Expert Review

Recent Developments in Cyclic Acetal Biomaterials for Tissue Engineering Applications

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Abstract. At an ever increasing pace, synthetic biomaterials are being developed with specific functionalities for tissue engineering applications. These biomaterials possess properties including biocompatibility, mechanical strength, and degradation as well as functionalities such as specific cell adhesion and directed cell migration. However, synthetic polymers are often not completely biologically inert and may non-specifically react with the surrounding *in vivo* environment. An example of this reactivity is the release of acidic degradation products from hydrolytically degradable polymers based upon an ester moiety. In order to address this concern, a novel class of biomaterials based upon a cyclic acetal unit has been developed. Scaffolds suitable for the replacement of both hard and soft tissues have been successfully fabricated from cyclic acetals and a detailed characterization of scaffold properties has been performed. Cyclic acetal based biomaterials have also been used to repair bone defects and promote bone growth, displaying a minimal inflammatory response. This review will discuss the most recent research of current biomaterials and cyclic acetals, and particularly focus on the tissue engineering applications of these materials. Finally, this review will also briefly discuss polyacetals and polyketals for drug delivery applications.

KEY WORDS: biomaterial; cyclic acetal; polyacetal; polyketal; tissue engineering.

INTRODUCTION

Biomaterials fabricated from synthetic polymers have been exhaustively developed so as to possess both biocompatible and bioactive properties for biomedical and tissue engineering applications (1–3). Depending upon each application, a newly developed polymer needs to meet a specific set of requirements. As a result, numerous studies have tailored polymers for individual applications by precisely controlling their chemical and physical properties (4–8). For example, synthetic polymers have been fabricated into specific shaped materials with desired pore morphologies to promote tissue in-growth (9–11). Indeed, a number of synthetic polymers have been successfully developed, and are now used widely in clinical applications (12,13).

A major advantage of synthetic polymers is that they may be modified to support the incorporation of drugs, chemical moieties, cells, implants and devices, as well as micro- and macro-molecules (14–16). Furthermore, specific biological functions can be pre-programmed into polymer materials by incorporating any of a variety of molecules, including ligands, hormones, proteins, peptides, nucleotides,

drugs, enzymes, vectors, and antibodies (17–19). Together, these physical and biological properties can create an optimal biomaterial whose main function is to act as a tissue substitute. With the diversity of matrix components available, however, it may be possible for the polymeric biomaterial to provide additional functionalities so as to ultimately act as a tissue replacement, or engineered tissue. *In vivo*, polymeric biomaterials should facilitate cellular proliferation and differentiation, as precursors to the synthesis of a new organic extracellular matrix. To successfully promote cellular and tissue regeneration, synthetic polymers must first work in concert with the surrounding tissue, and thus elicit a short and mild inflammatory response. The surrounding tissue response is especially critical in the development of degradable polymeric biomaterials. In particular, these biomaterials should possess degradation properties that do not lead to a long and pronounced inflammatory reaction (20,21).

Recently, a number of investigators have shifted their focus to fabricating degradable, biomedical polymers that produce less toxic degradation products, therefore decreasing the inflammatory response of the surrounding tissue. For example, synthetic polymers based upon degradable units such as acetals, cyclic acetals, and ketals have been developed and shown to degrade via hydrolysis to produce hydroxyl and carbonyl terminals (22–24). While the specific chemical structure of each degradation product is monomer and reaction specific, the products are typically alcohols, carbonyls, aldehydes, and ketones. This review will discuss the current research, development, and potential applications of newly developed acetal, cyclic acetal, and ketal based

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polymers. Further, this review will describe some of the encouraging physical, chemical, and biological properties of the resulting polymeric biomaterials, making them attractive candidates for a wide range of tissue engineering and drug delivery applications.

CURRENT DEGRADABLE BIOMATERIALS

Polymeric biomaterials vary widely both in material properties and applications. Tissue engineering applications require the consideration of properties such as biocompatibility, mechanical strength, and degradation. In the related field of drug delivery, however, the emphasis on mechanical strength is often replaced with the ability to release bioactive molecules. Overall, the importance given to each property is often application dependant and while many materials fulfill individual needs, there is still a requirement for a universally ideal material.

Polyesters

Polymers based upon a repeating ester unit are probably the most widely investigated biomaterials for biomedical and tissue engineering applications. Polyesters have been found to be largely biocompatible, along with possessing a wide range of mechanical and degradation properties. The simplest polyester is poly(glycolic acid) (PGA). PGA can easily be synthesized via the ring-opening polymerization of glycolide (25). PGA is most notably used in the clinical setting as resorbable sutures, but is currently being investigated in several other biomedical applications (26). PGA is a hydrophilic polymer which has a highly crystalline structure (26). PGA degrades via bulk degradation, where mass loss occurs throughout the material while initial dimensions (or volume) of the material remains mostly constant (27). Due to the mass loss, PGA materials exhibit a significant decrease in mechanical strength as the material degrades (26,28,29). In an effort to increase PGA's utility and slow it's degradation, PGA is often used as a co-polymer with poly (L-lactic acid) (PLLA) or poly(D,L-lactic acid) (PLA).

PLLA and PLA are structurally similar to PGA, with the exception of the presence of a chiral methyl group. PLLA and PLA have a semi-crystalline structure and are hydrophobic in nature. The increased hydrophobicity leads to an increase in degradation rate compared to PGA (26,30–32). To increase the hydrophilicity of PLLA and slow the degradation rate of PGA, co-polymers with PLLA have been developed, such as the widely investigated poly(D,L-lactic-co-glycolic acid) (PLGA). A significant clinical application of the PLGA copolymers is in drug delivery, where injectable PLGA microspheres are utilized to deliver leuprolide acetate in a controlled profile (30–32).

Poly(ε-caprolactone) (PCL) is a semi-crystalline polymer similar to PLA (26). PCL has been extensively used for drug delivery applications due to its high permeability to drugs and long term sustainability *in vivo* (26,33,34). The bulk degradation of PCL is a slow process on the order of one to three years. In an attempt to increase its degradation rate, PCL has been increasingly used in the synthesis of co-polymers and polymer blends with poly(ethylene glycol) (PEG), poly

(ethylene oxide) (PEO), poly(hydroxybutyrate-*co*-hydroxy-valerate) (PHBHV), PLLA and PLGA (35–38).

Poly(propylene fumarate) (PPF) is a linear polyester which hydrolytically degrades into fumaric acid and propylene glycol (39). Due to the presence of carbon-carbon double bonds within the repeating unit of PPF, PPF may be covalently crosslinked to fabricate a rigid biomaterial. Previous studies have demonstrated that PPF crosslinking may be initiated by either thermal or photo activated initiators (40,41). The physical properties of the PPF crosslinked networks, including the rate of degradation, are heavily influenced by the fabrication procedure (26,42). Particulate materials, including carbon nanotubes, have been incorporated within PPF to increase its mechanical strength, especially critical in bone tissue engineering applications (43–45). *In vivo* studies of both the tissue response to PPF and the functionality of PPF scaffolds have indicated that the polymer promotes a mild inflammatory response similar to other polyester materials (46,47).

Polyanhydrides

Polyanhydrides are synthesized from diacid monomers, as opposed to the polyesters' single acid monomer, and they degrade hydrolytically at the anhydride linkages into diacid products. Polyanhydrides are especially desirable due to their surface erosion degradation properties (26,48,49). Surface erosion occurs from the surface of the material, as opposed to bulk degradation which occurs throughout the material. Biomaterials that degrade through a surface mechanism retain their density, as mass is lost from the surface. The degradation rate of polyanhydrides has been shown to be largely controlled by the polymer backbone structure. Since the mechanical properties of polyanhydrides are generally modest, co-polymers and crosslinked polyanhydrides have been developed for bone tissue engineering applications (26,50). Polyanhydrides have also been used clinically as drug delivery materials (26,51,52).

While polyesters and polyanhydrides are all widely characterized and under development for biomedical applications, they are not biologically inert and may non-specifically react with the surrounding *in vivo* environment (53). Polyesters and polyanhydrides, as well as other similarly structured polymers, degrade via hydrolysis and give rise to products with carboxylic acid terminal groups. Thus their degradation may create an acidic regenerative environment which can prolong the inflammatory response and accelerate the degradation of the material, leading to premature loss of mechanical and structural properties (54,55). Previous studies have also shown that accumulation and increased concentration of acidic degradation products can induce tissue toxicity (28,29,56). To address these issues, a new class of synthetic, polymeric biomaterials based upon degradable units such as acetals, cyclic acetals, and ketals have been developed (22,24,53).

CYCLIC ACETAL BIOMATERIALS

Cyclic acetal biomaterials (CAB) are a novel class of biomaterials consisting of a six member ring structure based upon a cyclic acetal unit. The cyclic acetal unit hydrolytically

degrades, forming products terminated with diol and carbonyl end groups. Recent studies have described the development of CAB's for tissue engineering applications (22,57–59).

CABs are most easily fabricated by radical polymerization of the monomer 5-ethyl-5-(hydroxymethyl)-β,β-dimethyl-1,3-dioxane-2-ethanol diacrylate (EHD). Although available commercially through the early 2000s, to the best of our knowledge the EHD monomer is no longer commercially available. However, the EHD monomer may be easily synthesized in approximately 4 days (60). Briefly, isobutyraldehyde and formaldehyde are reacted with potassium carbonate. The product is then extracted using chloroform and is washed with water and brine. The resulting solution is dried under vacuum overnight, producing the solid product, 3-hydroxy-2,2-dimethylpropionaldehyde (HDP). HDP is then reacted with trimethylolpropane in 1 M hydrochloric acid. The solution is neutralized with sodium hydroxide and the resulting product, hydrolyzed EHD (HEHD), is extracted, washed with water and brine, purified by ether precipitation, and then dried overnight under vacuum. Finally acrylate terminal groups are added to the monomer. Here, HEHD is combined with triethylamine and acryloyl chloride. The final EHD product is extracted, washed, and purified by silica chromatography (60).

It should be noted here that although the EHD monomer does allow for the fabrication of a polymer network whose backbone is formed by hydrolytically degradable cyclic acetal units, the use of acrylates in the crosslinking chemistry will form degradation products with terminal carboxylic acids. Future development of CABs will attempt to eliminate the acrylate based crosslinking chemistry, and therefore completely remove acidic degradation products.

EH Networks

A number of disparate biomaterials may be fabricated from the EHD monomer. The simplest material is a EH network, where the EHD monomer is radically polymerized in to a network, using the initiator benzoyl peroxide (BP) and the accelerant N,N-dimethyl-p-toluidine (DMT) (Fig. 1).

A recent study focused on the effects of initiator, accelerant, and diluent content on the physical properties of the EH networks (22). Investigated properties included gelation time, reaction temperature, swelling degree, sol fraction, swelling degree, and cytotoxicity. Results showed that EH network gelation time varied between 33.3 and 193.9 s, with the gelation time decreasing with increased BP content. Maximum reaction temperature also increases from 31.9°C to 109.0°C with an increase in BP content. These gelation times and reactions temperatures are similar to the clinically relevant range for injectable biomaterials, however the utility of EH networks as an injectable biomaterial has not been fully investigated. Overall, results indicated that initiator and accelerant had the greatest effect upon the rate of reaction, as demonstrated by gelation time and maximum reaction temperature (22). As EH networks are hydrophobic, they do not swell in water, however swelling in organic solvent can be utilized to describe network formation. Results showed that EH network swelling varied between 29.9% and 48.3%, while network sol fraction varied from 22.0% to 45.0%. The results demonstrated that diluent content had the greatest effect upon swelling degree and sol fraction, and therefore most significantly affected the extent of the network forming reaction. Finally, results also indicated that EH networks could support the adhesion and viability of osteoprogenitor cells. There was a significant difference in osteoprogenitor cell viability between all experimental groups and the tissue culture polystyrene control at 4 h, however viability at 8 h was comparable to the control for the experimental group containing high amounts of initiator and diluent. Thus, the results imply that EH networks can be fabricated with controlled properties and also support osteoprogenitor cell adhesion and viability (22).

Additional investigations have characterized the degradation of the EHD monomer as well as EH networks. In terms of the monomer, EHD was degraded under acidic
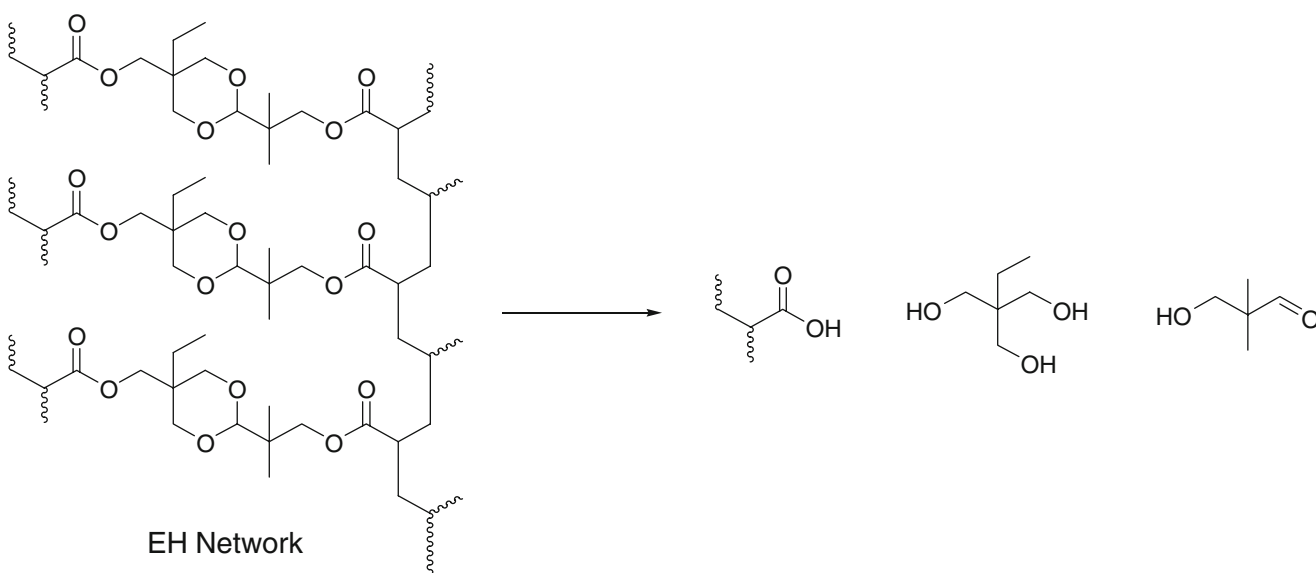

Fig. 1. Chemical structure of 5-ethyl-5-(hydroxymethyl)-β,β-dimethyl-1, 3-dioxane-2-ethanol diacrylate (EHD) cyclic acetal networks and its degradation products (22).

conditions (pH 2 and pH 4) and the solvent was analyzed for the degradation products of trimethylolpropane and HDP using ^{1}H NMR. Results showed that at temperatures of 65°C, 80°C and 90°C these products were indeed realized, and that their release followed first order kinetics (60).

Since the monomer does demonstrate hydrolytic degradation, the degradation rate of both porous and non-porous EH networks was evaluated. Macroporous EH scaffolds were prepared using a leachable porogen strategy. Briefly, macroporous networks were fabricated by incorporating a NaCl porogen (70, 75, and 80 wt%) into the EHD monomer solution prior to cross-linking. EH networks were formed around the crystals by radical polymerization, and the porogen was removed by water leaching. The results confirmed that while degradation occurred in all networks, the rate of degradation was enhanced with the addition of the macropores (Fig. 2a). Solid EH networks, which are highly hydrophobic and resist water absorption, lost approximately 3.5% of their mass after 28 days. By incorporating macropores however, the degradation rate was dramatically

Fig. 2. a The percent mass lost of from EH scaffolds and **b** change in solvent pH during *in vitro* degradation. All porous groups displayed similar degradation over 28 days, and a more dramatic degradation than the solid EH network. Results also confirmed the near constant solvent pH throughout the 28 days degradation study, demonstrating the lack of acidic degradation products produced by CABs. Values represent means and associated standard deviation (*n*=5).

increased, with the EH scaffolds displaying approximately 10% mass degradation after 28 days. The degradation rate was not found to be dependent on porogen content, however with only 10% mass lost for these groups after 28 days it should be noted that further testing is needed to determine the length of time required for complete degradation of the scaffolds. As described above, the use of acrylate chemistry in the formation of the EH networks will result in the formation of degradation products with terminal carboxylic acid groups. To investigate the acidity of the EH network degradation products, the pH of the solvent was monitored throughout the study and the solvent was not refreshed during the experimental time. The results demonstrated that the degradation of the EH networks was not associated with a significant pH change over the course of the 28 day study (Fig. 2b). Thus the study concluded that EH scaffolds hydrolytically degrade and produce minimal acidic products upon hydrolysis.

An initial application of EH networks has been in the area of skeletal muscle regeneration. Here, EH networks would act as platform for the recruitment of satellite cells, the proliferation and differentiation of satellite cells into myoblasts, and the ultimate formation of myotubes and myofibers. Therefore, initial studies examined the attachment and proliferation of putative myoblasts upon EH networks as well as the myoblastic response to EH network's release of insulin-like growth factor 1 (IGF-1) (59). To begin, two EH networks formed from 0.34 and 0.58 M initiator solutions were tested for myoblast attachment at 4 and 6 h. Both networks displayed a myoblast attachment similar to tissue culture polystyrene at both time points. Further testing was done to investigate the ability of the EH network to release growth factors and stimulate myoblast proliferation (59). IGF-1 was absorbed onto the networks' surface at concentrations of 0, 10, 50 and 150 ng/network, and then primary myoblasts were seeded onto the growth factor coated networks and grown in growth media for 3 and 5 days. Results indicated that on day 3, the IGF-1 loaded networks significantly increased myoblast proliferation in the highest loaded networks, and that the maintenance of this increased proliferation requires continuous IGF-1 release. Overall, this work demonstrated that EH networks support myoblast attachment as well as IGF-1 induced myoblast proliferation (59).

EH-PEG Hydrogels

In order to form a water swellable network based upon a cyclic acetal monomer, poly(ethylene glycol) was incorporated into the EH network polymerization reaction resulting in EH-PEG hydrogels (Fig. 3) (57,58,61). EH-PEG hydrogels were synthesized with varying molar ratios of EHD to PEGDA as well as with varying monomer concentrations so as to then investigate their effects upon the physical properties of the resulting hydrogel (58). Results showed that the EH-PEG hydrogel swelling degree was particularly dependent on the monomer concentration, with swelling increasing as monomer concentration decreased. Initiator concentration did not appear to be significantly dependent on the swelling degree of EH-PEG hydrogels. Results also demonstrated that low initiator concentrations did not produce sufficient amounts of radicals to propagate thorough
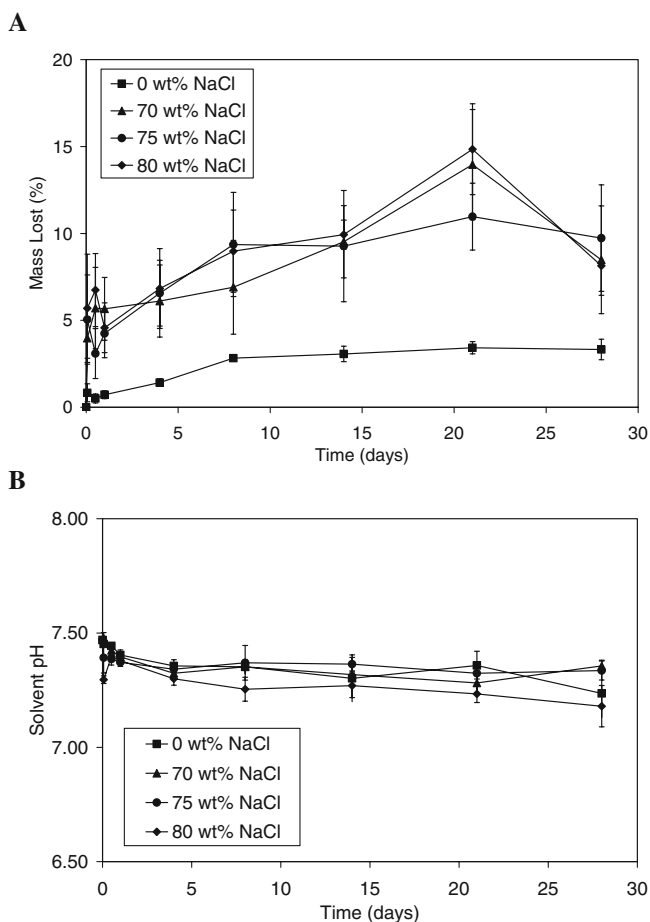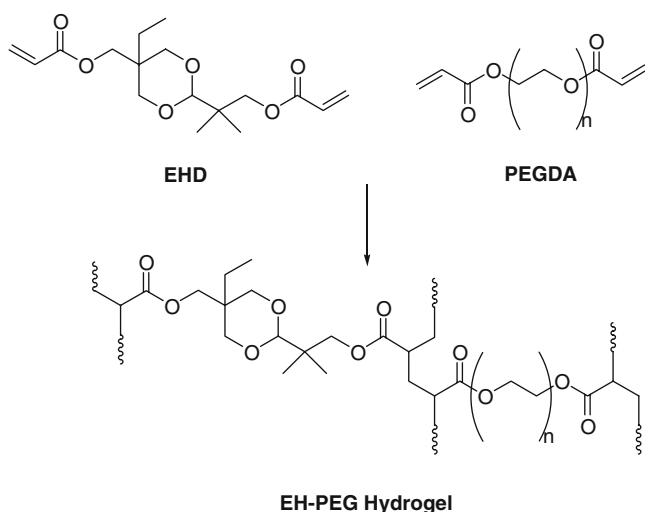
Fig. 3. Chemical reaction between poly(ethylene glycol) diacrylate (PEGDA) and 5-ethyl-5-(hydroxymethyl)-β,β-dimethyl-1, 3-dioxane-2-ethanol diacrylate (EHD) to form EH-PEG hydrogels (58).

crosslinking reactions. This lead to a higher sol fraction, due to unreacted monomers left within the gel (58). A study of water contact angle was also performed to examine the hydrophilicity of the surface of the EH-PEG hydrogels, with results indicating that the water contact angle decreased as the ratio of PEGDA increased. Thus, the addition of PEGDA strongly influenced the hydrophilicity of the material, due to its hydrophilic EH polymer main chain (58). Finally, the range of contact angle values was within the range of 50° to 75° where cell adhesion is generally thought to be promoted (62,63). This study concluded that the EH-PEG hydrogels can be easily fabricated with controllable properties and that these biomaterials may be suited for cell transplantation applications (58).

In order to investigate the utility of EH-PEG hydrogels as cell carriers, a series of studies were also undertaken to examine the viability and function of embedded osteoprogenitor cells (57). Specifically, this work examined (1) the effect of radical initiators on viability and metabolic activity of osteoprogenitor cells in monolayer, (2) the ability of the osteoprogenitor cells to differentiate after initiator exposure, and (3) the viability of osteoprogenitor cells embedded in the EH-PEG hydrogels. EH-PEG hydrogels were fabricated using the water-soluble redox, radical initiation system of ammonium persulfate (APS) and N,N,N′,N′-tetramethylethylenediamine (TEMED). To assess the effect of the initiator system on the metabolic activity, osteoprogenitor cells were cultured with the initiators at concentrations of 10, 15, and 20 mM and analyzed using a standard toxicology kit. Results indicate similar levels of metabolic activity between the 10, 15 mM, and control groups at early times and decreased activity for the 20 mM group. The effect of the initiator system on the differentiation of osteoprogenitor cells was examined by short exposure to the initiator system followed by culture in osteogenic media; differentiation was assayed by the expression of alkaline phosphatase. Results indicate that exposure to low concentrations of the initiation system does not affect the ability of the cell population to osteodifferen-

tiate. Lastly, osteoprogenitor cells were embedded in EH-PEG hydrogels, cultured in media for 7 days, and analyzed for viability using a fluorescent live/dead assay. Results quantitatively showed that the majority of the osteoprogenitor cell population was viable up to 7 days. This work indicated that the EH-PEG hydrogel system is a viable approach for cell carrier applications.

Finally, a recent study demonstrated the utility of EH-PEG hydrogels to repair craniofacial defects (61). The goals of the study were to repair the defect while studying tissue response to EH-PEG hydrogels and the extent of bone repair after loading the hydrogels with bone morphogenetic protein-2 (BMP-2). Results indicated a mild tissue response to the EH-PEG hydrogels and minimal cellular invasion around the implant. Prior to the *in vivo* study, BMP-2 release from the hydrogels was studied *in vitro*, demonstrating that the EH-PEG hydrogels do indeed release bioactive BMP-2 over the course of 12 h (61). For the *in vivo* study, two experimental groups (EH-PEG hydrogels containing either 0.25 or 2.5 µg BMP-2) and an unloaded EH-PEG hydrogel control group were implanted into an orbital defect created in the rabbit animal model. Histological results after 7 days indicated no difference in bone growth near the construct between both experimental groups. However, at 28 days the EH-PEG hydrogel containing 2.5 µg BMP-2 demonstrated higher levels of bone growth compared to the experimental and control groups. The results of this work demonstrated that EH-PEG hydrogels can be used for delivery of BMP-2 *in vivo* for bone tissue engineering applications (61).

Poly[poly(ethylene glycol)-*co*-cyclic acetal] (PECA) Hydrogels

Although EH-PEG hydrogels have a number of attractive properties for biomedical applications, there may be a need to fabricate water swellable, cyclic acetal based networks with a more defined, and therefore more controllable, macromolecular structure. Thus, a hydrogel formed from a copolymer of EHD and PEG may be advantageous, when compared to the random network of polymerized monomers and short chained polymers that form EH-PEG hydrogels. To this end, the copolymer poly[poly(ethylene glycol)-*co*-cyclic acetal] (PECA) and the resulting PECA hydrogels have been developed. The PECA copolymer is synthesized by co-polymerization of the EHD cyclic acetal monomer with PEG polymers (Fig. 4) (60). More specifically, EHD is first dissolved in tetrahydrofuran with sodium hydride at 0°C. Next, poly(ethylene glycol) (M_n=600 g/mol) ditosylate is added at 50°C. Water is added to the mixture, and then all solvents are removed by reduced pressure. The resulting PECA copolymer is dissolved in ethyl acetate, filtered, and then further purified by silica chromatography. The hydroxyl groups of the product were transformed into acrylate groups by acryloyl chloride and triethylamine. Diacrylated PECA was then crosslinked using APS and TEMED to form PECA hydrogels.

A series of studies investigated the effect of PEG length on the properties of the PECA copolymer as well as the resulting PECA hydrogels (60). Results confirmed that PECA hydrogels could be readily fabricated with water contents in excess of 90 wt%. The swelling and sol fraction
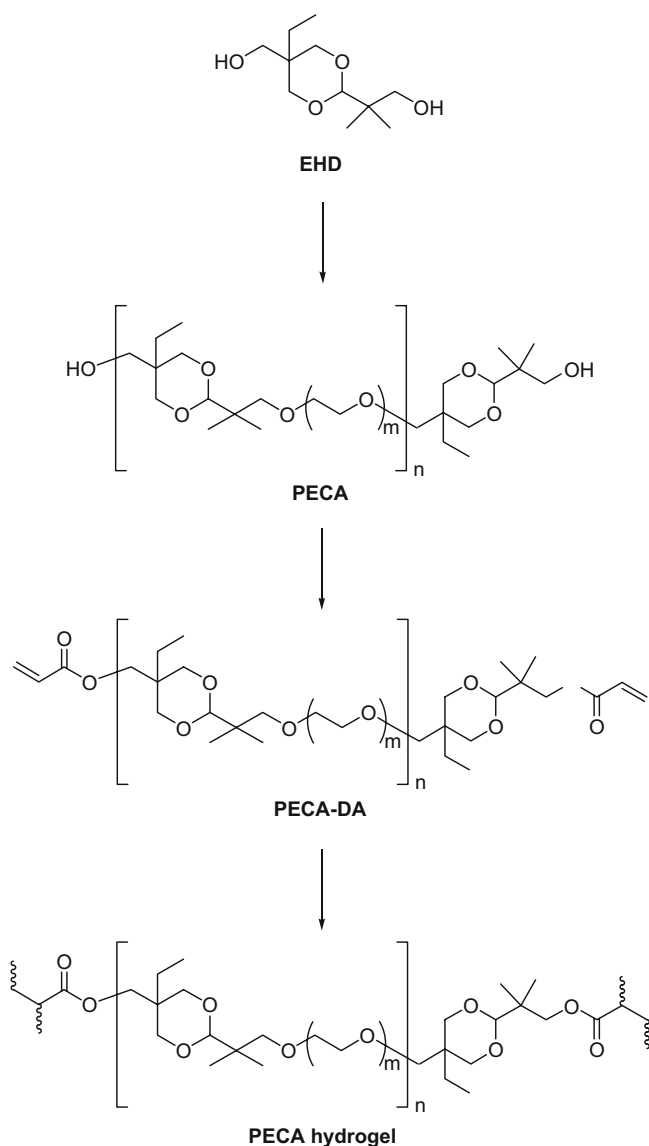
Fig. 4. Synthetic route for PECA and PECA hydrogels (60).

of PECA hydrogels were found to be dependent on the initial PEG chain length, initiator concentration, and polymer concentration. Swelling degree increased as the PECA concentration decreased, due to the mobility of the polymer chains during gelation and the crosslink density of hydrogels. Swelling degree also increased with an increase in PEG chain length due to the decreased hydrogel crosslinking. Degradation rate of the cyclic acetal segments was found to be dependent on the solvent acidity and temperature, where degradation rate increased with a decrease in temperature and acidity due to dependence of cyclic acetal hydrolysis upon hydronium ion concentration (60). When the cyclic acetal segments were degraded under simulated physiological conditions, the pH of the surrounding environment remained constant. Studies also showed that the dry weight of PECA hydrogels decreased by 30% after 5 months of *in vitro* degradation. Thus, this study revealed that both swelling ratio and degradation rate of PECA hydrogels were easily

controlled, and well suited for future drug delivery and tissue engineering applications (60).

POLYACETALS AND POLYKETALS

Another group of novel synthetic polymers includes the polyacetals and polyketals. The utility of biomaterials based upon polyacetals and polyketals are not limited to tissue regeneration, but are also useful in applications ranging from drug delivery to orthopedic implants. These biomaterials are often modified specifically to their desired function during synthesis using alcohols, ethers, aldehydes, and ketones (64). Consequently, the degradation products can also be tailored to consist of alcohols, aldehydes, and ketones, none of which significantly change the local tissue pH. Due to the variety of methods and reactants available for synthesis, there are near limitless applications for these biomaterials.

The majority of the work with polyacetal and polyketal based biomaterials is focused on drug delivery and tumor targeting. Current cancer therapeutics are often delivered systemically as opposed to selectively, leading to high levels of the drug found in tissues far from the intended site. Polyacetal and polyketal based biomaterials can take advantage of the fact that the local environment within a tumor has a lower pH than the surrounding tissue, and therefore induce the release of drugs at these sites, due to pH dependent degradation (24,65). A number of studies have recently shown that degradation and drug release rates are accelerated when in a low pH environment (23,24,66,67). This targeted release allows the carrier to remain in the blood and not release the therapeutic drug until it is taken up into the tumor, significantly decreasing administration of the drug to local healthy tissues (66). Also, the pH dependent behavior allows for the carrier to remain in the system longer than current carriers, and therefore deliver more therapeutic agent to the tumor (68). Additionally, by altering the reactants, carriers that have a $M_w < 40,000$ g/mol can be produced, allowing for the renal exclusion of degradation products (66).

Using the same principles, polyacetal and polyketal based biomaterials can be tailored to target other chronic illnesses. For example, macrophages can be targeted by these biomaterials for the delivery of anti-inflammatory drugs. The distinct pH difference between the blood (pH 7.4), endosome (pH 6.5), and lysosome (pH 5.5) allows for polyacetal and polyketal based biomaterial degradation within a specific compartment of the targeted cell (69,70). Taking the delivery one step further, Vicent *et al.* has shown that the therapeutic agent can be directly incorporated into the backbone of these polyacetal and polyketal polymer carriers (66). Through hydrolysis, the drug is freed as the polymer backbone is degraded.

Another application of polyacetal and polyketal based biomaterials is to create specialized structures that are polyfunctional. For example, Lemcoff and Fuchs showed that it is possible to create dendrimeric diacetals that had several potential uses, including guest inclusion, self assembly, and channel formation with controlled degradation (71). These structures are unique in the fact that each generation of the dendrimer is available for independent removal and can contain functional macromolecules that would become free upon degradation (71). This could be utilized in a multifaceted approach with each generation containing a different

macromolecule. Gillies *et al.* have also used these polyacetal and polyketal based dendrimer structures to create potential drug carriers (72). They have synthesized linear-dendritic block copolymers containing acetal degradable units that self assembled into micelles. To investigate the use of these micelles as controlled release drug carriers, studies were performed with Nile Red dye as a model. It was found that this dye, which was protected within the micelle's core, was subsequently released as the acetal groups were hydrolyzed and the micelle dispersed, therefore showing a degradation controlled release (72).

Polyacetals have also been used clinically in several orthopedic implants, most notably the Freeman all-polymer knee replacement and hip resurfacing prostheses (73,74). Current studies have discussed work on surface wear of hip joints and mechanical properties of these materials (73–75). A recent study published by Lee and Choi demonstrated that the properties of a porous polyacetal block were similar to that of bone (76). These studies have displayed the diverse function that these materials have in every aspect of tissue engineering.

CONCLUSIONS

Current synthetic biomaterials for tissue engineering applications are sufficient, yet they are far from ideal. Biomaterials based upon polyesters and polyanhydrides possess distinctive properties and are used extensively in clinical practice. While synthetic biomaterials can be tailored to meet many tissue engineering and drug delivery needs, many are not biologically inert. In an effort to develop alternative materials, extensive research is being done to synthesize polymers that have more desirable degradation properties. Cyclic acetals are an increasingly versatile group of materials that can be utilized for both soft and hard tissue repair. Properties of cyclic acetal biomaterials have been controlled by varying fabrication parameters to create highly hydrophobic EH networks. These networks have been shown to support a viable osteoprogenitor and myoblast cell population. Alternatively, water swellable EH-PEG hydrogels were able to sustain an encapsulated osteoprogenitor cell population for up to 7 days *in vitro* as well as deliver BMP-2 to bone *in vivo*. Finally, in an effort to create a more organized hydrogel structure EHD and PEG were co-polymerized to form PECA. PECA hydrogels have been shown to be a favorable material for both drug delivery and tissue engineering applications. Other groups of biomaterials are based upon polyacetals and polyketals, and have been shown potential in drug delivery applications due to their pH dependent degradation properties. The development of alternative synthetic polymers, such as those described here, is a critical step for the future success of many tissue engineering and drug delivery applications.

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