# Biopharmaceutics

Chapter-9

**NONLINEAR PHARMACOKINETICS**

# INTRODUCTION

- Linear models assumed that the pharmacokinetic parameters for a drug would not change when different doses or multiple doses of a drug were given.
- With some drugs, increased doses or chronic medication can cause deviations from the linear pharmacokinetic profile previously observed with single low doses of the same drug.
- This nonlinear pharmacokinetic behavior is also termed dose-dependent pharmacokinetics.

# Reasons for nonlinear pharmacokinetics

- Many of the processes of drug absorption, distribution, biotransformation, and excretion involve enzymes or carrier-mediated systems. For some drugs given at therapeutic levels, one of these specialized processes may become saturated
- Besides saturation of plasma protein-binding or carrier-mediated systems, drugs may demonstrate nonlinear pharmacokinetics due to a pathologic alteration in drug absorption, distribution, and elimination. For example, aminoglycosides may cause renal nephrotoxicity, thereby altering renal drug excretion.
- In addition, gallstone obstruction of the bile duct will alter biliary drug excretion.
- In most cases, the main pharmacokinetic outcome is a change in the apparent elimination rate constant.

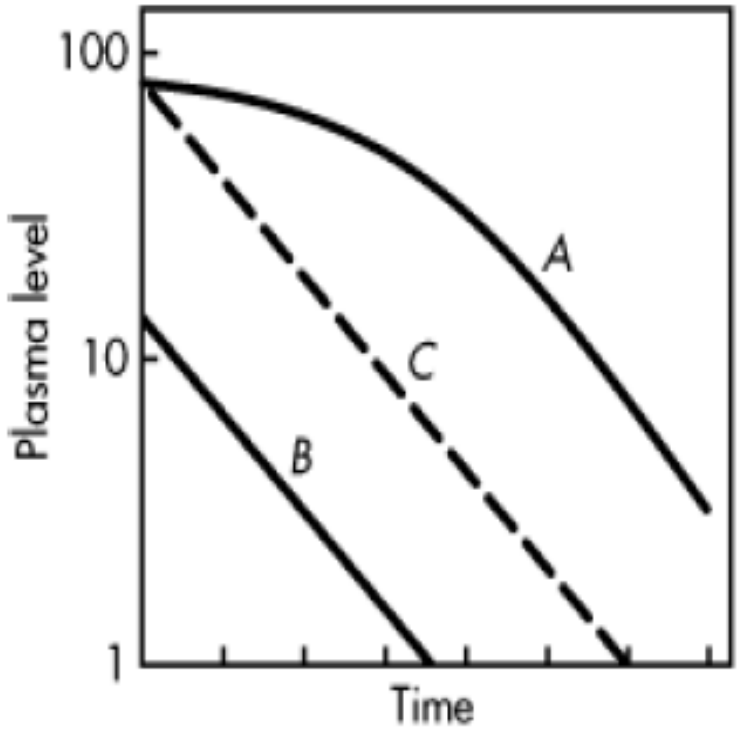
- A number of drugs demonstrate saturation or capacity-limited metabolism in humans. Examples of these saturable metabolic processes include glycine conjugation of salicylate, sulfate conjugation of salicylamide, acetylation of p-aminobenzoic acid, and the elimination of phenytoin.

**Drugs that demonstrate saturation kinetics usually show the following characteristics.**

1. Elimination of drug does not follow simple first-order kinetics that is, elimination kinetics are nonlinear.
2. The elimination half-life changes as dose is increased. Usually, the elimination half-life increases with increased dose due to saturation of an enzyme system. However, the elimination half-life might decrease due to "self"-induction of liver biotransformation enzymes, as is observed for carbamazepine.
3. The area under the curve (AUC) is not proportional to the amount of bioavailable drug.
4. The saturation of capacity-limited processes may be affected by other drugs that require the same enzyme or carrier-mediated system (i.e., competition effects).
5. The composition and/or ratio of the metabolites of a drug may be affected by a change in the dose.

- Because these drugs have a changing apparent elimination constant with larger doses, prediction of drug concentration in the blood based on a single small dose is difficult.
- Drug concentrations in the blood can increase rapidly once an elimination process is saturated.
- In general, metabolism (biotransformation) and active tubular secretion of drugs by the kidney are the processes most usually saturated.
- **Figure 9.1 shows plasma Level-time curves for a drug that exhibits saturable kinetics.** When a large dose is given, a curve is obtained with an initial slow elimination phase followed by a much more rapid elimination at lower blood concentrations (curve A). With a small dose of the drug, apparent first-order kinetics are observed, because no saturation kinetics occur (curve B).
- If the pharmacokinetic data were estimated only from the blood levels described by curve B, then a twofold increase in the dose would give the blood profile presented in curve C, which considerably underestimates the drug concentration as well as the duration of action.

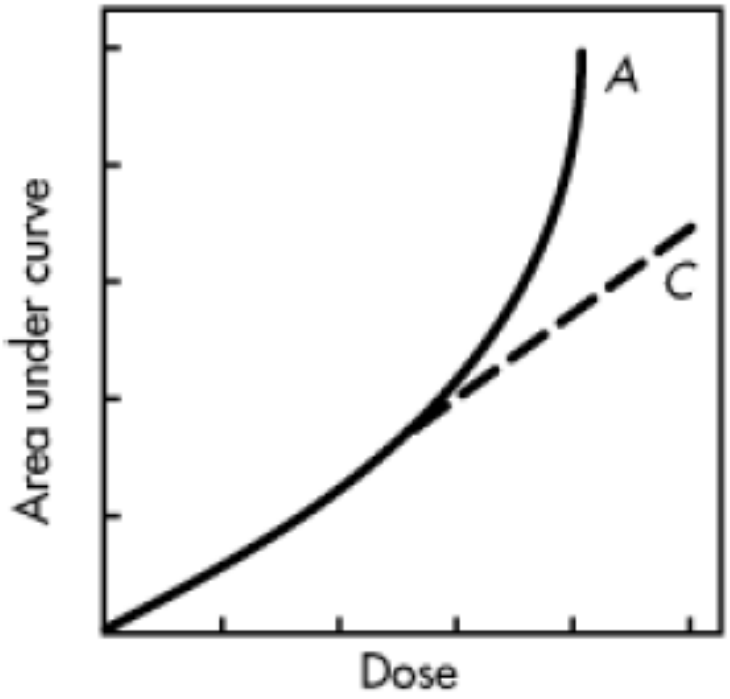
## Figure 9-1.




Plasma level-time curves for a drug that exhibits a saturable elimination process. Curves *A and B represent high and* low doses of drug, respectively, given in a single IV bolus. The terminal slopes of curves *A and B are the same. Curve C* represents the normal first-order elimination of a different drug.

- In order to determine whether a drug is following dose-dependent kinetics, the drug is given at various dosage levels and a plasma level-time curve is obtained for each dose. The curves should exhibit parallel slopes if the drug follows dose-independent kinetics. Alternatively, a plot of the areas under the plasma level-time curves at various doses should be linear (Figure 9.2).

## Figure 9-2.




Area under the plasma level-time curve versus dose for a drug that exhibits a saturable elimination process. Curve A represents dose-dependent or saturable elimination kinetics. Curve C represents dose-independent kinetics.

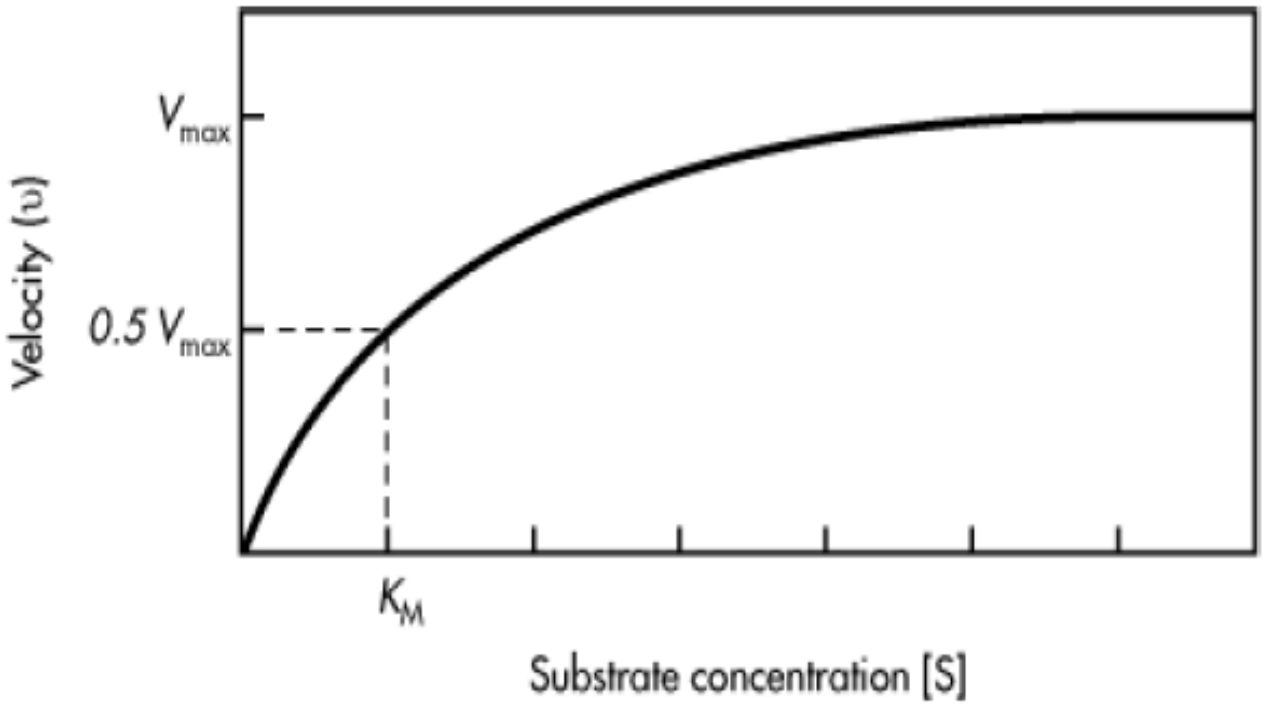
# SATURABLE ENZYMATIC ELIMINATION PROCESSES

- The elimination of drug by a saturable enzymatic process is described by Michaelis-Menten kinetics. If $C_p$ is the concentration of drug in the plasma, then

$$\text{Elimination rate} = \frac{dC_p}{dt} = \frac{V_{max} C_p}{K_M + C_p} \qquad (9.1)$$

- where $V_{max}$ is the maximum elimination rate and $K_M$ is the Michaelis constant that reflects the capacity of the enzyme system. It is important to note that $K_M$ is not an elimination constant, but is actually a hybrid rate constant in enzyme kinetics, representing both the forward and backward reaction rates and equal to the drug concentration or amount of drug in the body at $0.5V_{max}$. The values for $K_M$ and $V_{max}$ are dependent on the nature of the drug and the enzymatic process involved.

**Figure 11-2.**




Michaelis-Menten enzyme kinetics.

The hyperbolic relationship between enzymatic reaction velocity and the drug substrate concentration is described by Michaelis-Menten enzyme kinetics. The $K_M$ is the substrate concentration when the velocity of the reaction is at $0.5V_{max}$.

- The elimination rate of a hypothetical drug with a $K_M$ of 0.1 µg/mL and a $V_{max}$ of 0.5 µg/mL per hour is calculated in Table 9.2 by means of Equation 9.1.
- Because the ratio of the elimination rate to drug concentration changes as the drug concentration changes (i.e., dCp/dt is not constant, Eq. 9.1), the rate of drug elimination also changes and is not a first-order or linear process. In contrast, a first-order elimination process would yield the same elimination rate constant at all plasma drug concentrations.
- At drug concentrations of 0.4-10 µg/mL, the enzyme system is not saturated and the rate of elimination is a mixed or nonlinear process (Table 9.2).
- At higher drug concentrations, 11.2 µg/mL and above, the elimination rate approaches the maximum velocity ($V_{max}$) of approximately 0.5 µg/mL per hour. At $V_{max}$, the elimination rate is a constant and is considered a zero-order process.

## Table 9.2 Effect of Drug Concentration on the Elimination Rate and Rate Constant[a]

| Drug Concentration (µg/mL) | Elimination Rate (µg/mL per hr) | Elimination Rate/Concentration[b] (hrâ€“1) |
|---|---|---|
| 0.4 | 0.400 | 1.000 |
| 0.8 | 0.444 | 0.556 |
| 1.2 | 0.462 | 0.385 |
| 1.6 | 0.472 | 0.294 |
| 2.0 | 0.476 | 0.238 |
| 2.4 | 0.480 | 0.200 |
| 2.8 | 0.483 | 0.172 |
| 3.2 | 0.485 | 0.152 |
| 10.0 | 0.495 | 0.0495 |
| 10.4 | 0.495 | 0.0476 |
| 10.8 | 0.495 | 0.0459 |
| 11.2 | 0.496 | 0.0442 |
| 11.6 | 0.496 | 0.0427 |

[a]$K_M$ = 0.1 µg/mL, $V_{max}$ = 0.5 µg/mL per hour.

[b]The ratio of the elimination rate to the concentration is equal to the rate constant.

$$\text{Elimination rate} = \frac{dC_p}{dt} = \frac{V_{max} C_p}{K_M + C_p} \qquad (9.1)$$

Equation 9.1 describes a nonlinear enzyme process that encompasses a broad range of drug concentrations. When the drug concentration $C_p$ is large in relation to $K_M$ ($C_p >> K_m$), saturation of the enzymes occurs and the value for $K_M$ is negligible. The rate of elimination proceeds at a fixed or constant rate equal to $V_{max}$. Thus, elimination of drug becomes a zero-order process and Equation 9.1 becomes:

$$-\frac{dC_p}{dt} = \frac{V_{max} C_p}{C_p} = V_{max} \qquad (9.2)$$

# Practice Problem

Table 9.2

Using the hypothetical drug considered in ($V_{max}$ = 0.5 µg/mL per hour, $K_M$ = 0.1 µg/mL), how long would it take for the plasma drug concentration to decrease from 20 to 12 µg/mL?

## Solution

Because 12 µg/mL is above the saturable level, as indicated in Table 9.2, elimination occurs at a zero-order rate of approximately 0.5 µg/mL per hour.

Time needed for the drug to decrease to 12 $\mu g/mL$

$$= \frac{20 - 12\ \mu g}{0.5\ \mu g/hr} = 16\ hr$$

Note:

Zero order:

$dCp/dt = -k$

$Cp = - k\ t + Cp_0$

$t = Cp_0 - Cp\ /\ k$

- A saturable process can also exhibit linear elimination when drug concentrations are much less than enzyme concentrations.
- When the drug concentration $C_p$ is small in relation to the $K_M$, the rate of drug elimination becomes a first-order process.
- The data generated from Equation 9.2 ($C_p \leq 0.05$ µg/mL, Table 9.3 ) using $K_M = 0.8$ µg/mL and $V_{max} = 0.9$ µg/mL per hour shows that enzymatic drug elimination can change from a nonlinear to a linear process over a restricted concentration range. This is evident because the rate constant (or elimination rate/drug concentration) values are constant.

## Table 9.3 Effect of drug concentration on the elimination rate constant [a]

| Drug concentration (Cp) (µg/mL) | Elimination rate (µg/mL per hr) | Elimination rate/concentration ($hr^{-1}$) |
|---|---|---|
| 0.01 | 0.011 | 1.1 |
| 0.02 | 0.022 | 1.1 |
| 0.03 | 0.033 | 1.1 |
| 0.04 | 0.043 | 1.1 |
| 0.05 | 0.053 | 1.1 |
| 0.06 | 0.063 | 1.0 |
| 0.07 | 0.072 | 1.0 |
| 0.08 | 0.082 | 1.0 |
| 0.09 | 0.091 | 1.0 |

[a] $K_M$ = 0.8 µg/mL, $V_{max}$ = 0.9 µg/mL per hour.

[b] The ratio of the elimination rate to the concentration is equal to the rate constant.

The first-order rate constant for a saturable process, $k'$, can be calculated from Equation 9.3:

At drug concentrations below 0.05µ g/mL, the ratio of elimination rate to drug concentration has a constant value of 1.1 $hr^{-1}$. Mathematically, when $C_p$ is much smaller than $K_M$, $C_p$ in the denominator is negligible and the elimination rate becomes first order.

$$-\frac{dC_P}{dt} = \frac{V_{max} C_P}{C_P + K_M} = \frac{V_{max}}{K_M} C_P \qquad (9.3)$$

$$-\frac{dC_P}{dt} = k' C_P$$

The first-order rate constant for a saturable process, k', can be calculate
from Equation 9.3:

$k' = V_{max} / K_M = 0.9 / 0.8 = 1.1\ hr^{-1}$

$$k' = \frac{V_{max}}{K_M} = \frac{0.9}{0.8} = \sim 1.1 \text{ hr}^{-1}$$

Table 9.3

This calculation confirms the data in , because enzymatic drug elimination at drug concentrations below 0.05 µg/mL is a first-order rate process with a rate constant of 1.1 hrâ€" 1. Therefore, the $t_{1/2}$ due to enzymatic elimination can be calculated:

$$t_{1/2} = \frac{0.693}{1.1} = 0.63 \text{ hr}$$

## Practice Problem

How long would it take for the plasma concentration of the drug in to decline from 0.05 to 0.005 µg/mL?

Table 9.3

**Solution**

Because drug elimination is a first-order process for the specified concentrations,

$$C_P = C_P^0 e^{-kt}$$

$$\log C_P = C_P^0 - \frac{kt}{2.3}$$

$$t = \frac{\log C - \log C_P^0}{k}$$

$\log Cp = \log Cp^0 - kt/2.3$

$\log Cp - \log Cp^0 = kt/2.3$

$t / 2.3 = (\log Cp - \log Cp^0) / k$

$t = 2.3 (\log Cp - \log Cp^0)/k$

Because $C^0_p = 0.05\ \mu g/mL$, $k = 1.1\ hr^{-1}$, and $C_p = 0.005\ \mu g/mL$,

$$t = \frac{2.3(\log\ 0.05 - \log\ 0.005)}{1.1} = \frac{2.3(-1.30 + 2.3)}{1.1} = \frac{2.3}{1.1} = 2.09\ \text{hr}$$

When given in therapeutic doses, most drugs produce plasma drug concentrations well below $K_M$ for all carrier-mediated enzyme systems affecting the pharmacokinetics of the drug. Therefore, most drugs at normal therapeutic concentrations follow first-order rate processes. Only a few drugs, such as salicylate and phenytoin, tend to saturate the hepatic mixed-function oxidases at higher therapeutic doses. With these drugs, elimination kinetics are first-order with very small doses, mixed order at higher doses, and may approach zero-order with very high therapeutic doses.