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Novel Drug Delivery Systems

Fundamentals
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Developmental Concepts
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Biomedical Assessments

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Preface

The idea guiding the writing of this book, as in my chapters written for Sustained and Controlled Release Drug Delivery Systems (J. R. Robinson, Dekker, 1978) and Drug Delivery Systems—Characteristics and Biomedical Applications (R. L. Juliano, Oxford, 1980), is to present a comprehensive and coherent treatment of the science of controlled, prolonged administration of therapeutic agents with a total integration of the basic concepts, fundamental principles, biomedical rationales, and potential applications.

Development of a viable drug delivery system with controlled-release characteristics requires not only a fundamental understanding of, but optimization of physicobiomedical sciences—pharmaceutics, pharmacokinetics, and pharmacodynamics. Therefore, controlled-release technology is an expansive science encompassing areas of interest germane to many physical and biomedical disciplines. There is, in fact, a body of information dealing with the basic concepts, and biomedical principles that has been generated to provide a foundation for the understanding and development of controlled-release drug delivery systems for the effective treatment of illness.

The purpose of this book is to provide a concise source of that core knowledge of controlled-release technology that can be shared by all wishing to acquire an understanding of how controlled-release technology can be utilized in the development of drug delivery systems with controlled-release characteristics, following sound pharmacokinetic and pharmacodynamic principles, for optimum bioavailability and maximum therapeutic efficacy.

This book is written for individuals of diverse backgrounds who are interested in the conceptualization, development, and/or optimization of drug delivery systems or who are involved in the laboratory testing,

clinical evaluation, or use of drug products. To provide readers with a broad spectrum of scientific information in a concise, systematic manner, the book is divided into 10 chapters, ranging from the logic of controlled-release drug administration (Chap. 1) to the physicochemical principles of controlled-release drug delivery (Chap. 9), and the regulatory considerations involved in controlled-release medication (Chap. 10). The drug delivery systems developed on the basis of controlled-release technology in recent years are analyzed according to the routes of administration—ocular (Chap. 2), vaginal (Chap. 3), uterine (Chap. 4), skin (Chap. 5), parenteral (Chap. 6), and implantation (Chap. 7) and a special chapter for veterinary medicine (Chap. 8). Each chapter itself is a systematic treatment of a body of scientific literature from diverse fields of pharmaceutics, pharmacokinetics, and pharmacodynamics. This nonconventional approach to the new frontier of biomedical sciences will, to my belief, lead the readers into a more comprehensive and coherent understanding of the theoretical and practical aspects of controlled-release drug administration in an integrated form.

This book was begun in the last year of my employment with Searle Laboratories, G. D. Searle & Co., continued during my years with Endo Laboratories, E. I. duPont de Nemours & Co., and was completed after I joined the College of Pharmacy faculty at Rutgers—The State University of New Jersey. In all, it took more than three years to complete the task. I was very fortunate to have Dr. B. E. Cabana of The Food and Drug Administration and Dr. S. E. Mares of Searle Veterinary R&D Division to provide authoritative views and expertise in coauthoring and reviewing two important chapters of this book.

Yie W. Chien

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Controlled-Release Drug Administration: Logic

I. WHY A NEW PHARMACEUTICAL RESEARCH AND DEVELOPMENT STRATEGY IS INDISPENSABLE

One of the most pressing problems facing the U. S. pharmaceutical industry today is that in the past few years, only a very limited number of new drug products have been approved for marketing by the Food and Drug Administration (FDA). For instances, pharmaceutical companies in the United States spent $1 billion in research and development (R&D) in 1975 alone, but produced only seven new drug entities. In strong contrast, in the middle 1950s, about 40 new drug entities were introduced yearly by the U. S. pharmaceutical companies with total annual R&D expenditure of less than $100 million [1]. This decrease in productivity could well be related to the increasingly stringent FDA regulations that must be met before a new drug product can be introduced into the U. S. marketplace.

In order to meet the present FDA standards, the cost of testing has increased to $10-40 million for each drug. The time span for the development of a new drug from the time when its therapeutic potential has been discovered to its market introduction has increased from an average of 2 years in the late 1950s to 10 years or more [2]. A recent report, 1978 U. S. Industrial Outlooks, by the Commerce Department pointed out that development of a new drug product runs an average net cost of $12 million. The lack of FDA-approved drugs, the high cost of new drug development, and the expiration of patents for existing drugs means many pharmaceutical companies will be faced with a decreasing number of patent-protected drugs from which they may generate revenue.

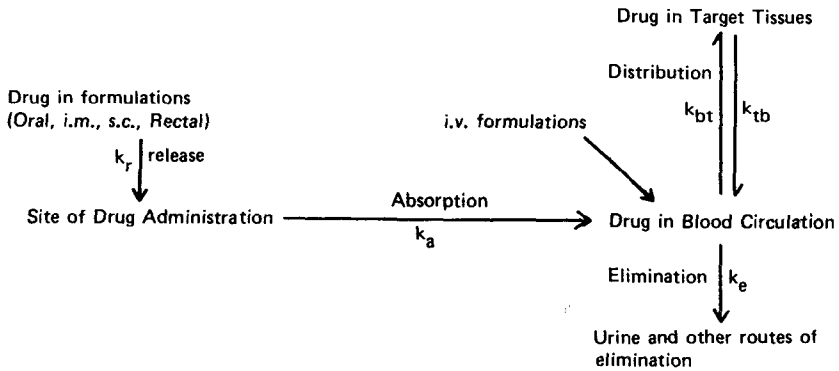
This dilemma, faced by all pharmaceutical companies today, calls for an immediate shift in R&D emphasis. Instead of a constant search for new drugs in the traditional random, hit-or-miss way [3], new R&D strategy must focus on making clinically established drugs do their therapeutic best.

Development of novel and patentable methods of delivering these drugs, by application of the concepts and techniques of controlled-release drug administration can not only extend the patent life of the existing drugs but also minimize the scope and expenditure of testing required for FDA approval. Requirements for the approval of controlled-release formulations will be elaborated in Chap. 10 on "Regulatory Considerations in Controlled-Release Medications."

II. WHAT POTENTIAL BENEFITS CAN BE DERIVED FROM CONTROLLED-RELEASE DRUG DELIVERY SYSTEMS

Controlled-release drug administration means not only prolonged duration of drug delivery, as in sustained release and prolonged release, but also implies predictability and reproducibility of drug release kinetics. The potential benefits that a controlled-release drug delivery system may bring to us can be appreciated by a consideration of prolonged and efficient delivery of therapeutically effective dosages, patient compliance, and localization of the therapy.

Optimal therapy of a disease requires the efficient delivery of active drugs to the tissues or organs that need treatment. Pharmacological activity and therapeutic efficacy are known to depend upon the concentration of the drug reaching the ailing tissue cells. It is usually desirable, from the standpoint of pharmacodynamics, to maintain the drug concentration in the ailing tissue cells at a constant level and within a therapeutically effective dose range for as long as the treatment requires. However, the availability of drug molecules to the cells is governed by a sequence of pharmacokinetic processes—release, absorption, distribution, and elimination (Scheme I).

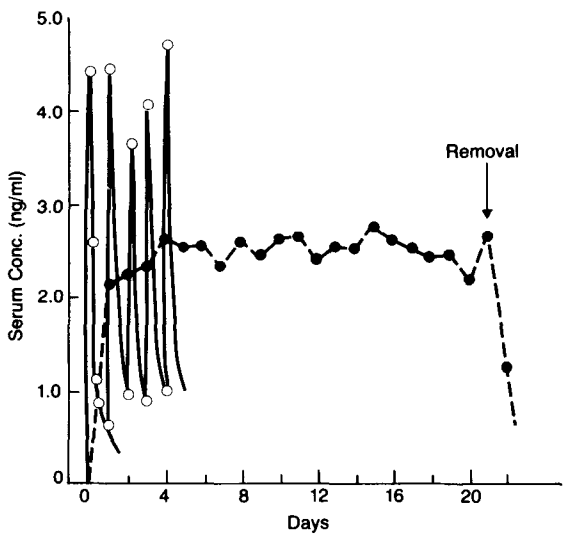


(SCHEME I)

These processes could, in some cases, result in the inefficient bioavailability of the drug to the target tissue cells. Very often, doses far in excess of those required in the cells have to be administered in order to achieve the necessary therapeutically effective concentration. Unfortunately, this massive dosing frequently leads to resistance and elicits undesirable immunological and toxicological effects in nontarget tissues. The bioavailability to a target tissue can be maximized and the adverse side effects in nontarget tissue can be minimized by applying the principles of controlled drug administration.

Administration of drugs in conventional dosage forms (except via intravenous infusion at constant rate) often results in see-saw fluctuations of drug concentrations in systemic circulation (Fig. 1) and tissue compartments. The magnitude of these fluctuations depends on the rates of absorption, distribution, and elimination, and dosing intervals. The "peak and valley" pattern is more striking for drugs with a biological half-life of less than 4 hr since prescribed dosing intervals are rarely less than 4 hr. On the other hand, a drug with a long half-life has the drawback of not

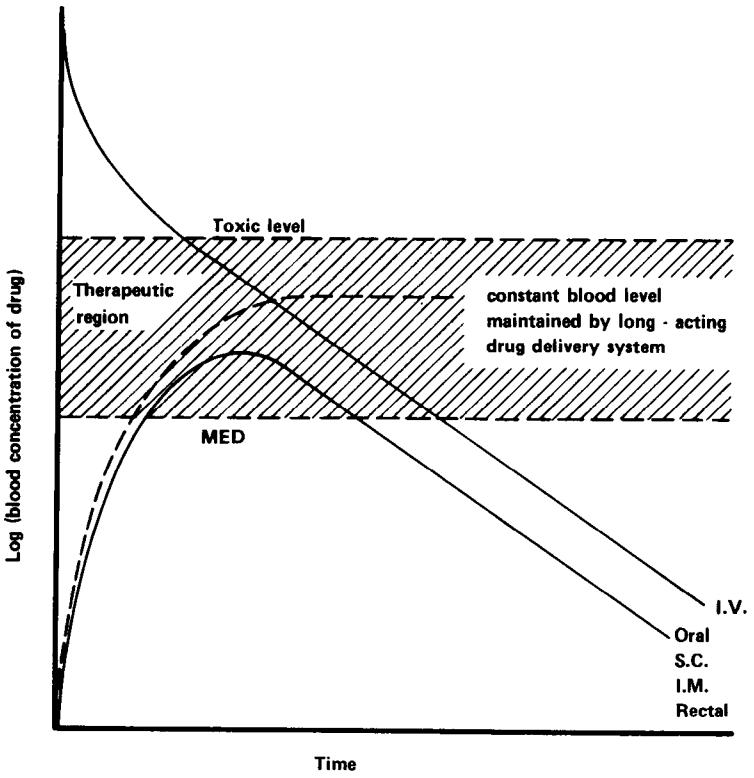
FIGURE 1 Comparative serum concentration profiles of medroxyprogesterone acetate in humans resulting from continuous delivery of medroxyprogesterone acetate from the intravaginal administration of one controlled-release medicated vaginal ring (each ring contains 100 mg of medroxyprogesterone acetate) for 21 days (●) and from daily oral intake of one Provera tablet (each contains 10 mg of medroxyprogesterone acetate) for 5 consecutive days (o). [Plotted from the data by Hiroi et al., Steroids, 26:373 (1975) and by Thiery et al., Contraception, 13:605 (1976).]



permitting rapid termination of therapy when adverse effects or other medical reasons dictate such a need. A well-designed, controlled-release drug delivery system can significantly reduce the frequency of drug dosing and also maintain a more steady drug concentration in blood circulation and target tissue cells, for example, the controlled release of medroxyprogesterone acetate from medicated vaginal rings (Fig. 1).

It has also been recognized that many drugs have relatively steep dose-response relationships. The usual range of therapeutic plasma concentrations of commonly used drugs is relatively narrow: the ratio of the upper to lower concentration limit is usually around 2, for example, 4 to 8 μg/ml for procainamide. The pronounced fluctuations resulting from the conventional drug administration are likely to yield periods of no therapeutic effect when the drug concentration is below minimum effective dose level (MED), and/or adverse reactions when the drug concentration exceeds the toxic dose level (Fig. 2). Drug concentrations can be maintained within a narrow

FIGURE 2 Theoretical illustration comparing blood drug concentration profiles of a long-acting controlled-release drug delivery system and immediate-release conventional dosage forms via various routes of administration.

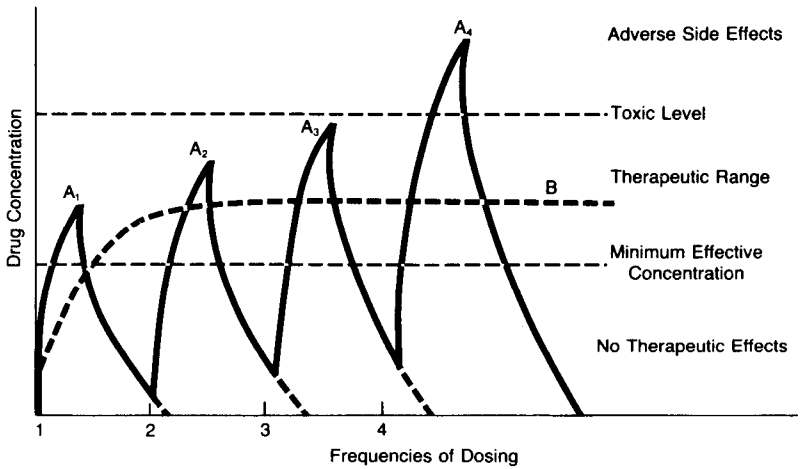


therapeutic range by the use of controlled-release drug delivery systems which will also minimize the incidence and severity of adverse side effects [4].

The success of drug therapy is critically dependent upon the ability of the patient to comply with the regimen. Lack of patient compliance with prescribed drug dosage regimens is a common cause of failure to respond to treatment. This occurs particularly often with long-term treatment of chronic diseases. A patient's compliance is affected by a combination of several factors, including his awareness of the disease process, his faith in the therapy, his understanding of the need to adhere to a strict treatment schedule, the complexity of the therapeutic regimen, the cost of therapy, and the magnitude of local and/or systemic drug side effects. The problem of lack of patient compliance can be resolved with the use of controlled-release drug delivery systems. The prolonged release characteristics of the controlled-release drug delivery systems minimize the need for frequent drug intake (Fig. 3) and thus assures better compliance with the prescribed medication regimen. The medicated vaginal ring for cyclic contraception, for example, eliminates the need for daily oral administration of contraceptive pills (Chap. 3).

The controlled-release drug delivery systems can be designed to release drugs in the vicinity of the target tissues that require treatment while drug exposure of other, nontarget tissue is minimized. The advantages of such selectivity are exemplified by the development of intrauterine contraceptive devices which selectively release contraceptive agents such as copper (Cu-7) and natural progesterone (Progestasert) to the endometrium, the desired site of contraceptive action (Chap. 4). The localization of drug

FIGURE 3 Theoretical illustration comparing blood drug concentration profiles resulting from administration of multiple doses of a conventional dosage form (A_1, A_2, A_3, . . .) and a single dose of a long-acting, controlled-release drug delivery system (B).



administration directly to the target tissue significantly reduces the dose and therefore minimizes the drug concentrations in tissues which do not require any medication. The occurrence of adverse side effects from a drug is thus eliminated.

The therapeutic effectiveness of a drug, i.e., the overall pharmacological response per unit dose, can be enhanced by choosing the optimal drug delivery rate, the rate that yields the most effective drug concentration in the target tissue cells. This is exemplified by the pilocarpine-releasing ocular insert (Ocusert) for the treatment of glaucoma (Chap. 2). The use of controlled-release drug delivery systems maximizes the bioavailability and, therefore, the therapeutic effectiveness of pilocarpine and minimizes the incidence of drug concentration peaks and ineffective concentration valleys.

III. HOW TO ACHIEVE CONTROLLED-RELEASE DRUG ADMINISTRATION

The therapeutic efficacy of a drug, under clinical conditions, is not simply a function of its intrinsic pharmacologic activity. Of equal importance is the path the drug molecules must take in getting from the site of administration to the target site(s) of action. Various conditions the drug molecules encounter along the path of distribution may alter either the effectiveness of the drug or affect the amount of the drug reaching the site(s) of pharmacologic action [5].

As illustrated in the flow diagram in Fig. 4, the path followed by the drug molecules to their sites of action consists of a number of intermediate steps. Each of these steps may determine, to various degrees, the bioavailability of the drug to its target tissue and, therefore, the onset, intensity, and duration of its intrinsic pharmacologic activity. All of these intermediate steps can be grouped and classified into three main branches of the pharmaceutical sciences:

1. Pharmaceutics refers to the development/manufacturing of an efficient, economic, and palatable delivery system (dosage form), in which the drug has maximum physicochemical stability and optimum bioavailability.
2. Biopharmaceutics/pharmacokinetics refers to the study of the absorption, distribution, metabolism, and excretion of a drug before and after reaching the target site(s) of action, and the evaluation of the relationship between delivery system and therapeutic response.