Controlled-Release Technology

Pharmaceutical Applications

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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. Papers are reviewed under the supervision of the Editors with the assistance of the Series Advisory Board and are selected to maintain the integrity of the symposia; however, verbatim reproductions of previously published papers are not accepted. Both reviews and reports of research are acceptable, because symposia may embrace both types of presentation.

Preface

CONTROLLED-RELEASE TECHNOLOGY HAS RAPIDLY EMERGED over the past decade as a new interdisciplinary science that offers novel approaches to the delivery of bioactive agents. These agents include pharmaceutical, agricultural, and veterinary compounds. By achieving predictable and reproducible release rates of bioactive agents, particularly pharmaceuticals, to the target environment for an extended time, controlled-release delivery systems can achieve optimum therapeutic responses, prolonged efficacy, and decreased toxicity. Many delivery systems have already been developed; some of them have proven commercially successful in many fields, including medicine, agriculture, forestry, and consumer products. However, the pharmaceutical area has gained the most significant growth and rapid advances in recent years, as evidenced by the proliferation of publications, patents, and controlled-release products in this area.

This expanding field represents an interdisciplinary effort that requires input from chemistry, materials science, engineering, pharmacology, and other related biological sciences. Controlled release has been the subject of many books. However, most of them are published with a specific group of readers in mind, usually pharmaceutical, agricultural, or biological scientists. Because many of the disciplines needed in the area of controlled-release research are related to chemistry (including polymer chemistry; polymer physics; organic, medicinal, physical, and analytical chemistry, as well as chemical engineering), this publication, addressed to chemically oriented scientists, is timely. A review of the current status and future prospect of the field is provided.

The symposium on which this book is based represented an effort to examine recent advances in the field with particular emphasis on pharmaceutical applications within the context of basic science and engineering. The chapters in this book are selected from the 33 papers presented at the symposium. Each manuscript was thoroughly reviewed by leading experts in the field, edited for content and style, and revised by the authors as needed. The interdisciplinary nature of controlled-release technology is reflected in the diversity of subject areas presented here. To provide focus and cohesiveness, the chapters have been divided into six general areas. In addition, an overview chapter is included to provide perspectives on the current status and future prospects of the pharmaceutical applications of controlled-release technology.

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Chapter 1

Overview of Controlled-Release Drug Delivery

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During the past two decades, significant advances have been made in the area of controlled release as evidenced by an increasing number of patents, publications, as well as commercial controlled-release products for the delivery of a variety of bioactive agents ranging from pharmaceutical to agricultural and veterinary compounds. This proliferation of interest is a reflection of the growing awareness that by achieving predictable and reproducible release rates of bioactive agents, particularly pharmaceuticals, to the target environment for a desired duration, optimum biological responses, prolonged efficacy, decreased toxicity as well as reduction of required dose level as compared to the conventional mode of delivery can be effectively achieved.

So far, the controlled-release pharmaceutical area has gained the most significant growth as a result of intense interdisciplinary efforts involving contributions from chemistry, material science, engineering, pharmacology and other related biological sciences. By improving the way in which drugs are delivered to the target organ, a controlled-release drug delivery system is capable of achieving the following benefits: (1) maintenance of optimum therapeutic drug concentration in the blood with minimum fluctuation; (2) predictable and reproducible release rates for extended duration; (3) enhancement of activity duration for short half-life drugs; (4) elimination of side effects, frequent dosing, and waste of drug; and (5) optimized therapy and better patient compliance. A number of controlled-release drug delivery systems have been developed and some are already commercialized. These include, for example, transdermal nitroglycerin delivery systems for the prevention of angina and oral osmotic pump devices for the delivery of a variety of therapeutic agents.

The purpose of this overview chapter is to provide perspectives in the current status and future prospects of controlled release drug delivery. This is accomplished by examining various delivery systems from a mechanistic point of view, exploring applications of these systems, and discussing relevant biopharmaceutical parameters. A major section of this book is devoted to fundamental issues and applications of transdermal and transmucosal delivery systems (Chapter 6,8,17-23). Other developing systems of future potential

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are addressed by various Chapters of this book involving self-regulating insulin delivery systems (Chapter 13), hydrogels (Chapters 5,10-12), drug-polymer conjugates (Chapter 14), and biodegradable microspheres (Chapters 15,16). To provide a broader scope on the physicochemical basis of controlled release, the fundamental aspects of diffusion in polymers (Chapters 2-4), polymer and delivery system characterization (Chapters 7,9) as well as other related applications of delivery systems (Chapters 24,25) are also discussed.

Classification of Controlled-Release Drug Delivery Systems.

An ideal drug delivery system is one which provides the drug only when and where it is needed, and in the minimum dose level required to elicit the desired therapeutic effects. In practice, such a system should provide a programmmable concentration-time profile that produces optimum therapeutic responses. This goal can only be achieved to a limited extent with conventional dosage forms.

Recent development in polymeric delivery systems for the controlled release of therapeutic agents has demonstrated that these systems not only can improve drug stability both in vitro and in vivo by protecting labile drugs from harmful conditions in the body, but also can increase residence time at the application site and enhance the activity duration of short half-life drugs. Therefore, compounds which otherwise would have to be discarded due to stability and bioavailability problems may be rendered useful through a proper choice of polymeric delivery system.

A useful classification of controlled-release polymeric system based on the mechanism controlling the drug release is as follows:

A. Chemically-controlled systems
   a. Bioerodible systems
   b. Drug-polymer conjugates
B. Diffusion-controlled systems
   a. Membrane-reservoir systems
      - Solution-diffusion
      - Osmotic pumping
   b. Matrix systems
      - Matrix diffusion
      - Polymer erosion
      - Polymer swelling
      - Geometry
      - Concentration distribution

Most of the delivery systems described in this book can be described by one of the above classifications.

Chemically-Controlled Systems

Bioerodible Systems. In this system, the polymer matrix contains hydrolytically or enzymatically labile bonds and uniformly dissolved or dispersed drug. As the polymer erodes by hydrolysis or enzymatic cleavage, the drug is released to the surrounding environment. One major advantage of such an approach is the elimination of the need to surgically remove the device after application. However, depending on the specific polymer used, the erosion/degradation products may have different degree of toxicity. As a result of research on improved absorbable sutures, poly (lactic acid), poly (glycolic

acid), and lactic/glycolic acid copolymers, which hydrolyze to natural metabolites, have been developed for drug delivery purposes (1).

Often the terms "bioerodible" and "biodegradable" are used interchangeable. However, "bioerodible" is usually reserved for systems where the polymer erosion occurs in a time scale similar to that of the drug release. In other words, the erosion process has a direct effect on the drug release. On the other hand, "biodegradable" polymer is for systems where the polymer degradation occurs after the drug release is long completed. In this case, the degradation process has no direct effect on the drug release.

As pointed out by Heller (2), polymer erosion can be controlled by the following three types of mechanisms: (1) water-soluble polymers insolubilized by hydrolytically unstable cross-links; (2) water-insoluble polymers solubilized by hydrolysis, ionization, or protonation of pendant groups; (3) hydrophobic polymers solubilized by backbone cleavage to small water soluble molecules. These mechanisms represent extreme cases; the actual erosion may occur by a combination of mechanisms. In addition to poly (lactic acid), poly (glycolic acid), and lactic/glycolic acid copolymers, other commonly used bioerodible/biodegradable polymers include polyorthoesters, polycaprolactone, polyaminoacids, polyanhydrides, and half esters of methyl vinyl ether-maleic anhydride copolymers (3).

With respect to the mechanism of drug release, it is important to distinguish between two types of hydrolytic erosion of water-insoluble polymers. On one hand, homogeneous erosion occurs by having hydrolysis at a uniform rate throughout the matrix. This is often referred to as bulk erosion which is capable of increasing the drug permeability through the polymer as time proceeds and thereby producing an accelerated release via a combination of diffusion and erosion. On the other hand, heterogeneous erosion confines the hydrolysis to the surface of the device and therefore commonly referred to as surface erosion. This process is capable of giving rise to a zero-order drug release for devices with constant surface area.

Mathematical analysis of surface bioerodible systems has been presented by Lee (4)who recently also investigated the effect of non-uniform initial drug concentration distribution on the kinetics of drug release from polymer matrices of various geometries (5).

Drug-Polymer Conjugates. This system involves drug molecules chemically bounded to a polymer backbone. The drug will be released through hydrolytic or enzymatic cleavage. Such polymeric drug carriers are also referred to as polymeric prodrugs. The attachment of drugs to macromolecular carriers alters their rate of excretion from the body and provides the possiblity for controlled release over a prolonged period. Furthermore, it limits the uptake of drug by cells to the process of endocytosis, thus providing the opportunity to target the drug to the particular cell-type where its activity is needed (6).

Both natural polymers such as polysaccharides and synthetic polymers such as polylysine, polyglutamic acid, polyphosphazenes, copolymers of vinylpyrrolidone, copolymers of 2-hydroxypropylmethacrylamide, and etc. have been used as drug carriers. The structure of these polymers can be modified by the incorporation of hydrophobic units, sugar residues, or sulfonyl groups to achieve a specific tissue affinity.

The drug-polymer linkage may be covalent, ionic, or through some weaker secondary molecular forces. The polymer backbone may be either biodegradable or non-biodegradable. The drug can be part of the polymeric backbone or attached to the side-chain either directly or through a spacer group. The spacer group is generally selected in such a way that it may be hydrolyzed or degraded enzymatically under specific environmental conditions. Examples of such drug-polymer conjugates include the attachment of ampicillin, 6-amino-penicillanic acid, daunomycin, and puromycin to N-(2-hydroxypropyl)-methacrylamide copolymers (7,8), methotrexate to poly (L-lysine) (9), and norethindrone to poly(hydroxyalkyl)-L-glutamine (10). In addition to diffusion rate limitations as described in the next section, the drug release rate is primarily governed by the rate of cleavage of the drug from the polymer.

Diffusion-Controlled System

Membrane-Reservoir Systems. Diffusion controlled polymeric delivery systems are finding increasing applications in the area of controlled release pharmaceuticals. To achieve optimum therapeutic effects especially for drugs with short biological half-lives, it is often desirable to have a zero-order drug release. Membrane-reservoir devices, where the drug core is surrounded by a rate-controlling membrane, are often employed for this purpose. The presence of a saturated reservoir in this case is essential to maintain a constant rate of drug release.

The kinetics of drug release from such membrane-reservoir systems generally follows either a solution-diffusion mechanism or an osmotic pumping mechanism. In the solution-diffusion mechanism, the drug transport occurs by first dissolving in the membrane at one interface followed by diffusion down a chemical potential gradient across the membrane and eventually released from the second interface into the external medium. Such solution-diffusion mechanism is typically observed in non-porous membranes. A similar mechanism is also responsible for drug permeation through swollen hydrogel membranes as well as porous membranes. In the latter case the drug permeation takes place by diffusion through the solvent filled porous network.

Under steady state conditions, a membrane device having a saturated drug reservoir can maintain a constant thermodynamic activity gradient across the membrane for an extended period of time. As a result, a constant rate of drug release sometimes referred to as "zero-order release" of the drug is established. The rate of release from such a system is generally dependent on the device geometry and the nature, thickness and area of the membrane, whereas the duration of the release is governed by the size of the drug reservoir. The mathematical analysis of the kinetics of drug release from membrane-reservoir systems has been discussed extensively in the literature (11,12).

Before the establishment of a steady state, the membrane-reservoir device will exhibit initial release rate higher or lower than the steady state value, depending on the prior history of the device. Thus, immediately after fabrication, a finite time lag will be required to establish the steady-state concentration profile

within the membrane. However, after the device is stored for some time, drug will saturate the membrane and subsequently give rise to an initial release rate higher than the steady state value. This is the so-called burst effect. The magnitude of these transient effects is related to the drug diffusion coefficient in the membrane and the membrane thickness.

Membrane-reservoir systems based on solution-diffusion mechanism have been utilized in different forms for the controlled delivery of therapeutic agents. These systems including membrane devices, microcapsules, liposomes, and hollow fibres have been applied to a number of areas ranging from birth control, transdermal delivery, to cancer therapy. Various polymeric materials including silicone rubber, ethylene vinylacetate copolymers, polyurethanes, and hydrogels have been employed in the fabrication of such membrane-reservoir systems (13).

In addition to the solution-diffusion mechanism discussed above, the drug release from a membrane-reservoir device can also take place through an orifice in the membrane via an osmotic pumping mechanism, where a semipermeable membrane such as cellulose acetate is utilized to regulate the osmotic permeation of water (14). For a system of constant reservoir volume, the device delivers a volume of drug solution equal to the volume of osmotic water uptake within any given time interval. The rate of osmotic water influx and therefore the rate of drug delivery by the system will be constant as long as a constant thermodynamic activity gradient, usually derived from a saturated reservoir with excess solid, is maintained across the membrane. However, the rate declines parabolically once the reservoir concentration falls below saturation.

Such an osmotic delivery system is capable of providing not only a prolonged zero-order release but also a delivery rate much higher than that achievable by the solution-diffusion mechanism. The system is also capable of delivering drugs with a wide range of molecular weight and chemical composition which are normally difficult to deliver by the solution-diffusion mechanism. The delivery rate from such devices is generally regulated by the osmotic pressure of the drug core formulation and by the water permeability of the semipermeable membrane. Equations for predicting release rate from osmotic pumping devices have been discussed by Theeuwes (15).

Matrix Systems

Matrix Diffusion. Historically, the most popular diffusion-controlled delivery system has been the matrix system, such as tablet and granules, where the drug is uniformly dissolved or dispersed, because of its low cost and ease of fabrication. However, the inherent drawback of the matrix system is its first-order release behavior with continuously diminishing release rate. This is a result of the increasing diffusional resistance and decreasing area at the penetrating diffusion front as matrix diffusion proceeds.

The kinetics of drug release from matrix devices containing uniformly dissolved or dispersed drug are well documented. In a flat sheet geometry, where the surface area is relatively constant,

the amount of drug release follows a square-root-of-time relationship. For systems containing dissolved drug, the fractional drug release M/M_∞ can be expressed as (11)

$$M/M_\infty = (4/\ell)\,[Dt/\pi]^{\frac{1}{2}} \tag{1}$$

where M is the amount of drug released at time t, M_∞ the total amount of drug released, ℓ the thickness of the sheet, and D the drug diffusion coefficient in the matrix. Equation (1) is accurate to within 1% for up to approximately 60% of the total amount released.

For systems containing dispersed drug, where the drug loading per unit volume, A, is greater than the drug solubility in the matrix, C_s, the drug release kinetics can be analyzed by the familiar Higuchi equation (16):

$$M = [C_s(2A-C_s)Dt]^{\frac{1}{2}} \tag{2}$$

However, because of the pseudosteady state assumptions involved, Higuchi's equation is only valid when the drug loading is in excess of the drug solubility ($A \gg C_s$). At the limit of $A \to C_s$, Higuchi's equation gives a result 11.3% smaller than the exact solution. Lee (4) recently presented a simple analytical solution for this problem which is uniformly valid over all A/C_s values:

$$M = C_s(1+H)[Dt/3H]^{\frac{1}{2}} \tag{3}$$

where

$$H = C_s^{-1}[5A+(A^2-C_s^2)^{\frac{1}{2}}]-4$$

When Equation (3) is applied to drug release, the deviations from the exact results are consistently one order of magnitude smaller than those of Higuchi's equation. As $A/C_s > 1.04$, Equation (3) has an accuracy within 1% of the exact solution. Therefore, Equation (3) is much more accurate than Equation (2), particularly at low A/C_s values. The latter case occurs quite often in delivery systems involving hydrophilic polymers and drugs of high water solubility.

In cases where well-defined pores ranging in sizes from a few hundredths to several hundred microns exist throughout the matrix, the kinetics of drug release can still be described by Equations (1)-(3) provided that an effective diffusion coefficient is used. When the drug diffusion only takes place through the solvent filled porous network, the effective diffusion coefficient is further related to the matrix structure by:

$$D_{eff} = \frac{D_s \varepsilon}{\tau} \tag{4}$$

where ε is the porosity expressed as the volume fraction of the void space in the matrix, τ the tortuosity factor expressed as the ratio of the effective average bath length in the porous medium to the shortest distance measured along the direction of mass flow, and D_s

the diffusion coefficient of the drug in the pore solvent. Since the ratio ε/τ is equivalent to the fractional area available for drug release, an increase in porosity or a decrease in tortuosity will certainly increase the amount of drug released at any given time.

Polymer Erosion. The release of a dissolved or dispersed drug from an erodible polymer matrix can be controlled by a variety of mechanisms ranging from hydrolysis/enzymatic cleavage as discussed in the previous section to swelling and dissolution. The situation where polymer erodes by a purely heterogeneous process, namely surface erosion, is of special interest because the drug release from such devices having constant geometry (sheet geometry) will be of constant rate (2). Unfortunately, the corresponding releases from both the cylindrical and spherical geometries all exhibit decreasing rates with time (17).

In cases where the diffusional contribution is present in addition to surface erosion, it has been shown (4)that the release from sheet geometry generally starts with typical first order kinetics then shifts toward zero-order kinetics. Apparently, a synchronization of both the diffusion and erosion front velocities at large time gives rise to the observed constant rate of drug release. Recently, Lee (5)has shown that by building in a non-uniform initial drug concentration distribution, a variety of release profiles ranging from zero-order to pulsatile delivery can be achieved from surface erosion controlled matrices in various geometries.

Geometry Factors. To overcome the inherent first-order release behavior with continuously diminishing release rate from matrix systems, geometry factors have been utilized to compensate for the increasing diffusional distance and decreasing area at the penetrating diffusion front generally encountered in matrix systems.

A hemispherical polymer matrix that is coated on all surfaces with an impermeable coating except for an aperture in the center face has been demonstrated to provide near constant rate release profiles (18). Another approach consists of a cylinder with impermeable wall and a cavity having a circular sector cross section. The center of the circular sector lies outside the cylinder, thereby producing a slit for drug release from the drug containing matrix in the cavity. The release profiles from this system also show a substantial constant rate region (19,20). It is clear that, in both systems, the increase in diffusional distance and consequently the decrease in diffusion rate have been balanced by the increase in area at the diffusion front thereby giving rise to a near constant rate region.

Polymer Swelling. Swelling phenomena are generally encountered in both the hydrophilic and hydrophobic polymer matrices during the release of entrapped water soluble drug in an aqueous environment. If the polymer is crosslinked either chemically through covalent bonding or physically through extensive entanglement or crystallite formation, the swelling will continue to some equilibrium state at which the elastic and swelling (or osmotic) forces balance each other.

Depending on the relative magnitude of the rate of polymer swelling to the rate of drug diffusion, various release profiles may be possible. The situation where the polymer structural rearrangement takes place rapidly in response to the swelling solvent as compared to drug diffusion generally leads to typical Fickian diffusion characteristics and the so-called first-order release behavior. The case of particular interest is the glassy hydrogel system where, upon water penetration, a slow macromolecular relaxation process at the glass/rubbery swelling front in addition to diffusion provides an additional mechanism to alter the release kinetics from the inherent first-order behavior. The prospect of having zero-order release kinetics from glassy polymer matrices via such a swelling controlled mechanism has stimulated an increasing number of research studies, publications and patents in this area involving the controlled-release of both small molecular weight and macromolecular bioactive compounds (21-28).

Mechanistically, as water penetrates a glassy hydrogel matrix containing dissolved or dispersed drug, the polymer swells and its glass transition temperature is lowered, and the dissolved drug diffuses through the swollen rubbery phase into the external releasing medium. At the same time, a sharp penetrating solvent front separating the glassy from the rubbery phase in addition to volume swelling is observed during the initial stage of the dynamic swelling process. Depending on the relative magnitude of the rate of polymer relaxation at the penetrating solvent front and the rate of diffusion of the dissolved drug, the drug release behavior may range from first to zero-order (21).

Various analyses and criteria have been reported in the literature for predicting whether drug release from swelling-controlled polymer matrices will be first or zero-order (diffusion or relaxation-controlled) (29). However, they have been successful only for limited situations of very low drug loading. In general, the drug loading level has a definitive effect on the release kinetics from swelling-controlled polymer matrices. Experimental evidences have shown that the presence of an additional component, namely the water soluble drug, alters both the swelling osmotic pressure and the associated time-dependent relaxation of the hydrogel network during the simultaneous absorption of water and desorption of drug (25). As a result, the drug release and solvent front penetration are observed to behave more Fickian as drug loading level increases. Such transition can be considered as a change of relative importance of the diffusion process versus the polymer relaxation as a function of drug loading.

Concentration Distribution. Despite the theoretical prospect of having a totally relaxation-controlled situation thereby achieving zero-order release from a glassy polymer matrix, hydrogels with pure relaxation-controlled (Case II) swelling kinetics are yet to be demonstrated experimentally. In addition, the inevitable geometry limitations and deviations from relaxation-controlled kinetics at higher drug loading levels further impair the flexibility in altering the release kinetics in such systems. This difficulty can be overcome by a recently reported, novel approach to constant rate of drug release from glassy hydrogel matrices via an immobolized