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PolyActives: Controlled and Sustained Bioactive Release Via Hydrolytic Degradation

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Abstract

Significant and promising advances have been made in the polymer field for controlled and sustained bioactive delivery. Traditionally, small molecule bioactives have been physically incorporated into biodegradable polymers; however, chemical incorporation allows for higher drug loading, more controlled release, and enhanced processability. Moreover, the advent of bioactive-containing monomer polymerization and hydrolytic biodegradability allows for tunable bioactive loading without yielding a polymer residue. In this review, we highlight the chemical incorporation of different bioactive classes into novel biodegradable and biocompatible polymers. The polymer design, synthesis, and formulation are summarized in addition to the evaluation of bioactivity retention upon release via *in vitro* and *in vivo* studies.

Graphical Abstract

This review discusses recent advances in the chemical incorporation of a wide range of bioactives into completely biodegradable and novel polymers
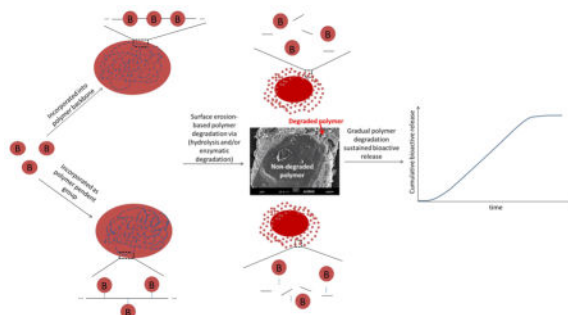
1. Introduction

Typically, small molecule drugs have short half-lives and undergo rapid and avid metabolism once implanted *in vivo*. To achieve an effective and therapeutic dose, repeated administration is often needed, which can contribute to a myriad of side effects, potential toxicity, and low patient compliance. Polymer-based delivery systems offer a solution to these issues. Many polymer-based bioactive delivery systems are physical admixtures of the active within the release-controlling polymer or encapsulations of the active within

polymeric carrier molecules.[1–12] However, physical incorporation of bioactives into polymeric matrices can suffer from low drug loadings as well as a burst release in which the vast majority of active is released after a short time.[13, 14]

Chemical incorporation of bioactives into polymeric systems addresses the potential limitations of physical admixtures; this approach offers higher drug loading in addition to sustained and tunable bioactive release. Many polymeric systems utilizing chemical incorporation have the bioactive covalently attached to polymethacrylamide backbones.[15–17] While many of these polymeric prodrug systems are water-soluble, they ultimately do not degrade, which may be a drawback; nonbiodegradable systems may require removal or additional modification once introduced *in vivo*. Nevertheless, polymeric delivery systems exhibit controlled release and have been successfully commercialized. Covalent bioactive attachment to commercially available or pre-made polymers such as poly(*N*- (2-hydroxypropyl)methacrylamide) (HPMA), poly(ethylene glycol) (PEG), and polysaccharides exhibiting sustained, controlled and targeted release has been reported in great detail.[15, 17–25] In this work, we focus on *completely biodegradable* and *novel* polymers in which the bioactive is chemically incorporated, whether attached as a pendant group or as a component of the polymer backbone (Figure 1). Additionally, bioactive attachment within the polymer backbone linker can follow one of two motifs: drug-linker-drug (i.e., two bioactives per repeat unit, Figure 2A), or linker-drug-linker (i.e., one bioactive per repeat unit, Figure 2B), depending on the available functionality of the drug. The linker molecule, often an inert, biocompatible small molecule, allows for the formation of bioactive-containing polymer precursors. In all examples, a bioactive-containing monomer is first synthesized and subsequently polymerized. Linker alterations and subsequent polymer property changes will be discussed in detail in Section 4.

The Uhrich group focuses exclusively on biodegradable and biocompatible polymers containing hydrolytically and enzymatically labile bonds (e.g., anhydrides, esters, and amides), with major focus on poly(anhydride-esters) (PAEs) and polyesters (PEs).. Polyanhydrides in particular are investigated due to their favorable properties for bioactive release. Because polyanhydrides are generally surface-eroding polymers exhibiting hydrolysis rates that are faster than diffusion rates, erosion is mostly limited to the outer surface of the polymer formulation. This erosion mechanism allows the polymer's interior structural integrity to be maintained throughout the degradation process and allows controlled polymer degradation and linear mass loss, both desirable properties for bioactive delivery.[26, 27] PAEs developed by the Uhrich group predominantly undergo surface erosion, which permits well-controlled polymer degradation with near zero-order bioactive release kinetics.[28]

In synthesizing polyanhydrides, other functional groups, such as amides and esters, can also be chemically incorporated into the backbone. For instance, our laboratory reported the synthesis of salicylate-based PAEs by melt-condensation and solution polymerization methods; these polymers are capable of achieving controlled and extended release of the salicylates through surface erosion.[29] Salicylate-based polymers are unique because non-steroidal anti-inflammatory drugs (NSAIDs) are chemically incorporated into the polymer backbone, instead of being physically admixed with the polymer.[30, 31] Likewise, the Uhrich

group has chemically incorporated other NSAIDs, such as ibuprofen and naproxen, as pendant groups into PE backbones through their propionic acid moiety.[32, 33]

To provide controlled therapeutic delivery, the Uhrich group has developed several types of polymeric bioactive delivery systems, namely PAEs and PEs. This review highlights the progress of polymeric bioactives investigated in our laboratory via two categories: pendant group and backbone attachments (Figure 1). In each of these categories, different classes of bioactives are explored. These bioactives include antioxidants (free radicals scavengers)[34], antimicrobials (microorganisms killing agents),[35] NSAIDs (providing anti-inflammatory, analgesic, and antipyretic effects),[36] antiseptics (kill microorganisms or inhibit their growth, especially on living tissue),[37] antibiotics (kill bacteria or inhibit their growth),[38] and opioids (potent analgesics).[39] Additionally, this review addresses methodologies to tune polymer hydrophobicity, alter bioactive release rates through chemical and physical modifications, and to formulate the polymers for different applications.

2. Pendant Group Attachment

The attachment of a bioactive molecule to a polymer backbone as a side chain can be achieved utilizing two major approaches: 1) post-polymerization modification in which a bioactive is covalently linked to a pre-made polymer backbone, and 2) polymerization of a bioactive-containing monomer. In this review, the latter case will be the major focus, as this methodology allows for higher drug loading and more tunable structures.

2.1. Propionic Acid NSAIDs

NSAIDs are a class of drugs with anti-inflammatory, analgesic, and antipyretic properties. Propionic acid NSAIDs, such as ibuprofen and naproxen, have short half-lives and may cause severe gastrointestinal side effects at high doses.[40] Thus, the sustained, localized release from a polymer could mediate these issues. Ibuprofen (**1a**) or naproxen (**1b**), both of which have a carboxylic acid moiety, was coupled to a protected tartaric acid derivative (**2**) via carbodiimide-mediated esterification (**3**).[32] Subsequent chemoselective deprotection afforded an NSAID-containing tartaric acid diacid (**4**). Using a linear aliphatic diol as comonomer (e.g., 1,8-octanediol, **5**) and stannous octoate as catalyst, two PEs were synthesized (**6a–b**, Scheme 1). NSAID release rate under physiological conditions (pH 7.4, 37 °C) in phosphate buffered saline (PBS) was slower and glass transition temperature was higher for the more rigid naproxen-containing PE (**6b**) when compared to the ibuprofen PE (**6a**). Cytocompatibility studies deemed the polymers nontoxic toward fibroblasts and proton nuclear magnetic resonance spectroscopy confirmed that the structure of the released NSAID was retained. This easily amenable methodology yields polymers whose ultimate degradation products yield a bioactive (ibuprofen or naproxen), sugar (tartaric acid), and biocompatible diol.

Using similar types of reactions, PEs containing ibuprofen attached to a malic acid backbone were also synthesized with the intent to minimize excess regents and utilize nontoxic solvents. Using the Twelve Principles of Green Chemistry[41] as a guide, a more environmentally friendly methodology to incorporate bioactives into polymer backbones was developed.[33] A solvent-free esterification of malic acid with ibuprofen followed by

catalytic deprotection in cyclopentylmethyl ether, a green solvent preferred by the personal care industry, yielded diacid. Polymerization with one of three aliphatic diol comonomers was accomplished via a commercially available lipase (lipase B from *Candida antarctica, CAL-B*) to afford three PEs with aliphatic chain lengths ranging from three to eight methylene units. Bioactive release rate and glass transition temperatures decreased with increasing aliphatic chain length. As with the tartaric acid analog, cytocompatibility was confirmed along with retention of drug composition. The reactions utilized here significantly reduce the amount of reagents and eliminate chlorinated solvents as outlined in previous methods.[42–44] Additionally, the tin catalyst often employed for polyesterification reactions was replaced with naturally-occurring and renewable lipase. The utilization of such green chemical processes for drug delivery and biomaterials can lead to a more environmentally friendly process.

Also utilizing CAL-B, Thompson *et al.* developed a novel polymer, poly(glycerol-adipate-*co*-pentadecalactone) (PGA-*co*- PL) in one step. The secondary hydroxyl group of PGA-*co*-PL, was then reacted with the acyl chloride derivative of ibuprofen to afford a polymer with pendant ibuprofen groups (Figure 3) with drug loading ranging from 3–13% for the three synthesized conjugates.[45] Thermal characterization via differential scanning calorimetry revealed that the amount of ibuprofen did not have a significant impact on melting or glass transition temperatures, which were on average 34 °C and −28 °C, respectively. Ibuprofen release was quantified by high performance liquid chromatography (HPLC); initially, a burst release (13 % over 30 min) was observed; however, over the next seven days, near-zero order release was observed.

Wang *et al.* also used CAL-B as catalyst to synthesize linear polyesters containing the NSAID ketoprofen as a pendant group.[46] Sebacic acid, glycerol, and PEG functioned as the backbone (Figure 4). Polymers with PEG molecular weights of 200, 400 and 800 Da ranged from ~16–30 % drug loading. Under physiological conditions and over two weeks, twice as much ketoprofen was released from the PEG 800 polyester compared with the PEG 400 polyester (22 % vs. 11 %). This observation is likely due to the increased hydrophilicity of the longer PEG chain, causing faster release. Polyester with PEG 800 and 4.5 kDa total Mw exhibited 16 % release over two weeks under the same conditions. However, a vast difference is noted between release in simulated gastric fluid when compared with simulated intestinal fluid: negligible release occurred in the gastric fluid while 100 % of drug was released within two days in intestinal fluid, with both studies lasting two weeks. This observation elucidates the potential for oral delivery of this polyester system.

2.2. Antioxidants and Antimicrobials

Oxidative stress and the production of reactive oxygen species and free radicals have profound implications on aging and age-related diseases.[34] Compounds with antioxidant properties can help eliminate free radicals and prevent oxidative stress.[47] Especially for consumer products such as food and cosmetics, oxidation can lead to browning as well as spoilage. Similarly, bacterial contamination remains a significant issue in personal care and food industries. Antimicrobial compounds with a wide range of activities and properties could prevent food spoilage.

Many phenols derived from natural sources exhibit both antioxidant[48] and antimicrobial[49] properties. Carvacrol, thymol, and eugenol are examples of such compounds isolated from the essential oils of oregano, thyme, and clove, respectively.[50, 51] The chemical incorporation of phenols into a polymer for bioactive sustained release has potential use in food packaging and personal care applications. Phenols have a single reactive moiety; however, dicarboxylic acids are often necessary as starting materials for PAE synthesis.[52] Thus, a phenol-containing small molecule precursor was initially synthesized (Figure 5A).[53] First, the ring opening of a cyclic dianhydride (e.g., pyromellitic anhydride, **8**) was investigated, affording the phenol-containing dicarboxylic acid, or diacid (**9**). The diacid subsequently underwent solution polymerization using triphosgene as coupling agent to make the PAE (**10**); here, the phenols are linked to the backbone via ester bonds, whereas the repeat units are connected through anhydride bonds. The general structure of repeat units follows a pendant group motif (Figure 1A) with a pyromellitic backbone. To ensure polymer safety, cell studies using fibroblasts indicated that the PAEs were cytocompatible.

Using a similar synthetic method, but replacing the pyromellitic anhydride with ethylenediaminetetraacetic (EDTA) dianhydride, a new series of PAEs containing carvacrol, thymol, and eugenol were developed.[54] These polymers are unique in that *all* polymer degradation products (i.e., phenol and EDTA) are active and found on the FDA's Generally Recognized As Safe (GRAS) list, leading to a high atom economy. Bioactive release via polymer degradation was determined under physiological conditions; polymer was completely degraded after 16 days. Additionally, it was determined via a 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical scavenging assay (Figure 5B) that all released bioactives retained their antioxidant activity after release from polymer. A disc diffusion assay also indicated that antimicrobial activity was preserved after release; in this assay, bioactive-impregnated discs are placed on bacteria-inoculated agar and incubated overnight. Antimicrobial activity is determined by the absence of bacterial growth surrounding the discs.[55]

3. Backbone Attachment

Previously, pendant group attachment (Figure 1A) of bioactives to a polymer backbone has been discussed in which the bioactive is conjugated to a monomer as a side group prior to polymerization. In this section, polymers in which the bioactives are chemically incorporated into the polymer backbone are discussed (Figure 2). Specifically, the bioactive is modified into a polymer precursor and subsequently polymerized, yielding high bioactive-loaded polymers. In the case of PAEs, this approach also offers fully biodegradable polymers capable of sustained, near zero-order bioactive release.

3.1 Anti-inflammatory Drugs

Salicylic acid (SA), a naturally occurring phenolic acid and active metabolite of aspirin, has an extensive tradition of medicinal use owing to its therapeutic effects, specifically its antipyretic, anti-inflammatory, and antimicrobial capabilities.[56, 57] While SA exhibits desirable therapeutic properties, its short half-life (~ 2 h) coupled with unwanted gastrointestinal side effects have limited its pharmaceutical use.[58, 59] To overcome such limitations and develop a controlled release drug delivery system, the Uhrich lab

incorporated SA into a polymer. SA-based PAEs were synthesized by first connecting two SA moieties through a linker molecule to acquire SA diacid, which is then activated and polymerized (Scheme 2).[60] SA-based PAE synthesis was achieved using a stoichiometric amount of pyridine to activate and selectively react a diacyl chloride (**12**) (linker molecule) with SA (**11**) to acquire SA diacid (**13**). SA diacid was then activated using excess acetic anhydride and subsequently polymerized at elevated temperatures under vacuum, ultimately acquiring a bioactive-linker-bioactive repeat unit (Figure 2B). This synthetic methodology is adaptable to a wide variety of salicylates such as aminosalicylates,[31, 61] iodinated salicylates,[62] diflunisal and salsalate among others.[30]

Polymer degradation studies conducted under physiological conditions revealed that SA-based (adipic) PAEs fully hydrolyzed into SA and adipic acid (**15**) (Scheme 3), both GRAS-listed compounds, over 8 days.[63] These studies also indicated a small lag period (1 day) in which a negligible amount of SA was released. Cytotoxicity studies conducted on polymer **14a** determined the SA-based (adipic) PAEs to be cytocompatible at 0.01 mg/mL.[64] To further investigate SA release, SA bioaccessibility was assessed using a dynamic *in vitro* gastrointestinal model (TIM-1).[65] Here, SA bioaccessibility from SA-based (diglycolic) PAEs was approximately 21% over 5 hours of simulated digestion.

As described above, SA contains a variety of therapeutic properties, including antimicrobial capabilities. To elucidate the efficacy against bacterial pathogens, our group evaluated SA-based (adipic) PAEs' ability to hinder biofilm formation. Polymer degradation was shown to significantly reduce *Pseudomonas aeruginosa* biofilm formation, preventing cell accumulation by five orders-of-magnitude when compared to an inactive control.[66] Similarly, SA-based (adipic) PAEs hindered the formation of *Salmonella* biofilms, offering a means to overcome traditional issues associated with bacterial biofilms.[67]

The anti-inflammatory properties of SA, specifically its decrease in pro-inflammatory cytokines production that are linked to compromised bone regeneration, have potential to be efficacious in bone repair.[68] SA-based (adipic) PAE/bone graft mixtures have been shown to significantly enhance bone fill percentage in rats relative to a bone graft control.[68] After four weeks, bone fill percentages in SA-based PAE bone graft mixtures were statistically greater than bone graft controls with diabetic and normoglycemic rats possessing 44 % and 37 % more bone fill than their respective bone graft control groups. Additionally, after 12 weeks, diabetic rats with SA-based (adipic) PAE/bone graft mixtures exhibited 43 % greater bone fill percentage than control rats and showed no statistical difference when compared to SA-based (adipic) PAE/bone graft mixture in normoglycemic rats (Figure 6).

Chandorkar *et al.* has also investigated incorporating SA into polymer backbones.[69, 70] Here, SA diacid is first synthesized using sebacoyl chloride, similar to Scheme 2, followed by activation with acetic anhydride and melt-condensation polymerization with mannitol to acquire a cross-linked, fully biodegradable PE (SAP). Curing SAP was found to decrease SA content, 40 % to 25 % (w/w), and SA release rate under physiological conditions, ~20 % in approximately 5 days to ~3.5 % over 4 months, when compared to noncured SAP. Positive *in vitro* cytocompatibility results culminated into subcutaneous implantation in mice to investigate SAP as a wound-healing matrix. Although an initial foreign body

response occurred, it subsided over the sixteen-week study as indicated by the reduction in systemic inflammatory cell density (i.e., neutrophil, macrophage and fibroblast) while vascularization surrounding the implant increased. Additionally, while poly(lactic-*co*-glycolic acid) (PLGA) displayed reduced foreign body response by the conclusion of the study, this result was likelydue to extensive bulk erosion. By sixteen-weeks, PLGA lost ~94 % of its mass whereas SAP had only ~8 % mass loss (Figure 7).

3.2 Antioxidants

As previously discussed, oxidative stress impacts a myriad of cellular functions, contributing to cardiovascular and neurodegenerative diseases. As such, antioxidants have been incorporated into PAEs, offering localized delivery to quench radical oxygen species. Two classes that have been investigated are phenolic acids and hydroxycinnamic acids (HCAs).

Two phenolic acids, syringic acid (SGA) and vanillic acid (VA), were integrated into a polymer backbone by first synthesizing diacid units and then undergoing solution polymerization.[71] Polymer degradation studies under physiological conditions found bioactive release to be controlled by polymer hydrophobicity; greater hydrophobicity decreased release rate. Released bioactive maintained antioxidant activity, as evident by a DPPH radical scavenging assay (Figure 8). Moreover, both polymers were found to be cytocompatible at higher concentrations (0.1 mg/mL) than those exhibited in the DPPH studies.

Whereas SGA and VA were incorporated into PAEs via a two-step approach, a modified synthetic method was necessary for HCAs (Scheme 4).[72, 73] HCAs, such as ferulic acid (FA), suffer from poor stability due to the double bond, readily undergoing decarboxylation and decreasing efficacy.[74] Consequently, HCA-based PAEs (FA and *p*-coumaric acid, *p*CA) were first synthesized as *t*-butyl protected derivatives (**15**), which were then reacted with a diacyl chloride to acquire *t*-butyl HCA diester (**16**). The diester is then selectively deprotected and the resulting diacid (**17**) subjected to solution polymerization to acquire HCA (adipic) PAEs (**18**)

Polymer degradation studies, conducted under physiological conditions, revealed that FA-based PAEs released more quickly than the *p*CA counterpart (6.2% vs 4.5%) over 30 days. Released bioactives were also found to maintain or possess significantly better antioxidant activity compared to free bioactives of identical concentration. Released bioactives from FA (adipic) PAEs were additonally tested for their antimicrobial activity against *Escherichia coli* and found to possess statistically similar antibacterial effects compared to free FA. Interestingly, in both FA and *p*CA (adipic) PAEs, polymers released their respective bioactives with no measurable decomposition occurring (Figure 9).

Whereas our lab has focused on incorporating antioxidants into PAEs, various hydrolytically labile bonds have been explored by others to integrate antioxidants into polymer backbones. Dziubla *et al.* utilized carbodiimide coupling to polymerize trolox, a Vitamin E analog, acquiring Poly(trolox ester) (PTx), a PE comprised solely of trolox.[75] PTx was further formulated into nanoparticles which displayed minimal cytotoxicity whilst possessing antioxidant activity *in vitro*. *In vitro* release studies measuring antioxidant activity revealed

that Trolox (Tx) was only released in a sustained manner when in the presence of carbonic anhydrase (CA). Cellular antioxidant activity was investigated and PTx nanoparticles found to inhibit protein carbonyl (a known marker of oxidative stress) content when compared to Trolox alone (Figure 10).[76]

Similarly, Lee explored PEs and PE derivatives for the inclusion of antioxidants into polymer backbones.[77–79] A unique feature of these systems is that the polymer itself possesses inherent bioactivity through the presence of aromatic peroxalate-esters, which are known to scavenge hydrogen peroxide.[77] Park *et al.* synthesized 4- hydroxybenzyl alcohol (HBA)-containing copolyoxalates (HPOX) by copolymerizing HBA and 1,4-cyclohexanedimethanl in the presence of oxalyl chloride.[78] HPOX hydrolysis kinetics studies revealed degradation to be pH-independent as both physiological and endosomal (pH = 5.5) conditions and possessed similar half-lives (~12 h). To further investigate drug delivery applications, HPOX was formulated into nanoparticles that displayed better hydrogel-peroxide scavenging activity than HBA alone (~50 % vs. ~20 % reduction at 1 mg/mL).[77] Additionally, intranasally delivered HPOX nanoparticles showed reduced instances of inflammation in ovalbumin sensitized mice. as indicated by inducible nitric oxide synthases (iNOS) staining.

Analogously, poly(oxalate-acetal) prodrugs of vanillin (PVO) have been synthesized and formulated into nanoparticles.[79] Vanillin was first protected at its aldehyde with 2-(hydroxymethyl)-2- methylpropane-1,3-diol to generate an acetal-containing vanillin prodrug diol which was subsequently polymerized with oxalyl chloride. Following nanoparticle formulation *in vitro,* release studies revealed faster vanillin release occurring under endosomal conditions compared to physiological conditions (~80 % to >40 %, respectively; Figure 11). Consistent with previous studies, PVO nanoparticles displayed greater hydrogen peroxide scavenging then vanillin alone owing to the peroxalate-ester presence. Furthermore, PVO nanoparticles inhibited iNOS and tumor necrosis facter-alpha expression while intravenous PVO nanoparticle injection reduced acetaminophen-induced acute hepatic injury.

3.3. Antiseptics

Heretofore, bioactives incorporated into PAE backbones have contained one phenolic and one carboxylic acid functionality, enabling a bioactive-linker-bioactive repeat unit. However, for bisphenol compounds, an alternate synthetic method is necessary (Scheme 5). To incorporate common antiseptics (e.g., catechol, fenticlor, and hexachlorophene) into PAEs, bis-phenols (**19**) were first reacted with cyclic anhydrides (**20**) to acquire antiseptic-diacids (**21**) which then underwent melt condensation polymerization.[80] The resulting antiseptic-based PAEs (**22**) contained linker-bioactive-linker repeat units (Scheme 5). A 12-week release study displayed varying release profiles (0–55 %), with catechol-containing PAEs (**22a**) degrading the fastest.

3.4. Antibiotics

While antibiotics remain essential to treat dangerous infections, overprescription and systemic delivery encourage the development of resistant bacterial strains.[81, 82] Local

delivery at an infection site can lower dosing necessary to eradicate the infection and, therefore, lower toxicity and the development of resistant bacteria.[83, 84] Ampicillin, a commonly used beta-lactam antibiotic, was chemically incorporated into a poly(anhydride-amide) backbone using a method similar to that described in Section 3.1 (Scheme 6).[85] Bearing a primary amine and a carboxylic acid moiety, ampicillin (**23**) was reacted with a diacyl chloride (e.g., sebacoyl chloride, **24**) to afford the diacid (**25**). Solution polymerization with triphosgene as coupling agent resulted in the poly(anhydride-amide) **(26)**. The antibiotic-based polymer was cytocompatible; however, polymer degradation/release studies revealed that the polymer did not completely hydrolyze to free ampicillin. Rather, the anhydride bonds hydrolyzed but the amides remained intact, i.e., only diacid **(25)** was observed in the polymer degradation media. Nonetheless, the disc diffusion assay showed that the diacid (**25**) exhibited antibacterial activity against *Staphylococcus aureus*. Although free ampicillin was not present in media, the diacid was determined to have antibacterial activity.

3.5. Analgesics

Opioids are a class of potent analgesic drugs used to treat severe pain.[86] Although they are widely used, opioids exhibit a short half-life,[87] necessitating frequent dosing, causing low patient compliance and a higher likelihood of tolerance development.[88] Moreover, opioids can be easily isolated from current formulations, leading to drug abuse and accidental overdoses.[89, 90] The chemical incorporation of opioids into a polymer backbone could decrease abuse potential all while providing sustained analgesia for patients. Morphine, the most widely used opioid, was chemically incorporated into a PAE backbone using a similar procedure outlined in Section 3.3.[91] Because morphine contains a phenol and secondary hydroxyl group, it was reacted with glutaric anhydride to produce the diacid. It was important to modify morphine such that the active groups (i.e., carboxylic acids) had equal reactivity, as the monomer underwent melt condensation polymerization to yield the PAE. Rather than a bioactive-linker-bioactive repeat unit motif, this PAE follows a linker-bioactive-linker motif (Figure 2B). Polymer degradation studies under physiological conditions revealed that free morphine was slowly released through hydrolytic cleavage of anhydride and ester bonds (Figure 12A). *In vivo* studies using intraperitoneal injection into mice determined that the analgesic effect of one dose of morphine-based polymer was sustained through 24 hours and for about 3 days, in comparison to the four hours of analgesia provided by free morphine (Figure 12B). Analgesia was evaluated via the tail flick latency (TFL) test, immersing the animal's tail in hot water and measuring pain response through the time it takes the rat to lift its out of water. Through chemical incorporation to a polymer, a therapeutic dose of morphine can be administered for days, a drastic improvement for patient care.

4. Tunability and Manipulations of PAEs

4.1. Linkers

Depending on the applications, different polymer degradation rates and bioactive release rates may be desired. When long-term bioactive release is required, such as medical device coatings and chronic disease treatments, polymers with slower degradation rates and longer

drug releasing windows are preferred. On the other hand, polymers with fast degradation rates are suitable where rapid bioactive release is needed, such as a cosmetic mask or topical cream. One effective way to control polymer degradation rate is to choose the appropriate linker molecule. PAEs with different linkers generally have different hydrophobicity and, thus, different hydrolysis rates. As an example, SA-based PAEs with a branched, hydrophobic diethylmalonic linker, released only ~18% of the SA incorporated in the polymer backbone in 30 days, whereas SA-based PAEs with a more hydrophilic malonic linker released 100% incorporated SA in 6 days.[63]

4.2. Copolymers and Blends

The combination of two polymer moieties, either through chemically copolymerizing two monomers or physically blending two polymers, can alter polymer mechanical properties, thermal properties and degradation rates, making them more versatile as needed for various applications. Chemical copolymerization of SA-based (sebacic) PAE and para-carboxyphenoxyhexane (pCPH) repeat units (Figure 13) yielded a copolymer with significantly higher T_g compared to the SA-based homopolymer (33 °C versus 27 °C), which greatly enhanced its processability at room temperature.[92] In addition, different ratios between the SA-based (sebacic) PAE and pCPH units resulted in different copolymer properties: higher pCPH percentage yielded copolymers with lower tensile strength, lower Young's modulus, lower ultimate elongation and lower toughness as the pCPH unit is more brittle than the SA-based unit.[92] Copolymers with more pCPH units were also more hydrophobic, which led to a slower hydrolytic degradation rate and, thus, less significant changes in polymer properties when incubated in PBS.[92] These parameters are important for choosing bioactive-releasing implant materials with stable properties after implantation.

Physical blending of polymers is another method to tune properties. For example, blending an SA-based PAE with a more ductile polymer, such as poly(lactic-*co*-glycolic acid) (PLGA) or polycaprolactone (PCL), can form flexible electrospun mats that is not possible with SA-based PAE alone as it is too brittle.[93] The physical combination of SA-based PAE and polyvinylpyrrolidone (PVP) yielded a much more hydrophobic system than SA-based PAEs yet was able to absorb a significant amount of water to form a hydrogel.[94] These different properties allow a broad range of applications of the SA-based PAEs, such as flexible wraps, wound dressing, nerve guidance conduits, etc.[93, 94]

4.3. Admixtures

Physical admix of bioactive compounds within polymer matrix has been intensively studied for decades by numerous laboratories. Taking the advantages of bioactive-based polymers and the various admixing methods, the Uhrich lab was able to physically incorporate secondary bioactive compounds into the bioactive-based polymers and generated dual-delivery systems, i.e. as the polymer degrades, both the admixed bioactive and the bioactive incorporated in the polymer are concurrently released. Molecules being admixed range from small molecules such as SA and antimicrobials (chlorhexidine, clindamycin, minocycline) to relatively bulky and complex proteins, such as insulin and fibroblast growth factor-2.[95–98] Concurrent release of the bioactive agents was observed (release time window ranging from ~6 days to ~2 weeks) with well-maintained chemical structures and bioactivities.[95, 96, 98]

Such dual-delivery systems are of particular interests to many applications. For example, SA-based PAEs with admixed antimicrobials delivers an antimicrobial and an anti-inflammatory drug at the same time, which may be an effective combination in treating infections. Furthermore, the combination of insulin and SA-based PAEs is a promising system to treat diabetes as the synergistic effects between insulin and SA have been clinically well-established.[99–106]

4.4. Versatility of Formulations

Polymers are well-known for their versatile formulations, such as films, hydrogels, microspheres, coatings, and fibers. These bioactive-based polymers can be formulated with high drug loading that is not feasible to achieve using free bioactive molecules alone admixed into polymer matrices. For example, salicylic acid can be formed into tablets, but it cannot be formulated into microspheres.

SA-based PAEs with various linkers have been formulated into microspheres using standard oil/water emulsion method and yielded microspheres with smooth surface and well-defined spherical geometry (Figure 14).[96, 98] Encapsulation of proteins into bioactive-based polymer microspheres was also achieved using the standard water/oil/water emulsion technique.[96, 98] One example is the encapsulation of insulin into SA-based PAE microspheres, which yielded microspheres with smooth spherical geometry, high insulin loading (4.1%) and high insulin loading efficiency (~82.6%). Insulin and SA were concurrently released from the microspheres in PBS for about two weeks and their *in vitro* and *in vivo* bioactivities were well maintained.[98]

Other formulations include compressed polymer disks, solvent-casted and spin-coated SA-based PAE films, and dip-coated tubes of SA-based PAE and poly(lactic acid) blends.[30, 67, 107] All these systems were able to release the bioactive in a sustained manner.

5. Future Directions

5.1. Green Chemistry and One-pot Synthesis

As the use of biodegradable polymers is continuously increasing toward various biomedical applications, the design and synthesis of these polymers with chemical approaches that eliminate the use or generation of toxic substances are essential. During biodegradable polymers synthesis, chemists can significantly reduce the risks to human health by implementing the Principles of Green Chemistry.[41] For instance, utilization of non-hazardous reactant monomers, safe solvents, and enzymatic catalysts could be investigated. Furthermore, simplification of procedures during polymer synthesis (i.e. reducing number of steps) is another way of applying green chemistry principles.

As illustrated in Section 2.2, green chemistry is one of the primary criteria considered in biodegradable polymer synthesis. In the previously described example,[33] solvent-free reactions and a naturally occurring catalyst were exploited to establish a green synthesis of PEs. Similarly, an alternative approach was developed for the preparation of the polymer precursor that minimized the number of synthetic steps and increased the overall yield. Scheme 7 demonstrates the three-step synthesis of SA-linker-SA type monomer with a less

than 50% overall yield. However, with the new approach the same monomer was obtained by a direct coupling of SA and acyl chloride in one step through the acyl-pyridinium intermediate formation. One-pot synthesis and simple purification methods for the diacid monomer greatly enhanced the overall yield up to 97%. Among several solvents evaluated, polar aprotic tetrahydrofuran (THF) was preferred due to its low boiling point. By using various alkyl- and aryl- based acyl chlorides in the place of sebacoyl chloride, a wide variety of similar diacid monomers have been prepared following this procedure.[60] Given the simplicity and ease of diacid isolation, this one-step method is the preferred choice for preparing a variety of diacids that will undergo melt condensation to yield PAE. This synthetic methodology was further improved by utilizing a one-pot method that eliminated solvent use and drastically decreased reaction time without impacting PAE properties.[64] This implementation not only minimizes the use of hazardous components, but also improves the overall efficiency and yield of the total process, which enables the industrial level scale-up and low-cost manufacturing.

5.2. Dual Delivery and Synergism of Bioactives

The synergistic treatment approach has emerged as an effective and promising strategy for therapeutic applications, especially for cancer treatments. Combined therapy through simultaneous administration of two or more drugs (i.e., a drug and a genetic component), is found to have greater therapeutic efficacy compared to individual use of each drug.[108] This enhanced therapeutic effectiveness is mainly due to the synergism amongst the drugs that suppress drug resistance (i.e., chemoresistance) following distinct biological mechanisms.[109] As delivery of therapeutic agents without a nanocarrier system results in its rapid degradation in the bloodstream and low accumulation levels at the tumor site,[110] a large number of biocompatible nanoscale delivery systems such as liposomes,[111] micelles,[112] nanoparticles[113] have been developed. Prolonged circulation half-lives, improved accumulation, and limited collateral damage on healthy tissue make these nanovehicles more efficient and safer drug delivery systems. In recent years, a great effort has also been dedicated to develop single nanocarrier systems for the co-delivery of multiple types of therapeutic agents. Although, some of them exhibit sophisticated designs, several have unique features that enable a great level of control over the delivery properties.[114]

Biodegradable salicylate-based poly(anhydride-esters) have proven to be excellent delivery platforms for bioactives - ranging from small antimicrobial molecules to relatively complex therapeutic agents, examples of which were discussed in Section 4.3. To date, sustained and concurrent release of encapsulated bioactives as well as salicylic acid has been successfully demonstrated. Currently, we are striving to chemically incorporate specific targeting groups to the polymeric backbone together with the bioactive moieties. The encapsulation of complex and bulky biotherapeutic agents within this type of polymer matrix, would make it a highly efficient and elegant biodegradable delivery system. Moreover, controlled and sustained release of the actives as well as achieved synergism among them would make this type of delivery systems very promising for dual treatment approach.

In this review, current progress in polymeric bioactives developed by the Uhrich group are highlighted. Both pendant group and backbone attachment approaches prove to be rational

strategies in the designing of bioactive-based polymeric systems. Examples of both type of systems illustrated in this review have successfully demonstrated the delivery of different classes of bioactives in a sustained manner. Moreover, reported dual-delivery systems to concurrently release multiple bioactives proved to be very promising in terms of certain applications Future works will include incorporating multifunctional bioactives and targeting moieties into PAEs while further exploring green chemistry synthetic methodologies. Research to develop more practical and efficient polymeric delivery systems is under progress in Uhrich group. With thousands of small molecule bioactives available, this approach can be applied to generate a plethora of new compounds.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Notes and references

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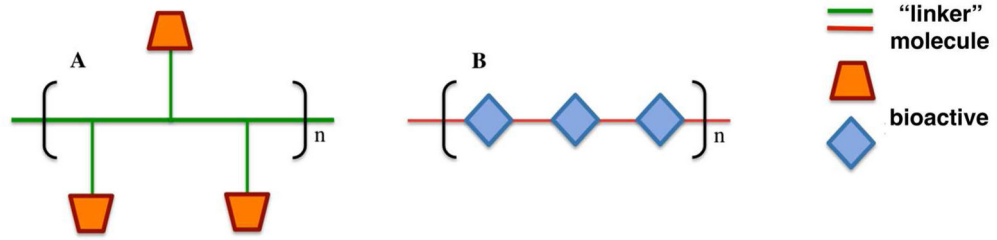
Figure 1.
Pendant (**A**) versus backbone (**B**) incorporation of drug to polymer
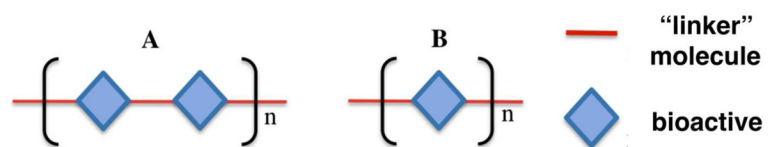
Figure 2.
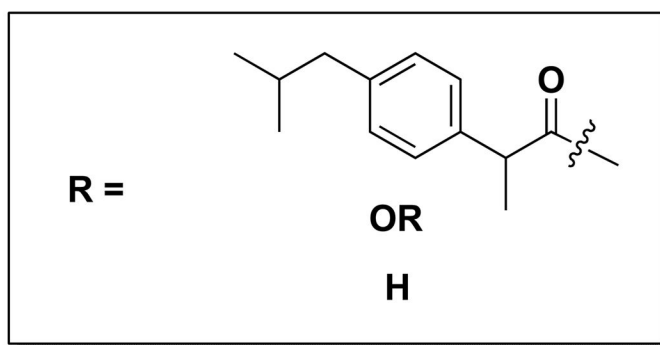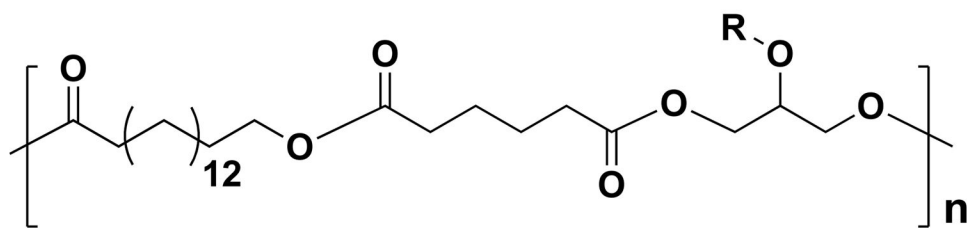Bioactive attachment within polymer backbone: drug-linker-drug (**A**) versus linker-drug-linker (**B**)

Figure 3.
Structure of PGA-co-PL with pendant ibuprofen. R group will vary between H and ibuprofen depending on drug loading
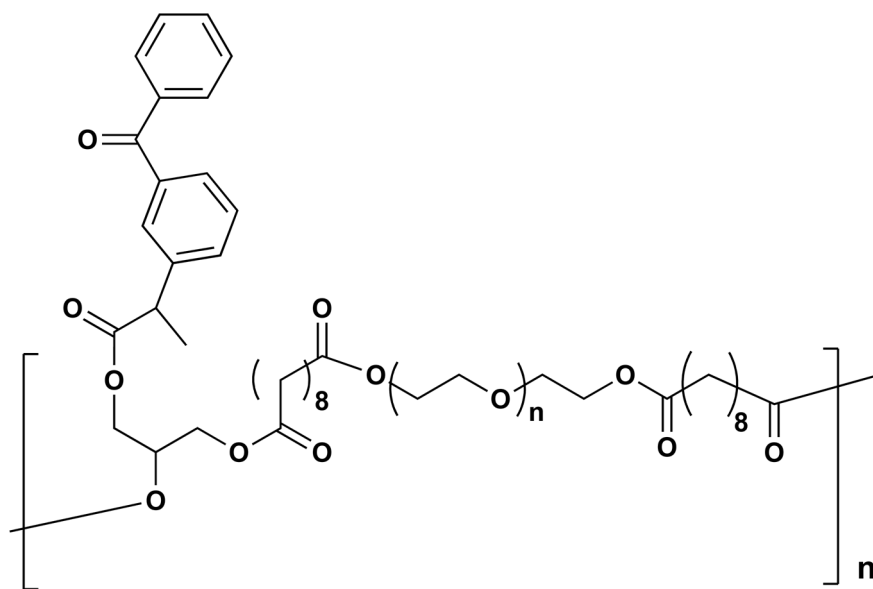
Figure 4.
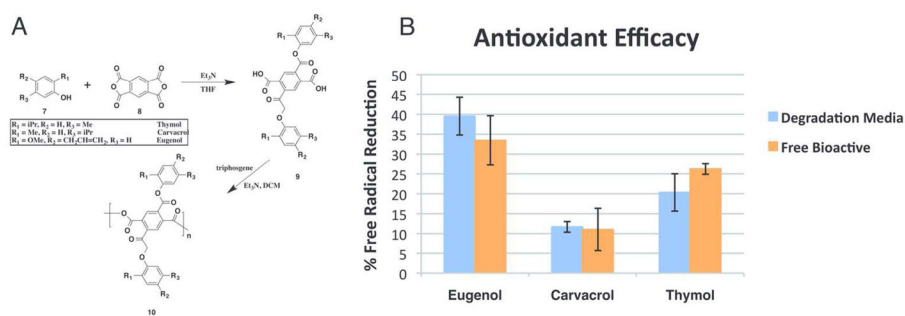Structure of ketoprofen polyester prodrug with sebacate, PEG, and glycerol backbone

Figure 5.
(**A**) Synthesis of phenol-containing PAEs with pyromellitic linker. (**B**) DPPH reduction results comparing phenols released from EDTA polymer with free phenols. Adapted with permission from Carbone-Howell A, et al. Biomacromolecules **2014**, 15 (5), 1889. ©2014 American Chemical Society
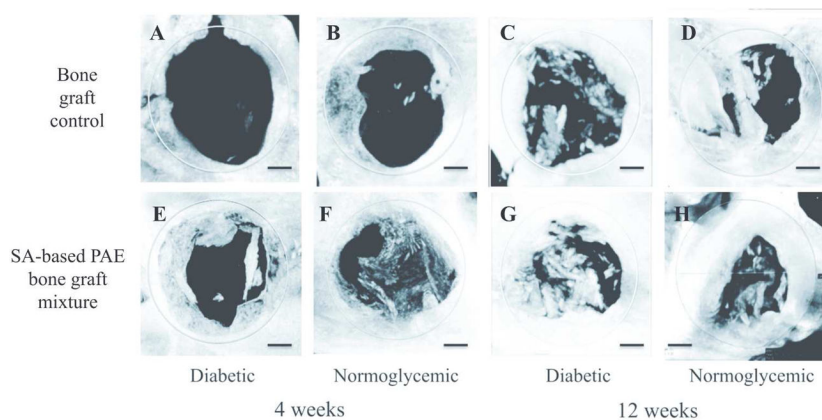
Figure 6.
Micro-CT images of bone formation within bone defect regions in diabetic (A, C, E, G) and normoglycemic (B, D, F, H) rats implanted with SA-based PAE and bone graft mixture (E, F, G, H) or with bone graft control alone (A, B, C, D). Scale bar = 1 m Adapted with permission from Wada K, et al. Journal of Controlled Release **2013**, 171 (11), 33. ©Elsevier B.V.
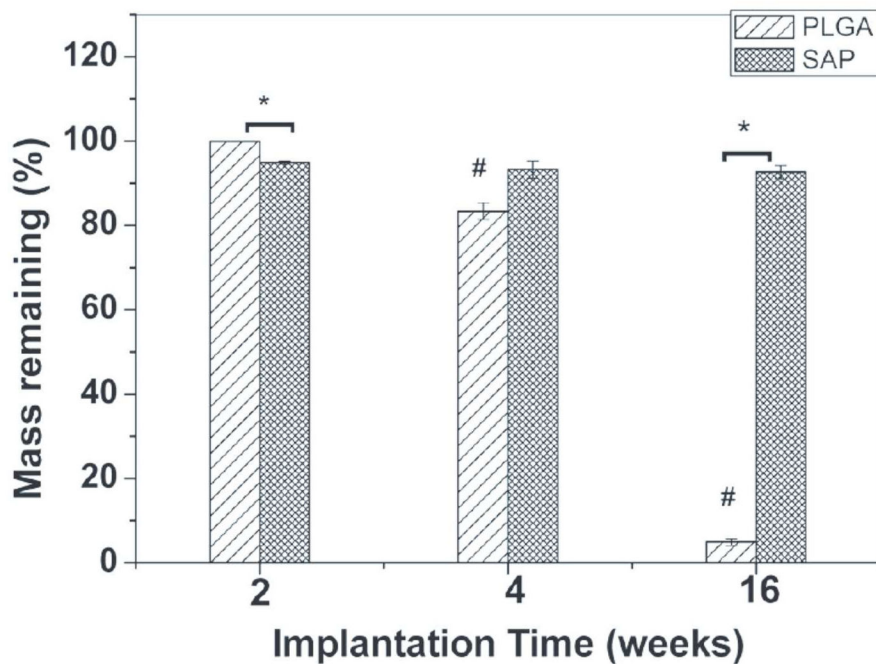
Figure 7.
Normalized in vivo mass loss of SAP and PLGA at weeks 2, 4, and 16 where * is statistical significance ($p < 0.05$) of SAP compared to PLGA and # is statistical significance ($p < 0.05$) is PLGA compared to PLGA 2 weeks post-implantation. Adapted with permission from Chandorkar Y, et al. Biomacromolecules **2015**, 16 (2), 636. ©2013 American Chemical Society
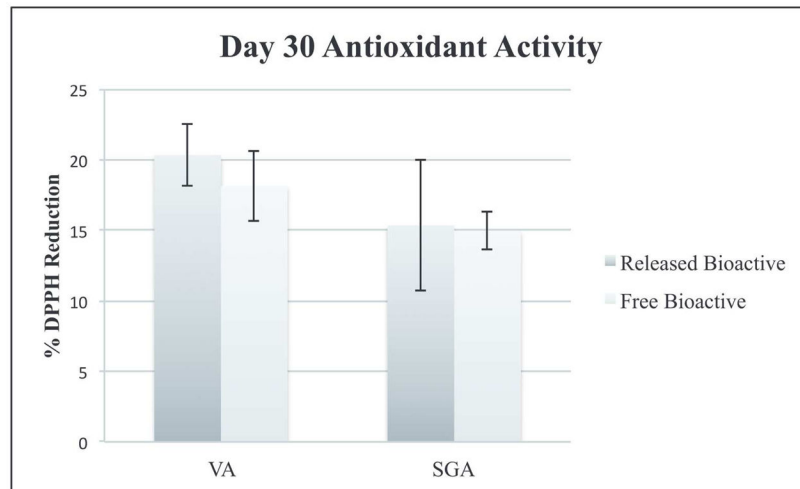
Figure 8.
Antioxidant activity of VA and SGA released from adipic-based PAEs compared to free bioactives at identical concentrations.
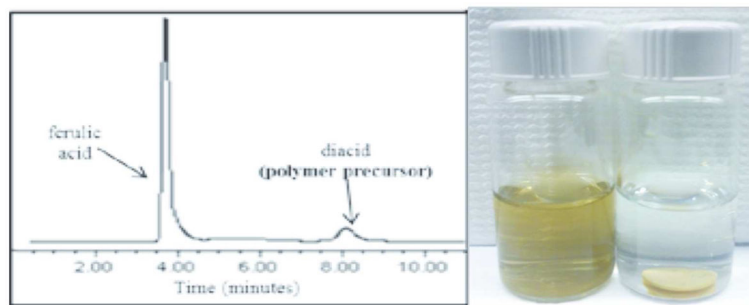
Figure 9.
A. FA (adipic) PAE high-performance liquid chromatography (HPLC) chromatograph demonstrating no FA degradation peaks. **B.** Free ferulic acid (left) and FA polymer containing the same amount of FA (right) after 20 days in PBS, illustrating a lack of yellowing indicative of decomposition in FA-based PAE media
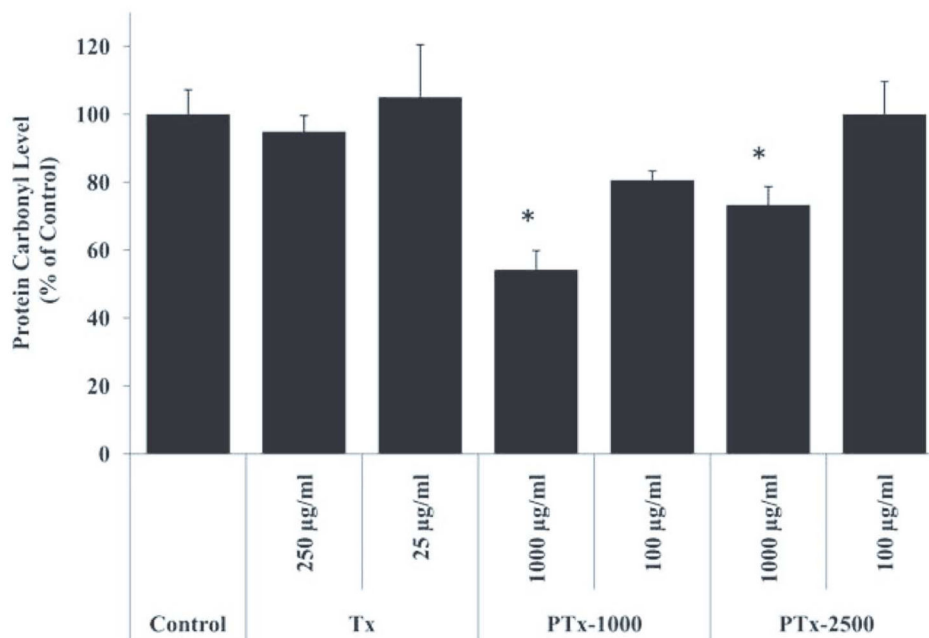
Figure 10.
Protein carbonyl content in human umbilical vein endothelial cells following 24 h treatment with two concentrations of Tx, and PTx. PTx treatment conducted with oligomeric PTx (PTx-1000) and polymeric PTx (PTx-2500). Protein was collected after lysing of cells and analyzed. A one-way ANOVA conducted on the data set revealed a significant trend (p < 0.05) for protein carbonyl levels Adapted with permission from Paritosh P, et al. Journal of Biomedical Materials Research **2011**, 99 (2), 184. ©2013 John Wiley and Sons
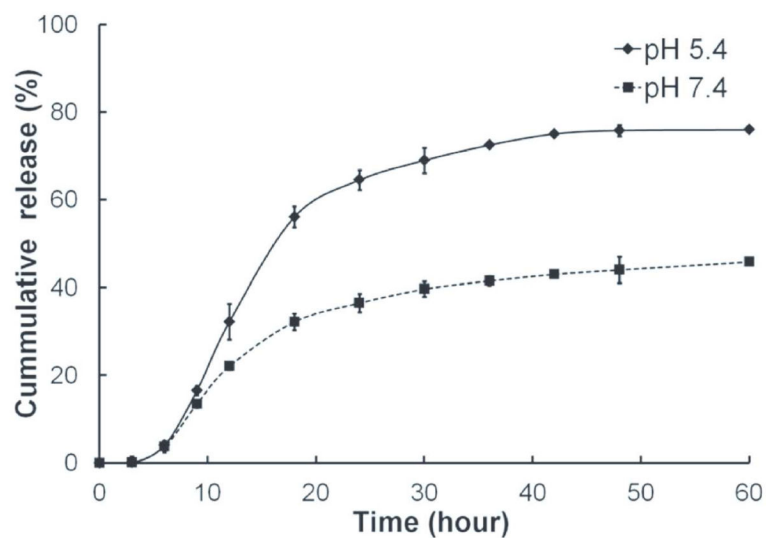
Figure 11.
Cumulative release of vanillin from PVO nanoparticles under physiological and endosomal conditions as determined by HPLC Adapted with permission from Kwon J, et al. Biomacromolecules **2013**, 14 (5), 1618. ©2013 American Chemical Society
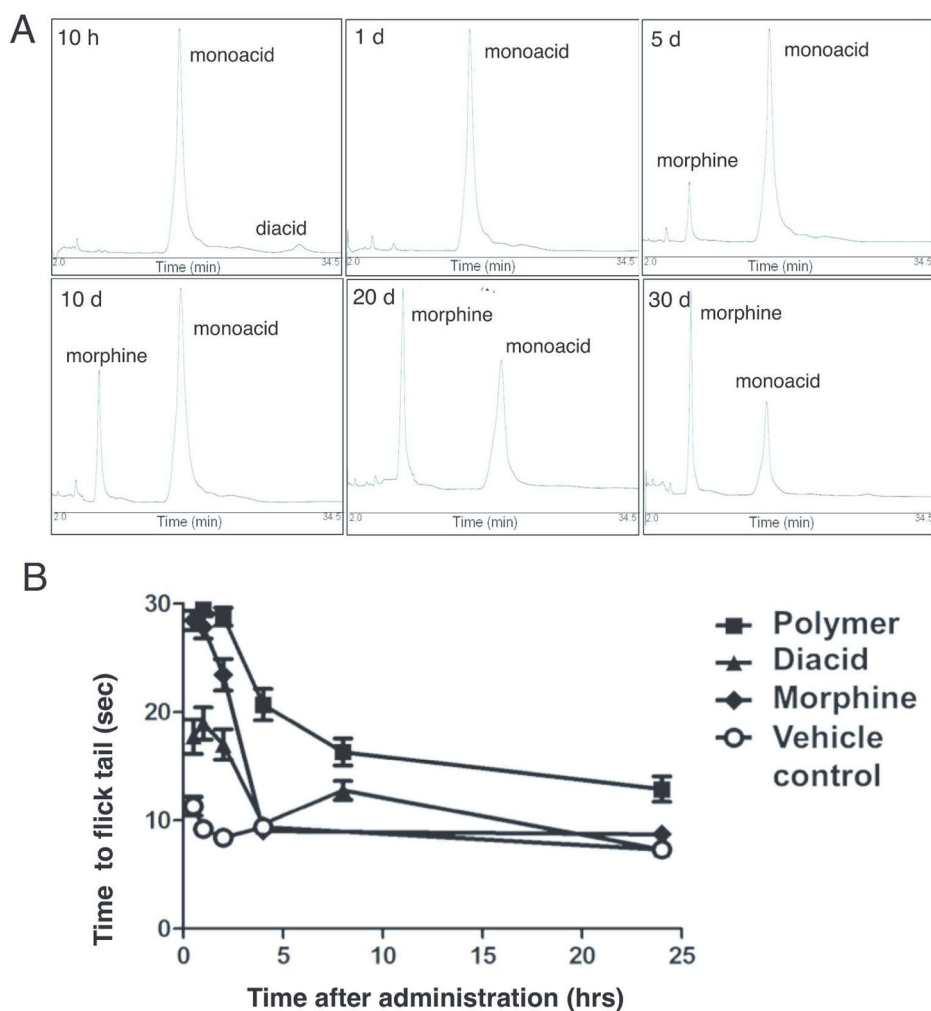
Figure 12.
(A) HPLC chromatograms from in vitro degradation study depicting morphine-based polymer breaking down into diacid, monoacid, and morphine at time points indicated in upper left; (B) In vivo TFL test results showing prolonged analgesia for morphine-based polymer compared to free morphine. Adapted with permission from Rosario-Melendez R, et al. Journal of Controlled Release **2012**, 162, 538. ©2012 Elsevier B.V.

carboxyphenoxydecanoate (CPD) repeat unit

para-**carboxyphenoxyhexane (*p*CPH) repeat unit**
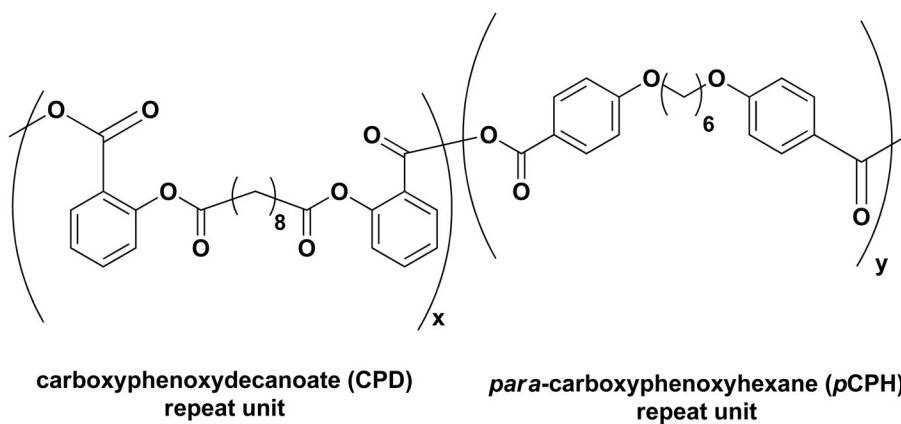
Figure 13.
Structure of SA-based (sebacic) PAE and pCPH copolymer
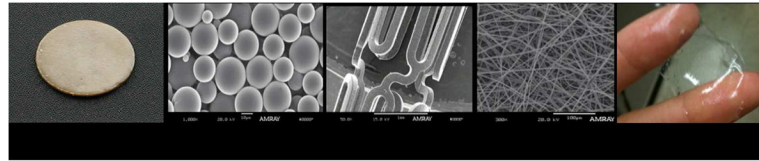
Figure 14.
Versatile formulations of SA-based PAEs
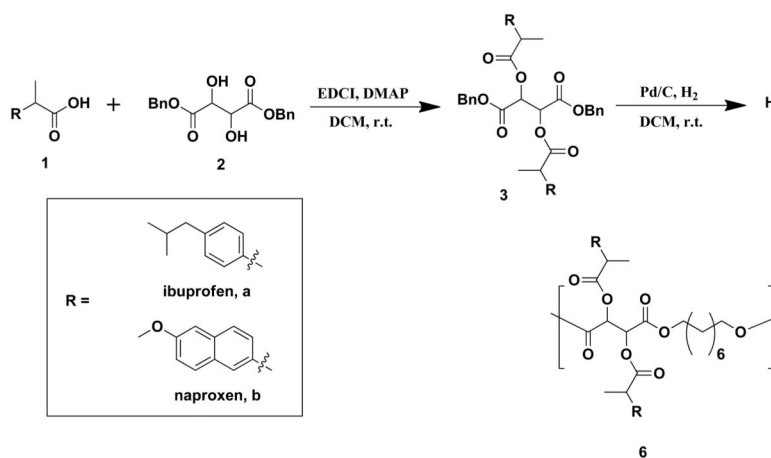
Scheme 1.
Synthesis of ibuprofen- and naproxen-containing PEs using tartaric acid as a backbone.
Adapted with permission from Rosario-Melendez R, et al. Macromolecules **2013**, 14 (10), 3542. ©2013 American Chemical Society
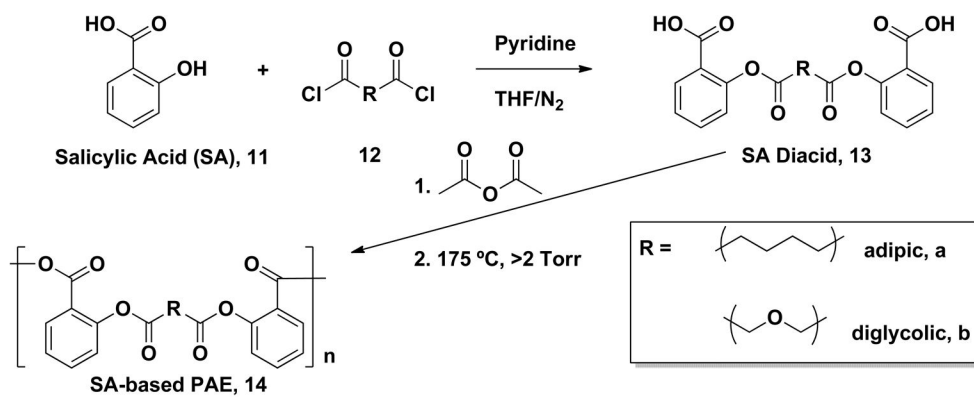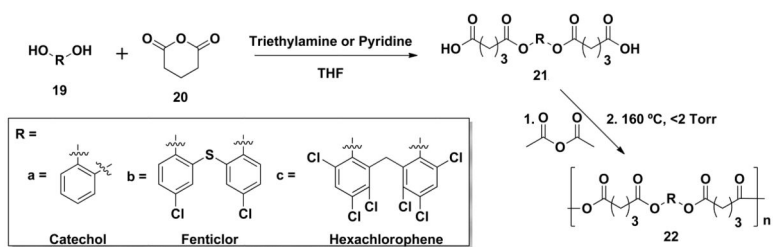
Scheme 2.
Synthetic scheme for SA-based PAEs with adipic (**a**) and diglycolic (**b**) linkages
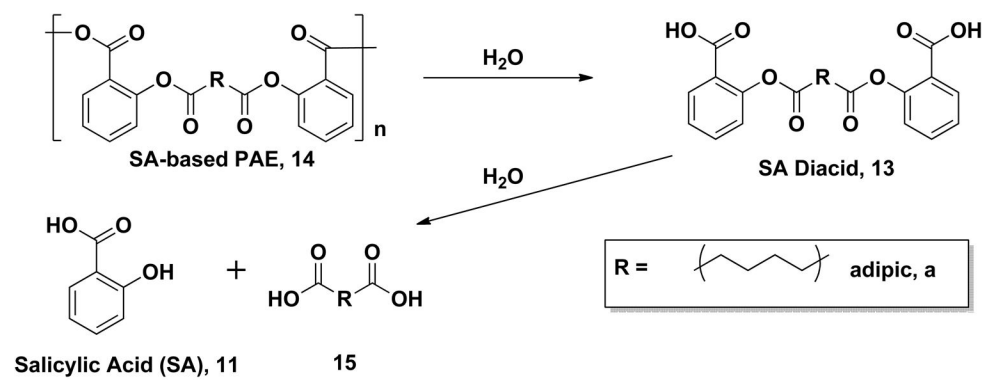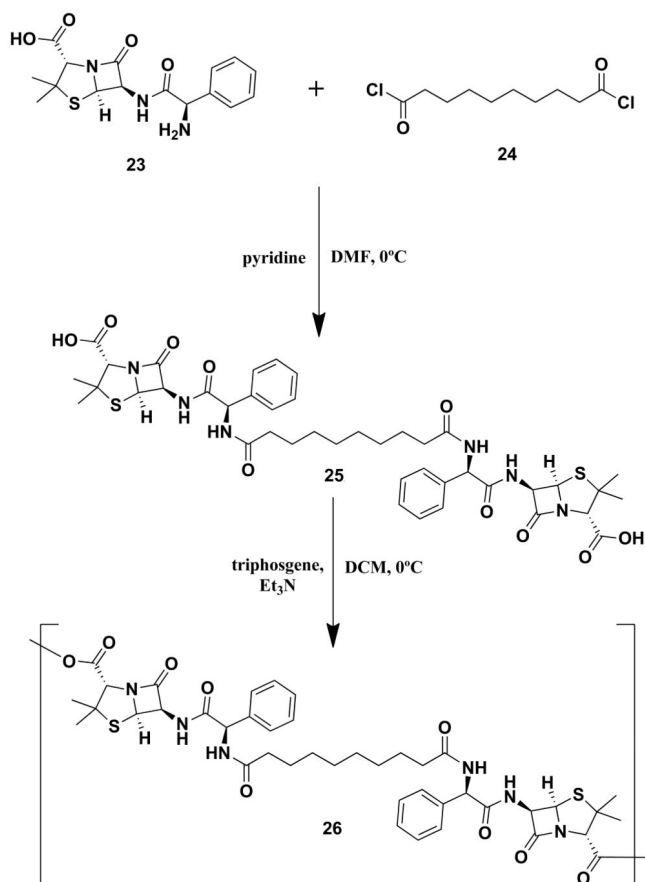
Scheme 3.
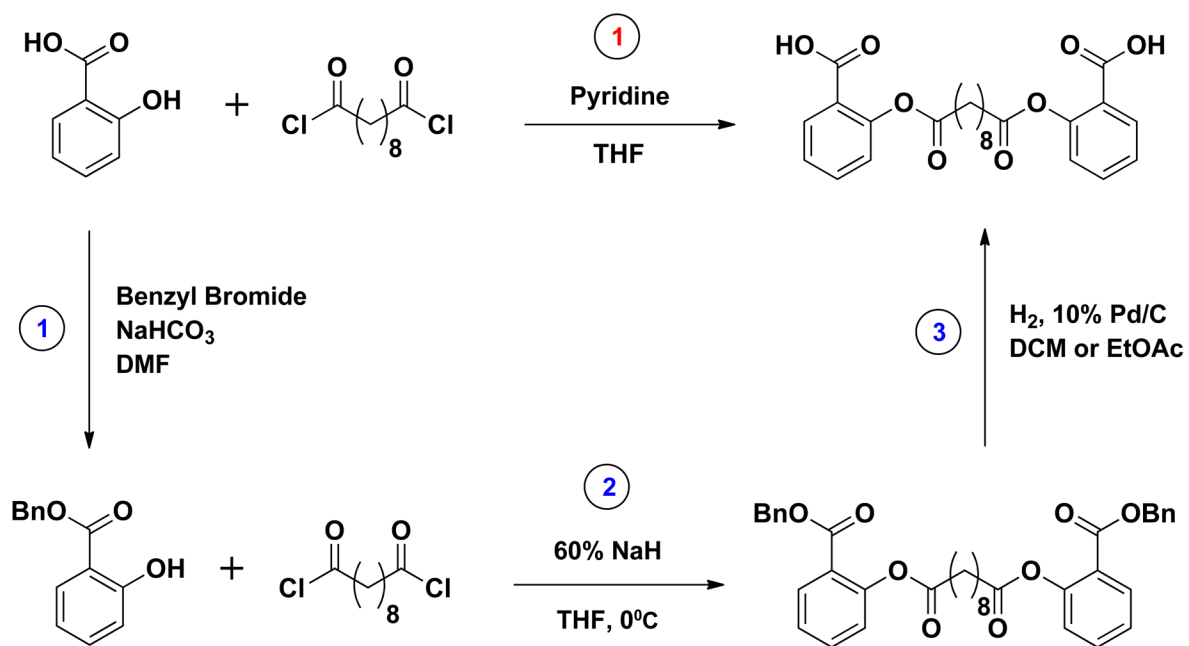Hydrolysis of SA-based (adipic) PAE into SA (**11**) and adipic acid (**15**)
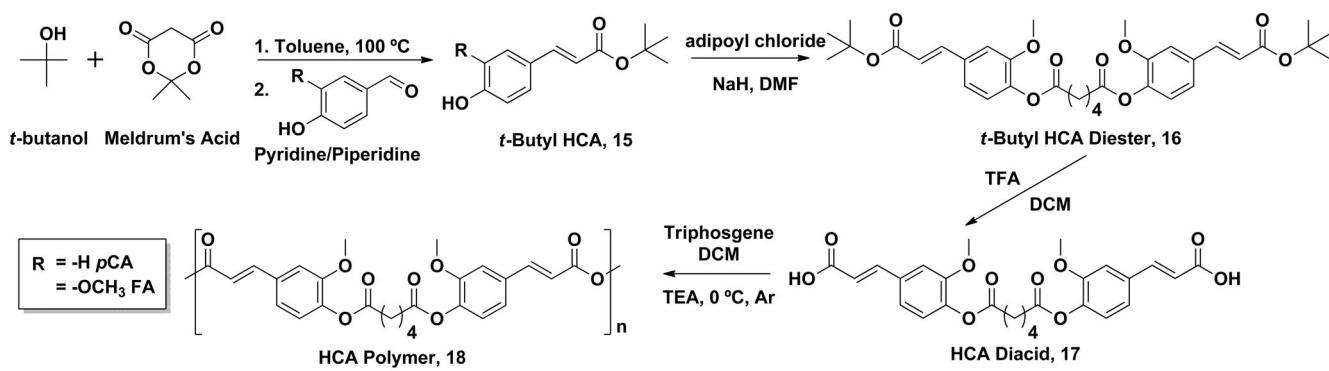
Scheme 4.
Synthesis of HCA (adipic) PAEs and polymer precursors.

Scheme 5.
Synthesis of bis-phenol, antiseptic-based PAE precursors (**21**) and polymer (**22**) through modified linker-bioactivelinker approach

Scheme 6.
Synthesis of ampicillin-containing poly(anhydride amide) (**26**)

Scheme 7.
Comparison of three-step method versus optimized one step method to synthesize salicylic acid sebacic diacid