AREA UNDER THE CURVE

What is "area under the curve?"

- The definite integral can be used to find the area between a graph curve and the 'x' axis, between two given 'x' values. This area is called the 'area under the curve' regardless of whether it is above or below the 'x' axis.

Importance of AUC

- **Toxicology :**
  - Measure of drug exposure
- **Biopharmaceutics :**
  - Comparison of drug products in BA/BE studies
- **Pharmacokinetics :**
  - Measure of Pharmacokinetic parameters e.g. Clearance, BA.

CLINICAL IMPLICATIONS

- TACROLIMUS – In Kidney transplantations
- Clearance and GFR for aminoglycosides like Gentamycin and tobramycin
- Variability of GFR to predict renal outcomes in CKD

- For assessment of Vancomycin safety.
- Glucose **AUC** as screening for glucose intolerance in outpatients.
- **AUC** for antimicrobials with concentration-dependent pharmacodynamics - daptomycin
- Cyclosporine estimation in pediatric hematopoietic stem cell transplantation.

- Aminoglycoside dosing in patients with obesity
- mycophenolate sodium - mycophenolic acid- **AUC** in adult kidney and liver transplant recipients
- Valganciclovir dosing using **AUC** in pediatric solid organ transplant recipients.
- receiver-operating-characteristic **AUC** - in mammography and radiology.

The most reliable measure of a drug's bioavailability is AUC.

Directly proportional to the total amount of unchanged drug that reaches systemic circulation.

Drug products may be considered bioequivalent in extent and rate of absorption if their plasma concentration curves are essentially superimposable.

- 5-fluorouracil **AUC** - pharmacokinetic dosing algorithm for colorectal cancer patients receiving FOLFOX6.

- Methotrexate **AUC** - prognostic factor - primary central nervous system lymphoma

- Mycophenolic acid **AUC** recovery time

- intravenous **busulfan** dose - **AUC**- hematopoietic stem cell transplantation.

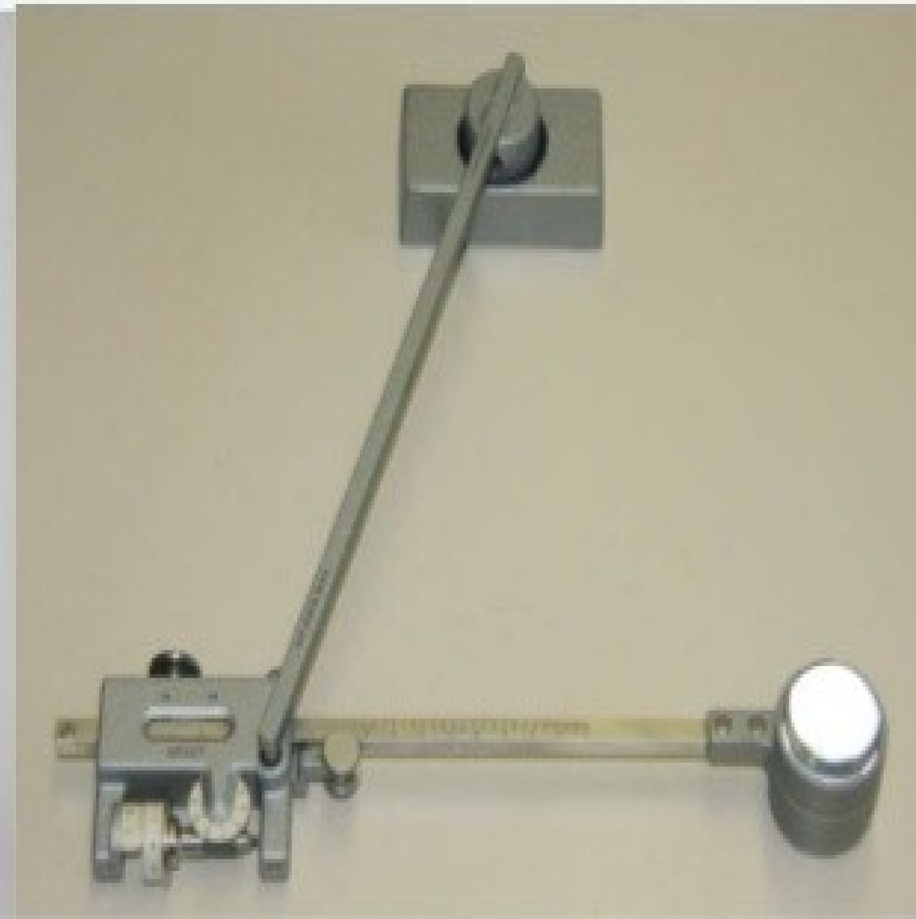
Calculation of AUC

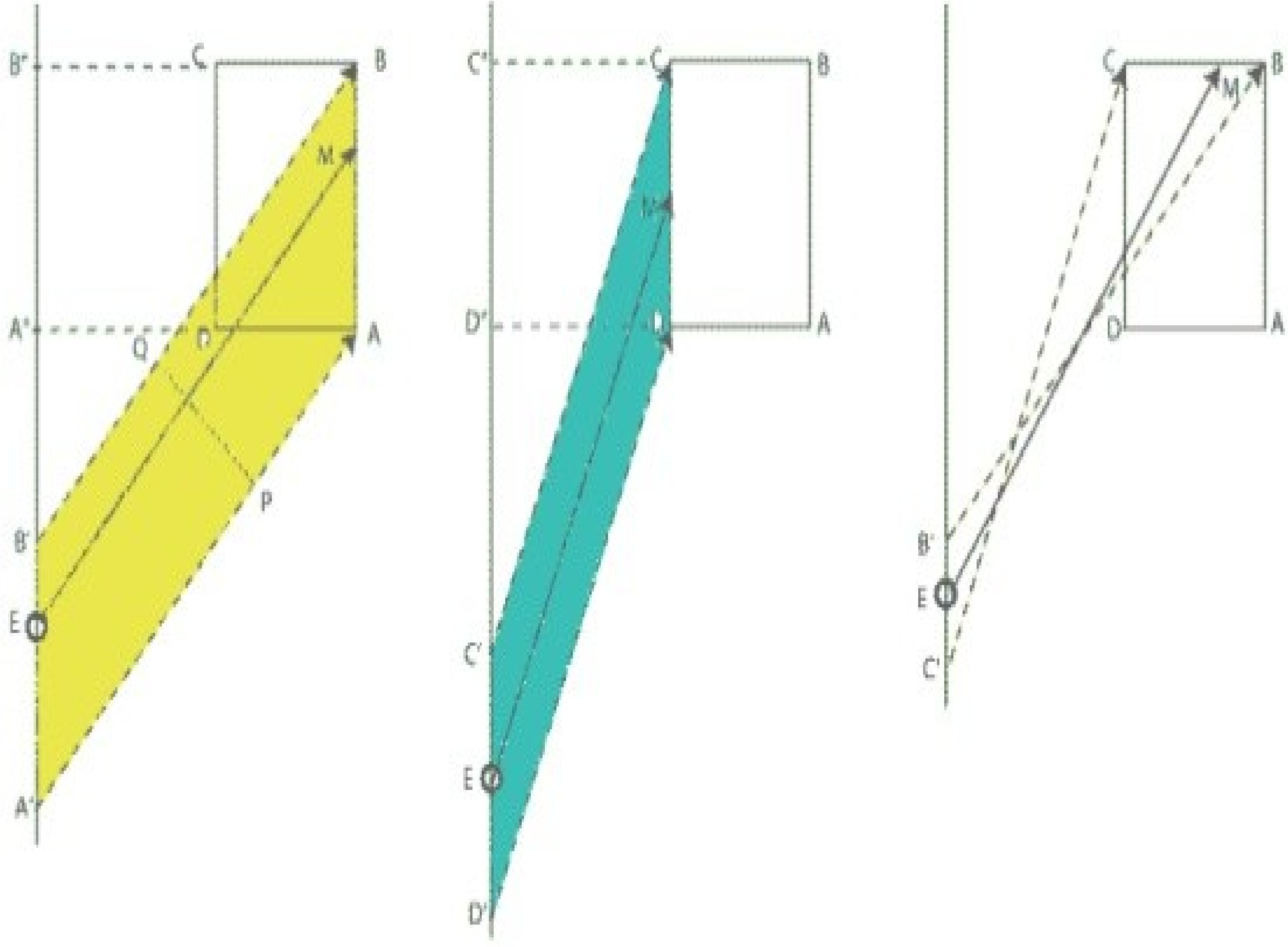
- **Planimeter :**
- **Cut & Weigh method :**
- **Mathematical :-** Trapezoidal rule
- **Counting Squares method :**

Planimeter

AKA **platometer**,

measuring instrument - to determine the area of an arbitrary two-dimensional shape





B'
C
B
M
A'
Q
D
A
P
B'
E
A'
C'
C
B
M
D'
D
A
C'
E
D'
C
M
B
D
A
B'
E
C'

CUT AND WEIGH METHOD

Plot the plasma profile vs time on graph paper

Cut the curve drawn carefully

Require an analytical balance

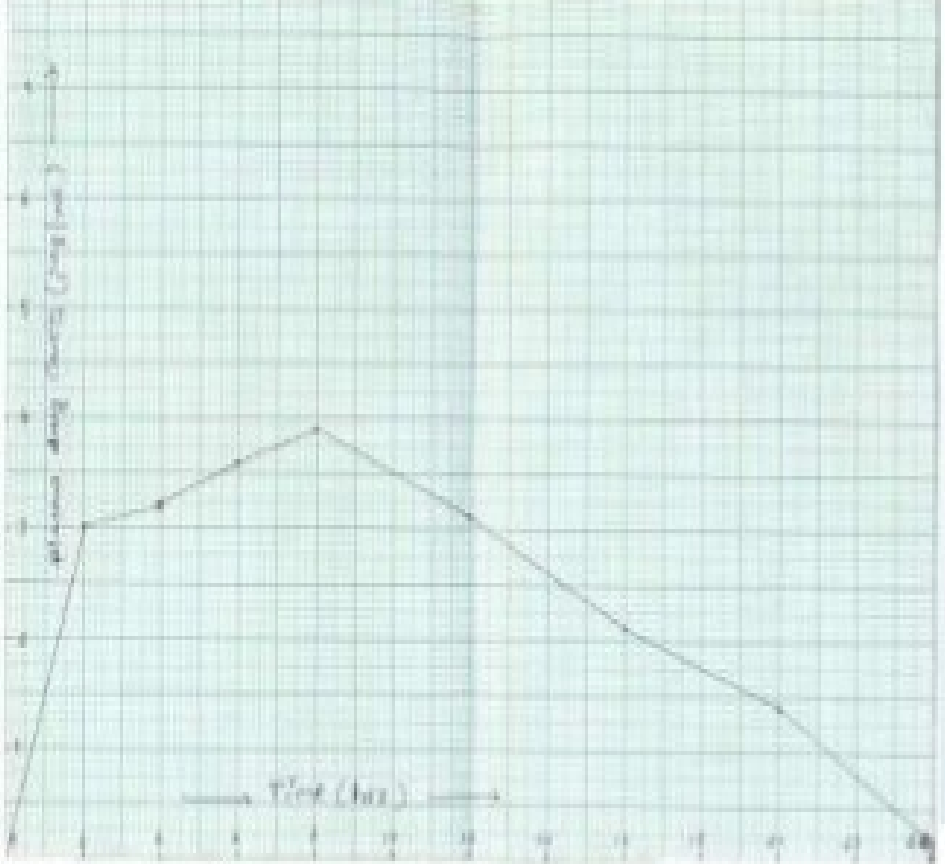
The weight of this cut portion is W1 so we presume

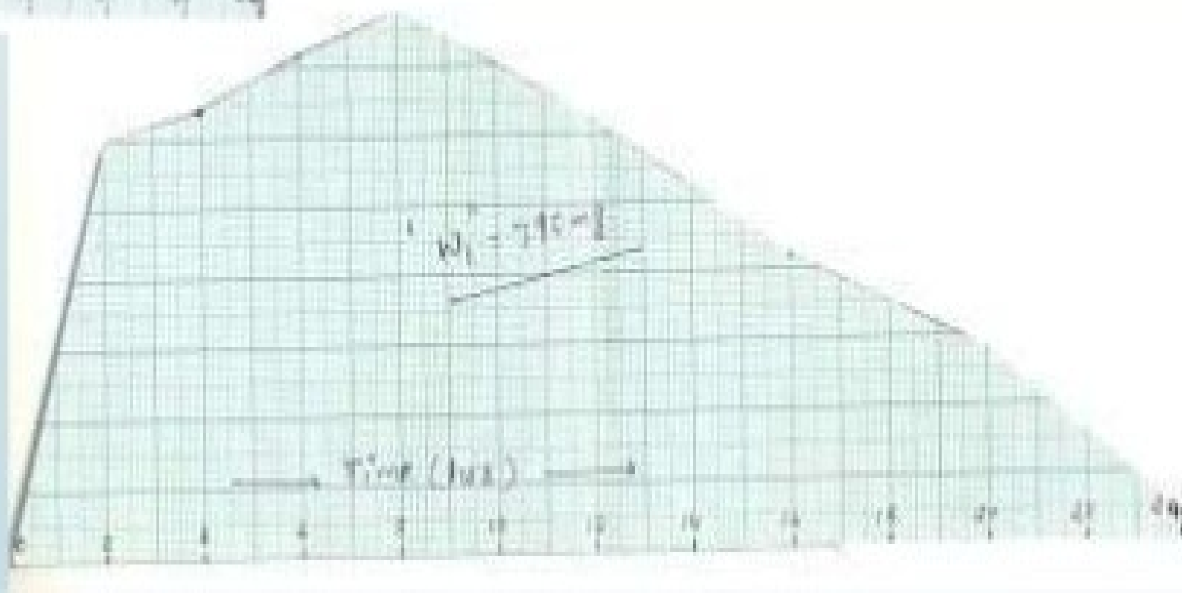
AUC1 @ W1

Weight of whole graph paper is W2

Area of whole paper = AUC2

Area= length X breath


Time (hrs)


Time (hrs)

$AUC_1 \alpha W_1$

$AUC_2 \alpha W_2$

AUC1/W1 = AUC2/W2

AUC2= 192 ug.hr/ml

W1= 790mg

W2= 2750mh

AUC1= [(192)(790) / 2750] = 55.15ug.hr/ml

Units Y axis ug/ml nd X axis is Hours so area is ug.Hr/ml

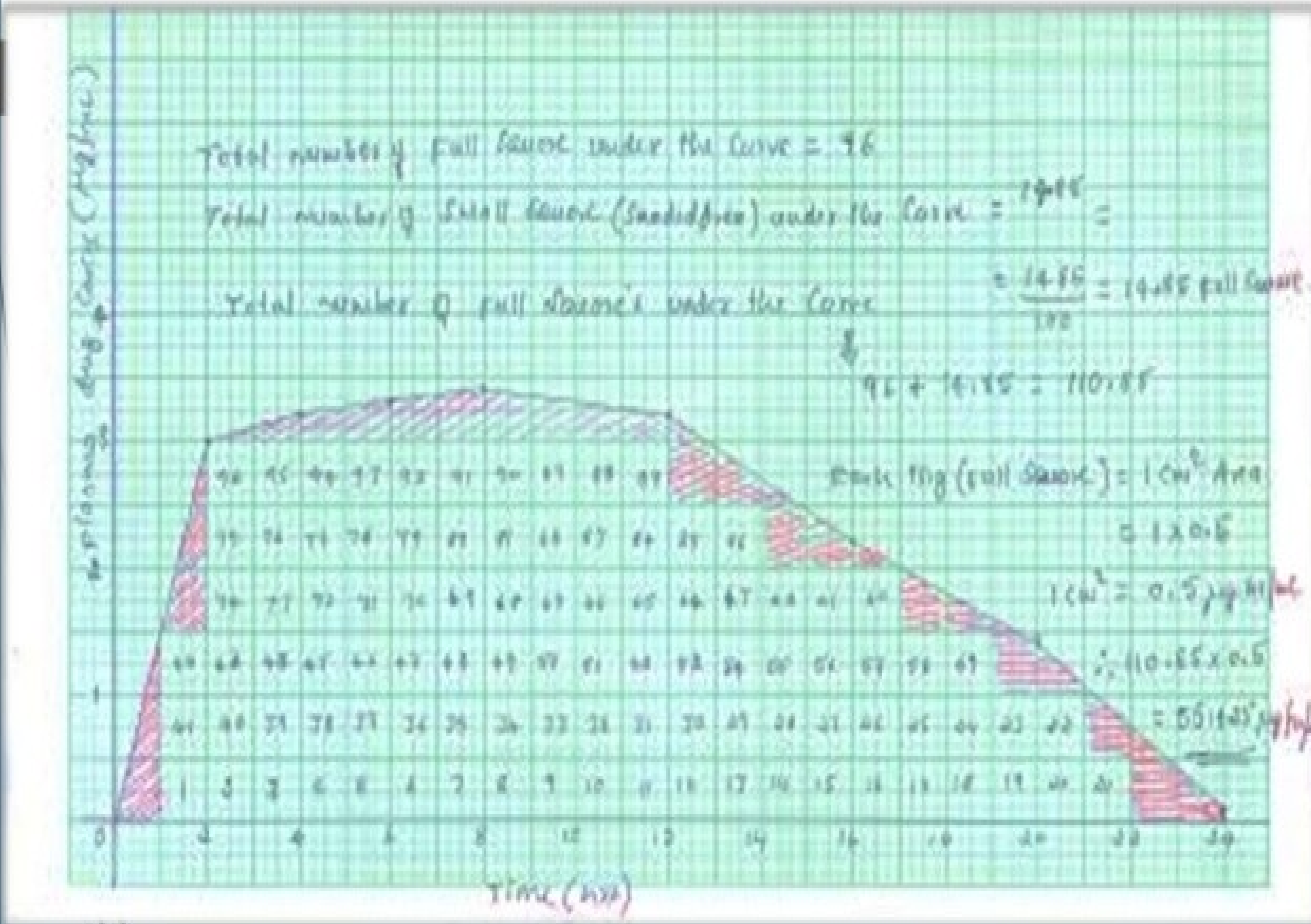
COUNTING SQUARED METHOD

The plasma concentration Vs time graph is plotted on graph paper

Total number of squares are counted

Area of each square is measured in cm or the units on x and y axis of graph

Total full squares counted and total number of small squares in shaded area counted to get total number number of full squares


Total number of full square under the curve = 96
Total number of small square (shaded area) under the curve = 1485
= 1485/100 = 14.85 full square
Total number of full square's under the curve
96 + 14.85 = 110.85
Each big (full square) = 1 cm² Area
= 1 x 0.5
1 cm² = 0.5 μg hr/ml
∴ 110.85 x 0.5
= 55.425 μg hr/ml
Time (hr)

FOR EXAMPLE

Total full squares=96

Total small squares in shaded area= 1485

Full squares in shaded area= 1485/100 = 14.85

Total full squares = 96 + 14.85 = 110.85

Concentration of each square 1cm2 area = 1X 0.5 = 0.5ug.hr/ml

AUC= 110.85 X 0.5 = 55.425ug.hr/ml

Trapezoidal Rule

Steps

Dividing whole AUC into trapezoidal segments

⇓

Counting the area of each segments separately

⇓

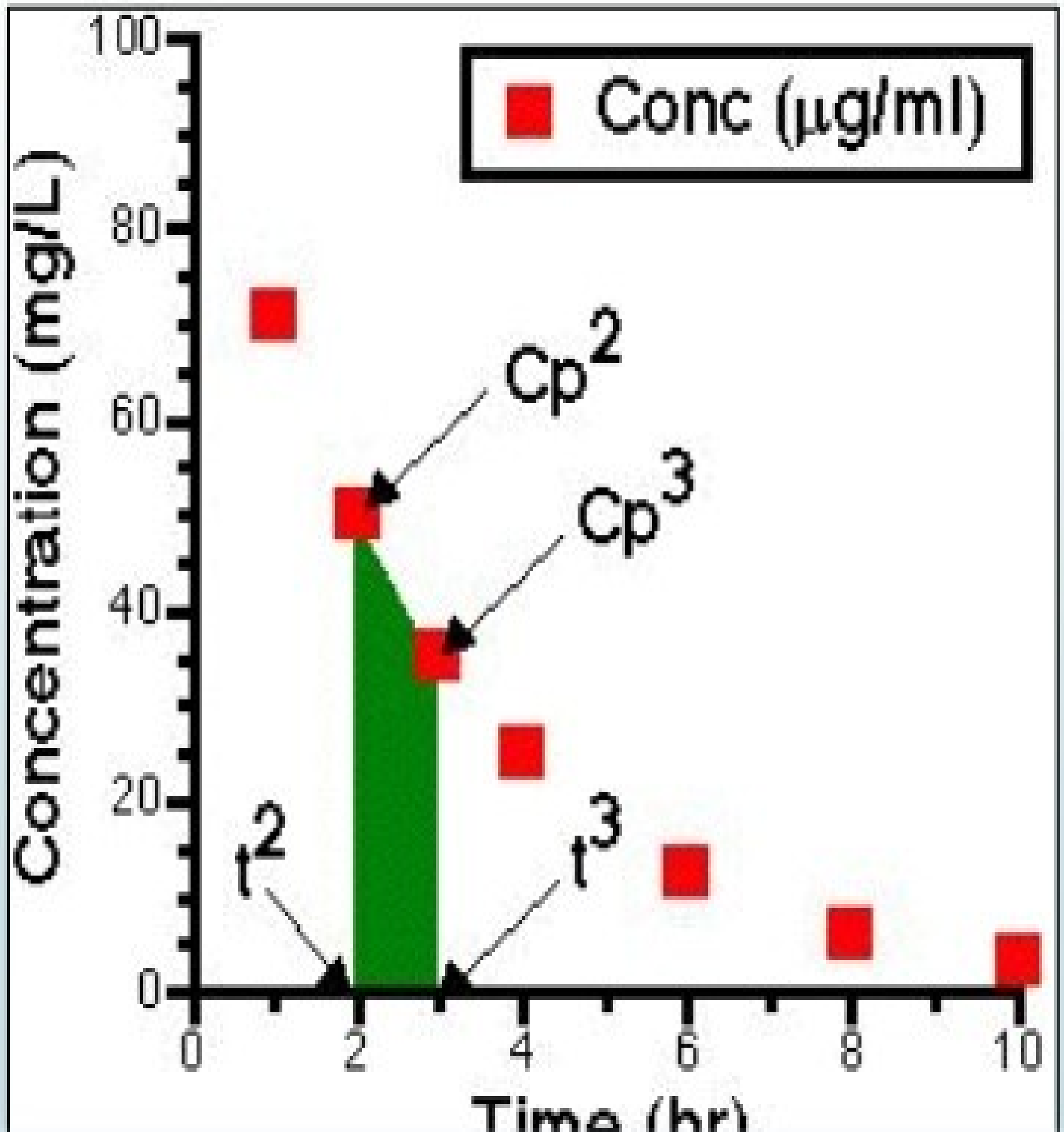
Summation of all the area

⇓

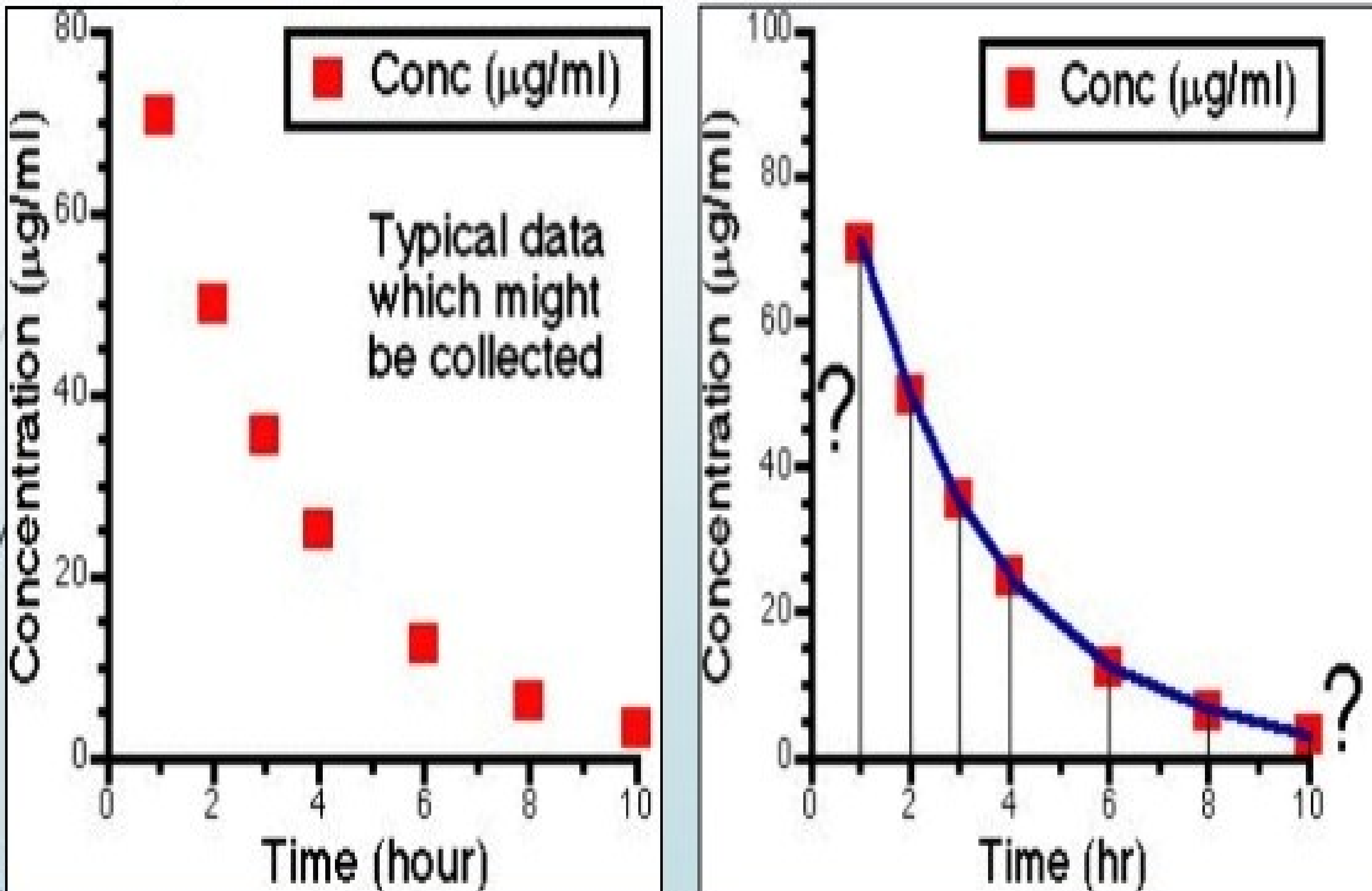
Total area

Trapezoid

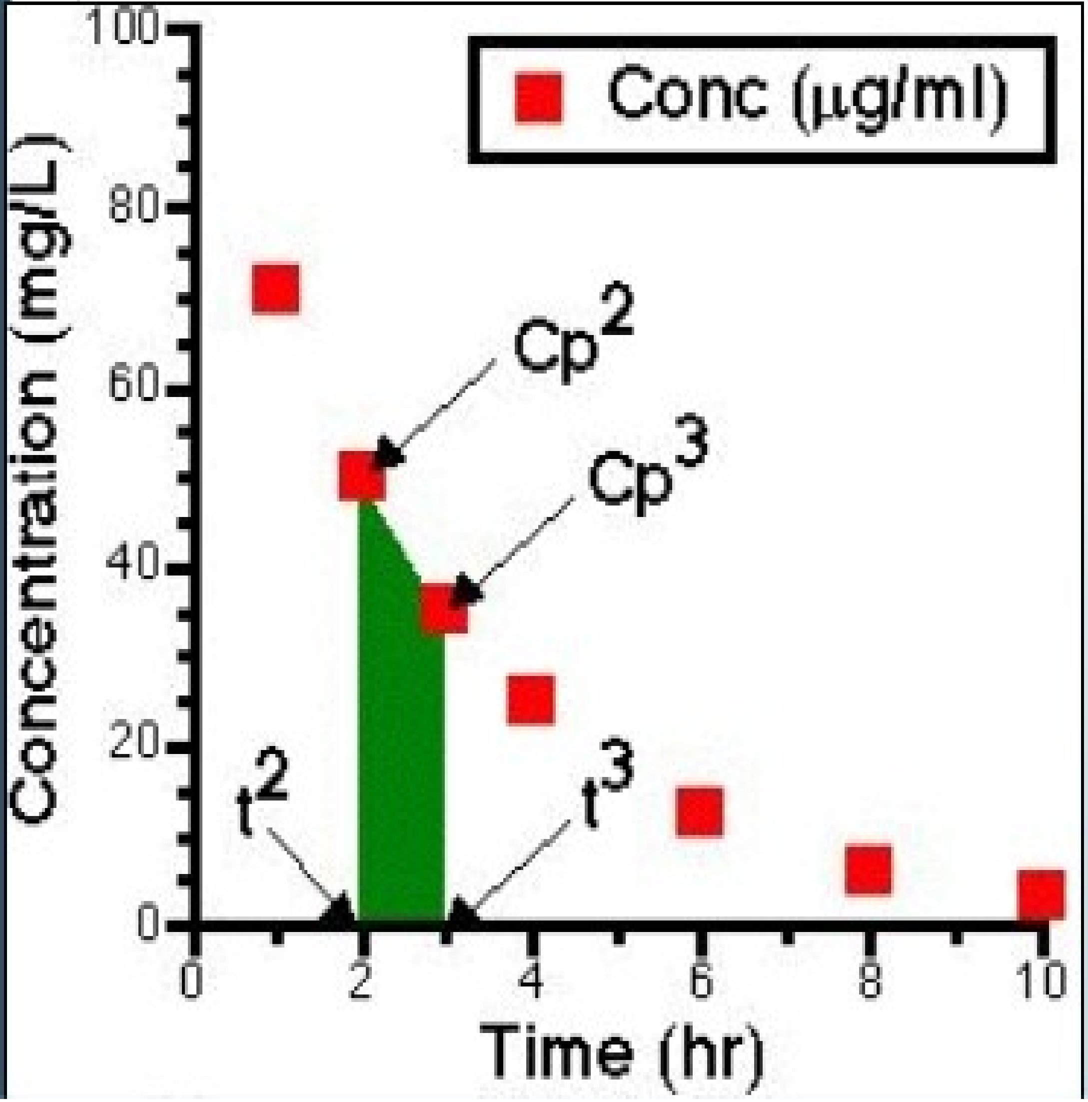
- Four sided figure with two parallel sides



- We can calculate the AUC of each segment if we consider the segments to be trapezoids

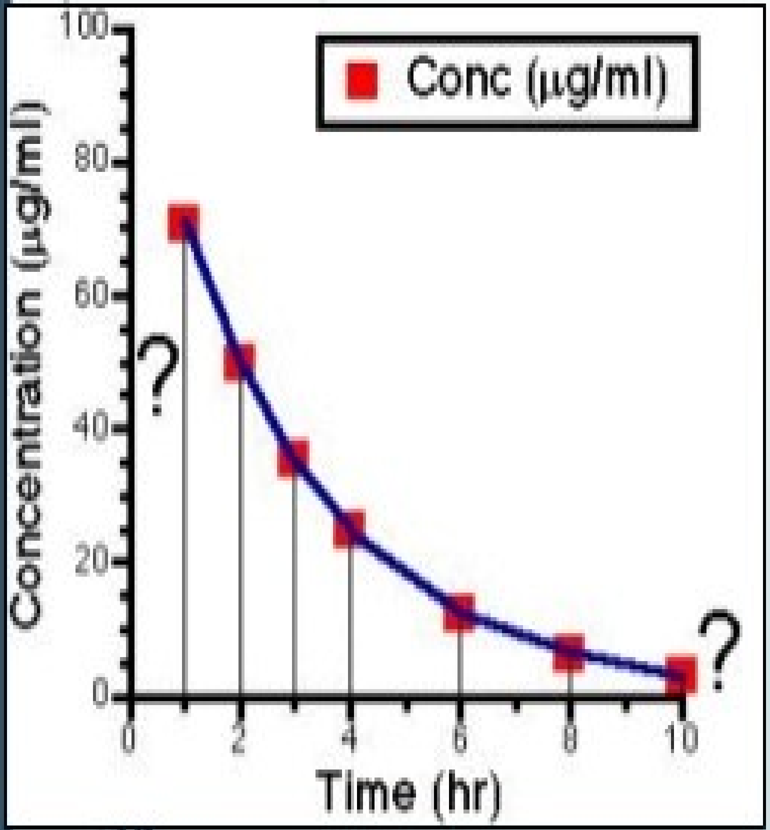


Calculation of a segment



$$AUC_{2-3} = \frac{Cp_2 + Cp_3}{2} \times (t_3 - t_2)$$

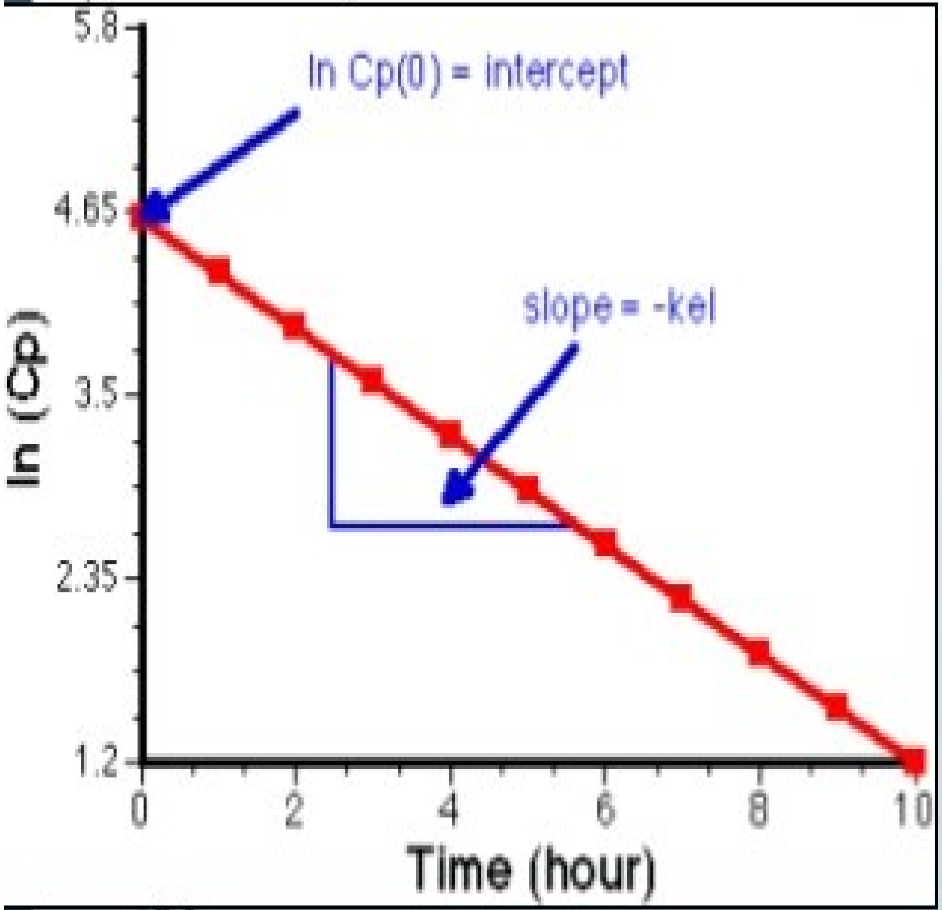
- The area from the first to last data point can then be calculated by adding the areas together



$$AUC_{1-n} = \sum \left\{ \frac{Cp_1 + Cp_2}{2} \bullet (t_2 - t_1) \right\} + \left\{ \frac{Cp_2 + Cp_3}{2} \bullet (t_3 - t_2) \right\} + \ldots$$

Calculation of First Segment

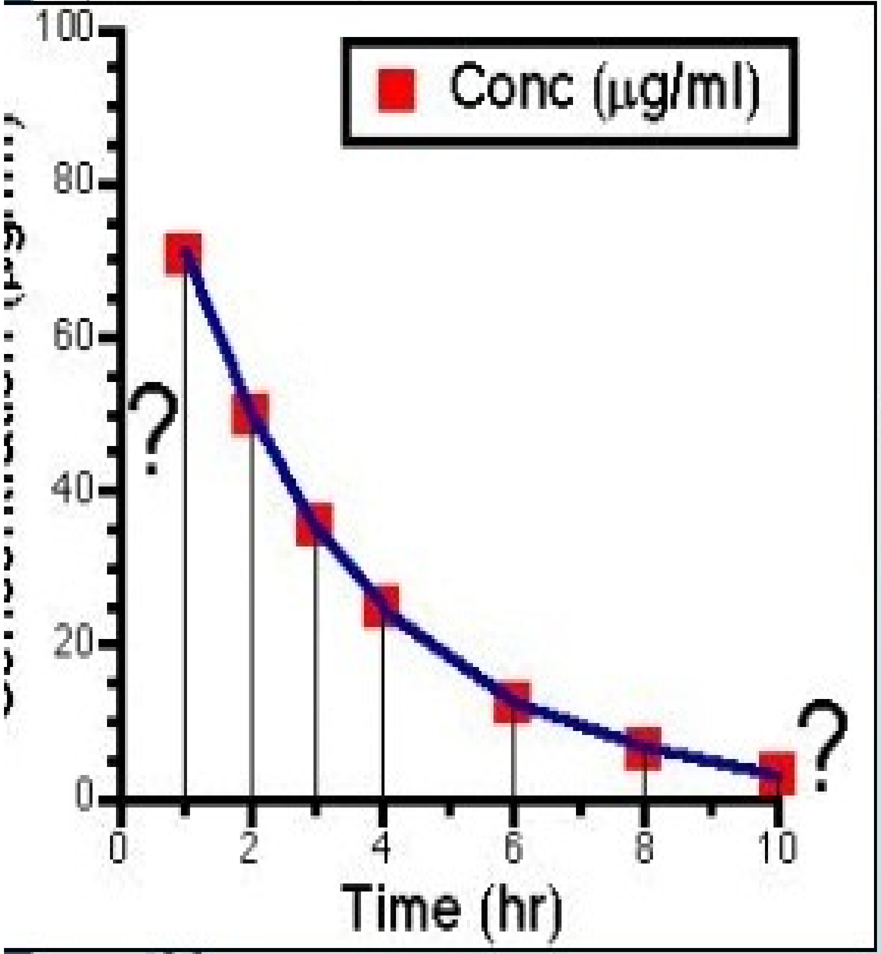
- The first segment can be calculated after determining the zero plasma concentration $\mathbf{Cp_0}$ by extrapolation



$$AUC_{0-1} = \frac{C_{p0} + C_{p1}}{2} \times t1$$

Calculation of Last Segment

- Final segment can be calculated from t_{last} to $t_{infinity}$



$$AUC_{t_{last}-\infty} = \int_{t=t_{last}}^{t=\infty} Cp \bullet dt = \frac{Cp_{last}}{kel}$$

Total AUC

$$AUC_{0-\infty} = AUC_{0-1} + AUC_{1-last} + AUC_{last-\infty}$$

$$= \frac{Cp_0 + Cp_1}{2} \bullet t_1 + \frac{Cp_1 + Cp_2}{2} \bullet (t_2 - t_1)$$

$$+ \frac{Cp_2 + Cp_3}{2} \bullet (t_3 - t_2) + \ldots + \frac{Cp_{last}}{kel}$$

NEWER ADVANCES IN AUC ESTIMATION

- Use of HPLC with mass spectrometry for plasma level calculation
- Use of two sample models to estimate AUC- reduces need for multiple puncturing and samples
- One sample Model is being researched
- Newer computer algorithms for calculating AUC – Graphical methods obsolete

Calculation of Observed Segments

- $AUC_{2\text{-}3} = \frac{Cp_2 + Cp_3}{2} \cdot (t_3 - t_2)$

Time	Concentration	AUC
0	100	
1	71	85.5
2	50	60.5
3	35	42.5
4	25	30
6	12	37
8	6.2	18.2
10	3.1 = Cp_{last}	9.3
???	???	???

Calculation of Last Segment

$$AUC_{t_{last}-\infty} = \int_{t=t_{last}}^{t=\infty} Cp \bullet dt = \frac{Cp_{last}}{kel}$$

$= 3.1 / 0.34$

$= 9.11$