Pharmacokinetic Calculations

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- Logarithm is a mathematical function that is the inverse of exponential functions.

$x = b^y$ $\log_b(x) = y$

If the base (b) is 10, the function is called **decimal logarithm**
or
general logarithm.

If the base **(b)** is **«e»**, then it is described as **natural logarithm (Ln)**

e= 2,7182

$x = b^y \qquad \log_b(x) = y$

$\log_2 8 = 3 \qquad \log_2 2^3 = 3$

$\log_{10} 1000 = 3 \qquad \log_{10} 10^3 = 3$

$\log 3 = \log_{10} 3$

Logarithmic Calculations

$\log_b (x.y) = \log_b x + \log_b y$

$\log_2 (32.8) = \log_2 32 + \log_2 8$

$= \log_2 2^5 + \log_2 2^3$

$= 5 + 3$

$= 8$

Logarithmic Calculations

$\log_b (x/y) = \log_b x - \log_b y$

$\log_2 (64/4) = \log_2 64 - \log_2 4$

$= \log_2 2^6 - \log_2 2^2$

$= 6 - 2$

$= 4$

$\log_2 16$

Logarithmic Calculations

$\log_b (x^p) = p \log_b x$

$\log_2 (2^6) = 6 \log_2 2 = 6$

$\text{Log } 1000 = 3$

$\text{Ln } 1000 = 6{,}9077$

$2{,}7182(e)^{6{,}9077} = 1000$

$\ln N / \log N = 2{,}303$

Anti-logarithm

- It is the opposite function of the logarithm.

Anti-logarithm of 0,028

$10^{0,028} = 1,0666$

To calculate the inverse of the natural logarithm:

$e^{-1,3} = 0,2725$

Differantial Equations

- Equations involving derivatives of one or more functions are called differantial equations.

- The description of most scientific problems involves the variation of some key variables relative to other variables.

- By expressing the rate of change of variables with derivatives, differential equations are obtained which provide definite (exact) mathematical formulations for physical principles and laws.

- Differential equations express a physical model and are called as mathematical model.

- **The derivative** is the amount of change at any time interval. It is used to measure **"the change".**

- **The integral** is used to express the total change in a given range, or the cumulative amount of range.

“The derivative is expressed by the slope of the tangent line drawn to a certain point on the graph.“

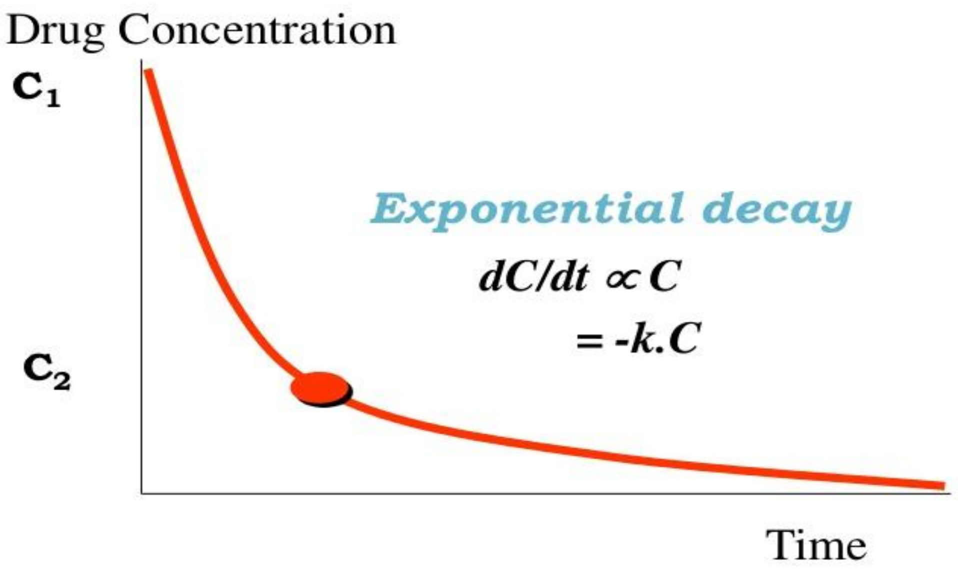
The more perpendicular the tangent is, the change is the faster.

The more horizontal the tangent is,

the change is the slower.

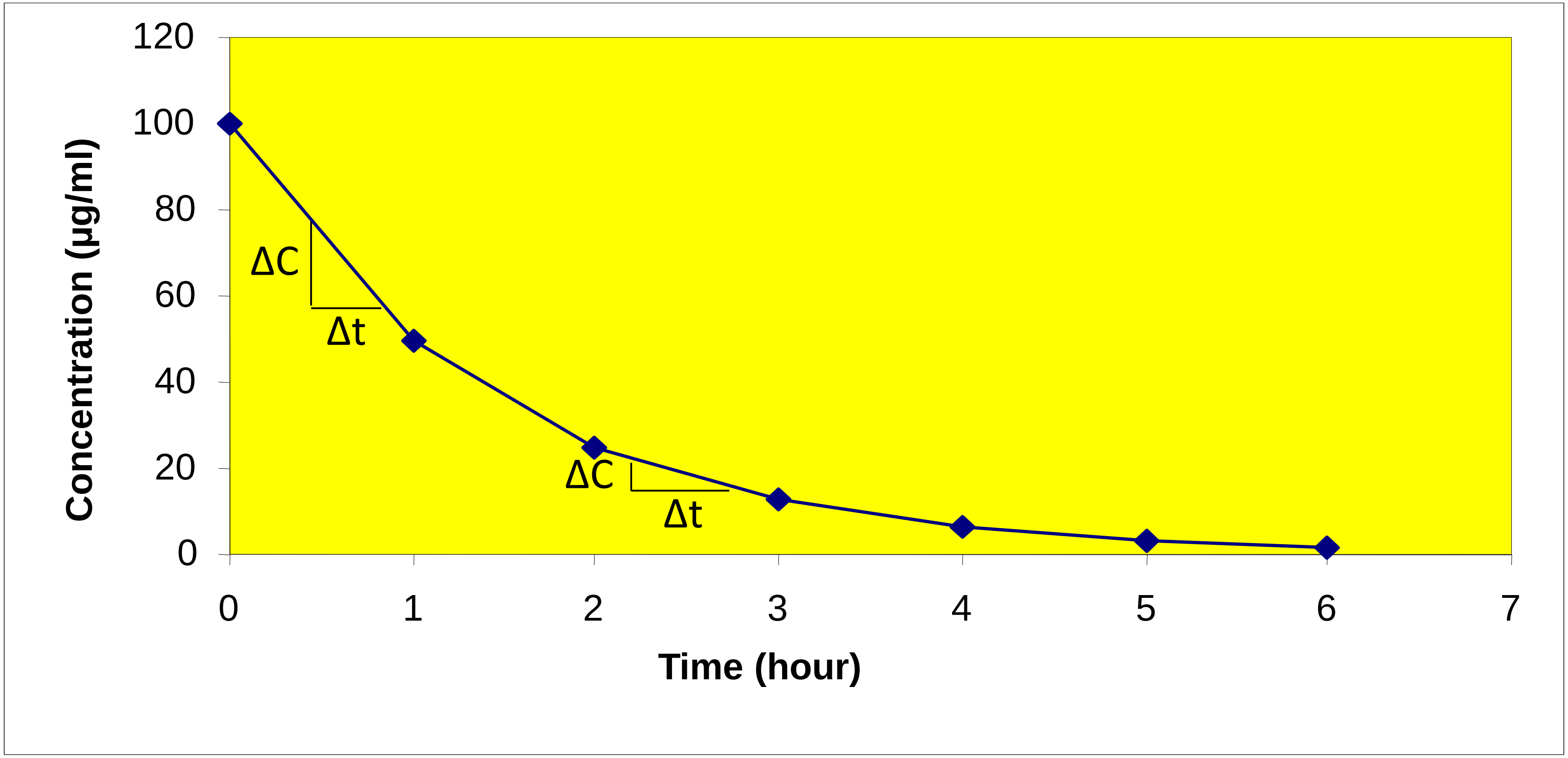
The amount of the active substance in the organism varies with time.
The quantity; is a dependent variable, the time is an idenpendent variable.
The amount which is eliminated at a time of unit can be described by **an elimination rate.**
The calculation of the speed is done by differantial functions.

Here, the purpose of the differential calculation is to determine the rate of change.



Determining the rate of change of a variable

Rate of concentration change dc/dt



The Slope of the Curve

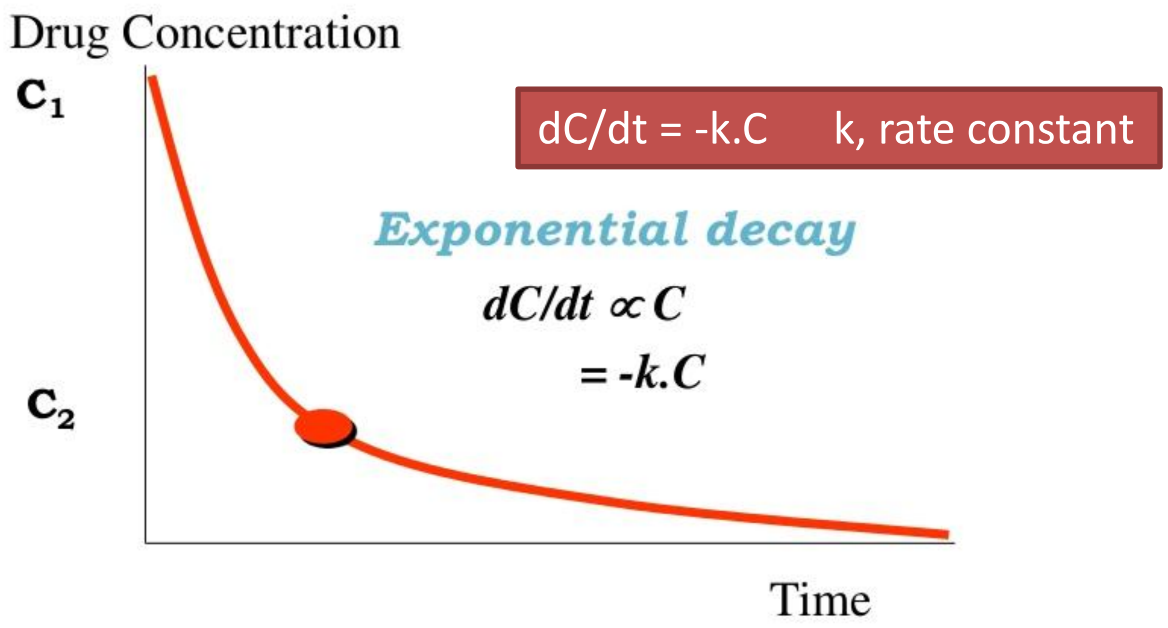
Time (hour)	Plasma drug const. (mcg/mL)
0	12
1	10
2	8
3	6
4	4
5	2

(10-8)/(2-1)

dc/dt = 2 mcg/mL/hour

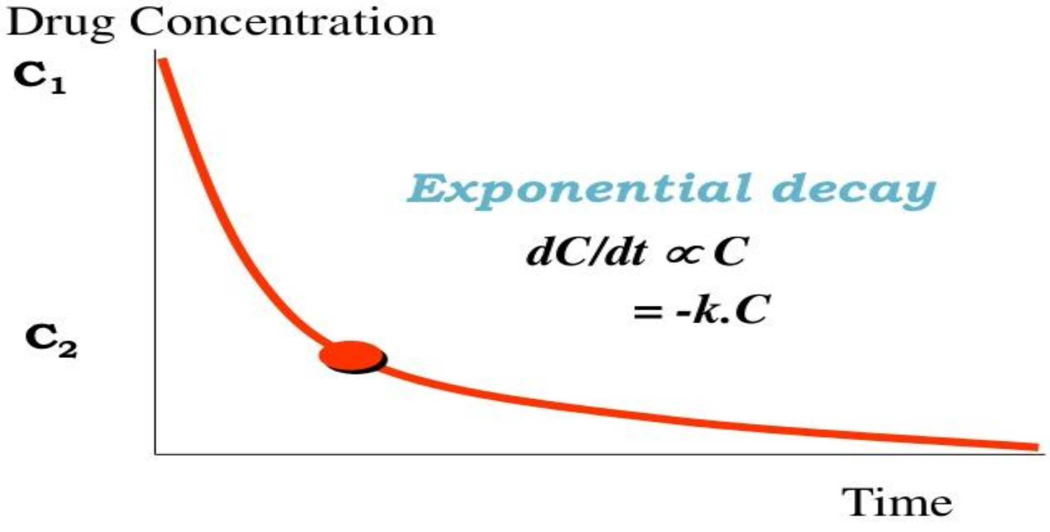
The integral function is based on integrating the differential equation.
Integral is obtained from the differential equation, which contains derivative, by using integration.

If the equation is integrated,
$C=C_o.e^{-kt}$ equation is obtained.



Determining the rate of change of a variable

- Here, it is seen that the decrease in the amount or concentration is faster at the beginning and slower with time.
- This reduction is an exponential decrease.
- C_0, is the drug concentration at the beginning (at t=0).



- **$C = C_0 . e^{-kt}$**
- If the **natural logarithms** of both sides are taken:

$$\ln C = \ln C_0 - k_{el} . t$$

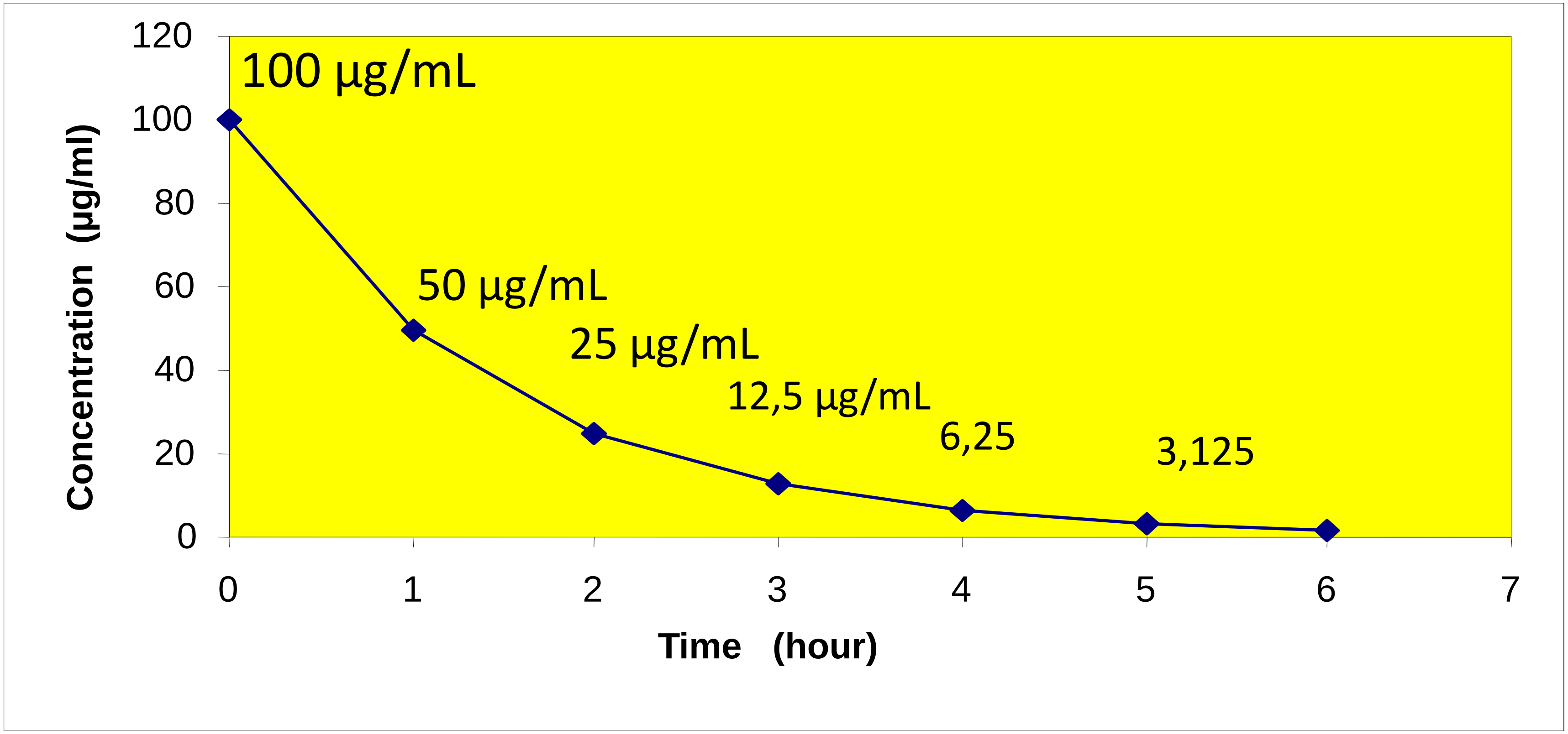
- $C=C_0.e^{-kt}$ equation can also be expressed logarithmically.
- If the **logarithms** of both sides are taken :

$$\text{Log } C = \text{Log } C_0 - (kt/2.303)$$

Example

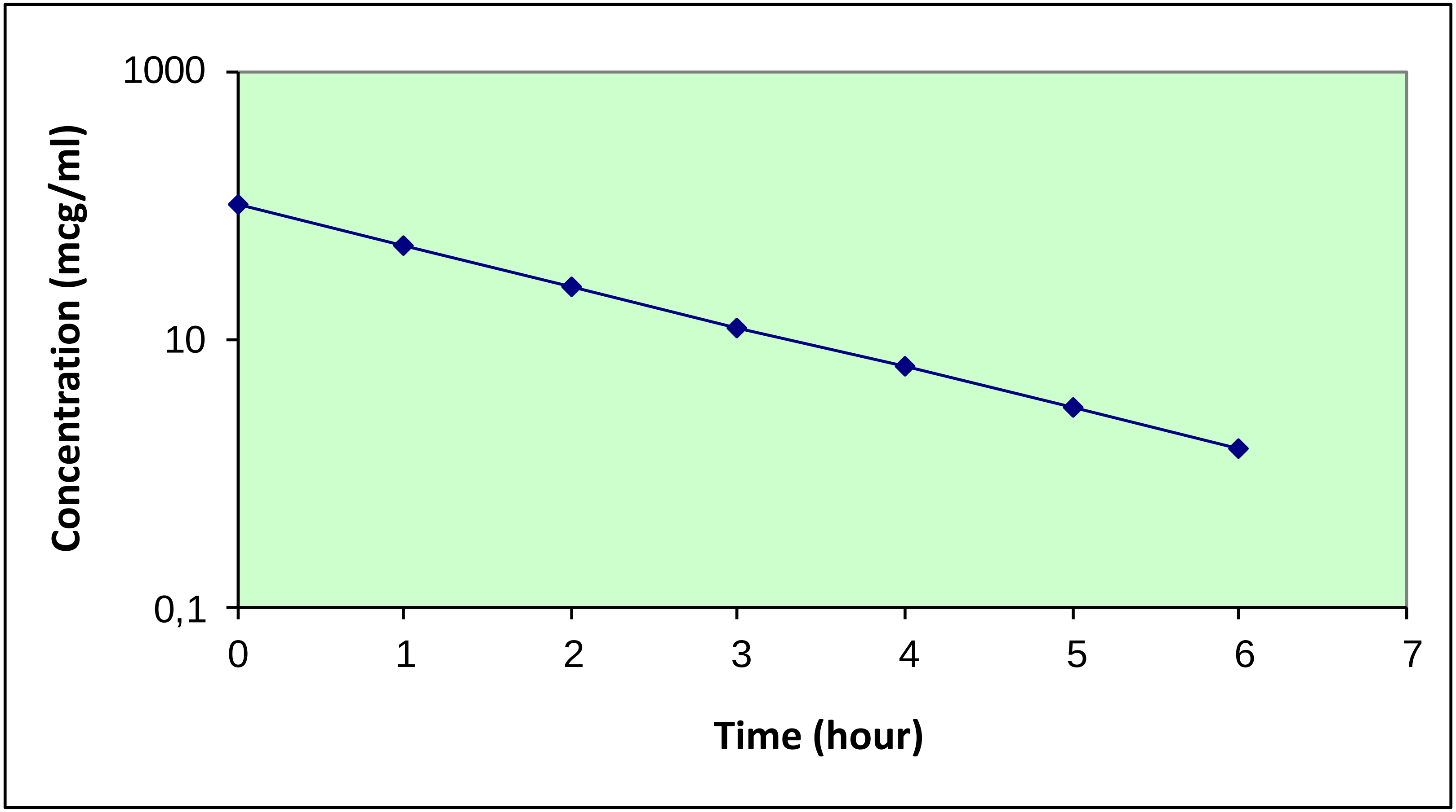
t (hour)	C (µg/mL)
0	100
1	50
2	25
3	12,5
4	6,25
5	3,125

Linear Graph



C_0= 100 µg/mL

Semi logarithmic graph



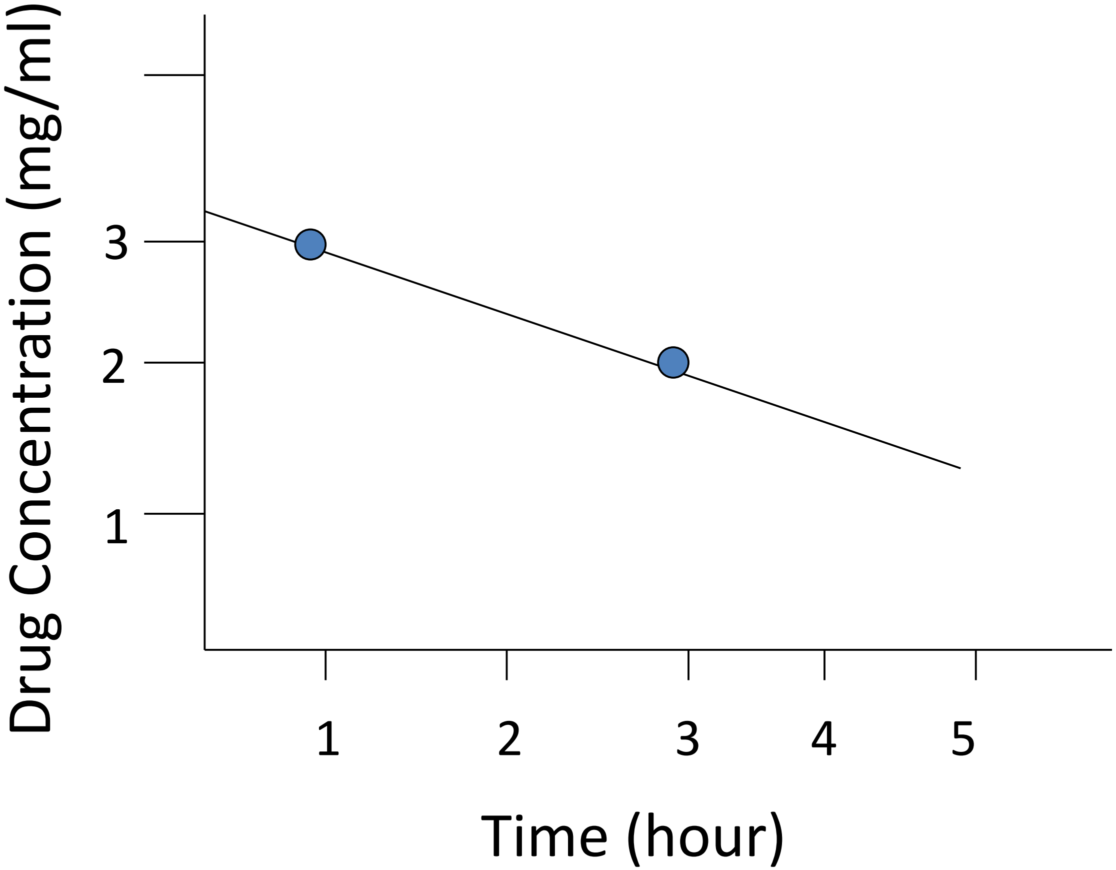
The important point is,
The values are marked without taking the logarithm.

Calculation of the elimination rate constant (k_{el})

- **$\ln C = \ln C_0 - k_{el} \cdot t$** equation gives a curve; **the slope** of the curve gives the **elimination rate constant (k_{el})** verir.

- k_{el}, can be found by a calculator or computer using ln-lineer regression function in Microsoft Office Excel.

Slope Linear



Slope= y2-y1/x2-x1

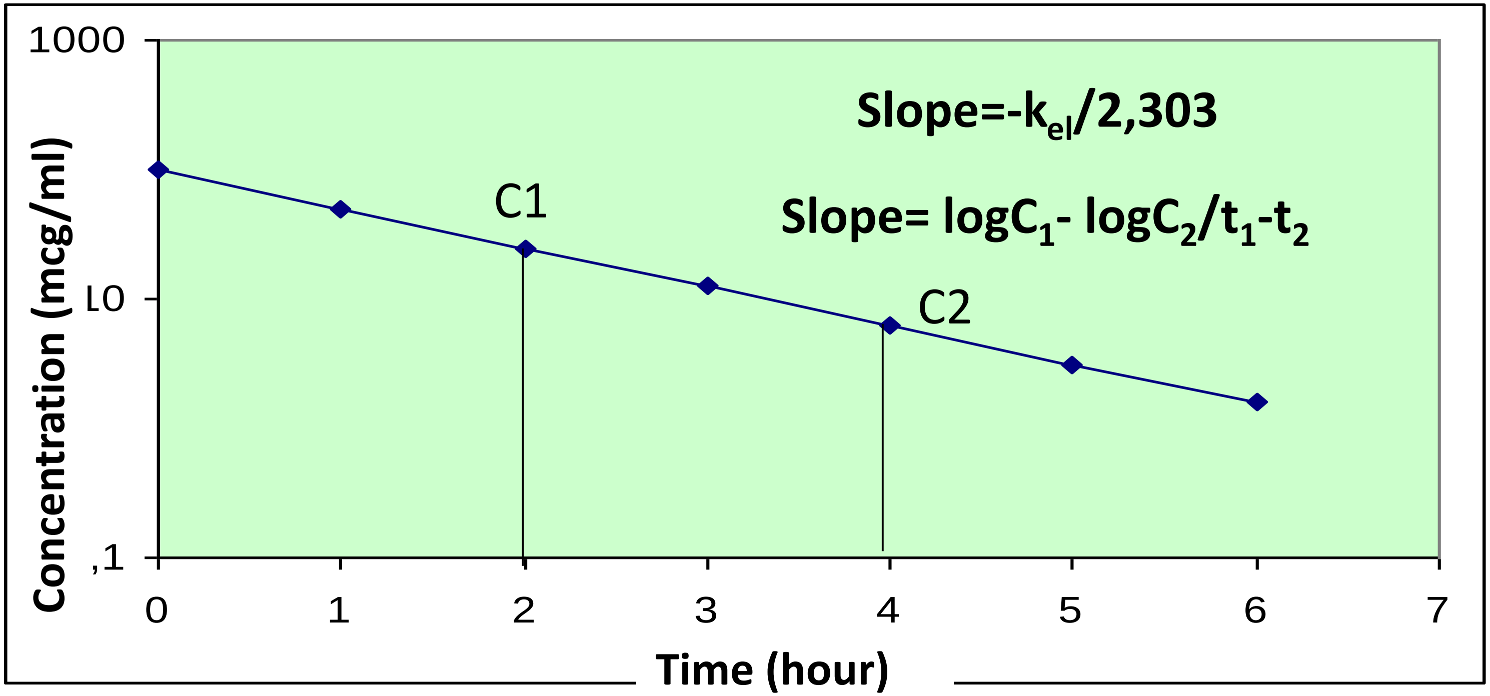
Slope= 2-3/3-1

Slope= - 1/2

y= -1/2x+3,5

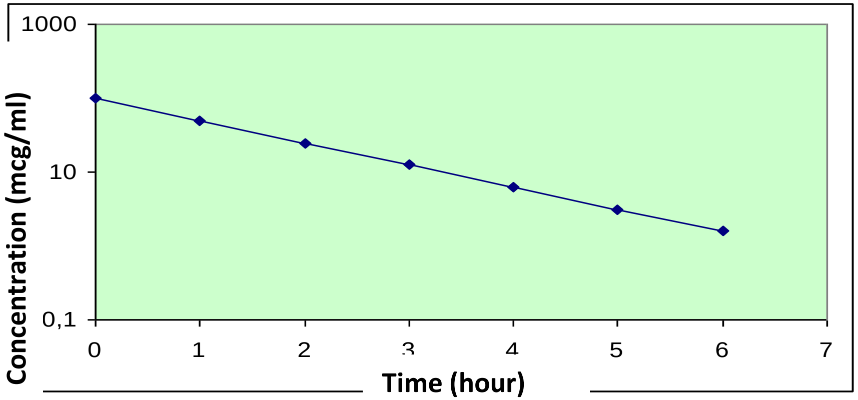
Calculation of the elimination rate constant (k_{el})

- The slope with log-linear regression = $-k_{el}/2,303$.
- In the ln-lineer regression, the slope of the line directly gives the **"k_{el}"** value.



t (hour)	C (µg/mL)
0	100
1	50
2	25
3	12,5
4	6,25
5	3,125

$$\text{Log } C = \text{Log } C_0 - kt/2.303$$



$$\text{LogC} - \text{LogC}_0 = -k.t/2.303$$

$$\text{LogC}_0 - \text{LogC} = k.t/2.303$$

$$\text{Log50} - \text{Log25} = k.\ (1\text{-}2)/2.303$$

$$1{,}6989\text{-}1{,}3979 = -k/2.303$$

$$0{,}301\text{X}2{,}303 = -k$$

$$k = -\ 0{,}\ 693$$

Calculation of the Elimination Half-Life

- The elimination half-life ($t_{½}$)of the drug in the plasma can be calculated from the following formula:

$$t_{½} = \ln 2/k_{el} = 0{,}693/k_{el}$$

- The half-life ($t_{½}$) can also be calculated using the graph.

Calculation of the Elimination Half-Life

- $\ln C = \ln C_0 - k_{el} . t$

The time until C_0 reach to $C_0/2$ is called as $t_{1/2}$.

- In the line equation, replace t with $t_{1/2}$ and C with C_0 /2,

  $\ln C_0 /2 = \ln C_0 - k_{el} . t_{1/2}$ or

  $\ln C_0 /2C_0 = - k_{el} . t_{1/2}$ or $\ln 2 = - k_{el} . t_{1/2}$

= $t_{1/2} = \ln 2 / k_{el}$

I.V. SINGLE DOSE ADMINISTRATION SINGLE-COMPARTMENT MODEL

- **QUESTION 1:** Drug ‘’A’’ is administered to a patient intravenously and blood was collected at certain time points. The following plasma concentrations were determined in these blood samples.

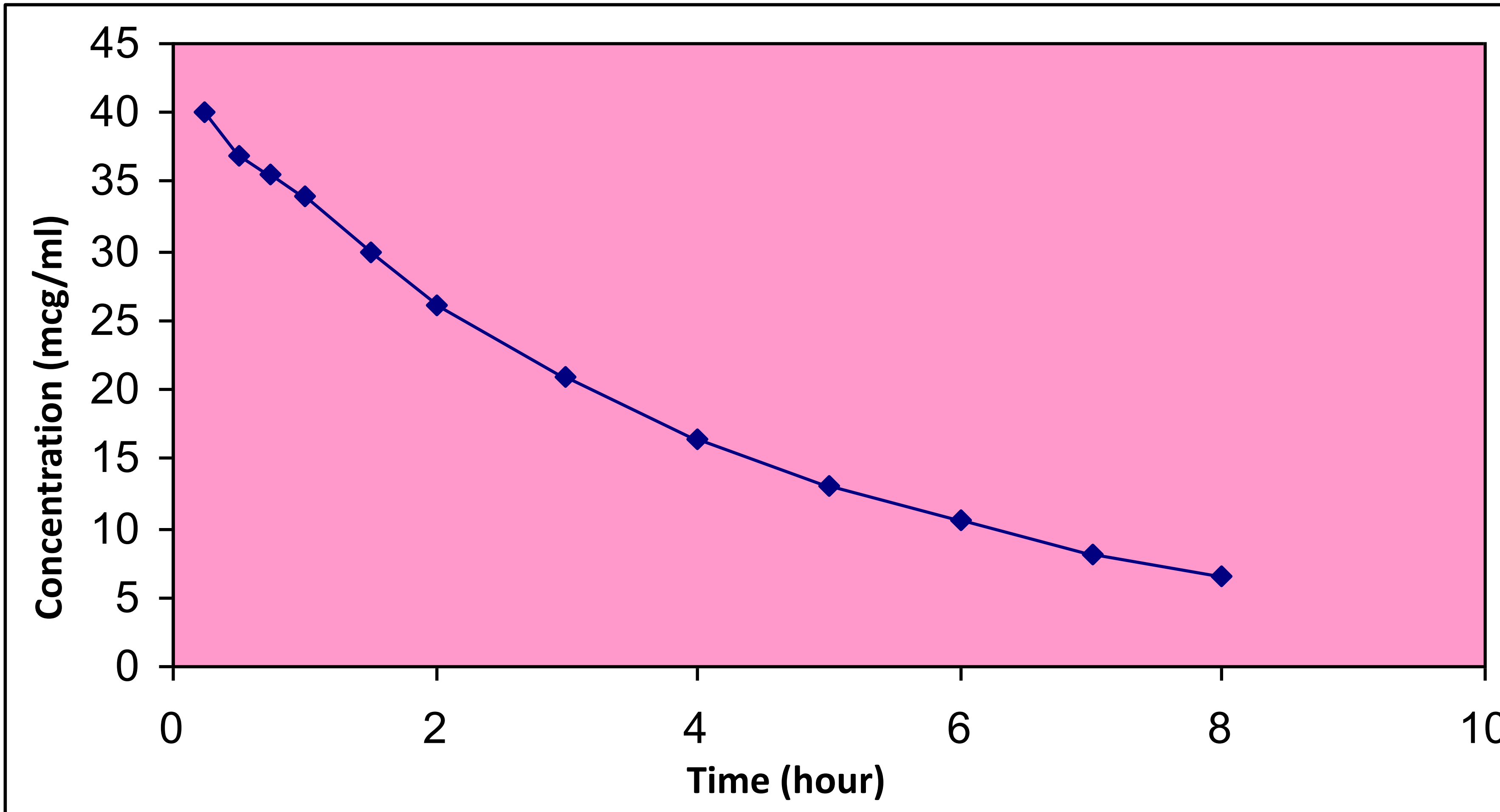
Plasma Data

t (hour)	0	0.25	0.5	0.75	1	1.5	2	3	4	5	6	7	8
C (μg /ml)	0	40	37	35,5	34	30	26	21	16,5	13	10,5	8	6,5

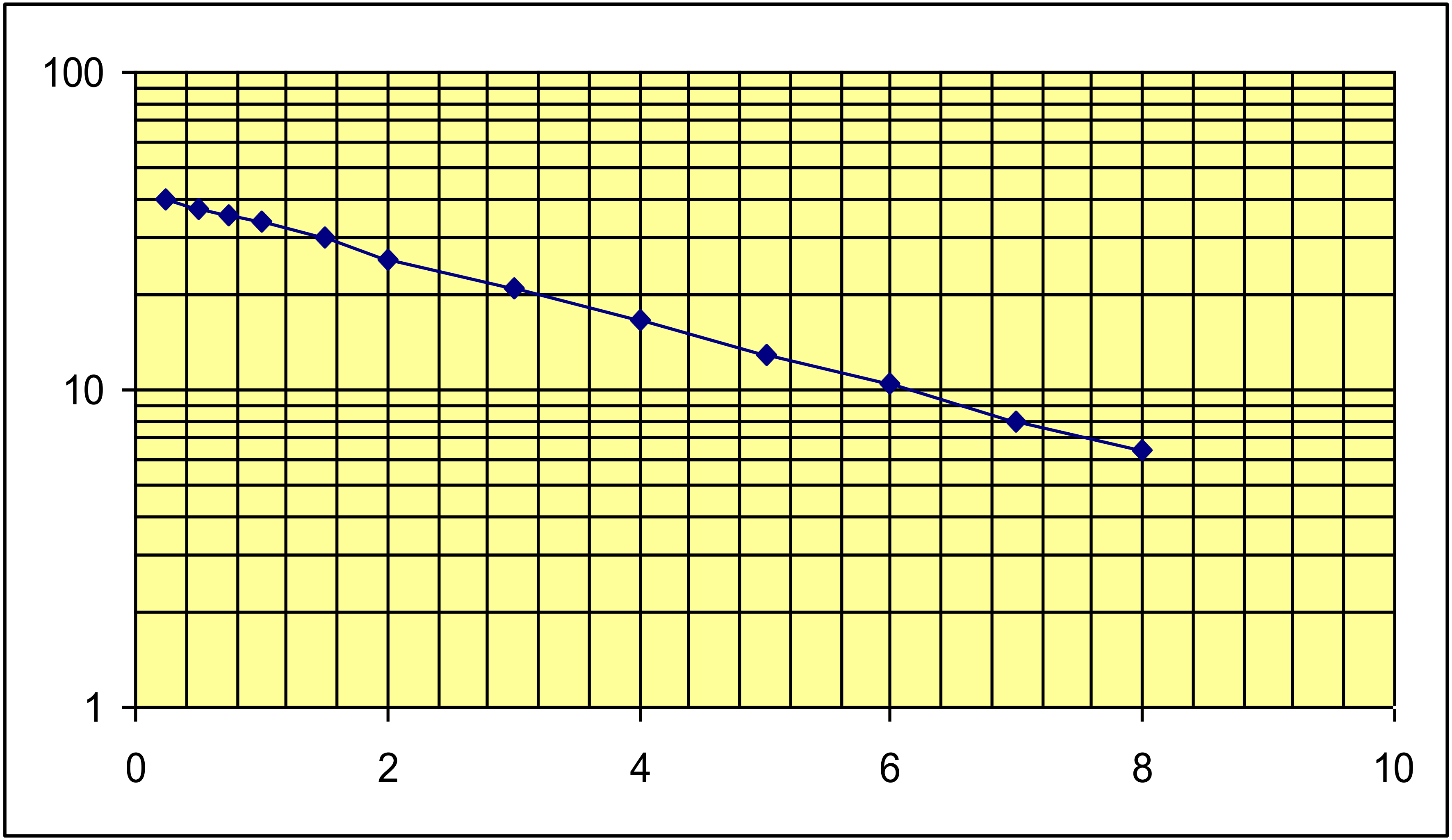
Questions

- Draw the graphs with the values in the table on normal paper and semi-logarithmic paper.
- Calculate the value ‘’C_0‘’.
- Calculate the elimination rate constant (k_{el}).
- Calculate the elimination half-life ($t_{½}$).
- Calculate the concentration at the time 3,5. hour.

Plasma const.-time curve



Semi logarithmic paper presentation



Calculation of C_0

- For the calculation of C_0 value, do ln-linear regression (LR) by using the last 4 points.

t (hour)	C (µg/ml)
5	13
6	10,5
7	8
8	6,5

- Find the point where the Y axis is cut.
- k_{el} value is equal to the slope of the curve. It is calculated as k_{el}= -0,24 hour^{-1} .

$$y = 42{,}3.e^{-0{,}24x}$$

Calculation of k_{el} value

t	Const.	Log const.
5	13	1.113943
6	10.5	1.021189
7	8	0.90309
8	6.5	0.812913

Slope = logc1- logc2/t_1-t_2

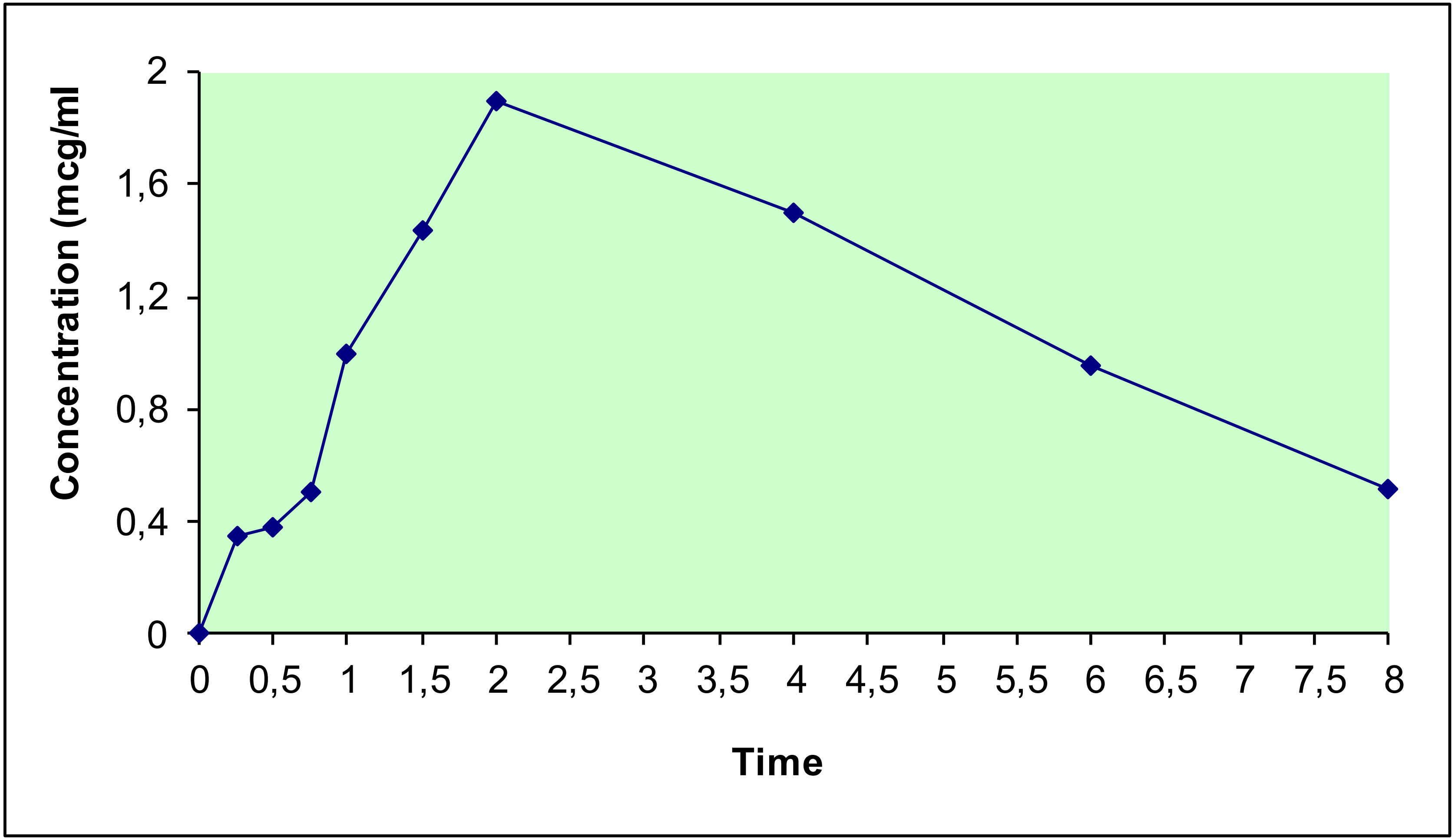
Slope = (1.02-0,81)/6-8

Slope = -0,104

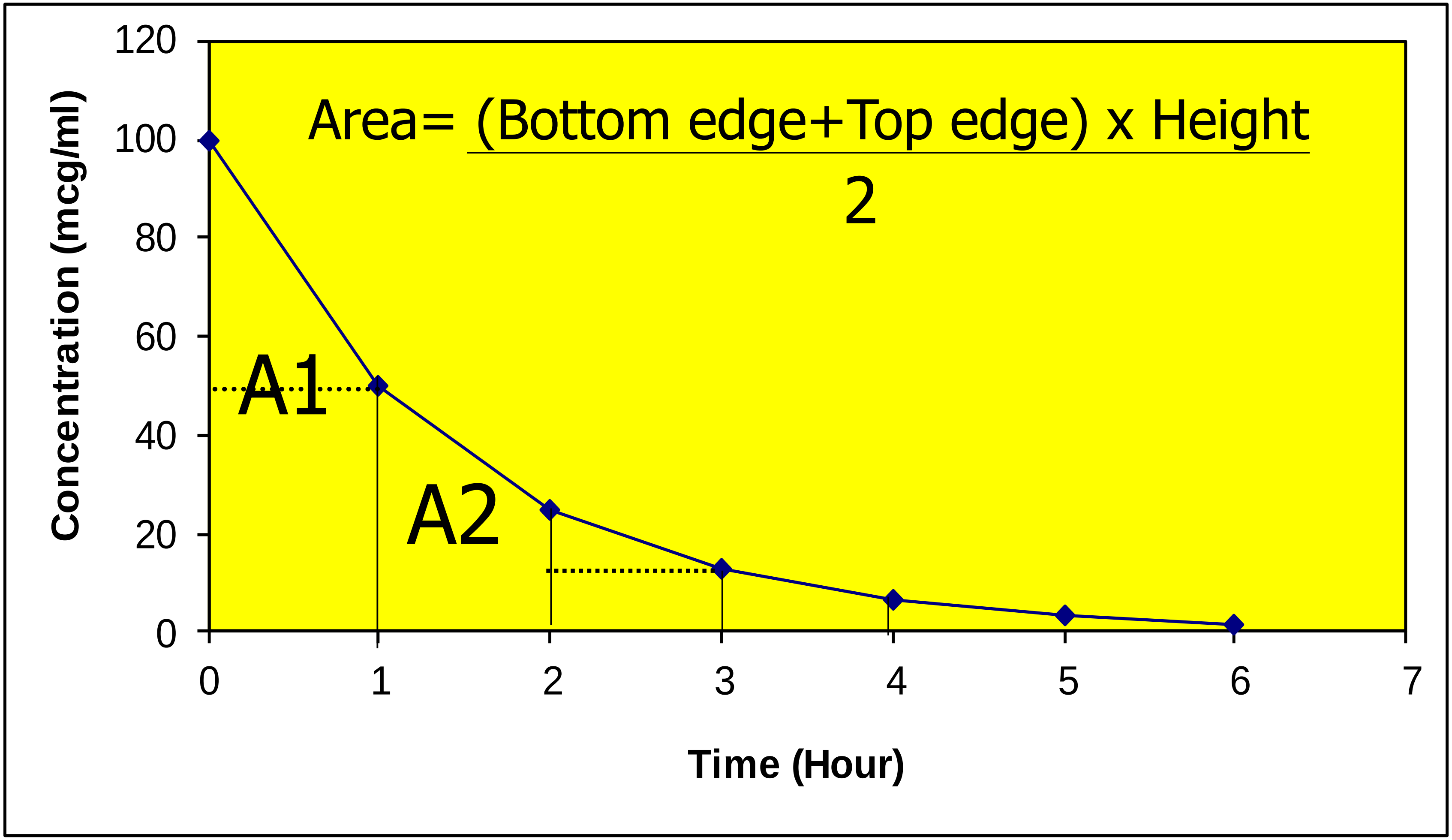
Slope = k_{el} / (2,303)

k_{el} = -0,24

Calculate the AUC values for the intervals of 0-8 ve 0-∞.



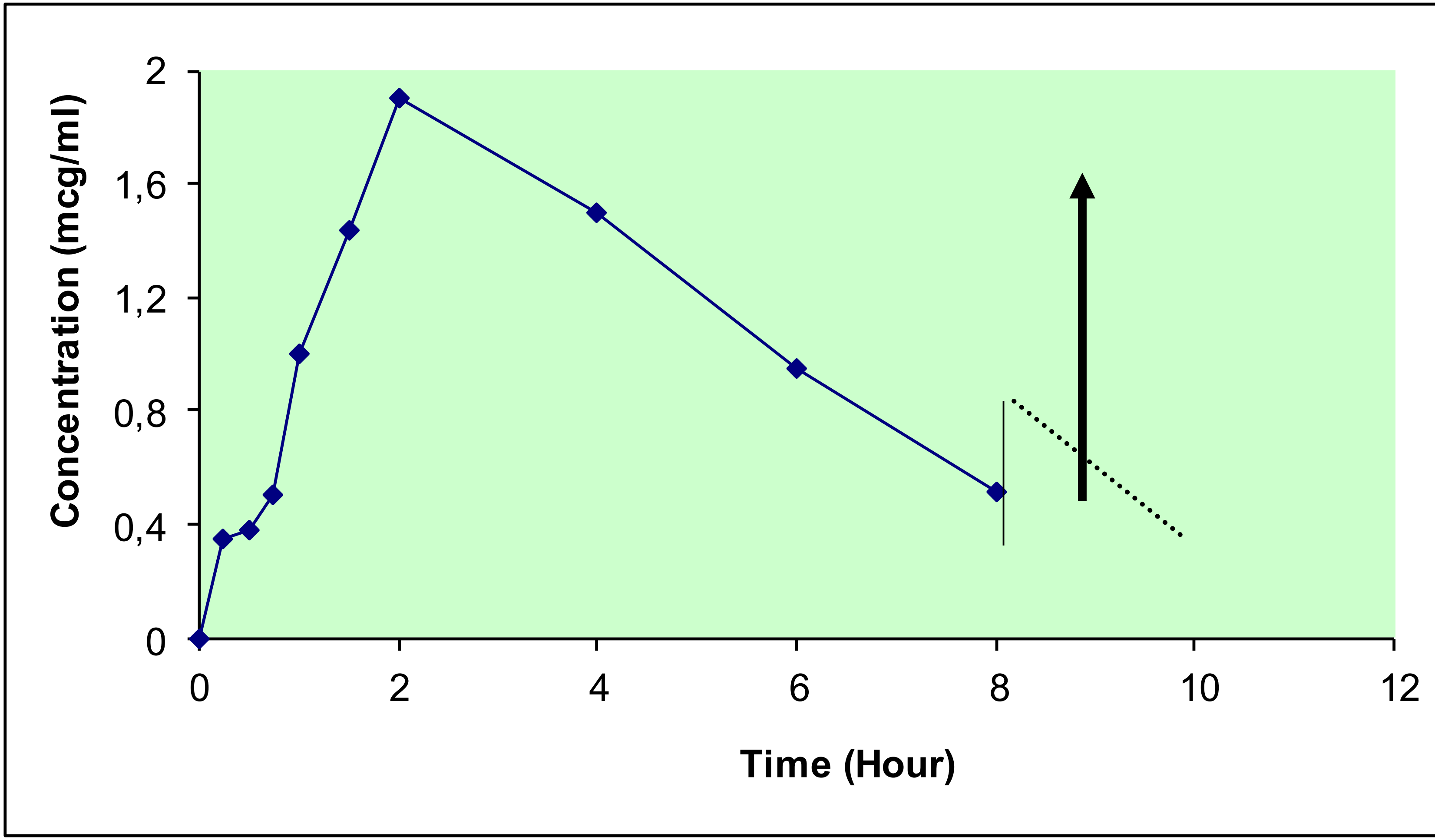
Calculation of AUC with Trapezoid Method



Calculation of AUC

- AUC_1 = 0,0437 µg.h/ml
- AUC_2= 0,090 µg.h/ml
- AUC_3= 0,109 µg.h/ml
- AUC_4= 0,187 µg.h/ml
- AUC_5= 0,61 µg.h/ml
- AUC_6= 0,835 µg.h/ml
- AUC_7= 3,40 µg.h/ml
- AUC_8= 2,45 µg.h/ml

$$AUC_{8-\infty} = C_8 / k_{el}$$



Calculation of AUC

- AUC_9 = 1,46 µg.h/ml
- $AUC_{0\text{-}8h}$ = 9,184 µg.h/ml

- **$AUC_{t-\infty} = C_t / k_{el}$**

  $AUC_{8-\infty} = C_8 / k_{el}$

= 0,51 / 0,266 = 1,96 µg.h/ml

- **AUC_{total} = 9,184 + 1,96 = 11,14 µg.h/ml**

ORAL SINGLE DOSE ADMINISTRATION
SINGLE-COMPARTMENT MODEL
HOMEWORK QUESTION

- **SORU-2 :** Drug ''A'' is administered to a patient via oral route and blood was collected at certain time points. The following plasma concentrations were determined in these blood samples:

t (hour)	0	0,25	0.5	0.75	1	1,5	2	4	6	8
C (µg /ml)	0	0,35	0.375	0.5	1	1,44	1,9	1,5	0,95	0,51

Homework

- Draw the plasma concentration-time curve as Linear (without using Excel) and calculate the Area Under the Curve (AUC).
- Draw the plasma concentration-time curve exponentially using the Excel program for the concentrations corresponding to the last 4 time points (2., 4., 6., and 8. hours). Add the output to your homework.
- Calculate the elimination rate constant (k_{el}) for the last 4 time points by using Log and compare it with the slope of the curve which you obtained from the Excel program.
- What is the elimination half-life ($t_{½}$) of the drug?

Do not forget to write your name, surname and number to your homework.
Give your homework in a transparent file.