Drug Delivery by Bioerodible Polymer System

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Ⅰ. Introduction

In recent Years, a significant progress has been made in the development of "programmed-drug-delivery" system for therapeutic use[1]. The concept of "programmed-drug-delivery" has been known for many years. But its emergence as an inter-disciplinary science of current interest is a relatively new-both in terms of academic interest and commercial applications. The purpose of a programmed release is to control the release rate of the drug in such a way that pre-determined concentration of drug (therapeutic amount of drug necessary to cure the disease in predictable time span) reaches the specific target site throughout the programmed time period. In kinetic terms, this would imply a "zero-order kinetics of durg release". For this reason, the term "programmed delivery" will be used in this writing instead of commonly used terminologies such as "controlled", "sustained", "slow release", etc., which represent only a partial or mislead meaning to the purpose.

There are several ways of achieving the stated purpose of "zero-order" kinetics: non-eroding and eroding reservoir devices made of polymeric membranes, dissolving devices, pumping devices based on the osmotic, elastic, electrochemical, and simple mechanical principles. However, for the reasons it will become apparent in the discussions follow, the present study will limit the scope of its presentation to dissolving devices made of bioerodible polymer systems.

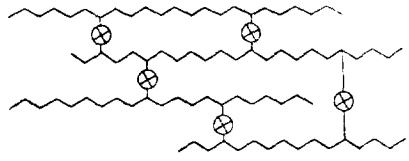
Ⅱ. Chemistry of Erodible Polymer Systems

1. Classical Erodible Polymer Systems

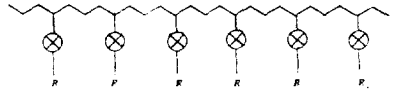
For the better understanding of the thought behind the present development a brief summary of classical erodible system is reviewed here.

The classical erodible polymer system may be devided into three categories from a structural view points as follows:

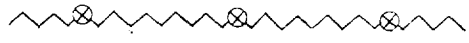
(1) Cross-linked systems



(2) Side chain erodible systems



(3) Main chain erodible systems



Where ⊗ denotes the hydrolytically labile linkage.

The cross-linked systems in general are too hydrophilic to be used in the "programmed-drug-delivery" system due to the intrinsic nature of hydrophilic character of substrate themselves. And also, their degradation patterns are often unpredictable arising from its random cross-linking with different functional groups.

Therefore, the use of cross-linked systems is limited to a certain specific applications of drug delivery systems where the drug is a relatively insoluble in aqueous medium. The mechanism of drug release is controlled by diffusion of drugs through hydrophilic cross linked gel-system.

Compared with cross-linked system, the erosion kinetics of side chain erodible polymers are more predictable. However, the main drawback of this system is that a pronounced boundary effect is observed. This is due to the fact that the diffusion of drug from the depot is retarded by a gel layer between water interface and un-hydrolyzed polymer-drug mixture. As a result, it is difficult to achieve a "zero-order" kinetics with such system.

Lastly, as one might expect from the structural and chemical considerations, the drug-delivery devices made from the condensation polymers works on the simple diffusion principle, while the polymer erosion itself proceeds independently, often lasting several months. In other words, the kinetics of drug release and the rate of polymer erosion are essentially independent of each other. The polymer in essence, acts as a simple holding depot for the duration of drug-release, and then, the polymer will slowly disintegrate into low molecular species in an uncontrolled manner.

2. Non-Classical Erodible Polymer Systems

It is apparent from the brief review of classical erodible polymer systems, the release rate of drug from a device made of classical erodible polymer is governed by diffusion principle and independent of matrix erosion: The diffusion of drug from the device precedes the erosion of matrix polymer. As pointed out earlier, all of these classical system exhibit a certain degree of a boundary effect due to the formation, of gel layer at the eroding front of drug-polymer mixture. As a result of the boundary effect the diffusion of drug will be retarded, and will result in a deviation from "zero-order kinetics"

To achieve the "zero-order kinetics" of drug release one must change the system from "diffusion-controlled" to "erosion-controlled" kinetics. In such system, the drug will be released from the eroding surface, and both drug and hydrolazates of matrix polymer being small molecules, will diffuse out to surrounding environment rapidly eliminating boundary effect problem. This relationship is illustrated in the Fig. 1 by simple schematic drawings.

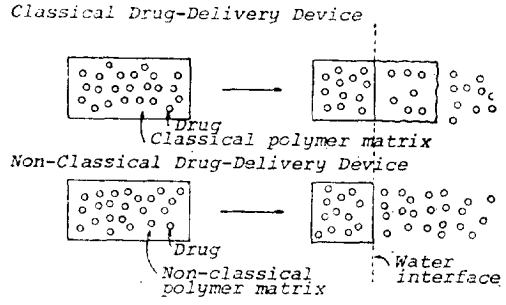


Figure 1. Classical and non-classical drug delivery devices showing the presence and absene of boundary effects.

It is also apparent from the practical point of view that the polymer itself has to be hydrophobic to retain the water soluble drugs for the programmed duration of drug release. One may now summarize the requirements for the ideal polymer matrix design as follows:

(1) In order to give "zero-order" drug release the matrix polymer should erode in such way that:

$$\text{Rate of polymer matrix erosion (surface erosion)} \gg \text{Rate of drug diffusion}$$

(2) The polymer should be sufficiently hydrophobic to retain a hydrophilic drug;

(3) Backbone structure of the polymer matrix should be such that the main chain can be hydrolyzed readily into a small, water-soluble product(s); In addition to these requirements, the following considerations should be included in the design of matrix polymer for the biological application:

(4) Cleavage of chemical linkage should proceed via simple hydrolysis mechanism preferably at physiological pH (~7.0) and body temperature (~37°C);

(5) Both matrix polymer and erosion products should be biocompatible-non-toxic, non-allergenic, anti-thrombogenic, etc.;

(6) In addition, the polymer must simultaneously satisfy other general requirements such as mechanical durability, appropriate thermal and physical properties for fabrication process.

At the time of undertaking of the present study, no such polymeric systems had been known. Therefore a new tailor-made polymeric system had to be developed to meet the aforementioned requirements. The first and the most difficult problem was the selection of proper functional group (s) which could erode rapidly at pH around 7 and near physiological temperature of 37°C. A close examination of organic functional groups had revealed that ortho-ester, ortho-carbonate, and amide acetal groups could undergo such a rapid hydrolytic cleavage under the physiological environment. Three new families of polymeric systems were developed, and named as "CHRONOMER™"[2] series to represent their characteristics-time (CHRONO) dependent erodible polyMER.

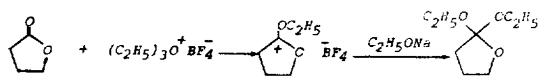
(a) Orthoester polymers

Triethyl oxonium fluoroborate

$$4(C_2H_5)_2O \cdot BF_3 + 2(C_2H_5)_2O + 3ClCH_2-\underset{\diagdown O \diagup}{CH-CH_2} \longrightarrow$$

$$3(C_2H_5)_3O^+BF_4^- + B(\underset{|\atop CH_2Cl}{O CH}-CH_2OC_2H_5)_3$$

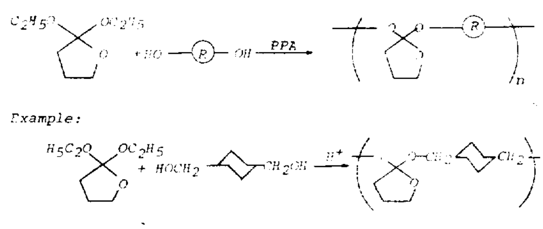
2, 2-Diethoxytetrahydrofuran (DETHF)



2, 2-Diethoxytetrahydrofuran (DETHF)

A key starting material, for the ortho-ester polymer synthesis was prepared by reaction of γ-butyrolactone with triethyl oxonium fluoroborate followed by sodium ethoxide treatment. Since one of the ether linkage in DETHF was incorporated in the 5-membered ring system (THF), it was effectively reduced to bifunctional monomer. The two labile ethoxy groups could undergo transetherification with diols in the presence of an acid catalyst.

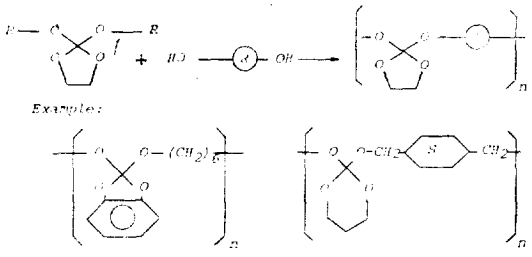
A linear polyorthoesters can be prepared readily by the reaction of DETHF with diols in the presence of acidic catalyst as follows;



A series of homopolymers were prepared by the transetherification of DETHF and its analogs with appropriate diols. As expected, polyorthoester having different physical properties can be prepared easily by proper choice of starting materials.

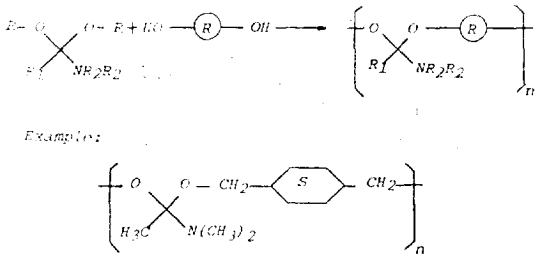
(b) Orthocarbonate Polymers

Similarly, orthocarbonate polymers were prepared by transetherification as follows:



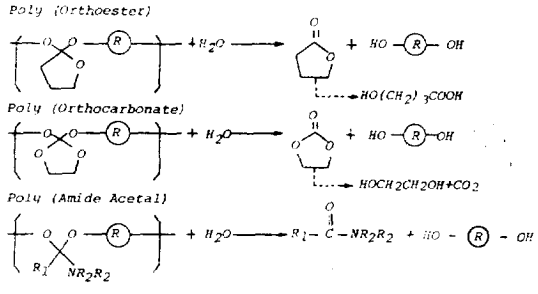
(c) Amide Acetal Polymers

Amide acetal polymers were also prepared by transetherification under similar reaction conditions as follows:



3. Hydrolytic Cleavage and Kinetics of CHRONOMER™ Degradation

As one might expect from the structures of polymers, the CHRONOMFR™ in vitro eroded to the corresponding lactones, cyclic carbonates, and amides with diols: In vivo experiments, the lactones, cyclic carbonates, and some cyclicamides were further hydrolyzed into corresponding *w*-hydroxyacid, diols and carbon dioxide, and *w*-amino acid, respectively.



Kinetic courses of drug release and CHRONOMER™ erosion were studied simultaneously using a combined means of high pressure liquid chromatography, UV spectrophotometry, and differential refractometer. The relationship between the erosion rate of CHRONOMER™ and drug release was established according to the following:

$$\frac{dD}{dt}=A\cdot C\cdot E$$

where:

$\frac{dD}{dt}$: Drug release rate (μg/day)

A : Exposed surface area (cm^2)

C : Concentration of drug in the polymer matrix (μg/cm^3)

E : Erosion rate of polymer (cm/day)

Fig. 2 shows experimental results of a typical in vivo study of drug release device made of CHRONOMER™ matrix.

A linear relationship between the rates of drug release and the matrix erosion is demonstrated here providing an unequivocal proof that drug release is solely governed by surface erosion of polymer matrix;

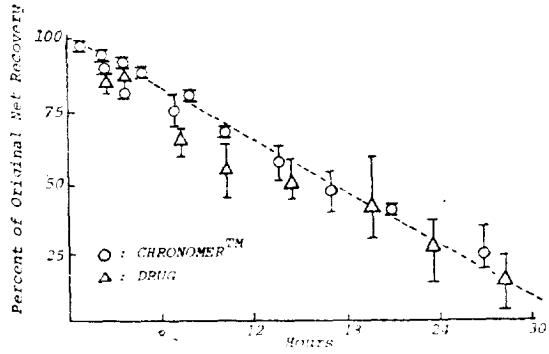


Figure 2. Net release from prototype system in subcutaneous tissue of rat.

Ⅳ. Prognosis

At the present time, the CHRONOMER™ series are produced in pilot scale (for medical use) by Alza Corporation, a subsidiary of Ciba-

Geigy. The CHRONOMER™ are being tested for various applications as drug delivery matrices, eg. for contraceptive applications by WHO, anti-cancer drug delivery devices and narcotic-antagonist implantation devices by NIH, ocular insert devices, transdermal drug delivery systems, and other applications by pharmaceutical industries. Beside pharmaceutical applications, application of CHRONOMER™ system in such diverse areas as electronic industry, printing and photographic industries may also be possible, and it is left to the imagination of scientists and engineers to broaden its scope of applications.

References

(1) A. Zaffaroni, The 31st International Congress of Pharmaceutical Science, September 7-12, 1971, Washington, D.C., "Optimizing Drug Activity"; A. Zaffaroni, V.A. Place, The B.C. Centennial symposium on the development and control of new drug products, October 1-2, 1971, Vancouver, Cannada.

(2) N.S. Choi and J. Heller, U.S. 4,079,038 (Mar. 14, 1978); ibid., U.S. 4,093,709 (June 6, 1978); ibid., U.S. 4,131, 648 (Dec 26, 1978); ibid., U.S 4,138, 344 (Feb. 6, 1979); ibid., Six U.S. Pats. Pending.

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1979年 10月 23日~24日 양일간에 걸쳐 韓國科學技術研究所에서 大盛況리에 끝마친 第一回 韓日共同심포지엄(最近의 高分子材料의 研究動向)에 參席하지 못한 會員여러분의 요청에 의하여 發表論文全文을 "폴리머"誌에 揭載키로 하였읍니다. 每回 2編程度 계속 게재키로 하였으니 많은 參考되시기를 바랍니다. 編輯委員會