Progress in Contraceptive Delivery Systems
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BIODEGRADABLES AND DELIVERY SYSTEMS FOR CONTRACEPTION

Edited by
E S E Hafez and W A A van Os

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Biodegradables and Delivery Systems for Contraception

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Editorial

The series *Progress in Contraceptive Delivery Systems* will include various volumes to be published during 1980–1983. Each volume contains in depth reviews of classical observations and contemporary research on the biophysics, physiology, ultrastructure, biochemistry, pathology and clinical parameters of biodegradables, intrauterine devices and all medicated delivery systems as they apply to fertility regulation in women and men, and to family planning.

In this series, observations which have been published in many different journals have been brought together and updated. Several scientists and clinicians from 28 countries have critically reviewed the literature in their field and added new observations of their own to every chapter. Each volume, multidisciplinary in nature, contains extensive illustrations (line drawings, photomicrographs, transmission and scanning electron micrographs) as well as numerous summary tables, and extensive bibliography. The chapters are grouped under general headings (sections) and within each section a wide range of related topics is covered.

Emphasis in this series is placed on the application of modern contraceptive technology to women and men under various environmental (nutrition, climate, parasites, health care), cultural and socioeconomical conditions. Non-human primates and experimental laboratory mammals are also considered where appropriate. No other series has as much depth or is as comprehensive. In addition no other series really attempts to combine both the basic science and clinical aspects of fertility regulation and delivery systems. Biologist, anatomists, biophysicists, physiologists, biochemists, pathologists, immunologists, gynecologists, epidemiologists, oncologists, and family planners will find much interest to them in this series.

In spite of the tremendous amount of research funds devoted for research to identify an 'ideal contraceptive', the progress in contraceptive technology in the past decade has been painfully slow. It is hoped that new horizons of future research are opened for the basic scientists. It is also hoped that a true exchange of ideas and methodology throughout the world will occur irrespective of regulatory policies of governments and national and international funding agencies.

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E. S. E. HAFEZ

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E. S. E. H.
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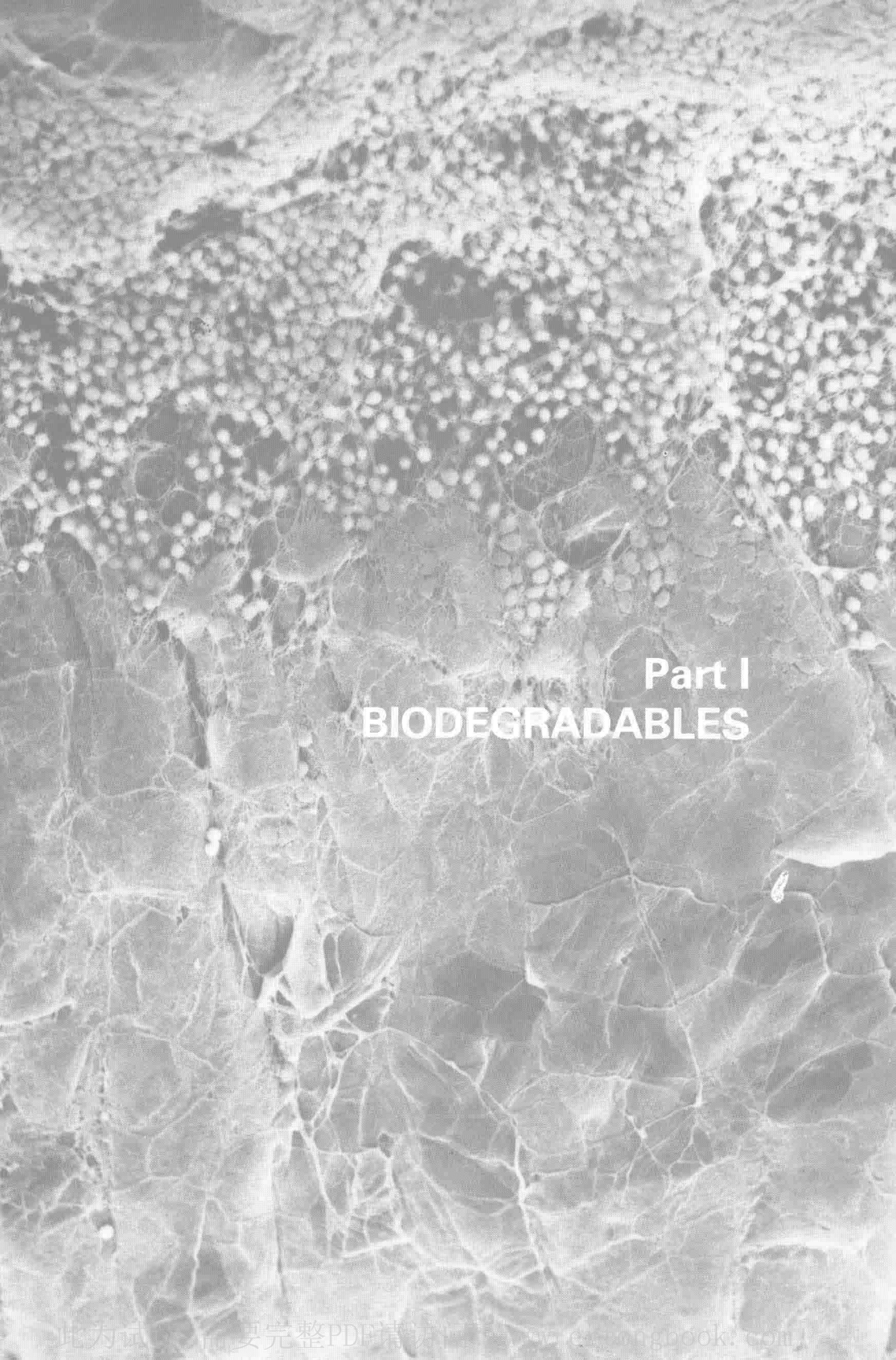

Part I
BIODEGRADABLES

1
Biodegradable delivery systems

W. E. SKIENS, F. G. BURTON AND G. W. DUNCAN

The pharmacologic approach to the control of fertility has developed primarily through orally administered steroids. Over the past few years implantable or injectable systems have been developed which permit controlled delivery of contraceptive drugs over relatively prolonged periods. Frequently, however, these systems deliver greater levels of drug than needed initially and then subsequently tail off to a much lower level of release. Progestogens, such as medroxyprogesterone acetate, may provide a number of months (up to 6) of contraceptive effectiveness after a single injection and are presently available in many countries. In this case, the duration of effect derives from the properties of the steroid itself and sustained release is thus limited to a very few compounds of specific chemistry. Also, injections of this type are not necessarily reproductive-organ targeted and are given in higher dose than may be necessary if introduced directly into or near the desired organ(s).

Systems in which the drug is delivered from a bio-inert carrier or vehicle have also been developed during the 1970s, and frequently permit the delivery directly to the desired area. Those systems which have been developed, generally based on biocompatible organic polymers, must usually be removed from the body after the drug reservoir is exhausted whether they were implanted intramuscularly or subcutaneously or placed in the reproductive tract. Much interest has developed recently in drug delivery systems based on polymers which will biodegrade in the body site and thus avoid removal. Such systems may deliver the drug either by a mechanism of drug diffusion through the polymer or delivery as the polymer matrix biodegrades (bioerodes) or a combination of both. Such systems, unlike the injectables, permit the delivery of a variety of synthetic or natural drugs without undue concern for the compound's structure or solubility in body fluids or tissues. It is desirable, of course, to have the delivery vehicle degrade and be absorbed within a relatively short time after the drug supply is exhausted.

It is necessary that biodegradable polymers have certain properties in order to be useful in contraceptive applications. These properties include: (1) ability to be formed into desired shapes; (2) release of contained drugs

by a suitable mechanism (diffusion, erosion); (3) adequate dimensional stability together with appropriate strength-loss characteristics; (4) little toxic response to either the polymer–drug system or degradation products; (5) complete biodegradation of the device and disappearance of material; and (6) sterilizability. Although it is possible to have the biodegradable vehicle disappear at the same time as the drug supply is exhausted, this relationship between completion of drug delivery and disappearance of the drug carrier is not usually attained. However, if the biodegradable delivery vehicle is absorbed relatively shortly after the reservoir is exhausted, with no residual tissue or toxic effects, this is generally satisfactory.

The biodegradable polymers of interest in drug delivery systems generally have some structural integrity. When these polymeric materials are placed in the environment of the body, a number of general changes occur which lead to degradation. Kronenthal (1975) suggests that biodegradable polymers do not simply erode away while still maintaining their initial strength and integrity, but undergo at least four major stages leading to degradation: (1) hydration – the disruption of tertiary and secondary structures by change in hydrogen bonding and van der Waals forces; (2) strength loss – covalent bond rupture of polymer backbone; (3) loss of mass integrity – additional bond rupture allowing initiation of absorptive or mass loss processes; and (4) solubilization of mass – polymer removed by dissolution of low molecular weight fractions and/or phagocytosis of fragments.

Although these restraints and requirements would appear to severely limit the available polymers that might be used in biodegradable delivery systems, it is apparent after review of suitable polymer materials that a fairly large number of systems providing the desired characteristics are being studied. Most of the studies of these materials are recent and in many cases only *in vitro* testing and *in vivo* results in animals have been reported. Clinical results on a number of promising biodegradable delivery systems should be forthcoming over the next few years.

MATERIALS

The application of biodegradable polymeric materials for use in the controlled delivery of drugs and other chemicals has been studied with great interest in the past few years. Such materials and systems have received the interest not only of those desiring to deliver contraceptive agents and other pharmaceuticals in both humans and animals, but also of those searching for new delivery systems for pesticides, fertilizers, pheromones, and marine antifoulants. The chemical to be delivered may be contained in the polymeric vehicle in a variety of ways: (1) dispersed homogeneously in a polymer matrix; (2) dissolved in the matrix; or (3) dispersed (or dissolved) in a liquid which is contained in a tube or cylinder fabricated from the biodegradable polymer. These delivery systems are frequently fabricated from synthetic polymers prepared from monomers which are naturally derived. This often permits the polymer vehicle based on such monomers to be enzymatically attacked and degraded to natural products in the body. The

resulting products are generally non-toxic, readily absorbed and removed systemically.

In theory it would be desirable to have the polymeric material degrade and disappear at the same rate as the drug is released; however, practically, this does not usually occur. The device is normally designed such that the delivery vehicle remains relatively intact until the drug reservoir is essentially exhausted, after which the polymeric implant should disappear as rapidly as possible.

Lactic and glycolic acids are frequently studied in the development of biodegradable delivery systems. Materials prepared from these monomers have been studied as the homopolymers, polylactides and polyglycolides (Nilsson *et al.*, 1975; Jackanicz *et al.*, 1973; Pitt *et al.*, 1977) as well as in copolymer systems (Boswell and Scribner, 1973; Pitt *et al.*, 1977; Wise and Rosenkrantz, 1977) for the release of contraceptive agents. The release of drug from these polymers has been observed to proceed both as a result of erosion or degradation of the polymer and by diffusion of drug from the polymer matrix.

Control of the ratio of lactic and glycolic acids in copolymers prepared from these monomers has made it possible to widely vary the rate at which these copolymers degrade (Miller *et al.*, 1977; Cutright *et al.*, 1974). Thus, it has been observed that in both bone and soft tissue the half-life of polylactic/polyglycolic (PLA/PGA) copolymer implants may be varied from 2 weeks to 6 months. Also, poly(($\pm$)-lactic acid) degrades more rapidly both *in vitro* and *in vivo* than the more highly crystalline poly(L-(+)-lactic acid), thereby providing another possible mechanism for control of degradation rate (Kulkarni *et al.*, 1971).

Contraceptive agents released from PLA, PGA and PLA/PGA copolymer delivery systems have been developed for administration from tablets (Boswell and Scribner, 1973); from cylinders (Wise and Rosenkrantz, 1977); from films (Pitt *et al.*, 1977); and from microcapsule systems (Nuwayser *et al.*, 1977; Gardner *et al.*, 1977). Microcapsule delivery systems have been developed in which a number of parameters may be varied to control quite extensively both the rate of release of drug and the rate of degradation of the polymer matrix.

Other biodegradable polymer and copolymer systems that hold promise in the sustained delivery of contraceptive agents have been studied. Such systems as homopolymers and copolymers of poly(ε-caprolactone), poly(DL-ε-decalactone) and poly(DL-methylethylglycolic acid) appear to provide desirable properties (Pitt *et al.*, 1979). These monomers copolymerized with lactic acid to produce a copolymer such as poly(ε-caprolactone-co-DL-lactic acid) seem to hold considerable promise. Steroid diffusion in such copolymers is similar to that observed in silicon rubber and lifespans of about 1 year have been estimated.

Copolymers prepared from glutamic acid and leucine have been studied as biodegradable vehicles for the delivery of progestogens. These two amino acids polymerized in a variety of molar ratios provide polypeptides which as random copolymers release progesterone and biodegrade quite slowly as soft tissue implants (Sidman *et al.*, 1977). Two preparative

techniques were tried: extrusion of a rod containing 40–60% progesterone dispersed in the polymer matrix, and coating a rod containing 60–80% progesterone with a thin layer of the polypeptide which acts as a rate-controlling barrier for drug release.

Polymers synthesized from other amino acids also offer a wide range of properties for use as biodegradable, sustained drug release implants. Some additional polypeptide materials studied by other workers include those prepared from L-aspartic acid, L-leucine, β-methyl-L-aspartate and DL-methionine in various copolymer ratios (Martin *et al.*, 1971; Marck *et al.*, 1977).

Other synthetic polymers such as polyvinyl alcohol and its derivatives (Dayer *et al.*, 1969; Fritsch, 1967) and copolymerized cellulosics (Kim *et al.*, 1976; Cook *et al.*, 1969) have been studied as biodegradable vehicles for the delivery of various drugs and chemicals. It is apparent that this combined field of polymer and pharmaceutical sciences is continuing to provide new biodegradable polymer–drug formulations as workers explore the basic properties of these systems.

The use of modified natural polymers has also provided another promising group of candidate systems for biodegradable delivery vehicles. Natural materials which have been studied fairly extensively include the polypeptides and collagen. Both biodegradability and drug delivery from collagen have been studied by a large number of workers (Stenzl *et al.*, 1975; Chvapil *et al.*, 1969). Bradley and Wilkes (1977) have studied the diffusion rate of the steroid, medroxyprogesterone, from collagen preparations and have controlled the release rate over a wide range by modification of the collagen with crosslinking and complexing agents. Other types of natural polymers that have been studied as biodegradable materials for sustained release include starches, the dextrans, and amylose modified by a variety of methods (Shasta *et al.*, 1976; Jarwenko, 1970).

As the need for definition of biodegradable polymers has progressed in recent years, scientists have developed materials with a wide range of properties. With the wide variety of polymer systems available and with a rapidly increasing understanding of biodegradable polymers it is to be expected that successful applications of these materials to the delivery of contraceptive agents, as well as other drugs and chemicals, will appear in the near future.

KINETICS OF RELEASE

Delivery systems designed using bioerodable polymers will usually contain the biologically active agent as a heterogeneous dispersion in the polymer matrix. Ideally the release of the agent is controlled by erosion of the polymer matrix; however, practically the release usually occurs by a combination of erosion and diffusion of the active agent through the polymer matrix.

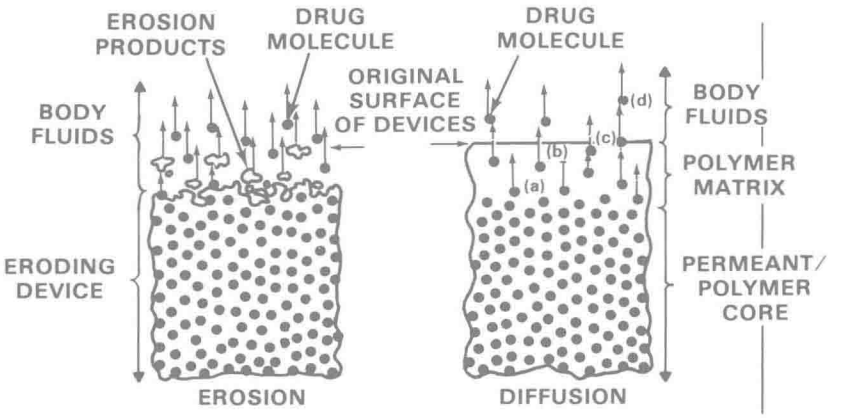

Figure 1.1 Schematic diagram of bioerodable and diffusional systems for drug delivery

Erosion kinetics

Kinetics describing the release of biologically active agents through the mechanism of erosion of polymeric matrices have not been as thoroughly studied as the kinetics of diffusional release. These two mechanisms of release (diffusion and erosion) are shown schematically in Figure 1.1. Hopfenberg (1976) has developed a related set of equations to describe, via an erosion mechanism, release of drug from a device (sphere, cylinder, or slab). The release of an agent is defined as a function of the amount of material released at time x (M_x), the erosion constant k_0, the initial concentration of agent in the polymer C_0, and the radius of a sphere or cylinder or, equally, the half-thickness of a slab, a. This relationship is

$$M_t/M_\infty = 1 - (1 - k_0 t/C_0 a)^n$$

where $n = 1$ for a slab, 2 for a cylinder, and 3 for a sphere. This is an idealized model and requires that the release kinetics are not affected by such phenomena as time-dependent diffusion of water to the site and diffusion of the active agent or degradation byproducts away from the site. However, in actuality these factors may significantly influence erosion (and drug release) rates and must be considered.

Diffusion–Permeation kinetics

The other major mechanism by which a biologically active agent may be delivered to the environment from a biodegradable polymer is diffusion of the agent through the polymer matrix to the boundary of the device. The mechanism of transport of a solute or permeant through a polymer barrier may occur either by viscous flow (dialysis or mass flow) or by diffusive flow (molecular transport) or by both simultaneously (Herzog and Swarbrick, 1970; Michaels, 1968; Flynn and Smith, 1972). If the polymer membrane barrier is neither macroscopically porous (fixed pores much larger than the