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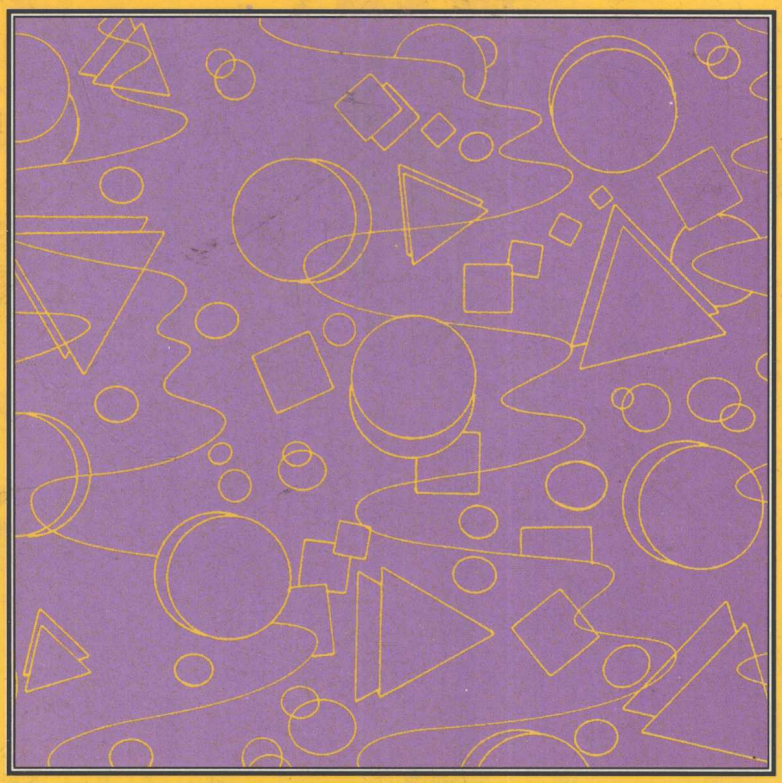
CONTROLLED DRUG RELEASE OF ORAL DOSAGE FORMS

JEAN-MAURICE VERGNAUD



CONTROLLED DRUG RELEASE OF ORAL DOSAGE FORMS

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ELLIS HORWOOD
NEW YORK LONDON TORONTO SYDNEY TOKYO SINGAPORE

First published in 1993 by
Ellis Horwood Limited
Market Cross House, Cooper Street,
Chichester, West Sussex, PO19 1EB, England
A division of
Simon & Schuster International Group

Printed and bound in Great Britain
by Bookcraft, Midsomer Norton

British Library Cataloguing in Publication Data

A catalogue record for this book is available from the British Library

ISBN 0–13–174954–4

Library of Congress Cataloging-in-Publication Data

Available from the publisher

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PREFACE

Therapeutic systems represent a new route for drug administration: as the drug is delivered continuously at a controlled rate over a predetermined period of time, uniform and constant blood level is achieved, smaller amount of drug is needed reducing the side effects, and the therapy is improved. Various people beyond the patient are concerned with this therapy, physicians and pharmacists in various areas of specialization, of course, but also bio-engineers and even workers in chemical engineering. Various oral therapeutic systems consist of a polymer matrix through which the drug is dispersed, and thus good knowledge of the matter transfers through the polymer is necessary when they are in contact with the gastric or the intestine liquid.These matter transfers being controlled by transient diffusion, the mathematical treatment of diffusion must be known when it is feasible in simple cases and especially for constant diffusivity. Morever, in complex cases and when the diffusivity is concentration-dependent, numerical methods with finite differences must be used instead of the mathematical treatment. Finally, in order to accustom the users with these ways of calculation, various mathematical or numerical models are built and tested in the study of different oral dosage forms. Thus a new way of working is developed, coupling the experiments with the models of the process, these experiments being performed in so called in-vitro tests which simulate the conditions in the body as much as possible.

The "drug", by using this term in the sense of a biologically active substance, is a chemical compound administered to the patient's organism, with which it develops a reciprocal interaction for therapeutic purposes. Generally, for many reasons, the drug is not used in the pure state. The supply form of presentation of the drug, or dosage form, is the complete medication. Conventional dosage forms consist of the drug, the active agent,

and auxiliary substances biologically inert, the excipients. The role of excipients is essentially of binding the drug, filling the dosage form in order to ensure the consistency and volume necessary for the patient use. When in contact with the gastric liquid, the drug is released from the dosage form used for the administration. Two factors determine the release of the drug: the solubility and the rate of dissolution. When the drug is released from the dosage form, it must pass through several barriers, before reaching the site of action. The driving force responsible for the transport of the drug through these membranes is the concentration gradient across the membrane, the process being controlled by diffusion. The amount of unchanged drug that is absorbed by the organism in a certain time and that arrives at the target site through the circulatory system, or bioavailability, depends on the dosage form, and thus may be altered by this dosage form. The drug conveyed by the bloodstream, leaving the intravascular compartment is distributed between extracellular and intracellular compartment where it can reach the receptors for drugs lying in the tissues. Finally the drug is eliminated either by chemical alteration of the molecule with formation of metabolites or by excretion via various organs. The time required for elimination of half the plasma content of the drug by metabolism or excretion, the biological half-time, is of high interest for the dosage regimen prescribed by the physician. An exact dosage regimen is of high importance when the concentration of the drug must be maintained constant in the tissues over a long period of time. Morever, the concentration of the drug must be kept between the median lethal dose (causing the deaths of 50% of experimental animals) and the median effective dose (effective in 50% of cases). The therapeutic index, equal to the ratio of these above concentrations defines the safety margin.

All conventional dosage forms made of a drug dispersed in excipients, release the drug according to the following pattern. The drug is very rapidly dissolved from the dosage form and quickly builds up to a maximum high concentration, which then falls exponentially with time because of the first order absorption. The result is an undulating concentration of the drug in the stomach or intestine, as well as in the blood and tissues, where high concentrations with overdosages alternate with low concentrations and underdosages. The limitations of conventional dosage forms made of drug and excipients appear then since they cause problems in maintaining therapeutic drug levels over only brief durations of time :

(i) The fluctuating drug levels with conventional dosage forms lead to an insufficient efficacy of therapy provoking an excessive use of the drug.

(ii) Overdosage appearing after dissolution of the drug may be responsible for a high frequency of side effects, leading to iatrogenic damage.
(iii) High frequency of administration of conventional dosage forms is limited by the reliability of the patient and the patient compliance (omission, wrong frequency)
(iv) A potent drug may largely lose its therapeutic efficacy through improper formulation, and thus a pharmacologically active substance is not necessarily an effective drug.

Oral dosage systems able to release the drug at a constant rate for a given time period are thus of interest. The result is then a constant uniform concentration of drug in blood and tissues over a given period of time, with the following advantages :
(i) Significant smaller amounts of drug are generally prescribed with a therapeutic system of drug delivery.
(ii) The reduced amount of drug administered reduces the problems of side effects, improving the safety of therapy.
(iii) The patient compliance is usually better with these types of dosage forms, as the frequency of administration is considerably lower.

Simple oral dosage forms capable of controlling the release of the drug are often and easily obtained with monolithic devices where the drug is dispersed in a biocompatible polymer. This polymer which can be either biodegradable or non degradable, plays the role of a polymer matrix. Not only the polymer brings the consistency to the dosage form, but also it controls the release of the drug. The process is generally as follows: the liquid (gastric liquid or intestine liquid) enters the polymer, dissolves the drug and enables the drug to leave out the dosage form through the liquid located in the dosage form. The matter transfers for the liquid and for the drug are controlled by transient diffusion, with concentration-dependent diffusivities, the diffusivity of the drug depending on the concentration of the liquid in the dosage form. The release of the drug being controlled by transient diffusion, exhibits a rather high rate at the beginning of the process which decreases with time in an exponential way. These dosage forms are very simple to prepare and rather inexpensive, but the process of release is controlled by diffusion, and the rate of release is far from being constant.

The drug delivery from the dosage form is studied by using in-vitro tests, these in-vitro tests being built up in such a way that they simulate as much as possible the story in the stomach or intestine of the patient. These in-vitro tests are very useful for many

reasons, and the most obvious are only given :
(i) The conditions of the in-vitro test are very well defined and standardized, enabling comparisons between various results.
(ii) They are easy to perform, and the effect of each parameter can be analysed separately.
(iii) In contrast with the in-vitro test, the in-vivo test is far more complex, as this latter is subject to a variety of influences that differ greatly among individuals.

There are several objectives in this book devoted to the study of the process of matter transfers in oral dosage forms with a polymer matrix able to control the release of the drug. As the driving force for the matter transfers of the liquid and the drug through the polymer is the gradient of concentration, the process is controlled by transient diffusion. Some emphasis is thus placed upon the mathematical treatment of diffusion in solids of various shapes, when the process is so simple that an analytical solution exists. As very often the process of matter transfers is rather complex, it must be studied by using numerical methods with finite differences. Finally, various examples are described by considering simple oral dosage forms with either a non-erodible or an erodible polymer matrix, and with more complex systems consisting of a core and shell. These studies are made by using the method coupling experiments with short tests and long real tests and modelling of the process.

The book is divided in three parts with sixteen chapters :

The first part presents an overview of the mathematical treatment of diffusion through a polymer in the elastomeric state. Various shapes are considered for the solid : thin plane sheets, rectangular parallelepiped, cylinders and spheres. In order to help the reader's understanding, some emphasis is placed upon the conditions in which the mathematical treatment is feasible constant diffusivity, uniform initial concentration, simple boundary conditions. For people wanting to improve their background knowledge of the mathematical treatment of diffusion, various examples are described in a didactic way in the first five chapters. Special consideration is given to the operational conditions : with a very high volume of the liquid in which the dosage form is immersed, or with a finite volume of this liquid ; with a very high coefficient of matter transfer on the surface leading to a constant concentration on the surface, or with a finite coefficient of matter transfer on the surface.

- In chapter 1, general equations of diffusion are given for various shapes of the dosage form, and basic considerations are described.

- In chapter 2, the mathematical treatment of diffusion is shown in various cases with a plane sheet and mono-directional diffusion.
- In chapter 3, the mathematical treatment of diffusion is given with a rectangular parallelepiped and three-dimensional diffusion.
- In chapter 4, radial diffusion through spheres is studied.
- In chapter 5, cylinders of infinite and finite lengths are considered with radial diffusion in the first case and radial and longitudinal diffusion in the second case.

The second part is devoted to numerical treatment of diffusion, in order to accustom the readers to this new and powerful way of working. This method is very useful, as very often no analytical solution can be obtained from the mathematical treatment, because of the complexity of the process : double matter transfers of the liquid and drug, concentration-dependent diffusivity. Explicit numerical methods with finite differences are developed, because of their easy use with microcomputers. Four chapters enable one to consider various shapes.

- In chapter 6, plane thin sheets are considered and classical examples of numerical analysis are developed in the following simple cases : the diffusivity is either constant or concentration-dependent, while various values of the coefficient of matter transfer on the surface are given.
- In chapter 7, numerical analysis is developed with a rectangular parallelepiped and a three-dimensional transfer.
- In chapter 8, numerical analysis for the radial transfer through a sphere is presented.
- In chapter 9, the matter transfers, either radial with long cylinders or radial and longitudinal with cylinders of finite length, are studied with the help of numerical analysis.

The third part examines various approches to industrial problems with practical purposes. A new method coupling experiments and modelling of the process is widely used.

Experiments are used for the following reasons :

- to get deep knowledge of the process
- to obtain the values of parameters, such as the diffusivities by using short tests
- to test the validity of the models.

Modelling of the process is widely used, either with the mathematical treatment when the problem is simple, or with the numerical treatment when the process is complex.

Each of these different cases are discussed in chapters 10 to 16, working through the difficulties encountered with experiments and calculation.

- Chapter 10 concentrates on the drug delivery from simple dosage forms consisting of a drug dispersed in a non-erodible polymer. Two matter transfers are considered with the liquid entering the polymer, dissolving the drug and enabling the drug to leave the dosage form through the liquid located in the polymer. These two transfers are connected with each other, and the diffusivity of the drug depends on the liquid concentration.
- Chapter 11 shows the complexity of the process of drying of dosage forms with a polymer matrix, the process being controlled not only by evaporation but also by diffusion of the liquid through the polymer. Various examples are described and the effect of factors such as the temperature or programmation of temperature, the pressure of the vapour in the surrounding atmosphere, is evaluated.
- Chapter 12 discusses the problem of drug delivery from dosage forms made of a drug dispersed in an erodible polyme matrix.
- Chapter 13 focuses on the interest of preparing dosage forms with constant rate of delivery. Typical dosage forms are presented with a core containing the drug dispersed in a polymer and with an erodible shell surrounding the core.
- Chapter 14 deals with dosage forms made of a core and shell, where the core contains the drug dispersed in a non-erodible polymer and the shell is a non-erodible polymer. The effect of the relative thickness of the shell is of high interest.
- Chapter 15 is devoted to special dosage forms able to deliver the drug from the dosage form when the drug is poorly soluble in the liquid. A swelling polymer is thus added in the erodible polymer matrix which helps the disintegration of the dosage form and thus dissemination of the drug in the liquid. As some polymers swell differently in gastric and intestine liquid, they allow the dosage form to deliver the drug partly in the stomach and intestine.
- Chapter 16 examines the problem of dosage forms where the drug is attached to a polymer, this branched polymer being dispersed in a polymer matrix.

ACKNOWLEDGEMENTS

A large part of this book covers various applications and industrial problems, as many people working in industrial firms have influenced this work through industrial contracts. I am glad to thank them for their interesting cooperation.

Many colleagues and students have supported my efforts and brought contributions worth noting.

Deep gratitude is extended to my colleagues M. Rollet who showed me round the world of galenic pharmacy as well as J. Bardon and C. Chaumat. I am grateful for the collaboration of my colleague J. L. Taverdet in the work concerned with the preparation and studies of dosage forms. I give my best thanks to my colleagues J. Bouzon for his participation in numerical analysis and modelling of the process, and J. P. Montheard who dealt with the polymerization problems in chapter 16. I appreciate the kind help of H. Liu and J. Paulet.

My best appreciation is given to my students :
Y. Armand, D. Bidah, N. Chaffi, A. Droin, A. Eddine, N. Farah, M. Kolli, N. Laghoueg, F. Magnard, P. Magron, Y. Malley, E.M. Ouriemchi, M. Saber, who did their best for preparating their Theses. Many thanks to D. Berthet for his efficient help in calculation and for his drawings, and to C. Cervantes, N. Fauvet, D. Ianna and M. Novais Da Costa for their competent typing of the manuscript.

Table of contents