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New strategies for polymer development in pharmaceutical science – a short review

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Abstract

We are developing synthetic polymers for pharmaceutical and medical applications. These applications can be broadly grouped on how the polymer will be utilized e.g. material, excipient or molecule. Our focus is to develop polymers with more defined structures that are based on biological, physicochemical and/or materials criteria. Strategies are being developed to more efficiently optimize structure–property correlations during preclinical development. We describe two examples of our research on pharmaceutical polymer development: narrow molecular weight distribution (MWD) homopolymeric precursors which can be functionalized to give families of narrow MWD homo- and co-polymers, and hydrolytically degradable polymers.

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Dedication: This paper is dedicated to Professor Mike Newton on occasion of his 65th birthday.

Introduction

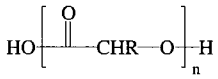
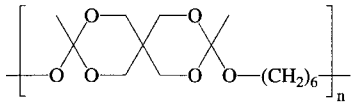
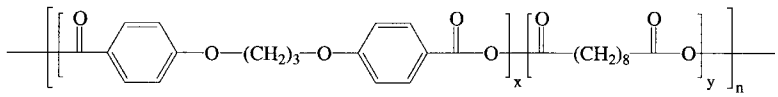
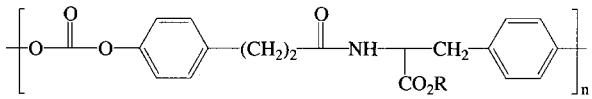
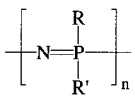
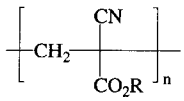
Synthetic polymers are being developed for a wide range of pharmaceutical and medical applications. One way to group these applications is how the polymer will be utilized e.g. material, excipient or molecule (Table 1). Broadly these applications span the use of polymers as materials to fabricate drug release matrices, gels and devices, as excipients in formulation development, and as physiologically soluble molecules utilized for the conjugation of bioactive compounds. While chemical structure and molecular weight characteristics of the polymer will influence structure–property correlations, there will be specific design criteria for each application endpoint. In ''material'' applications processing history may profoundly influence the bulk and surface polymer properties that define performance. To avoid long-term polymer accumulation and device removal after the therapeutic requirement has been met, degradable polymers have been and are continuing to be developed as materials (Table 2). Solution properties rather than processing history will be important for applications which involve the polymer being used as a ''molecule'' (e.g. drug and protein conjugation). Example structures are shown in Table 3.

Current challenges for the development of degradable polymers include optimization of structure–property correlations in respect to the biological profile and performance that are expected to change with time due to degradation processes, and maintenance of an acceptable toxicity profile over time. While there are many other important issues (e.g. manufacturing biomedical polymers at pilot scale under GMP conditions), regardless of the application or whether the polymer is degradable or non-degradable, toxicological considerations are crucial. A defining

Table 1 Applications of polymers in medicine and pharmaceutical sciences. These applications are broadly categorized by how the polymer will be utilized.

Polymer application group	Applications
Material	Site specific drug delivery; continuous and prolonged drug delivery Tissue/organ improvement, substitution or regeneration; prosthesis; dental restoration; ophthalmic devices Orthopaedic fixation; surgical devices
Excipient	Formulation stabilizers; adhesion enhancers; coatings Viscous oils
Molecule (large molecule therapeutics)	Physiologically soluble drug or protein–polymer conjugates; polyvalent ligands Sequestering agents Aggregating reagents for nano/macro particle fabrication; non-viral vectors; stimuli responsive agents

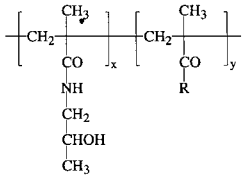
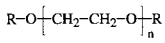
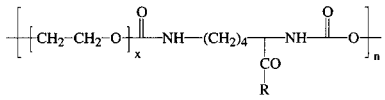
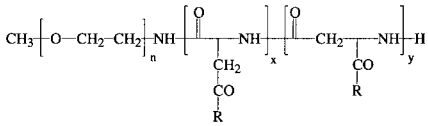
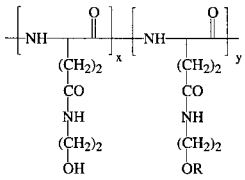
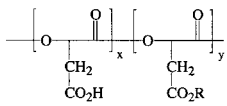
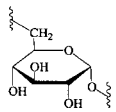
Table 2 Degradable polymers that have been developed for material type applications. This table is not comprehensive and while some of these polymers are used as gels or viscous oils, they tend to be fabricated into devices such as wafers, rods, and films.

Synthetic Polymers	Representative Structure
Polyesters (Domb *et al.*, 1997)	
Poly(orthoesters) (Heller, 1993)	
Polyanhydrides (Langer, 1998)	
Tyrosine derived pseudo-poly(amino acids) (Nathan & Kohn, 1994)	
Polyphosphazenes (Allcock, 1986)	
Poly(alkylcyanoacrylates) (Couvreur *et al.*, 1990)	

challenge to be met for biomedical polymer development is nested in the concept that these polymers are endowed with therapeutic attributes (i.e. they must meet a therapeutic need and optimally be biocompatible). Many important issues relating to toxicology (acute and cumulative) and metabolic fate apply to biomedical polymers. Like drugs, biomedical polymers must meet strict regulatory requirements.

Increasingly sophisticated biology and biotechnology are being utilized to discover new therapeutic targets and strategies. As new bioactive agents are discovered it is clear that many display limited pharmacokinetics and

Table 3 Representative examples of water-soluble polymers that have been used to conjugate drugs and proteins.

Polymer (example reference)	Representative Structure
Non-degradable mainchain	
N-(2-hydroxypropyl) methacrylamide copolymers (Duncan *et al.*, 1991; Putnam & Kopecek, 1995)	
Poly(ethylene glycol) (Greenwald *et al.*, 1996)	
Potentially degradable	
Alternating PEG-Lysine copolymer (Nathan *et al.*, 1993)	
PEG-aspartic acid block co-polymer (Kataoka, 1997)	
Amino acid derived polymers (Li *et al.*, 1998; Soyez *et al.*, 1996)	
Polyesters (Abdellaoui *et al.*, 1998; Ouchi *et al.*, 1990)	
Polysaccharides (Morgan *et al.*, 1995; Sezaki *et al.*, 1989)	

require a tailored delivery system to ensure clinical efficacy. In our view the development of the "delivery system" cannot be disassociated from the development of the therapeutic agent itself. This is especially true in respect to developing physiologically soluble conjugates. Until recently (Langer 1998), commodity synthetic polymers (e.g. Teflon, silicones, polyurethanes) have been used for many medical purposes including drug delivery. While in some applications such use may be appropriate, these polymers were not specifically developed to meet the complex multivariant challenges posed by medical use including drug delivery. It is now apparent that speciality polymers matched to a specific biomedical application are more appropriate candidates for development. Compared with naturally occurring and semi-synthetic polymers (e.g. polysaccharides and hydroxyethyl cellulose, respectively), the use of synthetic polymers offers the potential to elucidate optimal structure–property relationships matched to a specific application.

The technical and scientific paradigms used in drug development can be applied to the development of biomedical polymers. For example, combinatorial approaches have found application in the development of

therapeutic drugs. The appropriate use of combinatorial strategies for biomedical polymer development can lead to more efficient determination of structure–property correlations (Brocchini et al 1997, 1998). This research has demonstrated how simple, defined changes in monomer structure can produce libraries of A-B strictly alternating polymers. These libraries possess similar structural features (orthogonal homologation) which are not simply additive and that can be used to establish a multitude of structure–property correlations. This design paradigm can give families of candidate polymers that share many important properties (e.g. degradation mechanism, processability, biocompatibility) and display an incremental variation over a wide range for other properties (e.g. thermal, mechanical and surface properties). This approach to combinatorial development is a more accurate reflection of how in nature, structure and function are matched. For example all proteins share a set of properties (e.g. they are polyamides, water soluble, tend to have a hydrophilic surface) while at the same time other properties incrementally vary over a wide range (e.g. substrate selectivity, turnover, half-life). Although miniaturization, automation and IT advances are important for implementing combinatorial strategies, the exploitation of the combinatorial paradigm for biomedical polymer development requires that: (1) chemical structural features be designed so appropriate polymer and biological properties match the application endpoint; (2) characterization of the polymer and biological properties be conducted on both a global (e.g. determination of thermal properties, solution properties and toxicity) and application dependent levels (e.g. specific property matching to an application); (3) iteration be implemented (i.e. an experimental result be used as input to further optimize structure–property correlations); and (4) a library is designed so that only a limited number of polymers need be prepared as a basis to predict (e.g. by a neural network) the properties of many other related polymers that have not been prepared (Kohn, personal communication).

The biological rationale for the design of polymers is becoming better understood (Duncan 1997) and is a focus of much research for many of the applications listed in Table 1. Polymers continue to be needed that are tailored to match optimally the complex biological requirements for biomedical use. Our focus is to develop polymers that are based on biological criteria, have more defined structure and more efficiently optimize structure–property correlations during preclinical development. Reviewed in this article are two examples of our research in biomedical polymer development: narrow molecular weight distribution (MWD) homopolymer precursor which can be functionalized to give families of narrow MWD homo- and co-polymers, and polymers that undergo enhanced rates of hydrolytic degradation at acidic pH values.

A homopolymer precursor

There is considerable interest in the development of water-soluble polymers to conjugate therapeutic drugs and proteins. While there are other applications that are currently being examined (Table 1) for soluble polymers, conjugation of a bioactive agent to a polymer has been a focus of research for many years (Batz et al 1974; Ringsdorf 1975; Donaruma & Vogl 1978) and many reviews have been published (for example: Nucci et al 1991; Delgado et al 1992; Duncan 1992; Duncan et al 1996; Nishikawa et al 1996; Kataoka 1997; Alakhov & Kabanov 1998; Monfardini & Veronese 1998; Brocchini & Duncan 1999; Kopecek et al 2000). Possessing the knowledge that macromolecular uptake by cells is limited to the pinocytic route (Trouet et al 1972; deDuve et al 1974), and that soluble synthetic polymers could be used as blood expanders (Sprincl et al 1971, 1976), as prophylactics against radiation exposure (Ringsdorf et al 1971), and as pharmacologically active agents (Regelson 1968; Iliev et al 1974; Regelson et al 1974), Ringsdorf (1975) proposed that drugs and targeting moieties could be conjugated to water soluble polymers.

The purpose of the polymer component is more than just being a "carrier" to deliver the conjugated drug. The four components of a polymer-drug conjugate (Figure 1) together display a distinct profile of properties. The properties of the conjugate in solution are responsible for altering biodistribution by prolonging circulation half-life, exploiting permeability gradients in the body, defining mode and rate of cellular uptake, and for imparting favourable physicochemical properties

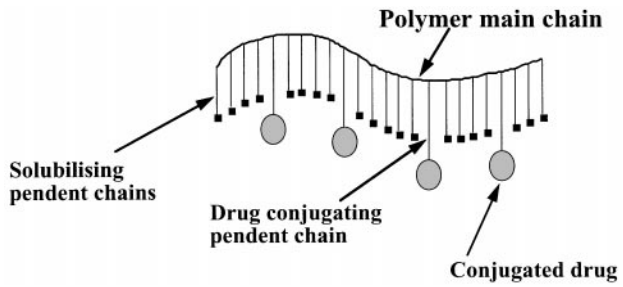
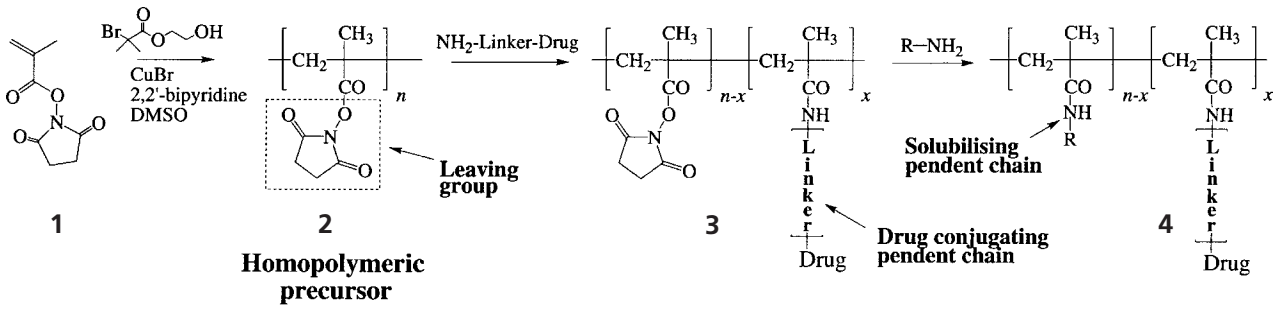
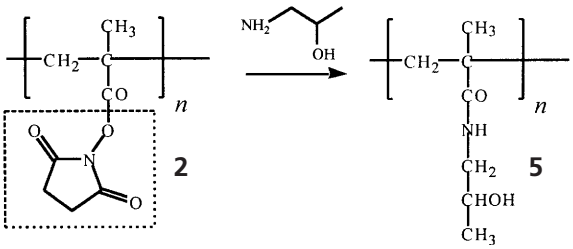


Figure 1 Depiction of a polymer–drug conjugate illustrating the four components that comprise this type of therapeutic agent (Ringsdorf 1975).



Scheme 1 Synthesis of narrow MWD polymer–drug conjugates **4** from the homopolymeric precursor **2**.



Scheme 2 Conjugation reaction of 1-amino-2-propanol with homopolymeric precursor **2** to give narrow MWD HPMA homopolymer **5**.

(e.g. increasing the water solubility of hydrophobic drugs). Many of these characteristics are related to properties indigenous to polymers. In this context, development of the polymer as a delivery system cannot be disassociated from the development of the therapeutic agent itself (i.e. a specific polymer–drug conjugate) and polymer conjugates are considered as "new chemical entities" by regulatory authorities (Duncan 1997).

Currently many polymer–drug conjugates are prepared by the conjugation of the drug to a copolymeric precursor by a polymer analogous reaction (reviewed in Putnam & Kopecek (1995)). This methodology has been essential to help systematically elucidate the biological rationale underlying many aspects for the development of polymer–drug conjugates for cancer treatment (Duncan 1997) and for developing numerous conjugates currently undergoing clinical evaluation (for example Vasey et al (1999)). In principle, this methodology can be limited by the need to make a copolymer precursor for each new conjugate needed for study. This requires optimization of the polymerization chemistry for each copolymer precursor to control molecular weight characteristics. Molecular weight distribution of these copolymer precursors tend to be broad and will be different for each conjugate that is prepared. Since there are only a few active pendent chains for conjugation, the product conjugates are frequently produced with significant structural heterogeneity in the pendent chain structure. Obtaining the necessary information during preclinical development about the fate of chemical species can be made more difficult by the differences in structure which inherently occur by using a co-polymer precursor.

More widespread clinical use of polymer conjugates will depend on the development of expedient paradigms that can be used to optimize efficiently structure–property correlations of a range of conjugates during preclinical development. One strategy for more effective preclinical development is to use a common homopolymer precursor **2** to prepare families of conjugates **4** for study. The use of a single homopolymer precursor can avoid molecular weight variation when preparing a family of polymer–drug conjugates. Only one precursor is required to give conjugates with varied drug loading, solubility and drug release properties. Each repeat unit in a homopolymer precursor is available for conjugation, so it is possible to conjugate the bioactive agent with its linker in an efficient manner and in ways to ensure linker structure is maintained.

We have developed the narrow molecular weight distribution (MWD) homopolymeric precursor **2** (Scheme 1) (Godwin et al 2000, 2001). Two critical issues have been addressed in developing this precursor: implementation of atom transfer radical polymerization (ATRP) to prepare the homopolymer precursor **2** with a narrow MWD, and examination of the conjugation chemistry of **2** to give families of narrow MWD conjugates and speciality polymers that cannot be prepared by any other process. The polymerization of acrylated active esters **1** to give active ester polymers which are then used to prepare functionalized polymers is well known (for example: Strohriegl 1993; Arshady 1994). A limitation has been the practical control of polymer molecular weight, which is difficult to achieve by

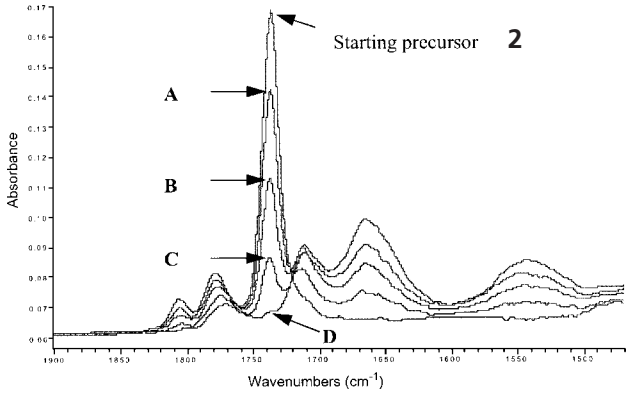


Figure 2 Conjugation of increasing stoichiometries of 1-amino-2-propanol with homopolymeric precursor **2**: trace A, 0.25 (0.26); B, 0.50 (0.53); C, 0.75 (0.76); D, 1.00 (0.99).

conventional free radical polymerization of active monomers. We can currently prepare narrow MWD homopolymer precursor **2** on 6-g scale in molecular weights ranging from 2000 to 50 000 g mol^{-1} with polydispersities ranging from 1.1 to 1.2.

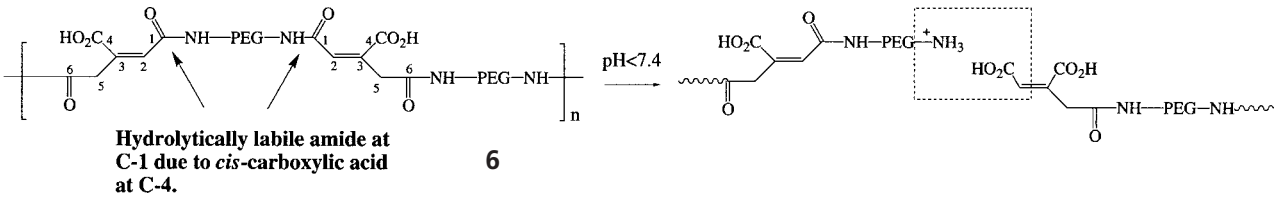
Conjugation reactions of precursor **2** with amines can be followed by FT-IR. For example, increasing stoichiometries of 1-amino-2-propanol correlated with a decrease in height of the imide band at 1735 cm^{-1} (Scheme 2, Figure 2). When an excess of 1-amino-2-propanol (2 equivalents) was added to a solution of precursor **2**, narrow MWD hydroxypropyl methacrylamide (HPMA) homopolymer **5** was isolated. HPMA copolymer conjugates have been instrumental in the development of polymer–drug conjugates. Currently it is not possible to prepare narrow MWD **5** or most other methacrylamide homo- and copolymers over a range of molecular weights except by tedious, and often difficult to reproduce, fractionation procedures. The homopolymer **5** prepared by conventional free radical polymerization is known not to be toxic (Putnam & Kopecek 1995). *In-vitro* cytotoxicity assays of HPMA homopolymer prepared by the method in Scheme 1 and by conventional free radical polymerization indicated that polymer prepared by either process was not cytotoxic.

The absolute molecular weight of **2** can be determined by hydrolysis to poly(methacrylic acid) (PMAA) followed by gel permeation chromatography (GPC) using PMAA standards. This provides a means to determine the degree of polymerization of **2** and any conjugate or speciality copolymer derived from **2**. By utilizing only the narrow MWD homopolymeric precursor **2**, families of narrow MWD polymer conjugates **4** and speciality copolymers are being prepared while keeping constant the absolute molecular weight characteristics of the polymer mainchain.

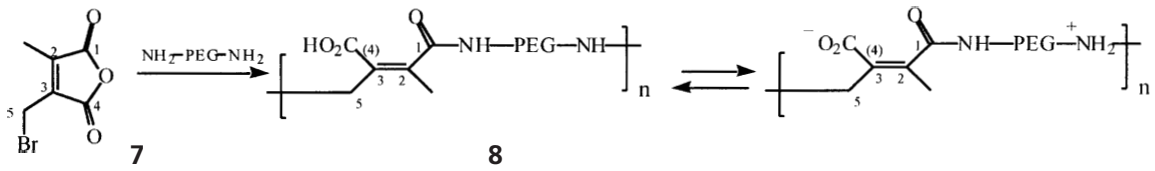
Hydrolytically degradable polymers

Degradable, synthetic polymers are being studied for a wide range of speciality biomedical applications (note Tables 2–3). For conjugation applications, it may be preferable that the polymers degrade by a hydrolytic mechanism rather than a proteolytic mechanism. In this way the degradation mechanism and its rate can potentially be broadly independent of the specific characteristics of the conjugate (e.g. degree of loading or type of drug/protein/targeting moiety conjugated to the polymer mainchain). With a degradable polymer it may be possible to increase and optimize the circulation time by increasing the molecular weight of the polymer (hence increasing its solution size). Permeability in some solid tumours can range to quite large dimensions (Yuan et al 1995; Hobbs et al 1998; Monsky et al 1998) resulting in the uptake of high molecular weight macromolecules (Seymour et al 1995; Noguchi et al 1998) and molecular aggregates which are beyond the renal threshold. For chronic conditions characterized by inflammation and where repeat dosing would be required, there is a need for polymers that can be degraded and cleared. Of the physiologically soluble, synthetic polymers which have been examined for the conjugation of proteins and drugs (e.g. amino acid derived polymers and certain polyesters; Table 3), it is not clear from the literature if there are any polymers that degrade within the cell and would potentially be expected to clear within hours after administration. These polymers simply do not have structural features to cause the acceleration of polymer degradation at acidic pH values found within the endocytic pathway or in certain regions of the body.

Concerning soluble, degradable polymers for conjugation applications there are two broad degradation pathways that can be considered. There is degradation of the polymer backbone to a molecular weight, which can be efficiently cleared, and there is degradation of the drug conjugating pendent chain to release the drug. Release of the drug must be optimized for maximal efficacy. If polymer degradation is too fast in the blood, then no advantage in exploiting the differential in vascular permeability is realised and both healthy and diseased tissue may be dosed. If the polymer degrades within acidic cellular organelles but degrades too slowly in circulation, then repeat administration is only possible if molecular weights below the renal threshold are used. These two degradation events need to be modulated as a function of polymer properties to optimize the bio-



Scheme 3 Assisted degradation of aconityl derived polymer **6** by the C-4 carboxylate to cause enhanced degradation of the amide bond at C-1. One bond cleavage reaction is shown. This mechanism is derived from early kinetic studies (Bender et al 1958; Kirby & Lancaster 1972) on related intramolecular acid assisted hydrolysis reactions of phthalamic and maleamic acid amide derivatives.



Scheme 4 Synthesis of zwitterionic polymers **8** possessing an aconityl-like degradable element in the polymer mainchain.

logical response. This is only possible if the structure of the polymer and/or the polymer conjugate is defined and can be incrementally varied by defined chemical derivatization.

Polysaccharides lack structural uniformity and exhibit the propensity upon chemical modification (i.e. drug conjugation) to become immunogenic or non-degradable (Vercauteren et al 1990; Shalaby & Park 1994). If a degradable biomedical polymer is to be used, then a hydrolytic mechanism will most probably be the preferred pathway for degradation leading to clearance in many applications. There is also a lack of structural uniformity in many potentially degradable polymer–drug conjugates derived from polysaccharides and synthetic polymers which have been studied to date because of the random incorporation of the drug conjugating pendent chains. This lack of structural uniformity results in a general inability to systematically modulate structure–property relationships and a limited capacity to use one polymer system to conjugate differing types of drugs in a defined structural way. In this respect, our goal is to prepare strictly alternating A-B polymers where pendent chain functionalization can be better controlled.

We are developing ''degradable elements'' designed to be transferable to a range of solution (molecule) and solid (excipient/material) pharmaceutical polymer applications. One example is the aconityl derived soluble polymer **6** (Scheme 3) which has a carboxylic acid (C-4) *cis* to a hydrolytic bond (C-1) (Clochard et al 2000). Such polymers have a pH dependent degradation profile

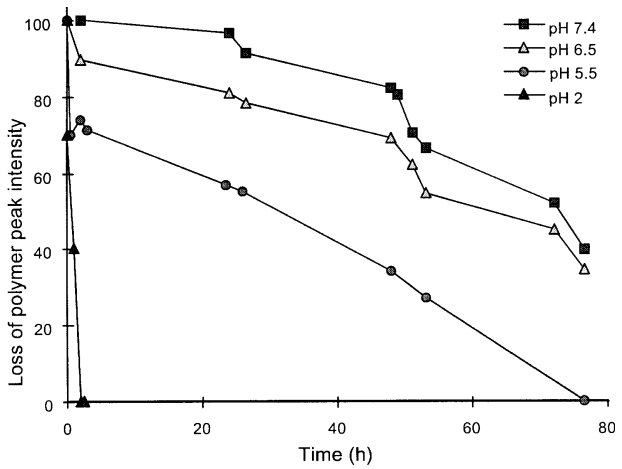
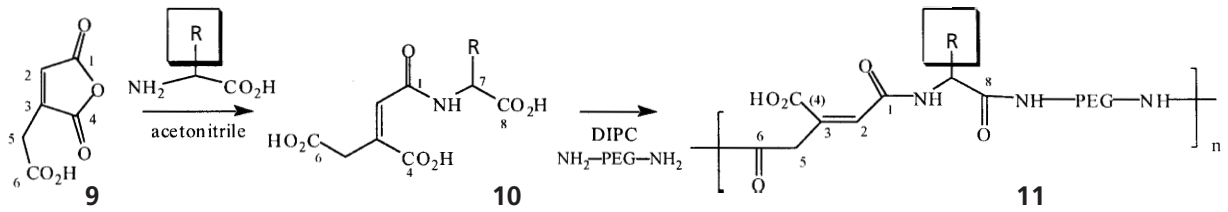


Figure 3 Degradation profile of zwitterionic **8** at acidic pH values.

with higher rates of hydrolysis at acidic pH values due to intramolecular assisted C-4 acid catalysed hydrolysis at the C-1 bond. The ''enforced propinquity'' (Woodward 1968) of the pendent carboxylic acid at C-4 is necessary to ensure intramolecular interactions facilitate hydrolysis at the C-1 amide (Scheme 3). Early kinetic studies (Bender et al 1958; Kirby & Lancaster 1972) focused on intramolecular acid assisted hydrolysis reactions of a defined structural motif which we have incorporated into a polymer mainchain with the expectation that degradation will occur at acidic pH values. *Cis*-aconityl acid derived linkers have been used



Scheme 5 Pendent chain functionalized, amino acid-aconityl derived polymers **11** (R = amino acid side chain; X = carboxylic acid activation group).

to conjugate bioactive molecules to macromolecules (Shen & Ryser 1978, 1981; Diener et al 1986; Dillman et al 1988; Franssen et al 1992; Hudecz et al 1992; Al-Shamkhani & Duncan 1995; Hoes et al 1996; Gaal & Hudecz 1998; Wirth et al 1998; Yang & Reisfeld 1988) and are known to degrade at enhanced rates at acidic pH values. Evaluation of the in-vitro biocompatibility indicated this first generation polymer **6** and its degradation products were not cytotoxic to B16F10 cells or caused red blood cell lysis. Preliminary degradation studies during the preparation and characterization of **6** indicated there were non-degradable aconityl derived elements in the polymer mainchain.

An improvement for preparing these polymers possessing the mainchain aconityl derived degradable element was to use the known compound **7** as a monomer (Scheme 4). This monomer **7** quickly yielded high molecular weight, aqueous soluble polymer **8** (polymerization time 6–12 h at ambient temperature; molecular weight averages within the range of 10^5–10^6 g mol^{-1}, PEG standards) (Clochard & Brocchini 2000). These zwitterionic polymers **8** displayed a pH dependent degradation profile with increased rates of hydrolysis occurring at increasing acidity (Figure 3).

The optimal strategy to prepare condensation polymers reproducibly with control over molecular weight is to use a well-characterized low molecular weight monomer. For many applications of interest pendent chain functionalization for drug conjugation is required, so a synthetic route is also required to incorporate this functionality. Compounds such as **10** (Scheme 5) are derived from *cis*-aconityl anhydride and amino acids (Simic et al 2000). Potentially they provide a means to incorporate functionalized pendent chains into these polymers. The direct polymerization of **10** with a carbodiimide reagent and diamino-PEG yields polymer (Scheme 5, R = hydrogen) which degraded within 30 min at pH 2.0 (25°C). This mode of polymerization is not yet optimal because of possible competing reaction at C-4. Our current efforts are focused on preparing well-characterized amino acid-aconityl monomers **10** activated at C-6 and C-8, which would then be directly polymerized to **11**.

Conclusion

Synthetic polymers provide a broad technology platform to address many applications in the pharmaceutical sciences and medicine. This has been recognized for a number of years (Batz et al 1974; Florence 1974; Ringsdorf 1975; Donaruma & Vogl 1978; Langer 1998). There are new advances being made in polymer science that are providing more defined polymer structure (for example: Sawamoto & Masami 1996; Deming 1997; Matyjaszewski 1997; Godwin et al 2001). Increasingly, the biological rationale for using polymers in medicine is becoming better understood. This is providing the opportunity for more efficient optimization of structure–property correlations of biomedical polymers (e.g. via combinatorial strategies). As the many disciplines that are traditionally involved in the pharmaceutical sciences become better known to the practitioners of polymer science and collaborations increase, then the "medicinal chemistry of polymers" will grow in importance.

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