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Review Article

BIODEGRADABLE DRUG DELIVERY SYSTEMS

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INTRODUCTION

During recent years there has been an upsurge of research into providing prolonged action formulations. Many approaches can be used and a considerable amount of work has been reported in this area where synthetic polymers constitute a major component in the formulation. Much of the pioneering research has employed non-degradable polymers; however, biodegradable polymers can be used to advantage in many applications. The most promising areas of application involve drug–polymer composites which are implanted, injected or inserted. The time scale over which the controlled release is envisaged can be in weeks and frequently months. The prolonged action brings with it the requirement for potent drugs due to limitations in the physical size of the formulation. The applications in which these biodegradable systems may be used range from contraceptive implants or injections which are required to provide constant release of steroid for up to one year to injectable formulations which concentrate the drug at a specific site using a targeting technique as proposed in some anticancer therapies.

In a recent overview of prolonged action dosage forms, Ballard (1978) has discussed the problems of terminology and abstracting from the literature, and Bagnall (1977) has proposed a possible classification of controlled drug-release devices. The amount of research in the general field of controlled release of biologically active compounds has led, of necessity, to classification and compartmentalization of the material (e.g. implants, injectable depots, hydrogels, polymeric drugs, affinity-labelled drugs with further groups including microcapsules and nanocapsules). Several publications are available in which most of these groups are treated in some detail (e.g. Tanquary and Lacey, 1974; Paul and Harris, 1976; Kostelnik, 1978; Robinson, 1978; Gregoriadis, 1979).

Information on biodegradable systems is rather limited at this time, most having been based on copolymers of lactic acid. However, there is a rapidly growing literature on biodegradation in general and on the use of polymers in biomedical applications. The terms bioabsorbable, bioerodible and biodegradable are frequently used interchangeably. In the case of bioerodible systems the device may erode by slow dissolution of the polymer as a result of side-group hydrolysis or ionization, while the polymer backbone remains undegraded (Heller et al., 1978).

In this review article only controlled release systems which involve polymers are considered. Due to the central role played by polymers in these systems some basic concepts of polymer chemistry are introduced using examples related to the pharmaceutical formulation of such systems. The important considerations of biodegradability and biocompatibility testing, processing to dosage forms and release mechanisms are treated in a general manner in separate sections and some examples of several types of polymer used in biodegradable systems are reviewed separately.

BIODEGRADATION AND BIODEGRADABLE POLYMERS

Traditionally, synthetic polymers have been designed to be inert and to resist degradation. Such has been the success that for several years there has been some concern regarding the ultimate disposal of consumer goods and packaging material prepared from synthetic polymers which accumulate in the environment at an ever-increasing rate. A recent review of this problem (Taylor, 1979) suggests that, due to the balance between social and economic considerations, several manufacturers have discontinued research and development programmes on degradable plastics. However, agricultural applications still continue to provide a considerable stimulus for research into biodegradable polymers (Dennenberg et al., 1978). Many reports on the microbiological deterioration of polymeric materials are available (e.g. Heap and Morrell, 1968) and a recent re-evaluation of polyethylene has shown it to be susceptible to a limited degradation (0.5% in 2 years) by soil fungi (Albertson, 1978). Blok (1975) has discussed methods of assessing biodegradation from a general point of view and Dagley (1978) reviewed the degradation of organic compounds from a biochemical point of view.

Two broad approaches can be used to prepare biodegradable polymers. The first involves the modification of polymers which are known to be degradable and the other concerns the design of novel polymers which are potentially biodegradable. An almost infinite range of polymers with different properties could be synthesised; however, due to the number of particular properties which may be required at the same time for application in a drug delivery system, progress in this field has been relatively slow. The difficulties may be illustrated by the work carried out to obtain synthetic biodegradable (absorbable) sutures, the first (Dexon) having been marketed in 1970 by Cyanamid. The suture was prepared by melt extrusion of high molecular weight poly(glycolic acid) (Fig. 1a) and was the result of 8 years of research (Anon., 1970). Closely related polymers (e.g. poly(lactic acid) Fig. 1b) have similar properties and the two monomers can be copolymerized to prepare a series of related polymers (Gilding and Reed, 1979). Studies of the in vivo degradation of poly(glycolic acid) sutures still continue (Pavan et al., 1979; Williams, 1980). Another class of biodegradable polymers, prepared from alkyl 2-cyanoacrylate monomers, has become established as biological tissue adhesives (Fig. 1c). The established use of these polymers in surgery has made them attractive candidates for application in experimental drug delivery systems. The poly(amino acids) form another class of polymers (Fig. 1d) which has been extensively studied in many disciplines, and other widely diverse polymers have been reported to be potentially biodegradable particularly in the patent literature.

Some considerations of the specificity of polymer degradation and the role of water,

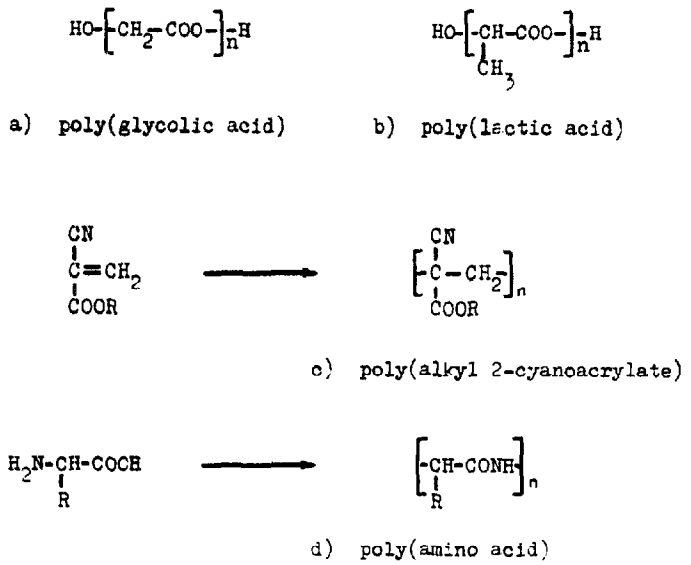

Fig. 1. Some examples of biodegradable polymers.

trace elements and enzymes in the macrokinetics of degradation in the living body have been discussed by Moiseev et al. (1979). Lipatova (1979) discussed some chemical aspects of resorption of polymers, mainly polyurethanes, while Livshitz (1972) presented theoretical considerations of the physical chemistry of resorption of implants in the body.

POLYMER CHEMISTRY

Synthetic polymers are composed of repeating monomeric units which are linked together by covalent bonds in the main chain backbone (e.g. C–C, C–O, C–N). When two or more different monomers are used the resulting polymer is termed a copolymer and its composition is generally dependent upon the reactivity ratio of the monomers. A recent study of the copolymerization of glycolide and lactide (Gilding and Reed, 1979) found that initially the copolymer is considerably richer in glycolide than the starting monomer mix, and that blocks of glycolide separated by single units of lactide occur. A physical mixture of the two homopolymers would exhibit modified properties compared to either alone but would not necessarily behave as the copolymer.

Generally the chemical composition of a polymer (i.e. the repeating monomeric unit) inadequately describes the material and the degree of polymerization (DP) must be considered. The degree of polymerization is the number of repeating monomeric units in the polymer chain which for high polymers is usually greater than 100. When DP is less than 10 the material is regarded as oligomeric rather than polymeric. Values of molecular weight determined by different methods give either a weight average (M_w) or a number average (M_n). The ratio M_w/M_n indicates the polydispersity of the fraction and a value of unity would correspond to a monodisperse system. Gilding and Reed (1979) have studied the effect of copolymer composition on the polydispersity of lactide and glycolide copolymers and have also reported an unexpectedly more rapid fall in M_n than M_w of

poly(glycolic acid) when it was irradiated (^{60}Co).

When poly(lactic acid) with molecular weights of about 150,000 and 450,000 was used to prepare implantable beads containing sulphadiazine, the amount of drug released after 90 days was about 80% from beads prepared from the lower weight material compared to 40% from the higher weight polymer (Wise et al., 1978a). However, Woodland et al. (1973) found no significant differences in the release rates of cyclazocine from composites prepared from poly(lactic acid) with molecular weights of 45,000 and 70,000.

Polymerization reactions can be divided conveniently into two types: (a) addition reactions; and (b) condensation reactions. Polymers prepared by addition reactions (e.g. substituted polyethylenes) have a backbone composed exclusively of C–C bonds which are normally resistant to hydrolysis and enzymic attack. This type was used by Wicherle and Lim (1960) to produce the well-known hydrogels (e.g. poly(hydroxyethyl methacrylate) or HEMA) which imbibe a considerable amount of water, are biocompatible and resist biodegradation. These materials, and other hydrogels, can be used as surgical implants and as soft contact lenses and are receiving considerable attention as potential drug delivery systems (Andrade, 1976). Polymers prepared by condensation reactions (Morgan, 1965) have a by-product (e.g. H_2O or HCl) formed as a result of the polymerization. A typical example is the interfacial formation of polyamides from the reaction of diamines with diacid chlorides with the formation of HCl. Other examples include polyesters, polyureas, polyurethanes, polysulphonates and polycarbonates. However, polyurethanes can be prepared without condensing out a small molecule by the reaction of di-isocyanate and a diol and some polyesters are preferably prepared by ring-opening of dimers (e.g. lactide). Both methods of preparation produce the same type of polymer which by virtue of the presence of a hetero atom in the chain, is potentially hydrolyzable.

The broad classification of groups of polymers by the presence of a particular chemical bond alone, while being of value when considering their preparation, is of little value in identifying polymers with particular properties. The polyesters are used to prepare sutures, catheters, artificial limbs, dental composites, dressings, syringes, clamps, forceps and cannulae and the polyacrylates are used in dental products, contact lenses and as adhesives (Mason, 1980). However, closely related polymers in any particular series, such as poly(glycolic acid) and poly(lactic acid), do exhibit gradual changes in properties.

Structure and properties of polymers

For controlled release applications two extreme situations can be encountered. In the first the polymer is initially insoluble in the body fluids and is used to prepare implants, microcapsules and similar types of devices in which the polymer acts as a physical carrier. The second concerns polymers to which drug molecules are attached (Ringsdorf, 1975). These can be regarded as chemical carriers and have the potential to both prolong release and to target the drug. In addition, synthetic water-soluble polymers can have biological activity (Regelson et al., 1960; Breslow, 1976) and it is possible to polymerize certain types of drugs such as steroids (Rabadeux et al., 1980). It is not always simple to distinguish between the various types and only the physical carriers will be considered here.

Three basic classes of polymers can be used in bioerodible systems: water-soluble polymers insolubilized by hydrolytically unstable crosslinks; polymers that are initially water-insoluble which become solubilized by hydrolysis, ionization or protonation of pendent

groups but which do not undergo backbone cleavage; and finally polymers which are water-insoluble and degrade to soluble products by backbone cleavage. The important consideration is whether the products are non-toxic and readily excreted by the body.

Crystallinity. High molecular weight linear polymers tend to undergo alignment to form crystallites when long sequences of the polymer chain have a stereoregular structure. With polymers of this type the presence of nucleating agents (perhaps the drug) or rapid cooling results in the formation of many small crystallites while slow controlled cooling allows crystal growth. Polymers are never 100% crystalline and the crystalline domains are separated by an amorphous region. The amorphous region can be in a glassy or rubbery state, at a particular temperature, depending upon the type of polymer. Poly(glycolic acid) and poly(L-lactic acid) have crystallinities of about 50 and 37% respectively (Gilding and Reed, 1979), while poly(DL-lactic acid) is totally amorphous.

The water uptake of a series of poly(glycolide–lactide) copolymers was studied by Gilding and Reed (1979). Low equilibrium water content was found with the more hydrophobic, crystalline poly(L-lactic acid) and with increasing glycolic acid content the degree of crystallinity and hydrophobicity decreased resulting in a rapid increase in the equilibrium water content up to a maximum of about 30% for the 70 : 30 copolymer (glycolide : lactide), thereafter with the onset of crystallinity the water content decreased. Clearly the presence of crystallinity may complicate both the rate of release of drug and the rate of degradation of the polymer and some of the implications of a biphasic matrix have been discussed by Gilding and Reed (1979). It was also found in that study that several lactide–glycolide homo- and copolymers crystallized partially when placed in a physiological environment (or water) for 24–72 h. Pitt et al. (1979a) have observed similar changes with poly(caprolactone) the crystallinity of which increased from 45 to 59% after 220 days and the effect of the change on the release rate of norgestrel was discussed.

Hydrophilicity/hydrophobicity. Since all biodegradable devices are in intimate contact with an aqueous environment the degree of hydrophilicity of the polymer is of considerable importance. The equilibrium sorption of water by polymers (Barrie, 1968) varies considerably depending upon the chemical nature, structure and the degree of crystallinity of the polymer (Moiseev et al., 1979). For systems which have drug release controlled by surface erosion of the device, the polymer should be hydrophobic. A limit of 5% water uptake based on the dry weight of the polymer has been suggested for poly(orthoester) and poly(orthocarbonate) devices (Choi and Heller, 1979).

When the balance between hydrophobic (e.g. $-CH_2-$) and hydrophilic (e.g. ester) groups allows appreciable water uptake, degradation may occur in the bulk polymer. In addition, the solubility and the diffusion of the drug in the polymer may be expected to alter due both to the presence of water soon after implantation and subsequently due to progressive degradation. The sorption of salts and other low molecular weight compounds along with water from the body fluids and the fact that degradation in the amorphous region is more rapid than in the crystalline domains complicates the pattern of biodegradation of poly(glycolic acid) (Moiseev et al., 1979).

Additives in polymers. Commercial polymers normally contain additives (e.g. initiators, catalysts, fillers, stabilizers and plasticizers) in addition to unreacted monomer. Williams (1973) has discussed some of the problems associated with the presence of addi-

tives in polymers when they are used in surgery. For biomedical applications the presence of additives should be avoided and when necessary should be strictly controlled.

In drug–polymer systems the drug may be present in considerable proportion and must be expected to affect the properties of the polymer in some cases. Loading levels of 30–50% have been used in many studies and beads (1.5 mm diameter) of a copolymer of lactic and glycolic acids containing 70% naltrexone have been studied in vivo and in vitro (Wise et al., 1978b). Schwope et al. (1975) found that naltrexone free base plasticized poly(DL-lactic acid) producing a tacky material which was not suitable for processing.

Tributyl citrate (5%) was added as a plasticiser of poly(lactic acid) in several studies (e.g. Yolles et al., 1975). Pitt et al. (1979b) studied the permeation of progesterone through films of poly(DL-lactic acid) finding a steady-state flux of 3.3×10^{-15} g cm^{-1} s^{-1}, when tributyl citrate (5%) was present in the films an initial value of 7.69×10^{-13} was found for 50 min after which the value changed to 1.10×10^{-14}, the effect being attributed to the partial loss of the plasticizer. In the same study glycerin (10%) was included in some films and the flux of progesterone was 5.6×10^{-13} g cm^{-1} s^{-1}, and the increase in permeability was attributed to the creation of a highly porous structure which was easily detected by the scanning electron microscopy.

BIODEGRADABILITY TESTING

In general when testing biodegradability one starts with the knowledge that a particular polymer, or series of closely related polymers, is potentially degradable and comparison with polymers which are known to be biodegradable is useful. In many cases a hydrolysis reaction is involved and frequently it is desirable to perform accelerated tests using extreme pH conditions, elevated temperature or enzymes.

In vitro experiments can be used in preliminary screening tests and can also provide more detailed information about the mechanism of degradation. Homogeneous degradation studies have been reported for the poly(alkyl 2-cyanoacrylate) series, in which the polymer was dissolved in acetonitrile, the presence of water being required for degradation to occur. The heterogeneous degradation was followed in boiling water systems. Both in vitro methods showed a similar trend, in which the methyl ester degraded fastest and as the size of the alkyl substituent increased the rate of degradation decreased, which was in broad agreement with limited in vivo studies using [^{14}C]-labelled polymer (Leonard et al., 1966). In a more detailed study of several members of the poly(alkyl 2-cyanoacrylate) series, Vezin and Florence (1980) found that the degradation rate was dependent on the surface area of the sample and suggested that degradation at the ends of the polymer chains was much faster than in the main chain.

The use of enzymes to assess whether a polymer is susceptible to enzymic degradation and to what extent a particular enzyme accelerates the degradation has been reported in several studies. Huang et al. (1977) have used several different enzymes to accelerate degradation of several different types of polymer. The same group (Huang et al., 1979) studied the chymotryptic degradation of a low molecular weight poly(ester-urea) containing phenylalanine using weight loss measurements and found it necessary to correct the results for hydrolysis due to the buffer salts present. A similar polymer derived from

glycine was found to resist chymotryptic cleavage. The effect of lipase on the degradation of several copolyamide-esters has been discussed by Tokiwa et al. (1979).

Other biological in vitro techniques involving organ cultures produced useful information about the degradability of poly(lactic acid) and several of the poly(alkyl 2-cyanoacrylates) in less than 24 h (Hegyeli, 1973). Kulkarni et al. (1971) reported a biological in vitro degradation study using chick embryo liver homogenates and found, in accordance with expectation, that the degradation of poly(DL-lactic acid) was faster than that of poly(L-lactic acid). In vitro homogeneous and heterogeneous hydrolysis studies were also reported.

In vivo studies are required at an early stage in any development programme to confirm the in vitro results and to begin assessment of the ultimate fate of the polymer and its metabolites. Simple methods such as weighing the residual polymer and microscopy of the polymer and implantation site after different time intervals are useful in preliminary assessment. Scanning electron microscopy can reveal important morphological changes and Vezin and Florence (1980) used this technique to demonstrate surface erosion, seen as pitting, of poly(alkyl 2-cyanoacrylates) when degraded in vitro. The decrease in molecular weight of poly(L-lactic/glycolic acid) copolymer (90 : 10) in the form of implanted beads in the monkey was followed by Wise et al. (1978b) who found a decrease from 37,000 to 18,000 after 28 days.

The use of radiolabelled polymer allows a convenient assessment of degradation and can be measured as per cent remaining after a given period of implantation or can be followed continuously as the label is excreted. The use of radiolabelled material also provides assessment of whether the degradation products, either molecules of low molecular weight derived from the monomer or oligomeric material which has diffused from the implantation site, concentrate in particular organs in the body. Brady et al. (1973) implanted blocks of [^{14}C]-labelled poly(DL-lactic acid) in the rat and found 36.8% of the radioactivity had been lost from the implant after 168 days. However, only 4.6% was recovered in the urine 2.8% in the faeces and less than 0.3% was found in tissues, and therefore it was suggested that the elimination of the radioactivity was mainly via respiration. Preliminary experiments on the degradation of poly(methyl 2-cyanoacrylate) in the dog used monomer labelled with ^{14}C at 3 different positions to allow a better understanding of the mechanism of breakdown and the possibility of hydrolysis of the ester group was noted (Wade et al., 1972). Using these types of approach during the development of a controlled release device a basic understanding of the polymer provides a background for detailed and extensive study of the drug–polymer in its final dosage form.

DRUG–POLYMER COMBINATIONS AND PROCESSING TO DOSAGE FORMS

Where polymers are used as physical carriers the drug–polymer combinations can be divided into two basic types as shown in Fig. 2. In the first the polymer acts as a membrane surrounding a core of drug while in the other the drug is dissolved or homogeneously dispersed in the polymer. Many diverse processes are available to prepare the various types of device and one of the first considerations is whether the polymer can be prepared, purified and fractionated prior to the admixture of drug and subsequent processing or whether the polymer is prepared in situ from the monomer in the presence of

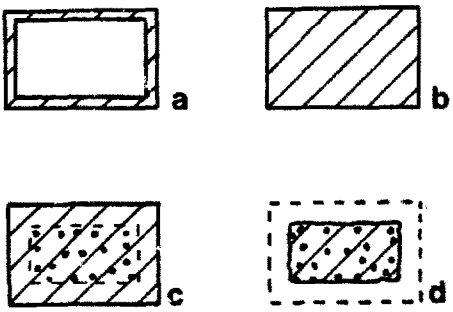

Fig. 2. Diagrammatic representation of drug–polymer combinations and release mechanisms. a: membrane device – polymeric membrane surrounding a reservoir of drug; b: solution device – drug dissolved in polymer; c: matrix device showing release of dispersed drug by diffusion; d: matrix device showing release of dispersed drug by erosion.

the drug. In the latter case, typical of highly crosslinked glassy polymers, casting and molding techniques are used. The polymerization can be carried out by thermal curing (Graham, 1979) or by polymerization of drug–monomer mixtures at low temperature by irradiation (Kaetsu et al., 1980). When linear thermoplastic polymers are used, the well-established polymer processing techniques (Tadmor and Gogos, 1979) are used to prepare devices. Poly(lactic acid) containing narcotic antagonists has been prepared as spherical beads by transfer molding and as cylindrical rods by extruding the melt (Schwope et al., 1975). Films of poly(lactic acid) incorporating several different drugs have been cast from common solvent systems, and where thicker films (>100 μm) of copolymers of lactic acid were required for permeation experiments, several films were stacked together and compression molded at 100–130°C (Pitt et al., 1979b). Spray drying of an antimalarial and a copolymer of glycolic/lactic acid from a common solvent produced finely divided (<125 μm) particles (Wise et al., 1976).

Microencapsulation has become used in a variety of applications (Gutcho, 1976) and pharmaceutical applications have been reviewed by Luzzi (1970) and Salib (1977). In addition to the coating of solid drug particles with a polymeric membrane, aqueous solutions of proteins can be microencapsulated bringing closer the concept of "artificial cells" (Chang, 1972, 1976, 1979). Microencapsulated enzymes have potential application in the therapy of hereditary enzyme deficiency disorders such as histidinaemia (Wood et al., 1979), in organ failure and as a treatment for substrate-dependent tumours.

Nanocapsules are of colloidal size and can be prepared by micelle polymerization (Birrenbach and Speiser, 1976). A coating of polymer around a solubilized core is produced by in situ polymerization of amphipathic monomers or alternatively nanospheres are produced by allowing polymerization to occur in the core of the micelle. The latter method was used to prepare poly(alkyl 2-cyanoacrylate) nanoparticles with diameters of about 200 nm which have potential as carriers of anticancer drugs (Couvreur et al., 1979).

The storage of biodegradable polymers may require strictly dry conditions in some cases to prevent degradation by atmospheric moisture. The presence of buffer salts where degradation is sensitive to pH or the presence of a degradation product in equilibrium with the polymer may essentially stop degradation until the formulation is administered. As an example of the latter, Florence et al. (1979) reported that the presence of a low

level of formaldehyde, a major degradation product, inhibited the degradation of poly-(butyl 2-cyanoacrylate) microcapsules in aqueous suspension. In a similar way to storage, the type of polymer may govern the method of sterilization used for the particular dosage form. In many cases steam sterilization would be totally unsuitable and a choice between dry heat, radiation or chemical sterilization could be made (Bruck, 1971). Gilding et al. (1980) studied the sterilization of a number of different polymers using ethylene oxide and noted that frequently this is the only suitable method. Poly(lactic acid) containing several different drugs has been sterilized by this method prior to in vivo studies (Yolles et al., 1976).

Routes of administration and promising drug therapies

Polymers have been used experimentally in dosage forms for most routes of administration. As mentioned previously, biodegradable polymers which undergo backbone cleavage may not offer significant advantage over non-degradable or bioerodible types for administration to the gastrointestinal tract. The use of bioerodible polymers has been suggested for administration to the eyes, vagina, uterus and rectum in addition to topical treatment of localized areas of the skin (Heller et al., 1978). Clearly most of these sites involve local action and even the rectal and vaginal routes have limited potential (de Blaey and Polderman, 1980). The potential of biodegradable drug delivery systems lies in the two main areas of depot formulation for prolonged release and in targeting drugs to specific sites, both requiring injection or implantation of the dosage form.

For prolonged action the 4 main types of drug which have been studied are steroidal contraceptives (Wise et al., 1980), antimalarials (Wise et al., 1979b), narcotic antagonists (Wise et al., 1978b) and anticancer drugs (Yolles, 1978). Several other drugs could be administered using similar systems, in particular psychotropics and drugs for the treatment of some tropical diseases. The currently available intramuscular formulations of psychotropic drugs (e.g. fluphenazine) are oily depot injections with duration of activity of up to 4 weeks. Florence et al. (1978) suggested that further extension of activity using oils was least promising and other approaches including the use of biodegradable polymers showed better potential in preliminary screening tests. Various arguments can be put forward for the use of implants as opposed to injectable depots, the main point in favour of implants being that they can be removed easily, for whatever reason, at any time during their useful lifetime while the removal of a fluid or particulate depot may present considerable difficulties. Indeed, a compromise situation has been suggested for the treatment of narcotic addicts by the implantation of up to 20 beads containing narcotic antagonist which would be less liable for illicit removal compared to a single implant (Wise et al., 1979a). Of course, the type of drug therapy and the desired duration of activity govern to a large extent the type of system required. At present injectable systems appear to prolong release for up to about 6 months while implants have the potential for a duration of activity in excess of 2 years.

The application of biodegradable polymers in targeting therapy has not been one of the prime topics of interest when using polymers as chemical carriers and several other approaches including the use of liposomes and binding drugs to proteins are being intensively studied (Gregoriadis, 1979). In many targeting studies the drug–carrier system is believed to enter cells by the process of endocytosis. The macrophage (Vernon-Roberts,

1976) is a type of cell which is present throughout all of the tissues of the body and which has a highly developed capacity for endocytosing large amounts of particulate matter of relatively large size, for example, bacteria and protozoa. After the material has been engulfed it is exposed to a variety of lysosomal enzymes. The highly developed ability of these cells to discriminate between particles of different type is readily appreciated if one considers their role in the removal or weak or damaged erythrocytes from the blood stream.

Polymer–tissue interactions

General and detailed accounts of the response of the body to injections (Gray, 1978) and implants (Williams, 1973) are available. The interaction of synthetic polymers, both soluble and insoluble, with living tissues has been discussed by Kalal (1979) and recently Bagnall (1980) has presented the "current understanding" of implant–tissue (blood and connective tissue) interactions. The response of the body to a particular material can be affected by its physical form, in particular whether it is porous or not and whether it is in the form of microscopic particles or a single macroscopic implant. An unexpectedly higher release rate of cyclazocine from poly(lactic acid) in the form of a film compared to a particulate form found in vivo was believed to be due to the different body response to the two physical forms (Yolles et al., 1974). Even different shapes of implanted rods of polymer can produce significantly different responses (Matlaga et al., 1976). Andrews and Kukulinsky (1979) have studied the role of surface charge on polystyrene thermoelectrets on foreign body carcinogenesis. However, in many cases implanted polymers produce minimal or bland responses and are encapsulated with collagen.

RELEASE MECHANISMS

Initially consideration must be given to whether a particular delivery system is designed to have release governed by surface erosion or by some other rate-determining step, particularly diffusion or partition of the drug. Diffusion of drug in non-degradable polymers has been widely studied; however, the effect of capillary channels and the solubility of the drug both in the polymer and the surrounding medium can be major variables in some cases.

Hopfenberg (1976) has considered controlled release from erodible slabs, cylinders and spheres. Where a single zero-order process controls erosion the theoretical equations can be rearranged in the form:

$$\frac{M_t}{M_\infty} = 1 - \left(1 - \frac{k_0 t}{C_0 a}\right)^n$$

where k_0 is the single zero-order rate constant for the erosion process, C_0 is the uniform initial concentration of drug, M_∞ is the total amount of drug present initially and M_t is the amount of drug released after time, t. For the slab n = 1 and a is the half-thickness; for the cylinder n = 2 and a is the radius and for the sphere n = 3 and a is the radius. From this analysis it is found that zero-order release is only obtained from the slab and that the delivery rate from the cylinder and sphere decreases with time. It is implicit in

the overall concept that the rate-determining step occurs at a boundary between the essentially unaffected host polymer and the previously degraded material. Specifically simple diffusion of the drug out of the matrix and water sorption by the polymer have negligible effect on the release rate. Bioerodible systems in which the release of drug is controlled by surface dissolution of a drug–polymer matrix have been reported (Heller et al., 1978); however, in those systems solubilization of the polymer occurred by hydrolysis and ionisation of side-groups and not by backbone cleavage. In a recent review, Heller (1980) has referred to work in progress (Choi and Heller, 1979) to develop bioerodible polymers suitable for implantation which release drug by zero-order kinetics.

When the duration of drug release is considerably shorter than the lifetime of the biodegradable polymer the mathematical treatment applied to non-degrading devices may be used. The mathematical treatment of such matrix-controlled systems (i.e. systems which do not change dimensions or physicochemical properties during release) has been the subject of many studies since T. Higuchi (1961, 1963) first proposed the mechanisms of release of dispersed drugs from ointment bases and inert granular matrices. Baker and Lonsdale (1974) have reviewed the basic types of release which have been proposed for non-degradable systems. The simplest type of release occurs by molecular diffusion of a drug molecule which is soluble in the polymer and approximations and exact solutions for the desorption are readily available for simple geometric forms (Crank, 1975). More commonly the amount of drug present in the system exceeds the solubility limit of the drug in the polymer and the drug is present as dispersed particles surrounded by polymer saturated with drug. When this situation is encountered the release kinetics can become complex, but in many cases the mechanisms involve simple dissolution and diffusion processes. Frequently a zero-order release profile is not predicted and the fraction released is related to the square-root of time ($Q - t^{1/2}$). Fu et al. (1976) and Cobby (1978) have developed mathematical models for the release of drug from different shaped tablets. The equations used in some of the more recent models are not suitable for hand calculation and require the use of computers. Several studies have shown good correlation between theoretical and in vitro experimental release profiles (e.g. Fu et al., 1976); however, quite restrictive assumptions are made in most models and their validity in real situations must be carefully considered. Chien and Lambert (1974) studied the release of ethynodiol diacetate form silicone devices and found a zero-order release ($Q - t$ relationship) when the steroid was poorly soluble in the eluting medium (e.g. water). When polyethylene glycol was added to the eluting medium to increase the solubility of the steroid the release profile changed from the partition-controlled ($Q - t$) to a typical matrix-controlled ($Q - t^{1/2}$) type.

Membrane devices utilize a polymeric membrane to control drug release and a constant rate of release can be obtained if diffusion through the membrane is the rate-determining step. This class of device is more difficult to fabricate than the monolithic or matrix types. For macroscopic devices the hollow cylinder or tube is perhaps the most easily formed and filled. Capsules of this type have been studied by Pitt et al. (1979a) to control the release of contraceptive steroid from poly(caprolactone). For microscopic (injectable) systems the microcapsule behaves as a membrane device. Theoretically a perfect coating of polymer can be applied to particles of drug but in practice it is difficult to establish a process of this type and the effect of defects and pores in the membrane can

overshadow the permeation of the drug through the membrane. Mason et al. (1976) prolonged the release of cyclazocine to about 8 days by encapsulating with poly(DL-lactic acid). However, calculations based on the permeability of the drug through cast films of the polymer predicted that the release from perfect microcapsules would have been 300 times longer, assuming that degradation of the polymer over the period was negligible.

Biodegradation in the bulk of the polymer, as with poly(lactic acid), complicates the release kinetics but has the fortuitous effect of compensating for the decline in the release rate with time associated with erodible and non-degrading devices. Wise et al. (1980) have developed a poly(lactic acid) implant which released [^{14}C]-labelled norgestrel, in the rat, for two years at a crudely constant rate. However, slight changes in the structure of the drug have been found to produce significant effects on release. Thus, the amount of naltrexone, cyclazocine and naloxone released from poly(lactic acid) particles after 60 days was 68, 38 and 26% respectively in vivo, while in vitro studies found considerably faster release rates (Yolles et al., 1974).

SOME EXAMPLES OF BIODEGRADABLE POLYMERS USED IN DRUG DELIVERY SYSTEMS

Polyesters

Poly(lactic acid) and come of its copolymers have been studied in prolonged action formulations for about 10 years and have repeatedly shown the potential of biodegradable drug delivery systems. Wise et al. (1979a) have reviewed the lactic/glycolic acid copolymer systems in some detail and Heller (1980), reviewing bioerodible systems, has included them as an example of bioerodible systems which undergo backbone cleavage. These systems, having been the most widely studied, have been used as examples throughout this article and will not be discussed further.

Other polyesters possess modified properties while retaining biodegradability. Recently poly(caprolactone) has been studied as a potential biodegradable polymer for prolonged release devices (Pitt et al., 1979). Ethicon (Doddi et al., 1977) have patented synthetic absorbable surgical devices, in particular sutures, prepared from poly(dioxanone) which while being rather similar to poly(lactic acid) can be sterilized by irradiation without loss of physical properties.

Polyamides and poly(amino acids)

Simple linear polyamides with a relatively high hydrocarbon content, such as nylon 6 (Roggendorf, 1976), have been examined in a range of biomedical applications and it is generally found that they are not suitable as inert implants but the time scale for complete reabsorption would be far in excess of that envisaged for drug delivery systems. Nylon 6 was found to resist enzymic degradation in a study by Huang et al. (1977). However, these workers were able to synthesize more hydrophilic polyamides which were susceptible to degradation by proteolytic enzymes.

The poly(amino acids) are rather different from the polyamides of the nylon-type in that the polymer backbone is composed exclusively of peptide (amide) bonds. While the in toto synthesis of an enzyme with ribonuclease A activity has been reported (Gutte and Merrifield, 1971), complex synthetic poly(amino acids) may be expected to present antigenic problems (Sela, 1969). However, due to the range of different amino acids available,

simple homopolymers or copolymers and derivatives offer a wide range of polymers, and few problems with antigenicity have been reported with the synthetic poly(amino acids) which have been studied.

Poly(glutamic acid) and its derivatives have been studied widely. Kovacs et al. (1960) reported that the methyl ester of poly(glutamic acid) had antitubercular activity. Increasing the degree of esterification of the polymer was found to delay the resorption of poly(glutamic acid) sutures (Miyamae et al., 1968). Anderson et al. (1974) found that esterified copolymers of glutamic acid and leucine were well tolerated in the rat and confirmed that removal of the ester groups resulted in a biodegradable matrix. Rowland et al. (1975) reported the use of poly(glutamic acid) as a carrier for *p*-phenylene mustard and an antibody; the conjugate subsequently suppressed tumour growth in mice. Hirano et al. (1979) used poly(glutamic acid) as a carrier for cyclophosphamide for cancer chemotherapy.

Poly(2-hydroxyethyl DL-aspartamide) has been studied as a non-toxic, non-immunogenic plasma expander which degrades in about 24 h (Neri et al., 1973). Copolymers of L-leucine and L-aspartic acid and some derivatives, prepared as solid subcutaneous implants, have varying degradation rates dependent upon their degree of hydrophilicity (Marck et al., 1977).

Poly(alkyl 2-cyanoacrylates)

The alkyl 2-cyanoacrylate monomers are used as "instant glues" and as tissue adhesives and as such have been the subject of a considerable amount of in vitro and in vivo study for over 20 years. The facile hydrolysis of the C–C backbone, generally very stable, is due to the presence of the particular substituent groups on the chain. The toxicity of the methyl ester is believed to be due to the rapid build-up of the degradation products; however, poly(butyl 2-cyanoacrylate) with a slower rate of degradation is well tolerated in vivo (Mungiu et al., 1979).

Florence and coworkers have studied the poly(alkyl 2-cyanoacrylates) as biodegradable polymers for controlled release applications for several years. The rapid polymerization (catalyzed by traces of water) allows the formation of films of the polymer at unstirred oil/water interfaces, the morphology of the films being dependent upon the type of organic solvent used (Florence et al., 1976). The ability of the monomers to polymerize rapidly was exploited to microencapsulate aqueous solutions of protein by in situ polymerization in water-in-oil emulsions (Florence et al., 1979). Detailed in vitro degradation studies on particles prepared from cast films showed that surface erosion occurred (Vezin and Florence, 1980).

Nanoparticles prepared using alkyl 2-cyanoacrylates have been found to adsorb several antineoplastic drugs (Couvreur et al., 1979) and their tissue distribution after intravenous injection in the rat has been reported (Couvreur et al., 1980). These nanoparticles by virtue of their size, structure, drug sorptive properties and biodegradability have considerable potential as lysosomotropic carriers.

The future

While the potential advantages of biodegradable controlled release systems are recognized to be wide-ranging and of significant value, many experimental studies have shown the complexities involved and clearly demonstrate the need for a multidisciplinary

approach. The recent rapid growth of polymer science and technology has provided novel materials for these systems which can be well-characterized. The problems associated with the long-term accumulation of non-degradable polymers in the body are minimized with the biodegradable types, but of course these require expensive, detailed long-term testing before they can be used widely.

In the near future, simple reproducible prolonged release drug–polymer devices, of the types already studied experimentally as contraceptives and for treatment of major tropical diseases, may become clinically and commercially acceptable. In the longer term, the potential offered by targeting systems is tremendous and progress is already being made to produce more stable drug–carrier complexes with greater targeting specificity.

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