# TREATISE ON CONTROLLED DRUG DELIVERY

## Fundamentals • Optimization • Applications

edited by
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*ConvaTec*
*A Bristol-Myers Squibb Company*
*Princeton, New Jersey*

Marcel Dekker, Inc. New York • Basel • Hong Kong

**Library of Congress Cataloging-in-Publication Data**

Treatise on controlled drug delivery: fundamentals, optimization, applications / edited by Agis Kydonieus.
p. cm.
Includes bibliographical references and index.
ISBN 0-8247-8519-3
1. Drugs--Controlled release. 2. Controlled release preparations.
I. Kydonieus, Agis F.
[DNLM: 1. Delayed-Action Preparations. 2. Dosage Forms. 3. Drug Carriers. QV 785 T784]
RS201.C64T74 1991
615'.6--dc20
DNLM/DLC
For Library of Congress 91-24646
CIP


This book is printed on acid-free paper.



**Marcel Dekker, Inc.**
**270 Madison Avenue, New York, New York 10016**

Current printing (last digit):
10 9 8 7 6 5 4 3 2 1

PRINTED IN THE UNITED STATES OF AMERICA

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# Oral Controlled-Release Delivery

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## INTRODUCTION

Among all the routes of drug administration that have been explored for the development of controlled-release (CR) systems, the oral route has by far achieved the most attention and success. This is due, in part, to the ease of administration as well as to the fact that gastrointestinal physiology offers more flexibility in dosage-form design than most other routes. Development of an oral CR dosage form for a given drug involves optimization of the dosage-form characteristics within the inherent constraints of gastrointestinal (GI) physiology.

Although significant clinical advantages have been obtained for CR formulations, most such dosage forms are still designed on an empirical basis. An understanding of varied disciplines, such as GI physiology, pharmacokinetics, and formulation techniques, is essential in order to achieve a systematic approach to the design of oral CR products. The scientific framework required for development of a successful oral controlled drug delivery dosage form consists of an understanding of three aspects of the system, namely, (1) the physicochemical characteristics of the drug, (2) relevant GI anatomy and physiology, and (3) dosage-form characteristics. The anatomy and physiology includes insight into the basic physiology of the gut as well as the absorptive properties of the GI mucosa. Often one encounters additional factors, including the disease being treated, the patient, and the length of therapy. Given that it is usually not practical to alter the physicochemical characteristics of the drug, design of controlled-delivery systems generally optimizes dosage-form characteristics relative to the GI environment.

The objective of this chapter is to review oral CR systems, with a focus on dosage-form characteristics and GI physiology. Since an understanding of the basic concepts of CR systems is vital for future development, particular emphasis will be on the rationale and mechanism of such delivery systems.

## Definitions

The term CR implies a system that provides continuous delivery of the drug for a predetermined period with predictable and reproducible kinetics, and known mechanism of release. Also included in this term are systems that provide control over movement of the dosage form through the GI tract and/or deliver the drug to a specific area within the GI tract for either local or systemic effect. This chapter will deal only with dosage forms intended to be swallowed orally and will thus exclude buccal and rectal areas of delivery.

## Advantages/Disadvantages of Oral CR Dosage Forms

The goal of oral CR products is to achieve better therapeutic success than with conventional dosage forms of the same drug. This goal is realized by improving the pharmacokinetic profile as well as patient convenience and compliance in therapy. Improvement is perhaps the major reason for so much attention being focused on drugs used in chronic therapy; e.g., diuretics, cardiovascular, and CNS agents. Some of the advantages of oral CR dosage forms are

1. Reduced dosing frequency
2. Better patient convenience and compliance
3. Reduced GI side effects and other toxic effects
4. Less fluctuating plasma drug levels
5. More uniform drug effect
6. Lesser total dose

The ideal system possesses all of the above advantages. In most cases, however, there is little direct evidence of a more uniform drug effect, and success has to be based on circulating plasma drug levels. Also, a lesser total dose is based on the assumption that the drug shows linear pharmacokinetics, which in many cases, as will be discussed below, may not be achieved.

On the other hand, oral CR formulations suffer from a number of potential disadvantages. These include:

1. Generally higher cost
2. Relatively poor in-vitro/in-vivo correlation
3. Sometimes unpredictable and often reduced bioavailability
4. Possible dose dumping
5. Reduced potential for dose change or withdrawal in the event of toxicity, allergy, or poisoning
6. Increased first-pass metabolism for certain drugs

Unpredictable and poor in-vitro/in-vivo correlations and bioavailability are often observed with such formulations, especially when the drug release rate is very low or drug absorption from the colon is involved. Dose dumping is a phenomenon where a large amount of the drug is released in a short period of time, resulting in undesired high plasma drug levels and potential toxicity.

## Drug Candidate Criteria

A number of drug characteristics need to be considered in evaluating drug candidates for oral CR dosage forms. Some of these characteristics are discussed here.

In both first-order- and zero-order-release systems, the time required to achieve desired drug levels in the body depends on the elimination-rate constant. The slower the elimination, the longer it takes to reach steady state.

## Bioavailability

Factors affecting the bioavailability of a drug after its oral administration include incomplete absorption from the GI tract, presystemic clearance (gut metabolism and liver first-pass effect), and degradation of drug in the gut lumen. These factors may vary in their magnitude depending on whether a drug is given as a conventional dosage form or as a CR formulation. Incomplete drug release from a CR dosage form will constitute an additional factor contributing to the loss of drug prior to its absorption. Among these factors, first-pass liver metabolism is particularly susceptible to change when changing the drug input rate.

### *First-Pass Liver Metabolism*

After absorption from the GI tract, the drug must first pass through the liver before it reaches systemic circulation. This is because blood drainage from the entire GI tract, with the exception of the buccal cavity and lower rectum, goes to the liver via the hepatic portal vein. Since the liver is the principal site of metabolism for a number of drugs, a fraction of the absorbed drug may be eliminated through metabolism by the liver before it reaches the general circulation. This fraction is a function of the susceptibility of the drug to liver microsomal enzymes for metabolism and is measured in terms of a parameter called extraction ratio. Because of this presystemic metabolism, which is also referred to as the ''first-pass'' effect, an oral dose of a drug may have incomplete bioavailability despite its complete absorption from the GI tract.

A number of drugs have been identified as having a significant first-pass effect, and many of these have been shown to obey Michaelis-Menten kinetics in the therapeutic dose range [29]. Factors that affect first-pass metabolism are (1) liver enzyme activity (2) blood flow (3) plasma protein binding, and (4) plasma drug concentration. All of these factors can play important roles, depending on the nature of the drug and its interaction with liver enzymes.

The major difference between conventional and CR oral dosage forms is the rate of drug input into the body. The amount of drug absorbed during any 24-h period is usually comparable. Therefore, if linear kinetics of drug metabolism are involved, one should expect no difference between the pharmacokinetic parameters of the two dosage forms. However, linear pharmacokinetics do not always apply in real situations. One such example is propranolol, which accumulates during repeated oral administration to a greater extent than predicted from its half-life and area under the curve after a single oral dose [30]. This type of nonlinearity is commonly referred to as ''dose-dependent kinetic.'' Such nonlinearity may also arise from other saturable processes arising during the course of drug absorption and disposition [31]. In addition, certain disease conditions, such as renal insufficiency, can also lead to dose-dependent kinetics for certain compounds.

Dose-dependent kinetics can be an important factor in considering the design and evaluation of CR systems. This is because the rate and pattern of drug delivery with a conventional dosage form are considerably different from those with a CR dosage form. Most important among saturable processes from an oral delivery standpoint is the saturable first pass liver metabolism effect. Experimental observations indicating dose-dependent and saturable first-pass metabolism include: (1) increase in dose-normalized bioavailability with increase in dose and (2) decreased clearance at steady state compared to a single dose. A consequence of dose-dependent kinetics is that bioavailability will decrease with

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