Lab 5

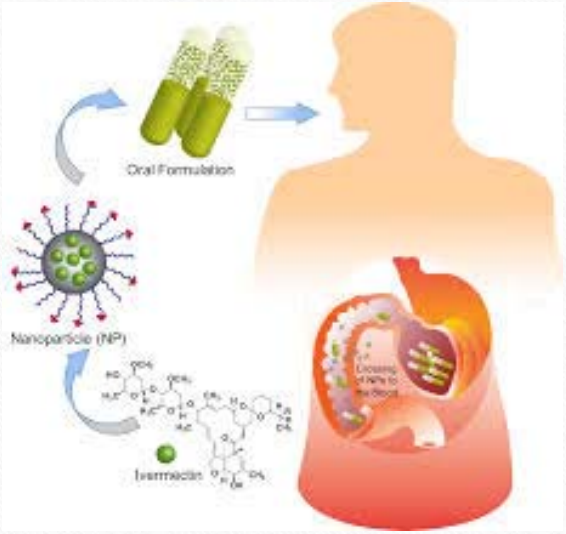
Determination of Absorption Rate Constants from Oral Absorption Data

Absorption Rate Constant

- The overall rate of systemic drug absorption from an orally administered solid dosage form encompasses many individual rate processes, including

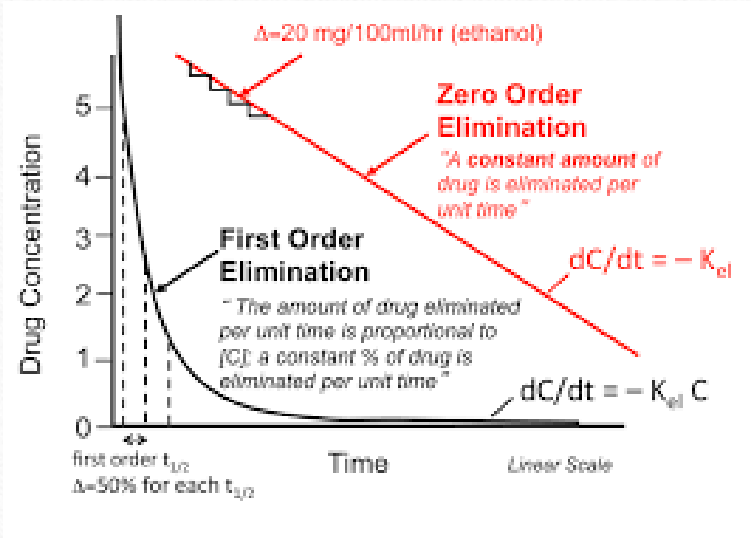
1. Dissolution of the drug,
2. GI motility,
3. Blood flow,
4. Transport of the drug across the capillary membranes and into the systemic circulation.

- The rate of drug absorption represents the net result of all these processes.



Absorption Rate Constant

- The selection of a model with either first-order or zero-order absorption is generally empirical.
- The actual drug absorption process may be zero order, first-order, or a combination of rate processes that is not easily quantitated.



Absorption Rate Constant

- For many immediate release dosage forms, the absorption process is first order due to the physical nature of drug diffusion.
- For certain controlled-release drug products, the rate of drug absorption may be more appropriately described by a zero-order rate constant.

Importance of Absorption Rate Constant

1. The calculation of ka is useful in designing a multiple-dosage regimen.
2. Knowledge of the ka and k values allows for the prediction of peak and trough plasma drug concentrations following multiple dosing.

Importance of Absorption Rate Constant

3. In bioequivalence studies, drug products are given in chemically equivalent (ie, pharmaceutical equivalents) doses, and the respective rates of systemic absorption may not differ markedly. Therefore, for these studies, tmax, or time of peak drug concentration, can be very useful in comparing the respective rates of absorption of a drug from chemically equivalent drug products.

Method of Residuals

- Assuming ka >> k in Equation (1) below:
- $C_p = \left(\frac{Fk_aD_0}{v_d(k_a - k)}\right) * (e^{-kt} - e^{-kat})$ 1
- The value for the second exponential will become insignificantly small with time (ie, e^{-kat} =0) and can therefore be omitted.
- When this is the case, drug absorption is virtually complete. Equation (1) then reduces to:
- $C_p = \left(\frac{Fk_aD_0}{v_d(k_a - k)}\right) * e^{-kt}$ 2

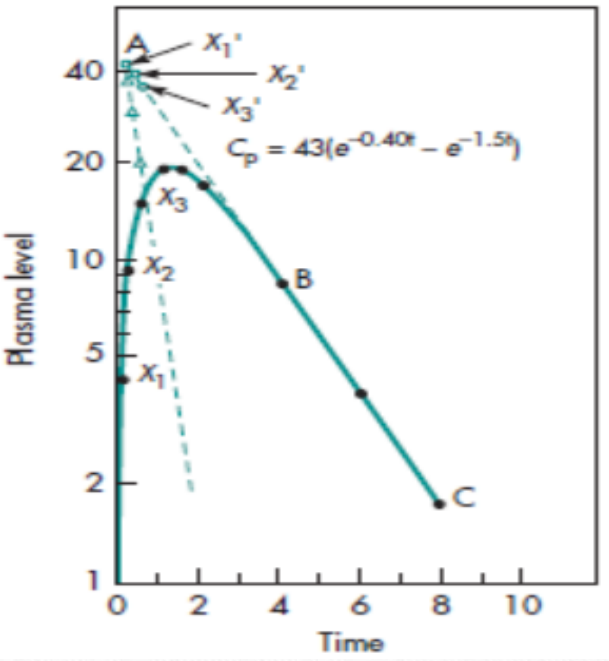
Method of Residuals

- From equation 1, one may also obtain the intercept of the y axis
- A= $\left(\frac{Fk_aD_0}{vd(k_a-k)}\right)$
- where A is a constant. Thus, Equation 2 becomes
- $C_p = Ae^{-kt}$ 3
- This equation, which represents first-order drug elimination, will yield a linear plot on semilog paper. In which the slope is equal to - k/2.3.

Method of Residuals

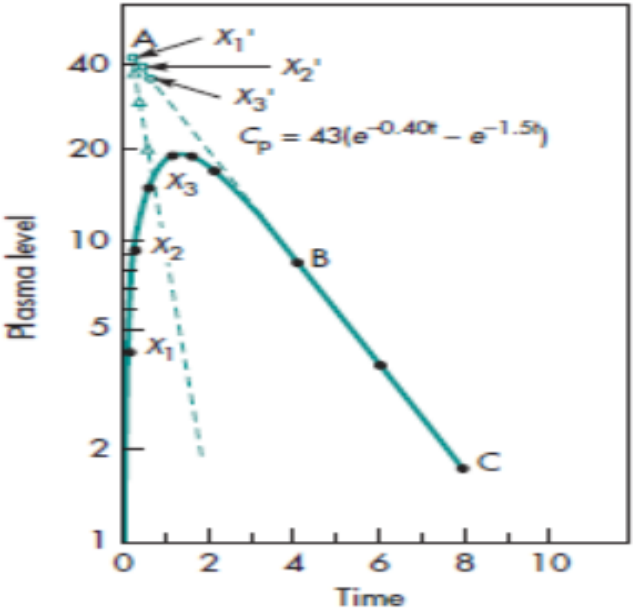
- The value for ka can be obtained by using the method of residuals or a feathering technique, by the following procedure:

1. Plot the drug concentration versus time on semilog paper with the concentration values on the logarithmic axis.
2. Obtain the slope of the terminal phase (line BC,) by extrapolation.



Method of Residuals

3. Take any points on the upper part of line BC (eg, x′1, x′2, x′3, …) and drop vertically to obtain corresponding points on the curve (eg, x1, x2, x3, …).
4. Read the concentration values at x1 and x′1, x2 and x′2, x3 and x′3, and so on.
5. Plot the values of the differences at the corresponding time points Δ1, Δ2, Δ3, … .
6. A straight line will be obtained with a slope of -ka/2.3.



Notes on Method of Residuals

- When using the method of residuals, a minimum of three points should be used to define the straight line.
- Data points occurring shortly after tmax may not be accurate, Because this portion of the curve represents the postabsorption phase,

Notes on Method of Residuals

- If drug absorption begins immediately after oral administration, the residual lines obtained by feathering the plasma level–time curve will intersect on the y axis at point A.
- The value of this y intercept, A, The value of A has no direct physiologic meaning.

Example

Drug concentrations in the blood at various times are listed in table. Assuming the drug follows a one compartment model.

Find the ka value by the method of residuals.

Time (hr)	Cp (mg/L)
0.1	0.429
0.3	0.936
0.4	1.051
0.5	1.139
0.7	1.189
0.8	1.226
1.5	1.082
3.25	0.697
5	0.449
6.5	0.308

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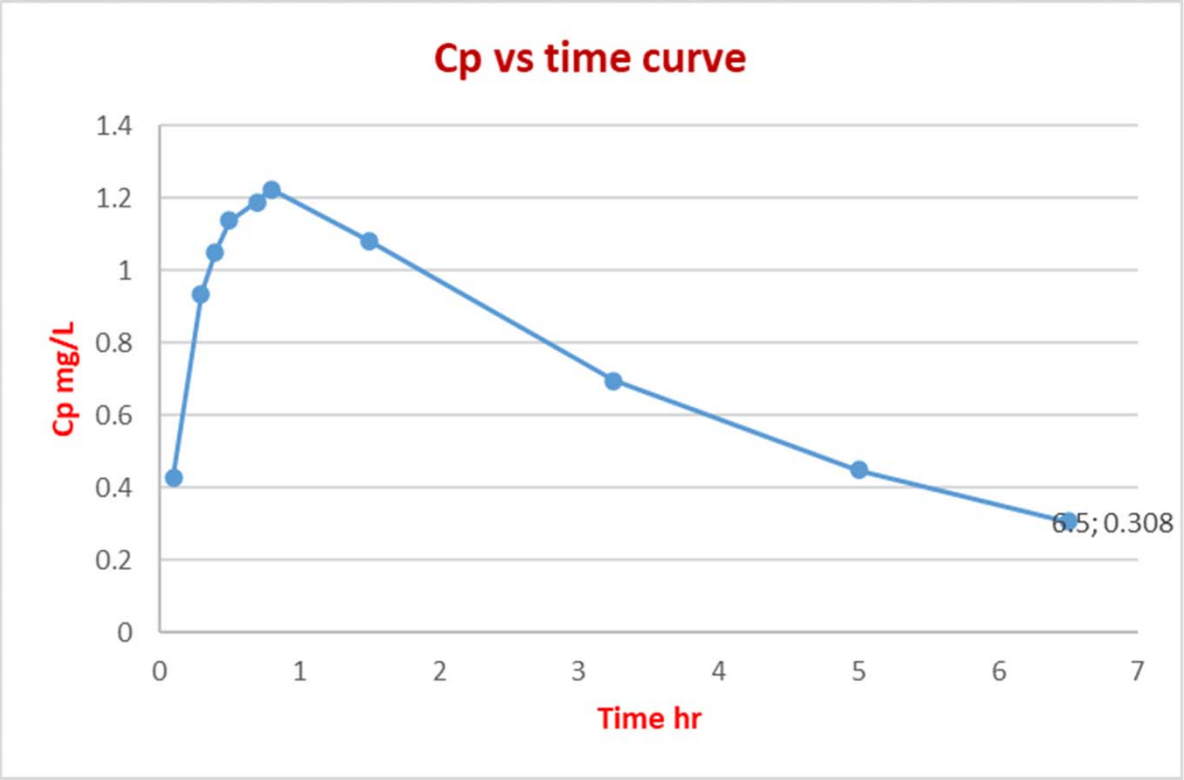

Time (hr)	Cp (mg/L)	Cp_{late} (mg /L)
0.1	0.429	1.538
0.3	0.936	1.462
0.4	1.051	1.426
0.5	1.139	1.391
0.7	1.189	1.322
0.8	1.226	1.29
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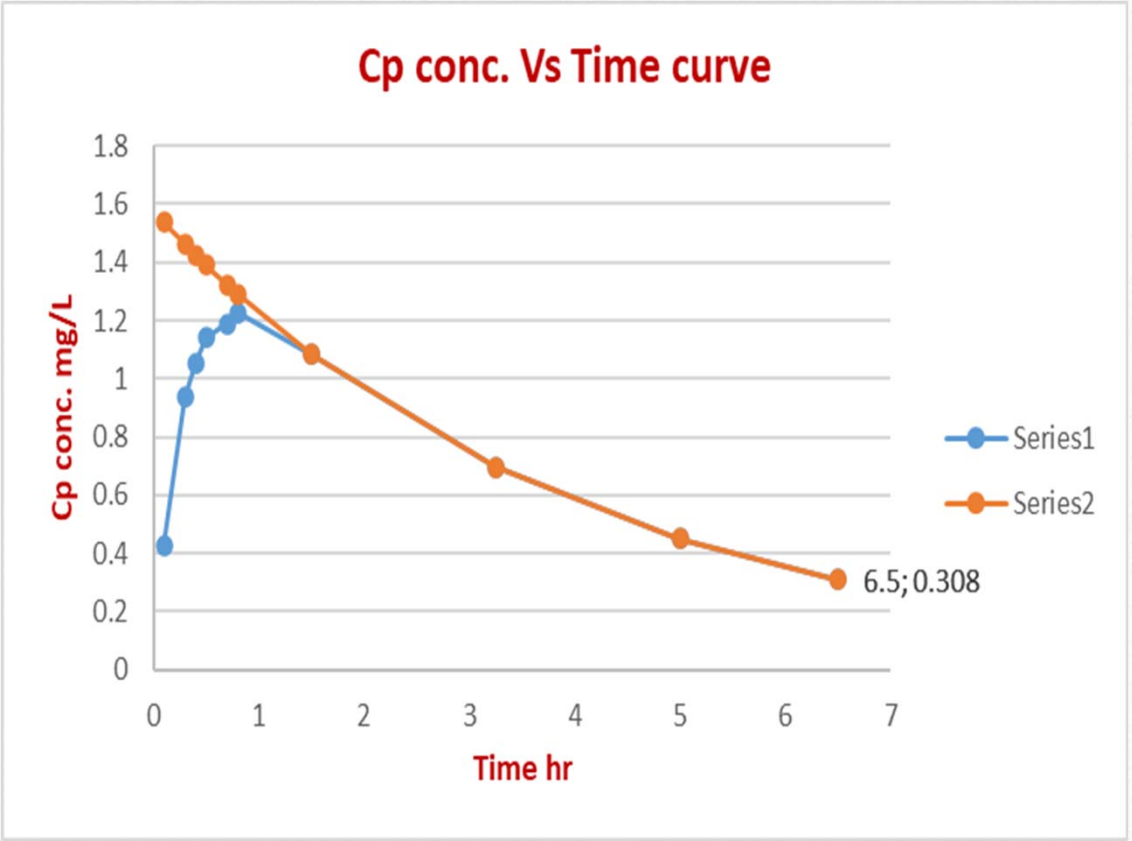

Time (hr)	Cp (mg/L)	Cp_{late} (mg /L)	Residual (mg/L)
0.1	0.429	1.538	1.108
0.3	0.936	1.462	0.527
0.4	1.051	1.426	0.375
0.5	1.139	1.391	0.252
0.7	1.189	1.322	0.133
0.8	1.226	1.29	0.064
1.5	1.082	1.082	-
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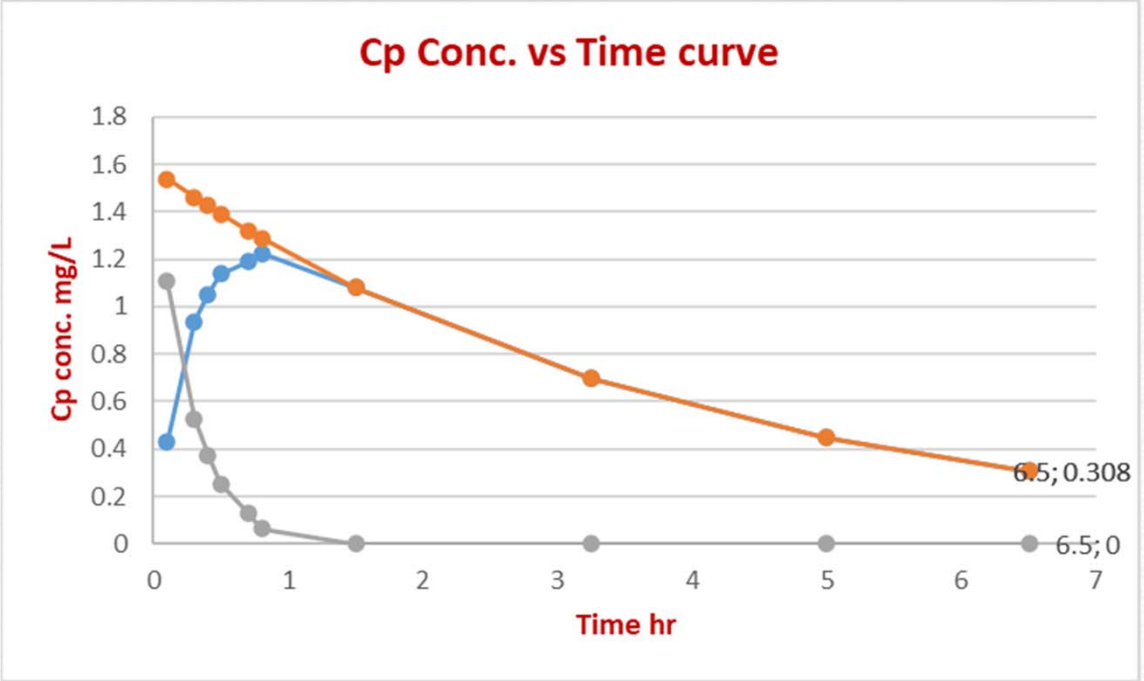
6.5	0.308	0.308	-



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$$Ka = -2.303\ slope$$

$slope = (\log cp2 - \log cp1)/(t2-t1)$

=(log 0.53-log 1.1)/(0.3-0.1)

= -0.322/0.2

=-1.61

So ka= -2.303* -1.61

=3.71

THANK YOU FOR YOUR ATTENTION