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Acid-Labile Thermoresponsive Copolymers That Combine Fast pH-Triggered Hydrolysis and High Stability under Neutral Conditions

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Abstract: *Biodegradable polymeric materials are intensively used in biomedical applications. Of particular interest for drug-delivery applications are polymers that are stable at pH 7.4, that is, in the blood stream, but rapidly hydrolyze under acidic conditions, such as those encountered in the endo/lysosome or the tumor microenvironment. However, an increase in the acidic-degradation rate of acid-labile groups goes hand in hand with higher instability of the polymer at pH 7.4 or during storage, thus posing an intrinsic limitation on fast degradation under acidic conditions. Herein, we report that a combination of acid-labile dimethyldioxolane side chains and hydroxyethyl side chains leads to acid-degradable thermoresponsive polymers that are quickly hydrolyzed under slightly acidic conditions but stable at pH 7.4 or during storage. We ascribe these properties to high hydration of the hydroxy-containing collapsed polymer globules in conjunction with autocatalytic acceleration of the hydrolysis reactions by the hydroxy groups.*

Polymers that degrade under specific conditions are attractive materials for biomedical applications.[1] For example, drug-loaded polymeric micelles that could release their cargo in a mildly acidic environment are interesting because of the lower pH values in, for example, tumor tissues or the endosomes/lysosomes in cells, where nanoparticles typically end up upon endocytosis.[2] For drug-delivery applications, acid-degradable polymers need to be stable at pH 7.4 in the blood stream. To enable subsequent degradation in acid medium, labile functional groups, such as ester[3] or cyclic-acetal/ketal[4] groups, are usually incorporated in the polymer backbone or side chains. However, owing to the relatively high stability of these groups, long degradation times are typically required to render these hydrophobic degradable polymers water-soluble. Less stable acid-labile functional groups, such as linear-acetal/ketal,[4b,5] orthoester,[6] or hydrazone groups,[7] have been reported to lead to faster acidic degradation, but notable hydrolysis of those polymers at pH 7.4 is usually also observed. Premature release of the cargo before it reaches the target tissue can potentially cause side effects resulting from systemic toxicity. Moreover, the instability of these more labile polymers make them very difficult to handle, since the polymer can degrade in aqueous solution or during storage under slight moist conditions.[8] Therefore, polymers with well-balanced stability, that is, fast hydrolysis in an acidic environment and high stability at pH 7.4 and during storage are highly desired for intracellular drug-delivery applications. However, as stability and degradability go hand in hand, the synthesis of such ideal polymers that are stable during storage or at pH 7.4 and quickly degrade under mildly acidic conditions appears to be impossible by simple tuning of the stability of the degradable moiety.

Stimuli-responsive polymers, also called “smart” polymers, are increasingly used as drug or vaccine carriers.[9] In particular, polymers exhibiting lower critical solution temperature (LCST) behavior with a hydrophilic-to-hydrophobic phase transition between room and body temperature are highly attractive candidates for the development of “smart” biomaterials. Poly(*N*-isopropylacrylamide) (PNIPAM),[10] poly(oligo(ethylene glycol)(meth)acrylate)s,[11] and poly(2-oxazoline)s[12] are prime candidates for such applications owing to their good biocompatibility.

Recently, we introduced a novel type of pH-labile thermoresponsive polymers based on an acid-labile acetal monomer, (2,2-dimethyl-1,3-dioxolan-4-yl)methyl acrylate (DMDMA).[4d,13] The cloud-point temperature (T_{CP}) of the DMDMA-based copolymers increased upon hydrolysis of the cyclic-ketal side-chain groups under acidic conditions, which was used to trigger the release of Nile Red or paclitaxel and to make transiently soluble polymer–protein conjugates. The main advantage of combining temperature responsiveness with degradability at certain pH values is that it allows homogeneous aqueous formulation or protein conjugation of the copolymers at low temperatures, whereas at 37 °C the polymer becomes hydrophobic and can induce encapsulation of the payload. For copolymers of DMDMA with methoxytri(ethylene glycol) acrylate (mTEGA; Scheme 1), the kinetics of hydrolysis and, thus, solubilization of the copolymers at 37 °C could be finely tuned by the composition of the copolymers; that is, copolymers with higher T_{CP} values close to 37 °C hydrolyzed faster, but their hydrolysis was still very slow at pH 5. The fast hydrolysis observed for polymers with a higher T_{CP} value was ascribed to the less efficient dehydration of these polymeric globules at 37 °C, so that the collapsed polymer globules still contain a significant amount of water molecules required for hydrolysis.

Inspired by these results, we hypothesized that faster hydrolysis might be promoted by incorporating hydroxy

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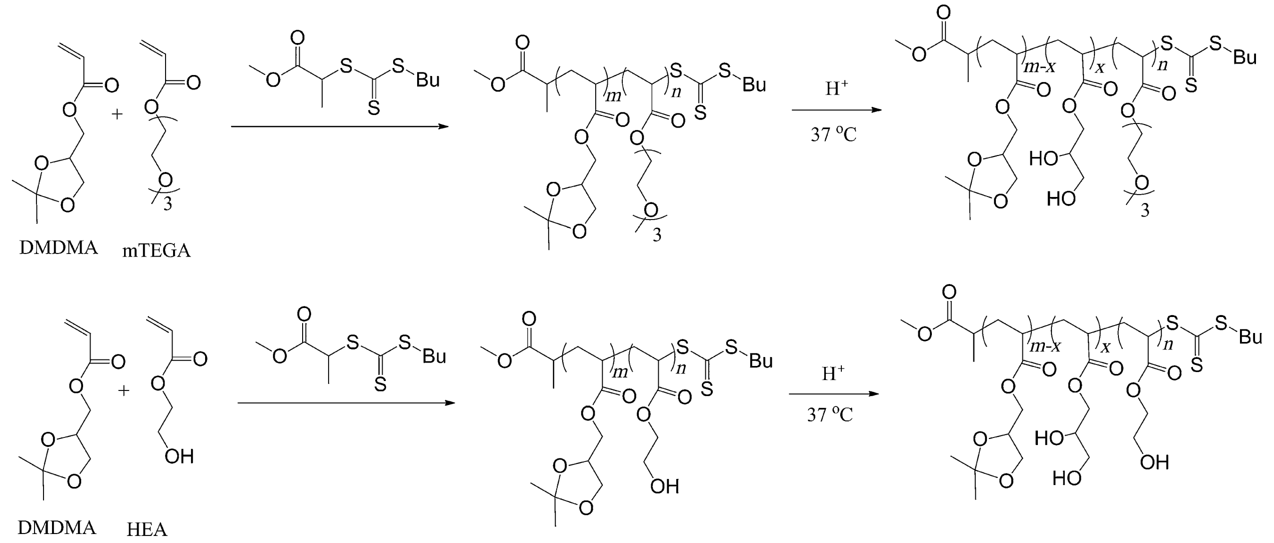

Scheme 1. Synthesis and (partial) hydrolysis of the mTEGA–DMDMA (top) and HEA–DMDMA copolymers (bottom).

Table 1: Polymer composition and properties of the synthesized copolymers.

Polymer	Theoretical DMDMA content[a] [mol%]	DP[b]		DMDMA content[c] [mol%]	DMDMA content[d] [mol%]/[wt%]	M_n[e] [kDa]	Đ[e]	T_{CP} [°C]
		HEA	DMDMA					
HP0	0	84	0	0	0/0	27.3	1.13	N/A[f]
HP5	5	81	2	2.4	4.3/6.7	27.0	1.11	N/A
HP12	12	75	8	9.6	10.0/15.1	24.4	1.20	70.0[g]
HP15	15	72	7	8.8	11.4/17.1	24.1	1.13	43.5
HP20	20	69	14	16.9[h]	15.5/22.7	26.2	1.11	30.1
HP22	22	71	12	14.5[h]	16.4/23.9	27.1	1.24	24.2
HP25	25	61	23	27.0	21.1/30.0	24.0	1.20	16.6
HP30	30	58	25	30.1	26.5/36.6	26.2	1.29	9.0
HP35	35	55	29	34.5	35.5/46.9	24.9	1.27	insoluble

[a] Proportion of DMDMA expected in the copolymer according to the feed ratio of the two monomers. [b] The degree of polymerization was calculated by GC with DMA as an internal standard. [c] Proportion of DMDMA in the copolymer according to the degree of polymerization of the two monomers. [d] Proportion of DMDMA in the copolymer as determined by ^{1}H NMR spectroscopy. [e] The number-average molecular weight and dispersity were determined by size-exclusion chromatography in DMA. [f] No phase transition was detected when the polymer was heated to 100 °C. [g] The T_{CP} value was determined by the use of a fast heating ramp; slow heating (1 °C min^{-1}) led to no phase transition. [h] The reversal observed in the DMDMA content of HP20 and HP22 by GC could be considered as the error in the GC measurement owing to the poor solubility of DMDMA in methanol. DMA = dimethylacetamide.

groups into the acid-degradable copolymers, since hydroxy groups can increase hydration in the collapsed globules by hydrogen bonding with water molecules, as we recently found for polymeric temperature sensors.[14] Moreover, it is generally known that acidic hydrolysis is accelerated when the water concentration is increased.[15] Therefore, in this study, DMDMA was copolymerized with 2-hydroxethylacrylate (HEA), whereby it was expected that only a small amount of the very hydrophilic HEA would be required to introduce LCST behavior in the HEA–DMDMA copolymers, although homopolymers of both HEA and DMDMA are not thermoresponsive. The copolymers were prepared by reversible addition–fragmentation chain transfer (RAFT) copolymerization[16] to ensure the formation of defined copolymers and thus facilitate the correlation of their thermoresponsive behavior with the molecular structure (Scheme 1). First, a kinetic study with HEA (25 mol%) and DMDMA (75 mol%) revealed controlled copolymerization with near-ideal random comonomer distribution (see Figure S1 in the Supporting Information). Subsequently, the synthesis of a series of copolymers with varying ratios of HEA and DMDMA yielded well-defined copolymers with a wide range of monomer compositions (Table 1).

The thermoresponsive behavior of these HEA–DMDMA copolymers was evaluated in MilliQ water by turbidimetry at 5 mg mL^{-1}. The resulting T_{CP} values are plotted versus DMDMA content in Figure 1; the T_{CP} values of our previously reported mTEGA–DMDMA copolymers are also shown for comparison.[4d] Surprisingly, there is only a rather narrow composition window that yields a thermoresponsive polymer, namely, from 10 to approximately 30 mol% DMDMA. The incorporation of less DMDMA yielded fully soluble polymers, as expected, since PHEA is water-soluble,[17] whereas the use of more DMDMA rendered the polymers insoluble. Moreover, within this specific range, the T_{CP} value correlates exponentially, instead of linearly as in the case of mTEGA–DMDMA copolymers, with DMDMA content. Comparison of P(HEA–DMDMA) with P(mTEGA–DMDMA) generally revealed lower solubility, that is, a lower T_{CP} value, for P(HEA–DMDMA) within its

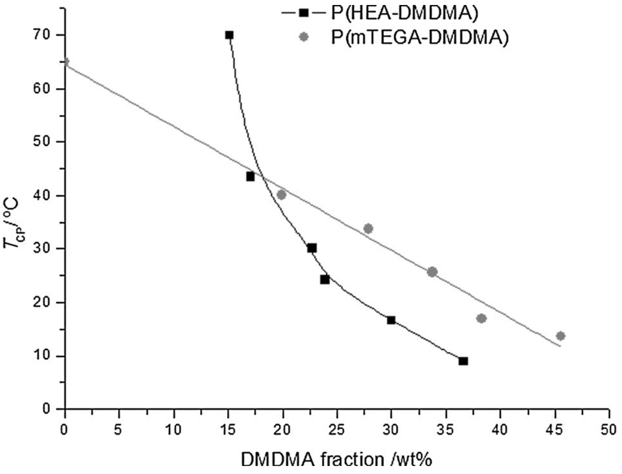

Figure 1. Evaluation of the cloud-point temperature (T_{CP}) as a function of the weight fraction of incorporated DMDMA content for P(HEA–DMDMA) and P(mTEGA–DMDMA)[4d] in MilliQ water (5 mg mL^{-1}). Lines are a guide for the eye, and all polymers have the same end groups and a similar degree of polymerization.

thermoresponsive regime. This observation is rather unexpected, as PHEA is more hydrophilic than PmTEGA, thus indicating that the thermoresponsive behavior of these copolymers is not solely governed by their hydrophilicity–hydrophobicity balance.

When comparing the schematic polymer structures of P(HEA–DMDMA) and P(mTEGA–DMDMA), it becomes evident that the observed differences in thermoresponsive behavior may result from the copolymer configuration that originates from its structure (Figure 2). P(HEA–DMDMA) is a near-ideal random copolymer in which the HEA side chain is smaller than the DMDMA side chain. The P(mTEGA–DMDMA) copolymer is also a near-ideal random copolymer, but it can be considered to be a graft copolymer with larger methoxytri(ethylene glycol) side chains that can cover and shield the hydrophobic DMDMA side chains from the aqueous solution. Therefore, it is proposed that the exposure of the hydrophobic DMDMA units to the aqueous medium is considerably higher in P(HEA–DMDMA) than in P(mTEGA–DMDMA), thus leading to a stronger hydrophobic contribution of DMDMA to the overall solubility behavior of P(HEA–DMDMA). This effect is in agreement with our recent observation that the introduction of more hydrophobic side chains into poly(2-oxazoline)s causes a larger decrease in the T_{CP} value than the introduction of a more hydrophobic polymer backbone.[18]

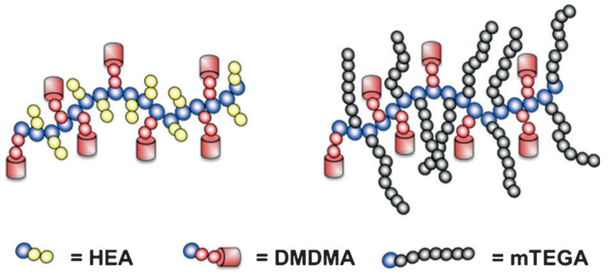

Figure 2. Schematic representation of copolymers P(HEA–DMDMA) (left) and P(mTEGA–DMDMA) (right).

Intrigued by this unusual solubility behavior of the HEA–DMDMA copolymers, we continued to investigate the influence of the unique configuration on the pH-dependent degradability of the copolymers. The hydrolysis of P(HEA–DMDMA) with $T_{CP} = 24.2$ °C in MilliQ (HP22; Table 1) at pH 5, 6, and 7.4 is discussed as a representative example for the HEA–DMDMA copolymer series (see Figures S2 and S3 for details of the hydrolysis of HP20 and HP25). The T_{CP} value of the HP22 copolymer was monitored over time as a measure of the extent of hydrolysis: the T_{CP} value increases as the dioxolane group is hydrolyzed into two hydrophilic alcohol groups with the release of acetone, thus leading to higher solubility.[4d,5b] For future use of these copolymers for pH-induced drug delivery, it will be important to know when the T_{CP} value increases beyond body temperature (37 °C), thus leading to dissolution of the copolymer. No major changes in T_{CP} occurred upon the incubation of HP22 at the physiological pH value of 7.4 for as long as 1000 h (42 days; Figure 3 a), thus indicating high stability of the copolymer at this pH value, which resembles the pH value in the blood stream. The slightly lower T_{CP} values of HP22 in pH buffers, as compared to MilliQ water, is ascribed to the influence of the pH value and ionic strength of the solution, as has also been observed for mTEGA–DMDMA copolymers and other thermoresponsive polymers.[4d,19] The high stability was expected considering the relatively high stability of the cyclic-acetal group and indicates that the introduction of the hydroxy groups does not compromise this stability.[4b,d] However, incubation of HP22 at the endo/lysosomal pH value of 5 resulted in a relatively fast increase in the T_{CP} value and solubility at 37 °C after approximately 200 h. Even incubation of the HP22 copolymer in a buffer solution at pH 6 led to a steady increase in T_{CP}, thus rendering the polymer soluble at 37 °C after about 1000 h. It was confirmed by ^{1}H NMR spectroscopy that the increase in T_{CP} directly correlates to the conversion of the acetal moieties (see Figure 3 a).

A direct comparison of the acid-catalyzed hydrolysis of HEA–DMDMA (HP22) and mTEGA–DMDMA (P42)[4d] copolymers with similar T_{CP} values of approximately 17 °C in pH 5 buffer shows a strikingly faster hydrolysis for P(HEA–DMDMA), although both copolymers contain exactly the same degradable acetal moieties (Figure 3 b). After 800 h, there was nearly no hydrolysis of P(mTEGA–DMDMA) even at pH 5, whereas P(HEA–DMDMA) was steadily hydrolyzed at both pH 5 and pH 6, while being stable at pH 7.4. These results indicate that the presence of hydroxy groups in the HEA–DMDMA copolymer allows faster hydrolysis under acidic conditions, whereas the stability at pH 7.4 is unaffected. A more detailed look at the data also revealed that the same degree of hydrolysis conversion led to a larger increase in T_{CP} for P(HEA–DMDMA) as compared to P(mTEGA–DMDMA).[20] This observation can be ascribed to the fact that the hydrolysis of DMDMA in P(HEA–DMDMA) not only results in the deprotection of two hydroxy groups, but also unveils the hidden alcohol groups of the HEA segments. A direct comparison of the hydrolysis in time of P(HEA–DMDMA) (HP22 with $T_{CP} = 16.2$ °C in pH 5 buffer) in pH 5 buffer with P(mTEGA–DMDMA) (P50 with $T_{CP} = 12.2$ °C in pH 5 buffer) revealed much faster

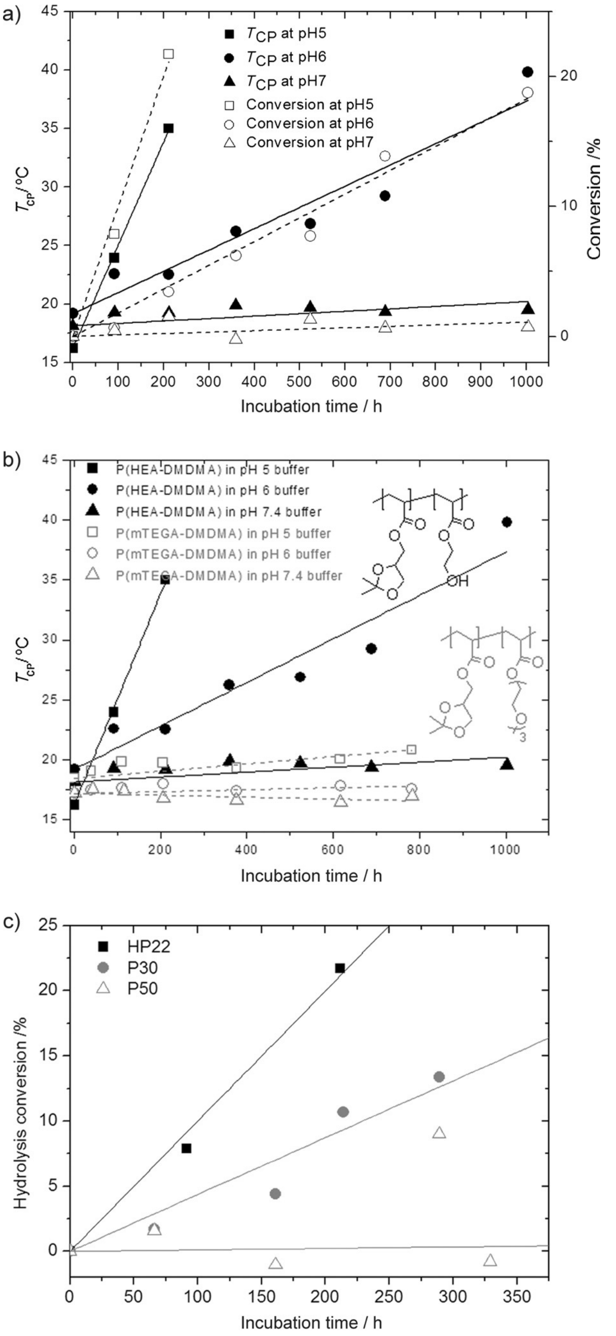

Figure 3. a) Plots of T_{CP} (solid symbols) and hydrolysis conversion (hollow symbols) versus time for HP22 incubated at pH 5, 6, and 7.4. b) Plots of T_{CP} versus hydrolysis time for HP22 and P42 at pH 5, 6, and 7.4. c) Plots of hydrolysis conversion as determined by ^{1}H NMR spectroscopy for HP22, P30, and P50. Data for P42, P30, and P50 were reported previously.[4d] Lines are a guide for the eye.

hydrolysis of HP22 than P50, in line with the previous observations (Figure 3c). To exclude the possibility that the lower T_{CP} value of P50 is partially responsible for the slower hydrolysis, a P(mTEGA–DMDMA) copolymer with much higher T_{CP} value (P30 with $T_{CP} = 32.2\,°C$ in pH 5 buffer) was also examined (Figure 3c). Even this more hydrophilic mTEGA–DMDMA copolymer showed much slower hydrolysis than HP22, thus demonstrating that the presence of HEA is the prime factor responsible for the fast hydrolysis.

Variation of the hydrophilicity of the microenvironment of the acid-labile groups has been proven to be an efficient way to accelerate polymer hydrolysis and to maintain the stability of the polymer during storage. For example, the research groups of Fréchet[21] and Murthy[22] have shown that the introduction of a more hydrophilic comonomer can accelerate the pH-induced hydrolysis of copolymers functionalized with ketal groups. We previously also found that more hydrophilic copolymers with higher T_{CP} values hydrolyze faster than those with lower T_{CP} values at the same pH value.[4d] The increased hydrolysis rate of the HEA–DMDMA copolymer (HP22) as compared to mTEGA–DMDMA copolymers (P50 or P30) is, however, conceptually different from the above-mentioned examples, since HP22 has similar hydrophilicity to P50 and P42, and is even more hydrophobic than P30, as evidenced by the T_{CP} values.

To understand the striking influence of HEA on the faster hydrolysis of DMDMA under slightly acidic conditions, we first evaluated the hydrolysis of HP22 and P50 at pH 4 and 5 in the soluble state at 7 °C, well below the T_{CP} value (see Figures S16–S19). The hydrolysis of both copolymers at both pH values was very similar, thus indicating that the observed acceleration only occurs in the collapsed polymer globules. Unexpectedly, the hydrolysis in the soluble state is much slower than the hydrolysis in the collapsed globules, thus indicating an accelerating neighboring-group effect for the hydrolysis reaction.

Next, a potential difference in the hydration of HP22 and P50 in the collapsed globules was studied by ^{1}H NMR spectroscopy in D_2O. The experiments revealed that the mobility of the side chains of P50 was highly restricted at 37 °C, whereas the side chains of HP22 still show high mobility at the same temperature (see Figures S14 and S15). This difference indicates that the hydroxy groups of P(HEA–DMDMA) lead to significantly higher hydration of the collapsed polymer globules than for P(mTEGA–DMDMA). This higher degree of hydration may enhance the hydrolysis.[15] However, the difference in hydration does not necessarily explain the large difference in hydrolysis rates, as the fully hydrated polymers revealed very similar hydrolysis rates below the T_{CP} value. Therefore, it is likely that the hydroxy groups of P(HEA–DMDMA) not only enhance the hydration of the collapsed copolymer globules, but also induce more pronounced acceleration of the hydrolysis in the collapsed polymer globules than for P(mTEGA–DMDMA), possibly by autocatalytic acceleration of the hydrolysis reaction.

In conclusion, we have demonstrated that by variation of the comonomer, the T_{CP} value and pH degradability of dioxolane-containing copolymers can be drastically altered. It was found that hydroxy-functionalized thermo- and pH-responsive copolymers, P(HEA–DMDMA), undergo significantly faster pH-triggered hydrolysis as compared to P(mTEGA–DMDMA), and maintain high stability under neutral conditions. This unexpected result is ascribed to the higher hydration of the polymer globules owing to strong hydrogen bonding between polymer hydroxy groups and water, in combination with autocatalytic acceleration of the

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hydrolysis reaction. Thus, the introduction of hydroxy groups into the copolymer chain enables the use of relatively stable pH-degradable moieties to obtain polymers that are highly stable at pH 7.4 but degrade readily at pH 5 and 6. This unprecedented concept makes it possible to bypass the direct correlation between stability at pH 7.4 and the hydrolysis rate under slightly acidic conditions. Therefore, the developed HEA–DMDMA copolymers are highly attractive for biomedical applications, such as intracellular drug or vaccine delivery.[23]

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[20] For example, only 22% hydrolysis of HP22 can contribute to an increase of 18.8°C in the T_{CP} value (from 16.2 to 35.0°C), whereas for P(mTEGA–DMDMA) with a T_{CP} value of 13.2°C, around 50% hydrolysis is needed for the same increase in T_{CP} (from 13.2 to 32.0°C). Even considering the difference in the T_{CP} values before hydrolysis and the influence of the pH value of the buffer solution (HP22 at pH 5, P(mTEGA–DMDMA) at pH 4), the difference in the degree of hydrolysis required for a similar increase in the T_{CP} value is remarkable.

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