Unit-5

Nonlinear Pharmacokinetics

Introduction:-

- The rate process of a drug's ADME are dependent upon carriers or enzymes that are substrate-specific, have definite capacities & susceptible to saturation at high dose concentration.

- "In such cases, an essential first-order kinetics transform into a mixture of first order and zero-order rate processes & the pharmacokinetics parameters change with the size of the administered dose. The pharmacokinetic of such drug are said to be dose dependent or Mixed order or capacity limited or nonlinear kinetics."

- Non-linearities in pharmacokinetics have been observed
  (i) Drug absorption eg- Vitamin C
  (ii) Drug distribution eg- Nabsoxen
  (iii) Drug elimination eg- Riboflavin

Factors Causing Non-linearity:-

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

(i) **Drug Absorption:**
Non-linearity in drug absorption can arise from 3 important sources:
(a) When absorption is solubility or dissolute rate limited.
eg- Griseofulvin

At higher doses, a saturated % of the drug is formed in the GIT or at any other extravascular site & the rate of absorption attains a constant value.

(b) When absorption involves carrier-mediated transport systems.
eg- Riboflavin, Ascorbic acid, Cyanocobalamin

(c) When presystemic gut wall or hepatic metabolism attains saturation.
eg- Propranolol, Hydralazine, Verapamil.

Other causes of non-linearity in drug absorption are changes in gastric emptying & GI blood flow & other physiologic factors.

(ii) Drug Distribution:
Non-linearity in distribution of drugs administered at high doses may be due to:
(a) Saturation of binding sites on plasma proteins.
eg- Phenylbutazone & naproxen

(b) Saturation of tissues binding sites.
eg- Thiopental, Diazepam

(iii) Drug Metabolism:
Two important causes of non-linearity in metabolism are -

(a) Capacity-limited metabolism due to enzyme & co-factor saturation.
eg- Phenytoin, Alcohol, Theophylline

(b) Enzyme induction. eg - Carbamazepine
Enzyme induction is a common cause of both dose & time dependent kinetics.

(iv) Drug Excretion :
The two active processes in renal excretion of drug that are saturable are :

(a) Active tubular secretion. eg - Penicillin G

(b) Active tubular reabsorption. eg. Water soluble vitamins & Glucose.

Other sources of non-linearity in renal excretion include forced diuresis, nephrotoxicity & saturation of binding sites.

∴ Michaelis Menten Equation =
The kinetics of capacity - limited or saturable processes is best described by Michaelis - Menten eqⁿ -

$$-\frac{dC}{dt} = \frac{V_{max}\,C}{K_m + C} \quad \text{---} \quad (1)$$

where, $-dC/dt$ = rate of decline of drug concⁿ with time

V_{max} = Theoretical maximum rate of the process
K_m = Michaelis constant

Three situation can be considered :
(i) When $K_m = C$:- under this situation, put the value in eqⁿ (1) reduce to :

$$-\frac{dC}{dt} = \frac{V_{max}}{2} \quad \text{---} \quad (2)$$

The rate of process is equal to one half its maximum rate.

(2) When $K_m \gg C$:- Here, $K_m + C = K_m$ & put the value in eq^n ① reduce to :

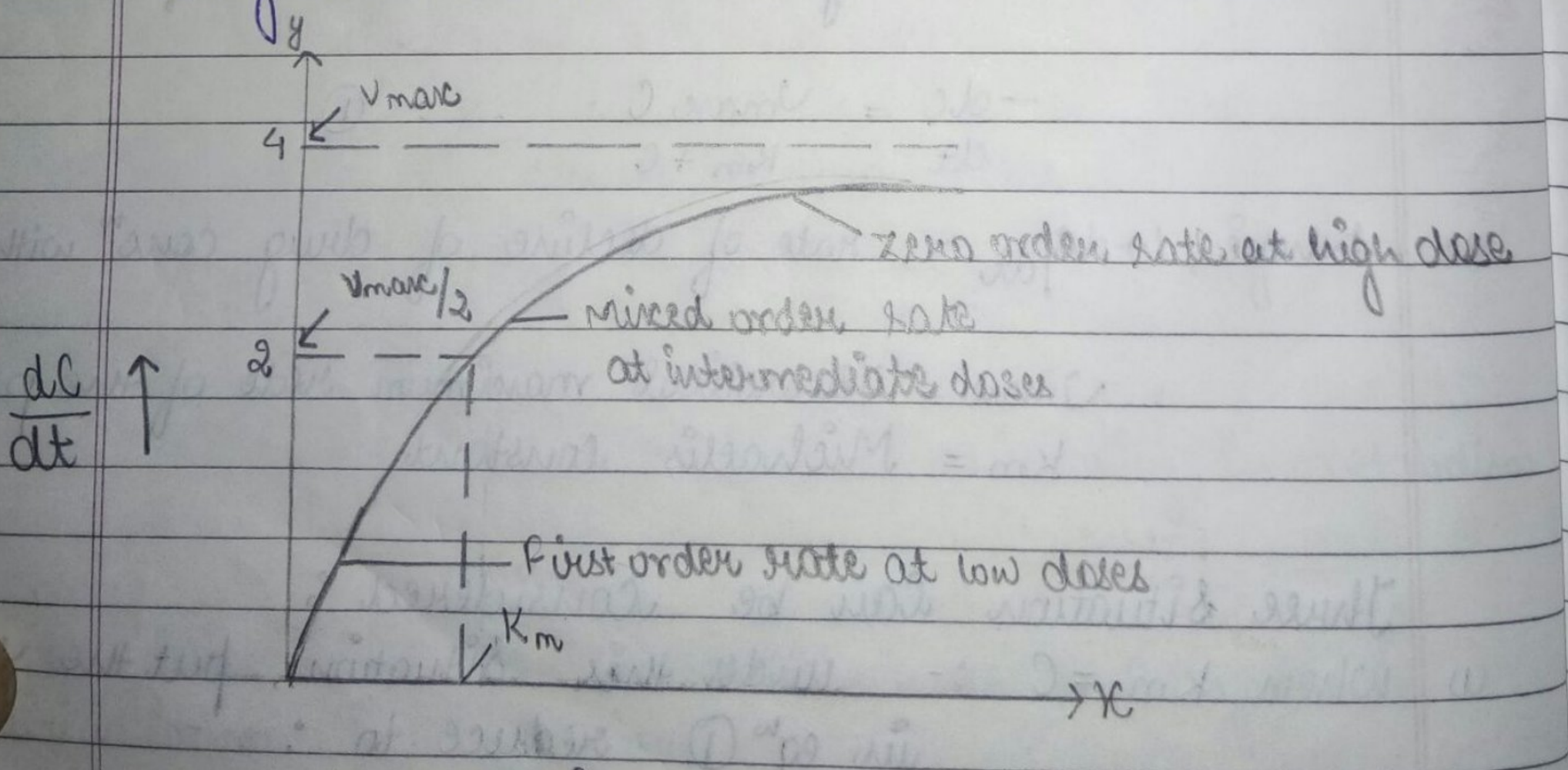
$$-\frac{dC}{dt} = \frac{V_{max}\, C}{K_m} \quad — ③$$

The eq^n ③ is identical to the one that describe first order elimination of a drug.

(3) When $K \ll C$:- Here, $K_m + C \equiv C$ & put the value in eq^n ① reduce to :

$$-\frac{dC}{dt} = V_{max} \quad — ④$$

eq^n ④ is identical to the one that describe a zero-order process. ie. the rate process occurs at a constant rate V_{max} & is independent of drug concentration.



A plot of Michaelis-Menten eq^n elimination rate '$\frac{dC}{dt}$' versus 'C'

Estimation of Km & Vmax -

The parameters of capacity-limited processes like metabolism, renal tubular secretion & biliary excretion can be easily defined by assuming one-compartment kinetics for the drug.

The parameters Km & Vmax can be assessed from the plasma conc^{n}-time data collected after i.v. bolus administration of a drug with non-linear elimination from Michaelis-Menten eq^{n} -

$$-\frac{dC}{dt} = \frac{V_{max}\, C}{K_m + C} \quad -(1)$$

On integration the eq^{n} (1) & conversion to log base 10 the eq^{n} becomes -

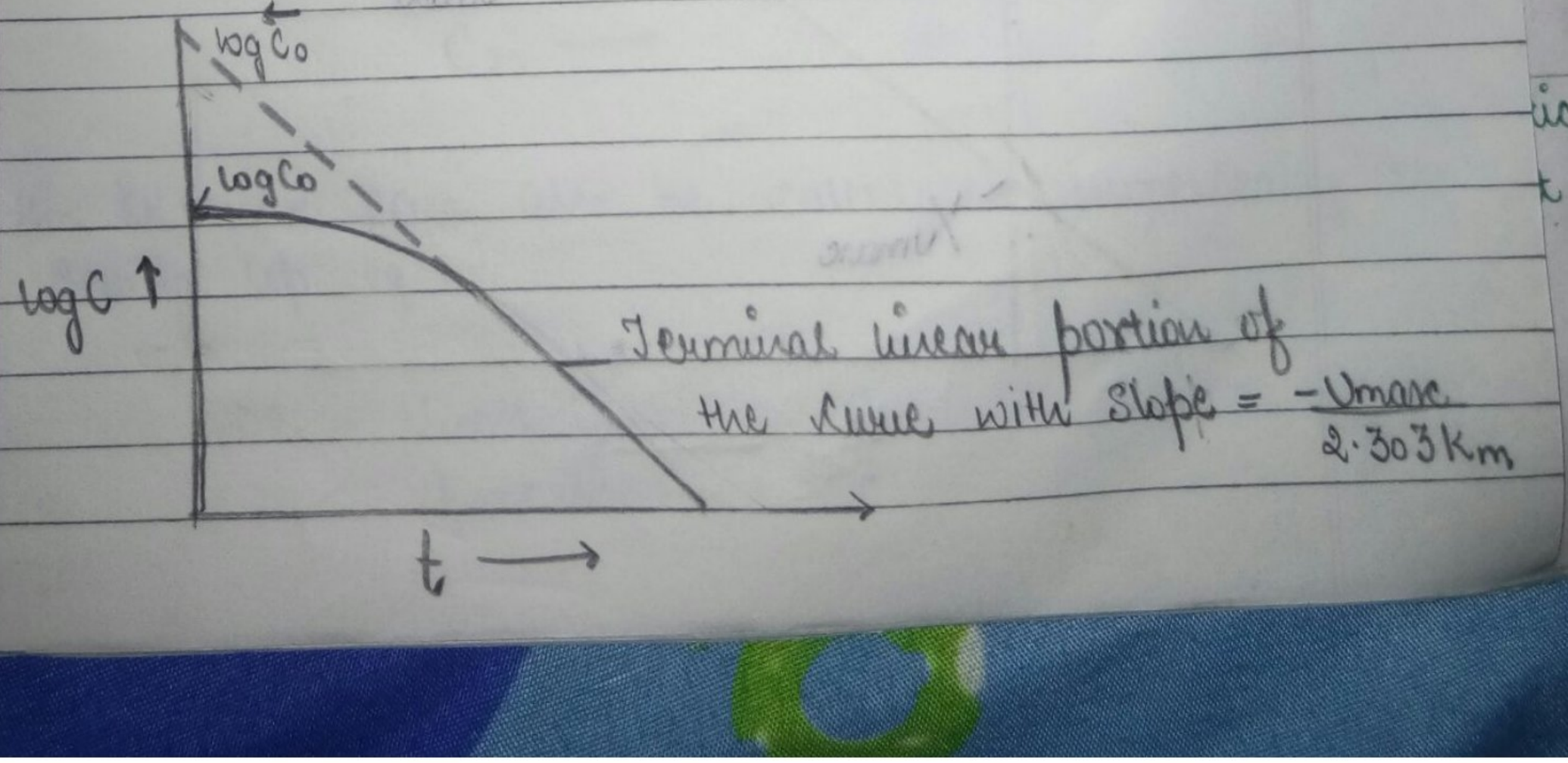
$$\log C = \log C_0 + \frac{(C_0 - C)}{2.303\, K_m} - \frac{V_{max}\, t}{2.303\, K_m} \quad -(2)$$

A Semilog plot of C versus t yields a curve with a terminal linear portion having slope $-\frac{V_{max}}{2.303 K_m}$ & when

Imp back extrapolated to time zero gives y-intercept $\log \overleftarrow{C_0}$

The equation becomes -

$$\log C = \log \overleftarrow{C_0} - \frac{V_{max}\, t}{2.303\, K_m} \quad -(3)$$



At low plasma conc^n, eq^n ② & ③ are identical equating the two & simplifying –

$$\frac{(C_0 - C)}{2.303\ K_m} = \frac{\log C_0}{\log C_0} \quad \text{—— ④}$$

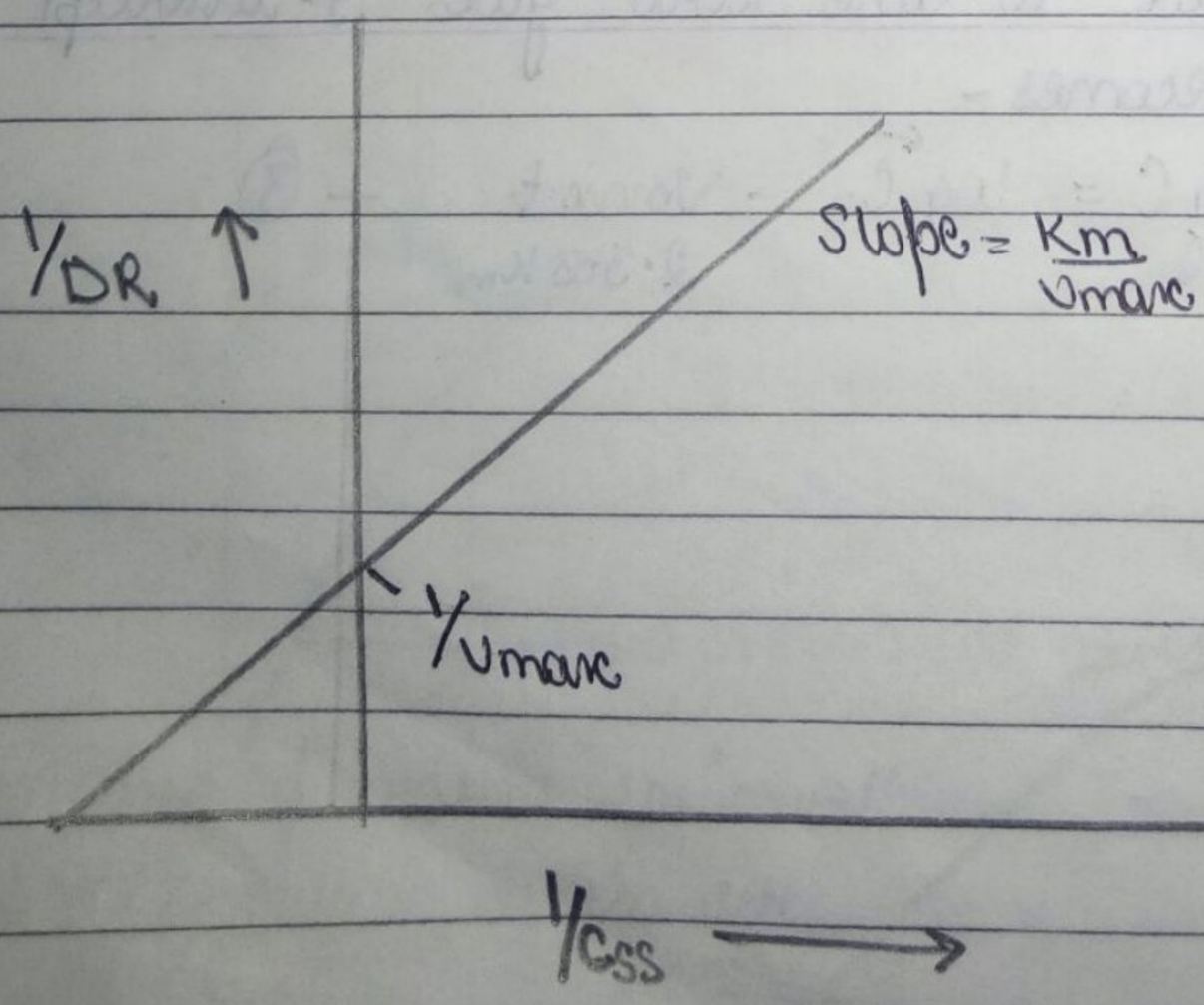
K_m can thus be obtained from above eq^n, V_{max} can be computed by substituting the value of K_m in the slope value.

→ Practically, we can graphically compute K_m & V_{max} by 3 ways –

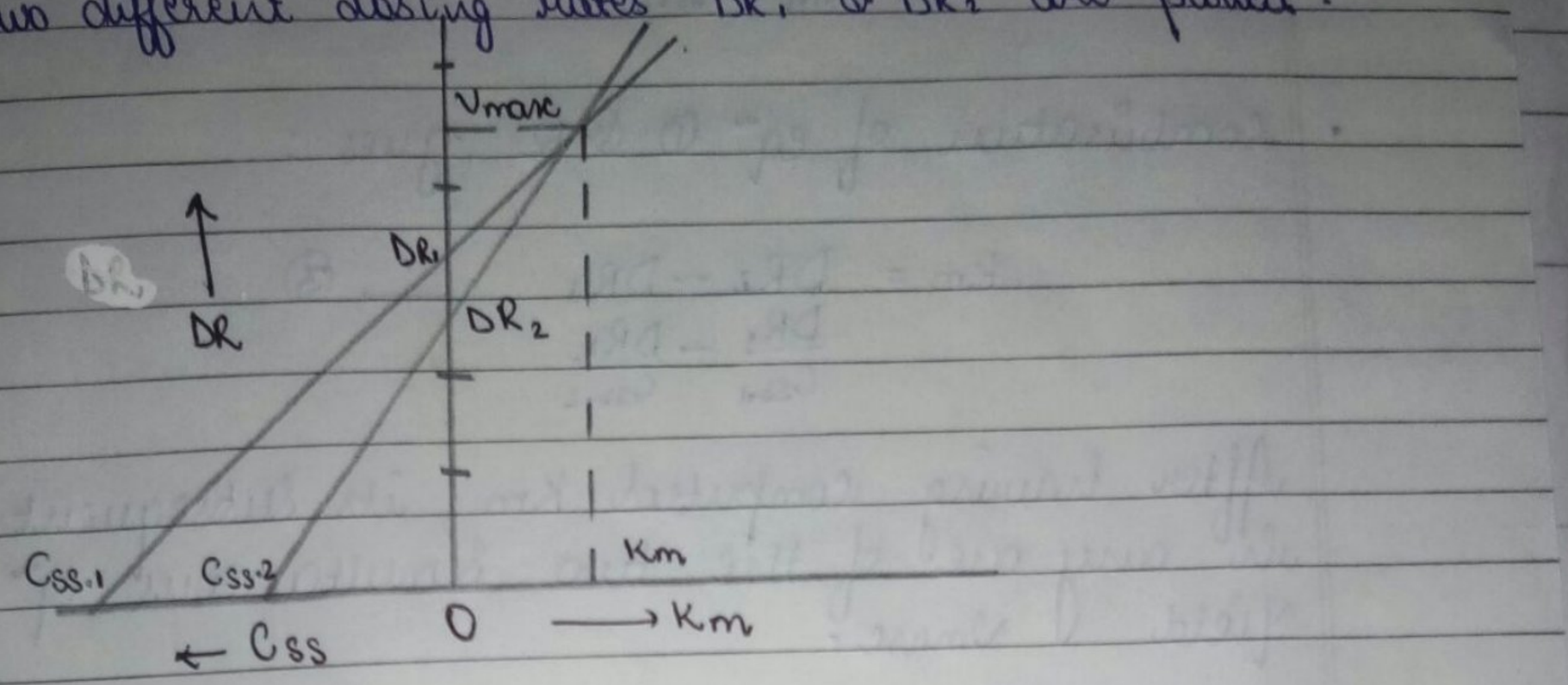
(1) Lineweaver - Burk Plot :

$$\frac{1}{DR} = \frac{K_m}{V_{max} C_{ss}} + \frac{1}{V_{max}}$$

A plot of $\frac{1}{DR}$ versus $\frac{1}{C_{ss}}$ yields a straight line with slope $\frac{K_m}{V_{max}}$ & y-intercept $\frac{1}{V_{max}}$



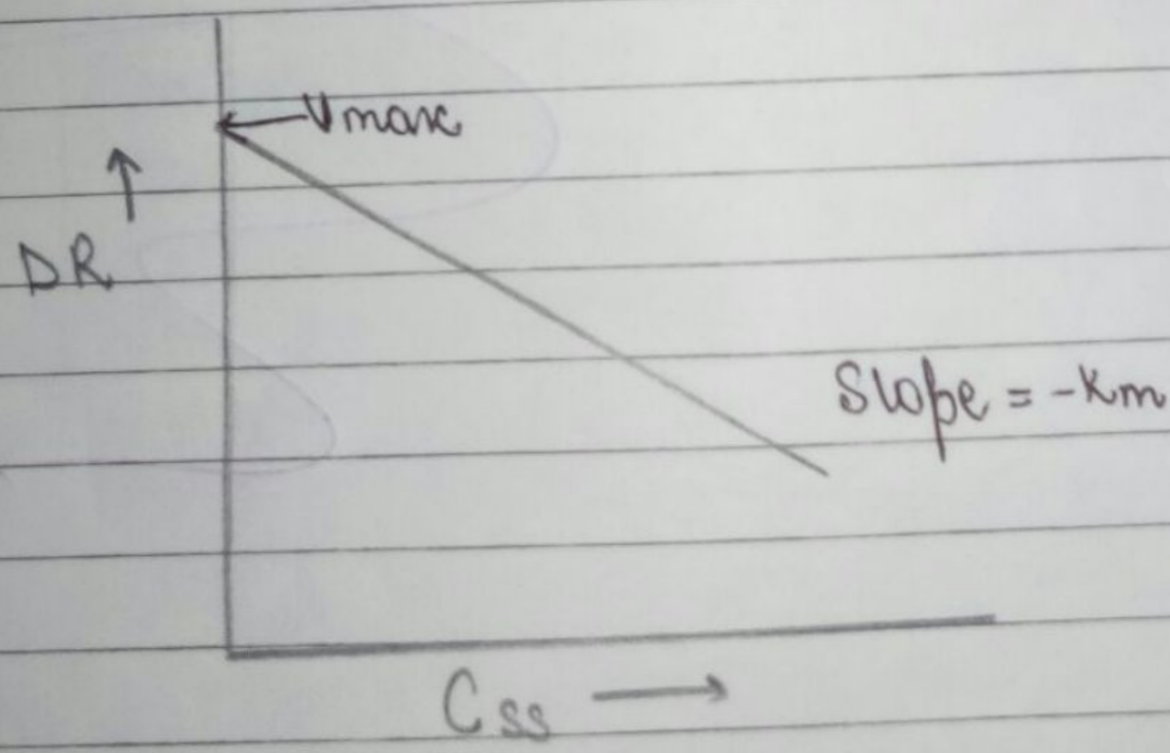
(2) Direct linear Plot : A pair of $C_{ss.1}$ & $C_{ss.2}$ obtained with two different dosing rates DR_1 & DR_2 are plotted.



(3) Graphical method :

$$DR = V_{max} - \frac{K_m DR}{C_{ss}}$$

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



- K_m & V_{max} can also be calculated numerically by setting up eqⁿ-

$$DR_1 = \frac{V_{max} C_{ss.1}}{K_m + C_{ss.1}} \quad \text{— (1)}$$

$$DR_2 = \frac{V_{max} C_{ss.2}}{K_m + C_{ss.2}} \quad \text{— (2)}$$

- Combination of eq^n (1) & (2), gives:

$$K_m = \frac{DR_2 - DR_1}{\frac{DR_1}{C_{ss.1}} - \frac{DR_2}{C_{ss.2}}} \quad \text{— (3)}$$

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

It has been observed that K_m is much less variable than V_{max}.