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Degradable vinyl polymers for biomedical applications

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Vinyl polymers have been the focus of intensive research over the past few decades and are attractive materials owing to their ease of synthesis and their broad diversity of architectures, compositions and functionalities. Their carbon–carbon backbones are extremely resistant to degradation, however, and this property limits their uses. Degradable polymers are an important field of research in polymer science and have been used in a wide range of applications spanning from (nano)medicine to microelectronics and environmental protection. The development of synthetic strategies to enable complete or partial degradation of vinyl polymers is, therefore, of great importance because it will offer new opportunities for the application of these materials. This Review captures the most recent and promising approaches to the design of degradable vinyl polymers and discusses the potential of these materials for biomedical applications.

After more than 50 years of continuous growth, worldwide production of synthetic polymers in 2013[1] was approaching 300 Mt, about half of which was obtained by free-radical polymerization (FRP) of vinyl monomers (~45% of manufactured plastic materials and ~40% of synthetic rubbers). FRP is certainly the most versatile and robust polymerization method because it requires undemanding synthetic conditions, is compatible with many organic solvents and water, and tolerates a wide variety of functional monomers; altogether this makes it relatively easy to translate to an industrial plant. The carbon–carbon backbones of vinyl materials (with the exception of poly(vinyl alcohol)[2]) resist degradation, which explains why the major industrial applications of vinyl polymers (for example, low-density polyethylene, poly(vinyl chloride), polystyrene, poly((meth)acrylic esters), poly(vinyl acetate) and fluoropolymers) are structural, such as packaging and building materials. But this very durability prevents hydrolysis or enzymatic degradation of the materials in biological environments, leading to waste disposal problems and environmental issues (of which the Great Pacific Garbage Patch is one of the most striking illustrations). Vinyl-based polymers are also employed in an increasing number of higher-added-value and specialty applications, especially in the area of microelectronics (for example, positive or negative resists in microlithography) and biomaterials (for example, drug delivery devices, tissue engineering scaffolds), for which degradability is often essential. Indeed, unlike polyesters and polypeptides, which contain labile groups in their main chain enabling cleavage into small pieces, the persistence of vinyl polymers employed for biomedical applications requiring degradable materials may cause toxicity and hamper their translation to clinical settings and, eventually, to the market.

This would be unfortunate in regards to the massive amount of work devoted to macromolecular engineering towards biomedical applications, especially since the advent of controlled radical polymerization (CRP)[3–6]. This general term gathers several techniques that enable a high degree of control (for example, predictable molar mass, low molar mass distribution, high chain-end fidelity, and so on) and functionalization to be reached, while maintaining all the advantages of FRP (for example, ease of use, applicability to a broad range of vinyl monomers, tolerance to numerous processes such as bulk, solution, emulsion, dispersion, and so on). As a result of these advanced polymerization methods, the past few years have been marked by a surge in the design of innovative and more sophisticated vinyl materials. Some of these are intended for applications in different bio-related areas, such as drug delivery, diagnostics or tissue engineering. Despite significant advances from synthetic and conceptual points of view, some very encouraging results and even improved performance compared with traditional systems, the persistence and non-degradability of the vast majority of these materials may cause unwanted immune responses and toxicity, and eventually result in a deadlock regarding regulatory requirements and risk–benefit analysis.

Biodegradable polymers strictly refer to polymers that degrade by biological activity (that is, action of cells) via lowering of their molar masses, whereas the term degradable is preferred when the degradation results from the action of water (hydrolysis), whether it is *in vitro* or *in vivo*, enzymes *in vitro* (enzymatic degradation), or when the mechanism of chain scission is unknown or not proven as cell mediated[7]. The term bioresorbable is used when an injected polymer is fully assimilated or eliminated *in vivo*, for instance through renal or biliary pathways. Note that *in vivo* degradation or biodegradation are necessary prior to bioresorption for high molar mass polymers (a commonly accepted renal excretion limit is ~40–60 kDa)[8]. Degradability is a key safety issue when choosing materials for specific biomedical applications (for example, drug delivery, tissue engineering, and so on). For instance, implantable biomedical devices must be biocompatible but stable in biological environments to perform their functions in the long term. Conversely, polymers for use as tissue-engineered implants or as nanocarrier materials for drug delivery applications need to degrade eventually and ideally be excreted so that no polymer remains in the body after treatment. The nature of the degradation products is also crucial since their toxicity will determine the ultimate biocompatibility of the materials. If *in vivo* degradation results in the release of naturally occurring monomeric components, they can also be metabolized by natural processes such as the Krebs cycle. This eliminates the risk of complications associated with the long-term presence of a foreign material. For tissue engineering applications, the degradation timescale should match with the tissue healing processes (from weeks to years), whereas

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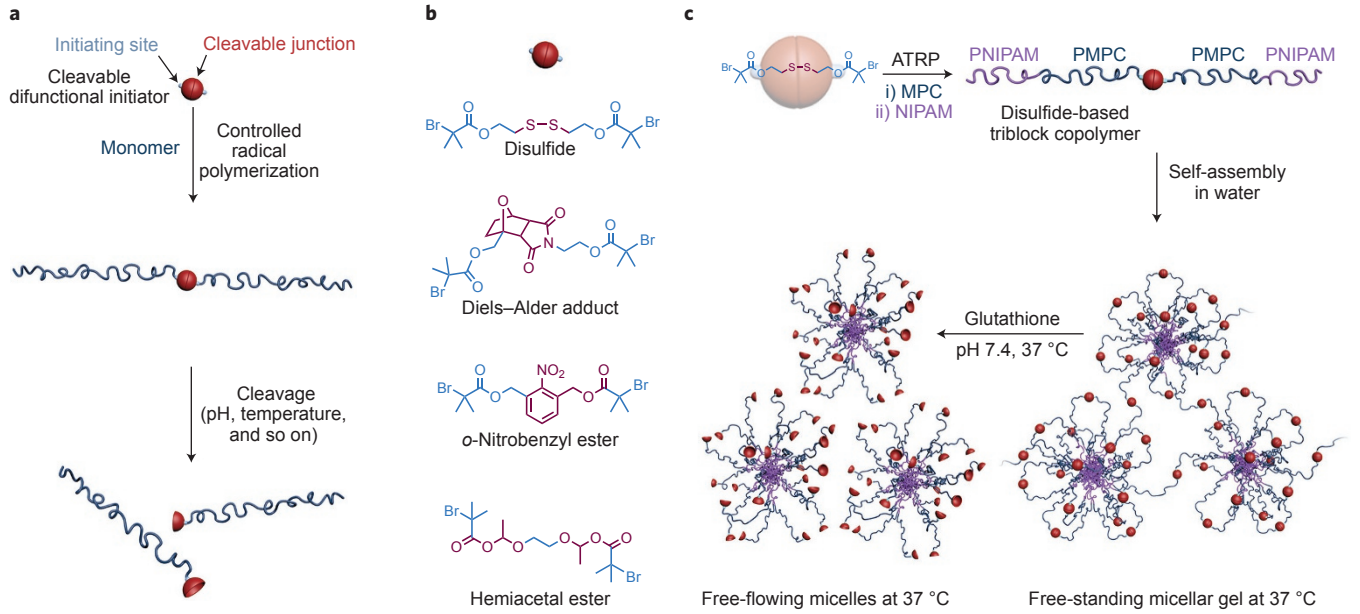

Figure 1 | Cleavable difunctional initiators to prepare mid-chain degradable polymers. a, General synthetic pathway for the insertion of mid-chain degradable functionalities within a polymer backbone from a cleavable controlled radical polymerization (CRP) difunctional initiator. **b**, Representative cleavable difunctional atom-transfer radical polymerization (ATRP) initiators containing disulfide, Diels–Alder, *o*-nitrobenzyl ester and hemiacetal ester groups. **c**, Synthetic route to a disulfide-based thermo-responsive PNIPAM-b-PMPC-b-PNIPAM triblock copolymer gelator from a cleavable difunctional ATRP initiator. Panel **c** adapted from ref. 21, Wiley.

for drug delivery purposes, it should ideally start after the nanocarriers have reached the diseased site and proceed in parallel with the drug release (from hours and days to months). Once the nanocarriers have reached their target tissue, polymer degradation can facilitate drug delivery by enabling the release of physically encapsulated drugs.

In this very demanding context, strategies conferring degradability to vinyl materials are of paramount importance and may represent the missing link between the design of advanced vinyl materials and their safe use in biomedical applications. This Review discusses recent and promising synthetic strategies for degradable vinyl polymers and emphasizes potential candidates for biomedical applications. Even though each degradation mode may not find direct application in the biomedical field and pharmacokinetic aspects or potential toxicity issues are not discussed, all pathways leading to chain scission will be covered, with a particular focus on hydrolytic, enzymatic and reductive degradations, because they can mimic biological conditions (for example, pH found in certain cellular subcompartments or associated with some pathological situations, presence of specific enzymes or reducing agents in cells).

Degradation of the polymer backbone

The obvious approach to confer degradability to macromolecules is to introduce labile units within the polymer backbone. A small number of degradable links can cause a significant decrease in molar mass, providing they are homogeneously distributed along the chain. For instance, a single cleavable unit will enable a reduction of the number average molar mass (M_n) by half after degradation. While multiple cleavable units are necessary for complete degradation, some applications require only partial degradation, and can be designed by combining degradable and non-degradable blocks.

Discrete insertion of main-chain degradable groups. The insertion of a single, typically central, degradable functionality into a vinyl polymer backbone became possible with the advent of CRP techniques, such as nitroxide-mediated polymerization (NMP),[3] atom-transfer radical polymerization (ATRP)[4,5] and reversible addition-fragmentation chain-transfer polymerization (RAFT)[6]. The high degree of structural control and chain-end fidelity of CRP-derived polymers allows for the use of difunctional initiators containing a cleavable function[9], followed by divergent chain growth, to position one degradable junction between two polymer blocks (Fig. 1a). In this instance, the disulfide bond appears to be the redox-sensitive linkage of choice (although the redox properties of selenium are receiving increasing interest[10]) for triggering cellular delivery applications by means of glutathione (GSH), one of the main reducing agents inside cells and the most abundant in the cytosol. However, it should be noted that the real biological situation is more complex, featuring subtle differences in redox potential within cells and a variety of different reducing agents[11]. To be translatable to the clinic, these characteristics should be considered in detail when developing redox-sensitive materials. Disulfide-containing polymers can be designed by different CRP methods from various disulfide difunctional initiators[9,12]. Addition of GSH or dithiothreitol (DTT) is usually performed to demonstrate the cleavage. Other difunctional CRP initiators (whose cleavage conditions are perhaps less biologically relevant) were also considered (Fig. 1b), based on a Diels–Alder adduct (thermal degradation)[13], a hemiacetal ester group (acid hydrolysis)[14], or an *o*-nitrobenzyl moiety (photodegradation)[15]. Interestingly, the photocleavable nature of *o*-nitrobenzyl moieties enables the use of a non-invasive method of degradation that can be temporally and spatially controlled[16,17]. One can also take advantage of the susceptibility of trithiocarbonate to aminolysis as a means to centrally cleave polymers made from symmetrical trithiocarbonate RAFT agents[18].

Owing to the simultaneity of the divergent chain growth, the use of cleavable difunctional initiators is restricted to the design of polymer blocks of the same nature, leading to symmetric architectures with a central degradable function. For instance, a single polymerization step will give a homopolymer, whereas consecutive polymerizations of different monomers will lead to an ABA triblock copolymer[19,20]. This has been illustrated by the preparation of disulfide-based poly(*N*-isopropyl acrylamide)-b-poly(2-methacryloyloxyethyl phosphorylcholine)-b-poly(*N*-isopropyl acrylamide) (PNIPAM-b-PMPC-b-PNIPAM)

triblock copolymer micelles forming a free-standing gel due to the establishment of disulfide bridges between the micelles. Nearly quantitative central cleavage by DTT caused irreversible dissolution of the micellar gel (Fig. 1c)[21]. This degradation was expected to be achieved under physiologically relevant conditions in the presence of naturally occurring oligopeptides, such as GSH. The method can also be adapted to multifunctional initiators containing degradable moieties to access complex architectures. For instance, tetrafunctional ATRP initiators with a central disulfide linkage and four ester groups bearing the initiating sites yield four-arm star polymers with two levels of degradability: reductive environments cleave the polymer into two symmetric parts, whereas alkaline conditions cut the four arms off[22]. This concept could be well adapted for drug delivery applications, as increasing the number of cleavable arms can result in unimolecular, degradable drug delivery vehicles, such as poly(ethylene glycol) (PEG)-based star-comb polymers[23] or star-shaped polymers made of a β-cyclodextrin core and multiple polymethacrylate chains[24].

Macromolecular coupling approaches are also convenient for preparing polymers with central cleavable groups embedded in them. A typical example are thermo-labile alkoxyamine functionalities, which cleave at high temperature and can be inserted by a variety of different techniques[25–27]. In a more biorelevant context, disulfide groups can also be positioned at the junction of AB diblock copolymers, thus enabling degradation under mild, reducing conditions. The methodology relies on the synthesis of two different ATRP-derived pyridyldisulfide (PDS) α-functional polymers; one of them being further reduced to react with the one still containing a PDS functionality to form the disulfide bridge, whose cleavage has been shown in organic solution in the presence of DTT[28]. Owing to the broad variety of different PDS-terminated polymers that can be designed, multi-stimuli sensitive amphiphilic block copolymers have been prepared by connecting a temperature-responsive block and a pH-responsive one[29]. Supramolecular interactions can also efficiently connect two polymer chains together, thereby affording dynamic and reversible structures, whose cleavage can be governed by a broad range of stimuli (for example, redox potential, electric field, temperature, competitive ligand)[30]. In the field of vinyl materials, most recent work stems from the design of well-defined polymers end-terminated by complementary moieties from the supramolecular toolbox (for example, hydrogen bonding, metal coordination, host–guest interactions) that are further reacted together[31–34]. The robustness of this approach has especially been illustrated by a one-pot orthogonal self-assembly using two concomitant orthogonal hydrogen-bonding recognition pairs, leading to supramolecular ABC triblock copolymers[35]. Such a strategy may find applications as stimuli-responsive colloidal structures for drug delivery[36], providing cleavage can be implemented *in vivo*. They can be formed and disassembled on demand on alternate ultraviolet–visible light exposure or electric stimulation, as shown for the latter with polystyrene-β-cyclodextrin (PS-βCD) and poly(ethylene oxide)-ferrocene (PEO-Fc) supramolecular vesicles (Fig. 2)[37]. Despite encouraging results and proofs of concept, it would be important to test these systems in more relevant biological contexts to assess their *in vitro* and *in vivo* degradability.

Multiple insertions of main-chain degradable functionalities. These are required to achieve significant or complete degradation, which is particularly relevant for biomedical applications where the polymer material must eventually be excreted. For this purpose, macromolecular coupling approaches can be adapted to produce multisegmented degradable polymers by using difunctional precursors. For instance, although typical cleavage temperatures should be lowered for biomedical applications, alkoxyamine-containing multisegmented polymers can be obtained by atom-transfer nitroxide radical coupling (ATNRC) from ATRP-derived α,ω-dihalogenated polymers and dinitroxides[38] or by nitrone-mediated radical coupling (NMRC) from similar polymer precursors[39]. Dinitroxides can also contain ester or disulfide moieties, thus conferring additional chemical and redox degradable properties, respectively, which could be well adapted for conferring degradability *in vivo*. On the other hand, disulfide-containing multisegmented polymers can readily be obtained by reacting together dithiol-terminated polymers under $FeCl_3$ or O_2 oxidation[12,40]. These materials are generally synthesized by ATRP (after nucleophilic substitution of the halide group of the corresponding dibromo-terminated polymers)[12] or by RAFT (after aminolysis of the RAFT end groups)[40,41]. Multiple disulfide functionalities can also be inserted by a polycondensation, step-growth procedure from a RAFT-derived macromonomer with a pyridyl disulfide end group, yielding polydisulfides with selective degradability *in vitro* in the presence of intracellular concentrations of GSH[42].

An alternative to the formation of degradable junctions between polymer blocks is the incorporation of degradable moieties in the polymer backbone. This has been achieved by ATRP of divinyl monomers with dibromo compounds bearing disulfide or ketal functionalities[43], or by multiple insertions of an enzymatically degradable peptide sequence (GFLG) in a vinyl polymer

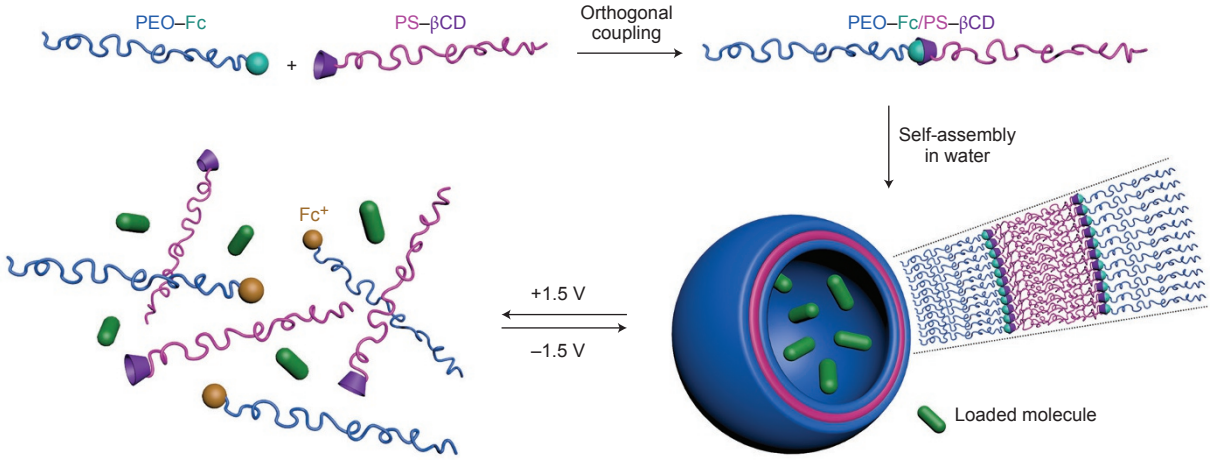

Figure 2 | Voltage-responsive polymer nanocapsules. End-functionalized polystyrene–β-cyclodextrin (PS–βCD) and poly(ethylene oxide)–ferrocene (PEO–Fc) are able to orthogonally form PS–βCD/PEO–Fc diblock copolymers by βCD–Fc host–guest interaction. They can further self-assemble into supramolecular nanocapsules in aqueous solution whose assembly and disassembly can be reversibly controlled by means of an electric field through the association and disassociation of the central supramolecular junction. Figure adapted from ref. 37, ACS.

chain. The latter approach was applied to water-soluble poly(*N*-(2-hydroxypropyl) methacrylamide) (PHPMA) coupled to doxorubicin (Dox)[44], which was the first polymer prodrug to enter clinical trials[45]. However, the non-degradable PHPMA–Dox prodrug showed marginal efficacy during phase II trials, possibly due to the relatively low molecular weight tested (~28 kDa). Conferring degradability to this system enabled the administration of higher molecular weight polymers, which were still excretable after degradation, and resulted in enhanced polymer prodrug accumulation in the tumour tissue by the enhanced permeability and retention effect. To do so, α,ω-telechelic PHPMA chains prepared by RAFT polymerization were linked together by means of a difunctional GFLG sequence via copper(I)-catalysed azide–alkyne Huisgen cycloaddition (Fig. 3) or thiol–maleimide coupling[46,47]. This versatile method allows for additional GFLG sequences to be inserted in the polymer structure, either in the middle of each PHPMA chain by using a GFLG-containing difunctional RAFT agent, or on the side chain between each drug and the polymer scaffold to promote the drug release. This system was proven to be biodegradable and bioresorbable by means of pharmacokinetics and biodistribution studies[48] and has been applied to various anticancer agents (for example, Dox, gemcitabine, paclitaxel, platinum drugs)[48–52] and prostaglandin E1 as an anabolic agent in bone[47]. Star PHPMA-drug conjugates have also been prepared by linking PHPMA chains to poly(amidoamine) (PAMAM) dendrimers via GFLG sequences acting as degradable spacers[53].

To circumvent the inherent constraints of consecutive macromolecular coupling, polyaddition and polycondensation reactions (for example, multistep processes, high dispersities), which may limit the applicability of the polymer, new polymerization concepts have emerged with the common feature of directly inserting multiple degradable functionalities in the course of the polymerization. This not only simplifies the synthetic pathway, but also gives more flexibility and robustness to the polymer design. In this respect, metal-catalysed step-growth radical polymerization of monomers possessing unconjugated C=C and active C–Cl bonds is an appealing strategy[54]. Such monomers can incorporate ester groups, leading to degradable vinyl homopolymers[55], but they can also be copolymerized with traditional vinyl monomers using an ATRP catalyst (this method is then termed simultaneous chain- and step-growth radical polymerization) for novel degradable architectures[54,56]. Although this system suffers from broad molar mass distributions (which is inherent to step-growth polymerization), it has been applied to the design of self-degradable antibacterial polymers via the copolymerization of an amine-functionalized acrylate[57]. However, their *in vivo* degradability still needs to be demonstrated to make them potential candidates for biomedical applications requiring this feature. Interestingly enough, though molecular oxygen is frequently viewed as inimical to radical polymerization, its copolymerization with vinyl monomers by oxidative polymerization affords polyperoxides that degrade at high temperatures (~60–150 °C)[58]. These copolymerizations can also proceed under CRP conditions using reversible chain-transfer catalysed polymerization (RTCP)[59] and produce biocompatible materials that can be cleaved by enzymatic degradation of the –O–O– sequence, which is encouraging regarding its potential degradability *in vivo*[60]. The use of polytrithiocarbonates, which can be seen as 'polyRAFT agents', can lead to well-defined polymers with multiple cleavable trithiocarbonate functionalities in the backbone after a single polymerization step[61]. The number of cleavable junctions is governed by the degree of functionality of the polyRAFT agent.

Despite these achievements, radical ring-opening polymerization (rROP) of cyclic monomers remains the radical polymerization technique of choice for incorporating degradable groups into the polymer backbone and enabling complete degradation. Thanks to its radical ring-opening mechanism, rROP possesses both the versatility of radical polymerization and the ability to introduce functional groups into the polymer backbone. The resulting polymers show low shrinkage, which is important for applications where constant volume is desirable, such as tooth fillings, coatings, and accurate moulding of electrical and electronic components. Several classes of cyclic monomers capable of undergoing rROP have been developed. Among them, cyclic ketene acetals (CKAs) are the most-studied family (Fig. 4a) and were the subject of extensive research by Bailey and co-workers in the early 80s[62]. Although homopolymerization of CKAs is not straightforward, these monomers have aroused renewed interest over the past decade as comonomers to confer degradability to vinyl polymers via insertion of ester groups (Fig. 4b)[63]. The advantages offered by this approach are many: (i) different structures of CKAs can be synthesized (even mimicking traditional polyester repeat units once opened, such as polycaprolactone (PCL)), thus offering flexibility regarding the materials properties, although the number of efficient CKAs is still limited; (ii) despite unfavourable reactivity ratios requiring a large excess of CKAs in the

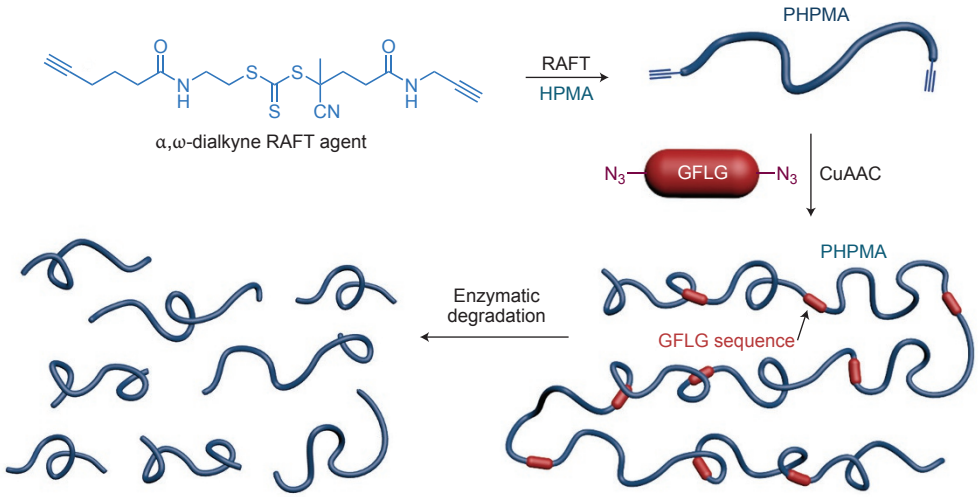

Figure 3 | Multisegmented polymer comprising biodegradable sequences in the main chain. Synthesis of multisegmented poly(*N*-(2-hydroxypropyl) methacrylamide) (PHPMA) copolymer by a combination of reversible addition–fragmentation chain-transfer (RAFT) polymerization of HPMA followed by copper-catalysed azide–alkyne Huisgen cycloaddition (CuAAC) between the resulting α,ω-dialkyne PHPMA and α,ω-diazide GFLG peptide sequence. Figure adapted from ref. 46, ACS.

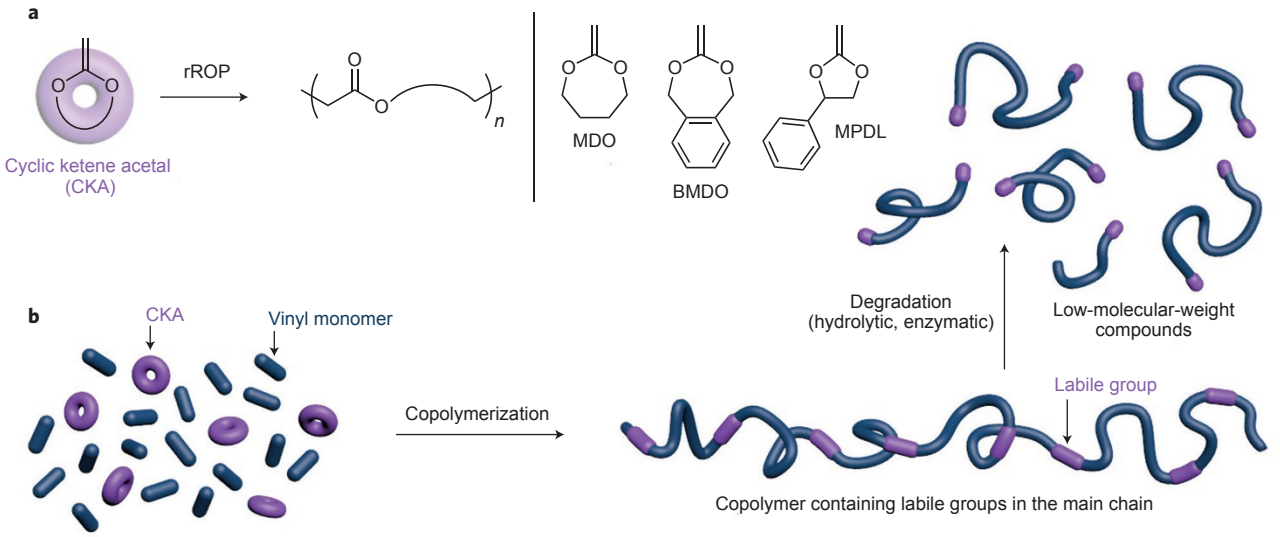

Figure 4 | Radical ring-opening polymerization (rROP) to insert ester groups in the polymer backbone. a, rROP of cyclic ketene acetals (CKAs) and structures of three representative CKAs (MDO = 2-methylene-1,3-dioxepane; BMDO = 5,6-benzo-2-methylene-1,3-dioxepane; MPDL = 2-methylene-phenyl-1,3-dioxolane). **b**, Synthesis of a copolymer comprising multiple ester functions by radical copolymerization between a vinyl monomer and a CKA polymerized by rROP.

comonomer feed, these monomers can be copolymerized with several traditional vinyl monomers both by FRP and CRP techniques, for designing well-defined, complex macromolecular architectures, such as block, grafted or star copolymers; and (iii) CKAs are randomly distributed into the copolymer backbone, which enables fine-tuning of the degradability of the materials simply by adjusting the monomer feed. The flexibility of this approach has been illustrated by the synthesis of a variety of different copolymer structures[64–69], which are intended to find applications in drug delivery, tissue engineering or hydrophobic coatings. Other families of cyclic monomers for performing rROP have been investigated as well, but to a lesser extent. Besides several methylene–dioxolane derivatives that lead to the insertion of ketones with potential photodegradability[70], cyclic allylic sulfides have shown promising results, especially since they can be used to incorporate ester, thioester and disulfide functionalities into the polymer backbone under controlled radical copolymerization conditions with traditional vinyl monomers[71,72]. Although rROP-derived polymers are currently attracting renewed interest, their degradability *in vivo* has not yet been shown. Current examples only refer to hydrolytic and *in vitro* enzymatic degradations, as well as degradation by composting[67].

While radical polymerization has captured most of the attention, living cationic polymerization can also be used to copolymerize naturally occurring aldehydes and vinyl ethers for the synthesis of alternating, degradable copolymers bearing acetal functions[73]. It is noteworthy that, due to the alternating structure, degradation on acid hydrolysis is observed down to monomer-unit molecular weight. Also, the broad structural diversity of vinyl ethers gave access to a wide range of different copolymers exhibiting water solubility and pH- and thermo-responsiveness[74].

Copolymers with non-vinyl degradable blocks. An efficient way of producing degradable vinyl-based materials consists of combining a CRP technique with a polymerization method leading to well-known degradable polymer segments, such as ring-opening polymerization (ROP), either of lactones or *N*-carboxyanhydrides. Although here the vinyl block is persistent, the resulting copolymer will contain polyester or polypeptide chains that can be degraded *in vivo* hydrolytically or by specific enzymes, thus ensuring substantial degradability of the whole material. An important advantage is that synthetic polyesters, such as poly(lactic acid), poly(lactic-co-glycolic acid) and PCL, are well-known US Food and Drug Administration-approved biodegradable materials. By varying the combination of polymerization methods, the nature of the monomers and the synthetic strategies, a large range of degradable architectures with unique properties can be designed owing to structurally different blocks. For example, hydroxyl or amine functional CRP initiators can be used for combining ROP and CRP by divergent chain growth to produce partially degradable diblock copolymers[75–78], and for some of them in a one-step process providing appropriate conditions are applied (Fig. 5a)[79]. This strategy can be extended to ABA triblock copolymers comprising a degradable central block by starting from a difunctional polyester macroinitiator for CRP[80,81]. From such block copolymers, potential biomedical applications have been suggested, including nanoparticles[82], micelles[75,83], nanocages[84] and porous membranes[81] for drug delivery, and hydrogels[80] for tissue engineering. Other partially degradable morphologies have also been investigated. For instance, a range of selectively degradable core crosslinked star (CCS) copolymers that can find applications in drug delivery or membrane formation have been synthesized, including arm-degradable CCS, partially arm-degradable CCS and core-degradable CCS polymers (Fig. 5b)[85,86]. The multiplicity of the possible grafting strategies enables great variation of the final macromolecular structure and ensures different levels of degradation. A typical example are bottle-brush macromolecules, which received considerable attention due to their potential for intramolecular nanoengineering, such as templates for inorganic nanoparticles or nanowires. Three efficient pathways have been developed for the synthesis of bottle-brushes comprising degradable segments: (i) the 'grafting from' method, for which vinyl chains are grown under ATRP conditions from polymer scaffolds based on halogenated ROP monomers, such as α-chloro-ε-caprolactone (α-Cl-ε-CL) or *N*-ε-bromoisobutyryl-L-lysine *N*-carboxyanhydride (Br-Lys-NCA)[87]; (ii) the opposite 'grafting from' method, which uses hydroxyl-decorated vinyl backbones suitable for initiating ROP[88]; and (iii) the 'grafting through' method, which relies on the CRP of degradable macromonomers, such as (meth)acrylate-terminated poly(D,L-lactide) and PCL[89]. By combining and permuting different coupling and polymerization (ROP and CRP) steps, all kinds of partially degradable vinyl-based brushed architectures are virtually accessible[88,90]. Even though all these examples reported vinyl architectures comprising segments

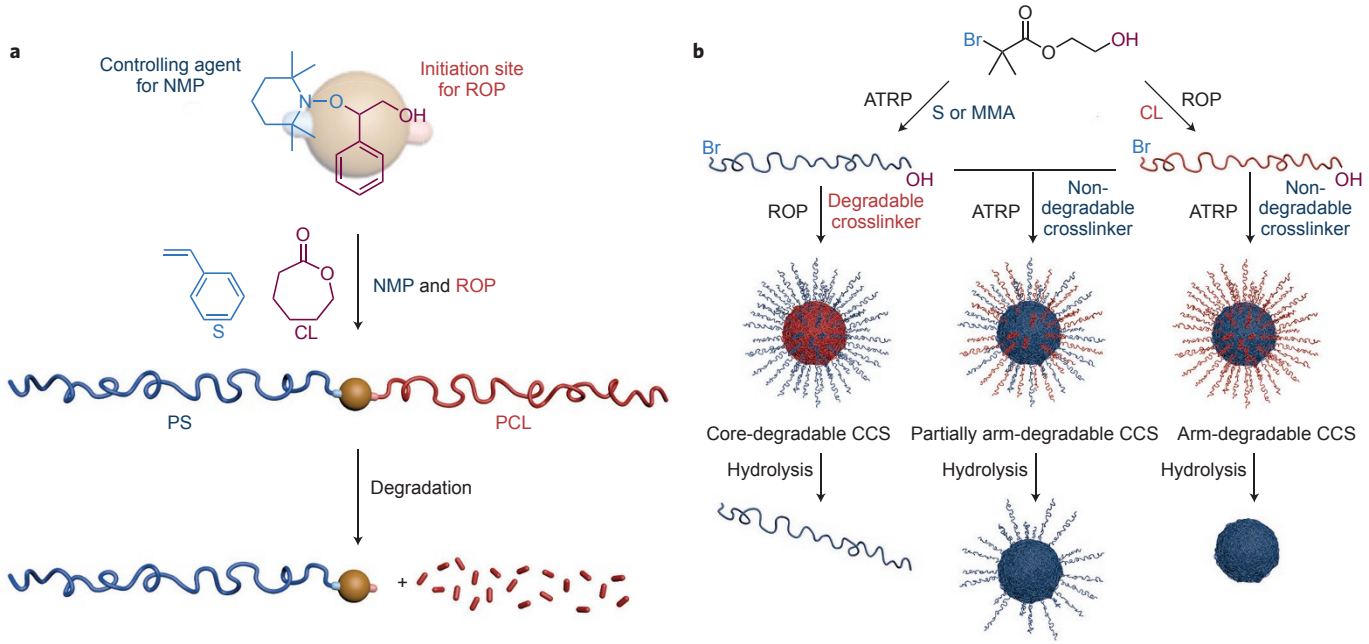

Figure 5 | Copolymers with non-vinyl degradable blocks from heterodifunctional initiators. a, Simultaneous nitroxide-mediated polymerization (NMP) of styrene (S) and ring-opening polymerization (ROP) of ε-caprolactone (CL) from a hydroxyl functional alkoxyamine for a one-step approach to PS-b-PCL diblock copolymers. **b**, Synthesis of a selectively degradable core crosslinked star (CCS) polymer from a hydroxyl functional atom-transfer radical polymerization (ATRP) initiator and subsequent hydrolysis to remove the labile component (MMA = methyl methacrylate). Panel **b** adapted from ref. 85, ACS.

based on well-known degradable polyesters and polypeptides, only hydrolytic degradation has been performed and their *in vivo* degradation or biodegradation still needs to be confirmed. The polycondensation of disulfide-containing diacids and diols combined with ATRP also received some attention as a means to prepare reductively degradable block copolymer nanocarriers[91].

Degradation of the polymer side chain

Side-chain cleavage of vinyl polymers is an important lever to confer degradation, especially to nanoparticulate systems. Even though the average polymer chain length is not affected, the substantial structural modifications that occur can either make the polymer hydrophilic, thus leading to nanoparticle degradation, or trigger the disassembly of colloidal structures. This facilitates their excretion from the body and thus makes them well adapted for drug delivery applications.

Degradation leading to water solubility. Certain acrylic polymers can undergo ester side-chain hydrolysis *in vivo* by means of esterases to become water soluble, which makes their excretion possible. The only two polymer classes that fall into this category are poly(methylidene malonate) and poly(alkyl cyanoacrylate) (PACA) (Fig. 6a). The presence of two electron-withdrawing groups in the α-carbon to the double bond makes the corresponding monomers extremely reactive towards nucleophiles, such as anions or weak bases, resulting in quasi-instantaneous anionic polymerization[92]. Initially used as surgical glue (Dermabond) or super glue for do-it-yourself activities (Loctite), PACA polymers from long alkyl cyanoacrylate monomers (for example, *n*-butyl, isobutyl, isohexyl, and so on) have been extensively investigated as biodegradable drug nanocarrier materials since the 80s (Fig. 6b)[93]. A typical example is the development of Dox-loaded poly(isohexyl cyanoacrylate)

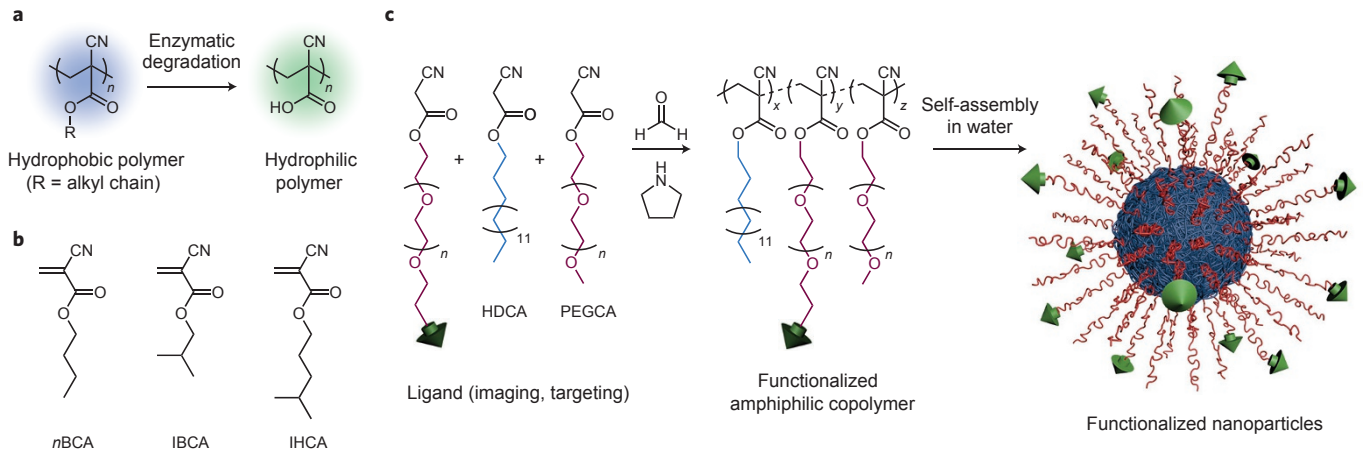

Figure 6 | Poly(alkyl cyanoacrylate) as a biodegradable polymer. a, General structure and side-chain degradation pathway of poly(alkyl cyanoacrylate) polymers. **b**, Structure of three representative alkyl cyanoacrylate monomers (*n*BCA = *n*-butyl cyanoacrylate; IBCA = isobutyl cyanoacrylate; IHCA = isohexyl cyanoacrylate). **c**, Design of functionalized, PEGylated nanoparticles by tandem Knoevenagel condensation–Michael-type addition from hexadecyl cyanoacetate (HDCA), poly(ethylene glycol) cyanoacetate (PEGCA) and its functionalized counterpart.

nanoparticles obtained by anionic emulsion polymerization that are currently under phase III clinical trials for the treatment of primary liver cancer[94]. A downside to the high reactivity of these monomers is the notable difficulty to design engineered and functionalized (co)polymers. This obstacle can be bypassed, however, by using cyanoacetate derivatives as monomer precursors. By tandem Knoevenagel condensation–Michael addition, the corresponding cyanoacrylate monomers are obtained *in situ* and can be further polymerized (Fig. 6c). From a mixture of hexadecyl cyanoacetate, rhodamine cyanoacetate and PEG cyanoacetate, this method enabled the formation of amphiphilic fluorescent copolymers that self-assembled into narrowly dispersed PEGylated nanoparticles, used for cell imaging and tracing purposes[95,96]. Increased sophistication was witnessed by positioning at the extremity of the PEG chains some targeting ligands directed against overexpressed cancer cell receptors or the amyloid-β peptide. This resulted in a versatile, nanoparticulate platform that exhibited stealth, fluorescent and targeting abilities against cancer and Alzheimer's disease[97].

Cleavage triggering colloidal disassembly. Side-chain cleavage can also activate rapid colloidal disassembly. For instance, amphiphilic diblock copolymers comprising a hydrophobic poly(methacrylate) block bearing pendent disulfide linkages formed drug-loaded micelles and released their load in aqueous solution due to complete disintegration in response to excess of thiols[98]. The system is versatile, as an equimolar thiol amount led to core crosslinked nanoparticles via thiol–disulfide exchange reactions. Cleavable side chains may also be attractive for gene delivery applications. Brushed copolymers composed of a methacrylate backbone onto which poly(2-(dimethylamino)ethyl methacrylate) (PDMAEMA) chains were grafted via a hydrolyzable carbonate linker were shown[99] to condense plasmid DNA into positively charged polyplexes of about 100–200 nm. Hydrolysis in physiological conditions (pH 7.4 at 37 °C) triggered the disintegration of the polyplexes and the subsequent release of plasmid DNA. This material is presumed to be bioresorbable as the molecular weight of the degradation product was found to be very close to that of the starting PDMAEMA, which is probably below the renal excretion limit. The method has been adapted to the grafting of cleavable PDMAEMA brushes onto polyaspartamide backbones[100].

Connecting polymer chains via degradable junctions

Instead of introducing degradable units in the polymer backbone or side chains, an appealing alternative consists of connecting polymer chains together via degradable or reversible linkages. This results in a variety of different architectures and structures that can be degraded at the chain connection sites. They can therefore find applications in the biomedical field, particularly drug delivery applications. If bioresorbable materials are also targeted, the remaining chains should be small enough to be below the renal excretion limit and be cleared *in vivo*, unless they also contain main-chain degradable moieties.

Degradable crosslinkers. A straightforward strategy to connect polymer chains together relies on the use of difunctional vinyl comonomers, usually termed crosslinkers. In the field of degradable vinyl polymers, a significant amount of work has been devoted to the development of crosslinkers with labile functionalities embedded to implement the degradability of the resulting materials. It offers significant advantages over other approaches: (i) a broad range of different crosslinkers are readily accessible by varying the nature of both the polymerizable group and the degradable functionality; (ii) the resulting polymer is rather easy to obtain as the synthesis only requires the addition of the crosslinker in the reaction medium; and (iii) depending on the experimental conditions, different architectures and nano-objects can be prepared.

For instance, star polymers with a degradable core are obtained via the 'arm first' method, which either generates the core of the star macromolecule by coupling monofunctional 'living' polymeric chains with cleavable crosslinkers,[101] or alternatively by direct copolymerization of a macromonomer with a degradable crosslinker. The latter approach was illustrated by the copolymerization of a PEG-based macromonomer with a disulfide methacrylate

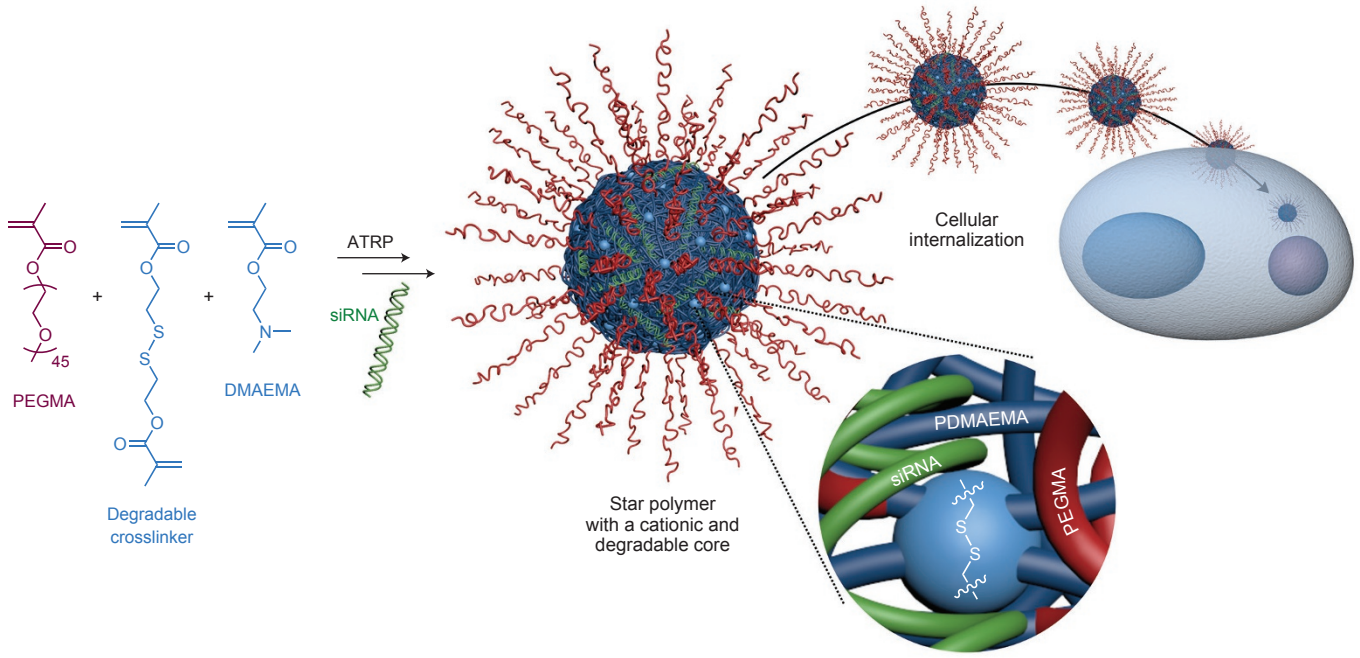

Figure 7 | Using a cleavable crosslinker to prepare degradable star polymers. Copolymerization of poly(ethylene glycol)methyl ether methacrylate (PEGMA), 2-(dimethylamino)ethyl methacrylate (DMAEMA) and bis(2-methacryloyloxyethyl) disulfide as a cleavable crosslinker to prepare biocompatible PEG-based star polymers with a cationic and degradable PDMAEMA core via atom-transfer radical polymerization (ATRP) and the 'arm first' method for the delivery of siRNA.

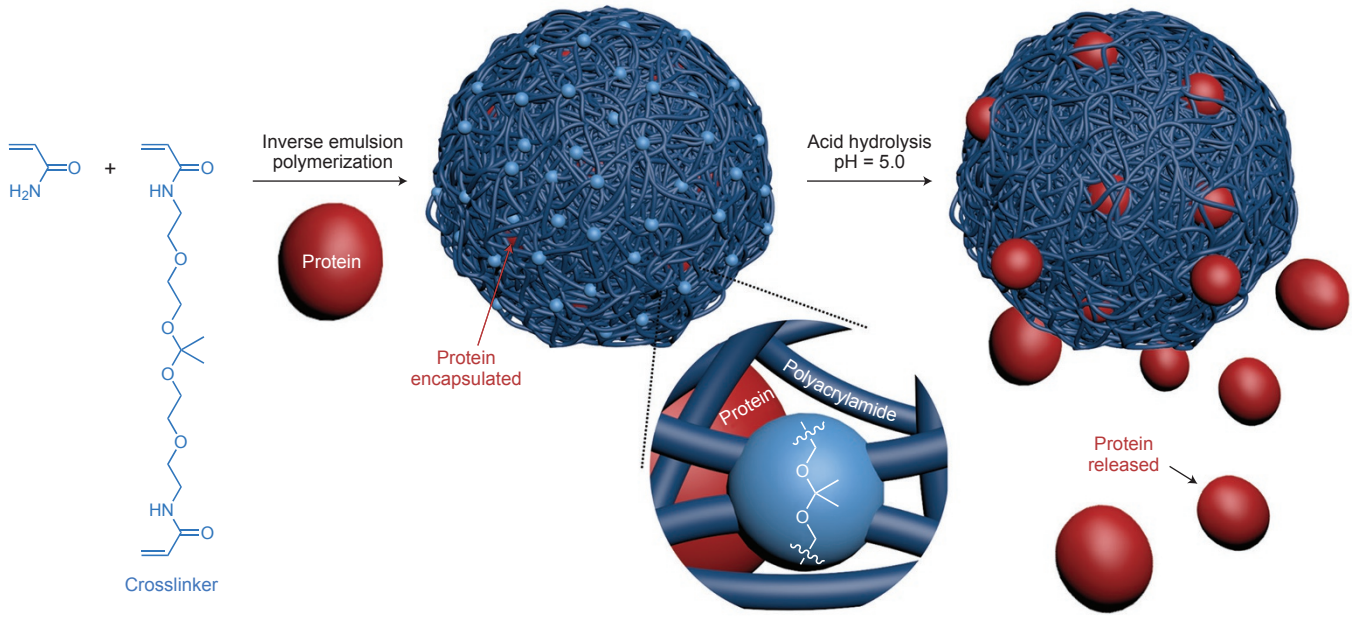

Figure 8 | Acid-degradable microparticles from a cleavable crosslinker. Inverse emulsion copolymerization of acrylamide and an acetal crosslinker to prepare acid-degradable crosslinked polyacrylamide microparticles for protein-based vaccines. The protein is released through degradation of the crosslinker.

and 2-(dimethylamino)ethyl methacrylate (DMAEMA) as a cationic vinyl monomer. Star copolymers for the delivery of small interfering RNA (siRNA) were prepared and degraded into individual polymeric chains in aqueous solution under reducing conditions (Fig. 7)[102].

Similar difunctional vinyl comonomers can also lead to (hyper) branched structures, which have recently received much attention due to numerous applications in which a large density of functionalities is desirable, including reactive adhesives and coatings, imaging, and drug delivery. Conferring them with degradable features appears essential for drug-delivery purposes. Interestingly, the branching process is better controlled if the synthesis is performed under CRP conditions. For example, when a redox sensitive crosslinker is employed in combination with ATRP or RAFT, the degraded polymer obtained after reduction by DTT in organic solution exhibits a nearly similar molecular weight distribution as the linear counterpart obtained in the absence of any divinyl reagent[103,104]. It was also shown that careful selection of the primary chain length enabled the production of poly(hydroxyethyl methacrylate) (PHEMA) fibres by electrospinning that could be further cleaved into linear PHEMA[105]. This may have biomedical applications considering that PHEMA can be degraded by macrophages[106].

If experimental conditions enable the gel point to be exceeded, fully crosslinked 3D polymeric networks with elastic properties are obtained. Among these, hydrogels have attracted most attention for controlled drug delivery applications and as scaffold materials, on account of their similarity to soft biological tissues and their highly tunable mechanical properties. Recent achievements in degradable hydrogels employed FRP[107–109] and CRP[80,107,110–113] techniques. CRP generally provides more homogeneous structures compared with those obtained by FRP and also lead to predetermined molecular weights and narrow molecular weight distributions of the decomposed fragments[107]. This is particularly relevant because it reduces the chance of non-excretable residues being released upon degradation. This was especially illustrated by the ATRP of HEMA[80], NIPAM[112] and DMAEMA[107] in the presence of a divinyl macromolecular crosslinker based on PCL, leading to hydrogels with different mechanical and physicochemical properties. Hydrolytic degradation was demonstrated and its rate was controlled by the crosslinking density, the PCL chain length and the primary vinyl chain length[80]. Original strategies leading to more sophisticated hydrogels have also been reported, among which are the use of a divinyl tetrapeptide sequence (CYKC) as a crosslinker for the preparation of protease-responsive hydrogels[114], the incorporation of cleavable poly(oligo(ethylene glycol) methyl ether methacrylate) (POEGMA) crosslinked nanoparticles into hydrogels[113] and the crosslinking of PVA macromonomers[115]. Despite all these promising results, more investigations are needed to demonstrate the *in vivo* degradability of such systems to make a critical step forward for applications in drug delivery or tissue engineering. The slow hydrolytic degradation of the ester bonds of PEG diacrylate-based hydrogels may also open new opportunities in this field[116].

When the copolymerization between a traditional vinyl monomer and a degradable divinyl crosslinker is performed in aqueous dispersed media (for example, dispersion, suspension, emulsion, and so on), degradable particulate systems that can find application as drug carriers are obtained. A typical example are acid-degradable crosslinked polyacrylamide microparticles for vaccine development, synthesized by inverse free-radical (micro)emulsion polymerization in the presence of acetal crosslinkers (Fig. 8)[109,117–120]. These particles allow for plasmid and protein encapsulation and can degrade under the mildly acidic conditions found in the phagosomes of antigen-presenting cells. By using ovalbumin as a model antigen, the system performances were further enhanced by the co-encapsulation[121] or surface attachment[122] of immunostimulatory CpG DNA to better mimic actual pathogens, and by the design of cell-penetrating peptide-modified microparticles to improve cell uptake[123]. Nanosized hydrogels (often termed nanogels), synthesized by inverse miniemulsion ATRP of OEGMA and a reducible divinyl crosslinker, also represent a promising reductively degradable system[124]. They have demonstrated not only high drug loading capabilities and efficient release upon degradation[125,126], but also the capacity to be surface functionalized with biologically active moieties[126]. Acetal crosslinkers can also be used on preformed block copolymer nanoparticles obtained by self assembly in aqueous solution[127], which represents a valuable alternative to direct polymerization in aqueous dispersed systems. The simplicity of these strategies and the efficiency of hydrolytic or reductive degradations are particularly appealing, but the *in vivo* degradability of the resulting carriers is still to be demonstrated.

Other strategies to insert degradable junctions. Many additional pathways have been proposed to connect polymer chains together in a degradable fashion. The use of degradable inimers (a class of molecules having both an initiator and monomer fragment) is appealing for its simplicity and robustness, as it readily enables the production of degradable hyperbranched structures. This has been notably illustrated by the use of a disulfide-containing ATRP inimer[128] and by the combination of two monomers that polymerize by different chemistries (ROP and ATRP) and bear initiating centres for the opposite types of chemistry. This leads to a concurrent one-step polymerization process[129]. Degradability was also conferred to polymeric capsules formed by layer-by-layer assembly[130] by means of degradable crosslinkers connecting together the different layers. This has been performed using a bisazide linker containing a disulfide bond, via copper(I)-catalysed alkyne–azide Huisgen cycloaddition, also termed 'click' chemistry[131]. This way, deconstruction of the capsules is expected to occur through exposure to a reducing environment, similar to that found in the intracellular cytosolic space. The concept has been further extended to the design of subcompartimentalized layer-by-layer capsules with selectively degradable carriers and subunits in response to multiple chemical stimuli. This was achieved simply by implementing degradable crosslinkers with different labile functionalities (for example, disulfide bond, vicinal diol group)[132].

Cleavable bioconjugates

Although on the fringe of degradable vinyl materials, polymer chain cleavage from organic substrates can also be seen as a form of degradability. This concept takes on its full meaning in the case of biological substrates, such as therapeutic proteins or peptides. Covalent attachment of PEG to proteins, termed PEGylation, confers indisputable pharmacological advantages to native proteins, such as improved solubility and stability, extended circulation time, and reduced proteolytic degradation[133]. However, their biological activity is often decreased because of stable polymer attachment. Therefore, it is desirable to efficiently release the protein therapeutics from the PEG chains to enhance their biological performances. Also, if the molecular weight of the released polymer is below the renal filtration threshold, its complete removal from the body will likely occur, which will not be the case for a stable linkage.

The 'grafting to' technique. Several linear PEGs have been attached to proteins via degradable linkages[134], allowing for the gradual release of the target protein and thereby overcoming the normal limitation of PEGylation. One can also take advantage of CRP techniques to design α-functional vinyl polymers for reversible protein bioconjugation[135]. In this sense, disulfide linkages have been advantageously utilized in several proofs of concept. A common strategy is to prepare pyridyl disulfide (PDS) end-terminated polymers for subsequent coupling under mild conditions with free cysteine-containing biological macromolecules, such as proteins (Fig. 9)[136,137] or siRNA[138]. Owing to the flexibility of CRP, the PDS moiety can also be positioned at the polymer mid-chain leading to branched bioconjugates with an expected improvement in masking the protein surface due to the so-called umbrella-like effect[139]. For targeting lysine residues, the disulfide functionality is incorporated in between a lysine-reactive moiety and the polymer chain[140]. This was illustrated by the design of thiazolidine-2-thione end-terminated POEGMA via RAFT polymerization, further reacted with lysozyme, used as a model protein. After cleavage of the polymer chains from the conjugates in aqueous tris(2-carboxyethyl) phosphine hydrochloride solution, the released protein displayed a marked increase in bioactivity. Interestingly, when the polymer is obtained from the copolymerization of OEGMA and 5,6-benzo-2-methylene-1,3-dioxepane by rROP, both reductive cleavage of the polymer chains from the protein and hydrolytic degradation of the polymer in the presence of base are observed[141]. This could be a valuable advantage compared with traditional PEGylation, as the polymer should be released from the protein and subsequently degraded, to allow for excretion of initially larger polymers. However, this promising combining strategy still requires validation *in vivo*.

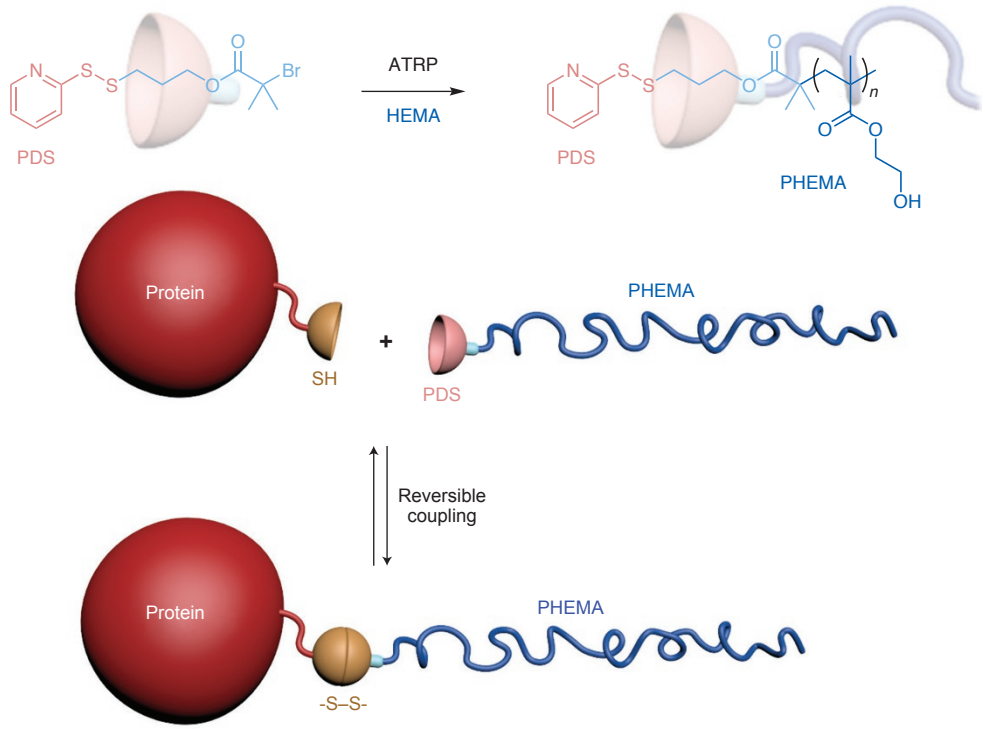

Figure 9 | Cleavable polymer–protein bioconjugates. Development of a bioreversible conjugation between cysteine-containing proteins and pyridyl disulfide (PDS) end-terminated PHEMA prepared by atom-transfer radical polymerization (ATRP) through the formation of a disulfide bond.

Table 1 | Main features of the synthetic approaches to design degradable and biodegradable vinyl polymers.

Architecture	Strategy	Polymerization technique	Degradable group (degradation modes tested)	Maximum M_n tested (kDa)	Expected M_n after degradation	Refs
Linear polymer with one central main-chain degradable unit	Difunctional, degradable initiator	ATRP, RAFT	Disulfide (reducing agent), hemi acetal (acid hydrolysis), Diels–Alder adduct (thermal), *o*-nitrobenzyl ester (UV light), trithiocarbonate (amynolysis)	50	$M_n/2$	9,13–15, 18,20,21
	Macromolecular coupling (formation of degradable junctions)	ATRP, RAFT	Alkoxyamine (thermal), disulfide (reducing agent), supramolecular pairs (competition, thermal)	30	$M_n/2$ if the two blocks have the same M_n	25–29, 31–37
n-Arm star polymer with *n* cleavable arms	Multifunctional, degradable initiator	ATRP, RAFT	*o*-Nitrobenzyl ester (UV light), ester (acid hydrolysis), hydrazone (acid hydrolysis), disulfide (reducing agent)	150	M_n/n	9,15,23, 24
Linear polymer with multiple main-chain degradable units	Macromolecular coupling (formation of degradable junctions)	ATRP + ATNRC/NMRC, ATRP + $FeCl_3$ or O_2, polycondensation + RAFT	Alkoxyamine (thermal), disulfide (reducing agent)	120	M_n of macromolecular precursor	12,38–42
	ATRPolyaddition between divinyl monomers and degradable dibromo compounds	ATRPolyaddition between divinyl monomers and degradable dibromo compounds	Acetal (acid hydrolysis), disulfide (reducing agent)	10 (160*)	MW of monomer unit	43
	Macromolecular coupling between macromolecules and degradable linkers	ATRP + ATNRC	Ester (basic hydrolysis), disulfide (reducing agent)	25	M_n of macromolecular precursor	38
	Macromolecular coupling between macromolecules and degradable linkers	RAFT + CuAAC (or maleimide/thiol coupling)	GFLG peptide sequence (enzymatic degradation, biodegradation)	40 (300*)	M_n of macromolecular precursor	46–52
	Metal catalysed step growth polymerization	Metal catalysed step growth polymerization	Ester (basic hydrolysis, methanolysis)	40	Oligomers	54–57
	Oxidative polymerization with O_2	FRP, RTCP	Peroxide (thermal degradation, enzymatic degradation)	15	Oligomers	58–60
	PolyRAFT agent	RAFT	Trithiocarbonate (aminolysis)	40	Oligomers	61
	rROP with vinyl monomers	rROP with vinyl monomers	Ester (basic hydrolysis, enzymatic degradation, degradation by composting), ketone (UV light), disulfide (reducing agent)	70	Oligomers	62–72
	Alternating copolymer aldehyde + vinyl ether	Cationic polymerization	Acetal (acid hydrolysis)	20	MW of monomer units	73,74
Linear copolymer with a degradable block	Heterobifunctional initiator	Combination CRP + ROP	Ester (acid hydrolysis, enzymatic degradation), amide (enzymatic degradation)	60	M_n of vinyl block	75–79,81, 82
	Symmetrical difunctional degradable macroinitiator	Combination CRP + ROP	Ester (basic hydrolysis, enzymatic degradation)	50	M_n of vinyl block	80
	Degradable macroinitiator	Combination CRP + ROP	Ester (acid or basic hydrolysis)	40	M_n of vinyl block	83,84
	Degradable macroinitiator	Combination polycondensation + ATRP	Disulfide (reducing agent)	15	M_n of vinyl block	91
Grafted copolymer with degradable side blocks or a degradable backbone	Multifunctional polymer scaffold	Combination ATRP + ROP	Ester (basic hydrolysis), amide (basic hydrolysis)	>1,000	M_n of vinyl backbone or side chain	87,88,90
	Degradable macromonomer	Combination ATRP + ROP	Ester (basic hydrolysis), amide (basic hydrolysis)	50	M_n of vinyl backbone	89
Polymer with cleavable side chains	Anionic polymerization of alkyl cyanoacrylates or polyaddition of alkyl cyanoacetates	Anionic polymerization of alkyl cyanoacrylates or polyaddition of alkyl cyanoacetates	Ester (enzymatic degradation, biodegradation)	8	Oligomers	92–97
	Cleavable side chains triggering colloidal disassembly	ATRP	Disulfide (reducing agent), carbonate ester (acid hydrolysis)	50	M_n of polymer scaffold without side chains	98–100

Continued

Table 1 | (continued)

Architecture	Strategy	Polymerization technique	Degradable group (degradation modes tested)	Maximum M_n tested (kDa)	Expected M_n after degradation	Refs
Star polymer with a degradable crosslinked core	Degradable crosslinkers in homogeneous media	ATRP + arm first method	Disulfide (reducing agent)	>500	M_n of arm	85,86, 101,102
Hyperbranched polymer with degradable branching points	Degradable crosslinkers in homogeneous media	ATRP, RAFT	Disulfide (reducing agent, oxidative agent)	70	M_n of primary chain	103,104
	Degradable inimers	ATRP	Disulfide (reducing agent)	5	Oligomers	128
	Degradable inimers	ROP + ATRP	Ester (acid hydrolysis)	30	Oligomers	129
Gel/hydrogel/ microgel with degradable crosslinking points	Degradable crosslinkers in homogeneous media	FRP, ATRP	Ester (acid or basic hydrolysis), disulfide (reducing agent), acetal (acid hydrolysis), CYKC peptide sequence (enzymatic degradation)	120	M_n of primary chain	80, 107–110, 112,114, 116
Crosslinked particulate system with degradable crosslinking points	Degradable crosslinkers in dispersed media	FRP, ATRP	Acetal (acid hydrolysis), disulfide (reducing agent)	70	M_n of primary chain	109, 117–120, 124–126
	Degradable crosslinkers on preformed block copolymer NPs	RAFT	Ketal (acid hydrolysis)	15	M_n of block copolymer	127
	Crosslinking polymer layers	RAFT + LbL	Disulfide (reducing agent), vicinal diols (reducing agent, oxidative agent)	n.d.	M_n of polymer chain	131,132

ATNRC: atom-transfer nitroxide radical coupling; ATRP: atom-transfer radical polymerization; CRP: controlled radical polymerization; CuAAC: Copper(I)-catalysed alkyne–azide Huisgen cycloaddition; FRP: free-radical polymerization; LbL: layer-by-layer; M_n: number average molar mass; MW: molecular weight; n.d.: not determined; NMP: nitroxide-mediated polymerization; NMRC: nitroxide-mediated radical coupling; NPs: nanoparticles; RAFT: reversible addition-fragmentation chain-transfer; ROP: ring-opening polymerization; rROP: radical ring-opening polymerization; RTCP: reversible chain-transfer catalysed polymerization. *After fractionation.

The 'grafting from' technique. The polymer chain also can be grown from the substrate by grafting a PDS-based ATRP initiator[142] or a RAFT agent[143] before the polymerization step. This 'grafting from' approach offers valuable advantages compared with the 'grafting to' method. For instance, the efficiency of the conjugation should be nearly quantitative due to negligible steric hindrance and purification of the conjugate might be easier since only the unreacted monomers have to be removed, as opposed to a preformed polymer. Importantly, the conjugates also retain their activities compared to the unmodified model proteins, meaning that the polymerization process is not detrimental to the biological substrates[142]. Additional studies performed *in vivo* to evaluate the value added by such degradable linkage would be strongly beneficial to this area.

Summary and outlook

This Review has summarized the recent progress in the development of groundbreaking strategies to confer degradability to vinyl polymers — a feature of paramount importance especially in several biomedical applications and for sustainable development. The vast majority of these achievements have been made possible by harnessing the robustness and versatility of modern polymerization methods and/or efficient ligation strategies to incorporate discrete or multiple cleavable functionalities. Beyond the degrability itself, which is crucial for toxicity concerns, intelligent placement of labile groups in a polymer structure can also trigger colloidal disassembly. This dual role is particularly relevant for drug delivery applications where the drug release from polymer nanocarriers should be governed by endogenous stimuli, such as pH or specific enzyme activity.

The main features of the synthetic approaches covered in this Review (except related to cleavable conjugates) are reported in Table 1. It includes the general strategies, the degradation modes tested, the highest molar masses investigated as well as the expected molar mass decrease after degradation, which gives an indication of the molar mass of the degradation products. Although the limits of these synthetic strategies have certainly not yet been reached, these data may be of great help for further synthetic developments to satisfy the requirements for other degradation modes, materials with higher molar mass or materials leading to lower molar mass degradation products. In general, the highest molar masses that have been tested ranged from several thousand to tens of thousands daltons, except for grafted and star polymers and macromolecular coupling approaches that enabled higher molar masses to be reached (typically above 100,000 Da). Combining radical polymerization and ROP from multifunctional polymer scaffolds enabled the preparation of higher molar mass materials (typically above 1 million Da) whose degradability is, however, restricted to polyester chains and backbones. Another important benefit of using CRP techniques is the ability to fine-tune the molar mass of the vinyl polymer, leading to great flexibility with regards to the desired application.

Among the different options to introduce labile groups in vinyl polymers, rROP appears to be one of the most efficient methods, but for decades received only intermittent attention. In recent years, however, there has been a real resurgence of interest, which could be explained by the possibility to copolymerize traditional vinyl monomers with monomers that polymerize by rROP, either by conventional or controlled radical polymerization. The full potential of this technique has not yet been fully exploited. The diversity of suitable monomers is still rather poor and there is a crucial lack of hydrophilic and functionalized structures. In copolymerization, owing to unfavourable reactivity ratios, a large excess of these monomers is required to incorporate significant amounts in the resulting copolymer. This displays a lack of 'atom economy', which is becoming more and more important. Furthermore, their homopolymerization is not straightforward and often fails to be controlled. Thus, some work remains to be done to allow rROP to approach the versatility of ROP, which is

still unparalleled in the biomedical context in terms of synthesis, properties, innocuousness and *in vivo* degradability.

It should be noted that the majority of vinyl polymers described in this Review (except PHPMA, PACA and rROP-derived polymers) have only been subjected to hydrolytic degradation (often accelerated in strongly acidic or basic environments), reductive degradation *in vitro* in the presence of reducing agents, or enzymatic degradation *in vitro* to prove their degradability. Yet, *in vivo* degradability or biodegradability is mandatory in the context of specific biomedical applications, such as drug delivery and tissue engineering. Although all these proofs of concept have already given solid indications of degradability, they must eventually be validated by undertaking appropriate *in vivo* degradability studies. This is crucial to discriminate between degradable materials that may find application in the biomedical field and those whose properties make them more appropriate for other types of applications (for example, nanolithography). Finally, future studies on newly developed degradable vinyl polymers should include in-depth investigations assessing their biocompatibility and the absence of toxicity, including those of their degradation products. These two major properties are often neglected, although they represent important steps to demonstrate the safety of these materials before any pharmaceutical or biomedical use.

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Competing financial interests

The authors declare no competing financial interests.