Feedback-regulated paclitaxel delivery based on poly(N,N-dimethylaminoethyl methacrylate-co-2-hydroxyethyl methacrylate) nanoparticles

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Abstract

pH-Sensitive poly(N,N-dimethylaminoethyl methacrylate (DMAEMA)/2-hydroxyethyl methacrylate (HEMA)) nanoparticles were prepared for the triggered release of paclitaxel within a tumor microenvironment. Tumors exhibit a lower extracellular pH than normal tissues. We show that paclitaxel release from DMAEMA/HEMA particles can be actively triggered by small, physiological changes in pH (within 0.2–0.6 pH units). Monodispersed nanoparticles were synthesized by forming an O/W emulsion followed by photopolymerization. Particles were characterized by transmission electron microscopy, dynamic light scattering, electrophoresis, and cytotoxicity. High release rates and swelling ratios are achieved at low pH, low crosslinking density, and high content of DMAEMA. Paclitaxel release is limited to 9% of the payload at pH 7.4 after a 2-h incubation at 37 °C. After adjusting to pH 6.8, 25% of the payload is released within 2 h. Cell viability studies indicate that pH-sensitive DMAEMA/HEMA nanoparticles are not cytotoxic and may be used as an efficient, feedback-regulated drug delivery carrier.

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1. Introduction

Stimuli-sensitive polymers that respond to temperature [1–3], pH [4,5], light [6,7], ionic strength [8], and electric [9] or magnetic fields [10] are attractive for use in drug delivery, diagnostics, and sensing. Much attention has been paid to the use of pH-sensitive polymers for oral drug delivery [11–13], gene delivery [14], and insulin delivery [15], where a physiological pH shift facilitates swelling. Because conventional pH-sensitive functional groups provide limited sensitivity within the blood pH range, their use in systemic drug delivery systems has been severely limited.

Common pH-sensitive polymers like poly(acrylic acid) [16] and poly(methacrylic acid) [17] incur swelling at high pH due to ionizable functional groups on the polymer backbone or side chain. Synthesized polymeric delivery vehicles [18] from these polymers exhibit similar swelling behavior, where swelling occurs at high pH. This mechanism is not useful for delivery to the acidic environments present in tumors. In this research, the drug delivery vehicles have a reversed swelling behavior from previously reported pH-sensitive nanoparticle systems; they swell under acidic conditions. Particles that have been reported to swell under acidic conditions [19] typically require a large pH change which limits their use.

DMAEMA has been used in the development of therapeutic drug delivery formulations [20]. Due to its pH-responsive characteristic, poly(DMAEMA) microgels have been synthesized with other co-monomers (i.e. polystyrene [21], acrylamide [22], and pyrrolidone [23]) for drug delivery applications. Satish and Shivakumar [24] investigated a self-regulating insulin delivery system based on poly(DMAEMA-co-HEMA) hydrogels within in vivo conditions. Hydrogel and micro-scaled formulations have size limitations and are unable to be used systemically. Thus, we have investigated...
monodispersed and nano-sized DMAEMA/HEMA particles for tumor-targeted delivery of paclitaxel, a chemotherapeutic agent. Tumors exhibit a lower extracellular pH than normal tissues [25]. It is hypothesized that this results from a chaotic vasculature and deregulation of glycolysis [26]. Drug delivery systems have been designed to use pH as a mechanism to improve delivery of chemotherapeutics [27]. Improved delivery mechanisms may reduce side effects and increase the quality of life of patients.

Paclitaxel is an effective chemotherapeutic agent against carcinomas of the breast, ovary, and lung [28–31]. Due to poor aqueous solubility, paclitaxel is dissolved in organic formulations such as poly(lactic-co-glycolic acid) (PLGA) nanoparticles [32], dehydrated ethanol [33], and polyethoxylated castor oil (Cremophor® EL) [34] for clinical use. Cremophor EL has been reported to cause toxic effects which are known to induce life-threatening anaphylaxis in up to 30% of treated patients [35–37]. Although antihistamines and glucocorticoids are administered to manage those toxic effects [38], these drugs also have the possibility of additional pharmacokinetic and pharmacodynamic interactions with paclitaxel. Controlled release of paclitaxel encapsulated within PLGA nanoparticles has been investigated to reduce these side effects [32]. Novel pH-sensitive delivery vehicles, that localize paclitaxel within the target site while minimizing side effects, may prove useful in the treatment of tumorigenic cancers.

In the present study, monodispersed pH-sensitive DMAEMA/HEMA nanoparticles were prepared by O/W emulsification followed by photopolymerization. These particles have been assessed by transmission electron microscopy (TEM), dynamic light scattering, electrophoresis, and cytotoxicity. We demonstrate pH-sensitive swelling for different ratios of DMAEMA to HEMA and different concentrations of the crosslinker tetraethylene glycol dimethacrylate (TEGDMA). Our study is the first attempt to characterize nano-scaled DMAEMA/HEMA nanoparticles and demonstrate their use as pH-triggered drug delivery carriers.

2. Materials and methods

2.1. Materials

The monomer 2-(dimethylamino)ethyl methacrylate (DMAEMA) and co-monomer 2-hydroxyethyl methacrylate (HEMA) were purchased from Acros (Morris Plains, NJ, USA). TEGDMA for crosslinking was obtained from Fluka (St. Louis, MO, USA) and 2,2-dimethoxy-2-phenylacetophenone (DMPAP) for photoinitiation from Aldrich (St. Louis, MO, USA). Monobasic and dibasic sodium phosphates used to prepare various pH phosphate buffers were purchased from Sigma (St. Louis, MO, USA). Pluronic F68 was obtained from BASF Corporation (Mount Olive, NJ, USA). For the controlled release experiment, paclitaxel was used as a model drug and purchased from Sigma (St. Louis, MO, USA). For the preparation of PLGA nanoparticles, poly (ε-caprolactone-glycolide) (PLGA, 50:50, Mn ~17,000–22,000) and polyvinyl alcohol (PVA, Mn ~25,000) were purchased from Polysciences, Inc. (War- rington, PA, USA) and ethyl acetate was purchased from Aldrich. Other reagents were commercially available and were used as received. All cell culture media and reagents, unless otherwise mentioned, were purchased from Invitrogen (Carlsbad, CA, USA). Deionized water (18.2 MΩ) used in all experiments was obtained from a Milli-Q purification system (Millipore Corp., Billerica, MA, USA).

2.2. Preparation of DMAEMA/HEMA nanoparticles

Pluronic F68 (150 mg) was dissolved in 10 mL of distilled water for the water phase. To form the O/W emulsion, 100 µL of a DMAEMA and HEMA solution (mixed at different molar ratios of 5/95 and 10/90, respectively) was added to the water phase. Three different mol% TEGDMA and 1 mol% DMPAP were added simultaneously to the water phase. The solution was sonicated (200 W, 20 kHz, Digital sonifier 250, Branson Ultrasonics Corp., Danbury, CT, USA) in a laminar flow hood over an ice bath for 10 min. Then, the DMAEMA/HEMA emulsion was exposed to a 365-nm UV energy source with 21,700 µW/cm² intensity (Model B-100 AP/R, UVP Inc., Upland, CA, USA) for 90 s for photoinitiation. DMAEMA/HEMA nanoparticles were collected by high-speed centrifugation at 39,000 × g for 20 min (Sorvall RC26 Plus, SA-600 rotor; Thermo Fisher Scientific Inc., Waltham, MA, USA). The particles were washed twice with pH 7.4 phosphate buffer to remove residual surfactant at the aforementioned operating conditions for the centrifuge. For the preparation of paclitaxel-loaded nanoparticles, paclitaxel was directly added to the DMAEMA/HEMA solution at 1 mM final concentration. It was followed by sonication and centrifugation, as discussed previously. Finally, nanoparticles were freeze-dried (FTS systems, Inc., Stone Ridge, NY, USA) and stored at 4 °C for later use.

2.3. Characterization of DMAEMA/HEMA nanoparticles

The size and morphology of DMAEMA/HEMA nanoparticles were analyzed by dynamic light scattering (ZetaPALS; Brookhaven Instrument, Holtsville, NY, USA) and transmission electron microscopy (JEOL 2100; JEOL Ltd., Tokyo, Japan). For TEM images, 0.05 wt% aqueous solution of DMAEMA/HEMA nanoparticles was dropped onto a copper grid (300 mesh, TED PELLA Inc., Redding, CA, USA) and Transmission Electron Microscopy (JOEL 2010) supporting a thin film of amorphous carbon. The excess liquid was swept away with filter paper and the grid was dried in the hood. To obtain the effective surface charge, 0.1 mg/mL of DMAEMA/HEMA nanoparticles in an aqueous solution was measured by electrophoresis (ZetaPALS; Brookhaven Instrument, Holtsville, NY, USA) at different pHs in N-[tris(hydroxymethyl)methyl]-2-aminoethanesulfonic acid (TES) buffer (pH 6.8, 7.0, 7.2, and 7.4, respectively).

2.4. Swelling of DMAEMA/HEMA nanoparticles

Swelling studies of DMAEMA/HEMA nanoparticles were performed in a buffered solution of known pH, composition, and temperature. The pHs of the buffered solutions were 6.8, 7.0, 7.2, and 7.4, respectively. A predetermined amount of freeze-dried DMAEMA/HEMA nanoparticles were put into a scintillation vial containing 10 mL of buffered medium. Samples were placed on a shaker (OS-500 orbital shaker, VWR, West Chester, PA, USA) with a shaking rate of 100 ± 1 rpm in an incubator maintained at 37 °C. The average nanoparticle diameter was measured by dynamic light scattering at 0, 1, 2, 4, and 24 h.

2.5. Controlled release of paclitaxel

Controlled release of paclitaxel from DMAEMA/HEMA nanoparticles was carried out in a buffered medium at either pH 6.8, 7.0, 7.2, or 7.4. A predetermined amount of freeze-dried DMAEMA/HEMA nanoparticles was placed into a 20-mL scintillation vial containing 10 mL of an aqueous release medium. During release experiments, the vial was placed in a shaker in an incubator with a shaking rate of 100 ± 1 rpm. Samples were collected from the...
tube once every hour until 6 h and then every 6 h until 24 h. The volume of each collected sample was 350 \( \mu L \). To maintain a uniform concentration of paclitaxel in the media, fresh buffer was added after sampling during the release studies. To demonstrate the controlled release of paclitaxel followed by a pH drop, an additional test was designed. Paclitaxel-loaded nanoparticles were added to a pH 7.4 buffered medium. After 2 h, the pH of the buffered medium was dropped to either pH 6.8, 7.0, or 7.2 by adding 1 N HCl. A 350-\( \mu L \) sample was collected every 30 min until 6 h. The concentration of released paclitaxel was directly determined by a UV/Visible spectrophotometer (SpectraMax Plus384; Molecular Devices Corp., Sunnyvale, CA, USA) at the absorption wavelength of 229 nm using a standard calibration curve.

2.6. Cell viability assay

To determine the toxicity profile of the newly investigated DMAEMA/HEMA nanoparticles, a Live/Dead viability/cytotoxicity assay for mammalian cells (Molecular Probes, Eugene, OR, USA) was used with HeLa cells (CCL-2, ATCC, Rockville, MD, USA). HeLa cells (10^5 cells/well) were added to a 96-well cell culture dish (Falcon) with 100 \( \mu L \) of Dulbecco’s Modified Eagles Medium (DMEM) supplemented with 5% fetal bovine serum (FBS) and 1% penicillin–streptomycin. After seeding the cells for 24 h, DMAEMA/HEMA nanoparticles were resuspended with growth medium and added into the cell culture dish. After a 24-h incubation, HeLa cells were rinsed twice with 100 \( \mu L \) of Dulbecco’s phosphate-buffered saline (D-PBS). The Live/Dead assay reagent, which contained 4 \( \mu M \) calcein AM and 2 \( \mu M \) Ethidium homodimer-1, was added to the cell culture dish. After a 30-min incubation at room temperature, cell viability/cytotoxicity was measured with a fluorescence microplate reader (SpectraMax Gemini XPS; Molecular Devices Corp., Sunnyvale, CA, USA). For the comparison of cell viability of DMAEMA/HEMA nanoparticles, PLGA nanoparticles which have been used for drug carriers in the literature [32] were also prepared as a control. In brief, 50 mg of PLGA was dissolved in 1 mL of ethyl acetate. The organic phase was mixed with 3 mL of a 1% aqueous PVA solution and sonicated in a laminar flow hood for 20 s at 200 W output. The formed emulsion was evaporated overnight under magnetic stirring to remove the organic solvent. The sample was collected by high-speed centrifugation at 39,000 \( \times \) g for 20 min. The particles were washed with deionized water 3 times. The nanoparticles were resuspended with 3 mL deionized water and freeze-dried overnight. All cultures were performed at 37°C, balanced with 5% CO_2 in air in a humidified incubator.

2.7. Statistical analysis

All of the experimental data were obtained in triplicate unless otherwise mentioned and are presented as mean±standard deviation. Statistical comparison by analysis of variance was done at a significance level of \( p < 0.01 \) based on Student’s t-test.

3. Results and discussion

3.1. Size and morphology

Nanoparticles were prepared with different molar ratios of DMAEMA to HEMA and increasing TEGDMA concentrations. DMAEMA/HEMA nanoparticles were analyzed by TEM and dynamic light scattering. Fig. 1 depicts the TEM image of 10/90 DMAEMA/HEMA nanoparticles crosslinked by 3 mol\% TEGDMA. Photomicroscopic examination of the nanoparticles reveals a uniform, smooth surface morphology. The average diameter of DMAEMA/HEMA nanoparticles was determined to be 230±30 nm by evaluating nanoparticles in at least 5 electron microscopic fields. The average diameter of nanoparticles with different molar ratios (either 5/95 or 10/90) and different TEGDMA concentrations (either 3, 5, or 10 mol\%) were not significantly different after synthesis or when hydrated at pH 7.4. These results were confirmed by dynamic light scattering.

3.2. Volume swelling ratio

Monodispersed DMAEMA/HEMA nanoparticles that exhibit pH sensitivity were successfully prepared by O/W emulsification and subsequent photopolymerization. Swelling studies of nanoparticles from different formulations were performed in phosphate buffer adjusted to the appropriate pH. The data are presented in the form of the volume swelling ratio, which may be described as the ratio of the nanoparticle diameter at a specific pH to the diameter at pH 7.4 (\( Q = d_{\text{pH7.4}} / d_{\text{pH7.4}} \)). The volume swelling ratio was measured as a function of time to analyze the effect of DMAEMA content, pH, and TEGDMA concentration on particle degradation, pH sensitivity, and matrix elasticity.

The swelling behavior of DMAEMA/HEMA nanoparticles varies by formulation and pH conditions. Fig. 2 shows the average particle diameters of DMAEMA/HEMA nanoparticles with molar ratios of (a) 5/95 and (b) 10/90 DMAEMA/HEMA after swelling as a function of pH and time. It was observed that the swelling ratio of nanoparticles significantly increased with decreasing pH values for both 5/95 and 10/90 DMAEMA/HEMA molar ratios. The diameter of the 10/90 DMAEMA/HEMA nanoparticles at pH 6.8 (394 nm) was larger than at pH 7.4 (246 nm) after 4 h of swelling.

The nanoparticle with 5% DMAEMA (Fig. 2a) had lower volumetric swelling relative to the 10% DMAEMA nanoparticles (Fig. 2b). For example, 5/95 DMAEMA/HEMA nanoparticles...
Despite the differences in volumetric swelling, after 24 h both 5/95 and 10/90 DMAEMA/HEMA nanoparticles degrade to approximately half their initial diameter. This is primarily due to bulk erosion, where the rate of diffusion is less than the rate of hydrolysis [44]. The erosion number is the ratio of the time for water to diffuse into the gel to the time required for hydrolysis. For polyesters, the erosion number is typically less than 1 (a hydrolysis dominated regime). Therefore, changes in surface area do not significantly affect degradation.

To determine the swelling ratio as a function of crosslinker concentration, DMAEMA/HEMA nanoparticles (molar ratio of 10/90) were prepared with 3, 5, and 10 mol% TEGDMA. Swelling studies were performed in a pH 6.8 buffered solution to obtain maximal swelling. As shown in Fig. 3, the volume swelling ratio of 10/90 DMAEMA/HEMA nanoparticles decreases with increasing crosslinking density. After 4 h, the volume swelling ratio at pH 6.8 is 1.7, 1.2, and 1.0 for 3, 5, and 10 mol% TEGDMA. The swelling rate (and thus sensitivity to pH) of 10/90 DMAEMA/HEMA nanoparticles decreases from 40 nm/h at 3 mol% TEGDMA to 15 nm/h for 5 mol% TEGDMA. Particle degradation is also influenced by the crosslinking density. The average diameter of 10/90 DMAEMA/HEMA nanoparticles remains unchanged after 24 h when crosslinked with 10 mol% TEGDMA. Here, the increase in crosslinking density slows hydrolysis-mediated degradation.

The equilibrium swelling volume is a balance between the osmotic pressure of the protonated polymer network and the elasticity of the network. Consequently, the amount of DMAEMA incorporated affects the degree of pH sensitivity due to the content of quaternizable tertiary amine groups. Increasing the crosslinking density reduces matrix elasticity and particle degradation.

(Fig. 2a) swelled 42.4 ± 6.4% after 4 h at pH 6.8 while the 10/90 DMAEMA/HEMA nanoparticles (Fig. 2b) swelled 68.7 ± 9.0% under the same conditions. Due to the increased concentration of protonated groups, the higher DMAEMA content nanoparticle results in larger volumetric swelling.

The pH sensitivity of each formulation may be addressed by looking at the swelling rate, or change in diameter as a function of time. The swelling rate after 4 h for 5/95 DMAEMA/HEMA nanoparticles crosslinked with 3 mol% TEGDMA at pH 6.8, 7.0, 7.2, and 7.4 was 25, 14, 13, and ~1 nm/h, respectively. The swelling rate increases with DMAEMA content. Thus, the swelling rate after 4 h for 10/90 DMAEMA/HEMA nanoparticles crosslinked with 3 mol% TEGDMA at pH 6.8, 7.0, 7.2, and 7.4 was 40, 25, 10, and 4.3 nm/h, respectively. Hence, even a small pH change of 0.2 units (pH 7.4 vs. pH 7.2) results in an approximate 10-fold increase in swelling for 5/95 DMAEMA/HEMA nanoparticles or a 2-fold increase in swelling for 10/90 DMAEMA/HEMA nanoparticles.
3.3. Zeta potential

To determine the effective surface charge of 10/90 DMAEMA/HEMA nanoparticles, the zeta potential was measured at 4 different pH values (pH 6.8, 7.0, 7.2, and 7.4) as shown in Table 1. The zeta potential of the nanoparticles is consistently negative between pH 6.8 and 7.4. The zeta potential was $-12.4 \pm 2.3 \text{ mV}$ at pH 7.4 and approaches 0 at pH 6.8, $-1.9 \pm 1.0 \text{ mV}$. The strong negative charge arises from deprotonated hydroxyl groups of HEMA ($-\text{O}^-$). As the pH decreases, a proportion of the hydroxyl groups become protonated ($-\text{OH}$). In addition, DMAEMA becomes positively charged as the pH decreases, reducing the strong effective negative charge. Similarly, Hu et al. [19] reports of poly(DMAEMA) microgels with an isoelectric point at pH 6. Below pH 6, the zeta potential of the microgels is positive. Negative zeta potentials were obtained at pHs above pH 6.

A strong negative charge stabilizes the particles from aggregation. As the particles approach pH 6.8, the particle charge approaches 0. However, no aggregation was observed at pH 6.8.

3.4. Controlled release

We investigated the controlled release of paclitaxel from 10/90 DMAEMA/HEMA nanoparticles crosslinked with 3 mol% TEGDMA. This formulation had the largest volume swelling ratio (Fig. 2b) and swelling rate. Controlled release of paclitaxel was monitored by incubating nanoparticles in media with different pHs as illustrated in Fig. 4a. The encapsulation efficiency of the particles was 76 ± 3%, where drug loss occurs during subsequent washing of the particles.

Paclitaxel release is described by different initial slopes, reaching an asymptote after approximately 4 h. The volume swelling ratio coincidently reaches a maximum after 4 h, which demonstrates the relationship between swelling and release. Large swelling ($Q = 1.7$ in 4 h, at pH 6.8) results in a large release (54%, 4 h); whereas small swelling ($Q = 1.1$ in 4 h, at pH 7.2) results in slow release (13%, 4 h). Thus, the design of particles with a large swelling ratio should coincide with fast release.

Generally, the drug release rate is dependent on several factors, including: the polymer structure, concentration of polymer and crosslinker, the volume swelling ratio, and the interaction between polymer and drug. Among these factors, the volume swelling ratio most closely predicts the ability of paclitaxel to be released. The swelling of the nanoparticle structure at a lower pH leads to an increase in the network mesh size [45]. Changes in the network structure allows paclitaxel to diffuse out of the matrix within a short time compared to the compact network structure at pH 7.4.

Figure 4b shows that paclitaxel release is dependent on the crosslinker concentration. At low crosslinking density (3 mol% TEGDMA), paclitaxel is released quickly relative to nanoparticles prepared with 5 and 10 mol% TEGDMA. Increasing the TEGDMA concentration results in a higher degree of crosslinking and a reduction in mesh size. Paclitaxel release is reduced by 67% by increasing the TEGDMA concentration.
from 3 to 5 mol%. Thus, paclitaxel release can be optimized by varying the DMAEMA content, extent of crosslinking, and the pH of the environment.

3.5. Triggered release

We investigated the ability of DMAEMA/HEMA nanoparticles to show a triggered release profile. Here, 10/90 DMAEMA/HEMA nanoparticles prepared with 3 mol% TEGDMA were allowed to release paclitaxel in pH 7.4 buffered media. After 2 h, the pH was shifted downwards to either pH 6.8, 7.0, or 7.2 relative to the control (pH 7.4). As shown in Fig. 5, the release of paclitaxel from the nanoparticles is identical until the pH is changed. After the drop in pH, the release varies with pH.

For delivery to tumors, we are interested in intravascular administration of paclitaxel-loaded nanoparticles in a pH 7.4 environment. At pH 7.4, we desire minimal release of the chemotherapeutic drug. In the vicinity of the tumor microenvironment, which has a lower pH, the DMAEMA/HEMA nanoparticle would then release its payload. This would alter the biodistribution of paclitaxel which may result in a decrease in side effects. We expect that uptake of nanoparticles by healthy cells will occur at equivalent rates to nonstimuli-sensitive nanoparticles such as PLGA nanoparticles which measure similar zeta potential (−13 mV) [46]. The DMAEMA/HEMA particles would degrade quickly within the acidic environment of the cell’s endosome.

After delivery of paclitaxel-loaded nanoparticles, approximately 10% of the paclitaxel is released within the first 2 h at pH 7.4. As time progresses, the release is dependent on the microenvironment of the particles. If the microenvironment remains at pH 7.4, then 16% of the paclitaxel will be released over the 6 h period. However, if the pH of the environment decreases, drops to 7.2 or 7.0, then release of paclitaxel over 6 h increases to 22 and 30%, respectively. In the most dramatic case, when the pH drops to 6.8, then 45% paclitaxel will be released after 6 h. Thus, DMAEMA/HEMA nanoparticles may be used to control the rate of release and to trigger release within a local environment.

Other pH-sensitive carriers exhibit shrinking or degradation upon acidosis. Sulfonamides swell under basic conditions and shrink under acidic conditions [47]. Polyketal-based nanoparticles have been designed to undergo acid-catalyzed hydrolysis, which focuses on the degradation mechanism and not swelling [48]. Our formulation has controlled swelling only upon acidosis within a narrow range.

We have designed DMAEMA/HEMA nanoparticles to immediately release their payload after contact with a local pH stimulus. Fig. 6 demonstrates that these carriers are nontoxic to cells and have similar cell viability to PLGA nanoparticles [32]. We believe systemic administration is the best method to induce the delivery response. DMAEMA/HEMA nanoparticles may be used for tumorigenic cancer therapies but may also be used as a nano-scaled pressure sensor as described [49]. In addition, pH-sensitive nanoparticles may be useful in the treatment of ischemia, diabetic ketoacidosis, and in morphine overdoses.

Several hydrogel or microgel formulations incorporate DMAEMA for insulin delivery [24,50]. The particles will respond quickly if necessary, and in the absence of the stimulus will degrade slowly.

![Fig. 5. Triggered paclitaxel release was observed by incubating 10/90 (mol/mol) DMAEMA/HEMA nanoparticles crosslinked with 3 mol% TEGDMA for 2 h at pH 7.4 (△) followed by a reduction in pH to either 6.8 (●), 7.0 (■), or 7.2 (○) for 4 h. The error is the standard deviation of the mean, where n = 3.](image1)

![Fig. 6. Cell viability assay. 5/95 and 10/90 (mol/mol) DMAEMA/HEMA nanoparticles crosslinked with 3 mol% TEGDMA were incubated with HeLa cells for 24 h and compared to a control (without nanoparticles) for viable cell number. PLGA nanoparticles (average diameter 169.4 ± 11.8 nm) were also tested for cell viability for comparison of DMAEMA/HEMA nanoparticles. The error is the standard deviation from the mean, where n = 3.](image2)
4. Conclusions

Monodispersed pH-sensitive DMAEMA/HEMA nanoparticles were prepared for the pH-triggered delivery of paclitaxel. From the swelling studies, the nanoparticles (average diameter 230 nm) showed a high volume swelling ratio at low pH, low crosslinking density, and high content of DMAEMA. From the controlled release of paclitaxel, it was found that the release rate directly depends on the pH of the buffered media and crosslinker concentration. Paclitaxel was released quickly at low pH and low crosslinker concentration due to nanoparticle swelling and degradation. The nanoparticles were not cytotoxic as indicated by cell viability studies. As a pH-sensitive carrier, DMAEMA/HEMA nanoparticles may be useful in therapeutic treatment which involves a physiologically relevant, but small pH change; i.e. cancer therapy, gene delivery, ischemia, diabetic ketoacidosis, and morphine overdose.

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