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EDUCATIONAL STRATEGIES

UNDERSTANDING AND APPLICATION OF CLINICAL PHARMACOKINETIC PRINCIPLES: SINGLE-COMPARTMENT PHARMACOKINETIC SIMULATION MODEL

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To simplify the principles of pharmacokinetics, we designed a single-compartment model with certain assumptions. Objectives of designing this model were to understand the basic principles of pharmacokinetics, to represent graphically the typical natural log concentration versus time curve for single-compartment model after (intravenous) dose, and to understand how to calculate the elimination half-life using graphical log concentration versus time curve as well as using a mathematical method.

INTRODUCTION

In clinical practice, pharmacokinetic principles are used to characterize the relationships between drug dosage regimens and drug concentration versus time profiles. Attainment of the correct dosage regimen is of fundamental importance: low doses are likely to be ineffective, whereas excessive doses are likely to produce toxic effects.

The pharmacokinetic phase covers relationship between the drug intake, which comprises adjustable factors such as dose, dosage form, frequency, route of administration, and the concentration achieved with time. In simple terms, it may be viewed as what body does to drug.

To simplify the principles of pharmacokinetics, we designed this single-compartment model with certain assumptions. In a single-compartment model

- drug enters the central compartment (or single compartment) from outside;
- drug then leaves the central compartment that is analogous to the drug leaving the body; and
- drug does not recirculate.

The single-compartment model considers the entire body, all of the organs and tissues are considered to be one compartment.

Objective of this model are:

1. To understand the basic principles of pharmacokinetics such as volume of distribution (V_d), clearance (CL), and plasma half-life ($t_{1/2}$).
2. To represent graphically the typical natural log concentration versus time curve after (intravenous) dose.
3. To understand how to calculate elimination half-life using graphical log concentration versus time as well as by using mathematical method.

MATERIALS AND METHODS

Materials

Marriott's bottle (reservoir), a 1-L container with outlet, $KMnO_4$, spectrophotometer, electric magnetic stirrer, iron pins, infusion set, and test tubes were used during the experiment.

Methods

A 1-L container with an outlet fitted at upper portion is kept on a platform of a magnetic stirrer and is completely filled with water. Few iron pins are kept inside the container, which stirs with magnet and mixes the drug ($KMnO_4$) uniformly. Marriott's bottle, which acts as reservoir, is filled with water and is kept 3 feet above the container. An outflow of water to the container is adjusted at a low rate. The water is filled

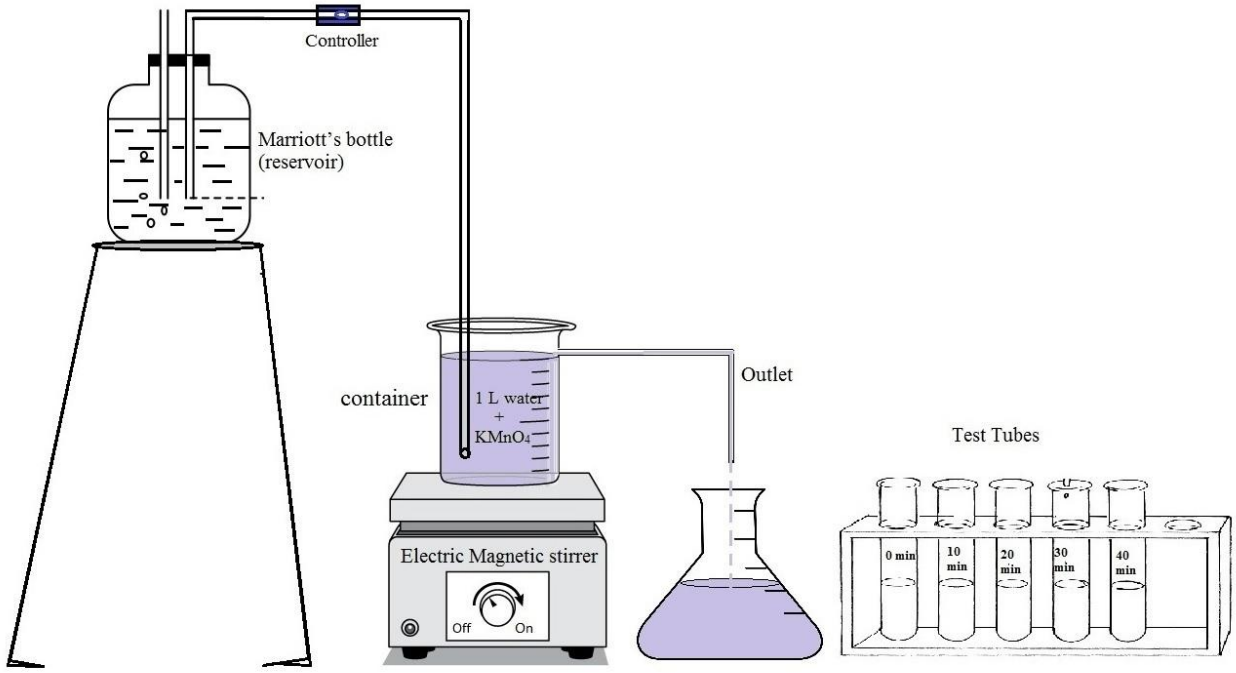

Figure 1: Assembly of single-compartment pharmacokinetic model

in the container and extra water flows out through the outlet. Obviously, outflow from the container will be equal to the inflow from the reservoir. The volume of water in the container remains same throughout the experiment.

Now, 100 mg $KMnO_4$ is added to the container. After dissolving the same, a sample is collected from the outlet of container to measure the concentration of $KMnO_4$ at 0 min. Subsequently, infusion of water from Marriott's bottle is started. Samples from the outlet of container are collected every 10 min for the next 90 min. To measure the concentration of $KMnO_4$ in a given sample, concept of spectrophotometer and optical density (OD), as applied in biochemistry, is used. Concentrations of $KMnO_4$ in these samples are measured. The time course of $KMnO_4$ concentration in the container is plotted on a graph, which shows area under curve (AUC). As total $KMnO_4$ added, initial concentration, and concentration at different time points are known, a standard graph is plotted using known serial dilutions of $KMnO_4$ and its OD. This graph is then used to obtain concentration of $KMnO_4$ from the measured OD of the sample.

RESULTS

Serial dilutions of $KMnO_4$ are prepared and their OD was recorded on spectrophotometer. Standard graph of OD versus $KMnO_4$ concentrations is plotted. This graph serves to identify unknown concentration of $KMnO_4$ from known OD.

Table 1: Optical density of the serial dilution of $KMnO_4$

Optical Density (OD)	1.101	0.525	0.258	0.130	0.070	0.030	0.006
Conc. of $KMnO_4$ (µg/ml)	100	50	25	12.5	6.25	3.125	1.56

Table 2: Optical density of sample collected at every 10 min and concentration of $KMnO_4$ obtained using standard graph

Time (min)	OD	Concentration of $KMnO_4$ (µg/ml)	Log conc. $KMnO_4$
0	1.101	100	2
10	0.824	75	1.91
20	0.586	54	1.74
30	0.390	38	1.56
40	0.270	28	1.39
50	0.193	21	1.19
60	0.111	12.5	0.95
70	0.067	10.5	0.71
80	0.050	8.5	0.65
90	0.040	7.5	0.54

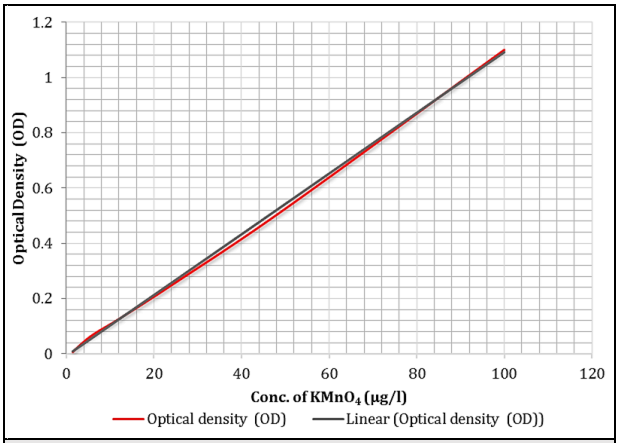

Figure 2: Standard graph: OD vs. concentration of $KMnO_4$ (µg/ml)

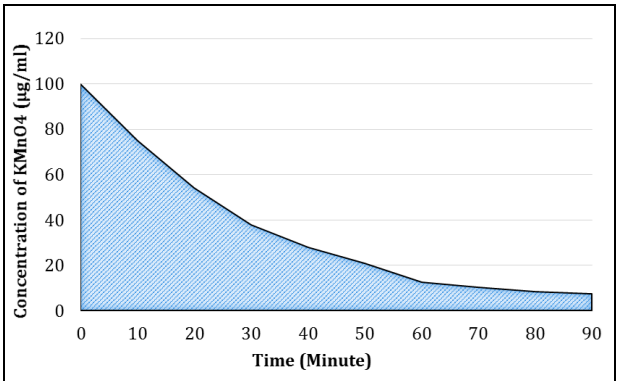

Figure 3: $KMnO_4$ concentration vs. time, showing AUC

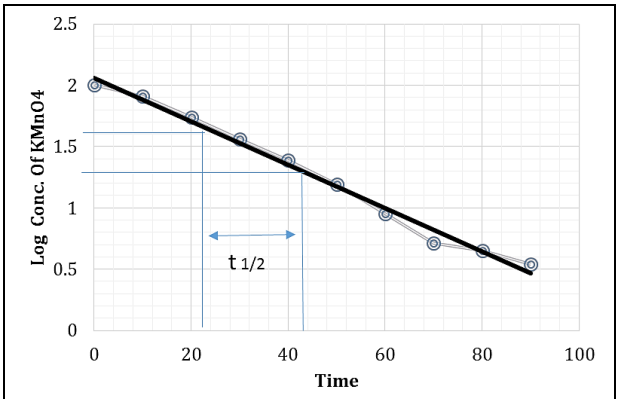

Figure 4: Log concentration of $KMnO_4$ vs. time. A typical straight line is seen in log concentration vs. time plot

$KMnO_4$ concentration versus time graph shows concentrations of $KMnO_4$ at different time points. This graph is similar to AUC of intravenously administered drug. This graph gives AUC of $KMnO_4$.

DISCUSSION

Volume of Distribution

Container represent the single compartment, contains 1 L water throughout experiment. So V_d in present situation is 1 L. A volume of 100 mg $KMnO_4$ (coloring dye as a drug) is added to the single compartment. So, initial concentration of $KMnO_4$ is 100 µg/ml. Constant quantity of fluid is added at slow rate from Marriott's bottle into the compartment. Peculiarity of this bottle is that irrespective of fluid level inside, water flows out at a constant rate. Magnetic stirrer mixes fluid uniformly and extra fluid flows out via outlet. Inflow and outflow remain equal.

Clearance

Experiment follows first-order kinetics, as elimination rate (outflow from single compartment) is constant and constant amount of fluid is entering container.

CL = Dose/AUC.

Dose is 100 mg, as 100 mg $KMnO_4$ is added. AUC is calculated from concentration versus time curve.

AUC in this case is 3050 µg/ml·min

So, CL = 100/3050 = 32.78 ml/min

Plasma Half-life

Any point on *Y* axis of log concentration versus time plot provides concentration at particular time. Time interval between the two points on graph where concentration become half is half-life and is evaluated by graphical method. In this experiment it is 20 min, as seen in Figure 4. Mathematically, $t_{1/2}$ is calculated using CL and V_d.

$$t_{1/2} = \frac{0.693 \times V_d}{CL} = \frac{0.693 \times 1000}{32.78} = 21.14 \text{ min}$$

Both graphical and mathematically calculated $t_{1/2}$ is approximately equal.

As mentioned earlier, the aim of the experiment was to simplify principles of pharmacokinetics with single-compartment simulation model. For better understanding of volume of distribution (V_d), clearance (CL), and plasma half-life ($t_{1/2}$), this model serves the purpose.[1–3]

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