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CHAPTER 91

Sustained-Release Drug Delivery Systems

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The goal of any drug delivery system is to provide a therapeutic amount of drug to the proper site in the body to achieve promptly, and then maintain, the desired drug concentration. This idealized objective points to the two aspects most important to drug delivery, namely, *spatial placement* and *temporal delivery* of a drug. Spatial placement relates to targeting a drug to a specific organ or tissue, while temporal delivery refers to controlling the rate of drug delivery to the target tissue. An appropriately designed sustained-release drug delivery system can be a major advance toward solving these two problems. It is for this reason that the science and technology responsible for development of sustained-release pharmaceuticals have been and continue to be the focus of a great deal of attention in both industrial and academic laboratories. There currently exist numerous products on the market formulated for both oral and parenteral routes of administration that claim sustained or controlled drug delivery. The bulk of research has been directed at oral dosage forms that satisfy the temporal aspect of drug delivery, but many of the newer approaches under investigation may allow for spatial placement as well. This chapter will define and explain the nature of sustained-release drug therapy, briefly outline relevant physicochemical and biological properties of a drug that affect sustained-release performance and review the more common types of oral and parenteral sustained-release dosage forms. In addition, a brief discussion of some methods currently being used to develop targeted delivery systems will be presented.

Conventional Drug Therapy

To gain an appreciation for the value of sustained drug therapy it is useful to review some fundamental aspects of conventional drug delivery.[1] Consider single dosing of a hypothetical drug that follows a simple one-compartment pharmacokinetic model for disposition. Depending on the route of administration, a conventional dosage form of the drug, eg, a solution, suspension, capsule, tablet, etc, probably will produce a drug blood level versus time profile similar to that shown in Fig 91-1. The term "drug blood level" refers to the concentration of drug in blood or plasma, but the concentration in any tissue could be plotted on the ordinate. It can be seen from this figure that administration of a drug by either intravenous injection or an extravascular route, eg, orally, intramuscularly or rectally, does not maintain drug blood levels within the therapeutic range for extended periods of time. The short duration of action is due to the inability of conventional dosage forms to control temporal delivery. If an attempt is made to maintain drug blood levels in the therapeutic range for longer periods by, for example, increasing the dose of an intravenous injection, as shown by the dotted line in the figure, toxic levels may be produced at early times. This obviously is undesirable and the approach therefore is unsuitable. An alternate approach is to administer the drug repetitively using a constant dosing interval, as in multiple-dose therapy. This is shown in Fig 91-2 for the oral route. In this case the drug blood level reached and the time required to reach that level depend on the dose and the dosing interval. There are several potential problems inherent in multiple-dose therapy:

1. If the dosing interval is not appropriate for the biological half-life of the drug, large "peaks" and "valleys" in the drug blood level may result. For example, drugs with short half-lives require frequent dosings to maintain constant therapeutic levels.
2. The drug blood level may not be within the therapeutic range at sufficiently early times, an important consideration for certain disease states.
3. Patient noncompliance with the multiple-dosing regimen can result in failure of this approach.

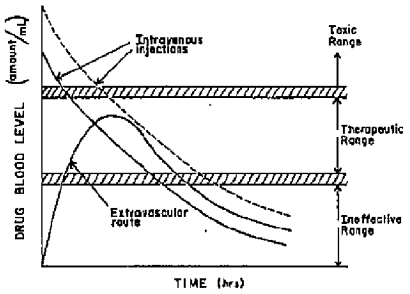

Fig 91-1. Typical drug blood level versus time profiles for intravenous injections and an extravascular route of administration.

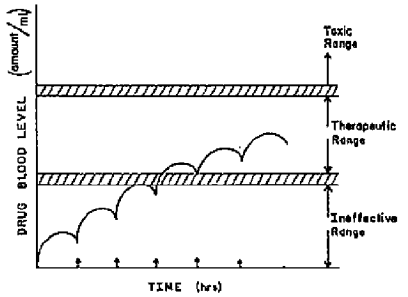

Fig 91-2. Typical drug blood level versus time profile following oral multiple-dose therapy.

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