Polymeric Delivery Systems

Properties and Applications

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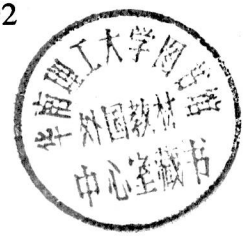

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Polymeric Delivery Systems

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Foreword

THE ACS SYMPOSIUM SERIES was first published in 1974 to provide a mechanism for publishing symposia quickly in book form. The purpose of this series is to publish comprehensive books developed from symposia, which are usually "snapshots in time" of the current research being done on a topic, plus some review material on the topic. For this reason, it is necessary that the papers be published as quickly as possible.

Before a symposium-based book is put under contract, the proposed table of contents is reviewed for appropriateness to the topic and for comprehensiveness of the collection. Some papers are excluded at this point, and others are added to round out the scope of the volume. In addition, a draft of each paper is peer-reviewed prior to final acceptance or rejection. This anonymous review process is supervised by the organizer(s) of the symposium, who become the editor(s) of the book. The authors then revise their papers according to the recommendations of both the reviewers and the editors, prepare camera-ready copy, and submit the final papers to the editors, who check that all necessary revisions have been made.

As a rule, only original research papers and original review papers are included in the volumes. Verbatim reproductions of previously published papers are not accepted.

M. Joan Comstock
Series Editor

Preface

POLYMERIC DRUG DELIVERY SYSTEMS are generating great interest in the scientific community. The thorough study of these systems is leading to increasingly frequent discoveries. However, equivalent systems for foods, cosmetics, and herbicide delivery are very hard to find. They have received a much smaller share of the fundamental research, especially from academia, and are still very much an applied art in the hands of the excellent, but unpublished, formulators of industry. Information on such delivery systems is lost as those formulators retire, their work never to be published or documented. Exceptions are found in the burgeoning work with polymeric delivery systems applied to skin. These research efforts started in pharmacology and are slowly moving into the cosmetic field.

The purpose of *Polymeric Delivery Systems* is to pull together the current work in the field as it applies to drugs, cosmetics, food, and herbicides. Although the editors have worked very hard to present a balanced view of the various disciplines, the resulting collection reflects the fact that most published work in the field is still on polymeric drug delivery systems—in itself a strong argument for such a book.

This volume is intended to inform and teach industrial technologists and academic researchers who are concerned with delivery systems for drugs, herbicides, and cosmetics. The advances described here are meant to stimulate new ideas for applying drug delivery technology to systems in cosmetics, food, pharmaceuticals, and pesticides. International authors representing academia, industry, and governmental research centers have provided a balanced perspective in their presentations on advances, basic research, and practical considerations of application techniques.

We put much thought into arranging the flow of the chapters so that they may help build the reader's knowledge in an orderly fashion. This book was not meant to be just a collection of papers for reference purposes, but a stimulus to the thinking process, designed to promote ideas and to present new developments in those areas lacking in the previously mentioned resource material.

The opening chapter outlines the scope of polymeric delivery systems: preparations, properties, and applications. Other topics include controlled release in the food and cosmetics industries, the general properties of various polymers used as delivery systems, and the processing of delivery systems. The contents continue on to applications in drugs, pesticides, and foods, starting with simple systems that can be widely applied (e.g., cyclodextrin–used to deliver water-insoluble drugs–has also been reported to carry cosmetics, herbicides, and flavors for beverages). Fol-

lowing discussion of the kinetics of release (vital to any polymeric delivery system), the book concludes with the more specialized polymeric drug delivery systems applied in vivo, i.e., polysaccharides such as biodegradable chitin, glycosylated dextran, and polylactides. *Polymeric Delivery Systems* presents varied aspects of the latest research on polymeric delivery systems in the hope that it will inspire more exchange, dialogue, and learning among the disciplines.

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Chapter 1

Polymer Delivery Systems Concepts

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Examples of successful applications of controlled release are mentioned and commonly used concepts are defined. The chapter describes how polymers are used in devices and how their properties affect device performance. Processes of wide applicability including those covered in succeeding chapters are summarized.

The task of controlled release is deceptively simple: get the right amount of the active agent at the right time to the right place. Controlled release is a term that represents an increasing number of techniques by which active chemicals are made available to a specified target at a rate and duration designed to accomplish an intended effect. In their most elegant implementation, these systems can mimic processes of living cells such as secretion of hormones or enzymes. Many other terms besides "controlled" have been used to describe somewhat different delivery system concepts from "continuous" release to "timed" release. Some of the terms are defined more precisely by Ballard (*1*). Only a few examples will be cited in the paragraphs following.

Controlled Release of Drugs. Controlled release is often used to extend the time the effective therapeutic dose is present at the target from a single administration, and to avoid or minimize concentrations that exceed therapeutic requirements. It also can decrease the needed dose of an expensive active ingredient. Protecting certain tissues is often desirable, e.g. the stomach from irritation. Targeting tissues may be desirable, avoiding toxic effects. This can make the administration of the drug less invasive. Taste-masking of a drug can improve patient compliance. Incompatibilities between ingredients can be mitigated. A few commercial examples may be mentioned: Occusert, a device for releasing pilocarpine, a drug to treat glaucoma, to the eye (*2,3*), an implantable osmotic pump capable of delivering a nearly constant 20 mg/hr of solution to the body for almost a day (*4*) and Norplant, a long-term contraceptive implant (*5*).

Controlled Release Pesticides. Controlled release can increase the effectiveness of an agent, and its specificity. It can decrease the possibility of damage to the environment.

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Penncap M and E, represent examples of microencapsulated forms of methyl and ethyl Parathion (*6*). Systems have been developed for releasing pheromones to confuse insects (*7*), collars to keep fleas away from pets (*8*), even keep mollusks from the hulls of ships (*8*).

Controlled Release Fertilizers. Controlled release can decrease the number of applications. It can make one application last longer. A reduction in run-off into rivers or aquifers may be another benefit.

Special Control Release Applications. "Carbonless carbon paper" was the first product involving microencapsulation. A latent dye, crystal violet lactone is contained in 5 to 25 micron microcapsules that are coated on the back of a page. The action of a sharp pencil, typewriter, or impact printer ruptures the microcapsules, releasing the lactone to react with an acid clay present on the copy sheet, activating the color (*9*).

Side effects in the treatment of diabetes would be decreased, if encapsulated implants of islets of Langerhans from the pancreas could be used. The islets could originate from a different species. Encapsulation would keep the islets from being destroyed by the immune system of the host, allowing the cells to release insulin in response to the concentration of glucose (*10*).

Improvements in oil well stimulation with hydraulic fracturing fluids have been realized with the use of controlled release viscosity breakers (*11*). Increasing the likelihood of germination of seeds under adverse conditions is another application of controlled release. Because controlled release is a rapidly changing field, new ideas are being generated and applications are being evaluated every day.

Functions of Polymers in Controlled Release.

Polymers are uniquely suited as materials of construction for delivery systems because their permeability can be modified and controlled. They can be shaped and applied relatively easily by a large variety of methods. Active ingredients and property modifiers can be incorporated either physically or chemically. In general, polymers have little or no toxicity. Despite the diversity of applications, they principally serve as membranes or envelopes, as matrices in which the active ingredient is dispersed or dissolved, or as carriers which are chemically attached to the active ingredient. Not all controlled release devices use polymers explicitely. For example liposomes do not.

Delivery Systems Terms.

Devices can range in size from as small as one molecule to coated tablets and boluses used in cattle.

Availability, or bioavailability is an important property of most drug-containing devices. Tests in glass-ware (*in vitro*) or in the living system (*in vivo*) must be conducted to ascertain that the active ingredient is available under specified conditions.

Biodegradable refers to polymers that under certain conditions undergo a decrease in molecular weight eventually disintegrating or dissolving in the medium. It is most often applied to polymers and copolymers of lactic, glycolic, hydroxybutyric acids as well as poly(ε-caprolactone). For these substances the degradation is hydrolytic and no enzymes are involved. Kinetics generally follow first order (*12*, *13*) and are often insensitive to pH. Natural polymers such as starch and cellulose are also biodegradable and enzymes are involved in these cases. Polyphosphazenes, polypeptides, and proteins have also been proposed for drug delivery. Other polymers mentioned as biodegradable were, poly(dihydropyrans), poly(acetals), poly(anhydrides) (*14*), polyurethanes, and poly(dioxinones).

Biocompatible devices are devices that can be applied without causing undesirable effects in living systems.

Bioabsorbable devices are those which are degraded by a living system and can be utilized or metabolized by it.

Erodible systems are designed to control the release of the active substance by erosion of the matrix.

Zero order release means the active substance is released at a constant rate. By analogy to reaction kinetics, the rate of release, $-dc/dt = k$. It can be approximated by a reservoir device containing a saturated solution of the active ingredient surrounded by a rate-limiting membrane. This requires a supply of undissolved active ingredient in the device and a non-changing or zero sink condition (*15*).

First order or pseudo-first order means the release rate is proportional to the concentration remaining in the device i.e., with a rate, $-dc/dt = kc$. This implies a decrease in rate with time. It would be approximated by a device in which the concentration decreased as the amount remaining in the device decreased.

Burst effect refers to the tendency of some devices to release the active substance more rapidly during some period, usually the initial test period, than during the steady-state, or a later period.

Time lag is observed when the rate limiting membrane must first establish a concentration gradient before releasing at the designed rate. Therefore some time elapses before the release rate reaches its designed value. Mathematical expressions of this and the above phenomenon are given in (*15*).

Reservoir devices consist of a drug or other active agent enclosed within an inert controlling membrane. Examples would be a tube filled with the active substance, where the wall of the tube would serve as the limiting membrane, a sphere of the active substance coated with a film controlling the diffusion of the active substance, or a slab

of the active substance closed off from the medium by a film which controls the diffusion.

Matrix devices in which the active drug is dispersed throughout the polymer are called monolithic devices or monoliths by a number of authors. One can distinguish between monolithic devices in which the active ingredient is dissolved, dispersed, located in connected pores, or granular. The equations describing the time behavior of such devices predict that initially the fraction released varies as $time^{1/2}$ and the rate of release is proportional to $time^{-1/2}$. Baker and Lonsdale (*15*) in their classic paper, treat each of the cases separately including the different geometries such as slab, sphere and cylinders. As time increases, the release rate is better approximated by an exponential decay (Late time approximation). A more recent review of this material by Roseman may be found in (*16*).

Targeting of drugs is a concept that is as old as the dream of the magic bullet of Paul Ehrlich (*17*). Thies (*18*) distinguishes between active and passive targeting. Passive targeting takes advantage of an existing body process such as the rapid concentration of particles smaller than 1 micron in the liver or spleen after intravenous injection. In active targeting, the natural tendency of the body to distribute the active substance is altered. The drug or carrier, because it has a special affinity e.g., by certain molecular interactions such as a lock and key mechanism, interacts with specific cells. If this could be implemented, it could improve cancer chemotherapy considerably.

Enteric coatings, coatings which are less soluble in acidic aqueous solutions than neutral ones, provide a means for a drug to by-pass the stomach and only become available in the intestine. This is a method to direct rather than target a drug. Many enteric coatings are based on polymers containing phthalic acid residues attached to cellulosic or vinyl polymer chains. Reverse enterics, on the other hand, do not dissolve in neutral media such as the mouth, but dissolve very rapidly in an acid medium such as the stomach.

Polymer Properties that Affect the Release of Active Substances.

Consider a polymer membrane and a diffusing active substance in solution. The amount of the substance which diffuses per unit time across the membrane at steady-state is proportional to the diffusion coefficient and to the concentration difference across the membrane measured on each side of the membrane just inside the membrane. (It is also proportional to the area and inversely proportional to the thickness of the membrane). Because the concentration inside the membrane is not known and is often much different from the concentration in solution, the concentration difference normally measured in the solution must be multiplied by the distribution coefficient. The distribution coefficient is the ratio of the solubility of the agent in the membrane to its solubility in the external medium. The permeability is the

product of the diffusion coefficient and the solubility coefficient. Its dimensions are the same as the diffusion coefficient, (length)^2/time.

It must be pointed out, as Baker and Lonsdale (*15*) have done, that the relatively low diffusivity and solubility of large molecules in polymers often constrain the release rates attainable with delivery systems which employ unplasticized dense membranes. Even silicone rubbers which have high diffusion coefficients and solubilities for many organic active molecules of interest, rarely permit maximum daily fluxes greater than 2.5 mg/cm^2 through a 0.1 mm thick membrane. For less permeable polymers, fluxes two orders of magnitude lower are typical. This is the reason why applications have favored silicone rubbers and only very potent drugs such as steroids. Some values of these parameters are listed in Table I. It illustrates the range of values encountered. The diffusion coefficient and the solubility (i.e. distribution coefficients) have very different dependencies in the polymer phase. This will be discussed below.

Table I. Selected Values of Diffusion Coefficients and Partition Coefficients in Polymers

Solute	Polymer	Diffusion Coefficient cm^2/sec	Partition Coefficient (polymer/water)
Acetophenone	Polyethylene	3.55×10^{-8}	3.16
Chlormadione Acetate	Silicone Rubber	3.03×10^{-7}	82
Estriol	Polyurethane Ether	2×10^{-9}	133
Fluphenazine	Polymethyl-methacrylate	1.74×10^{-17}	
Hydrocortisone	Polycaprolactone	1.58×10^{-10}	
17α-hydroxy-progesterone	Silicone Rubber	5.65×10^{-7}	0.89
Progesterone	Silicone Rubber	5.78×10^{-7}	45 to 60
Salicylic Acid	Polyvinyl Acetate	4.37×10^{-11}	

SOURCE: Adapted from ref. 16 with permission. Copyright 1980 CRC Press.

Hydrophilic polymers, or polymers that can swell in water or other solvents, are not subject to the limitations of the dense polymers in the above table and will be covered in a later section. Porous polymers also can have higher fluxes.