3 Polymeric Drugs


Dr. O. Vogl


Dr. D. Tirrell

Otto Vogl*[1]
David Tirrell*[1]

1 Introduction

The subject of polymeric drugs has recently achieved wide attention and is discussed among scientists interested in macromolecular science and in biological and pharmaceutical disciplines[1]). The general concept is also penetrating into regulatory authorities responsible for administering the areas of food and drng related subjects[2]. We are limiting our discussion on polymeric drugs to materials where the polymer consists entirely of synthetic polymers with functional groups of known or potential biological activity. Such drugs are defined to include any agent which, upon introduction into a living system, causes a physiological response. Not only curative but also prophylactic agents are included in this definition.

Polymeric materials which are biologically active have, potentially, both advantages and disadvantages in comparison with low molecular weight materials. The activity of a polymeric drug may be related to the functional groups present in the structure, or to the polymeric nature of the substance. An important area for biologically active synthetic polymers is in applications outside of the human body (e. g. topical application), as very little is known at the present time about the long-term effects of synthetic polymers in the body. The retention of synthetic polymers in tissues, the mechanism of the action of polymeric materials with biological activity, and the

*[1] Polymer Science and Engineering Department, University of Massachusetts, Amherst, Massachusetts 01003, U. S. A.
*[2] Department of Chemistry, Carnegie-Mellon University, Pittsburgh, Pennsylvania 15213, U. S. A.

metabolic fate of polymers, especially synthetic polymers, are still not well understood.

There are two highly desirable objectives in the development of new drugs: to enhance the drug specificity and to increase the duration of its action[3]. Enhanced specificity requires an increase in the therapeutic effect of the drug without a proportionate increase in side effects. Systematic chemical modification of known drugs has accomplished this goal to a varying extent in several classes of compounds. A different kind of specificity is achieved if cne can restrict the drug's penetration into undesirable parts of the system or limit the movement of the drug in the system. It is also desirable to be able to increase the duration of action of a single dose of the drug to increase the patient's tolerance. The establishment of this knowledge is important for prophylaxis and the treatment of diseases in inaccessible areas of the world. The increase of the duration of drug action can be accomplished by slow delivery, through slow dissolution from a crystalline depot, through diffusion from or dissolution of a matrix material, or through cleavage of the drug from a carrier molecule. These techniques potentially can avoid important undesirable side effects, particularly those associated with toxicity.

After the turn of the century, the effect of organic dyes on curing diseases was studied; the basic concept of chemotherapy, the treatment of infections with synthetic chemicals was developed. Enormous and continuous progress has been made over the years; it has included the discover:: of sulfa drugs, antibiotics and other synthetic materials for use against virtually all infectious diseases[4]. Only the virus diseases as a group have not yet been treated successfully by chemotherapy. Viruses are in general much smaller than bacteria and only selected viruses can be treated by chemotherapy, while bacteria and fcngi both can be effectively destroyed. The drug action is effected by agents affecting bacterial an3 other infectious diseases in various ways, (a) Acting on the cell wall. (b) Affecting the cell membrane. (c) Modifying replication or protein synthesis. (d) Affecting nucleic acid metabolism. (e) Affecting intermediary metabolism. Many antibiotics or synthetic materials are effective by acting in one or more of these individual points[5].

In this article we are not limiting the discassion of polymeric drugs and drug response to materials that prevent and cure microbial disease but we also include materials which might potentially prevent such undesirable affects such as toxic action in foods, weed induced damage to plants an3 sun induced damage to the skin.

A great number of polymers has been tested already for their biological activity

and polymers have been found with antibacterial, antifungal, interferon inducing, antiviral and antiparasitic activity. Polymeric materials effective as gastrointestinal, dermatological and antiulcer compositions have also been studied, as well as polymers which affect the immune response or act as antiinflammatory agents. Other polymers which were studied exhibited the following properties and activities: anthelmintic, narcotic, antitussive, hypotensive, antihistaminic, hypnotic, tranquilizing, analgesic, antisecretory, antispasmodic, antineoplastic, appetite suppressing, motor activity depressing, and muscle relaxing. Polymers were also found which have activity useful in treating circulatory, cardiac and blood diseases[2]. Steroids and vitamins have been incorporated, into polymeric systems and the larger group of herbicides and pesticides was and is being even more extensively investigated.

Polymeric compounds with biological activity are expected to differ from drugs of low molecular weight with respect to both effectiveness and toxicity. Of particular importance is the possibility that the polymeric drug has prolonged activity either directly or by sustained release, but greatly diminished toxicity.

The activity of a polymeric drug can be influenced by the characteristics of the macromolecular chain itself and is probably very readily influenced by the molecular weight and molecular weight distribution. Since some of the most interesting polymers are actually copolymers, modification of the activity can be visualized by manipulating the copolymer composition. In addition to the molecular weight and molecular weight distribution of the copolymer, the run number indicating randomness or blockiness of the polymer is very importznt. The stereospecificity or tacticity of the polymer or the cotacticity of copolymers has to be taken into account. The knowledge of design of polymers'with hydrophilic and hydrophobic groups as part of the chain or attached to the polymer chain also changes significantly the character and utility of **a** polymeric drug. Distribution of groups with hydrophobic/hydrophilic character, or transformation of the polymer into a polyelectrolyte by proper distribution of charges along the chain may play important roles in developing the optimum characteristics for biological activity. If synthetic polymers in crosslinked form are used as polymeric drugs, the degree of crosslinking and the swelling behavior of such materials are also of importance.

When a biologically active material is prepared in a polymerizable form and homo- or copolymerized, or the active compound attached to an already existing polymer chain, interesting comparisons of monomer activity versus polymer activity can be

made[6]). It would be expected that relative activities would be altered and (1) the activity of the polymeric drug could be less than that of the monomeric drug, (2) the activity of the polymeric drug could be greater than that of the monomeric drug or (3) the activity could be the same. These effects have been studied, and in actual fact all three effects have been noted. It was also found that inactive monomer could be polymerized to polymer with biological activity. Some drugs with toxic properties have been shown to become less toxic by inzoiporation into a polymer by copolymerization and consequently the copolymerization as potential technique for (a) enhancing the activity of a known drug or (b) decreasing the toxicity has become recognized.

2 Mechanism of Drug Action

Polymeric drugs have been shown to have various advantages in comparison with normal drugs; they may have delayed or prolonged activity (e.g., by sustained release), there are possibilities of getting such drugs to the desired organ in the right amounts at the right time, and the activity may be modified by attaching, at the same time, several types of drugs to the same molecule. Furthermore, possibilities exist for specific interactions of the polymeric drug with the cell walls of bacteria. Lower toxicity of a polymeric drug could also be a great advantage, although it is possible that toxicity could be accentuated by the polymer itself or by a biologically active agent attached to the polymer. The activity of a drug may be altered by changing solubility and consequently the rate of diffusion. Increased activity could be achieved by the use of the specific drug acting in combination with a polymer, as for example in the case of an antibiotic in the presence of polyacrylic acid. Specific side effects of a drug may be reduced, as exemplified by intolerance or irritation or other normal side effects which are caused by excessive dosage of a drug.

3 Drug Incorporation in Polymeric Structures

Several methods have been established to incorporate a drug into a polymer. A low molecular drug could be embedded in a polymeric matrix or it could be .completely encapsulated in polymer membranes. Such approaches should not alter the activity of the low molecular drug and these delivery systems show pharmacological activities

when the drug is released by dissolution, degradation or diffusion. The biologically active group in a polymer could be placed into a stereochemically restricted position to maximize activity and lead to a more potent drug; this approach is difficult, however, since steric restrictions in the interaction of the drug with receptor sites, resulting in a loss of activity or specificity must be avoided. With the polymeric forms of drugs it may be possible to manipulate or direct the drug's action to the specific organs where the biologically active agent is desired. Another possibility is that of using polymer drug complexes for substrates where enzymatic attack is possible. A slow release of the drug could lead to prolongation of biological activity and consequently reduction in toxicity which optimizes the potential of the drug. In all these cases it is very important to demonstrate that the polymeric drug as the active compound either as a polymer or through release of the active ingredients and that activity does not result from contamination by highly biologically active low molecular weight compounds.

The problem of incorporation of a pharmacon into a polymer would include such techniques as the preparation of polymeric gels, for example, hydrogels, which can incorporate and immobilize the small molecule in a macromolecular matrix of a crosslinked polymer. Encapsulation of biologically active materials in a polymeric capsule and the attachment of enzymes to crosslinked gels are also important developments. In this article on polymeric drugs we will consider only linear polymers with the biologically active group as part of the linear soluble (not necessarily water soluble) polymer chain[7]. The first class of polymeric drugs is that in which the macromolecule has an independent specific therapeutic effect. These polymeric drugs can be divided into two groups: (a) Drugs of polymeric nature whose activity and benefit is due entirely to their macromolecular properties; neither monomer nor low molecular weight material nor analogs exhibit any effects. Typical examples are plasma extenders poly(vinylpyridine-*N*-oxide) and synthetic analogs of heparin, and (b) polymeric drugs in which known drug structures are present either in the chain backbone or as pendent groups. In all cases, the distinguishing feature of this class of materials is the fact that the polymer itself exhibits biological activity, and need not be degraded to release low molecular weight active species[8,10-13].

A second class of polymeric drugs consists of drugs with a macromolecular vehiculum. This large group covers preparations represented by (a) Drugs which are attached to a carrier but which can be removed from the polymeric carrier by

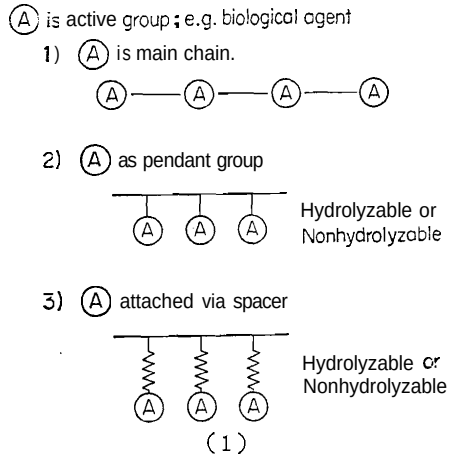
hydrolytic, enzymatic, or oxidative means.

(b) Noncovalent polymer drug complexes are another subgroup of this category, and ionic complexes of negatively charged polymers and basic drugs, for example, complexes of carboxymethylcellulose with quinine, procaine, diphenylhydramine, tripelennamine (pyribenzamine) and also complexes with non-ionic polymers, *e.g.*, poly(vinylpyrrolidone) and poly(oxirane).

Numerous polymeric drugs or drug forms have been prepared and clearly demonstrated. A short inspection of pharmacopoeias shows that very few of these polymeric drugs are, at this time, used in practice. It is clear that the general problems of lack of experience and prejudice must be overcome to open this wide and new prospective field for daily chemotherapeutical uses.

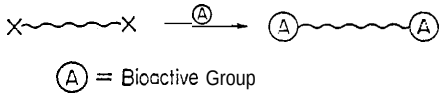
4 Incorporation of Drugs into Polymers

The synthesis of polymeric drugs as defined in this article depends on the way the biologically active material is incorporated in the polymer chain. The biologically active group, for example, a pharmaceutical, may be (a) part of the polymer main chain. This will require that the drug can undergo a polymerization reaction, and must therefore be bifunctional. For example, diamines or bisphenols can be allowed to react with dicarboxylic acid derivatives or bisisocyanates, bifunctional monomers capable of forming condensation polymers. (b) The active group might be linked to the main polymer chain as a pendant group which could either be linked directly or with a spacer group of some desired chain length[14,15] (Eq. 1). The biologically active agent may be at the end of a low molecular weight or moderate molecular weight polymer chain or attached to a high polymer. When polymeric drugs of relatively low molecular weights are desired, oligomers with reactive end groups such as hydroxyl groups, can be used as drug carriers and the biologically active group can he introduced by an endcapping reaction. Such reactions have been demonstrated with hydroxyl



(1)

terminated polyoxyethylenes or butadiene polymers[16,17] (Eq. 2). Whether incorporated as part of the main chain or as a pendent group, the biologically active agent may be attached irreversibly, or reversibly through an unstable linkage. The latter concept has become important because, by proper release kinetics, enhanced and prolonged effectiveness of the active agent may be achieved.



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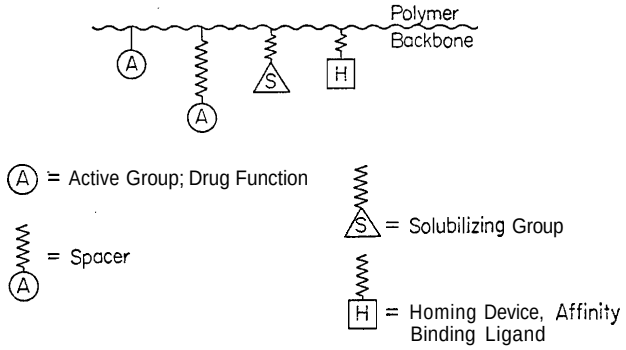
High molecular weight polymers can be functionalized in a number of different ways. The simplest is substitution of reactive groups of preformed polymer with desired functional groups of biologically active materials. Advantages of such polymer reactions are that the molecular weight and the molecular weight distribution of the polymers have already been established. One word of caution should be mentioned for polymers with degradable or potentially degradable backbone chains such as polyesters and polyethers: with these substrates the substitution must be carried out under mild conditions in order to avoid polymer degradation during the reaction.

If copolymers are used in the substitution reactions, run numbers of the reactive ccmonomer units have already been established in the original copolymer. Additional advantages of reactions on polymers include the possibility of introducing several different functional groups in sequence into the polymer. Groups to be introduced into a polymer include not only the biologically active group, but might also include solubilizing and compatibilizing group, anchoring groups, and groups with hydrophilic, hydrophobic or polyelectrolyte characteristics.

The attachment of a biolcgically active group to the backbone of a polymer may



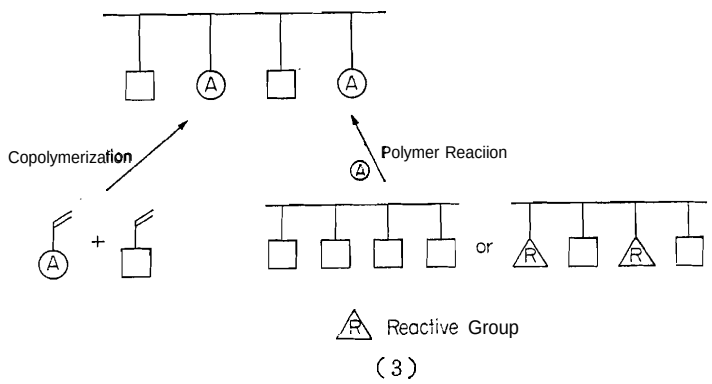
Scheme 1

be made by a degradable (temporary, hydrolyzable) linkage or by a non-degradable (permanent) linkage. The active component can be linked directly to the polymer chain, or with a spacer, solubilizing group or a "homing" group which may be selected for being specific or non-specific(Scheme 1).

Reactions on polymers offer the advantages discussed above, but they do suffer from several inherent problems; the reactions have to be carried out under mild conditions (near room temperature) and the yield for all the substitution reactions must be quantitative. Any 'error" in these reactions will result in the "error" being retained in the polymer chain. Examples of side reactions which occur in substitution reactions in polyepichlorohydrin may be dehydrohalogenation instead of nucleophilic displacement of chloride ion. Simple hydrolysis of an acid chloride or an ester to the acid are common undesirable side reactions for substitution reactions on activated acid groups. Other undesirable side reactions might result in color formation or crosslinking. It must also be realized that during the reaction the solubility of the initial polymer is often changed and precipitation of the final product may occur. A more favorable example is that of a starting polymer which has limited solubility but which dissolves during the reaction.

One of the limitations of reactions on polymers is the fact that the reactivity of a functional group may be unfavorable when it is directly attached to the main chain and suffers steric hindrance by neighboring side groups. Under these conditions the substitution reaction ti-ill not go to completion. Such problems can be overcome by spacing the reactive group several carbon atoms from the polymer main chain or by spacing the reactive group on a flexible polymer chain by more than the usual two carbon atoms, as for example, in the ethylene oxide backbone chain as compared to the normal polyethylene backbone chain. When chains other than polyethylene backbone chains are involved, the problem of thermal and oxidative stability of the backbone chain may become a problem in the substitution reaction.

The other approach to the synthesis of polymers with biologically active groups is the preparation of drug molecules with polymerizable functional groups for subsequent polymerization(Eq. 3). This approach has the advantage that the monomer can be highly purified and then polymerized or copolymerized with any number of desirable cornonomers. By adjustment of polymerization conditions, polymers of desirable composition and high purity can often be obtained in good yield. Functional monomers with a polyrnerizable vinyl group usually polymerize readily



(3)

as they often belong to the category of substituted styrenes.

Disadvantages of this approach can also be substantial and can sometimes not be overcome. The simplest and most significant problem with this approach arises if the biologically active monomer cannot be synthesized or if it can only be obtained by a cumbersome, multi–step synthesis ultimately giving very low yield of the material. It is most common that the polymerizable group is either a vinyl group or an epoxy group derived from such a vinyl group. These functionalities are often introduced in the last step, and this introduction is often difficult to achieve in the presence of many functionalities already present in the drug molecule. It may not be possible, consequently, to purify the monomer, or the monomer may not polymerize or copolymerize with the desirable comonomer. Copolymerization of monomers with spacer groups, unless they are acrylates or methacrylates, is sometimes difficult to achieve as in the case of all terminally substituted α-olefins. Although in principle an attractive approach, the polymerization of functional or biologically active monomers to polymers of optimum molecular weight, molecular weight distribution and sequence distribution may be achieved only with difficulty.

5 Oligomers Endcapped with Biologically Active Groups

The value of the oligomeric type of functional polymers has been demonstrated in a number of areas. The attachment of short paraffinic groups, for example, in ultraviolet stabilizers and antioxidants, has been shown to be an effective means of increasing compatibility and modifying solubility of the active components[18]. Such alterations in properties greatly improve the performance of the oligomeric materials as compared to monomeric functional compounds. The introduction of biologically active groups in oligomeric materials has been carried out by endcapping reactions.

Quite frequently, the oligomers are hydroxyl terminated oligomers, for example, low molecular weight poly(ethylene glycols) or butadiene oligomers terminated with hydroxyl endgroups.

Oligo (oxyethylene) glycols of low molecular weights (MW 60~400) were end-capped with *N,N*-dimethyl-*p*-aminobenzoate by a sodium methoxide catal zed ester interchange reaction of the corresponding glycol and the methyl ester of *N,N*-dimethyl-*p*-aminobenzoic acid. Bis-salicylates of ethylene glycol, diethylene glycol, and tetraethylene glycol were prepared from sodium salicylate by displacement reactions on the corresponding bis-*p*-toluenesulfonates in DMAc.

Oligomeric glycols were also used as the polymeric base for the preparation of higher molecular weight steroids. Since most steroids have a hydroxyl group as the functional group, the simplest way for attach such groups to a polymer with a hydroxyl group or reactive group is by preparing first the bis-chloroformate of the oligomeric glycol by allowing it to react with phosgene. The bis-chloroformate which is formed is isolated and then allowed to react with the drug alcohol. The attachment of the drug to the oligomer is then via a carbonate group; this method was used by Pinazzi[16] for such steroids as testosterone and others.

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6 High Molecular Weight Polymer Drugs

A number of reasonably high molecular weight polymers have been shown to be biologically active as polymers without elimination of an active small molecule.

The first category will include polymers which have biologically active groups in the polymer main chain which are nondegradable.

A number of polymers have been prepared from suitable biologically active compounds by reaction with formaldehyde[19]. Examples are aromatic amines, amides and phenols which formed copolymers with formaldehyde. The structure and molecular weight of these polymers has not always been determined. Copolymers of formaldehyde with various known sulfonamide drugs have been prepared, for example, those with sulfanilamide, sulfathiazole, sulfapyridine, sulfadiazine, sulfamerizine, sulfamethazine, sulfacetamide, sulfabenzamide and 4,4′-diaminodiphenylsulfone[20~24]. All compounds showed activity not only in the monomeric but also in the polymeric form.

Known quinoline antimalarials derived from 8-aminoquinoline, and salicylic acid derivatives when reacted with formaldehyde gave polymers which proved to be more

active than the monomer. Other polymers prepared from antimalarials are derivatives of tropolone which were again reacted with formaldehyde. The polymers of hinokitiol, 5–p–tolylazotropolone, 5–nitrosotropolone and 5–aminotropolone showed also activity in the polymeric form.

Antineoplastic activity of tropolones and their polymers with formaldehyde have been shown for 2–methacryloxytropone, tropolone itself, and hinokitiol. Other substituted tropolones showed the polymer to be less active or inactive. Some polymeric tropolones have also shown activity on the central nervous system; it was shown that the LD_{50} is at least twice that of the monomeric compound, as for example, in tropolone, 2–methacryloxytropone, 5-aminotropolone and 5–nitrosotropolone.

Anthelmintic activity (in *vitro*) of tropolone polymers has been shown in polymers of tropolone itself, 'hinokitiol and 5–aminotropolone. An increased inhibition of the development of strongyle eggs was noticed in the administration of tropolone-formaldehyde copolymers as compared to the individual monomeric compounds.

Antibacterial activity of sulfonamide drugs and their formaldehyde polymers was shown in sulfamerazine- and sulfabenzamide/formaldehyde copolymers. Antibacterial activity against a number of bacteria has also been demonstrated with tropolone-formaldehyde copolymers with tropolone itself, 5-aminotropolone, 5-*p*-tolylazotropolone and hinokitiol.

Fungistatic activity of tropolone–formaldehyde copolymers has been shown for 5-aminotropolone against several strains of fungi but tropolone in its polymeric form with formaldehyde was found to be less active. A number of sulfonarnide drug/formaldehyde polymers showed relatively little activity against *S. pyogenes*, E. *coli*, *A. aerogenes* and *P. aeruginosa.* As an important investigation of activity in polymeric systems, 4, 4′-diaminodiphenylsulfone-formaldehyde copolymers were studied for their activity as a function of molecular weight. Various polymers of molecular weight 4,000~10,000 were tested for their activities as antibacterials(*S. pyogenes*) and all polymers were found to be of equal activity. Similar results were found in catechol-*O*-methyl transferase inhibition, monoamine oxidase inhibition, xanthine oxidase inhibition and adenosine triphosphatase inhibition. Activity of changing degrees between monomeric and polymeric drugs of the sulfonamide type were shown also for the monamine oxidase inhibition. With most of the sulfonamide drugs described earlier, the xanthine oxidase inhibition exhibited does not differ significantly for the monomers and the formaldehyde copolymers, and similar results

were obtained for inhibition of catechol-o-cethyltransferase and adenine triphosphate.

The monomer activity was higher when the anthelmintic activities of various piperazine polymers, namely piperazine polyamides, were compared with piperazine itself. In some cases, piperazine polyamides showed activity as amebicidals.

Antifungal activity was shown by some polyamides of piperazine against three test organisms: *C. albicans*, *M. gypseum*, and *T. granulosum*.

Trichomonicidal activity was shown by two piperazine copolymers, poly-*N*-glutarylpiperazine and poly-A[1]-pimeloylpiperazine. against the test organism *T. vaginalis*.

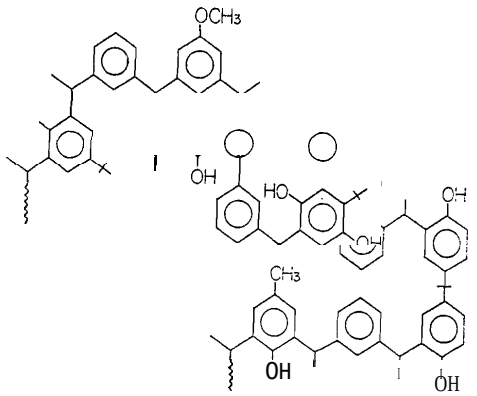
Some curative effect has been found with sulfonamide drug/dimethylolurea copolymers as antimalarials. The antimalzrial activity was studied as a function of molecular weight in the copolymer system sulfapyridine-formaldehyde. Activity was found even at 10 mgs. per kilogram body weight and it appears that not only the dose level but also the molecular weight increased the effectiveness of the drug. This was also demonstrated in the copolymer system 4, 4′-diaminodiphenylsulfone in the molecular weight range from 5,000~10,000; in a comparison of samples with molecular weights of 4,700, 7,600, and 10000, the highest activity was observed in the sample of an intermediate molecular weight.

Estrogenic activity was found in the estrone-formaldehyde copolymer system. These copolymers were active in the Allen doisy test and in the uterotrophic assay.

It may be seen from these data that certain properties, largely peculiar to polymer systems, may be related to biological activity. This may, in the long run, give rise to development of structure activity relationships for polymeric drug systems.

Problems which are conceptually similar to those of polymeric drug design are encountered also in the development of polymeric additives for food. This work is motivated by the prospect of reducing the toxicity of food additives such as antioxidants and colorants, through increase in molecular weight. For example, a useful antioxidant should have controlled biological absorption parameters, acceptable functionality in food systems and good solubility characteristics and stability characteristics[11]). This places important restrictions on the molecular weight of the polymer and its stability. Thermal stability is a key problem for antioxidants since they are used in high temperature operations, for example, frying at temperatures of 190℃. Other requirements for the stability of such materials are stability to phosphoric acid, a component of soft drinks, storage temperatures of up to 50℃., exposure to sunlight for unknown time, possible sterilization at temperatures up to 140℃., and

maintainence of activity at low moisture or high temperature in the presence of reducing sugars and proteins. Some individual foods are subjected to only some of these conditions, but food additives being produced for broad usage must withstand all of them. Finally the polymeric antioxidant must not distill with steam and must not be extracted by an organic solvent. Testing has begun recently on a polymeric antioxidant designed with these criteria in mind. This material is prepared by a condensation of divinylbenzene with a mixture of bisphenol A, *p*-cresol, p-tertiarybutylphenol and *p*-hydroxyanisole, giving a polymer which has a molecular weight of 5~10,000(Eq. 4).



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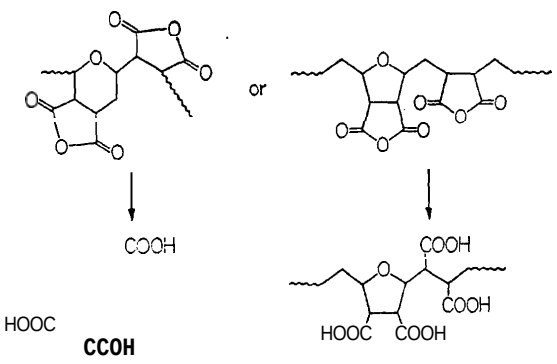
Polymeric dyes have been prepared from 1-aminoanthraquinones and 4-aminoanthrapyridones to provide red dyes suitable for human consumption. These dyes were attached to polyethyleneamino groups obtained by polymerization of acetamidoethylene followed by hydrolysis[26]. Several solubilizing monomers were evaluated in order to identify a composition with the greatest potential degree of chromophore substitution along with the proper solubility characteristics. The presence of an anionic group on the backbone significantly diminished the nucleophilicity of the amine and made full substitution on the polymer chain impossible.

Anionic and cationic polyelectrolytes of synthetic origin have been found to exhibit inhibitory effects on viruses, bacteria and enzymes[27~30]. Polyanions, in particular, have a wide range of biological activity and have received considerable attention in the area of oncology and virology. The prolonged protective action of synthetic polyanions when given prior to virus innoculation also has significant clinical potential. Most polyanions are water-soluble which is significant not only for transport but also for systematic administration, since injection of suspensions in the blood vessels can cause "colloido-clasmic shock" or "macromolecular syndrome", with major hypersensitive clinical toxicology. Water soluble polyanionic polymers can distribute themselves in a living system by blood or lymphatic circulation, by cellular transport through the involvement of mobile phagocytic cells or by absorption on cell surfaces. The compatibility of a polymer in blood requires that

it should not cause thrombosis or destroy cellular elements, alter plasma proteins, deplete polyelectrolytes or cause acute or delayed toxic or immune tissue damage(Eq. 5).



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Polyanions that enter into biological functions by distribution throughout the host behave similarly to certain biological materials that modulate a variety of biological responses related to bacteria and fungi and enhanced immune responsiveness. In relation to such immunologic and hormonal responses, inflammation, wound repair, blood clotting and tissue damage may be subject to the action of macromolecules[31,32]. Perhaps the most significant role of polyanions is their mitotic inhibitory effect and its functional role in antineoplastic processes.

The toxicology of polyanions is of prime importance to their medical applicability. Initially polyanions were found to be too toxic and clinical testing of pyran copolymers as anti-tumor agents was halted due to adverse side effects. The biological and clinical application of synthetic polyanions is again of major interest since recent evidence has shown that the toxicology is in many instances related to the higher molecular weight fractions.

Some synthetic polyanions have been tested for biological activity[28,30] including interferon induction, antiviral activity and growth inhibition which are caused by the high density of carboxylate groups that are pendant to a long polymeric backbone chain. The molecular weight should be greater than 1000 and the carboxyl groups can be on alternate or adjacent positions in the chain. Polganionic polymers in general have been found to be fairly stable and not readily biodegradable, which may account for their prolonged activity. Polymers with carboxylate functions bound by amidation or noncarboxylated polyethylene at comparable dosage are inactive. One of the most interesting and most widely studied polymers is a (1:2) copolymer of divinyl ether and maleic anhydride[34] ("pyran copolymer").

Acrylic acid-maleic anhydride copolymers have biological activity similar to that of the copolymer of divinyl ether and maleic anhydride but are not as biologically effective. These copolymers are prepared by radical polymerization of acrylic

acid and maleic anhydride. The resultant polymer after hydrolysis is a flexible straight-chain polymer with three carboxyl groups for every four carbons in the polymer chain. Maleic anhydride homopolymers are produced at high temperature using high concentrations of benzoyl peroxide (2~4%) to yield high molecular weight materials. This material is less toxic but also much less effective against tumor growth and viruses[35].

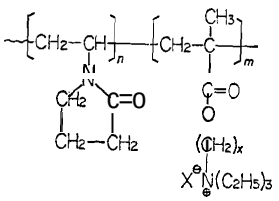
Most of the research on anionic polymers has been done without regard to either the average molecular weight or the molecular weight distribution of particular polymer samples. Polyanions that have been tested cover a range of molecular weight from 1000 to 500,000. Optimally, the polymer should be of sufficient molecular weight so as to delay body clearance (more than 30,000) but still below the kidney threshold (less than 50,000). Consequently, the molecular weight distribution will be more critical than the average molecular weight since very large molecules can cause erythrocyte aggregation[36] and changes of platelet or leukocyte distribution or morphology. It is possible to prepare pyran copolymers with low polydispersity through radical polymerization at low temperature in acetone[37]. It was found that low molecular weight samples of these pyran copolymers with narrow molecular weight distribution not only possessed lower toxicity but retained the antitumor activity exhibited by the higher molecular weight samples against both Erhlich adrenocarcinoma and Lewis lung carcinoma in mice.

Polyanions have shown antiviral activity, for example, against plant viruses and are now being developed for purification of water made impure from contaminating viruses. The mechanism of this antiviral activity has not been defined. Polyanions such as polyacrylic acid and pyran copolymers have also shown immunoadjuvant activity in several systems.

The action of polyanions as mitotic inhibitors and their functional role in neoplastic processes have been demonstrated. A possible mechanism for the activity of polyanions in tumor growth may be related to coupling of'the pol>-anion to tumor antigen. However, the action of polyanions on a wide range of enzymes, alteration of the isoelectric point, displacement of nuclear histone, macrophage activation and antiviral action, all indicate possible alternative concepts of antitumor action. Polyanions have also been shown to have an effect on phagocytosis in cell structures.

Quaternary ammonium salts which contain a lipophilic group having 8—28 carbon atoms are known to be effective germicides(Eq. 6). Several mechanisms have

been proposed for the action of such compounds. One mechanism suggests an interaction with, and perhaps' denaturation of, essential protein enzymes of the micro-organism. It has also been suggested that antibacterial action is related to the interaction of the cationic material with the cell membrane with release of enzymes, coenzymes and other intermediates from the cell.



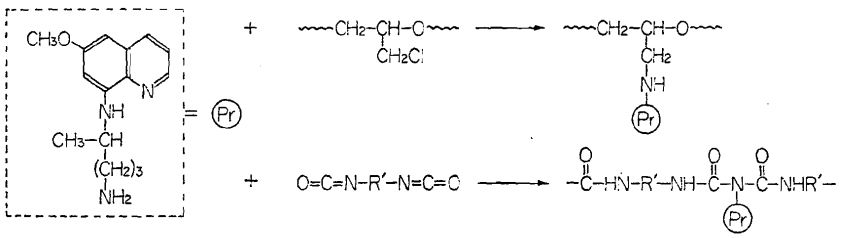
(6)

Polymeric quaternary ammonium salts have been proposed for such applications as disinfectants for wounds and abrasions and various types of skin infections. Copolymers of *N*-vinylpyrrolidone and 2-methacryloxyethyl-*N*, *N*, *N*-triethylammonium bromide and iodide showed activity increase as the content of the quaternary ammonium moiety increased[38]. Cationic polymers produced by the reaction of polyepichlorohydrin and various amines were found to be active against different types of staphylococcus, escherichia and salmonella[39]. Cumarone-indene polymers with quaternary ammonium groups attached hare been found to possess bactericidal and fungicidal properties[40].

Polymers from various fatty quaternary diallyl ammonium compounds with cateriostatic and fungicidal properties have been described. These polymers contain a lipophilic group and would be expected to have antibacterial properties. Polyionenes, in which the quaternary ammonium groups are located along the polymer chain, have been shown to have bactericidal properties.

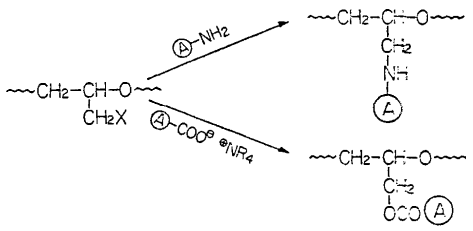
Various heavy metal salts used as therapeutic agents were once of great importance. A novel 10-(alkenyloxy)phenoxarsine based monomer and polymer have been reported[41] to be active against a variety of fungal and bacterial organisms. Polymers containing arsenic in the main chain include poly(triphenylarsenic pyrimidines)[42].

Penicillin, the first and most important antibiotic, has been incorporated into both natural and synthetic polymers. Polymeric salts of penicillin with vinylamine and



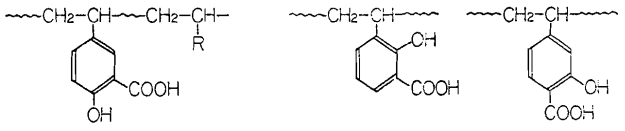
(7)

vinyl alcohol copolymers and arnides and hydrazides of penicillin have been demonstrated. These polymers have the same activity as the parent drugs in clinical studies[43,44]. Primaquine, a potent antimalarial drug, was attached to a polyepichlorohydrin[45] (Eqs. 7 and 8).



(8)

Several vinylsalicylic acid derivatives have been studied. Of the four possible isomeric vinylsalicylic acids, three isomers have already been prepared : the 3-\-inγ!. 4-vinyl, and 5-vinylsalicylic acids and their acetyl derivatives[6]'. These monomers have been synthesized and both the vinylsalicylic acids and vinylacetylsalicylic acids



5-vinyl salicylic acid 3-vinyl salicylic acid 4-vinyl salicylic acid

(9)

have been homopolymerized and copolymerized with a number of comonomers. Scme polymeric derivatives of vinylsalicylic acids have been tested against gram negative E. *Coli* and gram positive 'S. *Aureus* bacteria(Eq. 9). The significance of testing against two of these bacterial strains stems from the difference in the structures of the cell walls of the strains. Since an antibacterial agent must first interact with the cell wall, it is important to understand the influence of cell wall structure on antibacterial activities.

Several important conclusions may be reached from the results of these tests of antibacterial activity in vinylsalicylic acid polymers. It was shown that the specificities of the vinylsalicylic acid derivatives against E. *Coli* and *S. Aureus* are quite different. For example, poly (5-vinylacetylsalicylic acid) has specific activity against *E. Coli* while the monomer is nonspecific (it is very active against both gram positive and gram negative bacteria). This may have implications in the design of new specific antibacterial agents. A second observation concerns the influence of the molecular weight on antibacterial activity. Five samples of poly (4-vinylsalicylic acid) with inherent viscosities from 0.4～2.2 dl/g were examined and showed no

substantial difference among the samples, with slight activity independent of molecular weight. The same was found with homopolymers of 5-vinylsalicylic acid.

It has also been shown that 4–vinylsalicylic acid is a potent but nonspecific antibacterial agent and that the homopolymer is still active but nonspecific. Copolymerization of 4-vinylsalicylic acid with methacrylic acid produced a copolymer which has substantial specificity against *E.Coli*[46]. The same observation was found for a 5–vinylsalicylic acid derivative. These experiments demonstrate that the specificity of a given biological agent may be altered through copolymerization with a suitable but inactive comonomer and again imply the possibility of designing new biological agents of high specificity by using the appropriate comcnomers for copolymerization of a biologically active agent with a polymerizable double bond.

Other studies, in the new area of "polymeric affinity drugs"[47], are directed toward effective localization of activities of enzymes, cytotoxic agents, and other drugs of potential value for cardiovascular, urolithiasis and cancer therapy. The concept of targeting drugs for specific cells and tissues using carrier molecules having biospecific affinities originated in work done at the turn of the century[48]. Various serious problems have recently arisen with toxicity, antigenicity and instability associated with systemic administration of chemotherapeutic agents, especially for cancer or enzyme deficiency therapy, motivating research based on new approaches to such treatments.

Although drug delivery systems based on insoluble polymers have been successfully developed, soluble polymeric drugs have received much less consideration because the opportunities for localizing action and beneficially altering undesirable pharmacological behavior seem less obvious as compared to insoluble systems. Only soluble polymers, however, offer the prospect of taking advantage of known biospecific affinity binding properties. Such macromolecular bioactive materials have general principles in common with affinity chromatography.

Recent work with soluble polymeric drugs has produced cyclophosphamide and chlorambucil conjugates using modified hydroxyethylmethacrylates, polyvinylpyridine and poly (vinylpyridine–*N*–oxide) as hydrophilic carrier molecules. Only limited pharmacological information is available for these systems at this time.

A number of synthetic hydrophilic polymers are' available for consideration as carriers, including poly (hydroxyethylmethacrylate), poly (vinylpyridine–N–oxide), poly (hydroxypropylmethacrylate), poly (ethyleneglycol)[49], poly (vinylalcohol), and

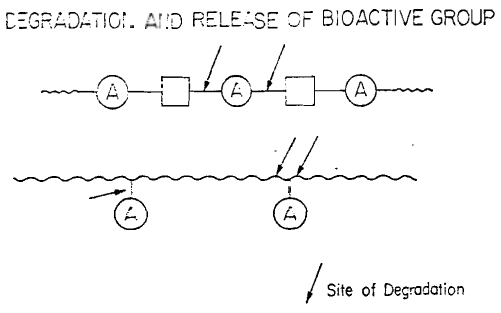
poly(ethyleneimine)(branched and linear).

The targeting of polymer bound litholytic agents to specific renal system surfaces requires identification of biospecific complexing partnerships and appropriate ligands for polymer attachment. Work on targeting drugs which could be useful for urolithiasis, cardiovascular/arteriosclerosis therapy and cancer therapy are in the early stages of development[50].

Recent work which has a direct impact on the general problem of polymeric drugs is the preparation of vinyl monomers containing purine and pyridine bases which can be polymerized and copolymerized[51]. The resulting polymers show base-pairing characteristics of the nucleic acids; complexes of poly(*N*-vinyladenine) and RNA or poly(uridylic acid) have been reported. The purine and pyrimidine bases of the nucleic acids have been attached directly or through spacers onto linear polyethylene imine[52].

7 Hydrolyzable Polymeric Drugs

Polymers with biologically active groups in the main chain are desirable when they can be hydrolyzed to the active component and inactive small molecules. Primary candidates for such polymer structures in this category include polyesters and polyamides, and especially polycarbonates and polyurethanes. Esters and amides of carbonic acid are of particular interest maybecause hydrolysis leads to the formation of the active molecule and carbon dioxide only. However, it may be desirable and necessary to introduce additional solubilizing groups into the polymer chain in order to increase the transport or solubility of the polymer in aqueous media(Eq. 10).



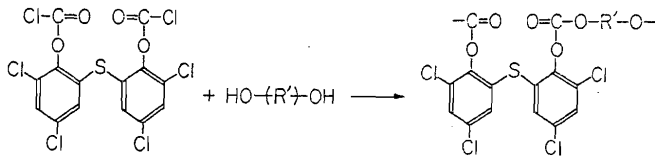
(10)

A piperazine/carbon disulfide copolymer has been prepared as a long lasting anthelmintic that in acid medium degrades slowly to monomer or oligomer giving sustained anthelmintic effect for the active monomers[52]. For the degradation by hydrolysis to occur at a significant rate not only must hydrolyzable groups such as ester, urethane or amide groups be present, but they must be accessible to the agents

controlling hydrolysis. In bulk form only polymers which are sufficiently hydrophilic will hydrolyze to a great extent. These include some polyamides, polyurethanes and the polyesters of phosphonic, phosphoric and phosphorous acid. In contrast, some normal polyesters such as poly(ethylene terephthalate) are quite stable to hydrolysis because of hydrophobicity and crystallinity. In solution or in a swollen state all of the effective linkages of the polymer chain are relatively accessible to water and other low molecular weight compounds. As the rate of hydrolysis is essentially controlled by the accessibility of the hydrolyzable linkage, hydrophilic groups must be introduced into the polymer chain to help solubilize and swell systems that are otherwise insoluble.

One of the best bactericides known today, bithionol [2,2′-thiobis (4, 6-dichlorophenol)] is a compound with a wide spectrum of activity against both Gram negative and Gram positive bacteria. It also has fungicidal properties and is used as an anthelmintic against certain types of worms and flukes in both animals and man[54]. Its exceptional bacteristatic activity closely resembles that of hexachlorophene, and it is effective in a great many antiseptics, soaps and solutions.

Bithionol is a bis phenol and the general polymerizability of this class of compounds is well known. Bithionol has now been polymerized with acid chlorides to polymeric aromatic polyesters[54]. The less soluble polyesters of bithionol, such as those of aromatic diacid chlorides (isophthaloyl or terephthaloyl chloride) gave polymers of relatively low molecular weight. High molecular weight polymers were obtained with diacids which have more flexible aliphatic groups (Eq. 11).



(11)

Bithionol was also polymerized to a polycarbonate of high molecular weight with phosgene, or better with diphenyl carbonate. An effective way of preparing polymers of the hindered bis-phenols is by transforming the bisphenol into the bischloroformate. Reaction of the bischloroformate of bithionol with glycols gave alternating copolycarbonates of bithionol with a variety of aliphatic and aromatic diols. Of particular importance were the copolyesters of poly(oxyethylene) glycols in the molecular range of 2,000 to 4,000, because these polymers formed tough transparent

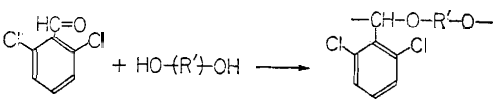
films which are water soluble and degrade slowly under physiological conditions (and faster at pH 4 and pH 9). This seems to be an excellent way of utilizing a bactericidal polymer with useful properties, which is also easily degradable.

The bischloroformate of bithionol when reacted with aromatic and aliphatic diamines gave polyurethanes. Bithionol was also allowed to react with phenyl phosphonic, phosphoric and diphenyl phosphorus acid chlorides to form the corresponding polyesters. These polymers were of low molecular weight.

Not all apparently bifunctional monomers can be used as bifunctional polymer intermediates; for example, the antimalarial primaquine has a priinary aliphatic amino group, and a secondary aromatic amino group in the molecule, but in spite of an extensive amount of effort[6], the diamine primaquine cannot be used as a bifunctional monomer. Attempts to incorporate primaquine, by reaction with various diacid chlorides, into polyamides failed and only A–B–A type molecules were formed with reaction only on the aliphatic amine group.

Primaquine could, however, be introduced into a polymer by allowing it to react with diisocyanates in one or two step reactions. Hexamethylene diisocyanate or methylene diphenyl diisocyanate (MDI) could be used as reactants, and polymers involving primaquine with biuret linkages were formed. Only the primary amino group of the primaquine molecule reacted, but it reacted as a difunctional moiety to form a biuret linkage with the bisisocyanate.

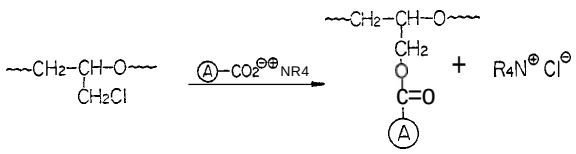
Efforts to use pesticides as controlled release formulations have led to the development of several good candidates[55]. Only a few will be mentioned here. The incorporation of pesticides into condensation type polymers has been described; for example, the preparation of polyacetals of 2,6-dichlorobenzaldehyde, a pesticide with strong herbicidal and moderate fungicidal activity (Eq. 12). Condensation type polymers with molecular weights of 1,000 ~ 5,000 could be achieved when 2,6-dichlorobenzaldehyde was condensed with 1,6-hexanediol, 1,10-decanediol, and diethylene and triethylene glycols. Linear hydroxy-terminated polyacetals formed from 2,6-dichlorobenzaldehyde and a,w-glycols which could be extended to polyurethanes with 1,6-hexamethylene diisocyanate. Hydrolysis experiments were carried out and the release of 2,6-dichlorobenzaldehyde demonstrated.



(12)

8 Pendant Hydrolyzable Active Groups

Polymers whose active groups are attached via a hydrolyzable or degradable link to the polymer chain, either directly or via a spacer group, are the most extensively studied release agents. In this case the polymer main chain is not attacked and remains as a polymer fragment. This approach suffers from many potential problems, particularly in applications in which the drug is to be introduced into the blood stream. Biologically active materials have been allowed to react with various reactive groups attached to polymer backbone chains. When polyepichlorohydrin is used as carrier, an ester group can be readily formed, for example[15], by performing a nucleophilic displacement reaction of the chloride with tetrzalkyl ammonium salts of a carboxylic acid; the introduction of the dimethylaminobenzoate group via this route has been demonstrated (Eq. 13).



(13)

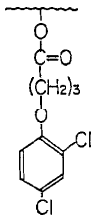
2, 6-Dichlorobenzaldehyde may be linked with polyamides derived from tartaric acid[55], or with poly(vinyl alcohol); in either case, 1, 3-dioxane rings are formed. This reaction has been used for the preparation of poly(vinyl butprals) for many years. Polymers which are derivatives of 5-nitro-2-furaldehyde (polyacryloyl hydrazone) were found to be antibacterially active in *vivo*[56]. The activity was much longer lasting than that observed for the 1-[(5-nitrofurfurylidene)amine]-hydantoin. The activity was ascribed to slow liberation of the active drug. A polymeric nitrofuran was also obtained from *N*-(3-vinylphenyl)-β-(5-nitro-2-furyl)acrylamide[57].

Antitubercular activity was found when 10 mol % of p-aminosalicylic acid was introduced into poly(vinylalcohol). Again the polymer was found to be more slowly eliminated than p-aminosalicylic acid itself and showed in *vitro* antitubercular activity[58].

Perhaps the most important effort in the area of release of polymeric drugs is in herbicides used in plant control[59]. Plants contribute a valuable renewable resource by virtue of their action as solar energy traps providing much of our food now and potentially an incrasing fraction of our industrial energy needs in the future. Obviously, since a healthy plant is a more efficient solar trap, attention must be given to proper plant nutrition and growth.

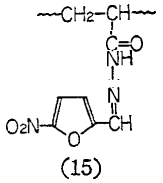
A polymer drug used as a release agent can be regarded as a type of prodrug. The concept of prodrugs originates in the human health field and is applied to substances that are themselves perhaps biologically inactive but are convertible to an active principle at some point between the locale of administration of the final target site. Aspirin is perhaps the most well known example of a prodrug where the acetyl group may 'simply modify solubility of the parent slaicylic acid so that it can more readily penetrate membranes and then hydrolyze to release the active drug and relieve pain.

The commercially available triethylamine salt of 2, 4-dichlorophenoxybutyric acid (2, 4-DB) is an excellent herbicide. It is oxidized in the cell to 2, 4-dichlorophenoxyacetic acid(2, 4-DA)which is much more toxic than 2, 4-DB itself. It has been shown that these polymeric plant drugs can be attached to bark, cellulose, lignin or sawdust and then administered on the ground. These polymeric drugs can then be hydrolyzed to release 2, 4-DB in a controlled and desirable way (Eq. 14). 2, 4-DB has been also attached to purified cellulosic materials.


(14)

The attachment of polymeric drugs and release at the proper rate depends on chain mobility and on the length of the, spacer which carries the active group. Fundamental studies have been carried out on methacrylamide polymers to which *p*-nitrophenylacetate groups were attached via spacers of varying length. These polymers were prepared and enzymatic hydrolysis was studied. It was shown that the bonds of the side chain were susceptible to enzymatic hydrolysis provided that the side chain had the proper length and was terminated by an enzyme-sensitive(e.g. chymotrypsin-sensitive)bond.

It was also shown that when the potentially active material is highly insoluble, hydrolysis cannot occur. It was consequently suggested that highly hydrophilic monomers be considered as solubilizing agents, and *N*-/tris(hydroxymethyl)methyl/ methacrylamide was proposed and found effective as a neutral hydrophilic comonomer[60]. It is very stable to hydrazinolysis and could be used as comonomer for studies of bactericide release from copolymers of the 5-nitro-2-furaldehyde hydrazone of polyacrylic acid(Eq. 15).


(15)

Many aspects of biologically active materials have been studied over the last few years. A number of symposia concerned with functional polymers, polymer reactions, polymeric drugs, and biologically and medically compatible materials have been held and slowly the picture of syn-

thetic polymers with biological and pharmaceutical activity is evolving. It is now time to identify the areas in which polymeric forms of drugs can solve problems associated with the ineffectiveness or toxicity of conventional drugs.

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