CONTROLLED RELEASE POLYMERIC FORMULATIONS

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Controlled Release Polymeric Formulations

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FOREWORD

The ACS SYMPOSIUM SERIES was founded in 1974 to provide a medium for publishing symposia quickly in book form. The format of the SERIES parallels that of the continuing ADVANCES IN CHEMISTRY SERIES except that in order to save time the papers are not typeset but are reproduced as they are submitted by the authors in camera-ready form. As a further means of saving time, the papers are not edited or reviewed except by the symposium chairman, who becomes editor of the book. Papers published in the ACS SYMPOSIUM SERIES are original contributions not published elsewhere in whole or major part and include reports of research as well as reviews since symposia may embrace both types of presentation.

PREFACE

The "controlled release" concept has made significant advances in the last decade because of substantial research efforts by private companies, institutions, and governmental agencies directed towards solving some specific problems by this method. While there are many recognized uses of controlled release, most of the above-mentioned programs have been concerned with either the prolonged delivery of drugs at optimal rates or control of a wide range of pests with minimal pollution of the environment. Previous symposia have focused on these application areas. A number of common techniques or concepts applicable to the different areas of application have emerged, each of which employs polymeric materials as a vital part of the controlled release mechanism. Therefore, controlled release technology has become a new area in which to apply or develop interesting concepts of polymer chemistry and engineering.

It was timely to organize a symposium on controlled release within the two divisions of the American Chemical Society most concerned with polymer chemistry and engineering for the purpose of focusing on the polymer-related aspects of this subject. The contents of this book are based on 25 of the 28 papers presented at this symposium. An attempt was made to include papers that traversed the spectrum from fundamentals to commercial products while also covering a wide range of applications and techniques. The individual papers deal with the role of the polymer to varying levels of detail, but the overall objective is served by the total collection of papers.

The manuscripts for this book were collected several weeks after the symposium so that the authors could incorporate their most recent results and take cognizance of the discussions that took place at the symposium. An introductory chapter, not presented at the symposium, is included here primarily as background and perspective for the reader who is new to this field and wishes to use this book as a beginning point to learn the state of the art in controlled release technology.

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Polymers in Controlled Release Technology

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Controlled release technology emerged actively from the 1960's with promises to solve a diversity of problems that have in common the application of some active agent to a system with the objective of accomplishing a specific purpose while avoiding certain other possible responses this agent might cause. A number of techniques for effecting controlled release have been identified and analyzed, and most of these have been considered for or embodied in commercial devices or formulations which already are or soon will be on the market. Most of these concepts have been described in the literature (patents, journals, books, etc.) The proceedings of previous symposia (1-3) and recent reviews (4-16) provide a rapid way to learn the present state of the art of this technology. One of the common features of many of these techniques or formulations is the judicious selection of a polymeric material to act as a rate controlling device, container, or carrier for the agent to be released. The contents of this book are the results of an American Chemical Society Symposium organized primarily to emphasize the role of the polymer and its selection as opposed to focusing on a particular application or methodology although aspects of the latter are included by necessity. The polymer choices in some cases are the result of sophisticated considerations while in others evolution from historical successes had dictated this selection. Both extremes illustrate the considerable opportunity for tailoring polymers to meet the demands of this developing technology.

The purposes of this introductory chapter are to make this book somewhat more autonomous and, therefore,

hopefully of more value to the reader by placing its contents in perspective by reviewing briefly previous developments in concepts, techniques, principles, areas of application, and commercial products. This purpose is largely fulfilled by including in the bibliography a compendium of symposium proceedings, review articles, books, and other references which have been selected to provide the reader with a quick introduction to the literature of this field. From these references and the comments that follow, the reader will see that the present papers deal with only some of the concepts which have developed in this area although a broad and important sampling is represented.

Rationale for Controlled Release

Conventionally, active agents are administered to a system by non-specific, periodic application. For example, in medicine drugs are introduced at periodic intervals by ingestion of pills, liquids, etc. or by injection and then distributed throughout much of the body rather than directed to a specific target. Similarly in agricultural practice, fertilizers, pesticides and the like are distributed to crops at periodic intervals by broadcasting, spraying, etc. Immediately following these application pulses the concentration of the active agent rises to high levels system-wide. In some cases, these initially high concentrations may produce undesired side effects either to the target area of the system and/or the environment around the target. As time passes after this spike of active agent, its concentration begins to fall because of natural processes such as elimination from the system, consumption, or deterioration. Before the next application, the concentration of the active agent may fall below the necessary level for the desired response. Thus periodic applications are frustrated by concentrations of active agent which may be alternately too high or too low within the same cycle when the time between doses is long while on the other hand more frequent application of smaller doses results in more inconvenience and expense of application. In addition, a cyclic regime is usually rather inefficient in that a considerable fraction of the active agent never gets to perform the intended function either because of deterioration or loss to the system

environment. In many cases the latter may be quite serious, and in all cases both factors inflate the cost of the treatment. Certainly a more desirable regime would be to release the active agent at a controlled rate that maintains its concentration in the system within optimum limits, and it would be even better to release this agent directly to the target area of the system if one exists or can be identified. The latter are the objectives of controlled release technology in general whether the active agent is a drug, pesticide, or sex attractant or whether the purpose is to control the growth of weeds or to prevent barnacles from forming.

Areas of Application

Controlled release technology has been considered for a wide variety of applications of which a large fraction are either medically related or for pest control. Some of the papers incorporated in this book are general in scope and the formulations or principles discussed might be applicable to a number of different areas; however, most deal with particular objectives. It is of interest, therefore, to summarize these objectives here and to mention examples of other specific problems of active interest which are not dealt with in this book.

In the medical area, contraception or fertility control has historically been one of the most publicized applications, and this is reflected in the papers which follow. However, also covered here more briefly, are formulations to deliver narcotic antagonists, fluoride for dental purposes and drugs to combat cancer and cardiac arrhythmia and a drug to induce hypertension for experimental studies. Many of these papers deal with techniques of general applicability as drug delivery systems. An example of a medical area not covered here is the recently commercialized device for control of glaucoma (8).

A number of the following papers deal with the control of pests such as snails, weeds, marine fouling organisms, roaches, flys through the release of toxicants or pheromones. None of the present papers deal in detail with the release of fertilizers, pesticides, or growth regulators for agricultural purposes but activities in these areas are summarized by one of the authors.

Techniques and Release Kinetics

One of the central problems in controlled release formulations is to combine the active agent with its carrier in an economical manner yet achieve a release profile that best fits the situation. These two desires are often in opposition of one another so compromises must be made. Frequently the desired release profile is a constant rate of delivery of the active agent which in analogy with chemical kinetics has become known as a "zero order" process since it does not depend on how much of the agent has been delivered or remains. Many of the formulations used in controlled release technology do not meet this objective. At this point it will be useful background to categorize as generally as possible the techniques of formulation that are employed in the subsequent papers and to discuss their inherent release kinetic characteristics. Following this, some other techniques not employed here will be mentioned.

The classification scheme preferred here divides the devices of interest into the following basic types which in some cases may be combined in various ways:

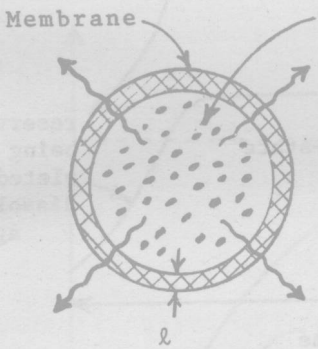
I. Erodible Devices that Disappear

In this category the active agent is released as the carrier is eroded away by the environment through physical processes such as dissolutioning or by chemical processes such as hydrolysis of the polymer backbone or crosslinks. The kinetics of release cannot be simply stated since they depend on the details of the erosion mechanism and geometry. The central distinction is the complete disappearance of the device in time which has obvious advantages providing the erosion products are of no health or environmental concern.

II. Membrane Encapsulated Reservoir Devices

In this category a rate controlling membrane completely encloses a cavity which contains the active agent appropriately dispersed. These systems have also been referred to as depot devices (8). The membrane may be porous or non-porous, and in the case of the latter the environmental fluids may or may not appreciably swell the membrane. The most useful situation is when the reservoir contains a suspension of the active agent in a fluid since this will maintain a

constant activity of the agent in the reservoir until the excess has been removed. This situation creates a constant steady-state release rate by diffusion across the membrane as illustrated below for an idealized situation:



$$\text{Release Rate} = SDC_s^m/\ell$$

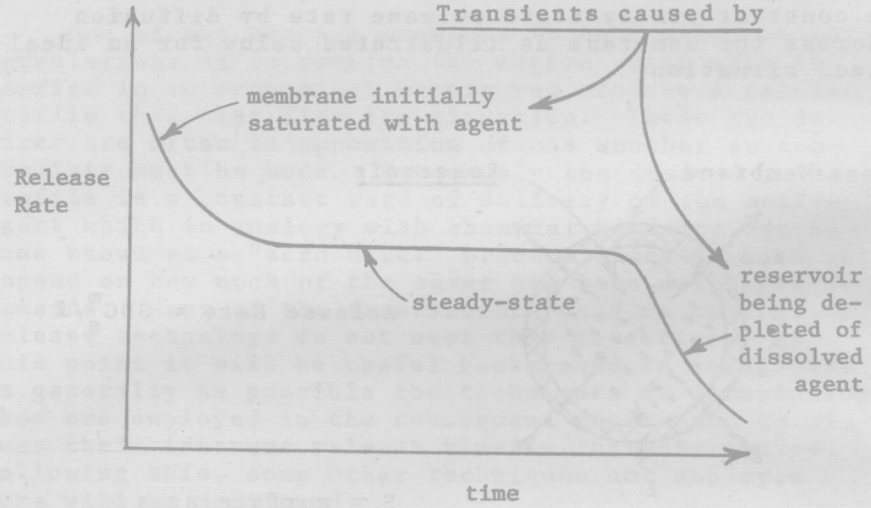
S = surface area
D = diffusion coefficient of active agent in membrane
C_s^m = solubility of active agent in membrane

If the active agent is totally dissolved in the reservoir fluid, then its activity will change and the release rate will decay more or less exponentially with time as expected for "first order" kinetics.

These devices may be rather large (macroencapsulation) or very small in which case microencapsulation is the usual terminology (10-16).

In general the release profile for encapsulated systems has the form shown by the graph at the top of the next page. The duration and rate for each of the three stages shown can usually be engineered within certain limits by the design of the device.

A special case of encapsulated devices depends on rupture of the membrane by some mechanical action to release the active agent (13).



III. Matrix Devices

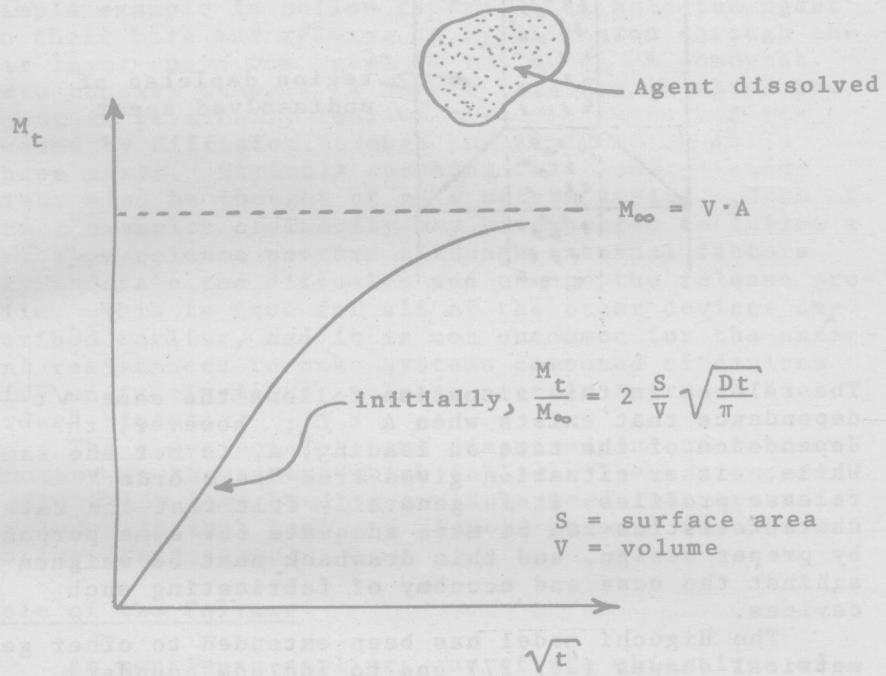
In this type of system there is no membrane per se but rather the active agent is dispersed in a carrier - usually a polymer - from which it is ultimately extracted. These have also been referred to as monoliths (8) and have obvious advantages of fabrication, but generally they do not yield "zero order" release kinetics. Matrix devices may be divided into two categories depending on the mechanism by which the agent is released:

A. Release Caused by Simple Diffusion of Agent. In this case the active agent always has some mobility within the carrier and its release depends on the juxtaposition of a suitable exterior sink. We can further divide this category depending on whether the initial loading per unit volume of the agent within the matrix, A, exceeds the agent's solubility in the matrix, C_s, or not

1. $A < C_s$

For this situation all of the agent at equilibrium is dissolved in the matrix and release involves its diffusion from the device following simple notions similar to desorption as treated in most classical works on diffusion (17-19, 22). The total amount

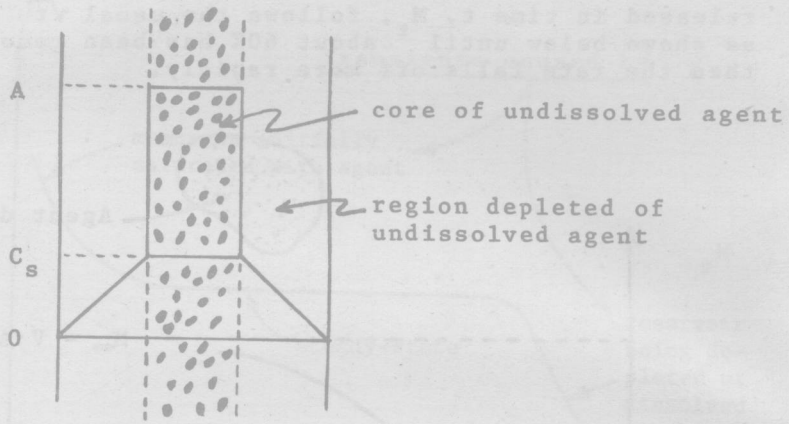
released in time t, M_t, follows the usual $\sqrt{t}$ relation as shown below until about 60% has been removed and then the rate falls off more rapidly.



2. $A > C_s$

In this case, the excess agent above that which is dissolved at equilibrium is dispersed in the matrix as small particles. The details of the extraction may be very complicated; however, for the usual case when diffusion is rate limiting rather than other processes such as dissolutioning, Higuchi (25,26) has shown that a very simple but extremely clever pseudosteady-state analysis describes the release rather accurately (30). The figure at the top of the next page shows the physical picture envisioned. The mathematical result Higuchi obtained for the release rate from planar geometrics is

$$\text{Release rate} = S \sqrt{\frac{DC_s(A - 1/2\ C_s)}{2t}}$$



The release in this situation follows the same $\sqrt{t}$ dependence that exists when $A < C_s$; however, the dependence of the rate on loading, A, is not the same. While neither situation gives true "zero order" release profiles, it is generally felt that the rate characteristics can be made adequate for some purposes by proper design, and this drawback must be weighed against the ease and economy of fabricating such devices.

The Higuchi model has been extended to other geometrical shapes (26, 27) and to include boundary layer resistances (28, 30).

B. Release Triggered by Ingression of Environmental Agent. In this case the agent may be dispersed within the matrix either physically or chemically bound to it, but in either case it is initially not mobile - for physical dispersions this may be owing to very small diffusion rates. Its release may be triggered by the penetration of some environmental agent, e.g. water, into the matrix. This event could lead to a chemical reaction to unbind the agent, e.g. hydrolysis, or simply to plasticize the matrix to allow physically bound molecules to diffuse. The release rate may be controlled by the penetration of the environmental agent or the reaction it produces or some combination thereof and then the exact form of the rate depends on the details of the particular system. This class of devices differs from erodible systems in that the matrix remains physically intact.

IV. Reservoir Devices Without a Membrane

This final category of devices covered in this book confines the active agent in a reservoir but does not employ any membrane to control its release. A simple example is hollow fibers which hold the agent in their bore and release it by diffusion through the air layer above the agent in the bore. A somewhat more complex example is porous networks in which the agent is physically imbibed into the pores and released by diffusion through the fluid which fills these pores. Strictly speaking this configuration might also be thought of as a matrix device. Both of these examples ordinarily may be expected to follow a $\sqrt{t}$ type release pattern although external factors may moderate the diffusion and change the release profile. This is true for all of the other devices described earlier, and it is not uncommon for the external resistances to make systems composed of devices with an intrinsic $\sqrt{t}$ release profile approach "zero order" kinetics.

The above concepts are discussed in one form or another in the papers which follow. There are concepts which have been or could be used that are not included in this book and "osmotic pumps" (8,29) are an important example.

Role of the Polymer

As mentioned earlier, one of the objectives of this book is to focus on the function and selection of the polymer used in the controlled release formulation. The requirements of the polymer are obvious in some cases but it is useful to summarize here what a few of the considerations in its selection might be:

1. Diffusion and solubility characteristics with the active or environmental agents to provide the desired release control (see e.g. 19,20,21,23,24,31).

2. Compatibility with the environment (e.g. not toxic or antagonistic in medical applications).

3. Stability in the environment (should not degrade or change undesirably).

4. Compatibility with the active agent (no