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REVIEWS

Biodegradable Polymeric Drug Delivery Systems

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Abstract.□The use of biodegradable polymeric materials as drug carriers is a relatively new dimension in polymeric drug delivery systems. A number of biodegradable or bioerodible polymers, such as poly (lactic/glycolic acid) copolymer, poly (α-amino acid), polyanhydride, and poly (ortho ester) are currently being investigated for this purpose. These polymers are useful for matrix and reservoir-type delivery devices. In addition, when chemical functional groups are introduced to the biodegradable polymer backbone, such as poly (N-(2-hydroxypropyl) methacrylamide), the therapeutic agent can be covalently bound directly or *via* spacer to the backbone polymer. These polymer/drug conjugates represent another new dimension in biodegradable polymeric drug delivery systems. In this paper, major emphasis is placed on clinical applications of biodegradable polymeric delivery systems. In addition, examples of biodegradable polymeric durg delivery systems currently being investigated will be discussed for the purpose of demonstrating the potential importance of this new field.

Polymeric materials were first introduced two decades ago for the use of sustained release tablets, based on an inert plastic matrix, and have since gained considerable attention in clinical use. The sustained release and slow dissolution in the GI tract of oral dosage tablets is controlled by using polymeric materials as a barrier to the dissolution process.

The general types of polymeric moderated controlled release devices (1) can be classified as; (i) those in which the therapeutic agents are dissolved or dispersed in an inert diffusion barrier (i.e. monolithic device); (ii) those in which the active agents form a core surrounded by an inert polymeric diffusional barrier (i.e. reservoir device); and (iii) those in which the therapeutically active agent is covalently bound to the polymer backbone producing a controlled release by the nature of chemical bonding between drug and polymer backbone and other properties of the polymer (e.g. molecular weight, hydrophilicity or hydrophobicity, nature of spacer group, etc.).

The physicochemical properties of both polymer and drug are important factors in the design of a controlled release delivery system. In addition, the toxicity, biocompatibility and immunogenicity of the polymeric devices are critical due to the fact that these devices interface directly with the biological environment in which they are injected, implanted or inserted.

The concept of prolonged release of therapeutically active agents combined with polymers has been in existence for decades. In 1964, Folkman *et al.*(2) reported that Silicone rubber is permeable to a variety of drugs and is also relatively compatible to the surrounding tissue. This report encouraged researchers to study sustained drug release monolithic devices for application other than simple oral medication. For example, implantable devices have been studied for sustained release of anesthetics (3), antimalarial and antischistosomal agents (4), atropine and histamine (5) and a variety of steroids for fertility control in female (6) or for inhibition of platelet adhesion on polymer surfaces (7-8).

Reservoir type devices are presently on the market for the controlled release of progesterone (PROGESTASERT) (8) and pilocarpine (OCUSERT) (9) developed by ALZA Corporation. These systems can be inserted in close proximity to the target organ sites and permit easy removal once the device's life is over. Many drug release devices, however, require surgical implantation and afterward retrieval, whereas a biodegradable polymeric device would eliminate this procedure.

Although the concept of utilizing biodegradable syn-

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thetic polymers ad drug carriers is attractive, the drawback is mainly due to the optimum requirements of polymer degradability, biocompatibility of the polymer and its concern on degradation products.

In an ideal situation, a biodegradable drug delivery device would release a therapeutic agent at a constant or controlled rate over predetermined time followed by degradation of polymer backbone into nontoxic, biocompatable subunits which would subsequently be metabolized or eliminated from the body. Furthermore, the system would not exhibit dose dumping at any time and would retain its physical characteristics until after depletion of the drug.

The advantages of biodegradable polymeric delivery systems over the traditional unit dose form are obvious. In general, they show the same advantages as nonbiodegradable polymeric delivery systems, such as aiming for constant release of drug, which eliminates the "sawtooth" effect of traditional dosage regimens. In addition, surgical removal of implanted devices after depletion of the therapeutic agent is not required in the biodegradable system, which is unlikely in a nonbiodegradable device. It must, however, also be recognized that there are disadvantages exhibited by the biodegradable system. In addition to the general disadvantages in the use of nonbiodegradable systems, some types of biodegradable systems exhibit substantial dose dumping at times following implantation or injection. This phenomenon is generally related to scission of backbone polymers or crosslinks, therefore the devices lose a integrity resulting in a release of substantial doses of the drug. Also the "burst effect" is typical of most systems. Additionally, if a biodegradable system administered especially by injection (particle forms) was nonretrievable, thus this system might be troublesome if the patient shows an adverse reaction to the drug or carrier.

The term "biogradable drug delivery systems" is not yet clearly defined. They have also been described as bioerodible and as bioabsorbable drug delivery systems. Degradation caused by enzymes and/or acid-base catalytic reactions should be well defined. While there are some differences, precise distinctions have not been made and the terms are frequently used interchangeably.

2. Monolithic Systems—Physically Dispersed Drug in a Biodegradable Polymer.

The release of drugs from these systems can be divided into the three general mechanisms shown in Figure 1. While the therapeutic agent is homogeneously dispersed in all of the following polymer matrices, the mechanism for drug release is controlled by (i) diffusion, (ii) polymer surface erosion, or (iii) a combination of diffusion and polymer surface erosion. A constant release (zero order release) is difficult to achieve due to the decrease of concentration, more precisely, a decrease in chemical activity of drug. As the drug is released from the polymer matix as in the case of (i) and (iii) in Figure 1, chemical activity or concentration of drug is decreased over time and affects the release rate to behave as first order release rather than zero order release. Most monolithic biodegradable devices currently in use rely on either mechanism (i) or (iii) shown in Figure 1.

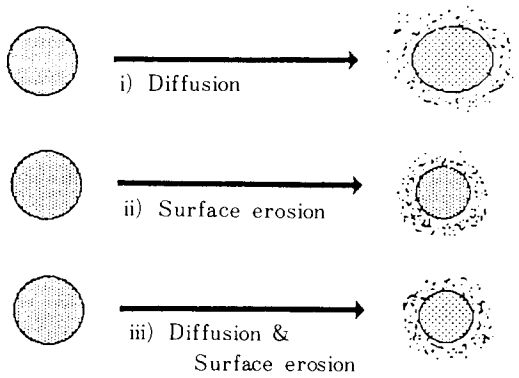


Fig. 1. Release mechanisms of biodegradable polymeric drug delivery systems.

It is obvious that a constant release of therapeutically active agents is very difficult to achieve with a monolithic type biodegradable system, since the release of drugs is mainly controlled by a diffusion process.

The most desirable biodegradable drug delivery system is one where the therapeutic agent is fully immobilized in a biodegradable polymer matrix where diffusional release is of little consequence and the bioerosion porcess is confined to the outer surface of the delivery device (mechanism ii, in Figure 1). Under these conditions release of the physically dispersed drug into the polymer matrix is controlled solely by surface erosion, therefore kinetics of release are predictable and amenable to precise control (21)

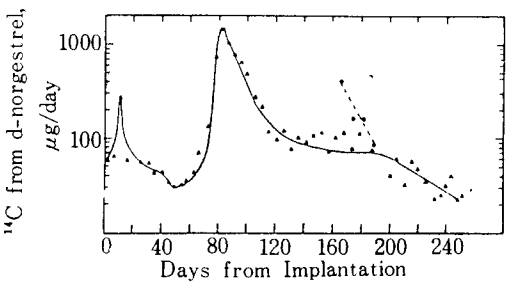


Fig. 2. Recovery of excreted ^{14}C-labelled d-norgestrel from dog with implants of 100 *dl*-lactide polymer (ref. 16).

A further consequence of surface erosion is that the amount of drug released is directly proportional to the loading percent of drug in the matrix and to the total surface area of the device. In addition, since erosion of the device occurs by the uniform movement of an eroding front, lifetime of the device is directly proportional to the thickness of the device. However, unless total area of the device remains constant, the rate of drug release will decline with the decrease of the total surface area of the device which is a consequence of the erosion process (22).

Poly (lactic acid) or poly (lactic/glycolic) copolymers have been developed by many researchers (10-17) for the purpose of investigating monolithic biodegradable polymeric drug carriers. In 1973, Jacknicz *et al.*(10) reported that thin films of d-norgestrel in relatively nonbiodegradable polymer of L(+) lactic acid lasted for several years and released nonuniformally approx. 50 μg/day of d-norgestrel at a rate of approximately 4 μg/day/cm^2. Because of the lower rate of polymer hydrolysis with respect to steroid release in this study, later investigations (16) were carried out using polymers with greater susceptibility to degradation. Results of this study (16) with cylindrical monolithic implants using dogs indicated that the polymer from 100L (+)-lactide released d-norgestrel at a uniform rate of approximately 4 μg/day/cm^2. However, this apparent diffusion controlled steroid release system appears to have a lifetime much greater than the desired six months.

In this same study, copolymers of 75 dl-lactide/25 glycolide, 75 L (+)/25 glycolide, and 90 dl-lactide/10 glycolide appeared to be so readily biodegradable that an implantable cylinder prepared from these polymers would not last for six months of continuous delivery of d-norgestrel. An implant of the 100 dl-lactide homopolymer provided a nominal d-norgestrel release of about 100 μg/day/cm^2 for about a period of less than one year (data shown in Figure 2). However, this system exhibited an initial burst at 10 days post-implantation and a second burst 83 days later, making this system unsatisfactory in its formulation.

The results of a 50 dl-lactide/50 L(+)-lactide copolymer show certain potential for a long term contraceptive delivery. This device, when implanted, had a lifetime of approximately one year with a nominal steroid release rate of approximately 20 μg/day/cm^2. this system was noted for having rather modest initial burst of drug as compared with the other systems tested (16).

In these studies (10, 16), the direct correlation of steroid release rate was not made with respect to either polymer molecular weight of steroid loading percent in the implant. However, it appears that the diffusion rate of steroid may be lower in 100 L(+)-lactide homopolymers (crystalline) than in similar but noncrystalline dl-lactide homopolymers and lactide/glycolide copolymers. This may be the case for the crystalline 100 L(+)-lactide polymers, since the chain segments have restricted mobility. It is interesting to note that 90 dl-lactide/10 glycolide copolymers was found to have a slower release rate of d-norgestrel than the 75 dl-lactide/25 glycolide copolymers according to the independent study (18). It is likely that increasing lactic acid percentage in copolymer composition resulted in decreasing the hydrophilicity of polymer system. When comparing the chemical structures of lactic and glycolic acid, it can be seen that lactic acid has an α-methyl group making more hydrophobic. This increased hydrophobicity limits accessability of highly aqueous physiological fluids into the polymer matrix. Similar results were also reported (17) in an antinarcotic release system by using a lactide/glycolid copolymer as the drug carrier. In this study, it was found that the duration of naltrexone release from the 90 dl-lactide/10 glycolide beads was almost twice that as from the 75 dl-lactide/25 glycolide beads.

Aliphatic polyesters have been developed by the Research Triangle Institute (19). Homopolymers and copolymers of ε-caprolactone, ε-(+,–)-calactone, pivalolactone, and (+,–)-dilactide have been prepared an characterized. It was found that poly ((+,–)-lactic acid) and copolymers of ε-caprolactone with (+,–)-lactide, ε-(+,–)-calactone, and pivalolactone degrade rapidly losing mechanical strength and significant weight (> 10%) within 6 months. The delivery lifetime of the poly (ε-caprolactone) device can be controlled by a choice of the initial molecular weight of the implant and useful release lifetimes of 9 to 12 months have been achieved with these copolymers.

Synthetic polypeptides consisting of copolymers of glutamic acid and leucine have been used by Sidman *et al*, (20), as a biodegradable delivery carrier for narcotic

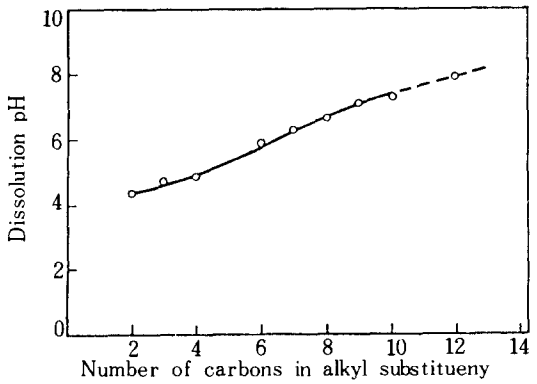


Fig. 3. Relationship between pH of precipitation and size of ester group in half-esters of methyl vinyl ether-maleic anhydride copolymers (ref. 30).

antagonists. A delivery system in film form was prepared from copolymers containing 10% to 40% naltrexone by weight. The naltrexone was found to be released by a diffusional process, exhibiting diffusion coefficients which varied as a function of the glutmatic acid content and the initial naltrexone load.

The uniform surface erosion of a polymer matrix can be achieved by one of three different methods. The first method requires the use of hydrophobic polymers which contain highly hydrolytically labile linkages. A well known example is polyanhydrides (23-25) which are currently being investigated by Langer's group at MIT. These polymers exhibit well known lability of the anhydride bond and the ability to make polymer matrices of varying degrees of hydrophobicity by combining aliphatic and aromatic monomer units (26).

The second method requires the use of polymers in which surface linkages are more reactive than linkages in the interior of the matrix. Materials in this category include currently used enteric coatings generally represented as polyacids. One of the most widely studied systems is a partially esterified copolymer of methyl vinyl ether and maleic anhydride or a partially esterified copolymer of ethylene and maleic anhydride (27-29). In unionized form these copolymers are water insoluble, whereas upon ionization of the carboxylic acid functional group they become water soluble. These materials characteristically exhibit a pH range above which they are soluble and below which they are insoluble. This pH range is quite narrow, approximately 0.25 pH units, as shown in Figure 3, and changes linearly with the number of carbon atoms in the ester side group of the copolymer (30). This behavior can be readily understood by considering the hydrophobicity of the polymer

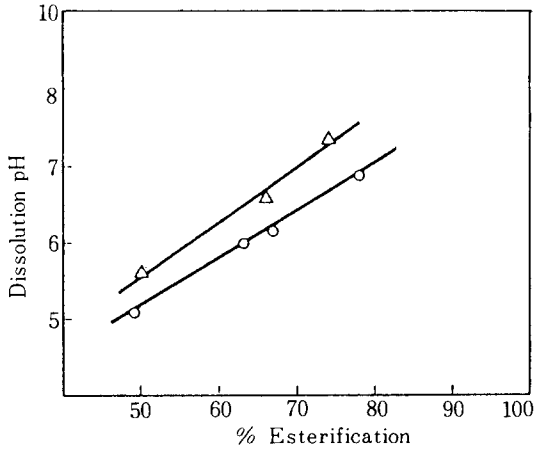


Fig. 4. Relationship between pH of precipitation and degree of esterification for n-butyl and n-pentyl half-esters of methyl vinyl ether-maleic anhydride copolymers (ref. 30).

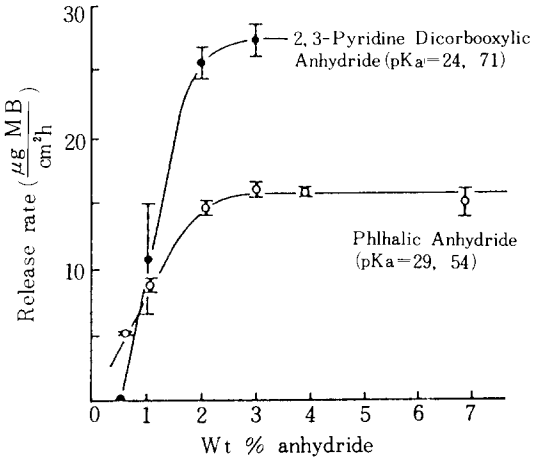


Fig. 5. The effect of anhydride content on the methylene blue release rate from 65: 35 1,6-hexanediol (HD)/trans-cyclohexanedimethandiol (t-CDM) poly (ortho ester) disks containing 0.2% methylene blue (ref. 37).

matrix. With relatively small ester groups, a low degree of ionization is sufficient to solubilize the polymer, therefore the dissolution pH is low. Whereas the size of the alkyl group increases, so does the hydrophobicity, and progressively more ionization is necessary to solubilize the polymer, requiring high pH for dissolution. The same argument also holds for polymers having the same ester group but a different degree of esterification as shown in Figure 4. The higher the degree of esterification, the more hydrophobic the polymer, and consequently requires a higher dissolution pH. Although these polymers were originally designed to dissolve abruptly with a significant increase in external pH, in a constant pH environment they undergo a controlled surface erosion; since the pK_a of the surface carboxyl groups, which are in an aqueous environment, is significantly lower then those in the interior of the hydrophobic matrix. This makes the surface carboxyl groups more reactive than those in the interior of th matrix.

A third method for achieving uniform surface erosion requires polymers that contain pH-sensative linkages and using excipients physically incorporated into the matix to bias the erosion process towards the surface of the device. Examples of such polymers are poly (ortho esters) (31-37). The primary rationale for using excipients physically incorporated into a polymer matrix containing pH-labile bonds is to lower the pH at the surface relative to the interior. This acts to catalyze the hydrolysis process at the surface layer only. When acidic excipients are used, water will slowly intrude into the highly hydrophobic polymer matrix. This excipient is activated either by a simple dissolution process of incro-

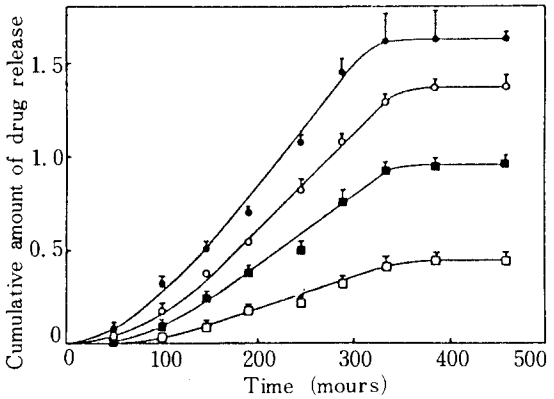


Fig. 6. The effect of drug loading on the drug release profile from 50: 50 1.6-hexanediol/trans-cycolhexanedimethanediol poly (ortho ester) disks containing 0.2% poly (sebacic anhydride) (37°C, pH 7.4). Drug loadings: 8% W/W (●), 6%(O), 4%(■), 2%(□), Ref. 37.

porated acidic salt such as calcium lactate or by the hydrolytic activation of an incorporated latent catalyst such as acid anhydrides. In either case, pH will be depleted within that zone. Poly (ortho esters) having useful release lifetimes from hours to about one month have been prepared by using acid anhydride excipients (37). As expected, the rate of polymer erosion and drug release depends on the pK_a of the diacid and its concentration in the matrix. This dependence is shown in Figure 5 for 2,3-pyridine dicarboxylic anhydride and phtahalic anhydride. Another method can be used by the incorporation of a slightly water soluble basic excipient, such as $Mg(OH)_2$, into the polymer matrix with the drug (32). Since these poly (ortho esters) are stable in base, no polymer backbone hydrolysis can take place until the incorporated basic salt is neutralized. The neutralization very likely occurs by water soluble $Mg(OH)_2$ out of the device where it is then neutralized by the external buffer. As a result of this process, a $Mg(OH)_2$ depleted layer develops at the outer surface of the device where polymer erosion can occur.

As mentioned previously, in a an ideal bioerodible polymeric drug delivery system, diffusional release should be minimized since diffusion occurs by first-order kinetics. Himmelstein *et al.* (37) reported that the acid anhydride catalyzed erosion of poly (ortho esters) is an ideal case of surface erosion. As shown in Figure 6, the rate of drug release is directly proportional to drug loading percent. Figure 7 shows that the lifetime of the device is directly proportional to the thickness of device; and in Figure 8, the rate of drug release is directly proportional to total surface area. The examples shown in Figures 6-8 indicate that the effect of diffusion on the release of drug from a bioerodible system can be minimized.

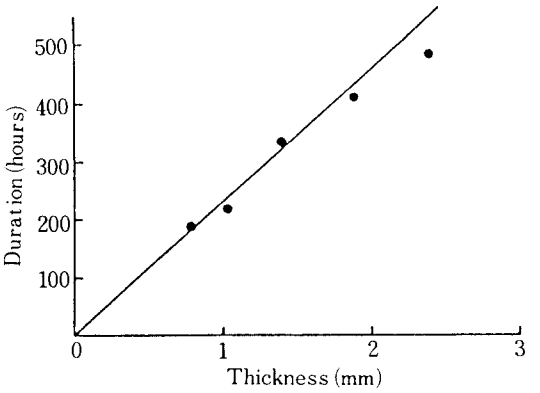


Fig. 7. The effect of poly (ortho ester) disk thickness on the duration of drug release from 50: 50 HD/t-CDM containing 0.2% poly (sebacic anhydride) and 4% drug (37°C, pH 7.4). Ref. 37.

The incorporation of a low water soluble basic salt into a poly (ortho ester) also provide a means for developing devices which have useful lifetimes of several months. Figure 9 shows cumulative weight loss and cumulative drug release from crosslinked poly (ortho ester)rods containing 30 wt. % levonorgestrel and 7 wt. % $Mg(OH)_2$ implanted subcutaneously in rabbits (32). Althought the data which were based on a single experiment show considerable scatter, polymer erosion and drug release occur concomitantly for 20 weeks after which drug release may accelerate. The accelerated release may be due to the inhomogenous mixing of ingredients into the polymer matrix and it is likely that the uneven distribution of ingredients contributed to the

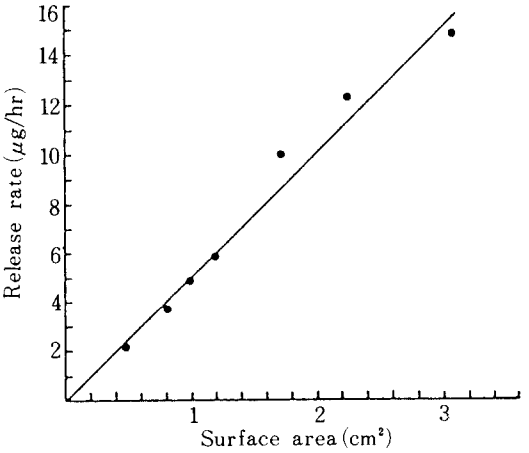


Fig. 8. The effect of poly (ortho ester) disk surface area on the drug release rate from 50: 50 HD/t-CDM containing 0.2% poly (sebacic anhydride) and 4% drug (37°C, pH 7.4). Ref. 37.

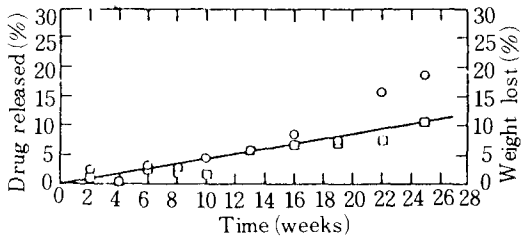


Fig. 9. *In Vivo* cumulative weight loss (□) and cumulative release of levonorgestrel (O) from crosslinked poly (ortho ester) rods, 2.4 × 20 mm, containing 30 wt. % levonorgestrel and 7.1 wt. % $Mg(OH)_2$. Total drug content 32.0 mg. Devices implanted subcutaneously into rabbits. Ref. 32.

scattering of data points. This reaffirms that homogeneous mixing is an another important factor in the formulation of monolithic-type bioerodible polymeric drug delivery system in order to achieve the controlled release.

3. Chemically Immobilized Drug/Biodegradable Polymeric Delivery Systems.

The incorporation of drugs via covalent bonding has only recently been described. Such systems can achieve a controlled release of therapeutically active agents by chemical immobilization of the drug onto a biodegradable polymeric backbone through a labile bond as shown in Figure 10. This system is different from the physically dispersed delivery system as discussed in the previous section. In this system the covalently bound drug is hydrolized and then free drug is released through the polymer matrix. If the diffusion coefficient is much greater than the hydrolysis constant of labile bond, the hydrolysis is the rate limiting step. The chemical activity of the immobilized drug is nearly constant (concentration of drugs remains constant), therefore constant release can be achieved.

Specific targeting can also be possible with this system. The attachment of specific targeting moieties as shown in Figure 11, such as a hapten or an antibody, to the polymeric backbone allows the localization of the delivery system to specific cells or tissues which express the particular antigenic determinant.

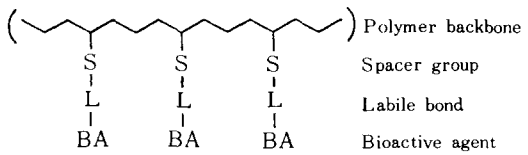
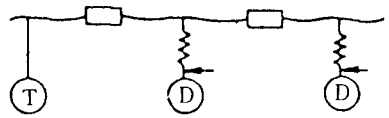


Fig. 10. Schematic representation of drug/biodegardable polymer conjugate.



Ⓣ targeting moiety
Ⓓ drug attached by an enzymatic degradable (←) bond via a spacer (-⋀⋀-)
□ degradable parts of the main chain

Fig. 11. Schematic representation of targeting drug/polymer conjugate.

3.1 Systemic Delivery.

The polymeric α-amino acids, poly (L-glutamic acid) and poly (hydroxyalklglutamine), have been extensively utilitized at the University of Utah and at Twente University in Netherlands (38-42) for coupling reactive functional groups of bioactive agents to spacer or directly to backbone polymer using drugs, such as norethindrone (contraceptive) or naltrexone (antinarcotic).

Although a variety of poly (amino acid) homopolymers, copolymrs, terpolymers and more complex combinations have been synthesized, those which have shown the greatest potential as chemically immobilized drug delivery systems are homopolymers of L-glutamic or L-aspartic acid and copolymers of these amino acids with L-leucine or L-valine. Since glutamic and aspartic acid are dicarboxylic acids, the polymer backbones contain free carboxyl groups after polymerization. The remaining functional group can be subsequently reacted with drugs, directly or via variety of spacers. Homopolymers of glutamic or aspartic acid are highly hydrophilic due to the side-chain carboxylic group. Even though the hydrophilicity can be regulated by copolymerization with less hydrophilic amino acids, such

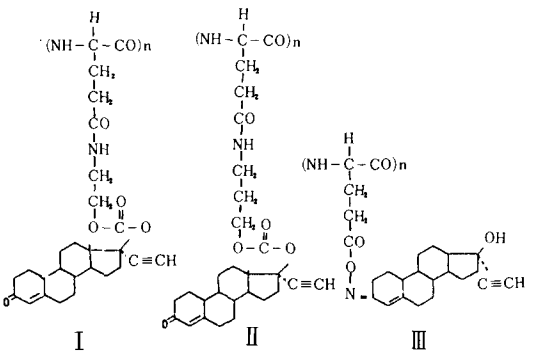


Fig. 12. Norethindrone/polymer conjugates:
I. norethindrone/poly (hydroxyethylglutamine) conjugate via carbonate linkage.
II. norehindrone/poly (hydroxypropylglutamine) conjugate via carbonate linkage.
III. norethindrone/poly (glutamic acid) conjugate via oximino linkage. Ref. 41.

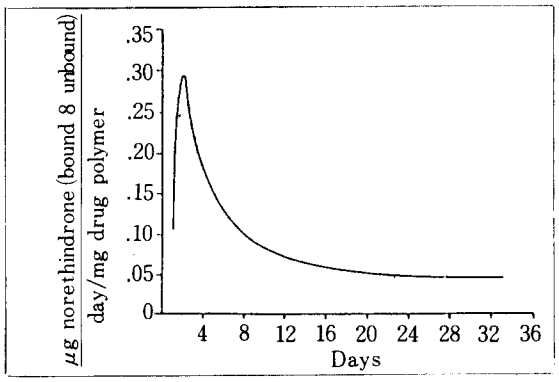


Fig. 13. *In vitro* release of norethindrone from poly (hydroxypropyl glutamine)/norethindrone conjugate in aqueous buffer. Ref. 41.

as L-valine or L-leucine, it must be noted that as the number of amino acids increases, the immunogenic reaction of polymers also increases (41).

Poly (L-glutamic acid) has been used by Mitra *et al.* (38) as a backbone polymer for direct attachment of norethindrone to the free carboxylic groups of the poly (glutamic acid) via oximino ester labile linkage (compound III in Figure 12). Norethindrone was also attached via alkyl spacer groups (compound I and II in Figure 12). These spacers groups were attached by reacting an α and ω hydroxyalkylamine with a poly (γ-benzyl-L-glutamine) imtermediate. The resulting poly (hydroxyalkyl-L-glutamine) contains a reactive terminal hydroxyl group on a variable-length alkyl spacer group through which norethindrone can be attached via a carbonate ester labile linkage (38-41). The length of the spacer group is dependent upon the chain length of the hydroxyalkylamine utilized.

A typical in vitro release curve using 14C-labelled norethindrone bonded to poly (hydroxalkylglutamine) is shown in Figure 13. It can be seen that, following an initial burst, likely due to physically entrapped norethindrone, release of the drug was relatively steady for about 30 days. There are five major parameters that can be varied to control the rate of drug release from this system (41): (i) hydrophilic character molecular weight of polymer; (ii) length of spacer group; (iii) the lability of

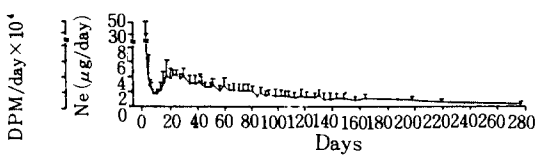


Fig. 14. *In vivo* release of norethindrone from compound I in Figure 12. 2.77 mg norethindrone/-10mg compound I/rat. 6 rat average + S.D. Ref. 41.

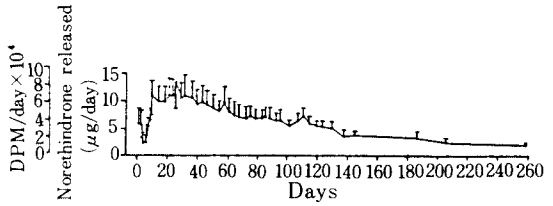


Fig. 15. *In vivo* release of northindrone from compound II in Figure 12. 3.88 mg norethindrone-/10mg compound II/rat. 6 rat average + S.D. Ref. 41.

the covalent bonding between polymer and drug; (iv) initial loading percent of drug; and (v) particle size and geometry of the powdered or fabricated polymer/drug conjugate.

Kim *et al.* (41) conducted a series of in vitro experiments, reporting that (a) the smaller the particle size, the faster the release rate; (b) as the initial load of norethindrone increases, the release becomes slower due to the increase of hydrophobicity of system (norethindrone is very hydrophobic); and (c) the shorter the spacer length, the faster the release rate.

In vivo release studies on the same compounds (Figure 12), subcutaneously injected as a suspension in rats, have been described by Fang *et al.*(41). The typical in vivo release profiles of 14C-labelled norethindrone from compound I and II are shown in Figure 14 and 15, respectively. There was an initial burst followed by a fairly constant but slightly declining rate of steroid release. The average in vivo release rates of steroids were 0.18 μg NE/mg compound I/day and 0.50 μg NE/mg compound II/day. It is interesting, however, to note that in vivo release rates of steroids from polymer/drug conjugate of carbonate type was more rapid when the spacer consisted of three carbons (compound II) as compared to the two carbon spacer unit (compound I). This apparent reverse correlation in vivo/in vitro results may be due to the increased esterase enzyme accessibility found in vivo when the spacer length is increased. The in vivo release study (Figure 16) of compound III which has no spacer showed that the

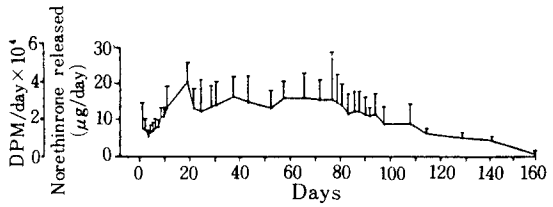


Fig. 16. *In vivo* release of norethindrone from compound III in Figure 12. 5.57 mg norethindrone/ 9mg compound III/rat. 5 rat average + S.D. Ref. 41.

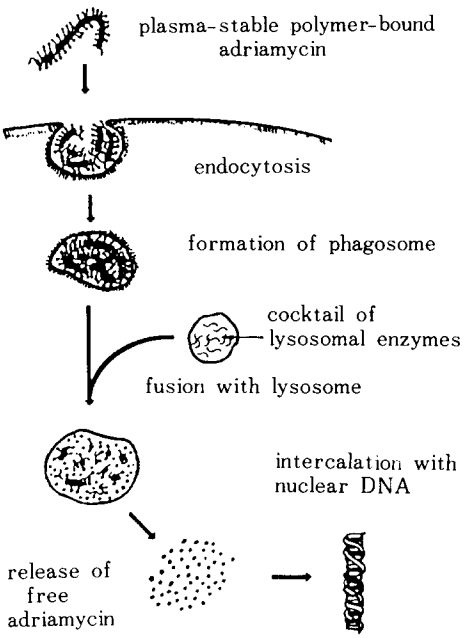


Fig. 17. Endocytosis and lysosomal digestion of polymer/drug conjugate.

steroid is more rapidly released than those of polymer/drug conjugates which contained spacers. In addition, reduction of average particle sized from 200 to 11 μm resulted in a tenfold increase in release rate *in vivo* (41).

3.2 Targeting Delivery.

A targeting drug delivery system, using a biodegradable polymer as the drug carrier, could be the best solution for the delivery of cytotoxic agents. Cytotoxic agents which are used for treatment of tumors and autoimmune diseases are not specific enough to suppress only maligant tissue or target cells. These agents often exhibit non-specific cytotoxic or cytostatic action on other normal cellular system. These unwanted side effects are therefore a limiting factor for the use of most therapeutically effective cytotoxic agents. This dilema, i.e., the search for more effective cytotoxic agents with a weaker non-specific side effect, could be solved by using a targeting drug carrier system which would ensure that the cytoxic agent will be delivered to and act only on the specific target clls.

Ideally the drug/carrier conjugates should be stable in the systemic circulation and should degrade only after uptake by the tumor cells. Tumor cells exhibit a high uptake of macromolecules by endocytosis (either pinocytosis or phagocytosis) (Figure 17) whereas normal tissue cells are poorly endocytotic (43). Thus the uptake of carrier/drug conjugate by tumor cells is expected to be higher than that of the normal cells. After iner-

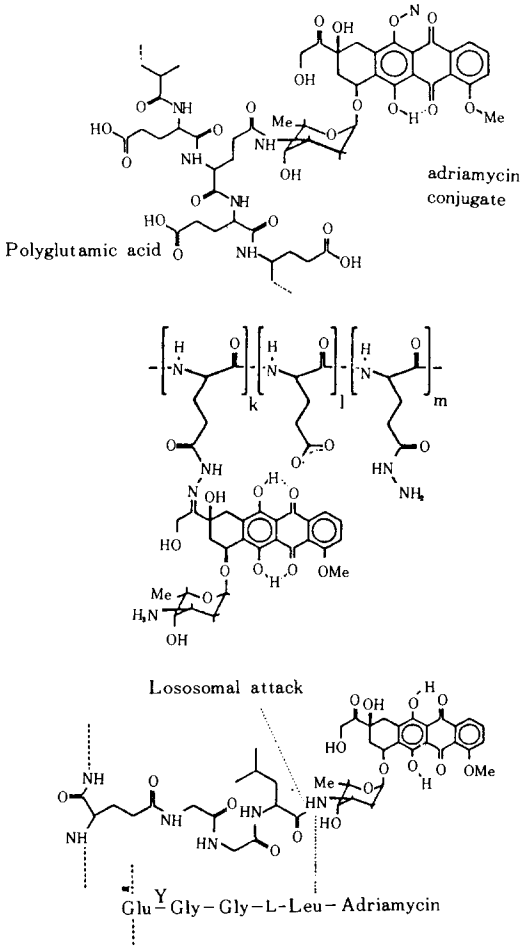


Fig. 18. Adriamycin/poly (glutamic acid) conjugates. Ref. 43.

nalization of macromolecule-drug conjugates by endocytosis, a phagosome is formed which is then fused with a lysosome. The drug/carrier is then exposed to some 40 or more digestive lysosomal enzymes and should release the cytotoxic drug in situ. These lysosomal enzymes are known to readily attack α-amino acid peptide bonds (Figure 17). The carriers which have been utilized in this approach are categorized as follows: (a) proteins or synthetic macromolecules which have been shown to localize in tumor cells in vovo, (b) lysosmotropic materials, namely the drug/carrier conjugates that have a tendency to accumulate in lysosomes, and (c) antibodies that specifically recognize antigenic determinants located in tumor cells (44, 45). A number of carrier systems, such as DNA (46, 48), liposome (40-52), bovine serum albumin and high molecular weight dextrans (53, 57), lectins (58, 61), copolymers of N-vinylpyrrolidone and vinylamine and copolymers of 2-methyl-5-vinlpyridine-

Table I. ID_{50} values of adriamycin and adriamycin conjugates obtained with the L1210 clonogenic -and the B16 assays.

Compound	Drug Code**	L1210 clonogenic assay		B 16 liquid assay	
		ID_{50} (ng/ml)	ID_{50} (ng Adria/ml)	ID_{50} (ng/ml)	ID_{50} (ng Adria/ml)
Free drug	Adriamycin	21/24*	21/24*	4-5	4-5
Conjugate (amide)	P_2A_1	19030/25821*	3045/4131*	–	–
	P_2A_2	5100/5400*	1122/1188*	–	–
Conjugate (hydrazone)	$P_3H_2A_1$	4455	71	–	–
	$P_3H_2A_2$	2062	53	–	–
	$P_3H_3A_1$	–	–	550	17
Spacer-Conjugate (amide)	P_3-GGL_2-A_1	6725	201	–	–
	P_2-GGL_1-A_1	–	–	1400	70

*Results of two independent experiments; **P=poly-α-L-glutamic acid, G=Gly, L=Leu, A=adriamycin; indices indicate batch numbers of PGA, hydrizide and/or spacer and adriamycin conjugate, respectively. P-H=hydrazide of poly-α-L-glutamic acid (ref. 43)

N-oxide and 2-aminoethylmethacrylate (62), poly-(-D-glutamic acid) (43, 63, 64) and N-(2-hydroxypropyl) methacrylamide (45, 65-77), have been studies. Among these carriers, synthetic polymers are advantagous since they could be moditied in a defined way to correspond exactly to the specificity of the individual lysosomal enzyme in contrast to a natural macromolecule.

Feijen's group has sythesized a series of adriamycin-macromolecule conjugates using poly (α-L-glutamic acid) as a carrier, and peptides of different length and composition as spacer units (Figure 18) to screen the cyctotoxic activity of conjugates with various assays (43, 63). Accoding to the resulst, the conjugates without spacers (amide linkage) exhibit very little toxicity towards L 1210 leukemia cells. Adriamycin connected directly to the carrier by means of hydrozone linkage showed higher cytotoxic activity than those of amide linkage although still less than corresponding amounts of free adriamycin. The ID_{50} values for adriamycin attached to the carrier through a Gly-Gly-Leu spacer were 5-10 times higher (i.e. less effective) than for free adriamycin as determined by both L 1210 clonogenic assay and B16 liquid assay. It was observed that the cytotoxic activities against the tumor cells are dependent upon the composition of the conjugates. However, the cytotoxic activities of the conjugate systems were always lower as compared to that of the free durg. In principle, this may be due to the slow uptake or no uptake at all of the conjugates by the tumor cell or to a very low rate of degradation of the conjugates after internalization by the tumor cell. Recently Feijen et al. (64) addressed the question of uptake and degradation by investigating the interaction of conjugates with mouse leukemia L1210 cells using laser flow cytometry and using papain as a model enzymer for the enzymatic degradation of carrier and the conjugates. In this study (64), it was found that i) adriamycin/polymer conjugate is strongly absorbed onto the leukemia L1210 cells; ii) adriamycin and adriamycin-peptide residues are released from polymer/drug conjugates by papain enzyme when tri-or tetrapetides were used as spacers; and that iii) the rate of enzymatic degradation of these conugates is in accordance with their cytotoxicity. It has been proven that the release of free drug from conjugate by enzymatic attack is a prerequisite to cytotoxic activity.

Taylor-made N-(2-hydroxypropyl) methacrylamide (HPMA) copolymers have been perpared and studied systemically by Kopecek's group (70, 71). HPMA copolymers are based on the N-(2-hydroxypropyl) methacrylamide backbone with variable oligopeptide spacers terminated in reactive p-nitrophenyl ester groups which allow these ester groups to bind by means of aminolysis with biologically active copound containing the aliphatic NH^2 group, e.g. cytotoxic agents or antibodies. Different spacers were studied with respect to their susceptibility to degrade by a number of proteolytic enzymes such as trypsin (75), chymotrypsin (76), papain (70) and lysosomal thiol proteinase such as cathepasin B, H, and L (65, 70). These experiments indicated that the enzymatic degradation of oligopeptide spacers depends not only on the length of the spacer, but also on the sequence of amino acids in the peptide spacer.

Recently, Kopecek et al. (45) have shown that the daunomycin attached to the copolymer of HPMA via a degradable sequence of oligopeptide spacers (Gly-Phe-Leu-Gly) and simultaneously carrying anti θ antibodies

exhibit a cytotoxic activity onto T lymphocytes at levels a hundred times greater than copolymers where daunomycin is bound via the nondegradable spacer (Gly-Gly). In addition, the anti θ antibodies bound to the copolymer of HPMA keep approximately 60% of their original activity. It appears that biodegradable targeting delivery systems can be developed but will require the systematic consideration of all aspects of this complex therapeutic approach. This includes development of nontoxic polymer backboone, synthesis of spacers which are specifically susceptible to lysosomal enzymatic attack and selection of targeting moieties that allow a high degree of cell specificity and can be chemically immobilized to the carrier system without reducing specificity.

4. Conclusion

Although the potential of a biodegradable polymer as a physical or chemical carrier of therapeutically active agents in controlled drug delivery systems has been demonstrated, its application is still in its infancy.

The use of biodegradable polymers is an advantage over nonbiodegradable polymers since removal of the device is not necessary after depletion of drug. However specific problems such as the toxicity of degradation products and the influence of the degradation of the matrix on the release rate of the drug have to be investigated before application. Using biodegradable polymers as chemical carriers of drugs offers many possibilities for a targeting delivery system.

In general, the toxicity of a durg is decreased when coupled to polymer backbones. This provides a method for introducing substantial amounts of drugs to specific parts of the body, which would not otherwise be possible with the pure drug only.

Future efforts should be directed toward the development of drug delivery systems with high specificity for target organs or cellular systems, predicatable and predetermined release rates, and the development and application of biodegradable polymers without side effects during and after treatment.

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