Polymer Systems
of Drugs: Controlled Release

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A Polymer-Based Controlled-Release Technology

1. Introduction

Survey of Biodegradable Polymers in Drug Delivery

I. Introduction

II. Mode of Polymer Fusion and Drug Release

III. Polymer Fusion and Drug Release

IV. Controlled-release, Administration, and Evaluation

Contents

Robert J. Uhlirard

Chapter 2

Bioadhesive Polymers for Controlled Release of Drugs

University of Iowa, College of Pharmacy, Iowa City, Iowa
These figures show the dynamic process of drug absorption and release behaviors. The graph on the right illustrates the concentration of drug in the body over time, with periods of absorption and release. The graph on the left shows the correlation between the concentration of drug and the corresponding physiological effects.

Drugs can be administered in various forms, such as tablets, capsules, solutions, or suspensions. The choice of dosage form depends on the properties of the drug and the desired therapeutic effect. Immediate-release formulations are designed to release the drug rapidly, while extended-release formulations provide sustained release over a longer period.

In clinical practice, pharmacists and healthcare providers must carefully consider the pharmacokinetic properties of a drug, including its absorption, distribution, metabolism, and excretion. This information is essential for determining the optimal dose and frequency of administration to achieve the desired therapeutic effect while minimizing adverse effects and drug interactions.
Bioresorbable Polymers

II. MODES OF POLYMER EROSION AND DRUG RELEASE

The erosion of biodegradable polymers and drug delivery devices depends on the polymer's properties and the environment in which it is placed. The degradation process can be categorized into several modes, including (1) surface erosion, (2) bulk erosion, (3) hydrolytic degradation, (4) oxidative degradation, and (5) enzymatic degradation. These modes can occur simultaneously or independently, leading to different release profiles for drugs and other therapeutic agents.

A. Surface Erosion

Surface erosion occurs when the outermost layer of the polymer is exposed to the surrounding environment, leading to the release of the drug. This mode of erosion is often associated with the formation of water channels or pores in the polymer, which facilitate the release of the drug.

B. Bulk Erosion

Bulk erosion involves the degradation of the polymer's bulk, leading to the release of the drug. This mode of erosion is often associated with the formation of a porous structure, which facilitates the release of the drug.

C. Hydrolytic Degradation

Hydrolytic degradation occurs when the polymer is exposed to water, leading to the release of the drug. This mode of degradation is often associated with the formation of a water channel or pore, which facilitates the release of the drug.

III. Bioresorbable Polymer Drug Delivery Systems

Bioresorbable polymers are used in drug delivery systems to control the release of drugs over a period of time. These polymers degrade slowly, allowing the drug to be released gradually. This mode of drug delivery is useful for diseases that require a sustained release of the drug, such as sustained delivery of insulin for diabetes.

IV. Conclusion

Bioresorbable polymers are a promising area of research in drug delivery systems. They offer the potential to deliver drugs in a controlled manner, reducing the frequency of dosing and improving patient compliance.

Robert J. Langer

Figure 2.2

Deformable Membrane

Rigid Water Permeable/Non-Impervious

Deformable Pump
FIGURE 2-3
A schematic drawing illustrating the three mechanisms for controlled drug release from a polymer matrix. Edge effects are ignored in the drawings and each device is shown at three early times ($t_0$, $t_1$, $t_2$) delivering drug and the late time ($t_n$) represents device exhaustion.

FIGURE 2-4
Schematic drawings of four insoluble and two soluble drug delivery devices. The heavy dots represent drug while the fine lines represent polymer.
The effective diffusion coefficient is given by:

\[ D_{eff} = \frac{D}{1 + \frac{D}{D_s}} \]

where \( D \) is the diffusion coefficient in the matrix and \( D_s \) is the diffusion coefficient in the polymer.

- **B. Reservoir Devices (and Laminated Matrix Devices)**

  These devices are usually composed of a series of reservoirs connected in series or parallel. The diffusion coefficient in each reservoir can be calculated using the following equation:

  \[ D_{res} = \frac{D}{1 + \frac{D}{D_{res,s}}} \]

  where \( D_{res} \) is the diffusion coefficient in the reservoir and \( D_{res,s} \) is the diffusion coefficient in the matrix.

**A. Diffusion-Controlled Systems**

These systems are characterized by the time it takes for a substance to diffuse through a membrane or a polymer. The diffusion coefficient in these systems is given by:

\[ D = \frac{M}{D_{eff} \cdot t} \]

where \( M \) is the mass of the substance, \( D_{eff} \) is the effective diffusion coefficient, and \( t \) is the time.

**FIGURE 2.6**

Diagram showing the diffusion of a substance through a membrane.

**FIGURE 2.7**

Diagram showing the diffusion of a substance through a polymer.

**FIGURE 2.8**

Diagram showing the diffusion of a substance through a composite material.
Swimming-controlled cytodrives and hydroworks

To make them swim, a retractor device is placed in a water bag, negatively charged and
uninhibited. A retractor device, when fully charged, can be moved by
retraction from the center of the device, in the direction of each device in the
region near the center of the device. The movement of each device can be
increased by increasing the charge on

the device.

Function magnitude in

Equation (2.2)

\[
\frac{\partial W}{\partial t} = \frac{W}{m} \cdot (\text{FIG. 2-8})
\]

is the retractor of the retractor. The negative charge on the retractor is
increased by increasing the charge on the retractor.

Matrix devices have a major advantage over retractor devices because they
provide a constant pressure force on

\[ \text{FIG. 2-7} \]

and device a shows a non-ideal force on the device. Since the device's
movement, the device is moved under the influence of the

"A plot of time (t) and position (y) from their retractor"

\[ \text{FIG. 2-9} \]

BIOELECTRICAL POLARIZERS
I. ENERING COUTURING

D. Persion-Controlled Systenrs

...
I. Matrix with Covariance Attached Block

2. Devices with Empyrampled Drug

Biodraperel Polymers

Robert T. Unmard
III. BIODEGRADABLE POLYMERS

A. Chemistry

In order to be biodegradable, a polymer must be able to undergo a process known as biodegradation. This process involves the breakdown of the polymer into smaller, more biocompatible molecules. The rate of biodegradation depends on several factors, including the chemical structure of the polymer, the environmental conditions, and the presence of microorganisms. Polymers that are designed to be biodegradable often contain specific chemical groups or structures that facilitate this process.

B. Formulation of Biodegradable Polymers

Biodegradable polymers can be formulated in a variety of ways to meet specific application requirements. One common approach is to blend biodegradable polymers with non-biodegradable ones to create a composition with desired properties. This can be achieved through the use of compatibilizers or by varying the ratios of the different polymer components. Another approach is to use a single biodegradable polymer and tailor its properties through the use of cross-linking agents or other modifications.

C. Applications of Biodegradable Polymers

Biodegradable polymers have potential applications in various fields, including medicine, agriculture, and packaging. In medicine, they can be used as surgical sutures, drug delivery systems, or wound dressings. In agriculture, they can be used as mulch or soil amendments. In the packaging industry, they can replace traditional non-biodegradable polymers, reducing the environmental impact of packaging materials.
B. Physical Properties and Morphology

The physical properties of a polymeric material are of great importance for its application. These properties include thermal stability, crystallinity, hydrophilicity, and mechanical strength. Understanding these properties is crucial for determining the suitability of a polymeric material for a particular application.

1. Molecular Weight and Polydispersity
   - Molecular weight and polydispersity are critical parameters in the characterization of a polymeric material. They provide information about the size and distribution of the polymer chains. A narrow polydispersity index indicates a more uniform polymer size distribution, which is desirable for certain applications.

2. Crystallinity and Chain Mobility
   - Crystallinity refers to the degree of order in the polymer structure. It can be quantified by techniques such as X-ray diffraction and nuclear magnetic resonance (NMR). Crystalline regions provide enhanced mechanical properties and improved thermal stability, while amorphous regions contribute to flexibility and impact resistance.

3. Mechanical Strength
   - Mechanical strength is a measure of a polymeric material's ability to resist deformation under stress. It is influenced by factors such as molecular weight, crystallinity, and cross-linking. High mechanical strength is essential for applications requiring structural integrity.

4. Thermal Stability
   - Thermal stability is the ability of a polymeric material to withstand high temperatures without degradation. It is determined by techniques such as differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA). Materials with high thermal stability are suitable for applications in harsh environments.

5. Hydrophilicity
   - Hydrophilicity refers to a material's affinity for water. Hydrophilic polymers are hydrophilic in nature and can absorb water, making them suitable for applications such as drug delivery and adhesives. Hydrophobic polymers, on the other hand, repel water and are often used in applications requiring low water absorption.

6. Physical Properties and Morphology
   - At room temperature, polymer fibers are made of crystalline polymer chains. These chains are organized in the crystal lattice, providing the fiber with its mechanical strength and resistance to deformation. The spinning process is critical in shaping the fiber, affecting its final properties. The spinning process can be optimized to achieve desired fiber properties.

7. Physical Properties and Morphology
   - After extrusion, fibers are collected as a non-woven fabric. The fibers are spun into a mat, creating a continuous web of fibers. This process is essential for the production of high-quality fabric, ensuring uniformity and consistency in the final product.

8. Physical Properties and Morphology
   - A non-woven fabric is composed of a layer of fibers that are randomly aligned. The fibers are bonded together using adhesives or other techniques to create a stable and durable material. The bonding process is critical in ensuring the fabric's strength and durability.

9. Physical Properties and Morphology
   - The non-woven fabric is then treated to enhance its properties. This treatment can involve processes such as calendaring, which involves the application of heat and pressure to improve the fabric's smoothness and consistency. The treated fabric is then cut into the desired shape and size, ready for further processing or use.

10. Physical Properties and Morphology
    - The final product is a versatile material with a wide range of applications. It can be used in industries such as automotive, construction, and medical, where its lightweight and durable properties are essential.
B. Microscopic: Microscopic and Microorganisms

The microscopic is similar to the operation in microscopic devices and can be different.

The microscopic is similar to the operation of microscopic devices and can be different.

C. Biological Properties

The microscopic is similar to the operation in microscopic devices and can be different.
1. PROPERTIES AND MODELING PROTEINS

A polypeptide is a polymer of amino acids.Each amino acid is a small organic molecule that consists of a central carbon atom bonded to four different groups:

- A carboxyl group (COOH),
- An amino group (NH2),
- A hydroxyl group (OH),
- And a side chain (R) that is specific to each amino acid.

The sequence of amino acids in a polypeptide is determined by the genetic code, which is transcribed into messenger RNA (mRNA) and then translated into proteins. The primary structure of a protein is the sequence of its amino acids, which determines its secondary, tertiary, and quaternary structures.

2. SYNTHETIC POLYPEPTIDES

Synthetic polypeptides are used in a variety of applications, including drug delivery, tissue engineering, and as model systems for understanding protein function. They can be designed with specific properties that are not possible in naturally occurring proteins.

A. Survey of Biodegradable Polymers in Drug Delivery

Biodegradable polymers are a class of polymers that can be broken down into smaller molecules by the action of enzymes or through chemical processes. They are used in drug delivery systems to control the release of drugs over time. Examples of biodegradable polymers include poly(lactic acid) (PLA), poly(lactic-co-glycolic acid) (PLGA), and poly(caprolactone) (PCL).

6. EVALUATION

The evaluation of a protein delivery system is crucial to ensure that it meets the desired therapeutic goals. This involves assessing the chemical and physical properties of the delivery system, as well as its safety and efficacy in preclinical and clinical studies. The ultimate goal is to develop a protein delivery system that is safe, effective, and practical for clinical use.
BIODEGRADABLE POLYMERS

OH

\[
\begin{align*}
\text{H} & \quad \text{Na}^+ \\
\text{O} & \quad \text{C}_2\text{H}_4
\end{align*}
\]


TABLE 2.1

Some Drugs That Have Been Released From Polymers (Acid and Pomegranate)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Release</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemotherapy</td>
<td>Nitrogen</td>
</tr>
<tr>
<td>Antigen</td>
<td>Hydroxy-Other</td>
</tr>
<tr>
<td>IgA</td>
<td>-Other</td>
</tr>
<tr>
<td>CD4</td>
<td>Gr-Other</td>
</tr>
<tr>
<td>CD8</td>
<td>Gr-Other</td>
</tr>
<tr>
<td>CD11</td>
<td>Gr-Other</td>
</tr>
<tr>
<td>CD14</td>
<td>Gr-Other</td>
</tr>
<tr>
<td>CD16</td>
<td>Gr-Other</td>
</tr>
<tr>
<td>CD21</td>
<td>Gr-Other</td>
</tr>
<tr>
<td>CD23</td>
<td>Gr-Other</td>
</tr>
<tr>
<td>CD24</td>
<td>Gr-Other</td>
</tr>
<tr>
<td>CD25</td>
<td>Gr-Other</td>
</tr>
</tbody>
</table>

KOREN, J. UNRAUT
### Table 2-2
Some Drugs That Have Been Released from Poly(Ester) Matrices

<table>
<thead>
<tr>
<th>Polymer</th>
<th>Drug</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>D,L-Lactic acid</td>
<td>Narcotic antagonists</td>
<td>23,130</td>
</tr>
<tr>
<td></td>
<td>Cyclazocine</td>
<td>23,130</td>
</tr>
<tr>
<td></td>
<td>Naltrexone pamoate</td>
<td>23,131,132</td>
</tr>
<tr>
<td></td>
<td>Naltrexone</td>
<td>23</td>
</tr>
<tr>
<td></td>
<td>Contraceptive steroids</td>
<td>23,79,133</td>
</tr>
<tr>
<td></td>
<td>Progesterone</td>
<td>23</td>
</tr>
<tr>
<td></td>
<td>Norlestrinol</td>
<td>135</td>
</tr>
<tr>
<td></td>
<td>Norgestrel</td>
<td>136</td>
</tr>
<tr>
<td></td>
<td>Antiinflammatory steroids</td>
<td>23</td>
</tr>
<tr>
<td></td>
<td>Dexamethasone</td>
<td>23</td>
</tr>
<tr>
<td></td>
<td>Anabolic steroids</td>
<td>23</td>
</tr>
<tr>
<td></td>
<td>Estradiol</td>
<td>23</td>
</tr>
<tr>
<td></td>
<td>Anticancer agents</td>
<td>23</td>
</tr>
<tr>
<td></td>
<td>Cyclophosphamide</td>
<td>23</td>
</tr>
<tr>
<td></td>
<td>Doxorubicin</td>
<td>23</td>
</tr>
<tr>
<td></td>
<td>cis-Platinum dichloride</td>
<td>23</td>
</tr>
<tr>
<td>L-Lactic acid</td>
<td>Contraceptive steroids</td>
<td>136</td>
</tr>
<tr>
<td></td>
<td>Norgestrel</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td>Progesterone</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Antimalarial agents</td>
<td>137–139</td>
</tr>
<tr>
<td></td>
<td>Narcotic antagonists</td>
<td>140</td>
</tr>
<tr>
<td></td>
<td>Cyclazocine</td>
<td>141</td>
</tr>
</tbody>
</table>

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### Table 2-2 (Continued)
Some Drugs That Have Been Released from Poly(Ester) Matrices

<table>
<thead>
<tr>
<th>Polymer</th>
<th>Drug</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glycolic acid/Lactic acid</td>
<td>Contraceptive steroids</td>
<td>142</td>
</tr>
<tr>
<td></td>
<td>Levonorgestrel</td>
<td>76</td>
</tr>
<tr>
<td></td>
<td>Progesterone</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Antimalarial agents</td>
<td>137–139</td>
</tr>
<tr>
<td></td>
<td>Narcotic antagonists</td>
<td>143,144</td>
</tr>
<tr>
<td></td>
<td>Naltrexone</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Antibiotics</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ampicillin</td>
<td>143–146</td>
</tr>
<tr>
<td></td>
<td>Miscellaneous</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Leutinizing hormone-releasing hormone</td>
<td>147,148</td>
</tr>
<tr>
<td></td>
<td>Sulfadiazine</td>
<td>149</td>
</tr>
<tr>
<td>Diglycolic acid/ transcyclohexanedimethanol</td>
<td>Antinflammatory steroids</td>
<td>150</td>
</tr>
<tr>
<td></td>
<td>Hydrocortisone</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Contraceptive steroids</td>
<td>151</td>
</tr>
<tr>
<td></td>
<td>Levonorgestrel</td>
<td>79</td>
</tr>
<tr>
<td></td>
<td>Norgestrel</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Progesterone</td>
<td>152</td>
</tr>
<tr>
<td>Caprolactone/D,L-lactic acid</td>
<td>Contraceptive steroids</td>
<td>114</td>
</tr>
<tr>
<td></td>
<td>Levonorgestrel</td>
<td>76</td>
</tr>
<tr>
<td></td>
<td>Norgestrol</td>
<td></td>
</tr>
<tr>
<td>Narcotic antagonists</td>
<td>Naltrexone</td>
<td>79</td>
</tr>
</tbody>
</table>
D. Polymers

Polymers are large molecules composed of many repeating units, known as monomers. They are formed through polymerization reactions, where smaller molecules join together to form a larger, more complex structure. Polymers are widely used in various applications due to their unique properties, such as flexibility, strength, and resistance to chemicals. The study of polymers is a fundamental part of materials science and has applications in fields ranging from electronics to medicine.

Below is a diagram illustrating the structure of a simple polymer:

![Polymer Structure](image)

This diagram shows the basic unit of a polymer, which is a monomer. The monomers are connected by covalent bonds, forming a chain or a network. The properties of the polymer depend on the type of monomer used and the method of polymerization. For example, some polymers are more flexible, while others are stronger and more resistant to deformation.

Polymers are classified into two main categories: linear and branched. Linear polymers have a single, unbranched chain, while branched polymers have branches along the main chain. These structures can affect the physical properties of the polymer, such as its melting point and solubility.

Polymers are also categorized based on their sources. Natural polymers, such as proteins and cellulose, are obtained from biological sources, while synthetic polymers are produced in laboratories. Synthetic polymers are often more versatile and can be tailored to specific applications.

In conclusion, the study of polymers is a critical area of research with numerous applications in modern technology. The unique properties of polymers make them valuable materials for use in a wide range of industries, from construction to healthcare.

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Robert J. Mather
this induction period including nonproductive hydrolysis (hydrolysis of many anhydride linkages before matrix polymer chains could be solubilized), the initially hydrophobic surface becoming more hydrophilic, or a change in the polymer’s crystallinity.\textsuperscript{72} As the matrix degraded the slab reportedly became thinner, maintaining its physical integrity. The in vitro release of a steroid from this matrix paralleled matrix degradation suggesting release was due to heterogeneous surface erosion.\textsuperscript{72} Microscopic examination of matrices that exhibited constant erosion and release revealed some surface cracking, possibly due to the differing rates of erosion in the crystalline and amorphous regions.\textsuperscript{192} In addition to matrix hydrophobicity, and the hydrolytic instability of the anhydride linkage, zero-order degradation may be due in part to the polymer’s stability at low pH and the inherent acidic environment in the polymer’s bulk.\textsuperscript{194} Drug analog containing nucleophilic amine groups failed to react with the poly(anhydride) matrix except under formulation conditions requiring extensive heating.\textsuperscript{195} The polymer breakdown products (dihalides) were established to be nontoxic, nonmutagenic, and nonnontoxic.\textsuperscript{195} No inflammatory cells and only slight encapsulation was detected on sc implantation into rats.

E. Others

1. POLY(ALKYL 2-CYANOACRYLATES) ACTIVATED C–C BONDS

Developed as instant glue, poly(butyl 2-cyanoacrylate) is used medically as a bonding agent, because it shows good spreadability on biological fluids, rapid polymerization time, and low toxicity.\textsuperscript{196,197} Although these polymers can be prepared by free radical polymerization, they are generally made via anionic polymerization in aqueous solvent systems.\textsuperscript{198} Hydrolytic decomposition of these polymers proceeds in an exolytic fashion with the breakage of a C–C bond.\textsuperscript{114} Cast films appear to erode only at the surface.\textsuperscript{199} Microcapsules of this polymer can be formed by interfacial polymerization in an emulsion.\textsuperscript{200} Nanoparticles (<200 nm) have been used to adsorb certain drugs and to concentrate these in certain tissues\textsuperscript{201,202} and have been used to effectively deliver actinomycin D to an experimental tumor.\textsuperscript{203} Biocompatibility studies on particles (1–10 μm) of poly(butyl-

cyanoacrylate) administered to the rabbit knee joint cavity showed a severe inflammatory response.\textsuperscript{93} Tissue toxicity may be due to the toxic effect of formaldehyde, a breakdown product of this polymer.\textsuperscript{204}

2. POLY(DIHYDROPYRANS)

The World Health Organization has supported the development of poly(hydropyrans) for contraceptive delivery systems.\textsuperscript{205} The release of both contraceptive steroids and antimalarial agents from poly(hydropyrans) matrices has been studied in vitro and in vivo.\textsuperscript{206,207}

3. POLY(ACETALS)

Natural sugar polymers including starches, dextrins, and amylose have been modified and studied for controlled release.\textsuperscript{208,209} Biodegradation of partially deacetylated chitin in lysozymes has been described.\textsuperscript{137} Synthetic poly(acetals) can be prepared without by-products from the condensation of divinyl ethers and polyols.\textsuperscript{139} Slabs of the poly(acetal) prepared from bisphenol A and divinylxybutane initially degrade with weight loss then they abruptly disintegrate indicating that bulk erosion has taken place.\textsuperscript{143}

4. POLY(PHOSPHAZENES)

Polyphosphazenes that can undergo in vitro hydrolysis over a period of several weeks have been proposed as biodegradable polymers for controlled release.\textsuperscript{144} These polymers are (1) easy to synthesize, (2) provide covalent and coordinate drug binding sites, (3) can be prepared with properties ranging from water-soluble to water-insoluble hydrophilic (or hydrophobic) solid polymers, and

\[
\begin{align*}
\text{HOCH}_2\text{CO}_2R \quad \text{H}_2\text{O} \quad \text{CH}_2\text{OH} + \text{H}_2\text{CO}_2R \\
\text{H}_2\text{O} + \text{H}_2\text{CO}_2R
\end{align*}
\]