

PHAR 7632 Chapter 8

Pharmacokinetics of Oral Administration

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Pharmacokinetics of Oral Administration

Student Objectives for this Chapter

After completing the material in this chapter each student should:-

- be able to draw the scheme and write the differential equations for a one compartment pharmacokinetic model with first order absorption
- be able to use the integrated equations for this pharmacokinetic model to calculate parameter values and dosing regimens
- be able to define, use, and calculate the parameters:
 - absorption rate constant, k_a
 - fraction absorbed, bioavailability, F
 - time of peak concentration, t_{peak}
 - maximum plasma concentration, $C_{p_{max}}$
- be able to describe the effect of changing k_a and/or F values on plasma concentration *versus* time curves including
 - with altered liver function on first-pass metabolism
 - with improved drug absorption through reformulation
 - with different dosage forms such solution, tablets and controlled release tablets

So far we have considered the pharmacokinetics of intravenously administered drugs, either as a bolus or by infusion. If we know k_{el} and V for a particular patient we can calculate appropriate doses or dosing rates (infusion rates) to produce the necessary therapeutic concentrations.

In the previous Chapter we considered a number of routes of drug administration. Most of the routes of administration were extravascular; for example IM, SC, and most importantly oral. With these types of drug administration the drug isn't placed in the central compartment but must be absorbed through at least one membrane. This has a considerable effect on drug pharmacokinetics and may cause a reduction in the actual amount of drug which is absorbed.

Most commonly the absorption process follows first order kinetics. Even though many oral dosage forms are solids, which must dissolve before being absorbed and absorption may occur at various parts of the GI tract, the overall absorption process can often be considered to be a single first order process. At least that's the assumption we will use for now.

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Scheme or diagram

This model can be represented as:-

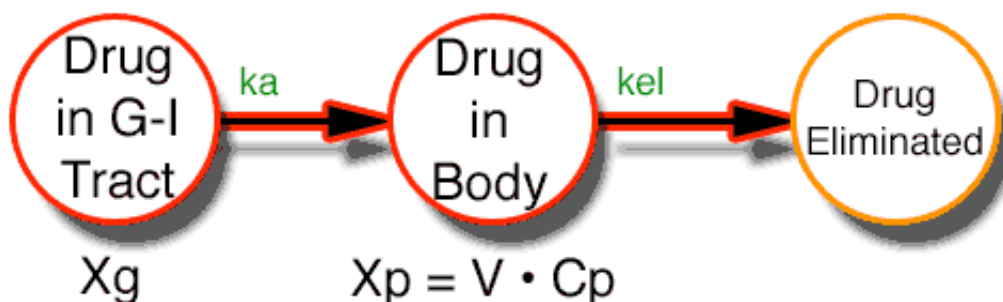


Figure 8.1.1 Representing Oral Administration, One Compartment Pharmacokinetic Model

Where X_g is the amount of drug to be absorbed, X_p is the amount of drug in the body, and k_a is the first order absorption rate constant.

Differential Equations

Drug Amount Remaining to be Absorbed, X_g

The differential equation for X_g is shown in Equation 8.2.1

$$\frac{dX_g}{dt} = -k_a \bullet X_g$$

Equation 8.2.1 Differential Equation for Amount Remaining in the G-I Tract

This is similar to the equation for dC_p/dt after an IV bolus administration.

Using Laplace transforms it is possible to derive the integrated equation.

$$X_g = X_g^0 \bullet e^{-k_a \bullet t} = F \bullet Dose \bullet e^{-k_a \bullet t}$$

Equation 8.2.1 Integrated Equation for Drug Amount Remaining in the G-I Tract available for Absorption

where F is the fraction of the dose which can be absorbed, the bioavailability.

We could therefore plot X_g (the amount remaining to be absorbed) *versus* time on semi-log graph paper and get a straight line with a

slope representing k_a , Figure 8.2.1.

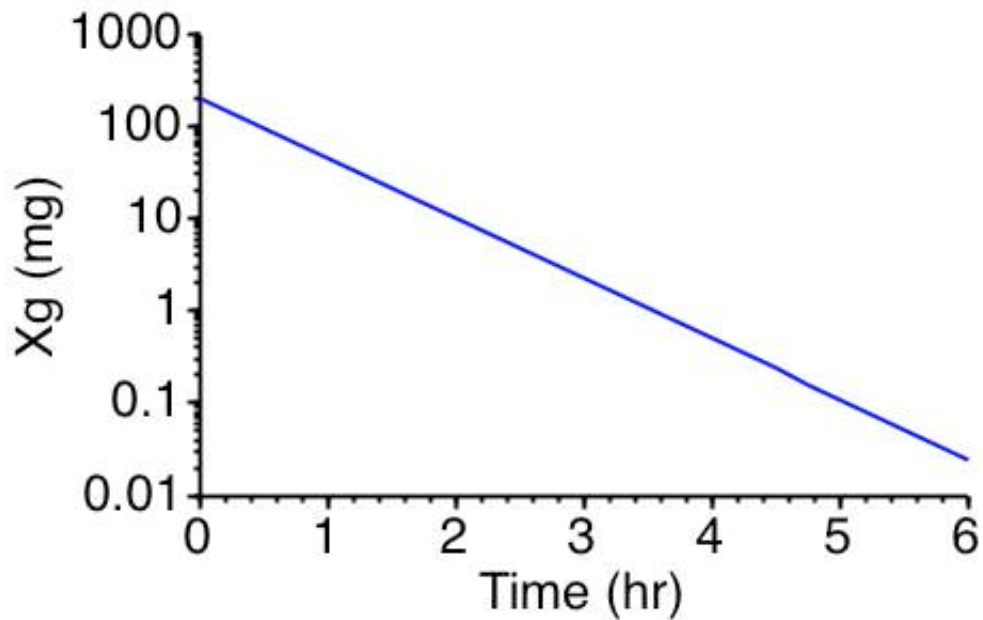


Figure 8.2.1 Semi-log Plot of X(g) versus Time

And as a linear plot.

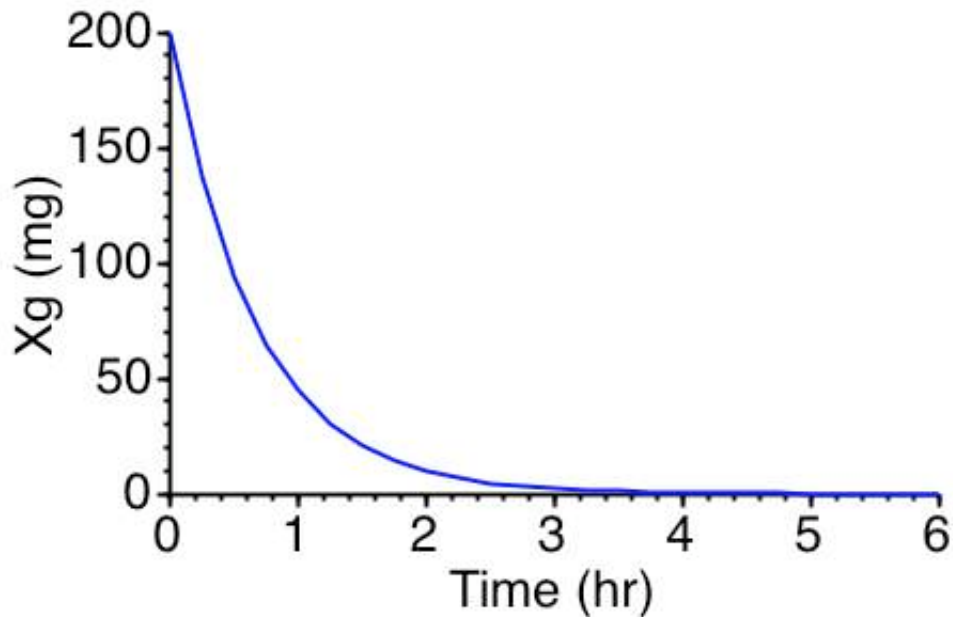


Figure 8.2.2 Linear Plot of X(g) versus Time

Drug Amount in the Body, X_p

For $X_p (= V \cdot C_p)$ the amount of drug in the body, the differential equation is shown in Equation 8.2.3

$$\frac{dX_p}{dt} = \frac{V \cdot dC_p}{dt} = k_a \cdot X_g - k_{el} \cdot V \cdot C_p$$

Equation 8.2.3 Differential Equation for Amount of Drug in the Body

The first term, $k_a \cdot X_g$, represents absorption and the second term, $k_{el} \cdot V \cdot C_p$, represents elimination

Even without integrating this equation we can get an idea of the plasma concentration time curve.

Shortly after the dose is administered X_g is much larger than $V \cdot C_p$ therefore the value of $V \cdot dC_p/dt$ is positive, therefore the slope is positive and C_p will increase. With increasing time after the dose is administered, X_g will decrease, while initially C_p is increasing, therefore there will be a time when $k_a \cdot X_g$ will equal $k_{el} \cdot V \cdot C_p$. At this time $V \cdot dC_p/dt$ will be zero and there will be a peak in the plasma concentration. At even later times X_g will approach zero, and $V \cdot dC_p/dt$ will become negative and C_p will decrease. It could be expected that the plasma concentration time curve will look like Figure 8.2.3.

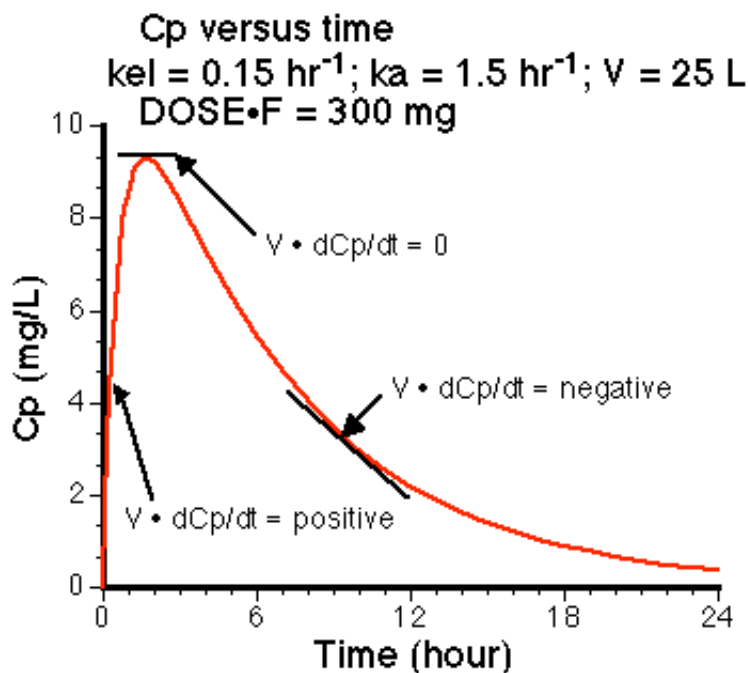


Figure 8.2.3 Linear Plot of C_p versus Time after Oral Administration Showing Rise, Peak, and Fall in C_p

Click on the figure to view the Java Applet window
 Java Applet as a [Semi-log Plot](#)

Using a JAVA aware browser you can create your own version of Figure 8.2.1.

Plasma Concentration versus Time Plots

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- [Semi-log](#)

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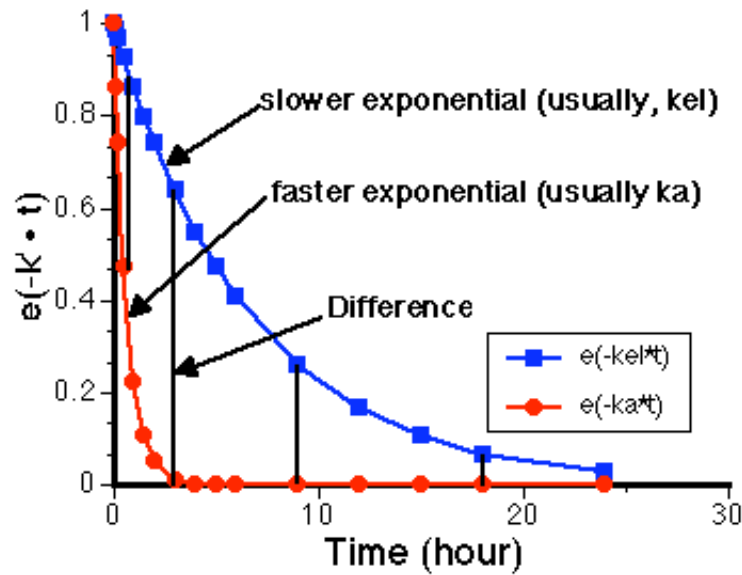


Figure 8.3.1 Linear Plot of $e^{-k' \cdot t}$ versus Time for Two Exponential Terms

Notice that the difference starts at zero, increases, and finally decreases again toward a value of zero.

Plotting this difference multiplied by $\frac{F \bullet Dose \bullet ka}{V \bullet (ka - kel)}$ gives C_p versus time.

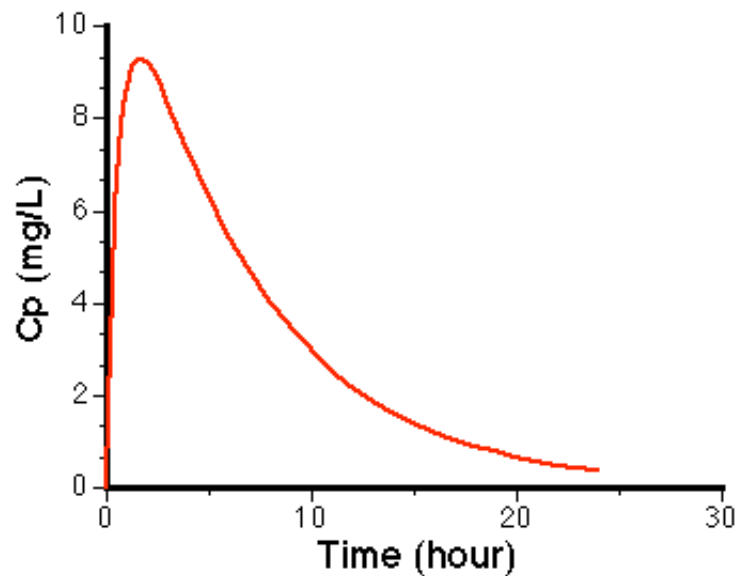
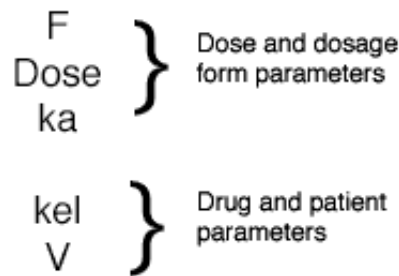


Figure 8.3.2 Linear Plot of Drug Concentration versus Time

We can calculate the plasma concentration at anytime if we know the values of all the parameters of Equation 8.3.1.



The parameters kel and V are dependent on the drug and the patient. Different patients will have different values for kel and V . This might depend on their age, weight, sex, genetic make-up (pharmacogenomics) and/or state of health. Different drugs can have quite different values of kel and V .

While dose is clearly a parameter associated with the dosage form, the parameters F and ka are partly determined by the drug and patient and also by the dosage form or route of administration. The rate (ka) and extent (F) of absorption can depend on the drug and patient with respect to transfer from the site of administration to the blood stream. The value of F may be reduced by poor solubility, drug instability, metabolism by intestinal flora, metabolism or reverse transport by various enzyme systems. The value of ka will be influenced by the drug dissolution rate and ability of the drug to move across any barriers between the site of administration and the blood stream. Both f and ka can also be influenced by the drug dosage form. Generally F is maximize but reduced values of ka may be desired to produce a sustained release effect.

Time of Peak Concentration

By setting the rate of change of C_p versus time, dC_p/dt , to zero and after some rearranging an equation for the time of peak can be derived.

$$t_{peak} = \frac{1}{(ka - kel)} \bullet \ln \left(\frac{ka}{kel} \right)$$

Equation 8.3.2 Time of Peak Concentration after an Oral Dose, t_{peak} or t_{max}

As an example we could calculate the peak plasma concentration given that $F = 0.9$, Dose = 600 mg, $ka = 1.0 \text{ hr}^{-1}$, $kel = 0.15 \text{ hr}^{-1}$, and $V = 30$ liter.

Using Equation 8.3.2

$$t_{peak} = \frac{1}{(1 - 0.15)} \times \ln \left(\frac{1}{0.15} \right) = 2.23 \text{ hour}$$

and now using Equation 8.3.1 we can calculate $C_{p_{peak}}$ or $C_{p_{max}}$ for a single oral dose

$$\begin{aligned} C_p &= \frac{0.9 \times 600 \times 1}{30 \times (1 - 0.15)} \times [e^{-0.15 \times 2.23} - e^{-1 \times 2.23}] \\ &= 21.18 \times [0.7157 - 0.1075] = 12.9 \text{ mg/L} \end{aligned}$$

As another example we could consider what would happen with $ka = 0.2 \text{ hr}^{-1}$ instead of 1.0 hr^{-1}

Using Equation 8.3.2

$$t_{peak} = \frac{1}{(0.2 - 0.15)} \times \ln \left(\frac{0.2}{0.15} \right) = 5.75 \text{ hour}$$

and now using Equation 8.3.1 we can calculate $C_{p_{peak}}$ or $C_{p_{max}}$ for a single oral dose

$$\begin{aligned} C_p &= \frac{0.9 \times 600 \times 0.2}{30 \times (0.2 - 0.15)} \times [e^{-0.15 \times 5.75} - e^{-0.2 \times 5.75}] \\ &= 72 \times [0.4221 - 0.3166] = 7.6 \text{ mg/L} \end{aligned}$$

Note the peak drug concentration is lower and slower with the smaller k_a value.

Calculator 8.3.1 Estimate Time of Peak C_p and the Peak C_p after Oral Administration

k_a	<input type="text" value="0.2"/>
k_{el} (Same Units as k_a)	<input type="text" value="0.15"/>
	<input type="button" value="Calculate t(max) or t(peak)"/>
Time of Peak C_p is:	<input type="text"/>
Dose	<input type="text" value="600"/>
Bioavailability, F	<input type="text" value="0.9"/>
Volume of Distribution	<input type="text" value="30"/>
	<input type="button" value="Calculate <math>C_p</math>(max) or <math>C_p</math>(peak)"/>
Peak C_p is:	<input type="text"/>

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Bioavailability Parameters, k_a and F

Absorption Rate Constant, k_a

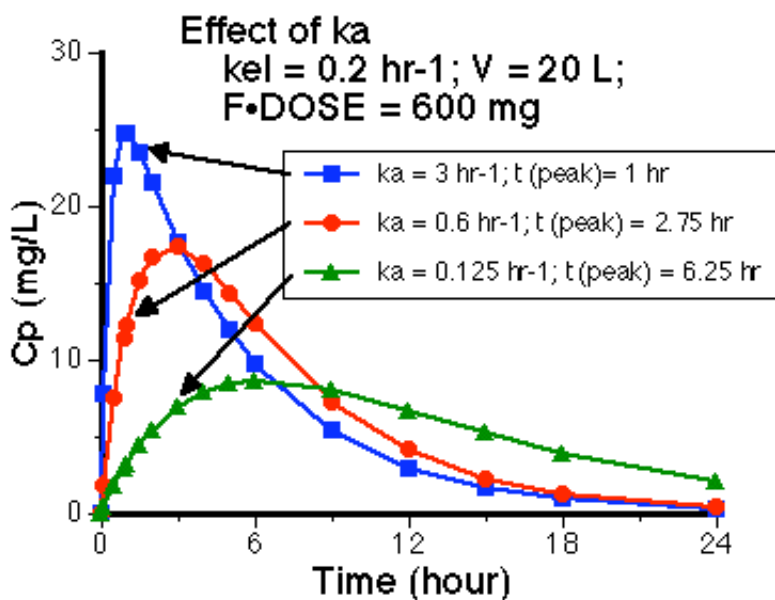


Figure 8.4.1 Linear Plot of C_p versus Time with $k_a = 3, 0.6, \text{ or } 0.125 \text{ hr}^{-1}$

Click on the figure to view the Java Applet window
 Java Applet as a [Semi-log Plot](#)

Before going on to calculate the parameters k_a , k_{el} , and F from data provided we can look at the effect different values of F and k_a have on the plasma concentration versus time curve. As k_a changes from 3, 0.6 to 0.125 hr^{-1} the time of peak concentration changes to 1, 2.75 and 6.25 hour. Notice that with higher values of k_a the peak plasma concentrations are higher and earlier.

Extent of Absorption or Bioavailability, F

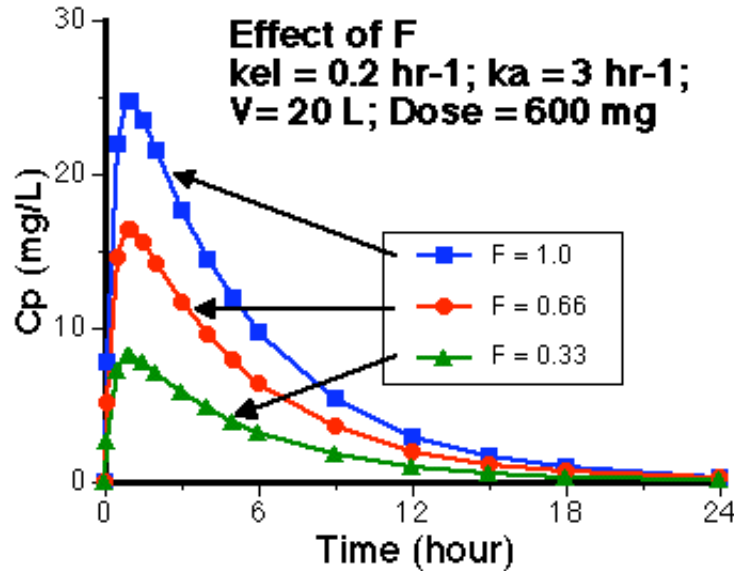


Figure 8.4.2 Linear Plot of C_p versus Time with $F = 1, 0.66, \text{ or } 0.33$

Click on the figure to view the Java Applet window
 Java Applet as a [Semi-log Plot](#)

Changing F values is equivalent to changing the dose. Thus the higher the F value the higher the concentration values at each time point. Since the values of k_{el} and k_a are unchanged the time of peak plasma concentration is unchanged.

Thus, $t_{peak} = 1, 1, \text{ and } 1$ hour. The same in each case.

Some items to consider

Item 1. A drug which undergoes extensive metabolism, with a high extraction ratio, may be subject to significant first-pass metabolism. In a healthy subject this would mean that the drug availability (F value) could be significantly lower than 1. In a patient with significant liver disease the first-pass metabolism could be reduced leading to a higher F value and more drug reaching the blood stream.

Consider a drug with the parameter values in healthy subjects: $F = 0.1$; $V = 725 \text{ L}$; $k_{el} = 0.105 \text{ hr}^{-1}$; $k_a = 3.0 \text{ hr}^{-1}$; $CL = 76 \text{ L/hr}$. Plot a concentration *versus* time curve after an oral dose of 100 mg. Contrast this with the results obtained with the same dose given to a patient with severe cirrhosis. Use the parameter values: $F = 1.0$; $V = 675 \text{ L}$; $k_{el} = 0.078 \text{ hr}^{-1}$; $k_a = 3.0 \text{ hr}^{-1}$; $CL = 54 \text{ L/hr}$. [Explore the problem as a Linear Plot - Java Applet](#) Pentikainen et al., 1978.

Item 2. A drug which undergoes extensive metabolism, with a relatively high extraction ratio, may be subject to significant first-pass metabolism. In a healthy subject this would mean that the drug availability (F value) could be significantly lower than 1. In a patient with significant liver disease the first-pass metabolism could be reduced leading to a higher F value and more drug reaching the blood stream. Other pharmacokinetic changes may modify this effect.

Consider a drug with the parameter values in healthy subjects: $F = 0.30$; $V = 290 \text{ L}$; $k_{el} = 0.173 \text{ hr}^{-1}$; $k_a = 3.0 \text{ hr}^{-1}$; $CL = 860 \text{ ml/min}$. Plot a concentration *versus* time curve after an oral dose of 80 mg. Contrast this with the results obtained with the same dose given to a patient with severe cirrhosis. Use the parameter values: $F = 0.42$; $V = 380 \text{ L}$; $k_{el} = 0.063 \text{ hr}^{-1}$; $k_a = 3.0 \text{ hr}^{-1}$; $CL = 580 \text{ ml/min}$. [Explore the problem as a Linear Plot - Java Applet](#) Wood et al., 1978.

Item 3. A drug with poor solubility has been marketed for some time. Peak drug concentrations after a single 0.5 mg (500 mcg) dose

were approximately 0.8 ng/ml (mcg/L). Drug intoxication was traced back to a change in dosage form formulation. Measured bioavailability went from approximately 30% to 75%.

Consider a drug with the parameter values in original product: $F = 0.30$; $V = 180 \text{ L}$; $k_{el} = 0.023 \text{ hr}^{-1}$; $k_a = 5.0 \text{ hr}^{-1}$; $CL = 69 \text{ ml/min}$. Plot a concentration *versus* time curve after an oral dose of 500 mcg (0.5 mg). Contrast this with the results obtained with the same dose but with the new formulation. Use the parameter values: $F = 0.75$; $V = 180 \text{ L}$; $k_{el} = 0.023 \text{ hr}^{-1}$; $k_a = 5.0 \text{ hr}^{-1}$; $CL = 69 \text{ ml/min}$. [Explore the problem as a Linear Plot - Java Applet](#) Danon et al., 1977.

Item 4. In this Chapter we have assumed that the absorption process is uncomplicated and can be represented as a single first order process. Occasionally an additional process may be necessary. With sustained release products an additional dissolution step may be necessary.

A drug was administered as an IV injection, and oral solution and two tablet formulations (one rapid and the other a slow release tablet). A dissolution step was included to model the two tablet formulations. Parameters values included $k_{el} = 0.077 \text{ hr}^{-1}$, $V = 81.3 \text{ L}$, $k_a = 0.113 \text{ hr}^{-1}$. The two tablet formulations required $k_d = 0.405 \text{ hr}^{-1}$ or 0.0261 hr^{-1} . The dose were 25000 mg (Dose1 IV bolus), 20300 mg (Dose2 Oral solution), 19000 mg (Dose3 Oral rapid release tablet) and 21600 mg (Dose3 Oral slow release tablet). Simulate the concentration *versus* time curves after each dose. Bevill et al., 1977. [Explore the problem as a Linear Plot - Java Applet](#)

Try graphing [linear](#) or [semi-log](#) plots of drug concentration after a single oral dose.

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