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pH- and Thermo-Sensitive Co-polymers Based on a Hyperbranched Polymers Core as Encapsulation and Release Carriers for Guest Molecules

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Abstract

Hyperbranched poly(3-ethyl-3-(hydroxymethyl)oxetane) (HPBO), modified by S-1-dodecyl-S′-(α,α'-dimethyl-α''-acetic acid) trithiocarbonate (DMP) to form a RAFT macroinitiator, and then two monomers, 2-(dimethylamino)ethyl-methacrylate (DMAEMA) and acrylic acid (AA), were polymerized to obtain novel pH- and thermo-sensitive polymers with a hyperbranched polymer core. These polymers exhibited phase transitions in response to pH and temperature. They were possible to harvest a bioactive molecule, indometacin, from solution using the phase transition of these pH- and thermo-sensitive polymers. Various parameters, such as percent loading of drugs, pH, temperature and nature of the release media on the release profiles, were investigated. The resultant polymer carriers can potentially be used for the controlled release of the anti-inflammatory drug indometacin.

Keywords

Hyperbranched polymer, pH-sensitive polymers, thermo-sensitive polymers, drug-delivery system, phase transitions

1. Introduction

Dendrimers and hyperbranched polymers have three-dimensional structures and unique properties that are different from those of linear polymers [1–4]. The unique architectural design of dendrimers and hyperbranched polymers, the high degree of branching, multivalency, globular architecture and well-defined molecular weight, clearly distinguishes these structures as unique and optimum nanocarriers in medical applications such as drug delivery, gene transfection, tumor therapy and diagnostics [5–7]. Despite the lower regularity of their branched backbone structures, hyperbranched polymers tend to have spherical structures and exhibit properties in

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common with dendrimers. In addition, hyperbranched polymers tend to be more easily prepared than dendrimers [8–10]. Thus, hyperbranched polymers may be more useful, from a practical viewpoint, than dendrimers. To increase the usefulness of hyperbranched polymers, it is crucial to impart desired functionality to target hyperbranched polymers with appropriate structure and properties. However, there have been only a few reports on the modification of hyperbranched polymers with functional groups [11].

Stimuli-responsive polymers are defined as those polymers which respond with dramatic physical or chemical alterations to small external changes in their environment. Such stimuli include temperature, pH, ionic factors, electric or magnetic fields, chemical or biological agents and mechanical stress [12]. In particular, temperature- and pH-responsiveness are of great importance for biomedical applications. The temperature of target sites, such as tumor tissues, in the body can be changed safely by hyperthermia. Also, it is known that some cellular compartments and tissues have lower pH environments than normal physiological pH. For those reasons many efforts have been made to develop hyperbranched polymers with temperature-sensitive and pH-sensitive properties for biomedical use [13].

To increase the potential usefulness of hyperbranched polymers in the biomedical and related fields, in the present study we have attempted to render biocompatible hyperbranched polymers sensitive to temperature and pH. We propose a novel method for imparting thermosensitivity to temperature-insensitive polymers, by which side-chain units of thermosensitive polymers are introduced to the target hyperbranched polymer core as temperature-sensitive moieties. Poly(dimethyoaminoethyl methacrylate), poly(DMAEMA), is a pH-responsive cationic polyelectrolyte containing tertiary amino groups, showing sensitivity to temperature [14]. The pendant tertiary amine groups of DMAEMA are easily protonated below its pK_a, and the polymer undergoes a hydrophilic-to-hydrophobic transition when heated above its lower critical solution temperature (LCST) in water [15]. In the present study, we have applied this method to biocompatible hyperbranched polyols (HPBO) and examined the effectiveness of the method for the temperature sensitization. We have also attempted to impart pH sensitivity to HBPO by the introduction of carboxyl groups. We have succeeded in making biocompatible hyperbranched polymers that respond to temperature and pH in ranges around normal physiological conditions, by controlling the relative proportions of the temperature-sensitive and pH-sensitive units.

2. Experimental

2.1. Materials

2-(dimethylamino) ethyl methacrylate (DMAEMA, 99%, Acros) was passed through a column of basic alumina to remove out the stabilizing agents. Azobisisobutyronitrile (AIBN, 98%) was purchased from East China Chemical and recrystallized twice from ethanol and dried in vacuum prior to use. Acrylic acid (AA, Aldrich) was used as received. S-1-Dodecyl-S′-(α,α'-dimethyl-α''-acetic

acid) trithiocarbonate (DMP) was synthesized according to a previously published procedure [16]. All other reagents and solvents were of analytical grade and used as received without further purification. MilliQ Water (18.2 MΩ/cm) was generated using a Millipore MilliQ Academic Water Purification System.

2.2. Synthesis of HBPO

Hyperbranched polyols (HPBOs) were synthesized by cationic polymerization of 3-methyl-3-oxetanemethanol directly initiated by $BF3 \cdot Et_2O$ according to the procedures described in the literature [10, 17, 18]. The M_n of the resultant product was 1.54×10^4 g/mol (by GPC).

2.3. Synthesis of HBPO-DMP Macroinitiator

DMP (2.1 g, 5.7 mmol) and HBPO (1.0 g, 10.0 mmol) were dissolved in 50 ml anhydrous dichloride methylene. Dicyclohexylcarbodiimide (DCC, 2.1 g, 10.0 mmol) and catalytic amounts of 4-(dimethylamino)-pyridinium 4-toluenesulfonate (DPTS) were added in one portion to the solution. The reaction mixture was stirred at room temperature in the dark for 24 h. A white by-product was removed by filtration. The filtrate was concentrated by evaporation, and the residue was purified by silica gel chromatography with ethyl acetate/hexane (1:4, v/v) as the eluent. A yellow solid was obtained (2.0 g, yield 74%). ^{1}H-NMR (DMSO-d_6, δ): 0.8–0.9 (–$CH_2C\underline{\boldsymbol{H}}_3$ in HBPO and –$C_{11}H_{22}C\underline{\boldsymbol{H}}_3$ in DMP), 1.3–1.5 (–$C\underline{\boldsymbol{H}}_2CH_3$ in HBPO and –$CH_2CH_2C_9\underline{\boldsymbol{H}}_{18}CH_3$ in DMP), 1.68 (–S–$CH_2C\underline{\boldsymbol{H}}_2C_{10}H_{21}$ in DMP), 1.75 (–S–$C(C\underline{\boldsymbol{H}}_3)_2COOH$ in DMP), 3.20 (–S–$C\underline{\boldsymbol{H}}_2C_{11}H_{23}$), 3.30–3.50 (–$C\underline{\boldsymbol{H}}_2OCH_2$– in HBPO).

2.4. Synthesis of HBPO-star-PDMAEMA

A series of multi-arm star co-polymers were synthesized in the presence of HBPO-DMP as macroinitiator. The general procedure was as follows. The HBPO-DMP (4.1 g, 0.5 mmol) and AIBN (0.016 g, 0.1 mmol) were placed into an oven-dried reaction flask, then dried 20 ml THF was added *via* a syringe. After the macroinitiator was dissolved completely, DMAEMA monomer (6.0 g, 38 mmol) was added. The solution was degassed for three cycles by pulling a vacuum and back-filling with nitrogen gas. The reaction was carried out at 80°C in a pre-heated oil-bath for 24 h. After cooling to room temperature, an amount of THF was added to the flask to dissolve the polymer completely. The excess THF was evaporated under reduced pressure and the product was precipitated from excess cold n-hexane, filtered and dried under vacuum to constant weight. The resultant product with M_n 8.26×10^4 g/mol (GPC, HBPO-star-PDMAEMA-1) was obtained in >90.3% yield after drying. ^{1}H-NMR ($CDCl_3$, δ): 0.8–1.0 (–$C\underline{\boldsymbol{H}}_3$ in HBPO, DMP and PDMAEMA), 1.0–1.5 (–$C\underline{\boldsymbol{H}}_2CH_3$ in HBPO and –$CH_2CH_2C_9\underline{\boldsymbol{H}}_{18}CH_3$ in DMP), 1.68–2.0 (–S–$CH_2C\underline{\boldsymbol{H}}_2C_{10}H_{21}$ in DMP, –S–$C(C\underline{\boldsymbol{H}}_3)_2COOH$ in DMP and –$C\underline{\boldsymbol{H}}_2$–$C(CH_3)$ in PDMAEMA), 2.2–2.40 (–$N(C\underline{\boldsymbol{H}}_3)_2$ in PDMAEMA), 2.50–2.80 (–$C\underline{\boldsymbol{H}}_2$–$N(CH_3)_2$ in PDMAEMA), 3.30–3.50 (–$C\underline{\boldsymbol{H}}_2OCH_2$– in HBPO), 4.00–4.20 (–$C\underline{\boldsymbol{H}}_2CH_2$–$N(CH_3)_2$ in PDMAEMA).

2.5. Synthesis of HBPO-star-PDMAEMA-b-PAA

A typical polymerization procedure is as follows: HBPO-star-PDMAEMA-1 (2.50 g, 0.03 mmol), AIBN (0.008 g, 0.05 mmol) and AA (0.65 ml, 9.0 mmol) were added to a dry flask, which was then immersed in liquid nitrogen for a while. Then, the reaction mixture was degassed three times using the freeze–pump–thaw procedure. Finally, the flask was flame-sealed under vacuum and placed in a pre-heated oil-bath at 80°C for 12 h. After cooling to room temperature, an amount of THF was added to the flask to dissolve the polymer completely. The excess THF was evaporated under reduced pressure and the product was precipitated from excess petroleum ether, filtered and dried under vacuum to constant weight. The resultant product with M_n 9.41×10^4 g/mol (GPC, HBPO-star-PDMAEMA-b-PAA) was obtained in >94.5% yield after drying. ^{1}H-NMR (DMSO-d_6, δ): 0.8–1.0 (–C$\underline{\boldsymbol{H}}_3$ in HBPO, DMP and PDMAEMA), 1.0–1.5 (–C$\underline{\boldsymbol{H}}_2CH_3$ in HBPO, –CH$_2$CH$_2$C$_9\underline{\boldsymbol{H}}_{18}CH_3$ in DMP and –CH$_2$–C$\underline{\boldsymbol{H}}$– in PAA), 1.68–2.0 (–S–CH$_2$C$\underline{\boldsymbol{H}}_2C_{10}H_{21}$ in DMP, –S–C(C$\underline{\boldsymbol{H}}_3$)$_2$COOH in DMP, –C$\underline{\boldsymbol{H}}_2$–C(CH$_3$) in PDMAEMA and –C$\underline{\boldsymbol{H}}_2$–CH– in PAA), 2.2–2.40 (–N(C$\underline{\boldsymbol{H}}_3$)$_2$ in PDMAEMA), 2.50–2.80 (–C$\underline{\boldsymbol{H}}_2$–N(CH$_3$)$_2$ in PDMAEMA), 3.30–3.50 (–C$\underline{\boldsymbol{H}}_2OCH_2$– in HBPO), 4.00–4.20 (–C$\underline{\boldsymbol{H}}_2CH_2$–N(CH$_3$)$_2$ in PDMAEMA), 12.20–12.35 (–COO$\underline{\boldsymbol{H}}$ in PAA).

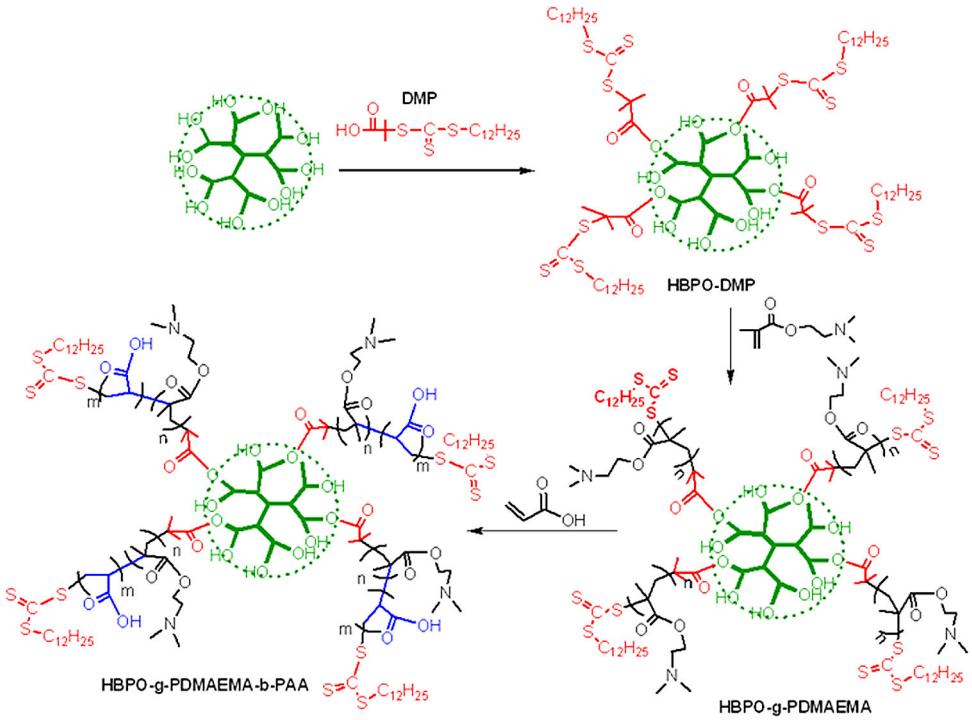
2.6. Characterization

The ^{1}H-NMR spectra were recorded on an Avance AV 400MHz Digital FT-NMR spectrometer operating at 400 MHz using $CDCl_3$ or DMSO-d_6 as the solvent. Gel-permeation chromatography (GPC) analysis was carried out using a Waters 1525 pumping system at a flow rate of 0.5 ml/min with an Ultrahydrogel 500 column (Waters). The eluent was THF. Fourier transform infrared (FT-IR) spectra were recorded on a Nicolet 5700 spectrophotometer using an ATR cell or KBr pellets for samples. The turbidity of solutions of HBPO-star-PDMAEMA-b-PAA in 10 mM phosphate containing 150 mM NaCl buffer (pH 5.0–7.4) was measured at 700 nm using a Jasco Model V-560 spectrophotometer equipped with a Peltier-type thermostatic cell holder coupled with an ETC-505T controller. The heating rate of the sample cell was maintained at 1.0°C/min. The cloud points were taken as the initial break points in the resulting transmittance *versus* temperature curves. The amount of release indometacin in the aqueous solution was analyzed by UV-Vis spectrometry. Through the comparison working curve, the concentration of indometacin was calculated. The release concentration of indometacin ($c = A/(\varepsilon \times d)$), where ε is the molar absorptivity of indometacin in an aqueous solution, and d the thickness of the sample pool ($\lambda_{max} = 320$ nm).

3. Results and Discussion

3.1. Synthesis of HBPO-star-PDMAEMA-b-PAA

The strategy for the synthesis of pH- and thermo-sensitive hyperbranched co-polymers is highlighted in Scheme 1. The RAFT chain-transfer agent (CTA), S-



Scheme 1. Preparation of novel pH- and thermo-sensitive hyperbranched co-polymers.

1-dodecyl-S′-(α,α′-dimethyl-α″-acetic acid) trithiocarbonate (DMP), was attached to the hyperbranched precursor (HBPO) by esterification between the hydroxyl and carboxylic groups using coupling reagents DCC and DPTS yielding RAFT agent. A large number of initiating sites on the HBPO core can be formed and used to initiate the polymerization. The hyperbranched polymer HBPO-DMP core with an average of 7.5 initiating sites, recorded by GPC data of HBPO and HBPO-DMP, was used to propagate. Subsequently, the new obtained hyperbranched RAFT agent was used to mediate the polymerizations of DMAEMA and AA. From the GPC data of HBPO-star-PDMAEMA and HBPO-star-PDMAEMA-b-PAA, we estimated the degree of polymerization of polymer chain on HBPO core. The results for all of the polymers that were synthesized are shown in Table 1.

The synthesized compounds were characterized by ^{1}H-NMR. The ^{1}H-NMR spectra of unmodified HBPO, HBPO-star-PDMAEMA and HBPO-star-PDMAEMA-b-PAA are shown in Fig. 1. The spectrum of HBPO-DMP reveals signals derived from DMP (0.85, 1.20 and 1.80 ppm) which indicated the introduction of DMP onto the hyperbranched core. Subsequently, the new obtained HBPO-DMP was used to mediate the polymerizations of DMAEMA and AA. The signals at 4.0–4.2 ppm and 2.5–2.8 ppm (methine and methylene, respectively) derived from the PDMAEMA and the signal at 12.2–12.3 ppm from the PAA (–COOH) indicate

Table 1.
Synthesis conditions, yields and characterization of various synthesized polymers

Sample	M_w ($\times 10^4$ g/mol)	PDI	Yield (%)	DP	
				DMAEMA	AA
HBPO	0.55	1.61	95.6	–	–
HBPO-DMP	0.82	1.58	90.2	–	–
HBPO-star-PDMAEMA	4.82	1.52	90.3	34.0 × 7.5	–
HBPO-star-PDMAEMA-b-PAA-1	5.09	1.45	94.5	34.0 × 7.5	5.00 × 7.5
HBPO-star-PDMAEMA-b-PAA-2	5.35	1.50	92.8	34.0 × 7.5	9.68 × 7.5
HBPO-star-PDMAEMA-b-PAA-3	5.20	1.48	92.5	34.0 × 7.5	6.80 × 7.5

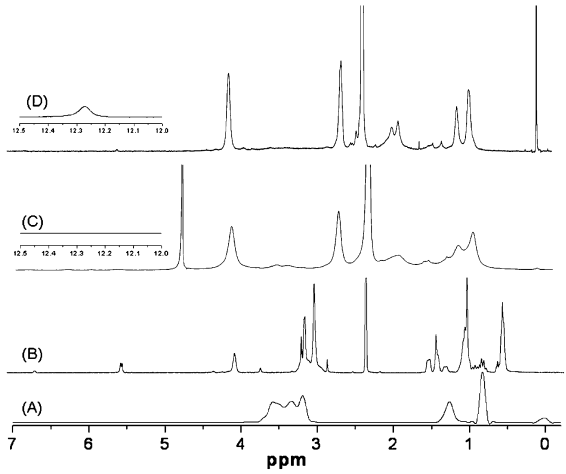


Figure 1. ^{1}H-NMR spectra of (A) HBPO, (B) HBPO-DMP, (C) HBPO-star-PDMAEMA and (D) HBPO-star-PDMAEMA-b-PAA-1.

that HBPO-star-PDMAEMA and HBPO-star-PDMAEMA-b-PAA have been synthesized successfully.

FT-IR analysis results of HBPO, HBPO-star-PDMAEMA and HBPO-star-PDMAEMA-b-PAA are shown in Fig. 2. Absorption bands at 1466, 1100 and 1052 cm^{-1} in Fig. 2A can be observed, which can be ascribed to the C–H and C–O stretching, respectively. The characteristic absorption peak of HBPO around at 3300 cm^{-1}, that is contributed to the O–H stretching vibration [10]. The C–H and C–O stretching is also verified in the FT-IR spectrum of HBPO-star-PDMAEMA. According to the FT-IR spectrum shown in Fig. 2B, the following characteristic peaks of PDMAEMA can be found: 1735 cm^{-1}, carbonyl (C=O) stretch vibration; 2920–2960 cm^{-1}, $-N(CH_3)_2$ stretch vibration; around 1476 cm^{-1}, $-N(CH_3)_2$ deformational stretch vibration [19]. Those absorptions, however, are absent in the FT-IR spectrum of HBPO. Comparing the relative intensity of the O–H stretching around at 3300 cm^{-1}, it is lower than that of HBPO and HBPO-star-PDMAEMA-

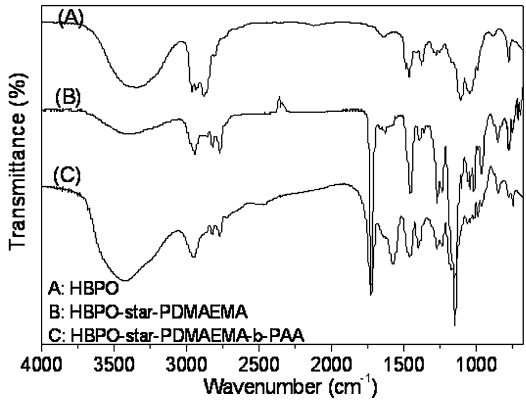


Figure 2. FT-IR spectra of (A) HBPO, (B) HBPO-star-PDMAEMA and (C) HBPO-star-PDMAEMA-b-PAA-1.

b-PAA samples which indicates a different amount of hydroxyl groups in the polymers. Thus, judging together with analysis by NMR spectrum, it demonstrated the successful polymerization of DMAEMA and AA.

3.2. Phase Transitions of HBPO-star-PDMAEMA-b-PAA

The phase transition of aqueous solutions containing the synthesized polymers was examined. However, HBPO-star-PDMAEMA-b-PAA exhibited thermosensitive behavior depending on the composition of resultant polymers. We firstly examined the influence of the degree of polymerization (DP) of PDMAEMA on the thermosensitivity of the polymers. We recorded the transmittance−temperature curves of a 1.0% sample in pure water (pH 7.0) during heating as shown in Fig. 3. The cloud points are 38.5 and 48.2 for two samples, for which the DP ratios of PDMAEMA and PAA are 3.5:1 and 6.8:1, respectively. It is thought that an increase of the DP ratios of PDMAEMA and PAA, terminal group density and van der Waals interaction might result in the higher cloud point of polymer.

The pH of the solution has a pronounced effect on the phase separation, as the charge densities of weak polyelectrolytes like PAA and PDMAEMA strongly depend on pH, and the stability of the phase separation depends on the charge densities. Because the carboxyl groups of the PAA can act as a pH sensor, we investigated the influence of pH on the thermosensitivity of the polymers. Increasing the pH resulted in a shift of the phase transition to lower temperatures and in sharper transitions. The cloud points of the sample at pH 4.5, 7.0, 7.5 and 8.0 were 36, 47, 63 and 68°C (Fig. 4), respectively. The decrease of cloud point with increasing pH of polymer solution is thought to be a larger proportion of carboxyl groups inducing the phase transition because of the enhanced hydrophobicity. The pK_a of PAA is 4.88 [20]; below this value of pH the –COOH groups of PAA associate and above this value the same groups dissociate. In the association state of –COOH groups there will be more interactions between these groups, which lead to lower

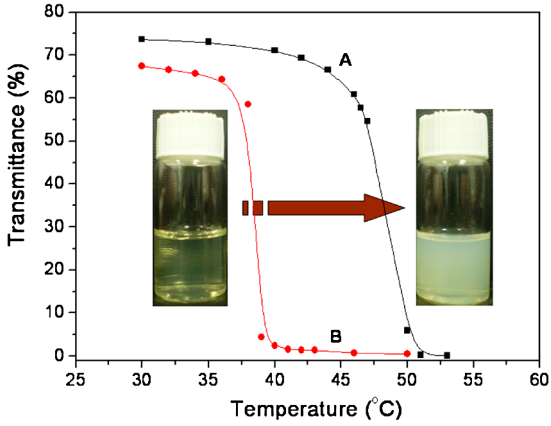


Figure 3. Temperature dependence of transmittance for solutions of HBPO-star-PDMAEMA-b-PAA with DP ratios of PDMAEMA and PAA of 6.8:1 (A, HBPO-star-PDMAEMA-b-PAA-1) and 3.5:1 (B, HBPO-star-PDMAEMA-b-PAA-2) at pH 7.0.

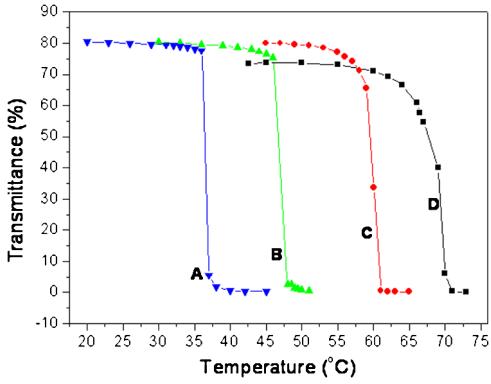


Figure 4. pH-sensitivity of HBPO-star-PDMAEMA-b-PAA-3. Temperature dependence of transmittance for solutions of HBPO-star-PDMAEMA-b-PAA-3 at (A) pH 4.5, (B) 7.0, (C) 7.5 and (D) 8.0.

cloud point of the resultant polymer. The observed pH effect on the cloud point behavior can be ascribed, to a large extent, to variations in the stabilizing effect of PDMAEMA blocks with changes of their degree of ionization [21]. Moreover, we observed under our experimental conditions an increase in the cloud points as the relative length of the PDMAEMA blocks increases, indicating an enhanced stabilization of hyperbranched polymer in the solution [22].

3.3. Effect of Temperature on Drug Release

Thermosensitive dendrimers can act as a nanocapsule for harvesting bioactive molecules [23]. We investigated the temperature-dependent encapsulation ability of HBPO-star-PDMAEMA-b-PAA to indometacin (INN), which is a type of non-steroidal anti-inflammatory drug commonly used to reduce fever, pain, stiffness and swelling [24, 25]. Drug-loaded complexes containing INN were prepared by a

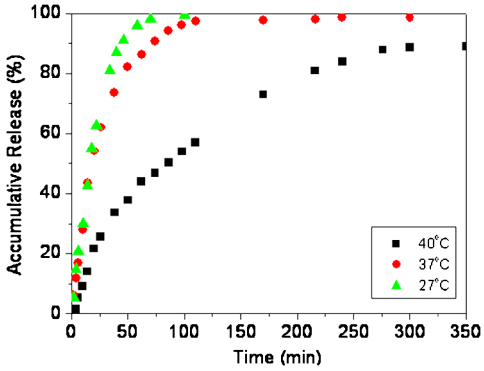


Figure 5. Effect of pH on the release profile of HBPO-star-PDMAEMA-b-PAA-3/drug complex. [complex] = 2.5 wt%, % loading = 20%, pH 7.0.

direct dissolution process. Briefly, the as-synthesized pH/temperature-sensitive hyperbranched polymers and INN were first dissolved in DMF with vigorous stirring at room temperature. After 24 h of stirring, the solution was dialyzed against distilled water at a certain temperature to remove the organic solvent and free drug completely. After dialysis, the solution in the dialysis bag was collected and freeze-dried to obtain drug-loaded complexes. The drug-loaded complexes were immersed in water incubated at different temperature with continuous shaking at a speed of 100 rpm. At specific time intervals, sample solutions were withdrawn from the release medium. The INN content of the samples was determined at 320 nm with an UV-Vis spectrophotometer.

Figure 5 shows the drug-release profiles of temperature with time at different temperature. It is observed that the drug-release rate is related to the temperature of the medium. The drug-release rate increases when the temperature value decreases. Comparing the drug-release profiles, it can be found that within 10 h the drug accumulative releases from these polymer carriers were 85, 97 and 99% at 40, 37 and 27°C, respectively. It is thought that PDMAEMA modification may cause the polymer carriers instability under the lower temperature (27°C) and the rapid release of encapsulated drugs. In contrast, at higher temperature polymer carriers exhibit a volume phase transition at a certain temperature, which causes a sudden change in the solution state [26]. These polymers become insoluble upon heating and the drug release from polymer carriers becomes slower. This finding corresponded well to our phase-transition reports.

3.4. Effect of % Loading on Drug Release

Another important aspect in using polymer carriers as drug vehicle is the effect of the drug loading levels on the drug release rates. Higher drug loading may be achieved either by using a highly concentrated drug solution or repeated soaking of polymer carriers in the drug solution and then drying them. In the present work, polymer carriers of defined composition were loaded with different amounts of INN

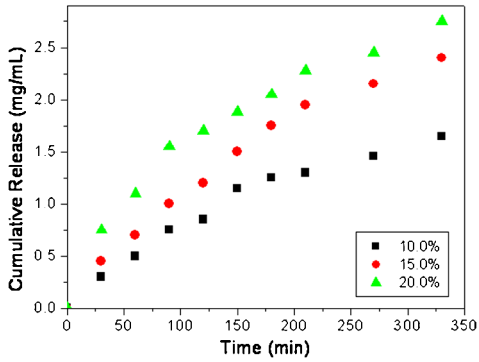


Figure 6. Effect of % loading on release profile of HBPO-star-PDMAEMA-b-PAA-3/drug complex. [complex] = 2.5 wt%, pH 7.0, $T = 37°C$.

by allowing the polymer carriers to swell in the drug solution of varying concentrations ranging between 10.0 and 2.0 wt%. The loaded polymer carriers were then allowed to release the entraped drug into the release medium. Drug-release results are shown in Fig. 6. The amount of INN released increases with increasing percent loading. Similar results were reported previously by us and others for different drug-release system [27–29].

3.5. Effect of pH on Drug Release

Since the pH change occurs at many specific or physiological sites in the body, it is one of the important parameters in the design of drug-delivery systems. Differences in pH in the target site may allow a specific drug to be delivered to that target site only [30]. The underlying principle for targeted drug delivery is the pH controlled swelling of hydrogel which normally results from the change in relaxation rate of network chains with changing pH of the medium. The pH profile of normal tissue is different from that of pathological tissues, such as cancerous and infected tissues [31]. In the present work, the release dynamics of the doxorubicin have been studied under varying pH conditions. The results are shown in Fig. 7. We found that less drug is released at physiological and acidic (pH 6.0) conditions, whilst the most efficient release is achieved at alkaline pH (8.0). These results are consistent with the phase-transition results. The reason behind the lower swelling of unloaded nanoparticles in acidic conditions is that the polymer carriers do not swell sufficiently. Drug-loaded polymer carriers swell better in the alkaline solution than at physiological pH or under acidic conditions. Similar results have been reported recently for pH-sensitive liposomes [31]. These were stable at physiological pH (7.4), but degraded to release active drug in target tissues in which the pH is less than physiological values, such as in the acidic environment of tumor cells.

4. Conclusion

Many anticancer agents have poor water solubility and, therefore, the development of novel delivery systems for such molecules has received significant attention. Hy-

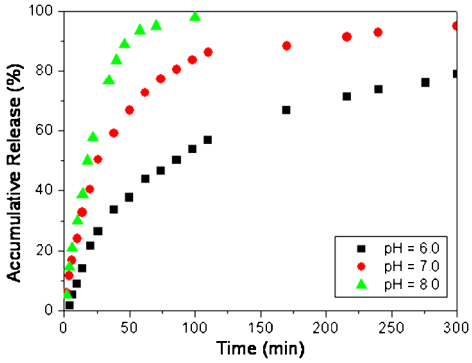


Figure 7. Effect of HBPO-star-PDMAEMA-b-PAA-3/drug complex. [complex] = 2.5 wt%, % loading = 20%, $T = 37°C$.

perbranched polymer carriers show great potential in delivering therapeutic agents into the targeted organs or cells and have recently emerged as a promising approach to cancer treatments. The aim of this study was to prepare and use pH- and temperature-sensitive co-polymers based on a hyperbranched polymer core for the controlled release of the anti-inflammatory drug indometacin. These polymers exhibited phase transitions in response to decreasing pH and/or increasing temperature, depending on the degree of polymerization and the ratio of AA to DMAEMA. It was possible to harvest a bioactive molecule, indometacin, from solution using the phase transition of thermo-sensitive hyperbranched polyols. We also studied the effects of various parameters such as percent loading of drugs, pH, temperature and nature of the release media on the release profiles of the drug. The resultant polymer carriers can potentially be used for the controlled release of the anti-inflammatory drug indometacin.

Acknowledgements

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