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pH-Responsive polymers

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In this review, we provide an analysis of some of the recent literature reports on the synthesis and applications of pH-responsive polymers. Depending on the solution pH, such copolymers can self-assemble and form various nanosized structures including core–shell micellar structures, micelles/reverse micelles, hollow spheres, vesicle structures, adsorbed species at the water–air interface, and more complex architectures. Their self-assembly behaviors open the door for the production of various novel nanostructures including shell/core cross-linked micelles, hollow spheres, hydrogels, microgels, layer-by-layer (LbL) nanofilms, controlled releasing systems, drug carrier systems, *etc*. The review consists of various major parts including types of pH-responsive polymers, synthetic methods for their synthesis and their solution behaviors, their nanostructures in aqueous media, applications as LbL nanofilms, delivery devices, controlled release systems, sensors, stabilizers, solubilizers, *etc*. In the last two decades, there have been great developments in synthetic methods and strategies for the preparation of novel pH-responsive polymers or polymeric materials providing possible materials for various applications including biotechnology, nanotechnology, colloid and surface science, materials science, *etc*.

Introduction

Stimuli responsive polymers are a class of polymers that can self-assemble or undergo phase transitions or morphology changes *via* physical or chemical changes in response to small external changes in the environment. They have also been named intelligent, smart, or environmentally-responsive polymers. These polymers can be responsive to a number of factors such as temperature, pH, biomaterials, solvent, ionic strength, chemical agents, light, electrical field, and magnetic field.[1–3] The field of pH-responsive polymers has gained great academic and commercial interest in the last two decades parallel to not only developments in the synthetic methodologies to make these materials but also their wide-span application potentials.

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pH-Responsive polymers are a group of stimuli-responsive polymers that can respond to solution pH by undergoing structural and property changes such as surface activity, chain conformation, solubility, and configuration. The term "pH-responsive polymers" is commonly used to describe polymers having ionisable acidic or basic residues whose ionization depends on solution pH. The subject of pH-responsive polymers has become very popular in recent years and new studies have been added year after year. These unique properties of pH-responsive polymer systems consequently make them very useful in various applications such as drug delivery, gene delivery, sensors, surfaces, membranes, and chromatography.[4–6]

pH-Responsive polymers can have linear, branched or network structures. They may show different responses to solution conditions and different self-assembly behaviors depending on their structures. For example, a pH change may cause (de)protonation of functional groups in polymer chains. In some cases, it may cause flocculation, chain collapse-extension, and precipitation for homopolymers. It may also cause self-assembly such as formation of micelles, unimers, gels, vesicles, swelling, deswelling, *etc*. Block (co)polymers, branched (co)polymers, and star (co)polymers having pH-responsive block(s) show surface active behaviors by pH change. Additionally, hydrogel and dendrimer like structures show (de)swelling behavior by pH change. Surfaces modified with polymers give a chance to obtain ionic surfaces and thin/thick layer formation by pH change. The changes observed in polymers of different architectures by pH change are shown in Fig. 1.

pH-Responsive polymers can be defined as polyelectrolytes that include in their structure weak acidic or basic groups that either accept or release protons in response to a change in the environmental pH. Polymers having acidic or basic groups like carboxyl, pyridine, sulfonic, phosphate, and tertiary amines are typically described as pH-responsive polymers because the ionization of the groups with pH change results in a change in the structure. In addition to their biotechnological applications, their pH-responsiveness or ionization allows us to tune their self-assembly behavior, hydrophilicity phase separation, polyelectrolyte nature, *etc*. It is possible to prepare a polymer having a pK_a between pH 1 and 14. In general, pH-responsive polymers of basic monomers behave as cationic polymers under acidic conditions and polymers with acidic monomers behave as anionic polymers under basic conditions. Depending on the application, it is necessary to choose one of these two types or a combination of them with the right composition. Apart from synthetic polymers, natural polymers have often been studied. The use of natural polymers is the most common focus of interest because of their abundance in nature, degradability, biocompatibility and ability to be modified. Synthetically, pH-responsive polymers can be produced from polypeptides such as poly(L-glutamic acid) (PLGA), poly(histidine) (PHIS), and poly(aspartic acid) (PASA). These polymers are biocompatible and degradable just like natural polymers. These natural polymers have great importance among pH-responsive polymers.[5,7,8] In this review, the type of pH-responsive polymer, synthesis methods, architectures, and their applications will be summarized in detail.

Classification of pH-responsive polymers

A large number of pH-responsive polymers can be designed using various electrolyte groups. There are two kinds of pH-responsive polymers. One is polymers with acidic groups and the other one is polymers with basic groups. Weak polyacids such as poly(methacrylic acid) (PMAAc) accept protons at low pH and release protons at neutral and high pH. Weak polybases such as poly[(2-dimethylamino)ethyl methacrylate] (PDMA) accept protons at low pH and form a positively charged polymer chain. In the following section, acidic, basic, and neutral pH-responsive polymers reported in the literature will be summarized.

pH-Responsive acidic polymers

Polymers having weak acidic or basic residues are utilized as pH-responsive polymers (Fig. 2). Such weak acidic/basic pendant groups accept protons at low pH and release them at high pH. Therefore, they gain polyelectrolyte nature at acidic or basic pH values depending on their pK_a values. Such an ionic/non-ionic transition allows us to tune their hydrophilicity in the aqueous phase. This tuning results in precipitation/solubilization of polymer chains, swelling/deswelling of their hydrogels, or hydrophobic/hydrophilic characteristic changes of such polymeric surfaces and their particles.

Carboxylic groups. The weak acidic carboxylic groups lose acidic protons at basic pH values, forming anionic polyelectrolytes. At low pH the carboxylic groups accept protons resulting in an uncharged macromolecule. Among pH-responsive polyacids, PAAc and PMAAc have been most frequently reported. AAc and MAAc can be easily polymerized *via* various polymer-

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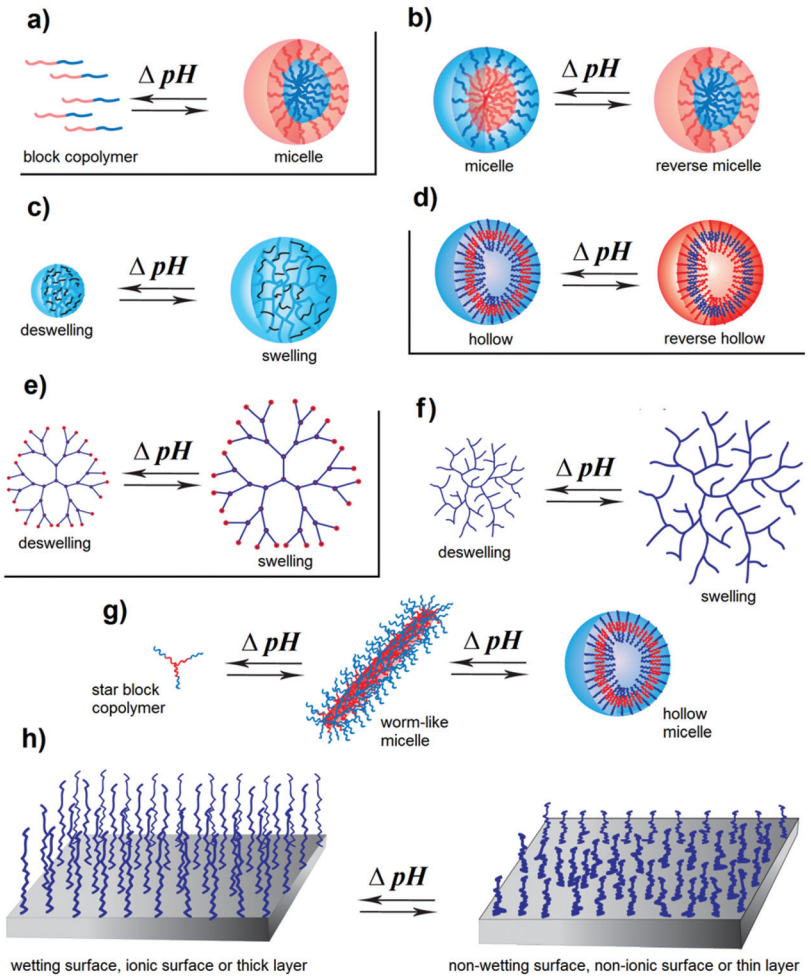

Fig. 1 pH-Responsive polymers of different architectures: (a) unimer–micelle, (b) micelle–reverse micelle, (c) nanogels or microgels, (d) hollow–reverse hollow, (e) dendrimer, (f) hyper-branched, (g) micelle morphology changes (from worm-like to hollow), and (h) polymer brushes.

ization techniques and are inexpensive. In some cases, protecting groups are also used during polymerization and followed by deprotection chemistry to obtain polymers with carboxylic groups. Leroux *et al.* have prepared an extensive review article about polycarboxylates containing pH-responsive polymeric structures such as vesicles, polymeric micelles, and nanospheres.[9] pH-Responsive dendrimers having carboxyl terminal groups are also produced.[10] Related carboxylic group containing polymers are shown in Fig. 2.

Sulfonic acid. The most widely used polymers containing sulfonic acid are poly(2-acrylamido-2-methylpropane sulfonic acid) (PAMPS) and poly(4-styrenesulfonic acid) (PSSA).[11] Polymers containing a sulfonic acid group are usually preferred in the preparation of hydrogels. Such hydrogels having sulfonic acid side groups swell very well when the pH is above the pK_a value of the related acidic groups. Such groups are well known to be more hydrophilic in their anionic form.

Phosphonic acid. Phosphorus-containing (meth)acrylate monomers are useful in many areas.[12,13] These monomers are usually used in the synthesis of hydrogels, which are swollen under basic pH conditions.[14–16] For the synthesis of phosphonic acid functionalized polymers, natural and synthetic polymers treated with different phosphonic acids are preferred.[17,18]

Boronic acids. Polymers containing boronic acid groups are used in applications such as self-healing gels and glucose sensors. As reported in the literature, phenylboronic acid moieties (Ph-B(OH)$_2$) containing polymers are very common and dominant among them.[19] Boronic acid based monomers can be polymerized with various polymerization techniques. In some cases, by using protected monomers, boronic acid based polymers can be obtained *via* additional deprotection chemistry.

pH-Responsive basic polymers

Weak polybases, which undergo ionization/deionization transitions from pH ~7–11, are utilized as pH-responsive polymers. The amine groups are located in their side chains. These groups accept protons at low pH values by forming polyelectrolytes and releasing them under basic conditions. The (meth) acrylate, (meth)acrylamide, and vinylic polymers containing tertiary amine, morpholino, pyrrolidine, imidazole, piperazine, and pyridine groups are shown in Fig. 3.

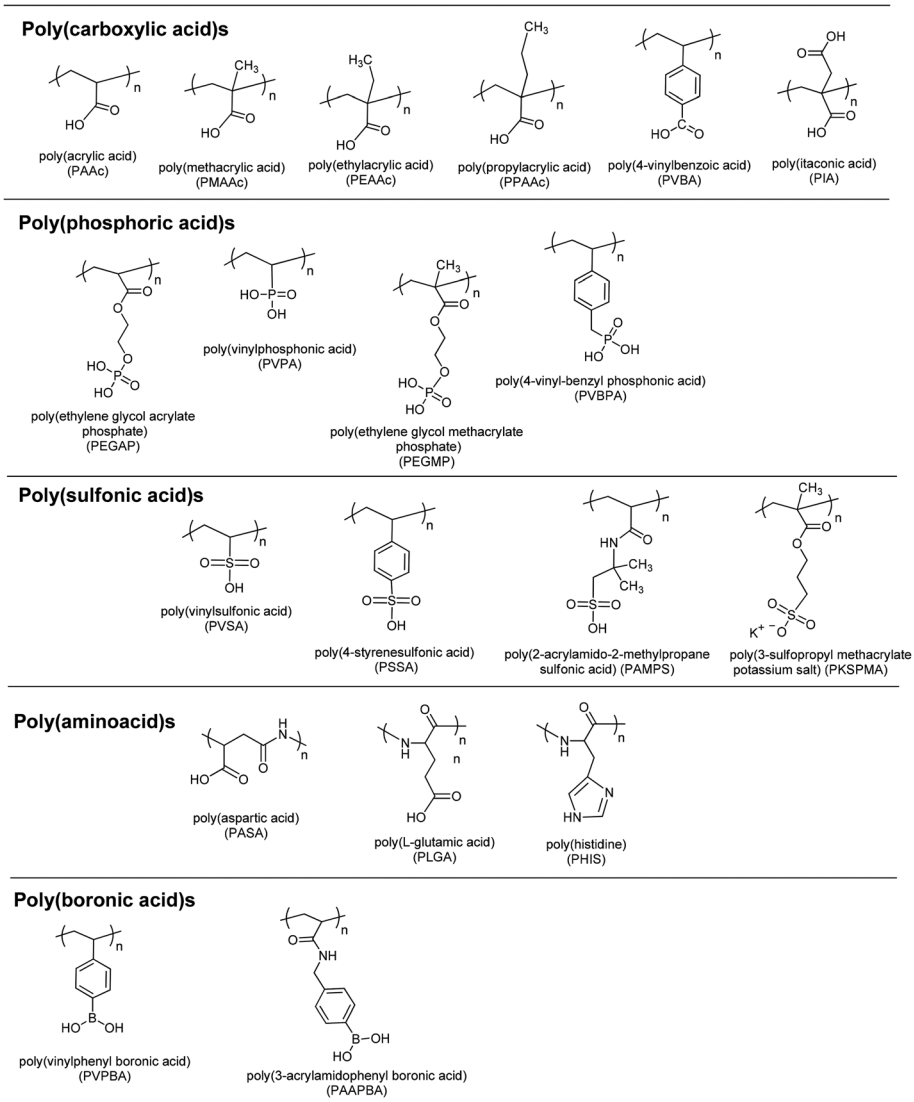

Fig. 2 Chemical structures of pH-responsive acidic polymers.

Vinyl, (meth)acrylamide, and (meth)acrylate polymers containing tertiary amine groups have also received great attention.[4,20–24] Tertiary amine methacrylate based polymers such as PDMA, poly[(2-diethylamino)ethyl methacrylate] (PDEA), and poly[(2-diisopropylamino)ethyl methacrylate] (PDPA) are the most preferred species among the basic polymers. Particularly, PDMA is the most popular weak basic polymer having not only pH-responsive nature but also thermo-responsive nature. Their polymers obtained from various techniques are commercially readily available. Poly (vinyl pyridine) based polymers are also widely used polymers which include poly(4-vinylpyridine) (P4VP) and poly(2-vinylpyridine) (P2VP). These polymers undergo a phase transition above pH 5 owing to deprotonation of pyridine groups.[25–27]

Other pH-responsive polymers are the polymers containing functional groups, such as imidazole,[28–32] piperazine,[33,34] pyrrolidine,[35] and morpholino.[31,36–38] Poly[(2-*N*-morpholino)ethyl methacrylate] (PMEMA) is an important polymer having morpholino groups and a response to pH, temperature, and ionic strength of the medium. Both Armes and Butun's groups have reported the synthesis of various PMEMA based polymers and investigation of their solution behaviors.[36,39–41] It is also necessary to mention that dendrimers such as poly(ethylene imine) (PEI), poly(propylene imine) (PPI), and poly(amidoamine) (PAMAM) can be classified as pH-responsive polymers. They can be modified with different functionalities and can be grafted with various polymers.[42–44] Some basic polymers are shown in Fig. 3.

pH-Responsive natural polymers

During the last decade, there have been great scientific developments in synthetic biodegradable polymers for various biomedical applications. Additionally, the use of natural biodegradable polymers has also gained great attention owing to

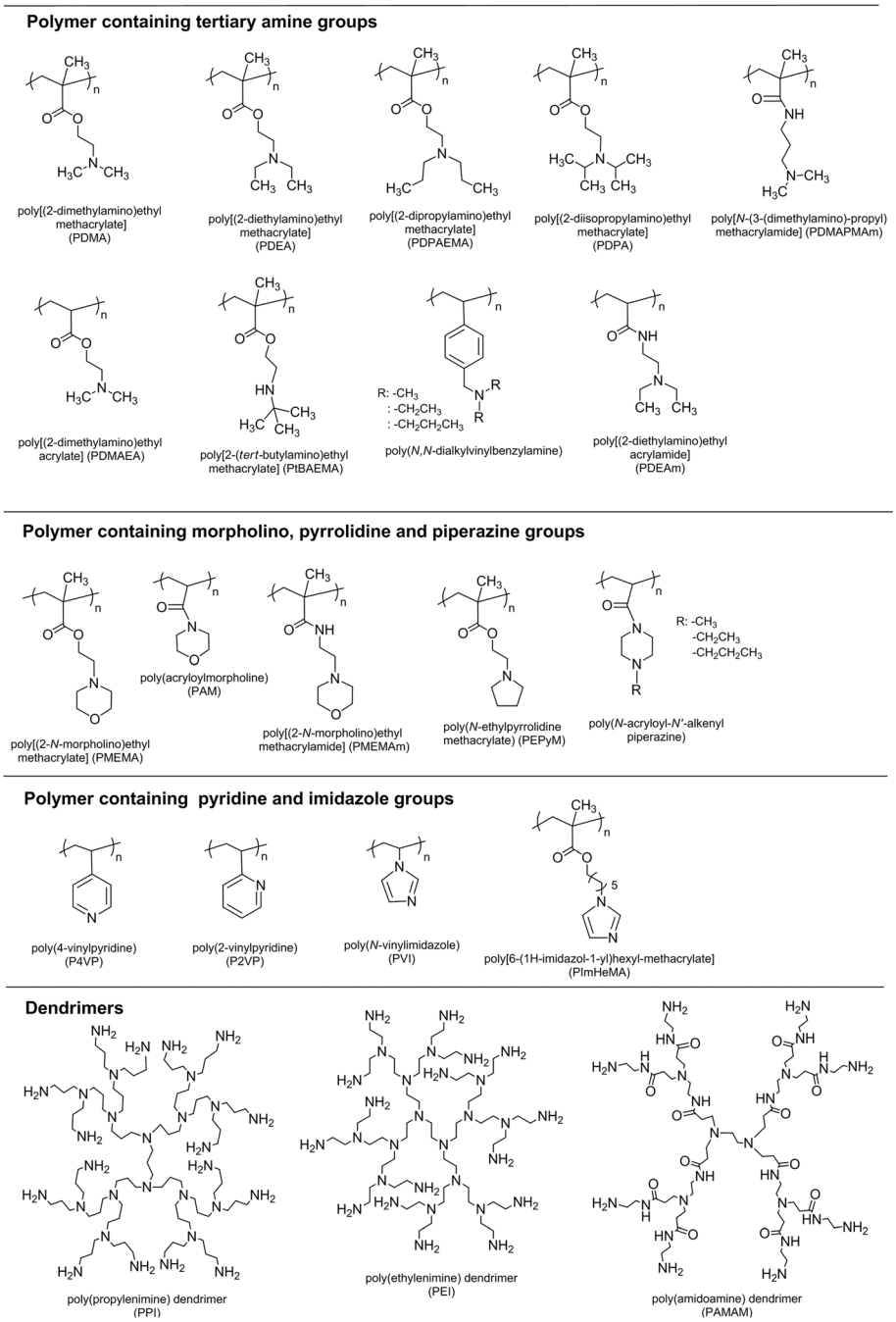

Fig. 3 Chemical structures of pH-responsive basic polymers.

their good biocompatibility and easy modification by simple chemistry. Some natural polymers are also used in the pH-responsive self-healing gel system.[5,7,45] Dextran, hyaluronic acid, alginic acid, chitosan, and gelatine are among the most widely used natural polymers (Fig. 4). On suitable chemical modification, these polymers can provide better materials for drug delivery systems. Another popular preparation strategy is the grafting of pH-responsive polymers onto a polysaccharide backbone. Hydrogels of these polymers in many studies using cross-linking agents have been produced. Chitosan has been the most studied species in such polymers.[46–51] Some of the natural and semi-natural polymers are given in Table 1.

Multi-responsive polymers

Multi-responsive polymers have recently become very popular. They give better results in various applications than other alternatives. Responsive polymers can have responses to a number of factors, such as temperature, pH, biomaterials, redox, light, electrical field, magnetic field, *etc.*[63,64] These polymers can be prepared by selecting two or more external impact

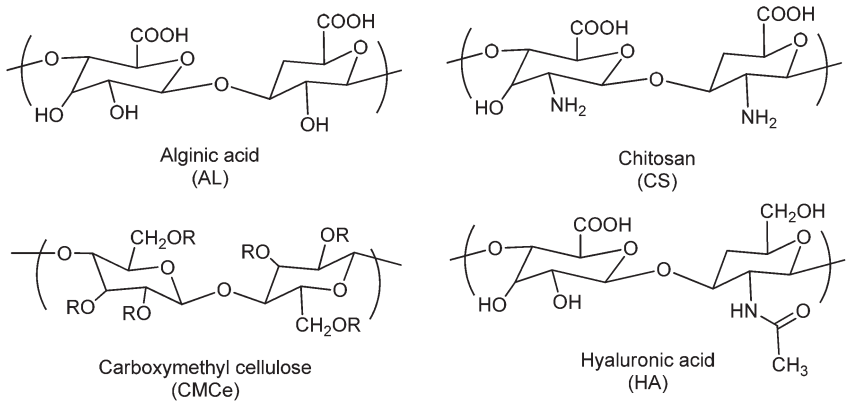

Fig. 4 Chemical structures of representative pH-responsive natural polymers.

Table 1 List of pH-responsive natural and semi-natural polymers

Natural polymers	Functional groups	Swelling pH	Ref.
Chitosan (CS)	$-NH_2$, –OH	Acidic	46–51
Guar gum (semi-natural)	–COOH	Basic	52 and 53
Alginic acid	–COOH, –OH	Basic	54–56
Hyaluronic acid (HA)	–COOH, –OH	Basic	57
Carboxymethyl dextran (CM-Dex)	–COOH, –OH	Basic	58
Carboxymethyl cellulose	–COOH, –OH	Basic	59–61
Gelatine A and B	$-NH_2$, –OH, –COOH	Acidic and basic	45 and 57
Tertiary amine starch ether	–N<, –OH	Acidic	62

Table 2 List of pH-responsive multi-responsive polymers

Responsive to	Polymers[a]	Type	Ref.
Glucose, pH, and thermo	PDMA-*co*-PAAPBA	Macrogel	67
Light, pH, and thermo	PDMA-*co*-PSP	Micelle	68 and 69
Glucose and pH	PVPBA-*co*-PDMAEA	Nanogel	70
Glucose and light	MePEGA-*b*-(PNBA-*co*-PAAPBA)	Micelle	71
pH and magnetic	PMAAc	Microgel	72
pH and electric	PAAc-*co*-PVSA	Macrogel	73
pH and reduction	PEO-*b*-(PMAAc-*g*-Hyd)	Micelle	74
	RPHA-*g*-coumarin	Micelle	75
Thermo and enzyme	PPDPMA-*co*-PTEGMA	Micelle	76
pH and thermo	PVI-*co*-PIMMA	Copolymer	30
	PNIPAm-*co*-PDMA	Nanogel	77
	PEPyM	Macrogel	35
	PNIPAm-*b*-PAAc	Micelle	78
	PEG-*b*-P4VP-*b*-PNIPAm	Micelle	79
	PNIPAm-*b*-PDEA	Micelle	66
	PDPA-*b*-PDMA-*b*-PDPA	Micelle	80
	PDMA-*b*-PAAc	Micelle	20
	PDMA-*b*-PDEA	Micelle	81
	PDMA-*b*-PDPA	Micelle	36
	[$PMEO_2MA$-*b*-(PDEA-*co*-PTPHMA)]	Micelle	82
	PEO-*b*-[PGMA-*g*-(PDEA)($PMEO_2MA$)]	Micelle	83
	PMAAc-*co*-PNIPAm	Yolk/shell	84
	PDMA-*b*-PMPS	Micelle	85
	PNIPAm-*b*-PLGA	Micelle	86
pH, thermo, and salt	PMEMA	Microgel	65
	PDEA-*b*-PMEMA	Micelle	87
	PQDMA-*b*-PMEMA	Micelle	88
	PβDMA-*b*-PMEMA	Micelle	89

[a] See abbreviations for the definitions of polymers and reagents.

sensitive specific monomers or polymers.[63–66] For example, PDMA and PMEMA polymers are both temperature and pH-responsive.[4,65] By combining two or more different monomers having different stimuli responsive behaviors, a number of multi-responsive copolymers can be prepared. Temperature and pH-responsive polymers are probably the most studied among multi-responsive polymers. Such copolymers can be fabricated from polymers having one block that is temperature responsive and the other block having pH-responsiveness. In general, PNIPAm is chosen as a thermo-responsive block due to its lower critical solution temperature (32 °C) in water, which is close to body temperature.[63] Some of the multi-responsive polymers are given in Table 2.

Most commonly used methods for the synthesis of pH-responsive polymers

Vinyl-based pH-responsive polymers can be synthesized with different polymerization methods such as free radical polymerization, cationic polymerization, anionic polymerization, group transfer polymerization (GTP), atom transfer radical polymerization (ATRP), nitroxide-mediated radical polymerization (NMP), and reversible addition–fragmentation chain transfer (RAFT) polymerization. Polymers with various molecular structures or shapes including random, gradient, block, star, branched, brushes and graft (co)polymers can be synthesized with these methods. Among them, free radical polymerization is the simplest one. But it is not suitable for the synthesis of polymers with controlled molecular weight, narrow molecular weight distributions, and well defined structures.

For well-defined polymers with narrow molecular weight distributions, controlled living polymerization techniques are developed. These methods include either ionic or radical chemistry. Webster *et al.* developed an anionic living polymerization chemistry, namely group transfer polymerization (GTP), in 1983.[90] GTP allows the living polymerization of (meth)acrylates at room temperature. Due to the strict reaction conditions and being not suitable for all monomers, the application of this technique is limited. In spite of difficult reaction conditions, pH-responsive polymers consisting of tertiary amine methacrylates such as DMA,[91–93] DEA,[81,92,94] DPA[36,39,80] and MEMA[36,39,94,95] have been prepared using GTP in a variety of architectures such as block,[36,91,93] star[96], branched,[92] *etc*. Functional monomers such as methacrylic acid cannot be used in GTP since their labile protons terminate the polymerization. In order to polymerize such monomers, the functional groups need to be masked using protecting groups that are readily converted back to the functional species after the polymerization.[91,97]

Using controlled/living radical polymerization (CRP or CLP) methods, well-defined polymers can be synthesized under mild conditions with predictable molecular weights and content, narrow molecular weight, end-functional, and different polymer architectures.[98,99] CRP is a chain polymerization that proceeds in the absence of chain transfer and termination reactions.[98] Among CRP methods, ATRP, NMP and RAFT are prominent in the preparation of pH-responsive polymers. Some examples of pH-responsive polymers with various architectures reported with the NMP method are P2VP-*b*-PNIPAAm,[100] PPO-*b*-P(DMA-*stat*-2VP),[101] PDEVBP-*b*-P2VP,[102] PDEVBP-*b*-P(NIPAm-*stat*-DMAAm),[102] PDMA-*ra*-PVBK,[103] and PAAc-*grad*-PS.[104]

Another CRP type ATRP chemistry was independently discovered by Matyjaszewski *et al.*[105] and Sawamoto *et al.*[106] in 1995. In recent years, it became the most popular CRP method which is suitable for a wide range of monomers, including (functionalized) styrenes,[107] (meth)acrylates,[107,108] and some (meth)acrylamides.[109–113] But it has some limitations on the polymerization of acrylamide and its derivatives. Unlike ionic polymerization, ATRP exhibits a tolerance of trace impurities, *e.g.* no moisture sensitivity and functional group tolerance. A wide variety of mono- and multi-functionalized ATRP initiators can easily be prepared or obtained commercially. Additionally, the polymers synthesized *via* ATRP can be used as a macroinitiator for further steps, which is another important advantage of ATRP. Due to easy production of pH-responsive polymers with various architectures such as block,[108] star,[114–116] gradient,[108,117] brushes,[118,119] and branched[120] (co)polymers, this method has been frequently used in the synthesis of pH-responsive polymers.

The first reports of the direct use of addition–fragmentation transfer agents to control radical polymerization appeared in the 1980s.[121–123] Reversible addition–fragmentation chain transfer (RAFT) polymerization is one of the most widely used processes for synthesizing well-defined blocks,[22,124] stars,[125–128] branches[128,129] and brushes[85,130–132] in recent years. The difference of this method from free radical polymerization is the addition of the transfer agent (RAFT-CTA) to the polymerization medium. RAFT polymerization is appropriate for (meth)acrylates, styrenics, and (meth)acrylamides, whereas RAFT reagents are not tolerant to primary and secondary amines.[133] Just as in the ATRP method, the polymer obtained by the RAFT method can be used as a macro-RAFT agent and can be easily obtained commercially. In addition, the polymers obtained by ATRP and RAFT methods have mono- or multifunctional end groups. These groups on polymers can also be modified to obtain different polymeric materials. As an example, Armes' group has prepared non-ionic PG2MA-*b*-PHPMA diblock copolymers which can exhibit pH-responsive behavior. This behavior is due to the fact that the carboxylic acid-functional RAFT agent is used in the synthesis of polymers.[134] Due to easy modification of silicon and gold surfaces with an ATRP initiator and/or RAFT agent, surface initiated-atom transfer radical polymerization (SI-ATRP) and surface initiated-reversible addition–fragmentation chain transfer (SI-RAFT) methods are used frequently in the synthesis of pH-responsive polymeric brushes.

Different sizes of pH-responsive crosslinked hydrogels (micro- and nano-) by emulsion polymerization techniques can be prepared.[135–138] Thanks to the developed techniques, the production of hydrogels with narrow size distribution and smaller size has provided more effective use. The type of monomer or monomers used in the synthesis of hydrogels is the most important factor that affects their swelling–deswelling behavior at pH changes. pH-Responsive degradable crosslinking agents which can be degraded by pH change have also been reported.[139–142]

Different architectures of pH-responsive polymers

The most common pH-responsive polymer structures described in the literature are linear homopolymers, amphiphilic, and double hydrophilic block copolymers which form micelles or vesicles, star, branched, and hyper-branched polymers, polymer brushes, dendrimer polymers, nanogels, microgels, and hydrogels (macrogels). The unique self-assembly properties of block, star, and branched (co)polymers make them a promising field of research for use in applications such as drug delivery. The diameter of the prepared pH-responsive polymers and their self-assembled structures are important factors in determining their applications. The polymeric materials used in biological applications are especially required to be biocompatible and less than 100 nm in diameter. These structures and their sizes are schematically depicted in Fig. 5. pH-Responsive polymer structures attracting attraction for different applications are underlined in this section.

pH-Responsive linear block copolymer

pH-Responsive linear polymer structures are generally reported to be in the form of homopolymers, random copolymers, amphiphilic, and double hydrophilic block copolymers (Table 3). pH-Responsive homo- and random polymers are not

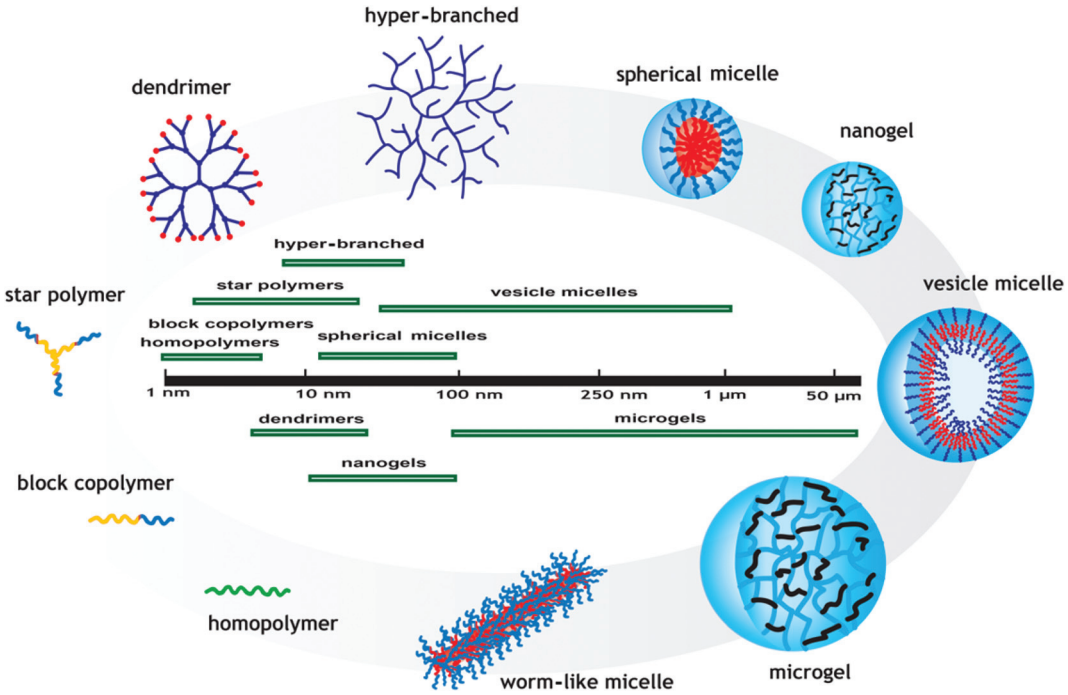

Fig. 5 Average sizes of pH-responsive polymers with different structures.

Table 3 Block types observed in pH-responsive linear diblock polymers

pH-responsive diblock copolymers[a]	
Double hydrophilic diblock copolymers (DHBCs) (hydrophilic–hydrophilic)	**Acidic-*b*-neutral block copolymers:** PEO-*b*-PMAAc,[147] PAAc-*b*-PNIPAm[78] **Basic-*b*-neutral block copolymers:** P2VP-*b*-PEG,[144] PNIPAm-*b*-PDEA,[66] PImHeMA-*b*-PG2MA[32] **Basic-*b*-acidic block copolymers:** PVBA-*b*-PMEMA,[148] PDMA-*b*-PAAc,[149] PMAAc-*b*-PDEA,[40] PAAPBA-*b*-PAEAm[150] **Basic-*b*-basic block copolymers:** PMEMA-*b*-PDEA[151] **Acidic-*b*-asidic block copolymers:** PNaAMPS-*b*-PAaH,[152] PNaStS-*b*-PNaVBA[153] **Acidic-*b*-zwitterionic block copolymers:** PNaSS-*b*-PSVBP[154] (no micelle by pH changes) **Basic-*b*-zwitterionic block copolymers:** PMPC-*b*-PDPA,[155] PMPC-*b*-PDEA,[156] PDPA-*b*-PβDMA,[89] PMEMA-*b*-PβDMA[89]
Amphiphilic diblock copolymers (hydrophilic–hydrophobic)	**Acidic-*b*-neutral block copolymers:** PS-*b*-PAAc,[157] PCL-*b*-PAAc,[158] PVPBA-*b*-PS[159] **Basic-*b*-neutral block copolymers:** PDMA-*b*-PS[107], PDMA-*b*-PMPS,[85] PPO-*b*-PDEA[160]

[a] See abbreviations for definitions of the terms used.

preferred in a lot of applications due to their only crash-dissolution behavior by pH changes. As is known, block copolymers consist of two or more different polymer segments. If one block is soluble in a solvent but the second block is not soluble, diblock copolymers tend to self-assemble into micellar structures by the insoluble block forming the core of the micelle and the solvated soluble block forming the corona. This self-assembly behavior provides a great possibility to scientists to prepare various micellar structures, nanoparticles and different materials.

Block copolymers which consist of both hydrophobic and hydrophilic blocks can behave as a surfactant. AB-type amphiphilic block polymers form micelles in aqueous solution by hydrophobic blocks moving to the interior to minimize their contact with water and hydrophilic blocks remaining on the outer surface of the micelles to maximize their contact with water (see Fig. 6). Various self-assembly structures such as spherical, flower, worm-like, and vesicle (hollow) micelles are formed by amphiphilic and double hydrophilic block copolymers by pH changes (Table 4).[4,80,143–145] The factors which determine the self-assembly and/or micelle morphology are temperature, pH, salt, polymer concentration, solvent type, and the structure/length of blocks.[146]

In addition to amphiphilic block copolymers, double hydrophilic block copolymers (DHBCs) can also form micelles due to their blocks with different stimuli responsiveness. These DHBCs can be responsive to pH in either block or in only one block. When the pH value is changed, these groups can accept or donate protons in aqueous solution and change the hydrophilicity of the related block. If there is a difference in pH-responsiveness of both blocks, pH changes may cause a self-assembly due to the dehydration of one block when the other one remains hydrophilic under related conditions. In contrast to the permanently amphiphilic block copolymers, so-called

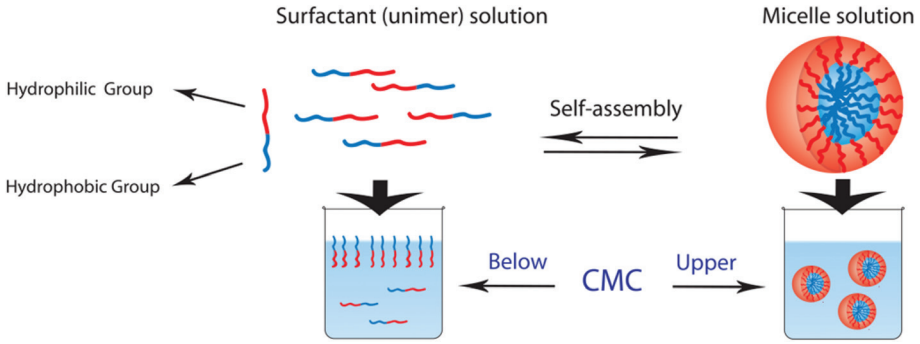

Fig. 6 Schematic representation of unimer–micelle equilibrium in water.

Table 4 Types of micelles obtained from pH-responsive linear block copolymers

Polymers[a]	Micelle type	Diameter	Ref.
Diblock copolymers (AB-type)			
P2VP-*b*-PEG	Spherical	100–170 nm	144
PPO-*b*-PDEA	Spherical	40–80 nm	160
PβDMA-*b*-PDPA	Spherical	~20 nm	167
PCL-*b*-PAAc	Spherical	100–200 nm	158
PLGA-*b*-PLL	Vesicle	120–180 nm	145
PB-*b*-PLGA	Vesicle	—	168
PEG-*b*-P(DEA-*co*-TMSPMA)	Vesicle	0.6–1.6 μm	169
Triblock copolymers (ABC- and ABA-type)			
PDPA-*b*-PDMA-*b*-PDPA	Flower	25–30 nm	80
PAAc-*b*-PS-*b*-P4VP	Vesicle	100–150 nm	170
PDMA-*b*-PMMA-*b*-PMAAc	Spherical	~11 nm	97
PDMA-*b*-PPO-*b*-PDMA	Worm-like	212 nm	143

[a] See abbreviations for definitions of the terms used.

pH-responsive double hydrophilic block copolymers offer an assembly strategy without the usage of a cosolvent.[4,161,162] Such amphiphilic pH-responsive block copolymer examples are given in Table 3.

There are different architectures of linear block copolymers, namely AB-type diblocks, ABA-type triblocks, ABC-type triblocks, and other multi-blocks (three or more).[163–165] In general, the ABA-type triblock copolymer can form flower type micelles at low concentrations and gels at high concentrations by pH changes. pH-Responsive ABA-type PDPA-*b*-PDMA-*b*-PDPA[80] having basic segments and PMAAc-*b*-PEG-*b*-PMAAc[166] having acidic segments triblock copolymers have also been reported as such systems. As an amphoteric triblock copolymer, the pH-responsive ABC-type PDMA-*b*-PMMA-*b*-PMAAc triblock copolymer has been reported by Patrickios *et al.* by examining its solution behavior.[97] In the following years, ABC, ACB, and BAC type triblock copolymers have also been demonstrated using hydrophobic MMA, basic DMA, and acidic MAAc monomers.[91] Some of the pH-responsive AB, ABC and ABA type block polymers are presented in Table 4.

The micelles can form or undergo a change of micellar morphology in an aqueous solution of block copolymers by pH changes. An example of the change of micelle morphology obtained by using schizophrenic polymers is micelles–reverse micelles.[161] In 1998, Armes' group reported a new type of pH- and salt-responsive block copolymer called "schizophrenic" AB diblock copolymers (PMEMA-*b*-PDEA, see Fig. 7). PMEMA-core micelles with cationic PDEA shells at pH 6.5 in the presence of Na_2SO_4 and PDEA-core micelles with neutral PMEMA shells at alkali pH have been successfully obtained in aqueous

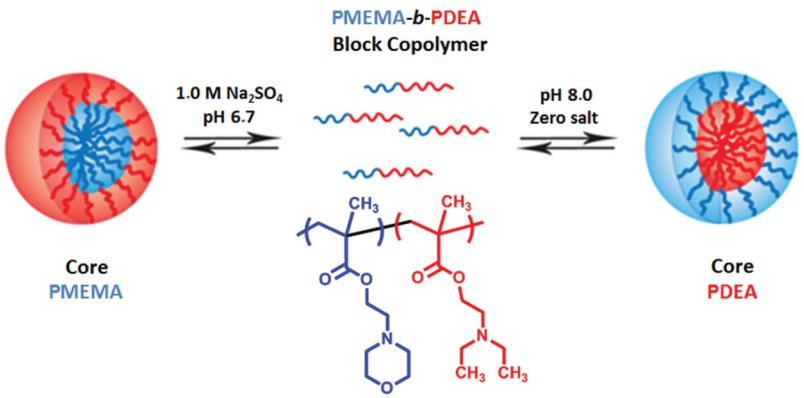

Fig. 7 Schematic representation of the formation of micelles and reverse micelles for a schizophrenic PMEMA-*b*-PDEA diblock copolymer in aqueous solution.[151]

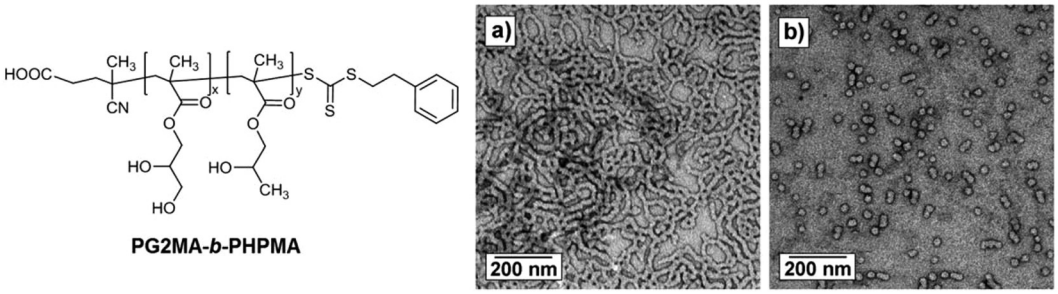

Fig. 8 TEM images obtained on addition of NaOH followed by dilution of a 10% w/w aqueous dispersion of a $PG2MA_{56}$-*b*-$PHPMA_{155}$ diblock copolymer prepared using the carboxylic acid functionalized PETTC RAFT agent: (a) pH 3.5 (initial worms); and (b) pH 6.0 (spheres) (Copyright 2015, Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, modified from ref. 134).

solution.[151] It is the first example of a pH and electrolyte responsive schizophrenic copolymer formed by a double hydrophilic block copolymer comprising weak polybase blocks. Later, the PDEA-*b*-PVBA block copolymer has been reported to be the only pH-responsive schizophrenic block copolymer formed by PVBA-core micelles with cationic PDEA shells at pH 2 and PDEA-core micelles with anionic PVBA shells in aqueous solution at pH 10.[171] Many pH-responsive schizophrenic polymers such as PVBA-*b*-PMEMA, PLGA-*b*-PLL, PPO-*b*-PDEA AB-type diblock copolymers and PDEA-*b*-PDMA-*b*-PMEMA and PAAc-*b*-PS-*b*-P4VP ABC-type triblock copolymers have been reported after these pioneering studies.[78,94,145,160,161,170,172] In later years, Lecommandoux and co-workers have succeeded in preparing schizophrenic vesicles using the PLGA-*b*-PLL diblock copolymer.[145]

In 2015, Armes' group achieved non-ionic PG2MA-*b*-PHPMA diblock copolymers which can exhibit pH-responsive behavior. This behavior is due to the fact that the carboxylic acid-functional RAFT agent is used in the synthesis of the PG2MA-*b*-PHPMA block copolymers. This study is a good report on the reversible transition from worm-like micelles to spherical micelles depending on pH change (Fig. 8).[134]

The practical applications of micelles are limited due to their structural instability since the micellar structure can hardly remain stable upon dilution or changes of external conditions such as changes in pH, ionic strength, type of solvent, and temperature.[173] In order to enhance the stability, cross-linking of the micelle core or corona by reacting functional groups of polymer chains with a bifunctional cross-linker was reported to be a useful approach. Based on cross-linking chemistry, core cross-linked micelles (CCL),[174,175] shell cross-linked micelles (SCL),[173–175] and intermediary layer cross-linked micelles (ILCL)[41,174] have been developed (see Fig. 9). In 1996, Wooley and co-workers reported the first example of covalently-stabilized block copolymer micelles. In this first example, polystyrene-*block*-poly(4-vinylpyridine) (PS-*b*-P4VP) block copolymers quaternized with 4-(chloromethyl)styrene have been used as building blocks to prepare conventional core–shell micelles using a THF/water cosolvent approach.[176] Cross-linked micelles (CLMs) are potentially useful as nano-sized vehicles for the delivery of various actives.[177] The CLMs

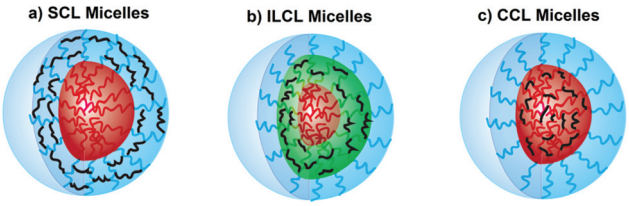

Fig. 9 Types of cross-linked micelles: (a) SCL micelles, (b) ILCL micelles, and (c) CCL micelles.

also show swelling–deswelling behavior with pH change. These CLMs are also called nanogels in the literature.[178,179] pH-Responsive cross-linked spherical micelles are the most studied species. Although limited in number, they have been made during the studies of the vesicle[169,180,181] and worm-like[143,181] micelles. CLMs have been obtained from various functional monomers such as TMSPMA, MPMA, and CMA[169,179,182] with various cross-linking agents such as BIEE, DVS, dicarboxylic acid, *etc.*[74,173–175,183] Degradable CLMs which are especially important for biomedical applications can be degraded by photo-, pH, biomaterials, and other chemicals.[75,173–175,184] Some of them are given in Table 5.

Spherical micelles and their SCL micelles were first prepared from PCL-*b*-PAAc diblock copolymers by Wooley and co-workers by first cross-linking of the PAAc shell. Then, the polyester core was degraded hydrolytically to obtain hollow spheres.[158] Similarly, Fustin and co-workers have reported hollow spheres by using PtBA-*hv*-PDMA block copolymers by cross-linking the PDMA shell followed by UV light irradiation of the PtBMA-core.[193] A CCL mixed micelle with dual responsive shells has also been constructed from two amphiphilic block copolymers P(MMA-*co*-MPMA)-*b*-PNIPAm and P(MMA-*co*-MPMA)-*b*-PDEA *via* a two-step process by Zhang and co-workers. PMPMA behaves as a cross-linker depending on solution conditions. Both block copolymers form core–shell mixed micelles in acidic aqueous solution at room temperature followed by using the inorganic "silica-based" cross-linking strategy without an additional cross-linker.[182] ILCL micelles from the MPEO-*b*-PAPMAm-*b*-PNIPAm triblock copolymer have been reported by McCormick and co-workers by

Table 5 List of cross-linked micelles obtained from linear block copolymers and types of CLMs

Block copolymers	Cross-linking moieties	Cross-linking agent	Core of micelle	Response	Ref.
Spherical CCL micelles					
$PMEO_2MA$-*b*-P(DEA-*co*-TPHMA)	TPHMA	$RuCl_3$	B/C	Low pH↑[a]	82
MPEO-*b*-PG2MA-*b*-PDPA	PG2MA	DVS	B	Low pH↑	185
PS-*b*-PAAc	PAAc	BIEE	A	—	186
P(QDMA-*co*-DMA)-*b*-PMEMA	DMA	BIEE	C	Low pH↑	187
P(MMA-*co*-MPMA)-*b*-PNIPAm	MPMA	Si–O–Si	A/B	Low pH↑	182
P(MMA-*co*-MPMA)-*b*-PDEA	MPMA	Si–O–Si	A/B	Low pH↑	
PAAPBA-*b*-PAEAm	AEAm	Dicarboxylic acid	A	Anionic/cationic	150
MPEO-*b*-P(DEA-*co*-CMA)	CMA	UV light	B/C	Low pH↑[b]	179
PEO-*b*-(PMAAc-Hyd)	MAAc-Hyd	DTE	B	High pH↑[a]	74
PVAm-*b*-PNIPAm	PVAm	Anthracene	A	pH degradable	184
Spherical ILCL micelles					
PDEA-*b*-PDMA-*b*-PMEMA	DMA	BIEE	A or C	Low pH↑	94
PDPA-*b*-PDMA-*b*-PMEMA	DMA	BIEE	A or C	Low pH↑	39
MPEO-*b*-PG2MA-*b*-PDEA	G2MA	DVS	C	Low pH↑[b]	188
MPEO-*b*-PDMA-*b*-PMEMA	DMA	BIEE	C	Low pH↑	41
PEG-*b*-P(CGMA-*co*-G2MA)-*b*-PDEA	CGMA	UV light	D	Low pH↑	189
MPEO-*b*-PG2MA-*b*-PDPA	G2MA	DVS	C	Low pH↑	185
MPEO-*b*-PAPMAm-*b*-PNIPAm	APMAm	TDA	C	pH degradable[a]	190
MPEG-*b*-P(LGA-*co*-CELG)	LGA	DTbDEA	B/C	High pH↑[a]	183
Spherical SCL micelles					
PDMA-*b*-P(MMA-*co*-CMA)	CMA	UV light	A	Desolve/low pH	191
PAAc-*b*-PDMA	DMA	BIEE	A	High pH↑	149
PSPMA-*b*-P(DEGMMA-*co*-CMA)	CMA	UV light	Both	High pH↑	178
PDMA-*b*-PMAAc	Both	BIEE	Both	—	40
(CNPBA-Dex)-*b*-PLA	CNPBA	CNPBA	B	pH degradable[a]	192
MPEO-*b*-PDMA-*b*-PMEMA	DMA	BIEE	C	—	41
Other micelle types					
MPEO-*b*-P(DEA-*co*-TMSPMA)	TMSPMA	Si–O–Si bond	B/C	Low pH↑[b]	169
PDMA-*b*-PPO-*b*-PDMA	DMA	BIEE	B	—	143
MPEO-*b*-P(DEA-*co*-GMA)	GMA	EN	B	Low pH↑	180

[a] Drug delivery. [b] Nanoreactors, (↑) represents the swelling (see abbreviations for the definitions of polymers and reagents). "A" represents the first block, "B" represents the second block and "C" represent the third block.

using terephthaldicarboxaldehyde as a cross-linker. ILCL micelles can be reversibly cleaved by simply adjusting the solution pH.[190] Such polymers are used in drug release studies.

pH-Responsive star polymers

Star polymers, containing several linear polymer chains connected to one central core, are another class of macromolecules with a precisely controlled architecture. Most commonly used synthetic approaches for the preparation of star polymers using different polymerization techniques are "core-first", "arm-first", and "coupling-onto" approaches.[194,195] There are different star-shaped segmented (co)polymers with a diameter between 7 and 30 nm.[196–199] Particularly, the so-called pH-responsive star polymers have attracted great interest since the stars bearing block/arms undergo sharp phase transitions upon responding to pH changes. These polymers can form micellar self-assembly or undergo a change of micelle morphology by pH changes. In vesicle, rod, spherical, and flower micelles morphology is obtained using star polymers.[96,114,115,200] For star polymers having very different segments, it is quite difficult to show the morphology of the micelles *via* self-assembly.[198] In addition, some of them may form gels by pH changes.[201] Some pH-responsive star polymers and their behaviors exhibited by pH changes are given in Table 6.

pH-Responsive star block copolymers are also good polymers for the preparation of hydrogels as reported by Armes and co-workers. They can be synthesized using 2-(methacryloyloxy)ethyl phosphorylcholine (MPC) as the inner block and followed by sequential monomer addition of various tertiary amine methacrylates or mixtures thereof such as DMA, DMA/DEA, and DMA/DPA. Star diblock copolymer gel agents having both thermo- and pH-responsive nature have also been reported by copolymerization of DMA with DPA.[201] Whittaker and co-workers have reported the successful synthesis of PPEGMA-*b*-P(TFEMA-*co*-DMA) degradable core cross-linked star (CCS) polymers through the arm-first approach. The related polymer could form nanoparticles in aqueous solution and the particle size is dependent on solution pH.[208] The *star*-$P(DEA\text{-}b\text{-}MMA\text{-}b\text{-}PEGMA)_6$ triblock copolymer has self-assembly behavior depending on pH change. The star copolymer can self-assemble into multi-compartment micelles at pH 10.5, vesicles at pH 7.4 and micelles at pH 2.0.[114] Multiarm star-shaped terpolymers based on PS_n–core-$(P2VP\text{-}b\text{-}PAAc)_n$ are known to be pH-responsive in dilute aqueous solutions (Fig. 10). A variety of amphoteric self-assemblies such as unimolecular micelles, multicore micelles, and worm-like micelles have been observed by pH changes.[202]

The miktoarm copolymer μ-(PtBA)(PCEMA)$(PEO)_{1.14}$ has been used for the preparation of various vesicles *via* a double

Table 6 List of pH-responsive star polymers and their types of micelles

Star polymers[a]	Micelle type	Core block of micelles[a]	Diameter of micelles	Ref.
PMPC-*b*-P(DMA-*co*-DPA)	Gel formation	—	—	201
star-P(DEA-*b*-MMA-*b*-PEGMA)	Multi-compartment spherical micelle	PDEA/PMMA	60–110 nm [b]	114
PS(PNIPAm-*b*-P4VP)$_2$	Spherical and rod	—	100–200 nm	115
SPCL-*b*-PCEMA-*b*-PDMA	Spherical-ILCL	SPCL	87–230 nm	127
PS$_n$(P2VP-*b*-PAAc)$_n$	Worm-like, spherical multicore	—	30–500 nm	202
PDMA-*star*-PDEA	Spherical	PDEA	25–50 nm	95
PMMA-*b*-P(NIPAm-*co*-DMA)$_3$	Spherical	PMMA	85–110 nm [b]	77
4AS-PCL-*b*-PDEA-*b*-PPEGMA	Spherical	PCL	60–220 nm [b]	116
MPEG-*b*-PtBA-*b*-PCL	Spherical	PCL	120–237 nm [b]	203
(PEO-*b*-PDEA)$_4$	Spherical	PDEA	21–56 nm	196
PEG-*b*-PMAAc-*b*-PDEA	Spherical	Both	57–94 nm	197
PEO-*b*-PDMA-*b*-PHEA	Spherical	PHEA	—[c]	204
PLL-*b*-(PLGA)$_2$	Spherical	PLL or PLGA	77–110 nm	205
μ-(PtBA)(PCEMA)(PEO)	Vesicle	—	188 nm	200
PDEA-*g*-CD-*g*-PNIPAm	Vesicle	—	30–85 nm	199
P2VP-*b*-PMMA-*b*-PAAc	Vesicle	PMMA	0.1–1.5 μm	206
MPEG-*b*-PHIS	Vesicle	PHIS	~70 nm	207

[a] See abbreviations for definitions of the terms used. [b] Drug delivery. [c] Enzyme carrier.

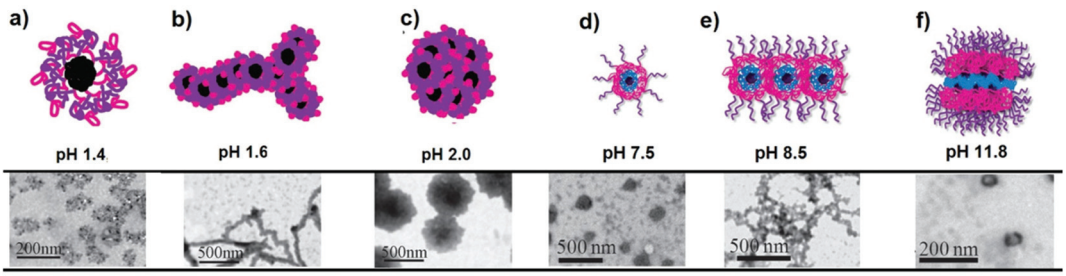

Fig. 10 TEM images of the PS$_n$_core-(P2VP-*b*-PAAc)$_n$ star conformation and the corresponding self-assemblies aqueous solution at: (a) pH 1.4 unimolecular micelle, (b) pH 1.6 worm-like micelle, (c) pH 2.0 multicore micelle, (d) pH 7.5 unimolecular micelle, (e) pH 8.5 unimolecular micelle association towards network-like assemblies, and (f) pH 11.8 multi-compartment multi-molecular micelle (Copyright 2011, The Royal Society of Chemistry, modified from ref. 202).

assembly strategy. PCEMA units have been used as photo cross-linkers and then hydrolysed PtBA units. These cross-linked vesicles exhibited pH-responsive reagent release in aqueous media.[200] Similarly, Lang and co-workers have also reported cinnamate-functionalized star amphiphilic triblock copolymers SPCL-*b*-PCEMA-*b*-PDMA which can self-assemble into core–shell-corona micelles in aqueous solution. The micelle stability has been improved by photo cross-linking by PCEMA units. pH changes provided swelling–deswelling on the cross-linked micelles.[127] The Y-shaped miktoarm star polypeptide PLL-*b*-(PLGA)$_2$ copolymer has also been reported to be an interesting polymer which can form both PLGA-core micelles at acidic pH and PLL-core micelles under alkaline pH conditions (Fig. 11). Thus, a pH-responsive self-association "schizophrenic" behavior of this segmented star polypeptide has been revealed in aqueous media.[205]

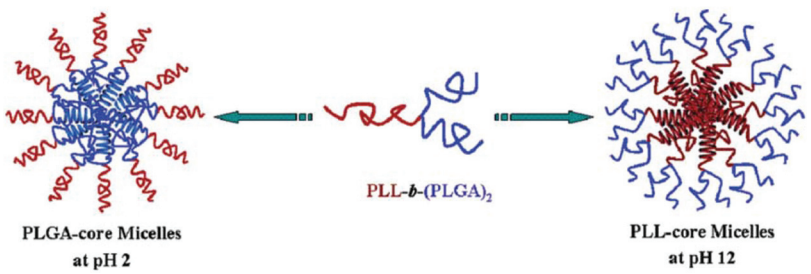

Fig. 11 pH-Induced micellisation of PLL-*b*-(PLGA)$_2$ associated with coil-to-helix transitions (Copyright 2008, The American Chemical Society, reprinted from ref. 205).

pH-Responsive branched and hyper-branched polymers

Among various polymer architectures, hyper-branched polymers are interesting materials since they have unique properties compared to their respective linear analogues. They have better solubility in a wide range of solvents due to their decreased chain entanglement, low melt and solution viscosities, reduced hydrodynamic volume, and critical phase transition behaviors. They also provide various advantages for further derivative materials due to the presence of a huge number of chain end functionalities.[209] In 1990, the first branched polymer using the Suzuki-type coupling of dibromoboronic acid monomers was reported.[210] In recent years, various branched and hyper-branched polymers have been reported with various application possibilities. Branched polymers have rather broad molecular weight distributions due to uncontrolled polymerization chemistry. However, novel approaches have recently been applied with controlled polymerization techniques which allow one to control the primer chain-length. Their synthesis *via* various polymerization methods such as GTP, RAFT, NMP, and ATRP became very easy.[92,209]

Table 7 List of pH-responsive branched polymers

Polymer contains[a]	Structure formed by pH change	Applications	Ref.
Hyper-branched polymers			
PEGMA-*co*-PDEA-*co*-PtBAEMA-*co*-EGDMA	(De)swelling	Drug delivery	214
P(Boc-VaI-HEA-*star*-MEO_2MA/PEGMA)	Multi-micelle	—	128
PEGMA/PDEA-PEG	Spherical micelle	—	216
P(BAC-AMPD)-PEG	(De)swelling	Drug delivery	215
BP(DMA-*co*-MAEBA-*co*-DTDMA)$(PMAGP)_n$	Spherical micelle	Drug delivery	126
HBPE-PDMA	Vesicle micelle	—	217
PAAc-*b*-PMEA-*b*-PNIPAm-*b*-MPEG	Vesicle micelle	Drug delivery	213
Branched polymers			
PBIEM-*g*-PDMA	Worm-like micelle	—	212
PNIPAm-*b*-P(EA-*g*-DEA)	Schizophrenic micelle	—	211
PEO-*b*-[PGMA-*g*-(PDEA)$(PMEO_2MA)$]	Schizophrenic micelle	—	83
PDEA-*b*-P(DMA-*co*-EGDMA)	Spherical micelle	—	92

[a] See abbreviations for definitions of the terms used.

These polymers can self-assemble and form micelles[211–213] and/or (de)swellable-particles by pH changes.[214,215] Worm-like, vesicles, and spherical micelles are obtained using pH-responsive branched and hyper-branched polymers. pH-Responsive branched and hyper-branched polymers and their solution behaviors are given in Table 7.

The hyper-branched polyethylene with thiocarbonyl thio moiety ends (HBPE-BSPA) can be used as a macro-RAFT agent for the synthesis of hyper-branched polyethylene amphiphiles, HBPE-PDMA, by RAFT polymerization of DMA. The resultant HBPE-PDMA can self-assemble to form supra-molecular polymer vesicles in aqueous solution. A preliminary investigation on the thermo- and pH-responsive behaviors of the polymer is also reported (see Fig. 12).[217]

The PEO-*b*-[PGMA-*g*-(PDEA)-$(PMEO_2MA)$] coil–rod diblock copolymer has been synthesized *via* a combination of ATRP and click reaction. This coil–rod diblock copolymer exhibits pH- and thermo-responsive supra-molecular aggregation behavior in aqueous solution. It behaves as schizophrenic and shows micelles–reverse micelles self-assembly at solution pH and temperatures (Fig. 13).[83]

A series of novel pH-responsive, amphiphilic branched copolymers based on PEGMA, DEA, and tBAEMA have also been prepared. Dynamic light scattering data indicated micelle formation with a diameter of about 16 nm by the formation of the hydrophobic PtBAEMA and PDEA core and the hydrophilic PEGMA corona above pH 8. With the decrease of pH from 8 to 6, a dramatic increase in the hydrodynamic radius of polymer particles from 16 nm to 130 nm has been observed, resulting from the protonation of the PDEA segment.[214]

pH-Responsive dendrimer polymers

Dendrimers are an important member of the class of polymers. The first report on dendrimer synthesis is attributed to Vögtle and co-workers[218] in 1978, followed by the work of Tomalia and co-workers in the early 1980s.[219] In later years, many dendrimers were reported with several application studies. They have great control over polydispersity, molecular weight and architecture with a high surface functionality. Their water solubility is an important property that makes them attractive for drug delivery and biomedical applications.[219–222] Among them, pH-responsive dendrimers have attracted great interest in recent years. Some dendritic molecules such as PEI, PPI, and PAMAM already show

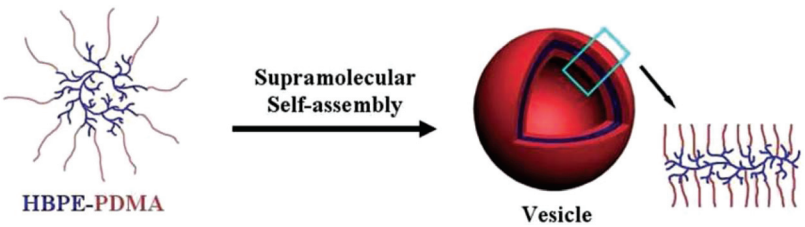

Fig. 12 A possible self-assembly mechanism for polymer vesicles (Copyright 2012, Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, modified from ref. 217).

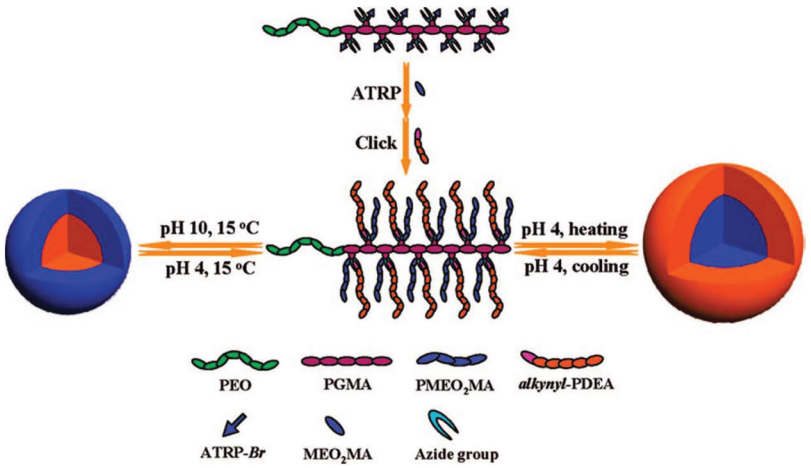

Fig. 13 Schematic illustration of the synthesis and multi-responsive supra-molecular self-assembly of a coil–rod double hydrophilic diblock copolymer: PEO-*b*-[PGMA-*g*-(PDEA)(PMEO$_2$MA) (Copyright 2009, The American Chemical Society, reprinted from ref. 83).

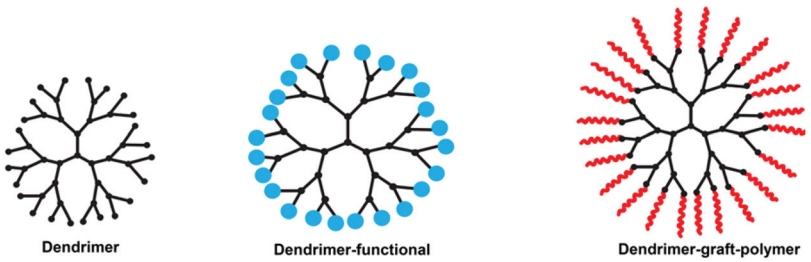

Fig. 14 Chemical structures of a dendrimer, a functional dendrimer and a dendrimer-*graft*-polymer.

pH-responsive behavior without requiring further modification. Depending on requirements, some dendrimers have to be modified to provide a different functionality. Despite the superior properties of dendrimers, their diameters being less than 15 nm cause some difficulties in some application processes. To overcome this problem, various polymers have been grafted onto dendrimers (Fig. 14 and Table 8).

Table 8 List of pH-responsive dendrimers, functional dendrimers and dendrimer-*graft*-polymers

Dendrimer contains[a]	Applications	Ref.
Dendrimer		
PAMAM	Drug delivery	223
PEI	—	224
PPI	Carrier	225
Funtional dendrimer		
PEI-sulfopropylated	—	226
PEI-phosphonated terminated	—	227
PPI-carboxylic acid terminated	—	228
HBPO-carboxylic acid terminated	—	10
Dendrimer-*graft*-polymers		
H40-PCL-*b*-PAAc-*b*-MPEG/PEG-FA	Drug delivery	229
PEI-*g*-(PLG-*b*-PEG)	Drug delivery	230
PEI-PLL-*b*-PEG	Protein carrier	231
PAMAM-*g*-PDMA	Drug delivery	232
PAMAM-*g*-PDMAPS	Drug delivery	233
PAMAM-*g*-PEG (vesicle micelle)	—	234

[a] See abbreviations for definitions of the terms used.

pH-Responsive brush and comb polymers

Polymer brushes are one kind of ultrathin polymer layers linked with one chain end to the surface of the solid substrate. As shown in Fig. 15, there are two common methods for the synthesis of such brushes on an inorganic surface. They are "grafting to" (attachment of the side chains to the backbone) and "grafting from" (grafting the side chains from the backbone).[235,236] In a "grafting to" method, pre-synthesized polymer chains are grafted to a backbone through the physicochemical adsorption or chemical reactions. On the other hand, during the last decade, the development of surface-initiated controlled/living radical polymerization (SI-CRP) provides a "grafting from" approach allowing one to tune the brush thickness, composition and architecture of brush polymers. Well-defined polymer brushes based on the "grafting from" strategy can be initiated directly from initiator-functionalized surfaces. The most commonly used polymerization techniques which have been applied in the "grafting from" approach *via* SI-CRP methods are NMP, RAFT, and ATRP.[235,236]

If any segment of related brushes has a response to external stimuli, it is possible to control the conformation, surface energy, and phase transition of a polymer brush by tuning the

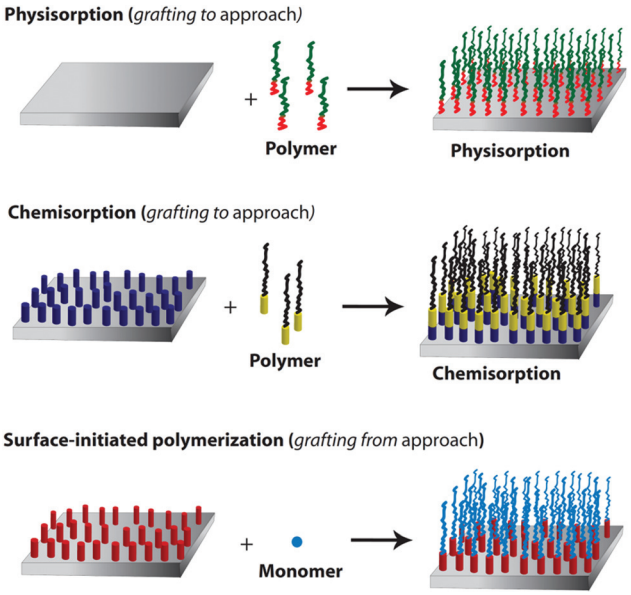

Fig. 15 Synthetic strategies for the preparation of polymer brushes: (a) physisorption of diblock copolymers (grafting to), (b) chemisorption (grafting to) and (c) polymer brushes grown *via* surface-initiated polymerization (grafting from).

composition, density and length of the brushes. There are a large number of reports in the literature that describe their pH-responsive nature.[235–237] These brushes contain ionisable pendant groups that can accept or donate protons in response to an environmental change in pH that leads to tuning of surface wettability. pH-Responsive brush polymers are used in many applications such as drug delivery or carriers,[238] non-biofouling,[239] membranes,[240] cell adhesive surfaces[239] and protein adsorption–desorption[241] (Table 9).

Similar to brush type polymer synthesis, there are various reports based on the synthesis of pH-responsive comb type polymers using both the "grafting from" and "grafting to" approaches (see Table 10). Additionally, the "grafting through" method with the usage of macromolecular monomers is also reported to be useful for the same purpose similarly to the "grafting from" approach.[252,253] The related reports are mainly based on PAAc, CS and PDMA type polymers. ATRP is the mostly preferred chemistry for the "grafting from" approach. In the "grafting to" pathway, chain ends of polymer molecules are commonly functionalized with alkyl-azide, thiol–ene and succinimide chemistries. As an example, the P(NVK-*co*-VBC)-*g*-P(DMA-*co*-AAc) comb polymer has been reported to be pH-responsive and has potential in drug delivery applications since it can self-assemble with pH change and form hollow micelles with different diameters at different temperatures.[254]

Table 10 List of pH-responsive comb polymers

Polymers[a]	Method for synthesis	Polymerization method	Ref.
P(MMA-*co*-HEMA)-*g*-PDMA	Grafting from	ATRP	255
Pluronic-*g*-PAAc	Grafting from	—	256
P(NVK-*co*-VBC)-*g*-P(DMA-*co*-AAc)	Grafting from	ATRP	254
Chitosan-*g*-PNIPAm	Grafting from	ATRP	257
PAMA-*g*-PLGA	Grafting from	ROP	258
PEGMA-*g*-PMAAc	Grafting through/from	ATRP	252
PEGMA-*g*-PDEA	Grafting through/from	ATRP	253
PNBC-*g*-PAAc	Grafting to	—	259
PNBC-*g*-PDMA	Grafting to	—	259
CS-*g*-PNIPAm	Grafting to	—	260
CS-*g*-PNIPAm	Grafting to	—	261
CS-*g*-PDMA	Grafting to	—	262
Alginate-*g*-PNIPAm	Grafting to	—	263

[a] See abbreviations for definitions of the terms used.

Table 9 List of pH-responsive polymer brushes

Polymers[a]	Method for synthesis	Applications	Surfaces	Ref.
Basic brush polymers				
PDMA	Grafting from	Protein ads.	Au coated quartz	242
PDMA	Grafting from	Wettability	Silicon substrates	243
PDEA and PDPA	Grafting from	Wettability	Silicon substrates	244
PNIPAm-*co*-PVI	Grafting from	—	Au coated silicon	119
PSPEA-*co*-PDMA	Grafting from	Catalyst surface	Silicon nanospheres	245
Acidic brush polymers				
PMAAc	Grafting from	Membrane	Silicon nitride	240
P(MAAc-*co*-DVB)-*g*-PNIPAm	Grafting from	Drug release	Silicon nanospheres	238
PAAPBA	Grafting from	Cell capture and release	Silicon nanowire	246
PEGMP	Grafting from	membrane	Silica film	247
PTMA-*co*-PCAA	Grafting from	Non-fouling and adhesive surface	Au chips and Au coated silicon	239
PKSPMA	Grafting from	—	Au coated silicon	248
Acidic–basic brush polymers				
PDMA-*b*-PMAAc	Grafting from	Protein ads.	Silicon wafer	241
PAAc-*b*-P2VP and PAAc-*b*-P4VP	Grafting to	—	Silicon wafer	249
Mixed PAAc-P2VP	Grafting to	Drug delivery	ITO glass and silicon	250
Mixed PAAc-P2VP	Grafting to/grafting from	—	Silica particles	251

[a] See abbreviations for definitions of the terms used.

pH-Responsive hydrogels (macrogels), microgels and nanogels

It is also worth mentioning that pH-responsive hydrogels are another type of pH-responsive polymer family. Hydrogels are network polymeric materials that have chemical or physical cross-linking among their macromolecular chains and remain insoluble in aqueous media.[264] Cross-linking of polymers can be carried out by electrostatic or molecular interactions between polymer chains (physical gels) or by chemically linking with cross-linking agents of polymer chains (chemical gels). Hydrogels are hydrophilic polymer networks and may absorb water up to thousands of times their dry weight. Hydrogel compositions can be divided into three classes: natural polymer hydrogels, synthetic polymer hydrogels and a combination of the two classes.[7]

Hydrogels can exhibit a phase transition with a change in external conditions such as pH, temperature, electric field, magnetic field, light, ionic strength, solvent, *etc*. and are known as 'stimuli-responsive' or 'smart' gels.[265] pH-Responsive hydrogels can be synthesized from pH-responsive polymers possessing ionisable functional groups which either accept or release protons in response to changes in environmental pH. As seen in Fig. 16, acidic hydrogels prepared with acidic monomers become negatively charged by releasing protons at high pH and swell. On the contrary, basic hydrogels prepared with basic monomers become positively charged by accepting protons at low pH and swell. Such ionizations cause their swelling due to an increase in hydrophilicity of related groups, changes in osmolarity and ionic interactions within the gel.[266] Swelling of a pH-responsive hydrogel is slow and takes hundreds of hours until it reaches equilibrium, but its deswelling is very fast (minutes). Amphoteric hydrogels such as PDMA-*co*-PMAAc contain both basic and acidic monomers, swell at low or high pH but deswell at isoelectric point.[267] Such hydrogels swell in a wider pH range compared to other hydrogels.[70,267–269]

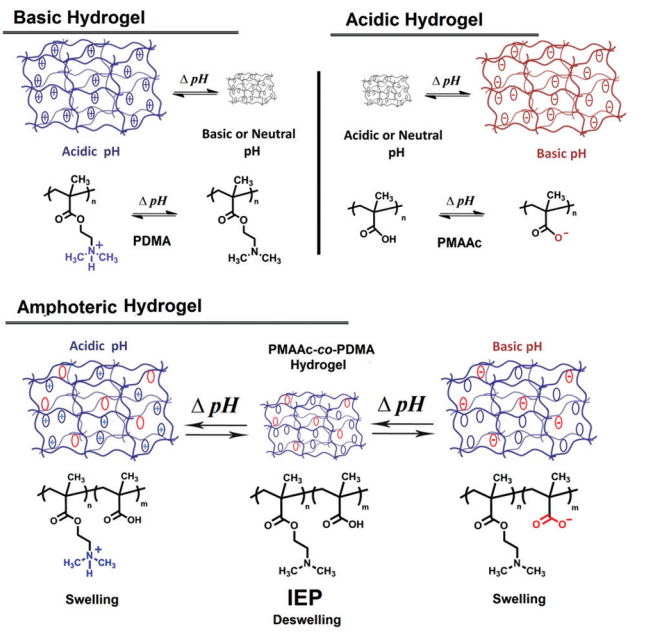

Fig. 16 Basic, acidic, and amphoteric hydrogels and their swelling–deswelling behaviors.

Hydrogels are also classified according to their size: macrogels (≥100 μm), microgels (0.1–100 μm) and nanogels (1–100 nm).[264] Various macro-, micro-, and nanogels have been synthesized containing different hydrophilic polymers. Nanosized PMMA-*co*-PAAc hydrogels were first prepared in 1991.[270] In 1996, a pH-responsive nanogel was developed for biomedical application as a drug delivery carrier by Gurny *et al.*[271] Such smart polymers are very promising polymers in drug delivery applications as a carrier and/or release system because of their high loading capacity, high stability and responsiveness to pH of the medium.[272] In the synthesis of pH-responsive hydrogels, synthetic polymers such as PDMA,[273,274] PAAc and PMAAc[84,142] and the natural polymer chitosan appear to be frequently used.[50,275] A few examples of pH-responsive hydrogels in natural, synthetic or combinations of the two classes with a diameter between 50 and 1000 nm are given in Table 11.

Recently, pH-responsive degradable hydrogels which can be degraded by biomaterial or physiological conditions,[139–142,277,278] oxidative processes,[183,279] and pH changes[276,279,280,292] have been reported. This behavior occurs by degradation of the polymer skeleton or cross-linking agents. The synthesis of biodegradable hydrogels which are used in medical and pharmaceutical applications has gained great importance in recent years.

As shown in Fig. 17, a successful synthesis of a boron containing hydrogel based on 4-arm PEG catechol and 1,3-benzenediboronic acid (BDBA) has been reported as a novel pH-responsive hydrogel. This hydrogel has been produced by complexation of a multifunctional catechol polymer with a bifunctional borate compound. The dynamic nature of the boronate ester linkages gives rise to self-healing hydrogels exhibiting high stability at alkaline pH (~9.0) and low stability at acidic pH (~3.0).[280]

As shown in Fig. 18, pH-responsive hollow P(MBA-*co*-MAAc) microgels have been successfully synthesized and used in drug delivery studies.[293] In another study, pH-responsive hydrogel fibers by the electrospin method have been reported by using PNIPAm and PAAc monomers.[294] In another study, enzymatically digested pig hair keratin has been modified by grafting copolymerization with a functional monomer, MAAc, which afforded an enzymatically digested pig hair keratin-based biopolymer hydrogel, a type of novel pH-responsive hydrogel. The hydrogel has been examined as a drug carrier, and its swelling and drug release properties have been defined.[295]

Application areas of pH-responsive polymers

pH-Responsive polymers are intelligent polymers that undergo changes in structures and properties such as volume, chain conformation, solubility, configuration and so on in response to changes in pH. pH-Responsive polymers have various potential application areas in biotechnology, nanotechnology, chromatography, membranes, coatings, *etc*. They can be used as gene

Table 11 List of pH-responsive macro-, micro-, and nanogels

Polymers[a]	Types	Response	Cross-linking agents[a]	Ref.
Mussel adhesive proteins	Macro	pH degradable	Fe^{3+}	276
CS-PVP	Macro	Low pH↑	GA	48
PAAc-PA-PBuAA-PMAGGONp	Macro	Low pH↑	ACDAAB	140 and 277
PHPMAm-*co*-PAAc-*co*-PBuAm PAM-*co*-PAAc-*co*-PBuAm PMA-*co*-PAAc-*co*-PBuAm PDMA-*co*-PAAc-*co*-PBuAm	Macro	Low and high pH↑	AB	278
PAAPBA-*co*-PVDT-*co*-POEGMA	Macro	High & low pH↑	PBAC	279
Dextrin/PAAc	Macro	High pH↑	MBA	141
PGH-PAAc, PGH-PMAAc PGH-PEAAc, PGH-PPAAc	Macro	High pH↑	Modified PLGA	142
4-Arm PEG catechol/BDBA	Macro	pH degradable	BDBA	280
PEGMP-PHEMA	Macro	High pH↑	—	14
PASA	Macro	High pH↑	—	281 and 282
PVP-*co*-PIA	Macro	Low pH↑	EGDMA	283
P2VP	Micro	Low pH↑	DVB	135
PEA-*co*-PMAAc	Micro	High pH↑	BDDA	284
PMMA-PMAAc	Micro	High pH↑	EGDMA	136
Chitosan/gelatin	Micro	Low pH↑	GA	285
PMAAc/PAAc-*g*-PPEGMA	Micro	High pH↑	TEG	286
PEG-chitosan	Micro	Low pH↑	PEG	50
PMEMA	Micro	Low pH↑	EGDMA	65
PMAAc-*co*-PNIPAm (yolk/shell)	Micro	High pH↑	EGDMA	84
PS-*co*-PtBAEMA	Micro	Low pH↑	DVB	287
PDMA	Nano	Low pH↑	EGDMA	274
PMMA-*co*-PAAc	Nano	High pH↑	EGDMA	270
MPEG-*g*-PDEA	Nano	Low pH↑	EGDMA	288
PNIPAm-*co*-PDMA	Nano	Low pH↑	MBA	273
MPEG-*b*-P(LGA-*co*-CLG)	Nano	Low pH↑	CLG	289
PMAAc-*g*-PPEGMA	Nano	High pH↑	TEG	290
PDEA-*co*-PTBAEMA-*g*-PPEGMA	Nano	Low pH↑	TEG	138
P2VP	Nano	Low pH↑	DVB	137
Lipoic acid modified PLL	Nano	Low pH↑	Lipoic acid	291

Arrows (↑) represent the swelling. [a] See abbreviations for definitions of the terms used.

delivery systems, controlled drug release systems, drug carriers, sensors, stabilizers, viscosity modifiers, *etc.*[4–6,9,296,297] The subject of pH-responsive polymers has become very popular in recent years and new studies have been added year after year.

One successful application of pH-responsive copolymers is their usage as stabilizers in dispersion and emulsion polymerizations.[297] Tertiary amine methacrylate based block copolymers can be used as stabilizers in heterogeneous polymerizations. For example, the PDPA-*b*-PMEMA diblock copolymer has been reported to be a good stabilizer in the production of monodisperse PMEMA microgels *via* emulsion polymerization.[298] As an example, MPEO-*b*-PDEA-*b*-PMPC is a successful stabilizer for such a purpose. The MPEO-*b*-PDEA-*b*-PMPC triblock copolymer can form micelles at pH >7.5 by the middle block forming micelle core and the outer blocks forming hydrated coronas. Nitrogen atoms of PDEA blocks are in the deprotonated form at pH >7.5 and PDEA blocks become insoluble due to dehydration. But both outer blocks show hydrophilic character over the entire pH range. Thus, this block copolymer provides successful stabilization for multi-responsive PMEMA microgels in aqueous media.[65] Another example, DMA and MMA monomers, can be used to prepare different types of polymers such as AB diblock, ABA and BAB triblock copolymers. With these copolymers, polystyrene latexes can be synthesized and these copolymers stabilize PS latexes well. At low pH, PS latexes have exhibited no surface activity, but showed surface activity at the air–water interface at high pH.[93]

Stabilization of inorganic particles which are metal oxides and metals is one of the most important problems in modern colloid chemistry and technology known nowadays as nanoscience and nanotechnology. The synthesis of nanoparticles with small size, narrow size distribution and long term stability requires the use of a stabilizer system that consists of small molecules and/or macromolecules. In the synthesis of inorganic particles, the use of polymers as a stabilizing agent is very common. Hydrogels, microspheres, nanospheres, homopolymers, dendrimers, brushes and block copolymers are widely used as stabilizer systems.[299–310] Among them, amphiphilic and double-hydrophilic block copolymers have attracted great attention since they allow inorganic particle formation within the core of their micelles. For such micellar systems, the block copolymer requires one block

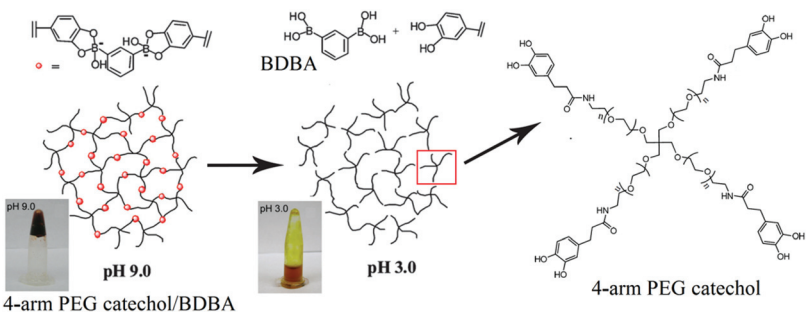

Fig. 17 Schematic illustration of pH-responsive hydrogels based on 4-arm PEG catechol and BDBA in aqueous solution at 20 °C (Copyright 2011, The Royal Society of Chemistry, modified from ref. 280).

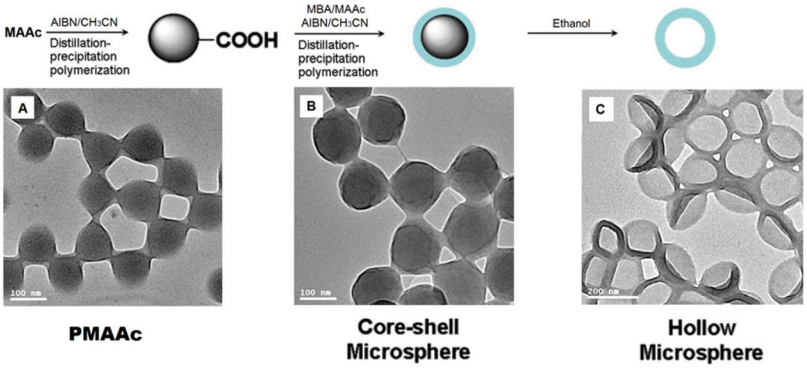

Fig. 18 Preparation of pH-responsive P(MBA-*co*-MAAc) hollow microspheres and TEM micrographs of polymer microspheres: (a) PMAAc seeds, (b) PMAAc/P(MBA-*co*-MAAc) core–shell microspheres, (c) hollow P(MBA-*co*-MAAc) microspheres with a cross-linking degree of 40 wt% (Copyright 2009, Elsevier Ltd, modified from ref. 293).

forming the micelle core by coordinating with metal containing ions and the second block forming the corona, which provides good stability in the solvent medium.[297,311,312]

Delivery and carrier of compounds studies. Temperature-, pH-, light-, magnetic-, electrical- or multi-responsive polymers have been studied very frequently in biomedical applications as delivery and carrier systems. Among them, temperature-, pH- and both temperature- and pH-responsive polymers are the most commonly preferred polymers in such applications. The key parameter for pH-responsive polymers for drug delivery is pH, which is used to determine the pH of the body site where the trapped drugs will be released. The pH values of the extracellular fluid of normal tissues and blood are, however, kept highly constant at 7.4 while the intracellular pH is maintained at 7.2. However, it is well known that there are some variations in the pH of several body sites and cellular compartments, such as the gastrointestinal tract, vagina and extracellular and endosomal/lysosomal microenvironments, intestine and skin.[265,313] In addition, the existing pH of tumor tissue has been considered an ideal trigger for the selective release of anticancer drugs in tumor tissues and/or within tumor cells. Compared to the extracellular pH of normal tissues and blood constant at pH 7.4, the measured tumor extracellular pH (pHe) values of most solid tumors range from pH 6.5 to 7.2, which is lower than the normal tissues.[314,315] pH-Responsive polymers have been used benefiting from these physiological features in biomedical applications.

Drug release by pH changes can occur by two different strategies. In the first strategy, polymeric materials containing pH-responsive groups release drug molecules due to swelling/deswelling behavior or degradation of the micelle structure with pH change. In the second strategy, polymeric materials release drugs with cleavage of covalent bonds between the drug and polymer by pH changes. pH-Labile bonds (Fig. 19), used in polymer structures, are hydrazone,[316–321] acetal/ketal,[322–325] *cis*-acotinyl,[326–330] imine,[184,331,332] substituted trityl,[333–335] orthoester,[336,337] and others.[338,339]

Storage and release of biomaterials, such as proteins, gene, enzymes and particularly drugs, can be carried out *via* the

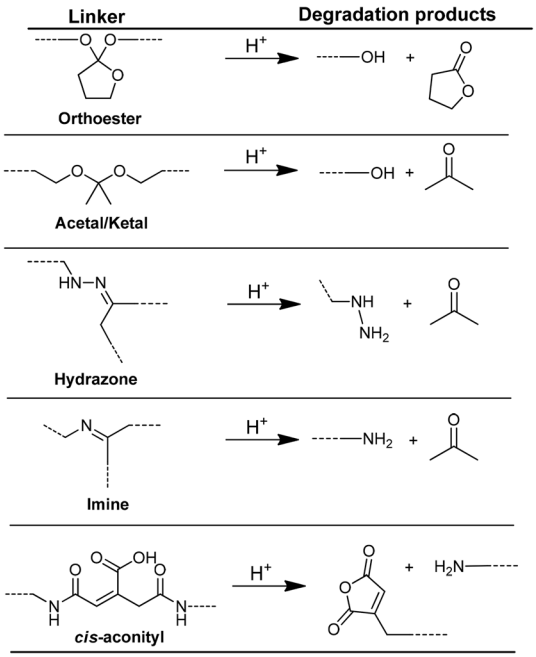

Fig. 19 Structures of pH-labile bonds and their degradation products.

usage of pH-responsive micelles and hydrogels.[293,296,313,340] Owing to pH-responsive groups in the structure, the release of various compounds is possible. Particularly smart polymers are very promising as delivery and carrier systems because of their high loading capacity, high stability, and responsiveness to change in environmental factors.[272] It is well known that micelles can solubilize some compounds which are not soluble in the aqueous phase.[296] Self-assembled pH-responsive vesicle structures are mostly used for drug transport and release.[341] Also cross-linked micelles have been used in the drug release study. These cross-linked micelles like nanogels can swell or deswell by pH changes and might be useful in drug release studies as releasing systems. There have been various reports on pH-responsive degradable cross-linked micelles and hydrogels in recent years.[139–142,178,190,192]

pH-Responsive polymeric micelles have also been used as controlled delivery systems for anticancer drugs in tumor-targeted studies. The micelles of poly(2-ethyl-2-oxazoline)-poly(D,L-lactide) have been used in the encapsulation of both the D-alpha-tocopheryl polyethylene glycol 1000 succinate (TPGS1000) and doxorubicin (DOX) drugs. The micelles had a high amount of drug encapsulation capability within the small size. They are reported to be perform well in drug release studies at low pH and in tumor targeting applications.[342]

Folic acid (FA)-functionalized well-defined PMPC-*b*-PDPA diblock copolymer (FA-PMPC-*b*-PDPA) micelles are reported to be useful to encapsulate the anti-cancer drugs tamoxifen and paclitaxel. *In vitro* cell viability studies demonstrated that both tamoxifen- and paclitaxel-loaded FA-MPC-*b*-DPA copolymer micelles are more toxic toward tumor cells in an acid environment. Such micelles dissociate at pH 5.5, thereby triggering drug release in the acid media. In contrast, minimal cytotoxicity is observed at body pH, because the drug-loaded micelles remain intact at this solution pH. Cell viability studies have been carried out on human chronic myelogenous leukemia (K-562) and colon carcinoma cell lines (Caco-2) in order to demonstrate that drug-loaded FA-PMPC-*b*-PDPA micelles exhibited higher cytotoxicities toward cancer cells than unfunctionalized PMPC-*b*-PDPA micelles. Uptake studies confirmed that folate conjugated micelles led to increased drug uptake within cancer cells, demonstrating the expected selectivity toward these tumor cells.[343] In another study, it has been reported that the PMPC-*b*-PDPA diblock copolymer is soluble molecularly in dilute acid solution, since the pH-responsive PDPA block is protonated and hence becomes hydrophilic under these conditions. On adjusting the copolymer solution to around pH 5–7, the PDPA blocks become deprotonated and hence hydrophobic, leading to the formation of micelles with dehydrated PDPA cores and hydrated PMPC coronas. These pH-responsive micelles have been used for encapsulation and controlled release of the dipyridamole drug.[344] Similarly, the controlled release of the same drug can be carried out by using amphiphilic MPEG-*b*-PDMA-*b*-PDEA triblock copolymers as well.[345] Tumoral acidic pH targeting of pH-responsive MPEG-*b*-PAE micelles has been examined for cancer targeting therapy. The anticancer drug, camptothecin (CPT), has been simply encapsulated into the pH-responsive micelles with higher loading efficiency and the CPT encapsulated pH-responsive MPEG-*b*-PAE micelles showed distinguished pH-responsive drug release characteristics under weakly acid conditions.[315]

A series of novel pH-responsive ABA triblock copolymers has been reported as a novel polymeric gelling agent. PDPA has been chosen as the A block while PDMA has been chosen as the B block. While the PDPA-*b*-PDMA-*b*-PDPA triblock copolymer is molecularly soluble in acidic aqueous media due to protonation of all tertiary amine residues, they formed either gels by the chain-end hydrophobic interactions with a relatively high polymer concentration (10 wt%) or near-monodisperse "flower" micelles with a low polymer concentration in neutral and basic aqueous solutions. A model hydrophobic drug release study has been carried out in a sustained manner from the gels at pH 7.4 by varying the polymer concentration, the polymer molecular weight, and the temperature of the medium. Studies indicate that both slow, sustained release and fast, triggered release of a model hydrophobic drug, dipyridamole, can be achieved by tuning the solution pH, polymer concentration, polymer molecular weight and temperature of the gel. In addition to pH, the thermo-responsive nature of the middle PDMA block has an important effect on the dipyridamole releases from the hydrogel.[80] PEG-*b*-PDEA-*b*-PCL amphiphilic triblock copolymers have been determined to be a good source for three layer micelle preparation in aqueous solution. The pH-responsive PDEA middle layer is hydrophobic and collapses on the micellar core at physiological pH (7.4) to prevent the premature burst drug-release. But it becomes positively charged below pH 6.5 and protrudes out at the solid-tumor interstitial pH. Its positive nature causes adsorption of nanoparticle onto the negatively-charged cell membrane and subsequently induces adsorptive endocytosis of the nanoparticle. After its transfer to a lysosome, PDEA layer is further charged, disrupting the lysosomal membrane to release the nanoparticles into the cytosol.[346] The pH-responsive glycol chitosan-*g*-3-diethylaminopropyl (GCS-*g*-DEAP) nanogel having both hydrophobic DEAP residues and hydrophilic GCS residues has been prepared and loaded with DOX. The release of DOX increased at pH 6.8 compared to that at normal body pH 7.4. This study showed that these self-assembled nanogels are appropriate for transport to the target cells and release of anticancer drugs.[347]

Duan *et al.* synthesized CS-*g*-PNIPAm based pH-responsive and biocompatible nanogels *via* free radical copolymerization. These nanogels have been evaluated as drug delivery systems. Nanogels have been loaded with oridonin (ORI) with a self-assembly method. ORI-loaded gels showed pH-responsive release behavior. Release of drugs from ORI-loaded gels is very slow at pH 7.4 but faster at pH 6.0–6.5.[348] Injectable hydrogels that have responses to pH and glucose have also been prepared with oxidized dextran and biocompatible phenylboronate ester. Imine residues behave as the pH-responsive part and phenylboronate ester behaves as the glucose responsive part of the polymer. The anticancer drug (DOX) can also be loaded successfully to the hydrogels.[349]

PHIS and PHEMA based synthetic polymers have been synthesized *via* ring opening polymerization and ATRP. PHEMA-*b*-PHIS polymers are both membranolytic and biocompatible. These pH-responsive polymers have been used as a drug carrier for tumor targets. Its nanosized micelles can be formed by self-assembly with changing solution pH and DOX which is encapsulated in the micellar system. Release of DOX has been studied under different pH conditions. PHEMA-*b*-PHIS micelles release DOX and do not lose their biological activity. At acidic pH, cancer cells have been killed by the DOX drug. The PHEMA-*b*-PHIS systems are suitable carriers of drug molecules for tumor targeting and productively encapsulating the chemo-therapeutic drug DOX.[350]

For a similar purpose, poly(2-(diethylamino)ethyl methacrylate)-*b*-poly(oligo(ethylene glycol) methacrylate)-coated silica

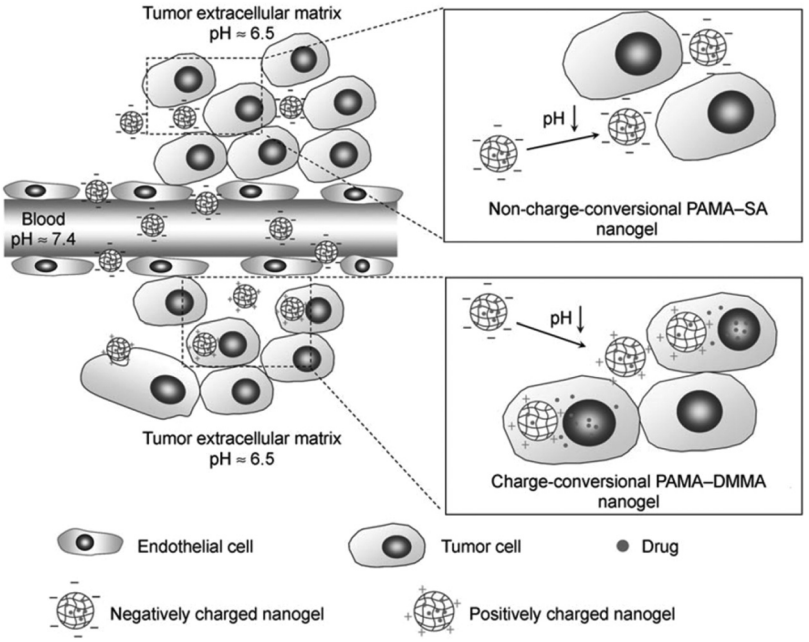

Fig. 20 Schematic illustration of the performance of the drug-loaded pH-responsive charge conversional PAMA-*co*-DMMA nanogel. In the acidic tumor extracellular environment, the PAMA-*co*-DMMA nanogel is activated to be positively charged and is thus readily internalized by tumor cells with subsequent intracellular drug release (Copyright 2010, Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, reprinted from ref. 368).

nanotubes (SNT-PDEA-*b*-POEGMA) have been prepared *via* surface RAFT polymerization. DOX has been loaded into this polymer and controlled release of DOX has been monitored by changing the pH (buffer solution pH = 4.0, 5.0, and 7.4). 13% of drug release has been observed at pH 7.4 whereas 77% of drug release has been observed at pH 4.0 within 24 h. PDEA chains being protonated and stretched in the open state provide easier release of DOX under acidic conditions.[351] Mesoporous silica-coated magnetic graphene oxide is another interesting material as a multifunctional drug nanocarrier. After attaching polyglycerol-*g*-polycaprolactone on the nanocarrier DOX is loaded to the system *via* electrostatic interaction between the DOX molecule and mesopores and adsorbed on graphene. Release of DOX has been examined at pH 7.4 (blood pH) and 5.5 (endosomal pH) at body temperature. The amount of drug release has been determined to be 86% at the endosomal pH for 48 h, but it is 61% at normal blood pH for the same period. This indicates faster release of the DOX at the acidic pH.[352]

In the last decade, another important application of such micellar systems was found *via* the layer-by-layer assembly method, which has also been widely applied in drug and different compound carrier systems using block copolymer micelles.[353] Tertiary amine methacrylate based copolymers have been determined to be good adsorbents on silica and glass surfaces, which results in the formation of nanofilms on the surface.[354–356] This nanofilm formation has opened the door for the preparation of LbL nanofilms on such surfaces as well.[357,358] Multi-layer films are prepared from block copolymer micelles such as PDMA-*b*-PDEA,[354,358–360] PMEMA-*b*-PDPA,[361] PβDMA-*b*-PDPA,[167,362–364] PDMA-*b*-PDEGMA,[365] PAMPS-*b*-PAAL[366] and PDEA-*b*-PNIPAm[367] loaded with various compounds by the layer-by-layer method with the release of these compounds by pH changes.

A novel pH-responsive nanogel with a pH-dependent charge conversion feature has also been developed for use as a possible anticancer drug delivery agent. The nanogel can be transformed from a negatively-charged to a positively-charged form in a slightly acidic tumor extracellular environment, which enhances the cellular uptake of the nanogel and promotes the efficiency of drug release in killing cancer cells. Positively charged DOX hydrochloride has been used to investigate the drug-loading capacity of the PAMA-*co*-DMMA nanogel (see Fig. 20).[368]

pH-Responsive polymer systems can behave as the host for the production of metal nanoparticles. For example, PEG-*co*-PMAAc gels can be used for Ni–Ag bimetallic NP production by the resulting core–shell hybrid system. These pH-responsive hybrid systems have also magnetic susceptibility with fluorescent pH sensing over the physiologically important pH range of 5.0–7.4. The hybrid nanogels could be used in pH-responsive delivery of the anticancer drug 5-fluorouracil (5-FU).[369]

Silica nanoparticles (SiNPs) are the most common materials for surface modification such as pH-responsive guanidine containing polymers (SiNP@PMCGH). Polymer coated silica particles do not form agglomerates after modification. The drug loading behavior of doxorubicin (+) and sulfasalazine (−) has been examined in a wide range of pH and drug loading and release has been determined to be dependent on the type of grafted polymer and its content on silica nanoparticles. The

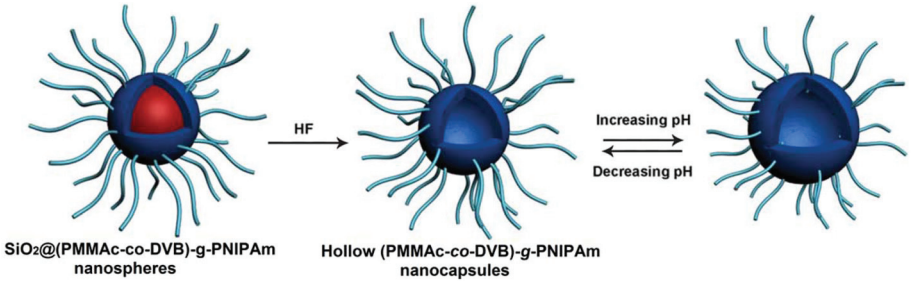

Fig. 21 Preparation of pH-responsive hairy P(MAAc-*co*-DVB)-*g*-PNIPAm nanocapsules (Copyright 2014, Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, modified from ref. 238).

rate and extent of drug release can be controlled by varying the values of pH. DOX solubility is low at low pH values. It can be released faster at pH 5 with the effect of solubility and electrostatic repulsion. Sulfasalazine is not a hydrophilic drug. Therefore, compared with DOX, sulfasalazine has a slower release profile.[370]

The hairy polymeric nanocapsules with a pH-responsive PMAAc-*co*-PDVB inner shell and temperature-responsive PNIPAm brushes can be successfully prepared as seen in Fig. 21. The hairy P(MAAc-*co*-DVB)-*g*-PNIPAm nanocapsules as a drug carrier show pH/temperature dual-responsive drug release behavior. Changing the external pH and temperature could effectively control the shell permeability for loaded drug molecules passing through the PMAAc-*co*-PDVB inner shell and the PNIPAm brush layer.[238]

The layer-by-layer (LbL) self-assembly technique has been successfully used to design superparamagnetic pH-responsive hybrid hollow microspheres [(CS-*g*-PEG/Fe_3O_4-CA)$_4$/CS-*g*-PEG]. DOX has been chosen as a model hydrophobic drug. The controlled release behavior has been investigated in *in vitro* studies by differing pH values. The release of DOX has been determined to be slower at pH 7.4 or pH 6.5 than at pH 5.0.[371] In another study, an acrylamide modified chitin based microsphere has been prepared and loaded with the vancomycin hydrochloride drug. Release behavior of vancomycin has been investigated under different pH conditions. In contrast to the previous work, in this study, release of the drug has been determined to be faster at pH 7.4 than under low pH conditions.[372]

Different sized chitosan coated magnetic nanoparticles have been synthesized and efficiently loaded with DOX for the *in vitro* targeted delivery applications on MCF (Michigan Cancer Foundation) breast cancer cells. The optimal loading efficiency, stability, and release profiles of DOX loaded nanoparticles have been determined. The DOX release profiles showed a pH dependent and slow release pattern. As the pH decreased, the swelling ratio of chitosan increased, therefore the drug release increased. The chitosan coated magnetic nanoparticles released most of the DOX at pH 4.2, while the nanoparticles are quite stable at pH 7.4.[373]

Biodegradable microgel systems based on glycerol-1,3-diglycidyl ether cross-linked TEMPO-oxidized potato starch polymers are capable of absorbing a large amount of lysozyme. The results provide insight into the factors that control the uptake and release of lysozyme by oxidized starch microgels. The protein uptake at saturation (Γ_{sat}) is the highest at high pH and low ionic strength. It is found that Γ_{sat} increases with increasing pH. This is due to the protein binding capacity which is mainly determined by charge compensation: with increasing pH, the positive charge on lysozyme decreases, while the negative charge on the microgel particle increases. Therefore, more protein molecules are required to neutralize for the charge on the gel and the binding capacity increases. The decreased Γ_{sat} with increased ionic strength is mainly due to the shielding effect on the electrostatic interaction between the gel and proteins caused by a high salt concentration. Protein release has been triggered by decreasing the pH and/or increasing the ionic strength, since the binding strength is the lowest at low pH and high ionic strength. The results suggest that oxidized microgels can be potentially applied in the controlled uptake and release of proteins.[374]

DMA and AAc copolymerized using free radical aqueous copolymerization and a series of pH-responsive hydrogels have been obtained. The reported formulations, being devoid of any chemical cross-linkers, remained dimensionally stable in buffer solutions of pH 1.2–7.4 with inter-locked nanogels being identified as the building blocks of the network structures. Swelling behavior and release kinetics of bovine serum albumin have been investigated for PAAc-*co*-PDMA in various buffer solutions that mimic the pH-metric hierarchy in the gastrointestinal tract. The PAAc-*co*-PDMA hydrogel has been prepared with different compositions and investigated for their possibile drug release behaviours.[375]

pH-Responsive polymers are also used in insulin transport systems. It is important that the right amount of insulin is used at the right time. Therefore the transport of insulin is very important. The oxidation of glucose to gluconic acid catalysed by glucose oxidase can lower the pH to nearly 5.8 when there is a rich glucose environment. This enzyme is generally used in glucose sensing and makes possible the use of different types of pH-responsive hydrogels for modulated insulin delivery.[376] Some of the polymers used in insulin release studies are PMAAc-*co*-PDMA microgels,[267] PVPBA-*co*-PDMAEA nanogel,[70] PLGA-*g*-PHEMA,[142] and PAAc-*g*-PEG and PMAAc-*g*-PEG.[286]

The pH-responsive polyacrylamide-modified hydroxypropyl methyl cellulose [*g*-HPMC (M)] graft copolymer has been synthesized *via* a microwave-assisted grafting method. This polymer has been examined as a drug release system for ornidazole. The drug is delivered to the colonic region with a copolymer at pH 7.4.[377] Poly(ethylene glycol)-*b*-poly(ε-caprolactone) (PEG-*b*-PCL) and folate-PDMA-*b*-PCL (Fol-PDMA-*b*-PCL) diblock copolymers form complex micelles in acidic water. When pH has been adjusted to above the pK_a of PDMA (pH 7.4), core–shell-corona (hydrophobic PCL-collapsed PDMA-soluble PEG) micelles have been obtained. After loading DOX into the micelle-core (PCL), the DOX release profile indicated that complex micelles with a core–shell structure showed a faster drug release rate at pH 5.5.[378] pH-Responsive NaAlg-*graft*-poly(*N*-vinyl-2-pyrrolidone) copolymer beads are another polymer which has been prepared with microwave-assisted synthesis in order to examine the release profile of the ibuprofen (IB) model drug. The release of IB has been determined to be much slower at pH 1.2 than pH 7.4 release.[379]

Gene delivery studies. Cationic polymers can efficiently condense negatively charged biomolecules, which are plasmid DNA (pDNA) and small interfering RNA (siRNA), *via* electrostatic interactions.[4] The cationic tertiary amine methacrylate-based polymers electrostatically interact with DNA. They are slightly cytotoxic and may be used to traffic DNA to cells. Thus, they have potential for use as a gene transfer agent.

PDMA with a high molecular weight has been very productive for condensed DNA.[4] When PDMA is copolymerized with any monomer, its cytotoxicity and transfection efficiency could be changed.[380–382] Various hyper-branched poly(ester amine) polymers have been synthesized and used as gene carriers. Such hyper-branched poly(ester amine)s, due to their highest transfection efficiency and low cytotoxicity, have been determined to be safe and productive gene carriers. In another work, PNIPAm-*co*-PDMA-*co*-PBMA copolymers have been synthesized and used as a gene carrier. Gene-transfection efficiency has been studied at different temperatures. When the temperature is decreased, the transfection efficiency is increased. This case demonstrated the effect of temperature changes during formation and dissociation control of the complexes.[383,384] Similarly, PDEA containing polymers such as PEO-*b*-PDEA and plasmid DNA binding interactions have been determined to be due to enthalpy change. A pH change causes a change in the DNA compaction. In this case, the binding force of DNA and polymers depends on the stoichiometric balance between the molar ratio of DNA nucleoids and amine groups on PDEA.

Polycations consisting of poly(L-lysine) (PLL) side chains and a PDEA backbone have been synthesized for use as a new pH-responsive DNA carrier. Polycations attached with several ligands, such as insulin, transferrin and antibody molecules, have been examined for the efficient internalization of DNA–ligand complexes. The copolymer has shown proton dissociation and dual ionic character. The copolymer has shown no significant turbidity even at pH 10, whereas the PDEA homopolymer precipitated at pH greater than 7.5 owing to the deprotonation of amino groups. The discontinuous turbidity change of DNA-PDEA-*g*-PLL solution at pH 7.5 suggested that the solubility of the complex varied with pH.[385]

Membrane studies. The rapidly increasing interest in functional materials with reversibly switchable physicochemical properties has led to significant work on the development of stimuli-responsive membranes, for which mass transfer and interfacial properties can be adjusted using external stimuli: temperature, pH, *etc*.[386,387] There have been many studies on the synthesis of pH-responsive membranes in recent years. These membranes in various structures and contents have been prepared from basic polymers such as PDMA, P4VP, *etc*. and acidic polymers such as PMAAc, PEGMP, PAMPS, PAAc, *etc*.[386–389]

Functionalized membranes with three different acidic polymers, PAAc, PEGMP, and PAMPS, have been prepared by UV initiated grafting of functional monomers in the pores of the poly(propylene) host membrane. The adsorptions of different ions in the functionalized membranes have been studied.[13] The design of hybrid interfaces based on the use of mesoporous thin films incorporating polymer brushes as versatile functional units offers major opportunities for controlling molecular transport through interfaces. They conducted charge-selective ionic transport *via* pH changes. A PEGMP brush was designed *via* the "growth from" approach after initiator-functionalization of the mesoporous silica surface.[247] Increasing pH from 4 to 8 led to a significant increase in (anion) permselectivity and (cation) preconcentration, thus reflecting the ability of the PEGMP brush-modified mesoporous silica thin film to act as a selective "electrostatic nanovalve" precluding and boosting the anionic and cationic transport, respectively (Fig. 22). On the other hand, the complexation/chelation of phosphate groups with Ca^{2+} ions also allowed the generation of gate-like hybrid ensembles.[247]

Chromatography studies. One of the applications of pH-responsive polymers is purification and separation technology. Different molecules, such as peptides, enzymes, proteins, *etc*., are currently separated by chromatography systems. pH-Responsive polymers contain acidic or basic groups such as carboxylic acids and amines attached to a hydrophobic backbone that either accepts or donates protons in response to change in the environmental pH. For instance, pH-responsive linear polymers allow easy protein separation through electrostatic interactions. The pH-responsive polymers can interact very well with oppositely charged proteins by complexation, which results in precipitation. By changing the pH of the medium, the precipitated proteins can be recovered. pH-Responsive chromatography materials have also been prepared using basic polymers such as PDMA, PVI, PDMAPAm, P4VP, PANMP, *etc*. and acidic polymers such as PMAAc, PAMPS, PAAc, PLL, *etc*.[390]

Surface studies. pH-Responsive brush polymer surfaces are used in many applications such as non-biofouling,[239,391] membranes,[240] cell adhesive surfaces,[239] and surface wettability.[392] Polymeric micelles such as polybetaine-based ones can be used to prepare a monolayer micellar film (BCMs) for investigating bacterial anti-adhesive properties. Monolayer films can be self-assembled at pH 7.5 when a polybetaine-based diblock copolymer is in the micellar form. These zwitterionic micellar

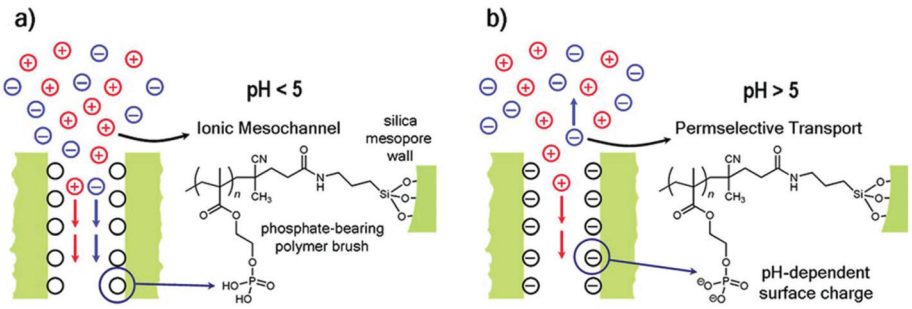

Fig. 22 Schematic depiction of the ionic transport processes taking place in the hybrid polymer–inorganic interfacial assembly at different pH values: (a) pH < 5, ionic mesochannel (no exclusion of ionic species) and (b) pH > 5, permselective transport of cations (Copyright 2012, The American Chemical Society, reprinted from ref. 247).

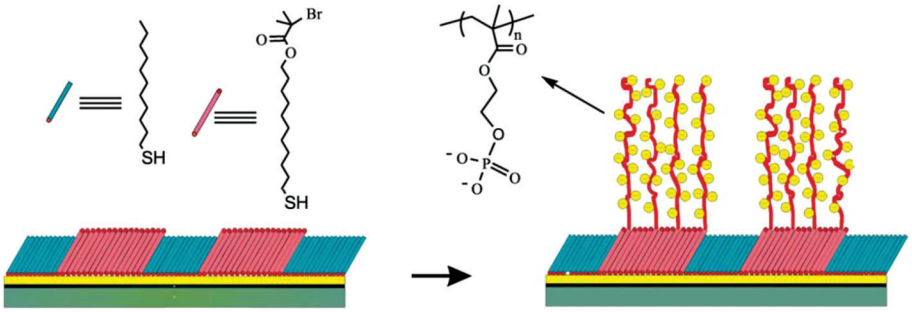

Fig. 23 Procedure for patterned polymer brush formation on gold substrates. Polymer brush growth from initiator modified areas (Copyright 2005, The Royal Society of Chemistry, modified from ref. 392).

coatings showed anti-adhesive properties against *S. aureus* bacteria. In addition to bacterial anti-adhesive properties, such coatings are expected to release antimicrobial agents when there is an infection induced local pH change.[363]

As an example, the pH sensitivity of PEGMP brushes bearing orthophosphoric acid with two ionization states for switching surface wettability (pK_{a1} in the range of pH 1–2 and pK_{a2} in the range of pH 6–7) has been well documented (Fig. 23). The phosphate groups are completely protonated (diacid) at pH 1, partly protonated when the pH is close to 7 and are in completely dibasic form when pH >7. The charges on the brush, the concentration of free counter ions and the degree of swelling can therefore all be tuned *via* the adjustment of the pH.[392]

A zwitterionic polymeric surface which has a tunable mixed-charge copolymer containing both positive quaternary amines and negative carboxylic acid residues has been determined to be useful for bacteria adhesive/resistance transition. The non-fouling properties of such a polymeric surface depend on the pH of the medium (Fig. 24). The surface has charge neutrality under neutral and basic conditions. It is positively charged under acidic conditions due to the protonation of the carboxylic acid and quaternary amine groups. This surface charge transition with respect to pH allows the surface to be switched from bacteria-adhesive to bacteria-resistant.[239]

Sensor studies. Most commonly, the performances of biosensors detecting the changes caused by pH changes are reversibly affected by the change of environmental pH.

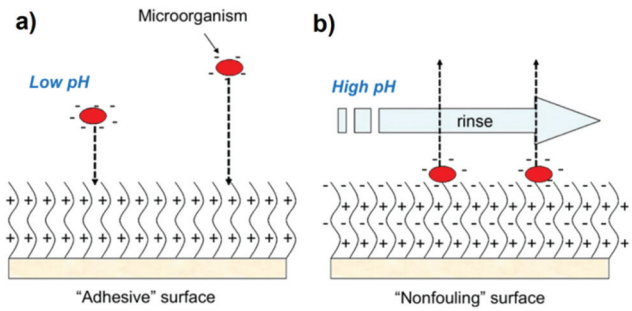

Fig. 24 A surface switching from fouling to non-fouling in response to pH change: (a) in low pH solutions where the surface bears a moderately positive charge, favoring the attachment of bacteria cells, and (b) in neutral or higher pH solutions where the surface becomes non-fouling, releasing the bacteria cells (Copyright 2010, Elsevier Ltd, reprinted from ref. 239).

Additionally, many biomedical applications have been designed in combination with pH-responsive polymers[124,393] or other biocompatible nanoparticles.[394] The pH-responsive polymer is a copolymer of isooctyl acrylate and acrylic acid. It shrinks or swells in response to decreasing or increasing pH values due to the dissociation of the branch carboxylic group at basic pH values. A wireless magnetoelastic glucose biosensor is fabricated by co-immobilizing glucose oxidase (GOx) and catalase onto a pH-responsive polymer coated magneto-

elastic sensor with chitosan as a supporting substrate. The glucose oxidase-catalyzed hydrolyzation of glucose produces gluconic acid, resulting in shrinking and a corresponding mass decrease in the pH-responsive polymer. This biosensor can be used to determine the amount of glucose in urine samples.[395] In another study, the sequential electrostatic adsorption of poly(*n*-butylmethacrylate)-*block*-poly[(2-dimethylamino)ethyl methacrylate)] (PnBMA-*b*-PDMA) diblock copolymer micelles and an enzyme, choline oxidase, leads to well-defined, highly active and stable biosensor coatings. Thereby, the pH during adsorption of PnBMA-*b*-PDMA and the charge density within the PDMA segment play a crucial role and the best results can be obtained if adsorption is carried out at pH 9–10. Under these conditions, the affinity of the material toward the hydrophobic surface is maximized. The subsequent adsorption of choline oxidase and, in turn, the activity of the generated biosensors mainly depend on the amount of pre-adsorbed PnBMA-*b*-PDMA though its charge at the stage of the enzyme deposition can also be important.[396] Both thermo- and pH-responsive multi-functional polymers can also be prepared *via* copolymerization of NIPAm with a fluorine based monomer. Under acidic conditions, the amino groups on the fluorine are protonated. Thus, no aggregation of the fluorine moiety has been observed and the fluorescence properties of the polymer have not been affected by the lower critical solution temperature transition. But aggregation is observed under basic pH conditions. When the amino groups of PDMA blocks are quaternized, this derivative cationic polymer can be used as a DNA biosensor due to quenching of the fluorescence intensity with the interaction of DNA and quaternized PDMA blocks as well.[397]

Closing remarks

The fascinating properties of pH-responsive polymers are likely to continue to generate more activities in scientific pathways. They are good candidates for further material and nanostructure developments. They can be used as stabilizers in heterogeneous polymerizations, hosts for nanometal dispersion preparation, and precursors of cross-linked micelles, hallow spheres, controlled drug-releasing systems, *etc*. In this review, we have highlighted some recently reported examples of pH-responsive monomers, polymers and their derivative nano- and micro-structures including copolymers, nanogels, microgels, hydrogels, cross-linked structures, LbL nanofilms, *etc*. We have also focused on their classifications, synthetic pathways for their synthesis, self-assembly behaviors depending on solution pH, nano-aggregates and further chemistries for their derivative nanostructures or materials, application possibilities in various fields, *etc*. Given the number of synthetic procedures and the variety of biocompatible monomers now available, it may be anticipated that biodegradable pH-responsive polymers will be the most prefered polymers in biotechnological applications owing to their response to biological conditions and favorable interactions with related biological environments.

Abbreviations

AAc	Acrylic acid
ACDAAB	*N*,*N*-(ω-Aminocaproyl)-4,4′-diaminoazobenzene
AMPD	4-(Aminomethyl)piperidine
AMPD	4-(Aminomethyl)piperidine
ATRP	Atom transfer radical polymerization
BAC	*N*,*N*-Cystaminebis(acrylamide)
BDBA	1,3-Benzenediboronic acid
BDDA	1,4-Butanediol diacrylate
BIEE	1,2-Bis-(2-iodoethoxy) ethane
Boc-VaI-HEA	*tert*-Butyl carbamate-L-valine-acryloyloxyethyl ester
BSPA	3-Benzylsulfanylthiocarbonyl sulfanylpropionic acid
CCL	Core cross-linked
CCS	Core cross-linked star
CELG	γ-2-Chloroethyl-L-glutamate
CLMs	Cross-linked micelles
CMA	4-Methyl-(7-(methacryloyl) oxyethyloxy)coumarin
CNPBA	3-Carboxy-5-nitrophenylboronic acid
CRP	Controlled radical polymerization
Dex	Dextran
DHBCs	Double hydrophilic block copolymers
DTbDEA	2,2′-Dithiobis(*N*,*N*-dimethylethylamine)
DTDMA	2,2′-Dithiodiethoxyl dimethacrylate
DVB	Divinylbenzene
DVS	Divinyl sulfone
EGDMA	Ethylene glycol dimethacrylate
GA	Glutaraldehyde
GTP	Group transfer polymerization
H40	Hyper-branched polyester
HA	Hyaluronic acid
HBPE	Hyper-branched polyethylene
HBPO	Poly[3-ethyl-3-(hydroxymethyl)oxetane]
Hyd	Hydrazine functionalized
ILCL	Intermediary layer cross-linked
ITO	Indium tin oxide
MAAc	Methacrylic acid
MAEBA	*p*-(Methacryloxyethoxy)benzaldehyde
MBA	*N*,*N*′-Methylene-bis-acrylamide
MePEGA	Poly(methoxypolyethylene glycol acrylamide)
MPEG	Methoxypolyethylene glycol
NMP	Nitroxide-mediated radical polymerization
P2VP	Poly(2-vinylpyridine)
P4VP	Poly(4-vinylpyridine)
PAAc	Poly(acrylic acid)
PAaH	Sodium 6-acrylamidohexanoate
PAAPBA	Poly(3-acrylamidophenylboronic acid)
PAEAm	Poly(acrylamidoethylamine)
PAMA	Alkyne-poly(2-aminoethyl methacrylate)
PAM	Poly(acryloylmorpholine)
PAMAM	Poly(amidoamine)
PAMPS	Poly(2-acrylamido-2-methylpropane sulfonic acid)
PANMP	Poly(*N*-acryloyl-*N*′-methylpiperazine)
PAPMAm	Poly[*N*-(3-aminopropyl)methacrylamide]
PASA	Poly(aspartic acid)
PBAC	*N*,*N*′-Bis(acryloyl)cystamine)

PBIEM	Poly[2-(2-bromoisobutyryloxy)ethyl methacrylate]
PBuAm	Poly(*N*-*tert*-butylacrylamide)
PCAA	2-Carboxy ethyl acrylate
PCEMA	Poly(2-cinnamoyloxyethyl methacrylate)
PCGMA	Poly(3-cinnamoyl glycerol monomethacrylate)
PCL	Poly(ε-caprolactone)
PDEA	Poly[(2-diethylamino)ethyl methacrylate]
PDEAm	Poly[(2-diethylamino)ethyl acrylamide]
DEGMMA	Methoxydi(ethylene glycol) methacrylate
PDEVBP	Poly(diethyl-4-vinyl-benzyl phosphonate)
PDMA	Poly[(2-dimethylaminoethyl) methacrylate]
PDMAEA	Poly[(2-dimethylaminoethyl) ethacrylate]
PDMAPAm	Poly[(3-dimethylamino)propyl acrylamide]
PDMAPMAm	Poly[*N*-(3-(dimethylamino)-propyl)methacrylamide]
PDPA	Poly(2-diisoprophylamino)ethyl methacrylate
PEAAc	Poly(ethyl acrylic acid)
PEG	Polyethylene glycol
PEGAP	Poly(ethylene glycol acrylate phosphate)
PEG-FA	Poly(ethylene glycol)-folate
PEGMA	Poly(ethylene glycol) methacrylate
PEGMP	Poly(ethylene glycol methacrylate phosphate)
PEI	Poly(ethylene imine)
PEO	Polyethylene oxide
PEPyM	Poly(*N*-ethylpyrrolidine methacrylate)
PG2MA	Poly(glycerol monomethacrylate)
PGMA	Poly(glycidyl methacrylate)
PHEA	Poly(2-hydroxyethylacrylate)
PHEMA	Poly(2-hydroxyethyl methacrylate)
PHIS	Poly(histidine)
PHPMA	Poly[*N*-(2-hydroxypropyl)methacrylate]
PHPMAm	Poly[*N*-(2-hydroxypropyl)methacrylamide]
PImHeMA	Poly[6-(1*H*-imidazol-1-yl)hexyl-methacrylate]
PIMMA	Poly[2-(isobutyramido)-3-methylbutyl methacrylate]
PKSPMA	Poly(3-sulfopropylmethacrylate potassium)
PLA	Polylactide
PLGA	Poly(L-glutamic acid)
PLL	Poly(L-lysine)
PMAAc	Poly(methacrylic acid)
PMAGGONp	Poly(*N*-methacryloylglycylglycine *p*-nitrophenyl ester)
PMAGP	Poly(6-*O*-methacryloyl-D-galactopyranose)
PMEA	Poly(2-methacryloylethylacrylate)
PMEMA	Poly(2-*N*-morpholinoethyl)methacrylate
$PMEO_2MA$	Poly[2-(2-methoxyethoxy)ethyl methacrylate]
PMMA	Poly(methyl methacrylate)
PMPC	Poly(2-methacryloyloxyethyl phosphorylcholine)
PMPMA	Poly(γ-methacryloxypropyltrimethoxysilane)
PMPS	Poly[3-(trimethoxysilyl)propyl methacrylate]
PNaAMPS	Poly[sodium 2-(acrylamido)-2-methylpropane-sulfonate]
PNaSS	Poly(sodium 4-styrenesulfonate)
PNBC	Poly(*S*-(*o*-nitrobenzyl)-L-cysteine)
PNIPAm	Poly(*N*-isopropylacrylamide)
POEGMA	Poly[oligo(ethylene glycol) monomethyl ether methacrylate]
PPAAc	Poly(propylacrylic acid)
PPDPMA	Poly[*N*-2(3-pentadecylphenoxy)ethyl methacrylamide]
PPEGMA	Poly[(poly(ethylene glycol) methyl ether methacrylate)
PPI	Poly(propylene imine)
PPO	Poly(propylene oxide)
PS	Polystrene
PSP	Poly(spiropyan-functionalized)
PSPEA	1′-(2-Acryloxyethyl)-3′,3′-dimethyl-6-nitrospiro-(2*H*-1-benzopyran-2,2′-indoline)
PSPM	Poly(3-sulfopropyl methacrylate)
PSPMA	Poly[1-3-[(2-methyl-1-oxo-2-propen-1-yl)oxypropyl] ester-*b*-poly(methoxydi(ethylene glycol) methacrylate)]
PSSA	Poly(4-styrenesulfonic acid)
PSVBP	Poly[4-(2-sulfoethyl)-1-(4-vinyl-benzyl)pyridinium betain]
PtBA	Poly(*tert*-butyl acrylate)
PtBAEMA	Poly[(2-(*tert*-butylamino)ethyl methacrylate)]
PTEGMA	Poly[2-(2-(2-methoxyethoxy)ethoxy)ethyl methacrylate]
PTFEMA	Poly(2,2,2-trifluoroethyl methacrylate)
PTMA	Poly[2-(acryloyloxy)ethyl] trimethyl ammonium chloride
PTMSPMA	Poly[3-(trimethoxysilyl)propyl methacrylate]
PTPHMA	Poly[4′-(6-methacryloxyhexyloxy)-2,2′:6′,2″-terpyridine]
PVBA	Poly(4-vinylbenzoic acid)
PVBK	Poly[9-(4-vinylbenzyl)-9*H*-carbazole)]
PVDT	Poly(2-vinyl-4,6-diamino-1,3,5-triazine)
PVAm	Poly(*N*-vinyl amine)
PVI	Poly(*N*-vinylimidazole)
PVP	Polyvinylpyrrolidone
PVPBA	Poly(vinylphenyl boronic acid)
PVSA	Poly(vinylsulfonic acid)
QDMA	Quaternized DMA
RAFT	Reversible addition–fragmentation chain transfer
ROP	Ring opening polymerization
RPHA	Reducible poly(β-hydroxy amine)s
SCL	Shell cross-linked
SI-ATRP	Surface initiated-atom transfer radical polymerization
SI-CRP	Surface initiated-controlled/living radical polymerization
SPCL	Star poly(ε-caprolactone)
TDA	Terephthaldicarboxaldehyde
TEMPO	2,2,6,6-Tetramethyl-1-piperidinyloxy
βDMA	Sulfobetaine DMA

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