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المادة باللغة الانجليزية	Practical Biopharmaceutics
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اسم التدريسي	م.م. علي فخري جميل
عنوان المحاضرة باللغة الانجليزية	Simulation of one compartment pharmacokinetic model
عنوان المحاضرة باللغة العربية	محاكاة نموذج الحركية الدوائية ذات حجرة واحدة
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المصادر والمراجع	Laboratory Manual of Biopharmaceutics and Pharmacokinetics, S. B. Bhise, R. J. Dias, S. C. Dhawale, K. K. Mali
	Applied Biopharmaceutics and Pharmacokinetics

محتوى المحاضرة

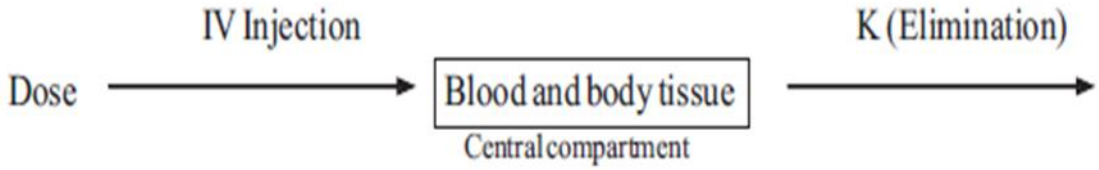
The one-compartment open model assumes that the body can be described as a single, uniform compartment that has no barrier to the movement of drug (i.e., one compartment), and that drugs can enter and leave the body (i.e., open model).

It's the simplest way to describe pharmacokinetics far away from the complex reality of human body.

The final distribution equilibrium between the drug in plasma and other body fluids is attained instantaneously and maintained at all time.

One compartment model assumes the declines in drug concentration in the plasma and tissues will be proportional .

IV bolus ensures entire administered dose to be reaching to the general circulation. (Without absorption)



By the following assumptions, we can simulate one compartment open model in lab and obtain pharmacokinetic parameters:

one-compartment model, first-order process.

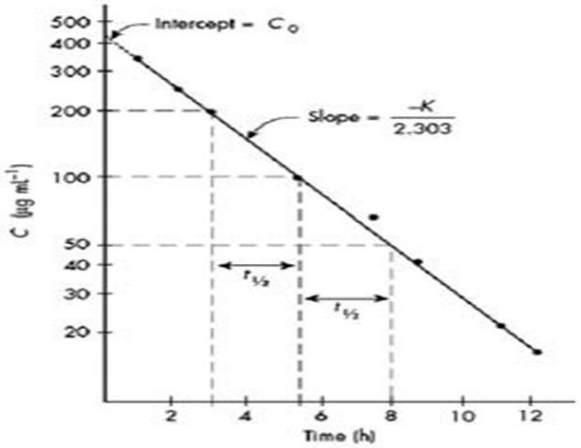
no metabolism takes place (elimination is 100% via renal excretion).

the drug is being monitored in blood (plasma) and urine.

Pharmacokinetic parameters:

Elimination half-life (t1/2) is the time required to reach the half of the initial amount of drug, in response to elimination processes.

$$t_{1/2} = \frac{0.693}{K}$$



Elimination rate constant (K) is the speed at which drug eliminates from body.

$$slope = -K = \frac{lnC2 - lnC1}{t2 - t1}$$

$$slope = \frac{-K}{2.303} = \frac{logC2 - logC1}{t2 - t1}$$

$$logC = logC_\circ - \frac{Kt}{2.303}$$

Apparent volume of distribution (VD) is the measure of the extent of distribution of drug in compartment. It represents the hypothetical volume of body fluid into which a drug is dissolved or distributed.

Note that:(VD) is simply a proportionality constant whose sole purpose is to relate the plasma concentration (C) and the mass of a drug (A) in the body at a given time. It is not a physiological volume.

$$V_D = \frac{A_\circ}{C_\circ}$$

Clearance (Cl) is theoretical volume of body fluid containing drug from which the drug is completely removed in a given period of time.

$$Cl = KV_D$$

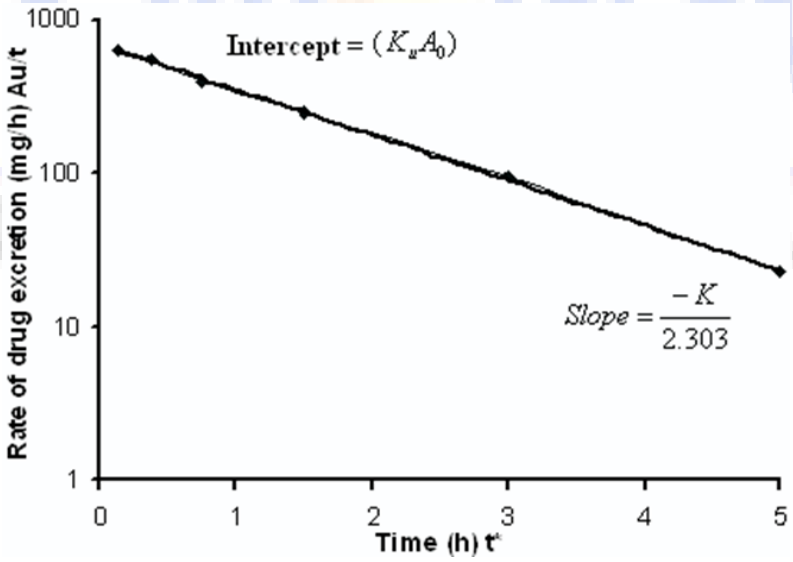
Calculation of K from urinary excretion data:

In this calculation the excretion rate of the drug is assumed to be first order.

$$\log \frac{dA_u}{dt} = \log(K_u A_\circ) - \frac{Kt^*}{2.303}$$

K_u is the excretion rate constant.

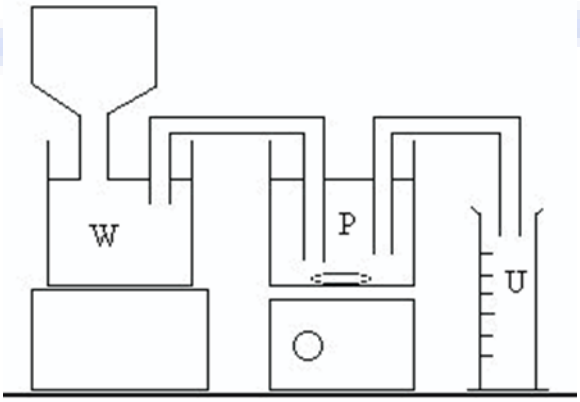
t^* is the average time between urine collection.



Experimental work:

By an arrangement of beakers and a constant head water reservoir, it is possible to simulate plasma concentrations and drug amounts in urine after IV bolus administration .

The constant flow of water through the system, causes a first order dilution of the marker, potassium permanganate.



The marker concentrations can be determined spectrophotometrically at 540 nm, by sampling the water from plasma compartment (P) and urine compartment (U) periodically.

The plasma concentration versus time is plotted on semi-log paper and the parameters; elimination rate constant, elimination half-life, plasma concentration at zero-time, volume of distribution, clearance and area under curve can be determined.

The rate of excretion versus time is plotted on semi-log paper and parameters; elimination rate constant, excretion rate constant and elimination half-life can be determined.

Prepare 100 µg/ml of potassium permanganate in distilled water. Further prepare 10 ml volumes of working solutions 10, 20, 40, 60, 80, and 100 µg/ml from the stock solution.

Measure the absorbance of each solution at 540 nm. Use distilled water as the blank. Plot calibration curve and determine slope and intercept.

Turn on the stirrer in the plasma beaker and adjust for gentle mixing. Establish water flow rate of 20 (15-25 is acceptable) ml/min.

Inject' the plasma beaker with the 'dose' of potassium permanganate (50mg dissolved in 1-2ml of water).

Collect plasma samples (5ml) at 2.5, 7.5, 12.5, 17.5, 22.5, 27.5, 32.5, 37.5, 45, and 55 minutes,

and urine samples at 5, 10, 15, 20, 25, 30, 35, 40, 50, and 60 minutes after the dose.

Arrange and label test-tubes to accommodate the samples.

At each time point for urine collection, replace the beaker with an empty beaker. Measure the volume collected, mix the contents of the beaker to obtain a uniform solution, and take 5ml sample for analysis.

Analyze each sample spectrophotometrically at 540 nm .

Note: early samples may need to be diluted to give absorbance readings below 1. Remember to apply this dilution factor in the analysis of the results.

Plot plasma concentration (C) versus time on semi-log graph paper. Calculate K from slope and $t_{1/2}$ from K. Calculate apparent volume of distribution by using C◦ and dose.

Plot rate of excretion $\left(\frac{dA_u}{dt}\right)$ **versus average time (t*) on semi log graph paper and calculate K.**

Construct a 'clearance' plot by plotting the rate of excretion $\left(\frac{dA_u}{dt}\right)$ **versus C (plasma concentration at the midpoint of the urine collection time). Measure the clearance as the slope of this line.**

Observations:

Calibration curve:

Concentration (µg/ml)	Absorbance
10	
20	
40	
60	
80	
100	
Slope	
Intercept	

Concentration of KMnO4 in plasma:

Time	Dilution factor	ABS	Conc.
2.5			
7.5			
12.5			
17.5			
22.5			
27.5			
32.5			
37.5			
45			
55			

Concentration of KMnO4 in urine:

Urinary Data								
Time Interval of urine collection	Time t	Time interval dt	Conc in Urine mg/ml	Volume of Urine collected (ml)	Amt of drug in urine ΔAu mg	Cumulative amount excreted Au (mg)	ΔAu/dt (mg/hr)	t* midpoint
0 5	5	5						2.5
5 - 10	10	5						7.5
10 - 15	15	5						12.5
15 - 20	20	5						27.5
20 - 25	25	5						22.5
25 - 30	30	5						27.5
30 - 35	35	5						32.5
35 - 40	40	5						37.5
40 - 50	50	10						45
50 - 60	60	10						55

Calculations:

Dilution factor = volume of diluted sample (ml)/ volume of sample removed (ml)

Sr. No.	Parameter	Plasma data	Urine data
1	Elimination half life ($t_{1/2}$)		
2	Elimination rate constant (K)		-
3	Excretion rate constant (K_u)	-	
3	Area under curve (AUC)		-
5	Volume of Distribution (V)		-
6	Clearance (Cl)		-

Exercise:

Plasma and urine data obtained after a bolus dose of 50mgof drug is given in following table:

Plasma data		Urine data		
Time (h)	Concentration (mg/l)	Time interval of collection (h)	Volume of urine (ml)	Concentration of unchanged drug in urine (mg/l)
1	2	0-2	120	133
3	1.13	2-4	180	50
5	0.70	4-6	89	63
7	0.43	6-8	340	10
10	0.20	8-12	178	18
18	0.025	12-24	950	2

Determine K, "t1/2", K_u, Cl, and VD.