# DRUG TRANSPORT AND PHARMACOKINETICS
## *For Chemical Engineers*

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The design and synthesis of a pharmaceutical agent that is able to induce the desired biological effect is a research area that requires expertise outside a regular undergraduate chemical engineering curriculum (*i.e.*, structures and functions of cells, protein, and receptors). Although concepts such as intermolecular forces would sound familiar to a chemical engineering student, a lack of basic understanding of signal transduction pathways would render the task of identifying suitable drug targets insurmountable. Drug delivery using compartmental models, however, is a more accessible option for ChE students with ample training in transport phenomena and especially in solving material balance problems involving single- and multiple-process units. Such perspective is indispensable for a sound understanding of pharmacokinetics, which focuses on drug absorption, distribution, metabolism, and excretion (ADME). In addition to binding properly to receptors and provoking a response, an active pharmaceutical ingredient (API) must be able to reach the target site in sufficient amount.[1] Knowledge of pharmacokinetics is therefore critical in drug discovery and development. For example, the rate of metabolism influences the bioavailability and clearance in humans and preclinical species.[2] This information, combined with the recognition of the enzymes that mediate the metabolism of the specific drug, is paramount at a very early stage in the discovery process. The present work describes a series of laboratory experiments, based on principles of chemical processes, to address questions of clinical relevance. Projects that draw analogies between the approach taken to understand the fate of drugs in the body and the methodology adopted to track materials through an entire chemical plant may offer new insights and opportunities to ChE students.

Engineering educators have already stressed the need to prepare a workforce with knowledge in drug delivery. Several experiments are made available to help students effectively apply principles of chemical engineering fundamentals (*e.g.*, chemical kinetics, mass transfer) to the study of factors influencing drug release from several delivery devices.[3] Cavanagh

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and Wagner[4] introduced to engineering students hands-on projects in drug delivery to illustrate flow and pressure through an experimental model of the circulatory system and the concept of drug dissolution. The learning objectives of this contribution are to assist students in i) applying knowledge of mass balances to the design of experiments focusing on the transport of medicaments in the body (*learning objective 1*), and ii) developing a knowledge of multiple IV doses and continuous IV infusion through well-stirred vessel experiments (*learning objective 2*).

The integration of laboratory activities into the study of drug transport and delivery can be beneficial for students majoring in chemical engineering as well as for biomedical engineering undergraduates. A fitting example is a Biotransport course (ChE427/BME427) taught at the New Jersey Institute of Technology. This three-credit class is mandatory for biomedical engineering students pursuing tracks in biomaterials and tissue engineering or biomechanics and is an elective for chemical engineering students. Concepts of transport phenomena, as applied to biological systems, are presented. Examples of topics covered are: body fluids, transcellular solute transport, basics of vectors and tensors, conservation relations, and momentum balances. During the semester, students are expected to develop and present simulation-based projects ranging from pharmacokinetic analysis to hemodialysis. Discussions of the results reveal knowledge of the physics as well as a firm grasp of real-life implications of several design alternatives and treatment regimens.

## LABORATORY DESCRIPTION

### *One-Compartment Model and Multiple IV Dosing Regimens*

The one-compartment model offers the simplest way to describe the kinetics of drug absorption and elimination in the body. Based on this representation, the body behaves like a well-stirred vessel (Figure 1).

After a rapid intravenous injection (IV Bolus), the pharmaceutic distributes to rapidly perfused tissues[5] and reaches the systemic circulation instantaneously. In addition, clearance commences immediately after the injection. A mass balance around the process in Figure 1 yields the following differential equation (*learning objective 1*):[5]

$$\frac{dVC_p}{dt} = D\delta(t) - k_{el}VC_p,\ C_p(0) = 0 \tag{1}$$

or

$$\frac{dVC_p}{dt} = -k_{el}VC_p,\ C_p(0) = C_p^0 \tag{2}$$

where D is the loading dose, V is the distribution volume, $k_{el}$ is the first-order elimination rate constant, $C_p$ is the plasma drug concentration at time t, and $\delta(t)$ is the Dirac delta function. The integration Eq. (2) gives:

$$C_p = C_p^0 e^{-k_{el}\times t}. \tag{3}$$

The elimination rate constant can be computed by measuring the slope of the straight line:

$$\ln(C_p) = \ln(C_p^0) - k_{el}\times t. \tag{4}$$

It can be shown that the time required for the plasma drug to drop to one-half of its initial value is:

$$t_{1/2} = \frac{0.693}{k_{el}}. \tag{5}$$

After a single-dose administration, the plasma drug level immediately rises above a minimum effective concentration. If a second dose is not taken at a specific time, however, the medicament may not produce any benefit as the plasma concentration drops well below the therapeutic level. Such a situation can be circumvented by prescribing a multiple-dosing regimen to the patient. This method of administration is not without its own challenge because the impact of each dose on $C_p$ has to be known *a priori* to achieve optimal clinical effectiveness and to minimize deleterious effects. Experiments were conducted to help chemical engineering students understand the influences of key parameters, such as the size of the dose, the administration time, and the elimination time constant on the plasma drug concentration.

Eq. (3) is used to calculate the plasma concentration at the end of the first dosing interval $\tau$:

$$C_{pl}^r = C_p^0 e^{-k_{el}\times\tau} \tag{6}$$

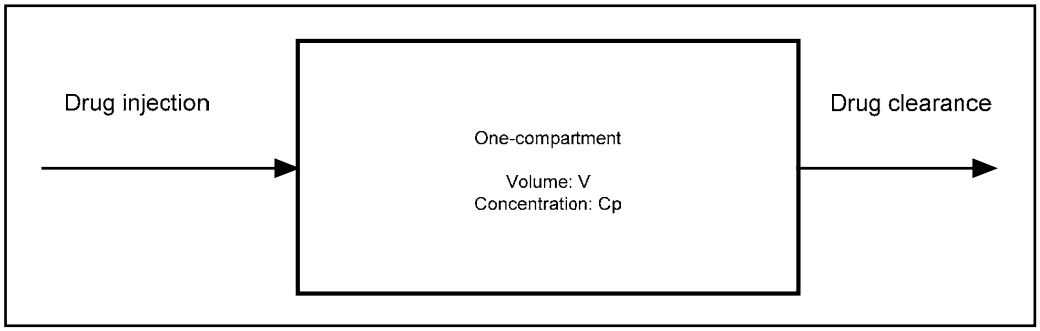


***Figure 1.*** *Representation of a one-compartment model.*

where $C_p^0$ is the loading dose. It can be shown that the concentration within the nth interval is:[1]

$$C_{pn}(t) = C_p^0 \left( \frac{1 - e^{-n \times k_{el} \times \tau}}{1 - e^{-k_{el} \times \tau}} \right) e^{-k_{el} \times t}. \quad (7)$$

At steady-state (*i.e.*, $n \to \infty$), the minimum and maximum $C_p$ values are:

$$C_{p\,min\,ss} = C_p^0 \left( \frac{1}{1 - e^{-k_{el} \times \tau}} \right) e^{-k_{el} \times \tau}. \quad (8)$$

and

$$C_{p\,max\,ss} = C_p^0 \left( \frac{1}{1 - e^{-k_{el} \times \tau}} \right), \quad (9)$$

respectively. The principle of superposition assumes that early doses of the medicament do not influence the pharmacokinetics of the subsequent doses.

### Materials and Experimental Procedure

The materials used in the experiments were: variable flow-rate pumps, 250-mL, 200-mL, and 4-L beakers, stopwatch, 10-mL graduate cylinders, pipettes, rubber tubes, magnetic stirrer, magnetic bars, potassium permanganate, spectrophotometer, cuvettes, laboratory stands, and clamps. The apparatus is shown in Figure 2. The beaker with the $KMnO_4$ solution was placed on a magnetic stirrer. A pump was used to mimic drug clearance from the body (*i.e.*, waste pump). Water was introduced at a rate similar to that of the waste pump in order to maintain a constant volume of liquid in the central compartment. The rubber tubes were fastened firmly with clamps (Figure 2).

Two main parameters were adjusted in developing a dosage regime: the size of the dose and the administration frequency. The study demonstrated why the drug strength and dosing interval are important for treatment. After initially adding 10 ml of $KMnO_4$ to the beaker, a new dose was added every 30 or 45 seconds. Samples were collected at regular 15-second intervals and analyzed with the spectrophotometer. The dose sizes were 0.0003657 g/mL and 0.000547 g/mL. In general, the ease with which samples are collected and the objective of a particular study determine the sampling interval. In this investigation, it was necessary to collect samples at a relatively fast rate to obtain a full picture of the system dynamics because of the short duration of each experiment. For the multiple IV bolus study, a new dose was added every 45 seconds. As a result, a sampling period of 15 seconds would allow a student to record the concentration before and after the addition of a new dose. A sample size of 1.3 mL was selected so that a constant volume was maintained in a 200/250 mL beaker. A larger dose would violate the constant volume assumption made in deriving the equations and, therefore, affect the analyses. The stirring rate was set sufficiently high to allow mixing to occur and low enough so that the formation of eddies did not influence the elimination rate causing inaccurate results.

### Results and Discussions

In practice, each drug has a therapeutic range in the human body. A medicament administered should not exceed the minimum toxic concentration (MTC) or fall below the minimum effective concentration (MEC). The maximum and minimum plasma concentrations should be kept within this window. Figure 3 shows that the dose strengths have a strong impact on $C_{p\,min\,ss}$ and $C_{p\,max\,ss}$ (*learning objective 2*). As a laboratory project, students can be asked to design drug-dosage regimens based on information regarding $C_{p\,min\,ss}$ and $C_{p\,max\,ss}$. Other hands-on activities may focus on investigating whether the number of doses required to reach a steady state is a function the dose size. Other worthwhile pursuits are to use

***Figure 2.*** *The experimental setup.*

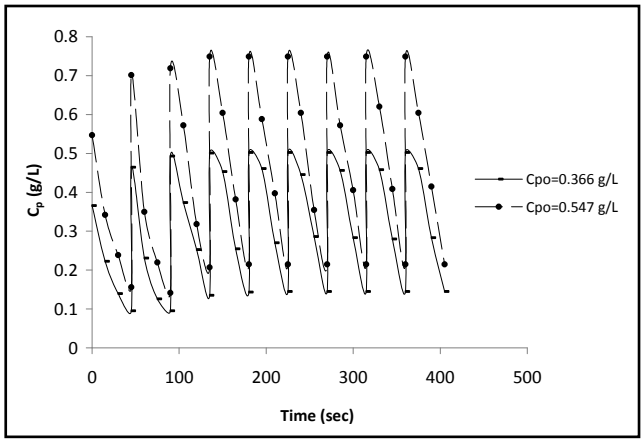


***Figure 3.*** *Concentration of $KMnO_4$ in the central compartment using nine IV boluses and two separate drug sizes: $k_{el}$ = 0.028 sec$^{-1}$, and $\tau$ = 45 sec, $C_p^0$ = 0.366 g/L (regimen 1) and $C_p^0$ = 0.547 g/L (regimen 2).*

the governing equations to predict the experimental profiles or to comment on the effect of drug clearance on the fate of the drug in the body.

### *Bolus Doses Followed By a Constant-Rate Infusion*

Drugs are administered intravenously in the form of a bolus dose or infused relatively slowly through a vein into the plasma at a constant or zero-order rate. One of the main advantages of an IV infusion is that an effective constant plasma drug concentration can be achieved, thereby eliminating the fluctuations observed in bolus IV dosing. Also, since the injected bolus dose takes 5 to 15 minutes to be completely diluted in the bloodstream,[1] a slow infusion is preferred, in some cases, to prevent an adverse effect caused by a high plasma drug concentration.

Eq. (1) is modified to account for the constant rate of infusion ($k_0$ in unit of mass/time) (*learning objective 1*):

$$\frac{dVC_p}{dt} = k_0 - k_{el} V C_p \tag{10}$$

For a constant volume and $C_p(0)=0$, the solution is:

$$C_p(t) = \frac{k_0}{k_{el} V}\left(1 - e^{-k_{el} \times t}\right). \tag{11}$$

The steady-state concentration:

$$C_{pss} = \frac{k_0}{k_{el} V} \tag{12}$$

is essentially achieved when $t=5\times t_{1/2}$. One of the consequences of this relationship is that medicaments with long half-lives take a long time to reach a desired steady-state level (or to be within a known therapeutic range). As a result, one of the strategies often used is to first administer bolus doses until the drug level is in a prescribed range. A continuous infusion ensues immediately to maintain an effective constant plasma concentration (*learning objective 2*).

Eq. (7) is first applied to calculate the plasma concentration during the multiple-dosing phase. Note that the value at the end of the last period N is given by:

$$C_{pN}(\tau) = C_p^0 \left(\frac{1 - e^{-N \times k_{el} \times \tau}}{1 - e^{-k_{el} \times \tau}}\right) e^{-k_{el} \times \tau} \tag{13}$$

where $\tau$ is the dosing interval. The solution to Eq. (10) with the initial condition defined by Eq. (13) gives the equation for the constant-infusion period:

$$C_p(t) = \frac{k_0}{k_{el} V} + \left(C_{pN}(\tau) - \frac{k_0}{k_{el} V}\right) e^{-k_{el} \times t} \tag{14}$$

### *Materials and Experimental Procedure*

The volume of liquid in the central compartment was kept at 200 mL. In one set of experiments, four boluses of $KMnO_4$ were administered at one-hour intervals followed by a constant-rate infusion. Operating conditions and kinetics obtained in a constant-rate infusion study were applicable in this case (*i.e.*, $k_{el}=0.014\ min^{-1}$, $C_{pss}=2.0$ g/mL, $k_0=5.6$ g/min). Samples of $KMnO_4$ solution were collected from the central compartment every 15 minutes until the concentration reached the steady-state value. Results of this investigation were compared to a different dosage regimen where two boluses were used prior to the continuous infusion.

### *Results and Discussions*

The concentration profiles for the two and four IV boluses with infusion are displayed in Figure 4. One key advantage of the multiple doses plus the infusion is a distribution of the total amount of injected medicament during the therapy.[6] The increase in the dimension of the input space, however, makes it difficult to develop the best drug-dosing strategy.

Several researchers have worked on such problems and proposed several algorithms to address the issue. Students should be given the opportunity to estimate the best injection times, drug dose sizes, and infusion rates. The sum of squared errors for the two and four boluses plus infusion are 0.306 and 0.576, respectively.

## SUMMARY OF EXPERIENCES

The educational objectives are formulated to fit courses, or programs, that provide an introduction to pharmacokinetics and drug transport. For example, in the case of IV bolus injections, not only do students need to understand that the blood concentration decreases faster for drugs with a shorter half-life but also why this process is important to patient compliance and administration protocols. Based on feedback and oral testimonies from students of ChE427/BME427, simulations—based on first-principle modeling—have been demonstrated to foster a better understanding of graduate courses in pharmaceutical engineering and some aspects of

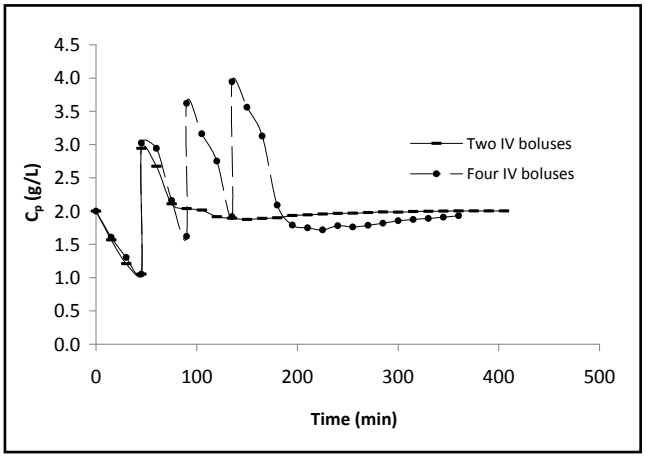


***Figure 4.*** *Concentration of $KMnO_4$ in the central compartment for two and four IV boluses followed by a constant-rate infusion of $k_0$ = 5.6 k g/min.*

current drug-delivery practices. In Spring 2009, three out of five projects were based on pharmacokinetics and dosing regimens. One group of students investigated the effects of drug half-life and multiple-dosing regimens on the maximum and minimum plasma drug concentrations. Another assignment focused on the impact of pharmacokinetic parameters on drug concentrations in the central and peripheral compartments of a two-compartment model. Simulations were also conducted to address several aspects of a continuous drug infusion (*e.g.*, time to achieve steady-state). The students from this group welcomed the idea of incorporating laboratory data from the constant rate-infusion experiment into their projects. Because of time constraints and the fact that some of the laboratory materials/experiments were not available at the time, students' requests for conducting multiple-dosing experiments were not met. Nevertheless, the entire class attended a demonstration in the laboratory on IV bolus experiments using well-stirred vessels. Initial responses indicated that the transition from simulation-based to experimental projects (*learning objective 2*) would be well-received.

## CONCLUSIONS

Several experiments were proposed to help chemical engineering students understand pharmacokinetic processes using familiar continuous-stirred vessels. In line with the educational objective of applying knowledge of fundamental physical principles (*learning objective 1*), these activities made extensive use of curriculum topics, such as mass balance equations and process dynamics, in an attempt to build on existing knowledge and to reinforce concepts taught in the classroom. Concentration-time profiles of potassium permanganate were monitored in a one-compartment stirred-tank model for single and multiple IV boluses. The influences of dose strengths and administration periods were investigated. The constant-rate infusion, although preferable to bolus injections for some medicaments, presents its own challenges, *e.g.*, the plasma drug concentration takes a long time to reach a steady-state. Experiments were designed to enable students to use their knowledge of process dynamics in developing drug-dosage regimens that meet certain criteria. Combined with multiple boluses, a continuous infusion may be appropriate for a series of drugs and treatments (*learning objective 2*). Designed laboratory activities would allow students to appreciate the benefits and overcome difficulties of this particular protocol. After participating in a demonstration of IV bolus injections, students, who worked on simulation-based projects in drug transport, were very supportive of the addition of a laboratory component to the Biotransport course.

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