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Objectives

The reader will be able to:

1. **Describe the characteristics of, and the differences between, first-order and zero-order absorption processes.**
2. **Determine whether absorption or disposition rate limits drug elimination, given plasma drug concentration-time data following different dosage forms or routes of administration.**
3. **Anticipate the effect of altering rate of absorption, extent of absorption, clearance, or volume of distribution on the plasma concentration and amount of drug in the body following extravascular administration.**
4. **Estimate the availability of a drug, given either plasma concentration or urinary excretion data following both extravascular and intravascular administration.**
5. **Estimate the relative availability of a drug, given either plasma concentration or urinary excretion data following different dosage forms or routes of administration.**
6. **Estimate the renal clearance of a drug from plasma concentration and urinary excretion data following extravascular administration.**
7. **Knowing the availability, estimate clearance, volume of distribution, and elimination half-life from plasma concentration data following extravascular administration.**

For systemically acting drugs, absorption is a prerequisite for therapeutic activity when they are administered extravascularly. The factors that influence drug absorption are considered in Chapter 9. In this chapter the following aspects are examined: the impact of rate and extent of absorption on both plasma concentration and amount of drug in the body; the effect of alterations in absorption and disposition on body level-time relationships; and the methods used to assess pharmacokinetic parameters from plasma and urinary data following extravascular administration.

Throughout this book, the term *availability* is used to express the completeness of absorption. Thus, availability is defined as the fraction, or percent, of the administered dose of drug that is absorbed intact.

rate. The absorption kinetics are then called *zero order*, because the rate of a
sorption is proportional to the amount remaining to be absorbed raised to th
power of zero. Differences between zero-order and first-order kinetics are illu
trated in Figure 4–1. Zero-order absorption, characterized by a constant rate
absorption, is essentially independent of the amount absorbed. A plot of th
amount remaining to be absorbed against time on regular graph paper yields
straight line whose slope is the rate of absorption (Fig. 4–1A). Recall fro
Chapter 3 that the fractional rate of decline is constant for a first-order proces
the amount declines linearly with time when plotted on semilogarithmic pap
In contrast, for a zero-order absorption process, the fractional rate of absorpti
increases with time, because the rate is constant but the amount remaini
decreases. This is reflected in an ever-increasing gradient with time in a sem
logarithmic plot of the amount remaining to be absorbed (Fig. 4–1B). A meth
of determining the kinetics of absorption following extravascular administrati
is given in Appendix C.

For the remainder of this chapter, and for much of the book, absorption
assumed to be first order. If absorption is zero order, then the equations d
veloped in Chapter 6 (Constant-rate Regimens) apply.

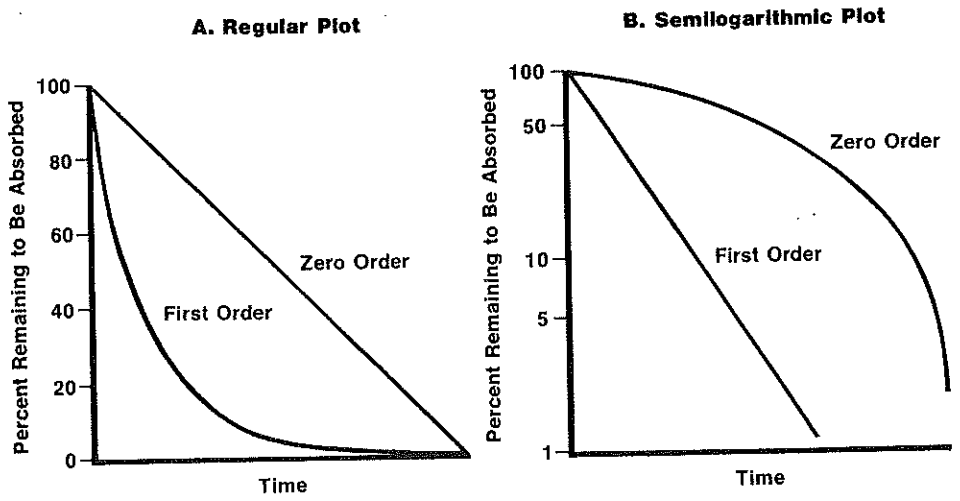

Fig. 4–1. A comparison of zero-order and first-order absorption processes. Depicted are: *A*, cartesian, *B*, semilogarithmic plots of the percent remaining to be absorbed against time.

in Figure 4–2. The rise and fall of the drug concentration in plasma are
understood by remembering that at any time

$$\underset{\text{Rate of change of drug in body}}{\frac{dA}{dt}} = \underset{\text{Rate of absorption}}{\frac{dAa}{dt}} - \underset{\text{Rate of elimination}}{k \cdot A} \qquad 1$$

where Aa is the amount of drug at the absorption site remaining to be absorbed. When absorption occurs by a first-order process, the rate of absorption is given by $ka \cdot Aa$.

Initially, with all drug at the absorption site and none in the body, the rate of absorption is maximal and the rate of elimination is zero. Thereafter, as drug is absorbed, its rate of absorption decreases, whereas its rate of elimination increases. Consequently, the difference between the two rates diminishes. However, as long as the rate of absorption exceeds the rate of elimination the plasma concentration continues to rise. Eventually, a time is reached when the rate of elimination matches the rate of absorption; the concentration is then at a maximum. Subsequently, the rate of elimination exceeds the rate of absorption and the plasma concentration declines.

The peak plasma concentration is always lower following extravascular administration than the initial value following an equal intravenous bolus dose. In the former case, at the peak time some drug remains at the absorption site and some has been eliminated, while the entire dose is in the body immediately

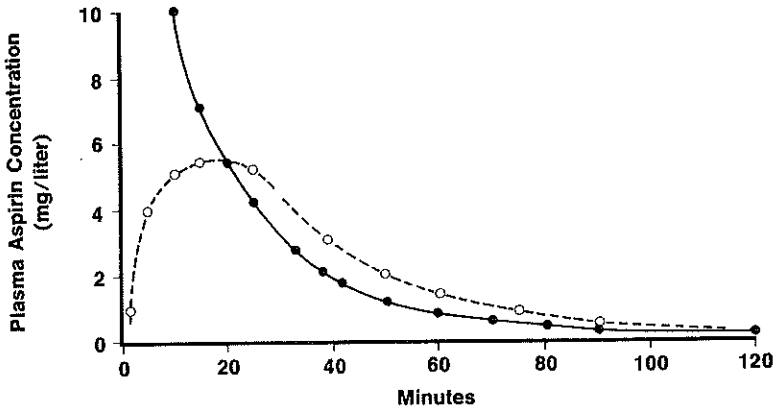

Fig. 4–2. Aspirin (650 mg) was administered as an intravenous bolus (●) and as an oral solution (○) on separate occasions to the same individual. Absorption causes a delay and a lowering of the peak concentration. (One mg/liter = 5.5 micromolar.) (Modified from the data of Rowland, M., Riegelman, S., Harris, P.A., and Sholkoff, S.D.: Absorption kinetics of aspirin in man following oral administration of an aqueous solution. J. Pharm. Sci., *61*:379–385, 1972. Adapted with permission of the copyright owner.)

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