JOURNAL OF Applied Polymer SCIENCE

Special Issue: Polycarbonates and Green Chemistry

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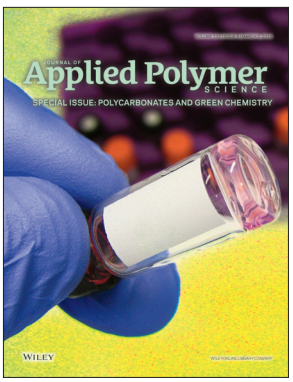

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Journal of Applied Polymer Science

REVIEW

Renaissance of Aliphatic Polycarbonates: New Techniques and Biomedical Applications

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ABSTRACT: Aliphatic polycarbonates (APCs) were discovered a long time ago, with their conventional applications mostly limited to low-molecular-weight oligomeric intermediates for copolymerization with other prepolymers or small molecules. Recent developments in polymerization techniques have overcome the difficulty in preparing high-molecular-weight APCs. These in turn, along with new functional monomers, have enabled the preparation of a wide range of APCs with diverse chemical compositions and structures. This review summarizes the latest polymerization techniques for preparing well-defined functional APCs and the new applications of those APCs, especially in the biomedical field. © 2013 Wiley Periodicals, Inc. J. Appl. Polym. Sci. **2014**, *131*, 39822.

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INTRODUCTION

Polycarbonates are polymers with backbones containing repeating carbonate [—O—C(O)—O—] linkages. Aliphatic polycarbonates (APCs) refer to polycarbonates with no aromatic groups between the carbonate linkages. APCs were initially prepared in Wallace Carothers' laboratory at DuPont around 1930.[1] With their characteristic low melting points and high susceptibility to hydrolysis, which were considered inferior to the properties displayed by many other polymers [e.g., polyester, polyamide, poly(methyl methacrylate)] developed in that era for fiber applications, APCs were not pursued commercially.[1,2] Unlike aromatic polycarbonates, which garnered immediate commercial attention when bisphenol A (BPA)-based polycarbonate was discovered in the 1950s and have been tremendously successful as consumer products,[1–3] APCs not only remained largely unexplored commercially but received little attention from the research field as well until the 1990s (Figure 1). Although APCs have been proposed as alternative materials for films, packaging, and rigid plastics applications, its current industrial applications are still limited as low-molecular-weight polycarbonate polyols, macromonomers for the production of polyurethanes, and other copolymers.

Earlier study on APCs has focused on the improvement of the mechanical properties and thermal stability of the readily available poly(trimethylene carbonate) (PTMC) through its blending with polymers with complementary properties for applications, such as engineering thermoplastics, albeit with limited commercial success. Increasing concerns over greenhouse gas pollution by carbon dioxide (CO_2) have motivated the incorporation of CO_2 into materials as a way to reduce greenhouse gas and as a means to alleviate the shortage of conventional petroleum fuel supplies. Polycarbonates have received significant renewed attention in this regard.[4–8] An increasing demand for more versatile, degradable biomaterials has also revived the interest in APCs for biomedical applications,[9,10] for which their degradability, low glass-transition temperatures (T_g's), and elasticity, which used to be perceived as major drawbacks, have turned into competitive advantages over many other polymers in a U-turn.[9,10]

Indeed, there has been a surge of reports on APCs in the past 2 decades (Figure 2); this has resulted from new progress on polymerization techniques,[7,11–16] functional monomer syntheses,[17–30] and the many new applications being explored.[31–36] In this review, we first update the latest progress on APC polymerization techniques and new insights on traditional techniques applied to APC preparation and then discuss recent biomedical applications of APC-based hydrogels and drug-delivery carriers. The information used in this review mainly comes from available scientific publications from the past 15 years, along with a few patents.

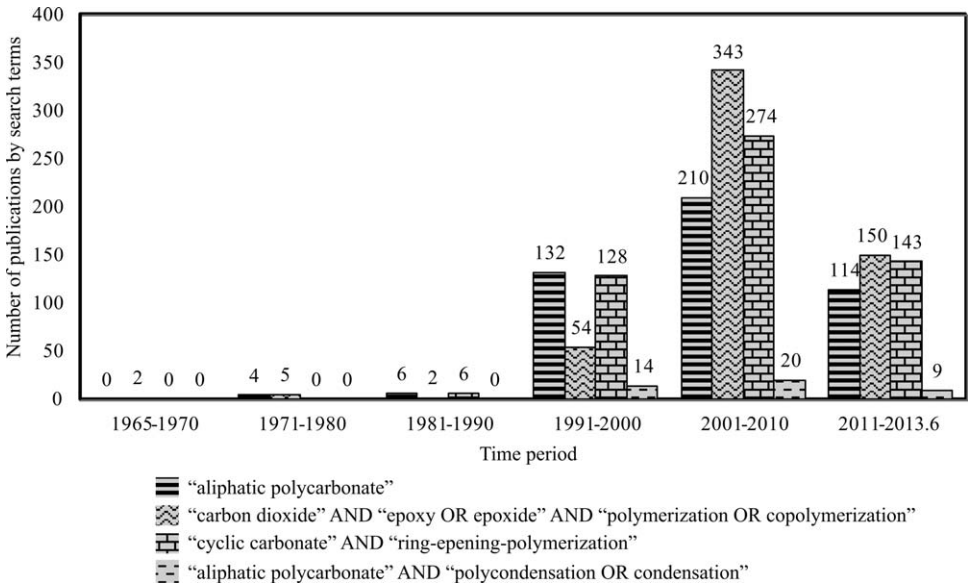

Figure 1. Number of scientific publications related to APCs versus the time period searched from the database of the Web of Science (Thomson Reuters) with various search terms.

PROGRESS ON APC POLYMERIZATION TECHNIQUES

The sharp differences in the mechanical and thermal properties between the most studied aromatic BPA-based polycarbonate and PTMC underscores the importance of the chemical composition of the main chains. The number-average molecular weight (M_n) and polydispersity index (PDI) also have a significant impact on the mechanical properties and degradation profiles of APCs. Through the alteration of these parameters, APCs with a wide range of properties have been developed with one of the three major polymerization techniques: (1) polycondensation between an aliphatic polyol with dialkyl carbonate [Figure 2(a)], (2) copolymerization of carbon dioxide with epoxides [Figure 2(b)], and (3) ring-opening polymerization (ROP) of cyclic carbonate monomers [Figure 2(c)]. Significant progress has been made to improve each method over the last 2 decades.

Polycondensation

APCs were initially prepared by the polycondensation method,[1] which involved toxic phosgene or its derivatives and aliphatic diols, and the resulting polymers usually suffered from poor control over the molecular weight and were characterized with broad molecular weight distributions. With the adoption of the nonphosgene aromatic polycarbonate preparation technique, APCs were later prepared with dialkyl carbonates instead of phosgene.[2,3,37] High-molecular-weight APCs were obtained via the polycondensation of dialkyl carbonates and aliphatic diols in the melt state, a two-step process involving an initial condensation and subsequent chain growth enabled by transesterification between the —OH and —OC(O)R end groups with transesterification catalysts.[37–39] The choice of catalysts, reaction temperature, and ratio of dialky carbonate to diol are all known to impact the polymerization outcome. With a novel TiO_2/SiO_2–poly(vinyl pyrrolidone)-based catalyst (TSP-44), three APCs, including poly(butylene carbonate), poly(pentamethylene carbonate), and poly(hexamethylene carbonate) with high weight-average molecular weights (M_w's $\geq$ 166,000 g/mol) and narrow PDIs ($\leq$1.86), were synthesized at yields greater than 85% by this method.[38] A recent study by Lee et al.[39] revealed that the formation of intermediate oligomers with a [—OCH_3]/[—OH] ratio of about 1.0 in the first step is the prerequisite for obtaining high-molecular-weight APCs with this method.

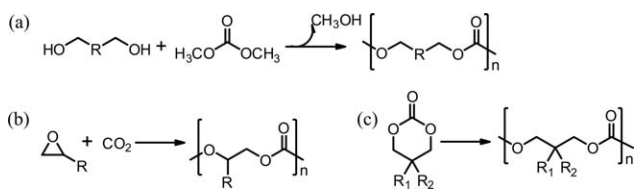

Figure 2. Common polymerization techniques for the preparation of APCs: (a) polycondensation between polyols with dimethyl carbonate, (b) copolymerization of carbon dioxide with epoxides and (c) ROP of cyclic carbonate monomers.

Polycondensation techniques can also be catalyzed by enzyme catalysts.[40,41] Enzymes provide distinct advantages over conventional catalysts for the preparation of functional polymers because of their milder reaction conditions, high tolerance for functional groups, and higher selectivity, which provides control over branching. However, enzyme-catalyzed polycondensations usually requires a high catalyst loading and a long reaction time, and the obtained polycarbonates suffer from a relatively low molecular weight and broad PDI.

A unique advantage of the polycondensation method over the other two APC preparation techniques is that it enables the straightforward preparation of APCs with different aliphatic linkages between the carbonates by the simple use of diols of different lengths during the polymerization.[39,42] High-molecular-weight aliphatic copolymers (M_w = 90,000–210,000)

incorporating multiple aliphatic linkages were prepared by the two-step melt polycondensation method with a mixture of 1,4-butanediol, 1,6-hexanediol, and cyclohexane-1,4-dimethanol.[39]

Alternating Copolymerization of Carbon Dioxide and Epoxy

Carbon dioxide (CO_2) is one of the most abundant and renewable carbon resources, and the selective transformation of carbon dioxide and epoxides into degradable polycarbonates has been regarded as a promising green and sustainable route to polycarbonates.[4,6,7,11,43–47] Since its discovery by Inoue et al. in 1969,[11] this copolymerization method has become one of the most well-studied and innovative technologies for the large-scale utilization of carbon dioxide in chemical syntheses. The search for highly efficient and selective catalysts for this process has been the focus. In addition to the earlier zinc-containing heterogeneous catalysts used by Inoue et al.,[11] a number of active homogeneous metal catalysts have also been reported, including the aluminum–porphyrin complex,[48] zinc–phenoxide derivatives,[49] β-diiminate–zinc catalysts,[50–52] chromium–salen derivatives,[53] and cobalt salen catalysts.[54–56] Studies of these well-defined transition-metal coordination complexes as catalysts have revealed much of the mechanisms underlying the alternating copolymerization of carbon dioxide and epoxy.

The copolymerization was initiated by epoxide ring opening by the metal catalyst, followed by CO_2 insertion into the metal–oxygen bond generated. Two side reactions that are detrimental to the desired alternating copolymer formation are (1) consecutive epoxide ring opening to form a polyether backbone and (2) back-biting reactions that lead to cyclic carbonate productions. Detailed mechanisms of the metal-catalyzed copolymerization of carbon dioxide and epoxides can be found in several excellent reviews.[43,47,57] Catalysts with a high reactivity toward polymerization with the capability of completely suppressing the two side reactions are highly desired. The most active catalysts reported to date are the single-component cobalt salen complexes bearing ammonium or nucleophilic substituents on pendant arms[55] and binary systems consisting of simple (salen)Co(III)X and a nucleophilic cocatalyst.[58] They exhibit a high reactivity under mild conditions (e.g., 0.1 MPa of CO_2 pressure) and give rise to copolymers with more than 99% carbonate linkages and a high regiochemical control (~95% head-to-tail content).

The mechanism of the copolymerization of cyclohexene oxide and CO_2 was studied quite extensively. The resulting poly(cyclohexylene carbonate), with a T_g of 115°C, however, had inferior mechanical and physical properties compared to BPA-based aromatic polycarbonate[59] and thus did not find practical applications as initially expected. Another widely studied system is the copolymerization between propylene oxide and CO_2 to generate poly(propylene carbonate), which has found application as a toughening agent for epoxy resins and sacrificial binder for ceramics because of its low T_g (40°C), sharp and clean decomposition above 200°C, and biodegradability.[60]

Unlike the expanding spectrum of catalysts, epoxides that can copolymerize with CO_2 to give truly alternating copolymers remain quite limited. Besides cyclohexene oxide and propylene oxide, styrene oxide, limonene oxide, indene oxide, and epichlorohydrin have been reported in successful copolymerization with CO_2. Polycarbonates with built-in side chain functionalities have rarely been prepared by this method.[61,62] Lukaszczyk et al.[61] copolymerized CO_2 with allyl glycidyl ether in the presence of diethyl zinc ($ZnEt_2$)/pyrogallol catalysts, which gave poly(epoxy carbonate) after oxidation. The epoxy-functionalized polycarbonate provides potential a functionalization handle for the covalent attachment of drugs and thus may be explored as a biodegradable drug carrier. Recently, Frey and Geschwind[63] and Grinstaff and Zhang[64] independently reported the preparation of poly(1,2-glycerol carbonate) with hydroxylated side chains. Both groups used a two-step method involving the copolymerization of protected epoxides with CO_2 followed by selective deprotection under mild conditions. In Frey and Geschwind's[63] report, the protected epoxide monomer was ethoxy ethyl glycidyl ether (EEGE) or benzyl glycidyl ether [BGE; Figure 3(a)], and the copolymerization of epoxide and CO_2 was carried out at room temperature for 72 h in dioxane in the presence of a heterogeneous catalytic system based on $ZnEt_2$ and pyrogallol at a molar ratio of 2:1, and a CO_2 pressure of about 20 bar. An alternating copolymer without an ether linkage ($M_n = 5000$–25,200 g/mol, PDI = 1.24–2.33) was obtained. The protecting groups were removed via acid cleavage and hydrogenation for EEGE and BGE, respectively, with little (EEGE) and no (BGE) backbone degradation. In Grinstaff and Zhang's[64] report, the atactic and isotactic linear poly(benzyl 1,2-glycerol carbonate)s were first synthesized via the copolymerization of *rac*-/(*R*)-BGE with CO_2 at 22°C for 4 h with a series of Co–salen complexes and a CO_2 pressure of 220 psi (15.2 bar). High-molecular-weight *rac*-/*R*-poly(benzyl-1,2-glycerol carbonate) ($M_n = 32{,}200$–48,100 g/mol) with greater than 97% carbonate linkage selectivity and a narrow PDI (<1.2) was obtained. Deprotection with hydrogenation afforded poly(1,2-glycerol carbonate).

Frey and Geschwind[65] further improved the preparation of hydroxyl-functionalized APCs by using a more labile epoxide monomer, 1,2-isopropylidene glyceryl glycidyl ether (IGG), for the copolymerization [Figure 3(b)]. A series of poly[(isopropylidene glyceryl glycidyl ether)-*co*-(glycidyl methyl ether) carbonate] random copolymers with different fractions of IGG units were obtained with greater than 99% carbonate linkages in this manner. The deprotection by acid ion-exchange resins [10 wt % in a methanol (MeOH)/tetrahydrofuran (THF) mixture at 40°C for 4 h] yielded 1,2-diol functionalized copolymers without any degradation in the polycarbonate backbone. In contrast to poly(1,2-glycerol carbonate), which degraded completely in THF after 2 weeks, the 1,2-diol-functionalized copolymers showed no degradation in THF even after 21 days.

More recently, Frey et al.[66] reported another versatile strategy for preparing functional APCs by the copolymerization CO_2 and propylene oxide with aliphatic alkene epoxides [Figure 3(c)]. The reactive double bond on the side chains of the resulting copolymers enabled the introduction of a wide range of functional groups through the thiol–ene reaction, which could alter the copolymer properties or provide suitable reactive sites for further grafting.

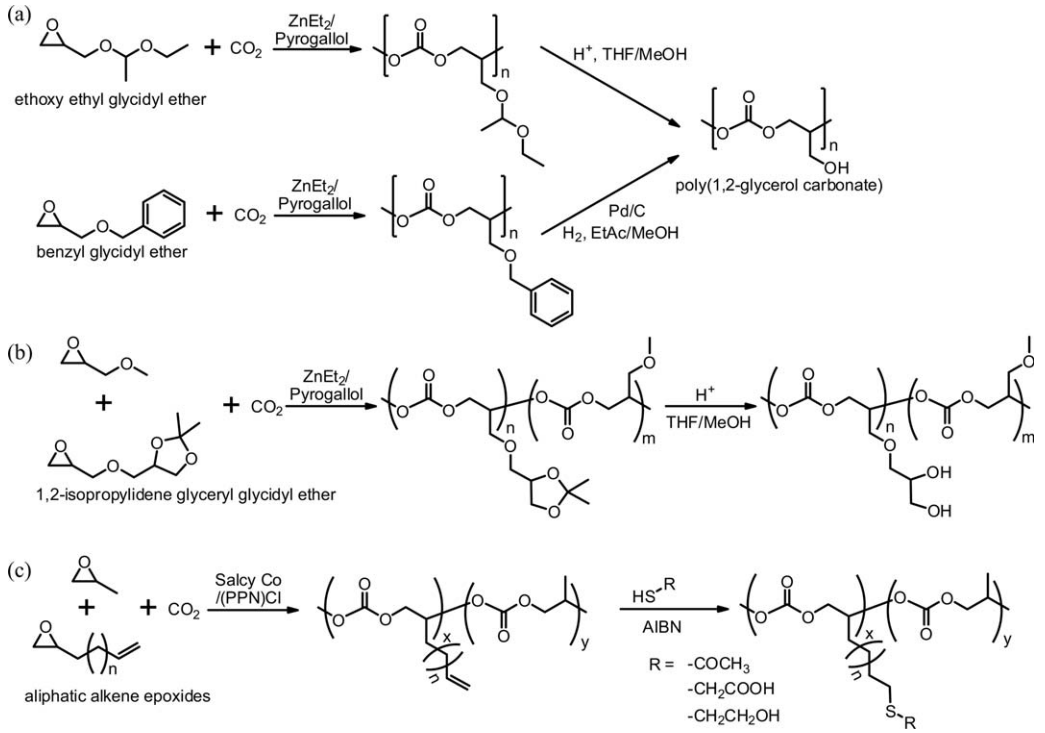

Figure 3. Synthetic strategies for the preparation of functional APCs by the copolymerization of CO_2 and epoxides: (a) preparation of poly(1,2-glycerol carbonate) (Adapted with permission from ref. 63. Copyright 2013 Wiley.), (b) synthesis of poly[(isopropylidene glyceryl glycidyl ether)-*co*-(glycidyl methyl ether) carbonate] copolymers and subsequent deprotection (Adapted with permission from ref. 65. Copyright 2013 Wiley.), and (c) preparation of polycarbonates with reactive double bonds and subsequent functionalizations via thiol–ene coupling (Adapted with permission from ref. 66. Copyright 2013 Wiley).

The lack of commercially available or synthetically readily accessible cyclic ethers beyond the three-membered cyclic epoxides commonly used in the alternating copolymerization of CO_2 and epoxides has largely limited the repeating units in the resulting copolymers to five carbons in length. Recently, a series of four-membered oxetane derivatives were successfully copolymerized with CO_2 with (salen)CrCl/onium salt catalysts to generate ether-free polycarbonates.[13,67–69] The copolymerization was found to proceed via the preformation of a six-membered cyclic carbonate intermediate. The equilibrium ratio of copolymer to cyclic carbonate decreased with the increase of the steric hindrance of the substituent on the oxetane.[69]

ROP of Cyclic Carbonate Monomers

The ROP of cyclic carbonates has become the most effective method to fabricate polycarbonates with good reproducibility and high quality (high molecular weight and low PDI). The ROP of cyclic carbonate monomers to prepare polycarbonate was mentioned as early as 1932 when the monomer TriMethylene Carbonate [TMC; **1** in Figure 4(d)] was discovered.[70] The polymerization was carried out in the melt with potassium carbonate as the catalyst, and it resulted in polymers with undesired decarboxylation. ROP techniques have gradually matured with the development of more effective catalysts for the industrial manufacturing of polyesters from cyclic ester monomers such as lactones. Almost all catalysts used for the ROP of lactones have been screened for the ROP of cyclic carbonate monomers because of the structural similarity between these cyclic monomers. Although many of them have also been active for the ROP of cyclic carbonates, the polymerization kinetics/mechanisms have varied because of the intrinsic difference in the electrophilicity of the carbonyl carbon in cyclic carbonates versus in that lactones.

ROP can be conducted in the melt or in solution by the variation of the mechanisms, including cationic, anionic, coordination–insertion, monomer activation, monomer and initiator dual activation, and enzymatic activation mechanisms. Catalysts available for the ROP of cyclic carbonates include transition-metal catalysts, alkyl halides, basic and acidic organocatalysts, and enzyme catalysts. Concerns over the toxic metal residues in the prepared polymers have motivated the development of a metal-free organocatalytic ROP, which has seen great progress in the last decade since Hedrick et al.[71] reported the use of 4-(dimethylamino)pyridine as the catalyst for the ROP of lactones. Basic organocatalysts[14,72] tertiary amines, guanidines, amidines, phosphazenes, *N*-heterocyclic carbine, and thiourea (TU)/amines, and the organic acidic catalysts diphenyl phosphate,[73] methanesulfonic acid,[74] and triflic acid (TFA)[75,76] have all been found to be effective in catalyzing the ROP of cyclic carbonates. Lipases as a class of biofriendly enzyme catalysts have also been explored for ROP.[12,77–82] Compared to their metallic and organocatalyst counterparts, however, lipases are generally less efficient and have poorer control over the PDI.

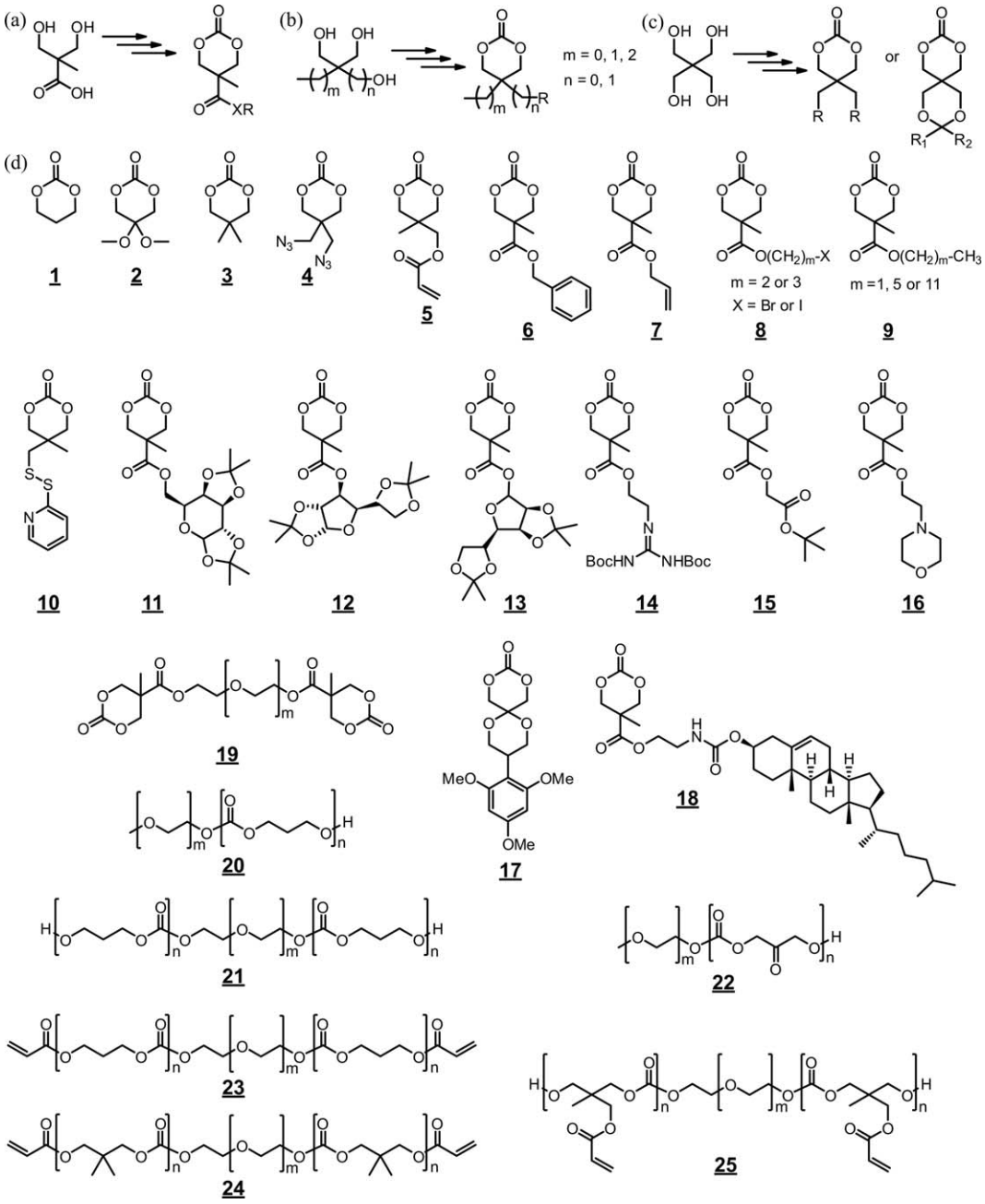

Figure 4. Preparation of six-membered cyclic carbonate monomers from (a) 2,2-bis(hydroxymethyl)propionic acid, (b) glycerol or trimethylolalkane, (c) pentaerythritol, and (d) representative chemical structures of functional cyclic carbonate monomers (**1–18**) and APCs-based macromers (**19–25**) used in the preparation of hydrogels and drug-delivery carriers.

Numerous cyclic carbonates, mainly six-membered cyclic carbonates with a variety of functional groups [e.g., **1–18** in Figure 4(d)], have been prepared and polymerized by means of ROP, as extensively reviewed by Zhang et al.[9] and Dove et al.[10] Most of these functional monomers were derived from compounds containing 1,3-diols. Among them, 2,2-bis(hydroxymethyl)propionic acid [bis-MPA, Figure 4(a)],[18,23,26] glycerol or trimethyolalkane [Figure 4(b)],[24,25,81,83–86] pentaerythritol [Figure 4(c)],[28,87,88] and their derivatives are the most used starting materials for deriving functional cyclic carbonates [**1–18** in Figure 4(d)]. The functionalities could be introduced via either protected monomers, which requires postpolymerization deprotection, or unmasked monomers when they are compatible with the carbonate structure and the polymerization conditions.

Compared to cyclic ethers and esters, there is greater functional diversity within cyclic carbonates. Combined with the development of ROP techniques with milder reaction conditions, this has enabled the facile preparation of a wide range of functional APCs. The degradability but slow degradation rate of APCs can be exploited to engineer desired degradation profiles of

polymers for biomedical applications by virtue of the incorporation of APCs with other nondegradable or faster degrading polymers.

APPLICATIONS

The advance of polymerization techniques, especially CO_2-based copolymerization techniques, makes it possible to prepare APCs at a relatively low cost on the industrial scale. These have been explored for a range of applications as thermoplastics, binders, electronics, coating resins, surfactants, foams, and others.[89–95] The relatively low thermal stability and poor mechanical properties associated with APCs have still limited them to applications that are less demanding in these properties in general. Of particular note, functional APCs with controlled architectures have been increasingly explored for biomedical applications in the last 2 decades, including as tissue engineering scaffolds in the form of electrospun fibers,[96,97] biodegradable elastomers,[98–103] hydrogels,[31,32,104–116] and drug-delivery carriers in the form of micelles,[34–36,88,117–128] polymersomes,[129–132] and polycomplexes.[33,34,111,133–135] Here, we review some representative applications of APCs as hydrogels and drug-delivery carriers.

Hydrogels

Hydrogels are three-dimensional polymer networks with the intrinsic ability to absorb/hold water,[136] and they have been widely used in personal care products,[137] wound dressings,[138,139] protein microchips,[140] drug and gene delivery carriers,[141] ophthalmic prostheses,[142] and tissue engineering scaffolds.[143–145] APCs themselves are usually hydrophobic; thus copolymerization with hydrophilic polymers is often required for the preparation of APC-based hydrogels. Both physically and chemically crosslinked APC-based hydrogels with various hydrophobicities, mechanical properties, and degradation profiles have been prepared.

Physically crosslinked hydrogels can be formed from diblock or triblock polycarbonate-containing amphiphilic polymers driven by hydrophobic interactions between the carbonate segments.[104–107] High-concentration aqueous solutions of the diblock copolymer PEG–PTMC [**20** in Figure 4(d)] with relatively short PEG and PTMC segments underwent a sol–gel transition as the temperature increased.[104] The sol–gel transition temperature could be tuned within the range 20–75°C by variation of the aqueous concentration, molecular weight, and composition of the polymer. Subcutaneous injection of aqueous polymer solutions (30 wt %, 0.5 mL) into rats led to *in situ* gelation, whereas the polymer was stable in Phosphate-Buffered Saline (PBS; pH 7.4) for over 90 days (e.g., no changes in molecular weight, pH, or gel mass). About 15 wt % mass loss due to the dissolution of lower molecular weight polymers from the gel was detected *in vivo* within the same time frame. To improve the mechanical properties of hydrogels formed from a diblock copolymer with a relatively low molecular weight that had storage modulus of only 10s of pascals, PTMC–PEG–PTMC triblock copolymers [**21** in Figure 4(d)] with longer hydrophilic and hydrophilic blocks were used for hydrogel preparation.[105] These triblock copolymers gelled upon cooling rather than heating and exhibited storage modulus values ranging from 220 to 4700 Pa, depending on the composition and concentration of the copolymer.

Cyclic carbonate monomers can be copolymerized with other hydrophobic monomers to improve the gelling characteristics. Compared to gels formed from the triblock copolymer poly(caprolactone-*b*-ethylene glycol-*b*-caprolactone) without APC segments, the poly(caprolactone-*co*-trimethylene carbonate)–PEG–poly(caprolactone-*co*-trimethylene carbonate) triblock copolymer hydrogel achieved better sol stability while maintaining the thermogelling property within a physiologically relevant temperature range of 10–50°C.[106] Subcutaneous implantation of the hydrogel in rats revealed substantial degradation, although the hydrogel was quite stable upon incubation in PBS (pH 7.4) for more than 50 days.[106]

Physically crosslinked hydrogels can be delivered in an injectable form because of dynamic physical crosslinking over time. Putnam et al.[107] prepared injectable hydrogels from a diblock copolymer consisting of monomethyl poly(ethylene glycol) (MPEG) and poly(2-oxypropylene carbonate) [pDHA; **22** in Figure 4(d)]. The copolymer was prepared by the MPEG-initiated ROP of 2,2-dimethoxypropylene carbonate (**2** in Figure 5), which was derived from the metabolic intermediate dihydroxyacetone, followed by deprotection under acidic conditions. pDHA is hydrophilic, even though it is insoluble in water. These injectable hydrogels were used for the prevention and alleviation of seromas (benign pockets of body fluids), a common postoperative complication following ablative and reconstructive surgeries. The MPEG–pDHA hydrogels were thixotropic, exhibiting decreasing viscosities with increasing shear rates, and thus allowed the hydrogels to be delivered to (potential) sites of seromas by injection. The *in vitro* degradation rate of the hydrogel in PBS (pH 7.4) was surprisingly rapid, complete degradation was achieved in 24 h, and the degradation rate decreased with increasing pDHA lengths. The *in vivo* degradation of the hydrogel in a rat mastectomy model was slightly slower than that *in vitro*, with complete degradation accomplished in less than 3 days. The seroma volumes decreased significantly when MPEG–pDHA was administered compared to the untreated control group. Moreover, the MPEG–pDHA gel and its degradation products did not adversely impact early wound healing.

Hydrogels usually suffer from inadequate mechanical properties without sufficient covalent or physical crosslinking. Covalently crosslinked APC-based hydrogels have been prepared by the photopolymerization of water-soluble, end-group acrylated PTMC–PEG–PTMC triblock copolymers [**23** in Figure 4(d)].[146] Varghese et al.[108] recently reported a mechanically tough biodegradable hydrogel prepared from the APC-containing macromer oligo(trimethylene carbonate) (OTMC)-*block*-PEG-*block*-OTMC diacrylate. A very tough hydrogel (TMC20, with 20 representing the number averaged molecular weight of PEG diol of 20,000 g/mol) was obtained from the photopolymerization of OTMC–PEG–OTMC with appropriate block lengths of the hydrophilic PEG ($M_n = 20{,}000$ g/mol) and the hydrophobic OTMC ($M_n = 325$ g/mol). The critical balance of hydrophilic–hydrophobic moieties resulted in hydrogels with enhanced toughnesses (215.3 ± 46.4 kJ/m^3) and moduli (14.9 ± 0.2 kPa) with good fracture strains

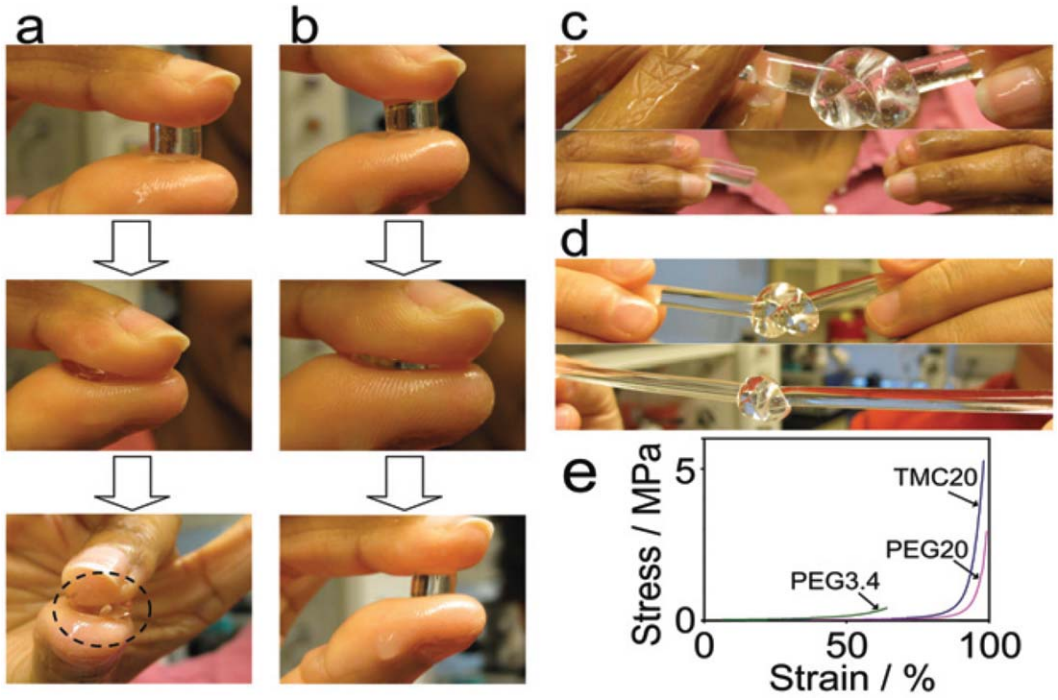

Figure 5. Photographs demonstrating how the TMC20 hydrogels better sustained compression, knot formation, and stretching compared to the PEG20 control: (a) PEG20 hydrogels deformed under compression and broke into pieces at higher stress. The dotted circle denotes the damaged hydrogel: (b) deformation and recovery of the TMC20 hydrogel under compressive stress, (c) knots formed from PEG20 hydrogels (top) were broken into pieces upon stretching (bottom), (d) TMC20 hydrogels knots (top) were able to withstand stretching/tightening (bottom), and (e) stress–strain profiles of the hydrogels under uniaxial compression. (Reproduced with permission from ref. 108. Copyright 2009 The Royal Society of Chemistry.). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

(98.2 ± 1.3%) compared with the hydrogel without the APC component (PEG20, with 20 representing the number averaged molecular weight of PEG diol of 20,000 g/mol), which exhibited a toughness of 130.2 ± 45.4 kJ/m^3, a modulus of 7.4 ± 0.8 kPa, and a fracture strain of 98.7 ± 3.5% (Figure 5). Moreover, these APC-containing hydrogels were shown to support the adhesion and spreading of human-bone-marrow-derived mesenchymal stem cells and primary bovine articular chondrocytes.[108,110] When chondrocytes were encapsulated in the TMC20 gel, they underwent spontaneous aggregation *in vitro,* which was not observed with cells encapsulated in the PEG20 control. More cartilage matrix (glycosaminoglycan and collagen) syntheses were observed with the aggregated chondrocytes in TMC20 than with those encapsulated in PEG20.

Triblock copolymer diacrylate with a more hydrophobic APC block, oligo(2,2-Dimethyltrimethylene carbonate)-*block*-PEG-*block*-oligo(2,2-Dimethyltrimethylene carbonate) DiAcrylate [DPD–DA; **24** in Figure 4(d)], prepared through the ROP of dimethyltrimethylene carbonate (**3** in Figure 5), was also photocrosslinked by Liao et al.[114] to form hydrogels. Although the hydrogel prepared from DPD–DA exhibited some good mechanical properties, their toughness was inferior to those of PEG20 and TMC20 reported by Varghese et al.,[108] probably because of the relatively low degree (~70%) of acrylation of the DPD precursor. A series of methacrylate-functionalized PTMC–PEG–PTMC triblock copolymers were also used for hydrogel preparation through photopolymerization. In contrast to the hydrogels reported by Varghese et al.,[108] these hydrogels, with similar lengths of PEG and PTMC blocks, only achieved modest mechanical properties with a compressive modulus of less than 15 kPa and a toughness of 25 kJ/m^3.

Multiple functional cyclic carbonates could also be directly crosslinked into hydrogels by ROP.[32,109,115] A pH-responsive APC-based hydrogel formed by covalent crosslinking and strengthened by secondary noncovalent interactions was reported by Mespouille et al.[32] Functional cyclic carbonates [methylcarboxy trimethylene carbonates (MTCs)] bearing tert-butyloxycarbonyl (BOC)-protected guanidines [GuaBOC; MTC–GuaBOC; **14** in Figure 4(d)] and *tert*-butyl-protected carboxylic acids [MTC–tBAc; **15** in Figure 4(d)] were first synthesized from 2,2-bis(hydroxymethyl)propionic acid. A PEG-based TMC crosslinker, poly(ethylene oxide) (PEO)–MTC [MTC–PEO–MTC, **19** in Figure 4(d)], was obtained by the esterification of PEO–α,ω-hydroxyl by 5-methyl-2-oxo-[1,3]dioxane-5-carboxylic acid. The hydrogel was formed by the organocatalytic ROP of the two functional cyclic carbonates, MTC–GuaBOC and MTC–tBAc, at various ratios with the MTC–PEO–MTC crosslinker in organic solvents. Monolithic and transparent hydrogels were obtained with high gel contents (>92%). The selective deprotection of the BOC- and *tert*-butyl protection groups resulted in hydrogels with guanidines and carboxylic acid side chains without the degradation of the polycarbonate backbone; pH-dependent swelling behavior was observed in the deprotected hydrogels because of the coexistence of the oppositely charged

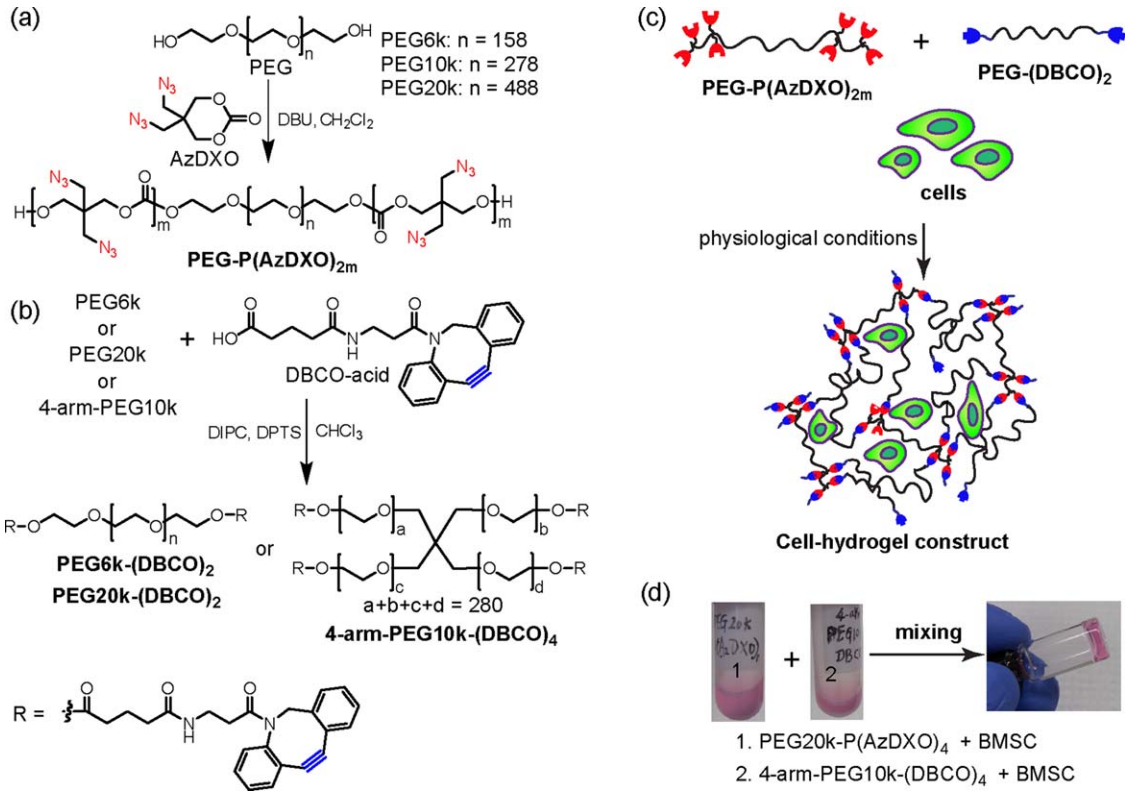

Figure 6. Macromer synthesis, crosslinking, and cell encapsulation strategies of a clickable APC-based hydrogel system: (a) ROP of AzDXO initiated by PEG, (b) synthesis of PEG–$(DBCO)_x$ using catalysts N,N'-diisopropylcarbodiimide (DIPC) and 4-(dimethylamino)pyridinium 4-toluenesulfonate (DPTS), (c) schematic illustration of cell encapsulation by crosslinking PEG–$P(AzDXO)_{2m}$ and PEG–$(DBCO)_x$ via SPAAC click reaction, and (d) a representative demonstration of the rapid gelation of the cell–hydrogel constructs within 1 min of mixing the BMSC suspension (10^6 cells/mL) in a PEG20k–$P(AzDXO)_4$ solution (10 w/v% in BMSC expansion media) and a 4-arm-PEG10k–DBCO solution (10 w/v% in BMSC expansion media). The BMSC expansion media consisted of alpha-minimum essential medium (α-MEM) with 20% fetal bovine serum (FBS). (Reprinted with permission from ref. 31. Copyright 2011 Wiley.). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

carboxylic acid and guanidine residues. The same group also reported morpholine-functionalized hydrogels through the copolymerization of 2-(morpholin-4-yl) ethyl-functionalized cyclic carbonate monomer [**16** in Figure 4(d)] with MTC–PEO–MTC.[115] Morpholine-containing hydrogels can be exploited for heavy-metal-ion sequestrations.

Strategies to directly encapsulate cells in hydrogels with tunable mechanical properties and degradability without harmful gelling conditions are highly desired for regenerative medicine applications. The gelling of most physically crosslinked hydrogels requires substantial changes in the environmental conditions (e.g., pH, temperature, ionic strength), which could be detrimental to the *in situ* encapsulated cells. On the other hand, the cytotoxicity of the crosslinking reagents and initiators and the heat or UV irradiation used to chemically crosslink the hydrogels can negatively impact the viability and long-term fate of the encapsulated cells. A hydrogel system that can be crosslinked under physiological conditions without external perturbations or cross-reactivities with cellular or tissue environment is highly desired. Functional APC-based hydrogel precursors carrying orthogonal reactive groups that can efficiently chemically crosslink to form functional hydrogels under physiological conditions without the use of a cytotoxic catalyst, heat, or UV irradiation are ideal for addressing such a critical challenge. To enable this strategy, our group recently developed an azido-functionalized six-membered cyclic monomer,[28] 5,5-bis(azidomethyl)−1,3-dioxan-2-one [AzDXO; **4** in Figure 4(d)], and prepared the azido-functionalized APC hydrogel precursors by ROP. A cytocompatile degradable hydrogel was then formed via a bioorthogonal azido–alkyne reaction with another alkynylated hydrogel precursor.[31]

Specifically, the hydrogel was formed from two orthogonal synthetic macromers, an azido-functionalized poly(azido carbonate) [$P(AzDXO)_m$]–PEG-*co*-$P(AzDXO)_m$ triblock copolymer and a dibenzocyclooctyne (DBCO)-functionalized PEG [PEG–$(DBCO)_2$ or PEG–$(DBCO)_4$], through copper-free, strain-promoted azide–alkyne cylcloaddition (SPAAC) click chemistry (Figure 6). The azido-functionalized triblock $P(AzDXO)_m$–PEG–$P(AzDXO)_m$ was prepared by the organocatalytic ROP of AzDXO under the catalysis of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), with PEG–diols (M_n = 6000, 10,000, and 20,000 g/mol) as initiators, in dichloromethane at room temperature [Figure 5(a)]. The triblock copolymer macromers with the expected molecular weight and narrow PDI (<1.1) were obtained with a high monomer conversion (~90%). The solubility of the $P(AzDXO)_m$–PEG–$P(AzDXO)_m$ macromers decreased

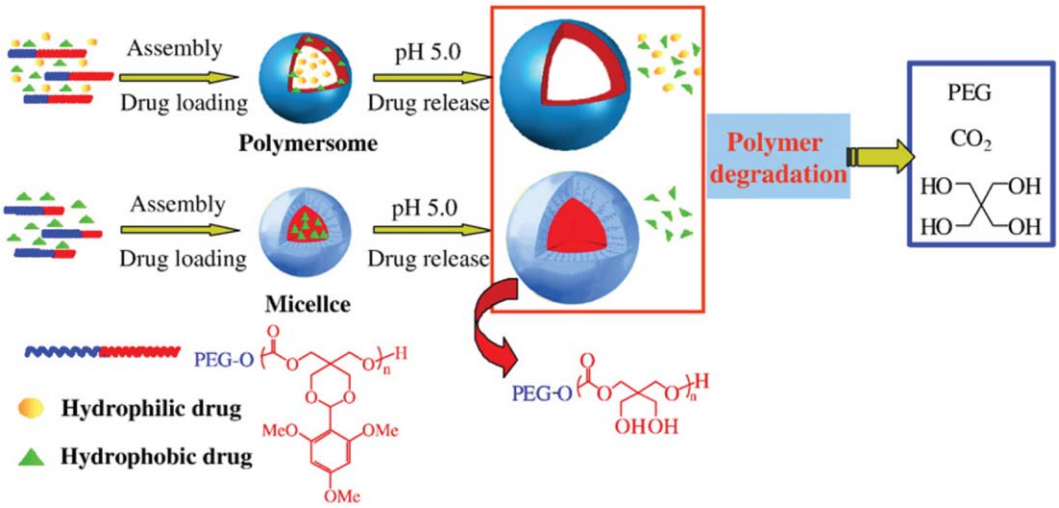

Figure 7. Illustration of pH-sensitive degradable polymersomes based on PEG–PTMBPEC diblock copolymers for the triggered release of both hydrophilic and hydrophobic anticancer drugs. In comparison, pH-sensitive degradable micelles are typically applied for the encapsulation and release of hydrophobic drugs only. (Reproduced with permission from ref. 129. Copyright 2010 Elsevier.). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

with increasing lengths of the polycarbonate block and was less dependent on the PEG block length. Water-soluble triblock copolymers with more than 14 azido groups were obtained. Robust hydrogels were formed upon mixing the azido-functionalized triblock copolymer macromers with the DBCO-functionalized PEG macromers [Figure 5(b)] in aqueous solutions. The gelation time, ranging from 20 s to 5 min, and the shear modulus, ranging from 200 Pa to 10 KPa, could be tuned by the polycarbonate block length, macromer concentration, temperature, and azido/DBCO ratio. The high fidelity and orthogonality of the SPAAC click chemistry and its high efficiency under physiological conditions present significant advantages over other *in situ* crosslinking chemistries for biological applications. The gelation could be carried out in water, PBS, and even cell culture media without noticeable compromises on the gelling kinetics. Rat bone marrow stromal cells (BMSC) were dispersed in the culture media containing DBCO- and azido-functionalized macromers, which rapidly gelled upon mixing [Figure 5(c,d)]. The encapsulated cells remained viable after 48 h at a greater percentage than those encapsulated in a conventional photopolymerized PEG hydrogel. These hydrogel formulations are being optimized in terms of their mechanical properties and degradation rates for potential cartilage tissue engineering applications.

Another hydrogel system based on reactive APC segments was reported by Zhong et al.[147] Acryloyl functionalized precursors, oligo(acryloyl carbonate) (OAC)-*b*-PEG-*b*-OAC (**25** in Figure 5) triblock copolymers, were prepared by the ROP of acryloyl cyclic carbonate (**5** in Figure 5). The hydrogel was formed between thiolated glycol chitosan (GC–SH) and OAC–PEG–OAC via a Michael-type addition reaction. Robust hydrogels were formed upon the mixture of aqueous solutions of GC–SH and OAC–PEG–OAC at relatively low total polymer concentrations of 1.5–4.5 wt % under physiological conditions. Hydrogels with gelation times ranging from 10 s to 17 min and storage moduli varying from 100 to 4300 Pa could be obtained by changes in the degree of thiolation of GC–SH, polymer concentrations, thiol/acrylate molar ratios, and pH. The hydrogels showed good hydrolytic stability in PBS (pH 7.4) at 37°C, whereas much faster degradation occurred in the presence of enzyme. No demonstration of this system for cell encapsulation has been reported yet.

Drug-Delivery Carriers

The use of functional APCs with well-defined chemical compositions and structures for drug-delivery applications was pioneered by Zhuo,[148–158] Jing,[159–166] Hedrick,[33,111,120,121,124,125,128,134,167–171] Yang,[33,34,111,120,121,124,125,128,134,155,167–173] Waymouth,[133,135,167,171,172] Wender,[133,135] and their colleagues. The ROP of functional cyclic carbonates enables an efficient strategy for exploring the chemical space to identify APC-based vehicles for optimal drug encapsulation and delivery. Here we review the recent progress in this area based on the encapsulation format of APC-based delivery vehicles.

Micelles for Hydrophobic Drug Delivery. The initial use of APCs for hydrophobic drug-delivery relied on the hydrophobic interactions between the drug and the polycarbonate segments. Hydrophobic drugs could be loaded directly onto bulk APCs. In the case where hydrophobic segments of the APCs self-assembled to form hydrophobic domains, the drugs could be more stably trapped within these hydrophobic pockets. The release kinetics of the drug is largely governed by the degradation rate or the dissociation of the self-assembled domains of the APCs.

Core–shell nanoparticles or polymeric micelles with a hydrophobic core can be formed through the self-assembly of amphiphilic copolymers in an aqueous environment. Diblock and triblock copolymers of PEG and PTMC with relatively long PEG blocks and short PTMC blocks have been shown to form micelles in aqueous solutions.[148,174] The critical micelle concentration (cmc) ranged from 35 to 100 mg/L and depended on the lengths of the PEG and PTMC blocks; it usually decreased

with increasing length of the hydrophobic PTMC segment. Drug loading efficiencies as high as 30% have been achieved.[148] The degradation rate typically increases with increasing PEG length.

Cyclic carbonate monomers have also been copolymerized with lactones to prepare amphiphilic copolymers to improve the stability of the self-assembled micelles through enhanced hydrophobic interactions. The diblock copolymer PEG-*b*-poly(carbonate-*co*-lactide) was prepared by the copolymerization of lactides and the 2,2-bis(hydroxymethyl) propionic acid (bis-MPA) derived monomer 5-methyl-5-benzyloxycarbonyl-1,3-dioxane-2-one [**6** in Figure 4(d)] with MPEG as an initiator.[119] The inclusion of the carbonate moiety facilitated the self-assembly of the copolymers, and the cmc values of these copolymers were up to 10-fold lower than those of polyethylene glycol-b-poly(L-lactic acid) (PEG-b-PLLA). A nonsteroidal anti-androgen for treating early stage prostate cancer, bicalutamide, was loaded in the copolymer micelles. The bicalutamide loading in the micelles, on the basis of the polycarbonate-containing diblock copolymer, was about fourfold higher than those achieved with micelles without the polycarbonate moiety.[119]

Temperature-sensitive and biodegradable self-assembled micelles were prepared by the linking of poly(*N*-isopropylacrylamide) (PNiPAAm) with hydrophobic APCs.[175] PNiPAAm and related copolymers are the most widely investigated temperature-sensitive polymers. Their copolymers with other poly(meth)acrylates were shown to form micelles in response to temperature triggers. However, the nondegradability of these micelles raised the concern of the inefficient clearance of the micelles from the body. Lee and Chen[175] reported the synthesis of degradable amphiphilic PNiPAAm-*b*-PTMC by the organocatalytic ROP of TMC [**1** in Figure 4(d)] or 5-methyl-5-benzyloxycarbonyl-1,3-dioxane-2-one [**6** in Figure 4(d)] with hydroxyl-terminated PNiPAAm as the macroinitiator.[175] The PNiPAAm-*b*-PTMC block copolymers showed temperature-dependent drug-release characteristics. At temperatures below the lower critical solution temperature, slow drug release was observed because of the higher stability of the micelles. The drug release became much faster when the temperature was increased to 37 or 43°C (higher than the lower critical solution temperature) to effectively disrupt the micelles. Because of the relatively high hydrophilicity of the PNiPAAm segment, the *in vitro* degradation of PNiPAAm-*b*-PTMC was much faster than that of PTMC.

Recently, disclike micelles were prepared from amphiphilic diblock copolymers containing hydrophilic PEG and hydrophobic cholesterol-functionalized APCs.[176] The amphiphilic block copolymers were synthesized through the organocatalytic ROP of cholesterol-functionalized cyclic carbonate monomer cholesteryl 2-(5-methyl-2-oxo-1,3-dioxane-5-carboxyloyloxy)ethyl carbamate [MTC-Chol, **18** in Figure 4(d)] with MPEG as an initiator. The copolymers exhibited unique self-assembly behaviors as a function of the hydrophilic/hydrophobic ratios. The $mPEG_{113}$-*b*-P(MTC–Chol)$_n$ (with 113 representing the units of ethylene oxide, corresponding to a number averaged molecular weight of 5000 g/mol) block copolymers formed disklike micelles when n was 4 and exhibited a stacked, disklike morphology when n was 11. These biodegradable disclike micelles were expected to exhibit unique biodistribution and cellular uptake patterns as drug-delivery carriers.[176]

Although the backbones of APCs are hydrophobic in nature, hydrophilicity may be introduced to APCs via side-chain functionalization. An amphiphilic graft copolymer comprised of hydrophobic poly(ε-caprolactone) (PCL) and hydrophilic polycarbonate segments were recently prepared as reduction-sensitive biodegradable micelles by Zhong et al.[177] This copolymer was prepared by a two-step process involving the preparation of a functional copolymer, PCL-co-P(pyridyl disulfide carbonate) [PCL-co-P(PDSC)], by the copolymerization of ε-caprolactone and a pyridyl disulfide functionalized cyclic carbonate monomer [PDSC, **10** in Figure 4(d)], followed by post-polymerization modification with thiolated PEG via a thiol–disulfide exchange reaction. The resulting amphiphilic, biodegradable graft copolymer, PCL-*g*-SS–PEG (with -SS- representing the disulfide linkage), formed micelles 110–120 nm in diameter and exhibited particularly low cmc values (<1 mg/L). These biodegradable micelles were prone to rapid shell shedding and aggregation under reductive conditions. Doxorubicin-loaded micelles showed redox-responsive drug releases and pronounced antitumor activity against HeLa cells.

Amphiphilic copolymers containing both hydrophobic and hydrophilic APCs were also developed to form micelles for targeted drug-delivery applications.[120] The sequential copolymerization of hydrophobic monomer TMC and hydrophilic diacetonide-protected, carbohydrate-based cyclic carbonate monomers [diacetonide protected glucose, galactose, and mannose, or **11**, **12**, and **13** in Figure 4(d)] yielded amphiphilic block copolymers with hydrophobic PTMC blocks and hydrophilic carbohydrate-functionalized APC blocks upon deprotection under acidic conditions.[120] These glucose- and galactose-functionalized block copolymers self-assembled into micelles that displayed a high density of sugar moieties on the surface. The delivery of doxorubicin via the galactose-functionalized micelles diaplayed enhanced cytotoxicity toward asialoglycoprotein receptor (ASGP-R) positive HepG2 cells, to which the micelles selectively targeted via the surface galactose moieties.

Polymersomes for Drug Delivery. Polymersomes are similar in microstructures to liposomes, which are formed by amphiphilic self-assembling lipids in aqueous media, and are characterized by a hydrophilic interior and a hydrophilic exterior separated by hydrophobic intermediate components.[178] Polymersomes may be exploited to deliver both hydrophilic (with the drug to be encapsulated within the hydrophilic interior) and hydrophobic (with the drug to be trapped within the hydrophobic domain) drugs and exhibit improved stability compared to liposomes. Whether an amphiphilic block copolymer can self-assemble into polymersomes is determined mainly by the hydrophobic/hydrophilic balance, molecular weight, and effective interaction parameter of its hydrophobic block with H_2O (χ).[178] Biodegradable polymersomes prepared from block copolymers based on PEG-*b*-poly(trimethylene carbonates) and PTMC-*b*-poly(L-glutamic acid)[130–132] have been reported.

Recently, Zhong et al.[129] reported a stimuli-sensitive degradable polymersome containing pH-responsive polycarbonate segments

(Figure 7). These polymersomes were based on the diblock copolymer of PEG and the APC containing, acid-labile trimethoxybenzylidene acetal-functionalized side chains (PTMBPECs). The copolymer with appropriate molecular compositions, PEG1.9k–PTMBPEC6k, was shown to spontaneously form polymersomes that were 100–200 nm in diameter in aqueous solutions. The copolymer with a longer PEG segment, PEG5k–PTMBPEC5.8k, on the other hand, formed micelles under the same conditions. The acetal protection groups on the APC side chains were stable at pH 7.4 but were rapidly deprotected at pH 4.0 and 5.0, exhibiting a half-life of 0.5 and 3 days, respectively. Both paclitaxel (PTX; hydrophobic) and doxorubicin hydrochloride (hydrophilic) could be loaded into the PEG1.9k–PTMBPEC6k-based polymersomes, whereas the PEG5k–PTMBPEC5.8k-based micelles could only be loaded with the hydrophobic PTX. Both carriers exhibited pH-dependent drug-release profiles, and the release rate increased significantly with lower pH. The PTX release from the polymersome was much faster than that from the micelles, likely because of the more significant dimensional changes in the polymersomes upon the cleavage of the acetal groups.

Temperature-induced fusion and fission of the polymersome prepared from PTMC-*b*-poly(L-glutamic acid) were also reported.[179] Polymersome budding and fission occurred when the temperature was increased above the melting temperature of the PTMC component, whereas fusion events were observed when the temperature was decreased. This phenomenon provided another potential strategy for the controlled release of therapeutics via polymersomes.

Degradable Polycationic Polycarbonates for DNA and Small Interfering RNA (siRNA) Delivery. Gene therapy has emerged as a promising strategy for the treatment of genetic diseases. Cationic polymeric nonviral vectors have received a lot attention for their potentially safer delivery of negatively charged DNA or siRNA cargos. Many earlier nonviral gene-delivery studies used commercially available, nondegradable polycations, such as poly(L-lysine), polyethylenimine (PEI), and polyamidoamine dendrimers, which exhibited fairly good transfection efficiency but significant cytotoxicity. Biodegradable, polycationic APCs have recently been explored as improved delivery vehicles for DNA (or siRNA).

Zhuo et al.[158] prepared a series of amine-functionalized APCs by a three-step process, including the lipase-catalyzed ROP of an ally-functionalized cyclic carbonate monomer, conversion of ally groups to epoxy groups, and finally, grafting of PEI to the polymer via the nucleophilic opening of the epoxy by the primary amine residues of the PEI [Figure 8(a)]. Poly(5-methyl-5-allyloxycarbonyl–trimethylene carbonate) (PMAC) was first synthesized in bulk by the catalysis by immobilized porcine pancreas lipase. Upon epoxidation of the allyl group by 3-chloroperoxybenzoic acid, the polymer was reacted with low-molecular-weight PEI_x at about 100% efficiency to give PEI-grafted polycarbonate (PMAC-*g*-PEI_x) with a controlled molecular weight and a slightly broad PDI. Because of the shielding effect of the PMAC backbone on the positive charge density, PMAC-*g*-PEI_x polyplexes exhibited much lower cytotoxicity compared to their PEI counterparts. PMAC-*g*-PEI_x could form positively charged nanosized particles (30–90 nm) with plasmid DNA (pDNA). *In vitro* transfection experiments in 293T cells showed that the PMAC-*g*-PEI_x/DNA complexes exhibited enhanced transfection efficiency compared with PEI25k.

Seow and Yang[34] also reported an amine-functionalized APC for gene delivery using a similar strategy [Figure 8(b)], which involved the organocatalytic ROP of protected carboxyl-functionalized cyclic carbonate monomer, deprotection to expose the carboxyl groups, and conjugation of aliphatic amines to the carboxyls by amidation. Specifically, a series of benzyl-protected polycarbonates with well-defined molecular weights and narrow PDIs ($M_n = 4500$–8400 g/mol, PDI < 1.20) were first prepared by the organocatalytic ROP of 5-methyl-5-benzyloxycarbonyl-1,3-dioxan-2-one. Carboxylic acid functionalized polycarbonate was then obtained after the removal of benzyl groups via palladium-on-carbon (Pd/C)-catalyzed hydrogenation. The amine-functionalized polycarbonate was prepared by further reaction with a variety of aliphatic amines (triethylenetetramine, tetraethylenepentamine, and pentaethylenehexamine). The degree of amine conjugation was estimated to be about 60%. These functional APCs readily formed nanoparticles upon direct dissolution in water. The cmc values ranged from 22 to 45 mg/L depending on the molecular weight of the copolymer and the type of aliphatic amine conjugated. These amine-functionalized APCs readily attracted DNA to form polycarbonate/DNA complexes 200 to 1000 nm in size. Transfection with these polymeric vectors mediated luciferase expression in the HEK293, HepG2, and 4T1 cell lines at efficiencies comparable or superior to that enabled by the PEI control. Moreover, the cytotoxicity of these polycarbonates much less compared to PEI.

The same group further optimized this DNA delivery platform by employing a two-step reaction instead of the three-step reaction [Figure 8(c)].[33] A series of cationic APCs with well-defined molecular weights and narrow PDIs were developed with the organocatalytic ROP of haloalkyl-functionalized cyclic carbonates derived from bis-MPA, followed by quaternization with bis-tertiary amine. The resulting cationic APCs were able to bind to and condense DNA to form polycarbonate/DNA nanocomplexes (83–124 nm). The nanocomplexes induced high luciferase expression efficiency in all four cell lines examined at relatively low N:P ratios in the presence of serum.

Cationic APCs have also been designed for the delivery of siRNA to induce RNA interference (RNAi). RNAi has been recognized as a general endogenous mechanism adopted by many organisms to silence the expression of genes that control various cellular events and to protect the cell from viral replication.[180] Synthetic siRNA are polyanionic, polar, and large, double-stranded RNA molecules, typically consisting of a 19–23-base-paired region with two 3′ overhanging nucleotides. The introduction of siRNAs into cultured cells can trigger highly efficient gene silencing through the degradation of the endogenous mRNA, whose sequence is complementary to the siRNA, making siRNAs a promising therapeutic modality for the treatment of cancer, viral infections, ocular disorders, and genetic diseases. The delivery of siRNA across the cell membrane and nucleus

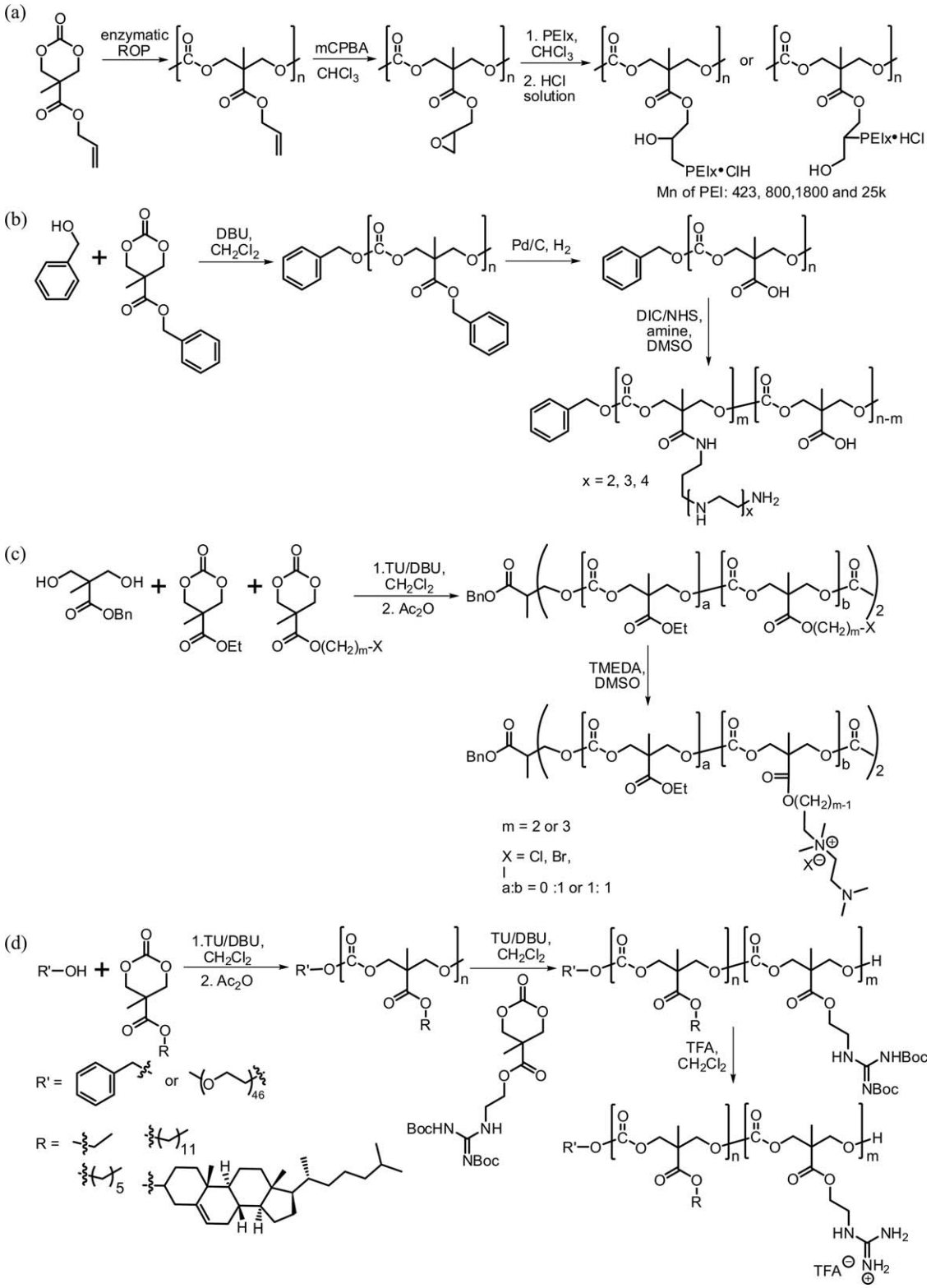

Figure 8. Representative preparations of degradable cationic APCs for DNA and siRNA deliveries: (a) a three-step method for preparing PEI-grafted polycarbonate (Reproduced with permission from ref. 158. Copyright 2009 Elsevier.), (b) a three-step method for preparing amine-functionalized polycarbonates (Reproduced with permission from ref. 34. Copyright 2009 Elsevier.), (c) a two-step method for preparing cationic APCs (Adapted with permission from ref. 33. Copyright 2011 Elsevier.), and (d) synthesis of a guanidinium-rich amphipathic carbonate co-oligomers (Adapted with permission from ref. 135. Copyright 2012 National Academy of Sciences.).

without degradation is the key to the success of RNAi therapeutics.

Wender et al.[135] successfully delivered siRNA into cells to achieve a 90% knockdown of a selected target protein with amphiphilic carbonate co-oligomers, which were composed of guanidinium-rich side chains for binding siRNA through electrostatic and hydrogen-bonding interactions and hydrophobic side chains for facilitating cellular entry.[135] The co-oligomers were prepared by the sequential or one-pot copolymerization of a series bis-MPA-derived cyclic carbonate monomers with biocompatible lipid side chains (ethyl, hexyl, or dodecyl) or cholesterol and BOC-protected guanidine monomers with benzyl alcohol or MPEG as an initiator [Figure 8(d)]. Block or random co-oligomers with a controlled composition and length were obtained. The removal of the BOC groups with trifluoroacetic acid yielded the desired amphiphilic carbonate co-oligomers containing both hydrophobic alkyl side chains and hydrophilic/charged guanidine groups. The size of the siRNA/co-oligomer complexes ranged from about 200 nm to 1.5 μm in diameter, depending on the co-oligomer type and the siRNA/co-oligomer ratio. A preliminary screening experiment on the delivery efficiency by siRNA/co-oligomer complexes showed that dodecylated co-oligomers achieved an average of 86% knockdown of the target protein with high specificity under serum-free conditions. Interestingly, the shorter co-oligomers were found to outperform their longer counterparts within each hydrophobic side-chain series. Random co-oligomers did not perform as consistently as their block co-oligomer counterparts. By mixing different co-oligomers with defined block compositions, an even greater diversity in the siRNA complexation system and, thus, siRNA delivery performances could be accomplished.

CONCLUSIONS

In summary, APCs, a type of long-known but underused degradable polymer, have been rejuvenated with new functionalities and properties. A wide range of APCs and APC-based copolymers have been prepared with a combination of improved polymerization techniques and novel functional monomers. Practical industrial applications of APCs, however, are still rare. The successful translation of APCs for industrial uses will require further improvements in many aspects, including the development of more universal/versatile catalyst systems, deeper understanding of the polymerization mechanisms and kinetics as a function of the monomer structure, and ultimately, the development of a predictive model to guide the rational/iterative design of functional polymers for the various targeted applications. With the flexibility provided by APCs in the adjustment of the polymer/copolymer degradation rate, hydrophilicity/hydrophobicity, and thermomechanical properties, many fundamental questions, such as those concerning the polymeric structure–properties relationship and cell–biomaterials interactions, can be more systematically interrogated, which willl ultimately benefit their biomedical applications and beyond.

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