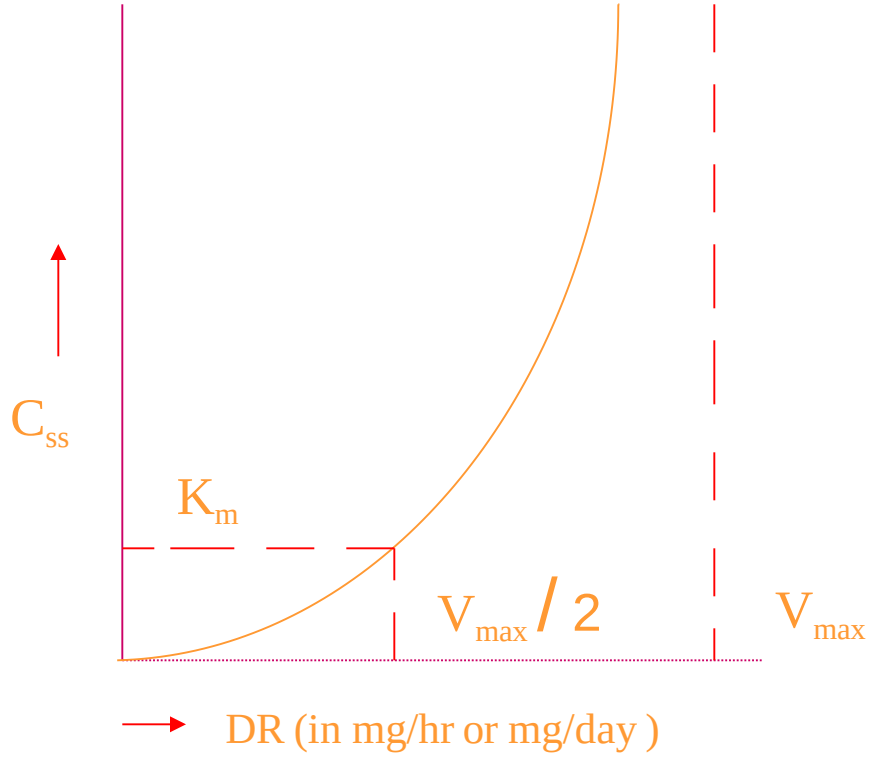

Figure 5

METHODS USED TO DETERMINE THE K_M & V_{MAX} AT STEADY-STATE

- There are three methods which are used to define the K_M & V_{max} at steady-state with appreciable accuracy:

1) Lineweaver-Burk Plot:- the reciprocal of eq. (2) we get

$$\frac{1}{DR} = \frac{K_M}{V_{max}\, C_{ss}} + \frac{1}{V_{max}} \qquad \ldots\ldots\ldots\ldots\ldots\ldots (3)$$

- If $1/DR$ is plotted against $1/C_{ss}$ a straight line is obtained having slope K_M/V_{max} & y-intercept $1/V_{max}$.

2) Direct linear plot:-

- Plotting a pair of C_{ss}, i.e. C_{ss1}, & C_{ss2} against corresponding dosing rates DR_1 & DR_2 we get following fig. 6 which gives values K_M & V_{max}

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Direct linear plot for estimation of K_M & V_{max} at steady-state conc. Of a drug, when it is administered at different dosing rates

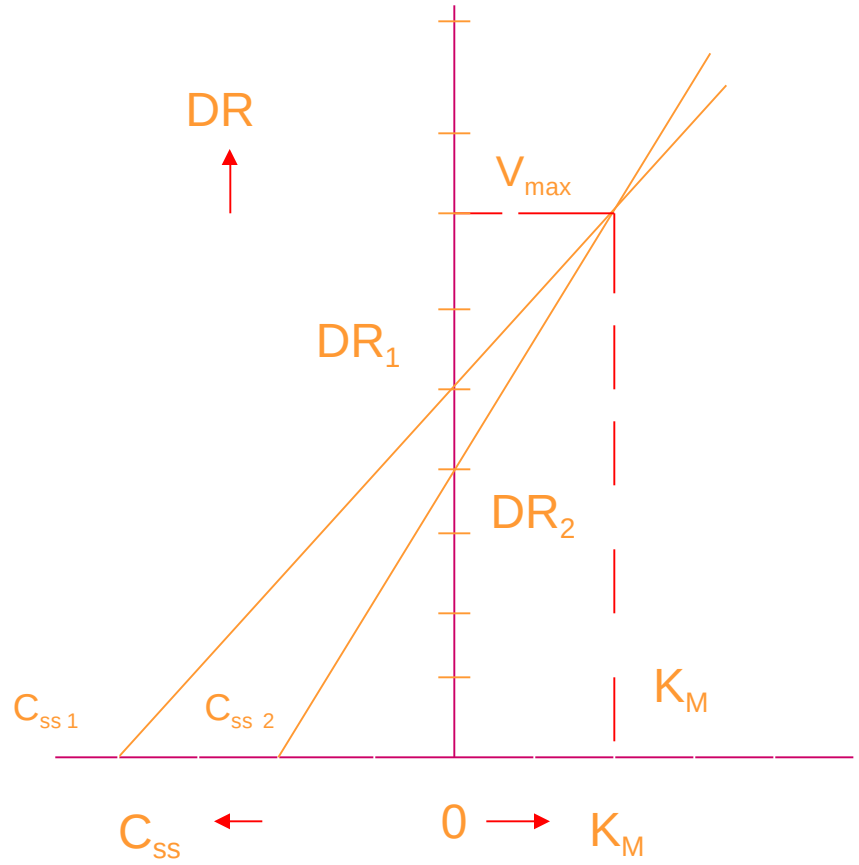

Figure 6

3) Graphical method:-

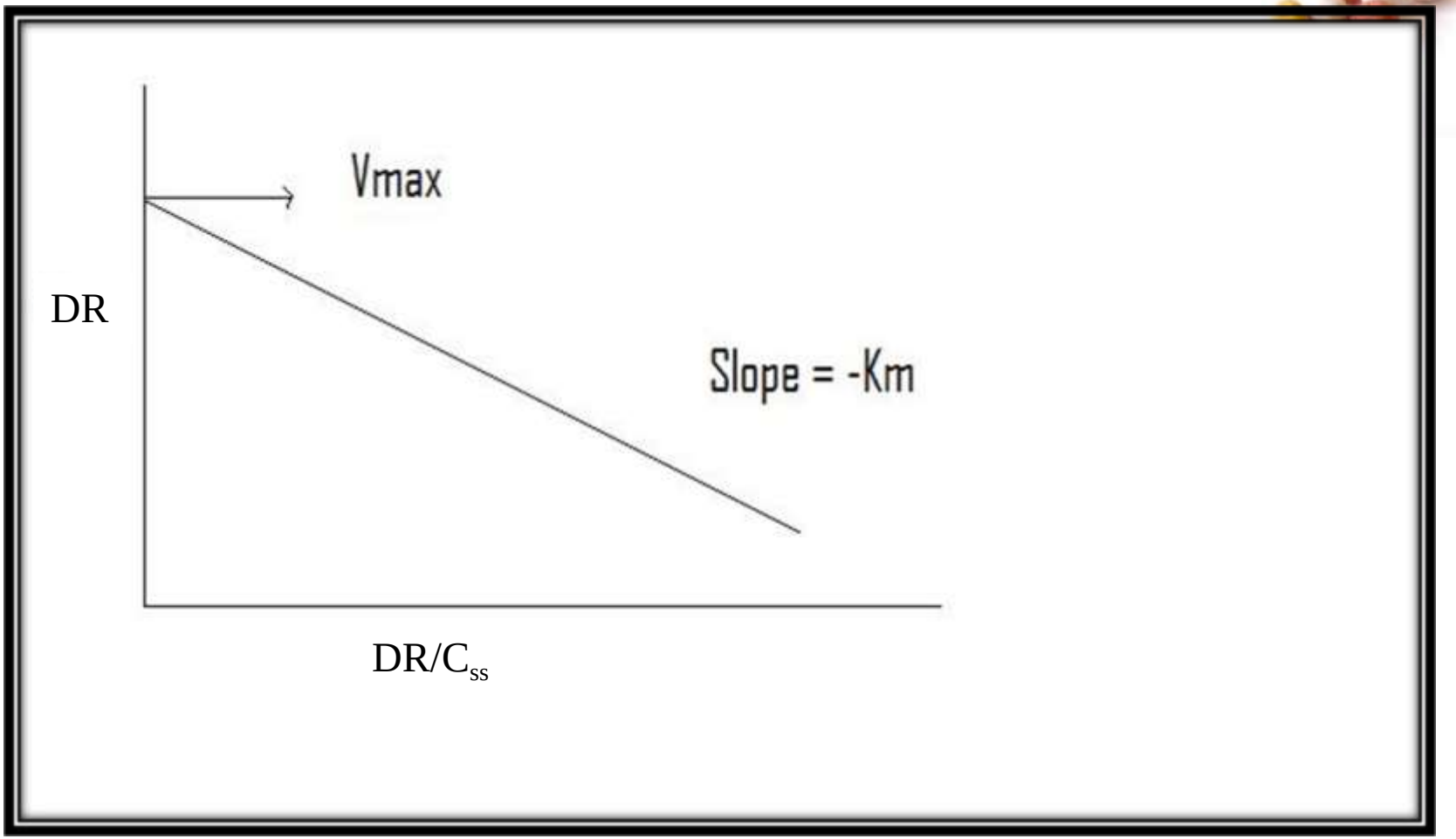

Figure 7

Plot of DR vs DR/C_{ss} for determining Km & Vmax

3) Graphical method:-

- In this method by rearranging eq. (2) we get

$$DR = V_{max} - \frac{K_M D_R}{C_{ss}} \qquad \text{..... (4)}$$

- In graph DR is plotted against DR/Css, a straight line is obtained with slope $-K_M$ & y - intercept Vmax.
- K_M & Vmax can be estimated by simultaneous eq. as

$$DR_1 = V_{max} - \frac{K_M D_{R1}}{C_{ss1}} \qquad \text{.....(5)}$$

$$DR_2 = V_{max} - \frac{K_M D_{R2}}{C_{ss2}} \qquad \text{..... (6)}$$

- On solving above eq. 5 & 6 we get,

$$K_M = \frac{DR_2 - DR_1}{\frac{DR_1}{C_{ss\ 1}} - \frac{DR_2}{C_{ss\ 2}}} \quad \text{..... (7)}$$

- By substituting values of DR_1, DR_2, C_{ss1} & C_{ss2} we get value of K_M & from K_M we can found value of V_{max} at steady-state concentration.
- From experimental observations, it shows that K_M is much less variable than V_{max}.

QUESTIONS

1. Explain the non-linear pharmacokinetics of a drug given through I.V. bolus injection. (‘07)

2. Write Michaelis-Menten equation. How is V_{max} and K_M estimated. (Sep’05)

3. Discuss Michaelis-Menten equation. (‘06)

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THANKS