TWO-COMPARTMENT PHARMACOKINETIC MODELS
for Chemical Engineers

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The absorption, distribution, metabolism, and excretion (ADME) of a drug, after single or multiple administrations, are usually represented by compartmental pharmacokinetic models. These compartments correspond to tissues and organs in the human body. The analysis of these processes can be very complex, as in the case of physiologically based pharmacokinetics (PBPK), where information on the weights, blood flows, and physicochemical and biochemical properties of a compound is necessary to describe concentration profiles in the tissues (*i.e.*, lung, brain, and kidney).[1] Although, in theory, a multi-compartment approach is better suited to describe the dynamics of most drugs in the body, clinicians prefer the simplicity of a one-compartment model[2] to predict the plasma drug concentrations and to design appropriate dosage regimens.

In a one-compartment model, the blood and surrounding tissues are lumped into a single process unit. As soon as the active pharmaceutical ingredient (API) enters this compartment, it is uniformly distributed throughout the body.[2] The mathematical representation of these systems involves a drug injection inlet stream, a constant-volume central compartment, and a clearance term. A series of experiments, inspired by this model, were designed to introduce chemical engineering students to pharmacokinetics and to stimulate their interest in research related to drug delivery.[3] Continuous intravenous (i.v.) infusion and i.v. bolus (single and multiple) administrations were illustrated with activities consisting mostly of a dye placed in a mixing vessel.

This contribution focuses on the applications of a two-compartment model for describing drug pharmacokinetics. Although the error in developing dosing regimens based on

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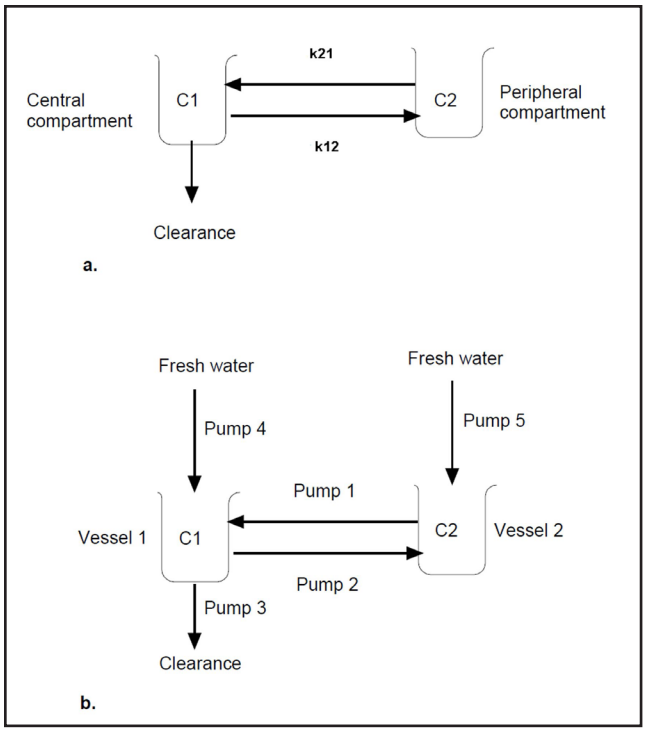

Figure 1. *Representation of a two-compartment model. Figure 1a is a schematic model of the process as introduced in a course in pharmacokinetics; Figure 1b is the two-unit process that is assembled to mimic the behavior of the two-compartment model.*

a single-compartment model is acceptable for most drugs, equations for two-compartment kinetics are more appropriate for a few pharmaceutical agents that are potent and/or exhibit a narrow therapeutic range.[3] Experiments, based on concepts learned in chemical engineering classes, are developed to introduce students to these processes. The learning outcomes of this project are to: i) illustrate a two-compartment pharmacokinetic model using continuous-stirred vessels, ii) derive total mass and component balances for the two compartments, iii) solve the derived differential equations using Laplace transform methodologies, iv) calculate the pharmacokinetic parameters, and v) conduct experiments to simulate a single i.v. bolus administration.

LABORATORY DESCRIPTION

Theoretical Foundation

The schematic of a two-compartment model is shown in Figure 1a. According to this representation, the human body is comprised of a central compartment consisting of the blood/plasma and well-perfused tissues (*e.g.*, liver, heart), and a peripheral compartment mainly composed of poorly perfused tissues (*e.g.*, skeletal muscles). Analysis of a blood sample would reveal the concentration in the first compartment. This measurement may be used by the physician to assess the effectiveness of a drug-dosage regimen.

Component balances in the two compartments (Figure 1a) yield:

$$\frac{d\left(C_1V_1\right)}{dt} = -k_{el}C_1V_1 - k_{12}C_1V_1 + k_{21}C_2V_2 \qquad (1)$$

and

$$\frac{d\left(C_2V_2\right)}{dt} = k_{12}C_1V_1 - k_{21}C_2V_2, \qquad (2)$$

where C is the drug concentration, V is the volume, and k is a mass transfer rate constant. The subscripts 1 and 2 represent the central and peripheral compartments, respectively. Drug elimination is shown by the subscript el. In addition, the subscript 12 denotes a transfer from compartment 1 to compartment 2 while drug transfer in the opposite direction is shown by 21. The parameter k_{el} is a first-order elimination rate constant, which is often used to represent clearance. It should be noted that more complex expressions (*e.g.*, Michaelis-Menten kinetics) are often appropriate for certain drugs. Since the volumes are constant, Eqs. (1) and (2) can be written as:[4]

$$\frac{d\left(C_1\right)}{dt} = -k_{el}C_1 - k_{12}C_1 + k_{21}\zeta_{21}C_2 \qquad (3)$$

and

$$\zeta_{21}\frac{d\left(C_2\right)}{dt} = k_{12}C_1 - k_{21}\zeta_{21}C_2 \qquad (4)$$

with $\zeta_{21} = \frac{V_2}{V_1}$.

Figure 1b. corresponds to the flowchart of a two-unit process designed to mimic the behavior of a two-compartment model. Several pumps are required to manipulate the flow rates. Fresh water streams are also added to the vessels. At this point, students may be asked to show that component balances around the units lead to the system described by Eqs. (3) and (4) (*objectives i and ii*). A total mass balance around vessels 1 and 2 yields:

$$\frac{d\left(\rho_1V_1\right)}{dt} = F_{w1}\rho_{w1} + F_{21}\rho_2 - F_{el}\rho_1 - F_{12}\rho_1 \qquad (5)$$

and

$$\frac{d\left(\rho_2V_2\right)}{dt} = F_{w2}\rho_{w2} + F_{12}\rho_1 - F_{21}\rho_2, \qquad (6)$$

respectively. The subscripts w1 and w2 indicate the fresh water streams into vessels 1 and 2. Assuming equal and constant densities, we have $\rho_1 = \rho_2 = \rho_{w1} = \rho_{w2}$. The relationships:

$$F_{el} + F_{12} = F_{w1} + F_{21} \qquad (7)$$

and

$$F_{21} = F_{w2} + F_{12} \qquad (8)$$

hold in order to maintain constant volumes in both tanks. In addition, potassium permanganate balances around the two units yield:

$$\frac{d\left(C_1V_1\right)}{dt} = F_{21}C_2 - F_{el}C_1 - F_{12}C_1 \quad (9)$$

and

$$\frac{d\left(C_2V_2\right)}{dt} = F_{12}C_1 - F_{21}C_2. \quad (10)$$

Dividing Eqs. (9) and (10) by V_1 results in Eqs. (3) and (4) with $k_{12} = \frac{F_{12}}{V_1}$, $k_{21} = \frac{F_{21}}{V_2}$, $k_{el} = \frac{F_{el}}{V_1}$, $\zeta_{21} = \frac{V_2}{V_1}$.

The experiments are conducted with V_1=V_2. As a result, Eqs. (3) and (4) become:

$$\frac{d\left(C_1\right)}{dt} = -k_{el}C_1 - k_{12}C_1 + k_{21}C_2 \quad (11)$$

and

$$\frac{d\left(C_2\right)}{dt} = k_{12}C_1 - k_{21}C_2 \quad (12)$$

The initial conditions are $C_1(0) = C_{10}$ and $C_2(0) = 0$ for a bolus injection. Using the Laplace transforms of the concentrations $C_1(t)$ and $C_2(t)$ (*i.e.*, $L\left\{C_1\left(t\right)\right\} = \bar{C}_1\left(s\right) = \int_0^\infty C_1\left(t\right)e^{-st}dt$ and $L\left\{C_2\left(t\right)\right\} = \bar{C}_2\left(s\right) = \int_0^\infty C_2\left(t\right)e^{-st}dt$) and applying the Laplace operator to both sides of Eqs. (11) and (12), the following equations are obtained:

$$s\bar{C}_1 - C_{10} = -\left(k_{12} + k_{el}\right)\bar{C}_1 + k_{21}\bar{C}_2 \quad (13)$$

and

$$s\bar{C}_2 = k_{12}\bar{C}_1 - k_{21}\bar{C}_2 \quad (14)$$

The system formed by Eqs. (13) and (14) is solved to give:

$$\bar{C}_1 = \frac{\left(s + k_{21}\right)C_{10}}{\left(s^2 + \left(k_{12} + k_{21} + k_{el}\right)s + k_{el}k_{21}\right)} \quad (15)$$

and

$$\bar{C}_2 = \frac{k_{12}C_{10}}{\left(s^2 + \left(k_{12} + k_{21} + k_{el}\right)s + k_{el}k_{21}\right)} \quad (16)$$

Partial-fraction expansion, or the residue theorem, may be used to invert the $\bar{C}_1$ and $\bar{C}_2$ (*objective iii*). Students are also encouraged to apply Laplace transform initial and final value theorems to verify the correctness of Eqs. (15) and (16).

Although the satisfaction of the initial conditions, $C_1(0) = C_{10}$ and $C_2(0) = 0$, is not sufficient to guarantee the accuracy of Eqs. (15) and (16), these equalities are necessary conditions. In addition, showing that $C_1\left(t \to \infty\right) = C_2\left(t \to \infty\right) = 0$ may lead to a discussion on the necessity for administering multiple bolus i.v. doses.

$$C_1\left(t\right) = \frac{\left(\lambda^+ + k_{21}\right)C_{10}}{\left(\lambda^+ - \lambda^-\right)}e^{\lambda^+ t} - \frac{\left(\lambda^- + k_{21}\right)C_{10}}{\left(\lambda^+ - \lambda^-\right)}e^{\lambda^- t} \quad (17)$$

and

$$C_2\left(t\right) = \frac{k_{12}C_{10}}{\left(\lambda^+ - \lambda^-\right)}e^{\lambda^+ t} - \frac{k_{12}C_{10}}{\left(\lambda^+ - \lambda^-\right)}e^{\lambda^- t} \quad (18)$$

with

$$\lambda^+ = \frac{-\left(k_{12} + k_{21} + k_{el}\right) + \sqrt{\left(k_{12} + k_{21} + k_{el}\right)^2 - 4k_{el}k_{21}}}{2} \quad (19)$$

and

$$\lambda^- = \frac{-\left(k_{12} + k_{21} + k_{el}\right) - \sqrt{\left(k_{12} + k_{21} + k_{el}\right)^2 - 4k_{el}k_{21}}}{2} \quad (20)$$

Given concentration data in the central compartment (or vessel 1), Eq. (17) can be applied to estimate k_{12}, k_{21}, and k_{el} (*objective iv*). Students may be given the opportunity to choose among three methods to compute these parameters:

1) Measurement of the flow rates: the pharmacokinetics are calculated using $k_{12} = \frac{F_{12}}{V_1}$, $k_{21} = \frac{F_{21}}{V_2}$, and $k_{el} = \frac{F_{el}}{V_1}$.
2) Regression of Eq. (17) to experimental $C_1(t)$ data: Eq. (17) is written in the form $C_1\left(t\right) = Ae^{-\alpha t} + Be^{-\beta t}$ with $\alpha > \beta$. Computational software packages such as Mathematica® (Wolfram Research, Inc., IL) or Matlab® (The MathWorks, Inc., MA) can be adopted to estimate A, B, α, and β. Algebraic manipulations show that $k_{21} = \frac{A\beta + B\alpha}{A + B}$, $k_{el} = \frac{\alpha\beta}{k_{21}}$ and $k_{12} = \alpha + \beta - k_{21} - k_{el}$.
3) Methods of residuals[5]: Data collected at long times are fitted to the equation $C_{1l}(t) = Be^{-\beta t}$ because $\alpha > \beta$. Parameters B and β are obtained from $\ln[C_{1l}(t)] = \ln(B) - \beta t$. The variable C_{1l} represents the concentration at a sufficiently long time. Similarly, data gathered at short times are fitted to $C_{1s}(t) - Be^{-\beta t} = Ae^{-\alpha t}$ where C_{1s} stands for the concentration a short time after the bolus injection. Parameters A and α are estimated from $\ln[C_{1s}(t) - Be^{-\beta t}] = \ln(A) - \alpha t$.

Any of the methodologies described above is implemented to study the influences of pharmacokinetic parameters on C_1 and C_2.

Materials and Experimental Procedure

Except for the increased number of pumps, the same materials required in the study of the one-compartment experiments[3] are used in this project (Figure 2) (*objective v*): variable flow-rate pumps, beakers, stopwatch, graduated cylinders, pipettes, rubber tubing, magnetic stirrer, magnetic bars, potassium permanganate, spectrophotometer, cuvettes, laboratory stands, and clamps. An i.v. bolus of 1.37 g of potassium permanganate was administered to the central compartment. Samples were collected every 15 minutes for both the central and the peripheral compartments and analyzed with a spectrophotometer set at 530 nm. A calibration curve was developed to relate the concentration with the absorbance reading: $y = 0.016 \times A$ where y represented the concentration in g/mL and A the absorbance. The volume of each vessel was maintained at 200 mL.

Results and Discussions

The data for the i.v. bolus administration are shown in Figure 3. Pharmacokinetic parameters determined from the three methods are $k_{12} = 1.80\ hr^{-1}$, $k_{21} = 2.94\ hr^{-1}$, and $k_{el} = 0.30\ hr^{-1}$ (measurement of the flow rates); $k_{12} = 1.42\ hr^{-1}$, $k_{21} = 2.37\ hr^{-1}$, and $k_{el} = 0.26\ hr^{-1}$ (regression in Mathematica®); $k_{12} = 1.80\ hr^{-1}$, $k_{21} = 2.92\ hr^{-1}$, and $k_{el} = 0.27\ hr^{-1}$(methods of residuals). The predicted concentrations plotted are the ones derived by the third method. Students may be given a project where they are expected to investigate the effects of the kinetic parameters on C_1 and C_2 to understand how drug transport is influenced by the distribution and elimination rate constants. This research also offers the opportunity to address the effects of the dose size on the plasma blood concentration. Multiple bolus-injections and constant-rate infusions can also be studied after a slight modification of the model and initial conditions.

The choice of one compartment or two compartments may be an important factor when designing appropriate drug-dosing regimens. To illustrate this point, three bolus injections of 1.10 g, 0.33 g, and 0.33 g of potassium permanganate were added to the central compartment at 0, 1.12, and 3.36 hours, respectively, as recommended by the results of an optimal dosing regimen for $KMnO_4$ (Figure 4). The optimization code, based on a two-compartment model and written in the Mathematica® environment, minimized the sum of squared errors between the concentrations in the central compartment and a desired $KMnO_4$ level of 3.46 g/L for an experimental duration of 5.75 hours. The following observations can be made: i) The predicted and experimental data agree very well and ii) the calculated doses were able to maintain the $KMnO_4$ concentration around 3.46 g/L. Simulations conducted under the assumption that $KMnO_4$ obeys one-compartment pharmacokinetics show that the predicted data deviate considerably from the true profile (Figure 4).

SUMMARY OF EXPERIENCES

A group of six students from an undergraduate course in biotransport worked on this project. The three-credit class is designed for biomedical engineering students pursuing tracks in biomaterials and tissue engineering or biomechanics.[3] Chemical engineering students may also select the course as an elective toward their degree requirements. A final report was produced after several meetings with the instructor during which the project was discussed. Although a graduate assistant helped design the experimental setup (Figure 2) because of time limitation, the group was required to draw a schematic diagram of the process similar to Figure 1b. The specific assignment was to study the effects of loading doses on the concentrations in the central and peripheral compartments. In addition to providing a background of the subject, the students were also responsible for deriving the model equations and estimating the kinetic parameters. They were not told about the methods that could be applied to determine

Figure 2. *The experimental setup of the two-compartment model. Potassium permanganate was added to the beakers. Fresh water in an Erlenmeyer flask was introduced to the two compartments.*

these parameters; the kinetic values were estimated from measurement of the flow rates. The results were also presented to the class and sources of errors, such as flow fluctuations, were identified.

CONCLUSIONS

Experiments in continuous-stirred vessels were designed to represent drug transport within the body. The processes governing equations were similar to those of a two-compartment model with linear first-order distribution and elimination kinetics. These activities gave students the opportunity to apply conservation principles learned in the classroom. In addition, Laplace transform techniques were implemented to solve the differential equations. Closed-formed expressions for the concentration of potassium permanganate in the central and peripheral compartment were obtained. Three methods of extracting the pharmacokinetic parameters based on experimental data were outlined. After administering an i.v. bolus of 1.37 g of potassium permanganate to the central vessel, the concentration profiles showed a pattern analogous to drug transport when a two-compartment model is used. The three parameter estimation methods yield comparable results. Students who worked on the project were able to model the process, solve the governing differential equations, and estimate the kinetics.

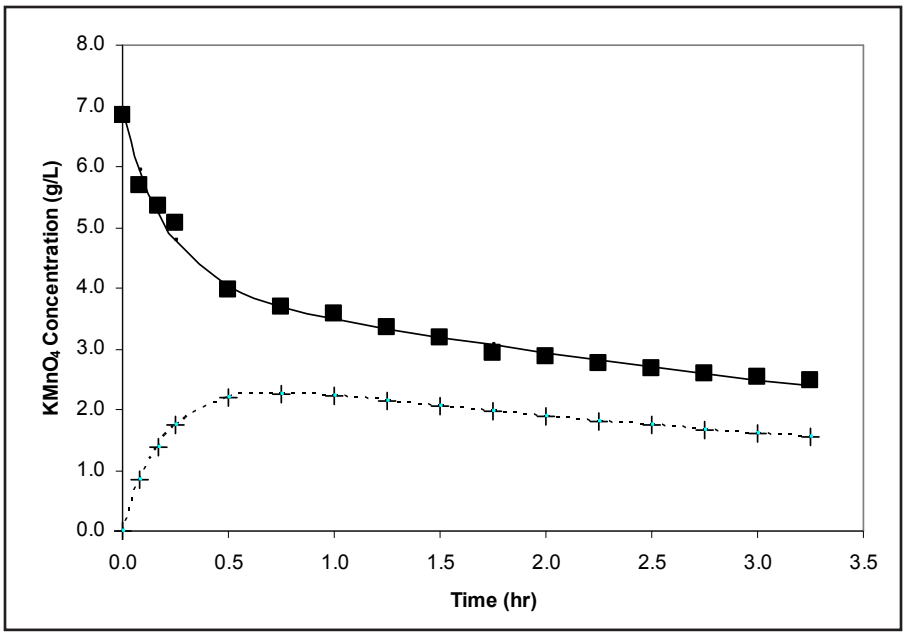

Figure 3. *Concentrations of $KMnO_4$ in the central (■) and peripheral (+) compartments. The parameters obtained by the method of residuals are k_{12} = 1.80 hr^{-1}, k_{21} = 2.92 hr^{-1}, and k_{el} = 0.27 hr^{-1}. Predicted concentrations in vessels 1 and 2 are shown by the symbols (—) and (-----), respectively.*

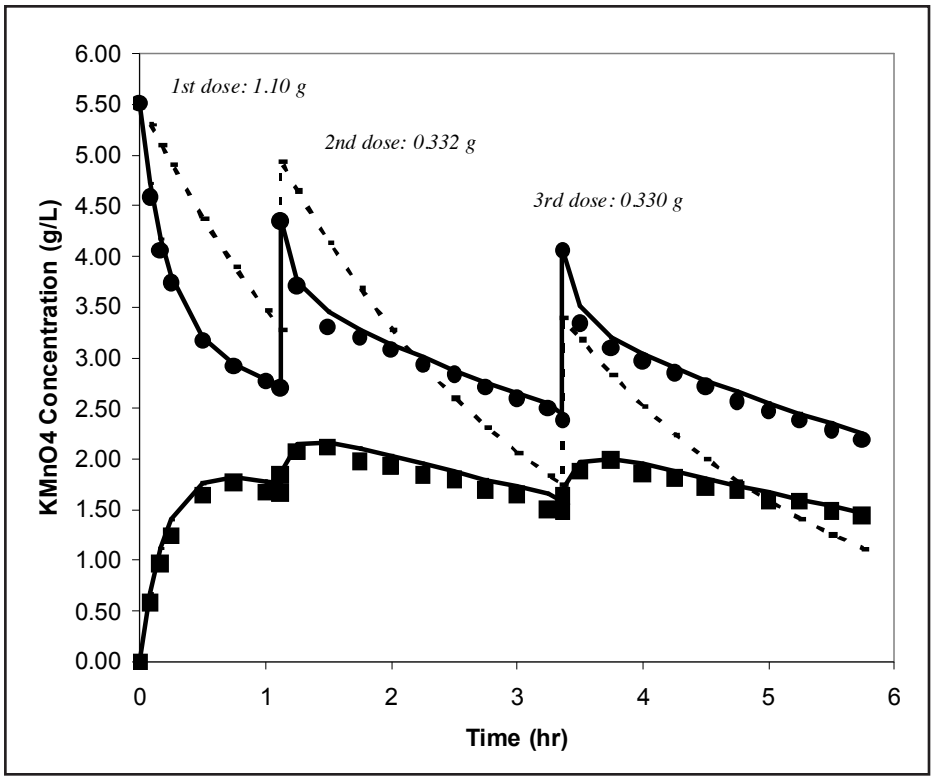

Figure 4. *Experimental concentrations of $KMnO_4$ in the central (●) and peripheral compartments (■). The predicted data are represented by the solid lines (____). The rate constants for the two-compartment model are k_{12} = 1.80 hr^{-1}, k_{21} = 2.92 hr^{-1}, and k_{el} = 0.27 hr^{-1}. The elimination rate constant for the one-compartment model (dashed line: -------) is k_{el} = 0.41 hr^{-1}.*

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