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Novel Thermosensitive Hydrogel Composites Based on Poly(D,L-lactide-*co*-glycolide) Nanoparticles Embedded in Poly(*N*-isopropyl acrylamide) with Sustained Drug-Release Behavior

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ABSTRACT: To reach sustained drug release, a new composite drug-delivery system consisting of poly(D,L-lactide-*co*-glycolide) (PLGA) nanoparticles (NPs) embedded in thermosensitive poly(*N*-isopropyl acrylamide) (PNIPAAm) hydrogels was developed. The PNIPAAm hydrogels were synthesized by free-radical polymerization and were crosslinked with poly(ethylene glycol) diacrylate, and the PLGA NPs were prepared by a water-in-oil-in-water double-emulsion solvent-evaporation method. The release behavior of the composite hydrogels loaded with albumin–fluorescein isothiocyanate conjugate was studied and compared with that of the drug-loaded neat hydrogel and PLGA NPs. The results indicate that we could best control the release rate of the drug by loading it to the PLGA NPs and then embedding the whole system in the PNIPAAm hydrogels. The developed composite hydrogel systems showed near zero-order drug-release kinetics along with a reduction or omission of initial burst release. The differential scanning calorimetry results reveal that the lower critical solution temperature of the developed composite systems remained almost unchanged (<1°C increase only). Such a characteristic indicated that the thermosensitivity of the PNIPAAm hydrogel was not distinctively affected by the addition of PLGA NPs. In conclusion, an approach was demonstrated for the successful preparation of a new hybrid hydrogel system having improved drug-release behavior with retained thermosensitivity. The developed systems have enormous potential for many biotechnological applications. © 2014 Wiley Periodicals, Inc. J. Appl. Polym. Sci. **2014**, *131*, 40625.

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INTRODUCTION

The most challenging task in curing diseases is the delivery of drugs in a specific amount at a proper targeted site over a predetermined duration of time. That is the reason for the intensive research on the development of drug-delivery systems.[1–4] The final goal of these studies is to control drug release by the encapsulation of drugs into a specific delivery system to maintain an optimal therapeutic level, reduce side effects through the targeting of specific tissues, and improve patient compliance through a decrease in the frequency of administration. Different formulations, such as hydrogels, nanoparticles, and microparticles, have been developed for localized drug delivery in a minimally invasive manner. Moreover, these drug-delivery systems can protect drug structures from being captured by nonspecific receptors or rapid degradation in the bloodstream.

Hydrogels are three-dimensional polymeric networks with the ability to swell to several times their dry weight through the absorption of water and other biological fluids. Their structural similarity to the highly hydrated macromolecular-based structures in the body assures biocompatibility. Hydrogels are currently being considered for numerous biomedical and pharmaceutical applications, including drug-delivery devices, contact lenses, tissue-engineering scaffolds, biosensors, sutures, and components of microfluidic devices.[5]

Hydrogels exhibiting a phase transition in response to a change in the external conditions, such as pH, ionic strength,

temperature, and electric currents, are known as *stimuli-responsive* or *smart gels*.[6,7] The most famous temperature-sensitive hydrogel is poly(*N*-isopropyl acrylamide) (PNIPAAm), which undergoes a phase transition at a critical temperature known as the *lower critical solution temperature* (LCST). This means that below this critical temperature, the hydrogel swells in water, and above that, it expels water and collapses into a smaller volume. Pelton[8] explained that PNIPAAm chains have hydrophilic and hydrophobic domains below and above the LCST, respectively. It was stated that temperature-dependent interactions between PNIPAAm and solutes arise because of changes in the local environment around the hydrophobic isopropyl domains.

Hydrogels based on PNIPAAm have been studied extensively for drug-delivery applications.[9–12] The release of drugs in a sustained manner is one of the most important concerns in drug-delivery systems. However, hydrogels typically release drugs, especially proteins, by rapid diffusion in an initial short-lasting burst, which is followed by a slow and relatively constant release rate.[13] This burst release limits their applications and can also injure tissues around the injection site.

Other systems that can also be used as drug-delivery vehicles are polymeric microparticles and nanoparticles (NPs). NPs are frequently defined as solid, colloidal particles in the size range of 10–1000 nm.[14–16] Poly(D,L-lactide-*co*-glycolide) (PLGA), in particular, is one of the most common biodegradable and biocompatible polymers used for the controlled delivery of drugs.[17–20] The loading of a drug into microparticles or NPs can have advantages, including the isolation of the drug, a slower drug-release rate, and the achievement of different drug-release profiles. However, such systems typically do not result in constant drug-release profiles. PLGA usually displays a biphasic or triphasic release profile. Drugs usually release from PLGA with an initial burst; probably as a result of surface-associated drugs, followed by a minimal release phase before they enter into an approximate linear release profile when sufficient polymer degradation has occurred.[21–23]

To obtain sustained drug release, a few composite drug-delivery systems have been introduced in recent years. For instance, Zhang et al.[24] developed a smart drug-delivery system based on hydroxyl-functionalized glycerol poly(ε-caprolactone) microspheres and a PNIPAAm hydrogel to obtain the prolonged release of ovalbumin with an adjustable function to external temperature changes.

The entrapment of PLGA NPs in poly(vinyl alcohol) (PVA) hydrogels was also done to deliver insulin.[25] This system showed a reduction in both the release rate and the total released amount of insulin. A nearly zero-order release profile was observed in this research. Liu et al.[25] attributed this behavior to the fact that microcrystalline PVA domains formed at the PLGA NP surfaces, and this, thereby, significantly decreased the ability of water to partition into the NPs and decreased polymer degradation and drug release.

Another studied microsphere/hydrogel combination system was based on bovine serum albumin (BSA) and contained PLGA microspheres mixed with alginate gels. Lee and Lee[26] suggested that the release of a drug from this system could be controlled by changes in the mixing ratio between the PLGA microspheres and the alginate hydrogels. No remarkable effects were observed in the release profile when the total BSA content and the size of the PLGA microspheres were changed. They also proposed that this combined system could be used to deliver two or more different protein drugs in a sequential manner. This PLGA microsphere/alginate hydrogel system was also used to deliver recombinant human vascular endothelial growth factor. It was observed that the released recombinant human vascular endothelial growth factor remained bioactive and substantially enhanced endothelial cell proliferation for prolonged time periods *in vitro*. It also protected muscles adjacent to ischemic sites from ischemic stress and effectively regenerated active new arterioles and capillaries *in vivo*.[27,28]

In this study, a new hybrid drug-delivery system based on PNIPAAm hydrogels and PLGA NPs and loaded with albumin–fluorescein isothiocyanate conjugate (FITC–albumin) as a model drug was developed to achieve a sustained drug-release behavior. It was hypothesized that a system based on a combination of PLGA NPs and hydrogels could compensate for individual disadvantages and release drugs in a controlled manner.

EXPERIMENTAL

Materials

N-Isopropyl acrylamide (NIPAAm), *N,N,N′,N′*-tetramethylethylenediamine (TEMED; 99%), poly(ethylene glycol) diacrylate (PEGDA), PVA, FITC–albumin, and PLGA with a D,L-lactide to glycolide copolymer ratio of 50:50 were purchased from Sigma-Aldrich. Ammonium peroxodisulfate (APS) was obtained from Fluka. All chemicals were used as received without further purification.

Synthesis of the PNIPAAm Hydrogel

The PNIPAAm hydrogel was synthesized by free-radical polymerization. First, an aqueous solution of the monomer (1 g of NIPAAm dissolved in 10 mL of Milli-Q water) was prepared and stirred. TEMED as an accelerator was added to this solution. Then, the monomer solution was gradually added to an initiator solution containing 5 wt % APS as an initiator and 5 wt % PEGDA as a crosslinker. The solution was stirred with magnet at 200 rpm in an ice–water bath. After the formation of the gel, it was kept at 5°C overnight to complete the polymerization. The prepared hydrogel was cut into $1 \times 1 \times 1$ cm^3 cubes. Then, these hydrogels were immersed in a large excess of deionized water at room temperature for 3–5 days, and the water was refreshed twice a day to wash out unreacted compounds. Before further use or characterization, the polymerized gels were dried in a vacuum oven.

Preparation of the PLGA NPs

The PLGA NPs were prepared by a water-in-oil-in-water (w/o/w) double-emulsion solvent-evaporation method.[29] The inner aqueous phase was prepared by the dissolution of 10 mg of FITC–albumin in 0.5 mL of phosphate-buffered saline (PBS; pH 7.4). This phase was added to 100 mg of PLGA dissolved in 5 mL of dichloromethane. The aqueous solution was emulsified in the intermediate organic phase with a probe sonicator for 60 s (Hielscher, UP400S, Germany) at 50% amplitude in an ice bath. To obtain the double emulsion, this water-in-oil emulsion

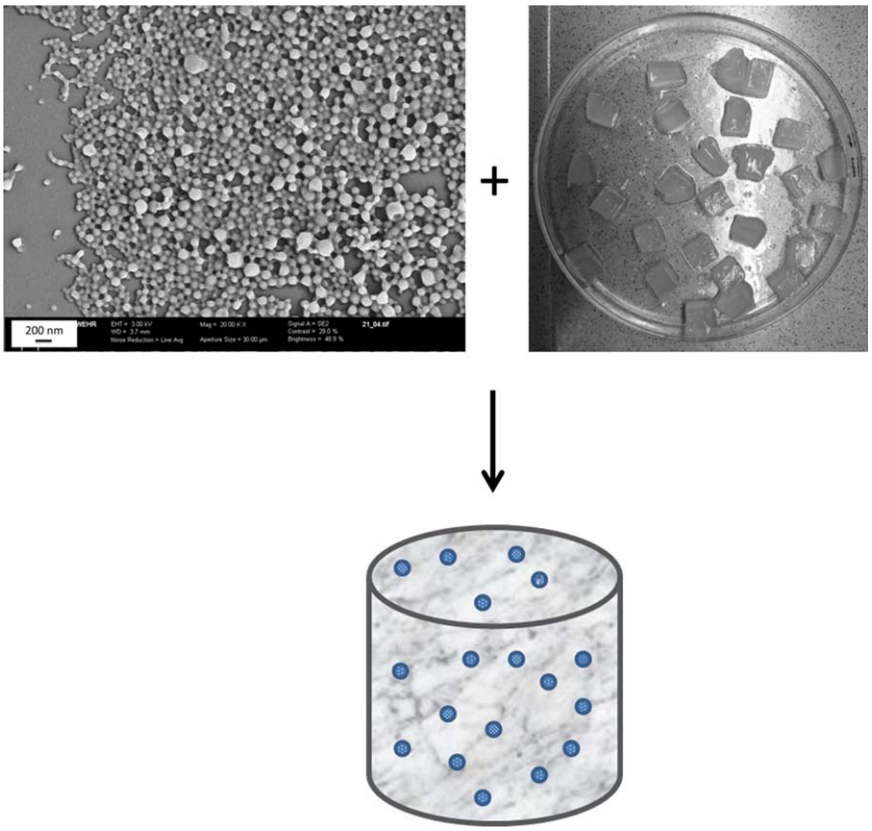

Figure 1. Schematic representation of the NP-loaded hydrogel. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

was emulsified with 20 mL of a second aqueous solution, which contained 400 mg of PVA. The homogenization was carried out with the same sonicator at 40% amplitude in ice bath and repeated three times, each for 40 s. To evaporate dichloromethane, the resulting double emulsion was stirred with a magnet for 4 h at room temperature. After that, the particles were centrifuged (Sigma 3K30, Germany) three times at 4°C each for 30 min at 20,000 rpm to purify them from residues of organic solvent and redundant PVA stabilizer. The particles were dried and collected by means of a Christ Alpha 1–2 LD lyophilizator.

Fabrication of the PNIPAAm Hydrogels Containing the Drug and Drug-Loaded PLGA NPs

To load the drug into hydrogels, the PNIPAAm dried gels were immersed in a drug aqueous solution with a concentration of 0.1 mg/mL drug for at least 3 days. Then, the swollen gels were taken out and washed with PBS.

To prepare the composite hydrogels (Figure 1), we added the drug-loaded PLGA NPs during the polymerization of NIPAAm in a manner similar to the procedure done by Zhang et al.[30] Aqueous solutions of the monomer and initiator were prepared as described earlier. In addition, the PLGA NPs, which were loaded with FITC–albumin, were dispersed in Milli-Q water. After the addition of the monomer solution to the initiator solution and before the gelation, the solution of PLGA NPs was added to the resulting solution. Mixing was continued until gelation occurred. The rest of the preparation procedure was the same as that of the neat hydrogels.

Characterization

Hydrogel Chemical Structure. The chemical structure of the synthesized hydrogels was confirmed by Fourier transform infrared (FTIR) spectroscopy. The PNIPAAm hydrogels were analyzed by an FTIR spectrometer (Bruker Equinox 55) in the region of 4000–400 cm^{-1} in the transmission mode. Before the tests, powdered samples were prepared by the grinding of the dried hydrogels. Then, about 1 part of the powdered samples was dispersed in 100 parts of KBr salt, and the obtained mixture was compressed to form disks.

Thermosensitivity of the Hydrogels. The LCST behaviors of the PNIPAAm hydrogel and the hydrogel containing PLGA NPs were tested by means of a differential scanning calorimetry (DSC) technique (Q 1000 Advanced TZEROTM Technology). Before the measurements, the hydrogels were immersed in Milli-Q water until they reached the equilibrium state. Thermal analysis was performed at a heating rate of 1°C/min from 0 to 50°C.

To measure the equilibrium swelling ratio, preweighted dried hydrogels were placed in 20 mL of PBS in a controlled temperature bath for 2 days. Then, they were removed, blotted with filter paper, and weighed again. This procedure was repeated three times, and the results are presented as the mean plus or minus the standard deviation.

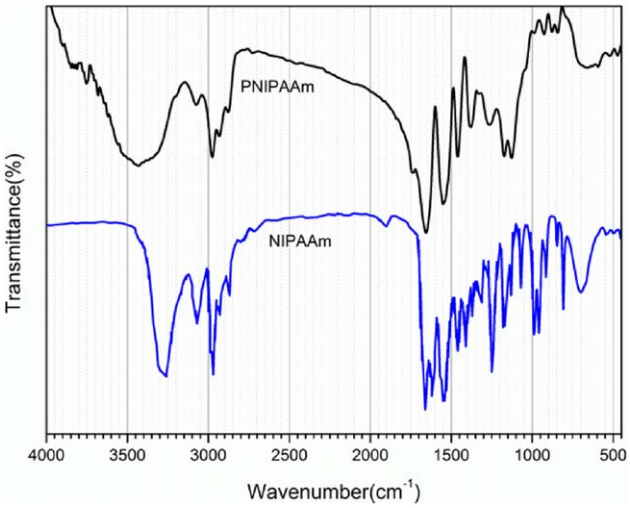

Figure 2. FTIR spectra of the NIPAAm monomer and the synthesized PNIPAAm hydrogel. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Morphological Studies. The size and morphology of the prepared PLGA particles and the microstructures of the composites system were measured and observed by scanning electron microscopy (SEM; Ultra Plus from ZEISS NTS). We prepared the SEM specimens by coating the samples with Pt. We measured the average particle size by measuring the diameter of over 100 particles with image analysis software.

***In Vitro* Drug Release.** To measure FITC–albumin release from the PNIPAAm hydrogels and the hydrogels containing PLGA, swollen samples were immersed in 10 mL of PBS at 37°C with mild stirring. At predetermined time intervals, 2 mL of the medium was withdrawn and replaced with fresh buffer. The concentration of drug in the collected samples was measured with an ultraviolet–visible (UV–vis) spectrophotometer (Specord 210 plus, Analytik Jena) at 490 nm.

To measure the drug concentration released from the PLGA particles, 15 mg of the dried particles was suspended in 10 mL of PBS and stirred with a magnet at 37 ± 1°C. At each scheduled time, 2.5 mL of released medium was removed. The released samples from the PLGA NPs were centrifuged for 5 min, and 2 mL of the clear supernatant of the released medium was collected. The precipitated particles were resuspended with 2 mL of fresh PBS and returned to the glass bottle. The supernatant was analyzed for the amount of released drug with a UV–vis spectrophotometer as described previously. The experiments were repeated three times. The average standard deviations were in the range of 1–5%.

RESULTS AND DISCUSSION

PNIPAAm hydrogels were synthesized by the free-radical polymerization of NIPAAm monomer. APS and TEMED were used as the initiator and accelerator, respectively. PNIPAAm hydrogels are usually crosslinked with *N,N′*-methylene bis(acrylamide). To obtain sustained release and a higher swelling ratio, some researchers have proposed PEGDA as a crosslinker.[31,32] Turturro et al.[12] prepared PNIPAAm hydrogels crosslinked by PEGDA and used them as an ocular drug-delivery system. They showed that the injection of this system to the retina did not have any long-term effects on retinal function. On the basis of these studies, in this study, PNIPAAm was crosslinked with PEGDA.

To confirm the formation of the hydrogels and to investigate their structure, the prepared PNIPAAm hydrogels were subjected to FTIR measurements. Figure 2 shows the FTIR spectra of the NIPAAm monomer and PNIPAAm hydrogel. As shown, the characteristic peaks of the NIPAAm monomer at 1407 cm^{-1} (CH_2═) and 1620 cm^{-1} (C═C) were not detectable in the FTIR spectrum of the synthesized hydrogel. This implied that the polymerization reaction had taken place. PNIPAAm showed a broad peak between 3200 and 3600 cm^{-1} due to N—H bond stretching. It was stated in the literature[33,34] that any change in the morphology of hydrogels changes their IR absorption spectra because of stretching and O—H vibration. The formation of coils or helixes, which is indicative of crosslinking, is indicated by the appearance of bands near 1648 cm^{-1}, which was observed in our PNIPAAm spectra at 1650 cm^{-1}.

The temperature sensitivity and LCST of the PNIPAAm hydrogels was observed by the investigation of their swelling behavior. The equilibrium swelling ratio of the hydrogels was measured gravimetrically on the basis of the following equation:

$$\text{Swelling ratio} = (W_s - W_d)/W_d \quad (1)$$

where W_s is the weight of the swollen hydrogel and W_d is the weight of the dry hydrogel.

Figure 3 shows the swelling ratio of the PNIPAAm hydrogels at different temperatures from 25 to 42°C. At room temperature, the equilibrium swelling ratio of PNIPAAm was around 28; this indicated that this hydrogel absorbed water to around 28 times its dry weight. As shown, a shift from water-swollen to a deswollen state happened between 31 and 34°C; this indicated the temperature range of the occurrence of the LCST. On the basis of the results from the FTIR and swelling ratio measurements, we concluded that the PNIPAAm hydrogels were formed and showed temperature sensitivity.

PLGA NPs were successfully prepared by the w/o/w double-emulsion solvent-evaporation method. The morphology of the

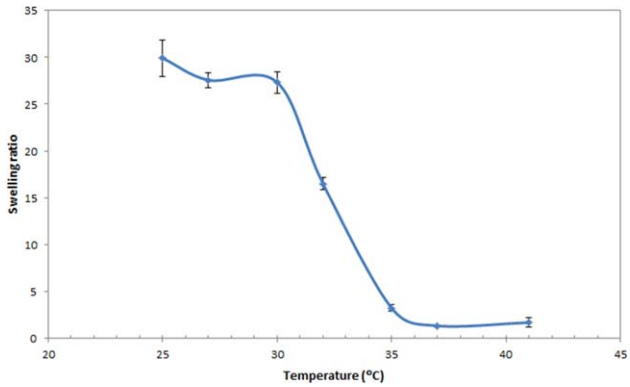

Figure 3. Equilibrium swelling ratio of the PNIPAAm hydrogels at different temperatures. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

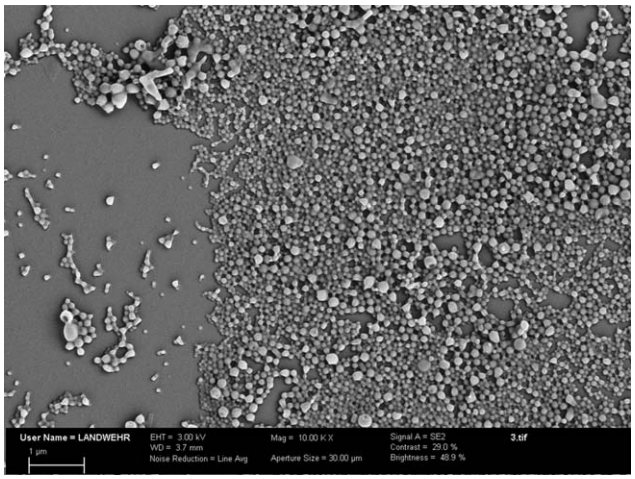

Figure 4. SEM images of the PLGA NPs prepared by the double-emulsion method.

NPs was observed by SEM (Figure 4). As shown in Figure 4, the particles had a smooth surface, and the average size of the particles was around 87 nm.

In the next step, hybrid systems based on drug-loaded PLGA NPs embedded in PNIPAAm hydrogels were fabricated. The SEM images presented in Figure 5 show the homogeneous dispersion of PLGA NPs within the PNIPAAm hydrogels.

To investigate the effect of the addition of PLGA NPs on the thermosensitivity behavior of the hydrogels, the LCSTs of the PNIPAAm hydrogel and hydrogel containing PLGA NPs were measured by DSC, and the results are presented in Figure 6. In the DSC diagram, the LCST is regarded as the intersection of the baseline and the leading edge of the endotherm peak, where

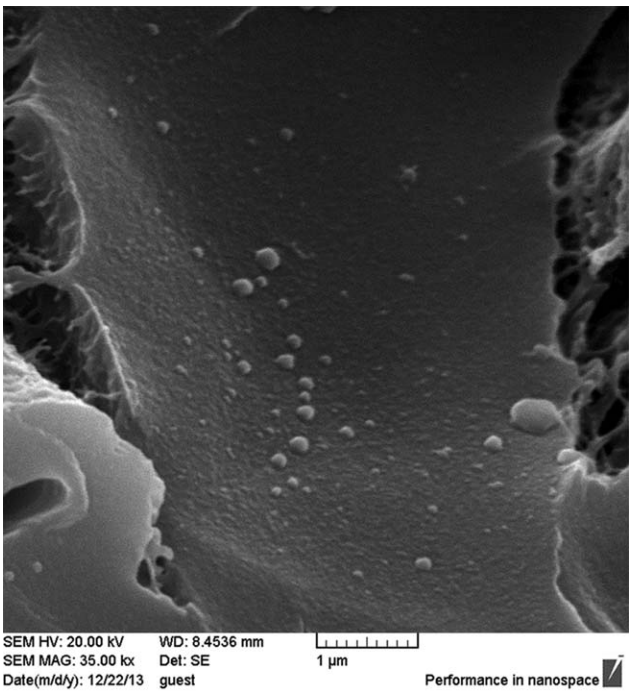

Figure 5. Interior morphology of the NP-loaded hydrogel system.

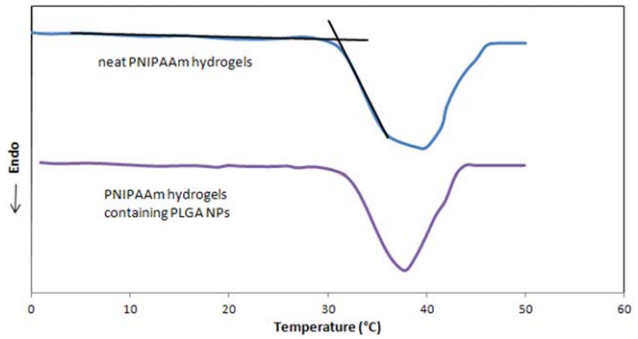

Figure 6. DSC results for the neat PNIPAAm hydrogels and the hydrogels containing PLGA NPs. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

the hydrophobic interactions of the isopropyl groups start to dominate the hydrophilic properties of the amide groups and the dehydration of the polymer chains occurs.[35] The results presented in Figure 6 indicate that the thermosensitivity behavior of hydrogel was not distinctively affected by the addition of the PLGA NPs. Compared to the neat hydrogels, the LCST of this composite system just increased by about 1°C.

The *in vitro* release behaviors of the drug-loaded hydrogels, NPs, and composite systems were studied in PBS solution at 37°C. The release of FITC–albumin from the PNIPAAm hydrogel versus time is demonstrated in Figure 7. As shown, when the drug was loaded directly into the hydrogels, an initial burst release occurred. This initial release was due to the compression of the hydrogel in response to temperature. About 60% of the loaded drug was released in the first few hours. Thereafter, the release of the remaining loaded drug continued for almost 10 days at a sustained rate.

On the other hand, when the drug was loaded into the PLGA NPs, the same behavior was observed with only a difference in the release duration. A huge initial release of FITC–albumin occurred during the first few hours. This type of initial burst release, which has also been observed by numerous other

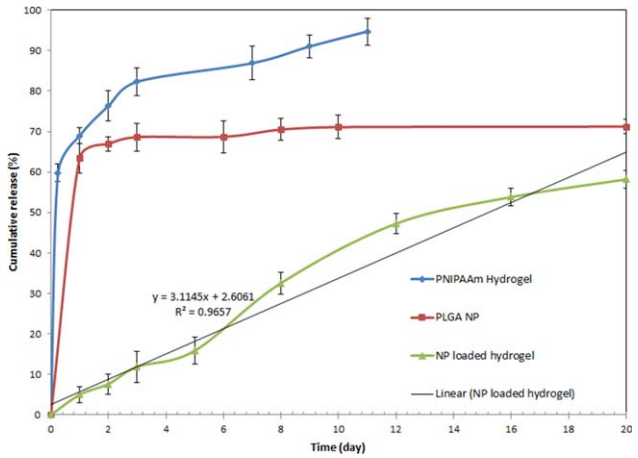

Figure 7. *In vitro* release of FITC–albumin from the PNIPAAm hydrogel, PLGA NPs, and PLGA–NPs entrapped in the PNIPAAm hydrogel (PBS, pH 7.4, 37°C). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

researchers,[21–23] has been attributed to the fraction of drug that is adsorbed or weakly bonded to the surface of the NPs.[18,36] The FITC–albumin-loaded PLGA NPs released the drug at a constant rate for a longer time (compared to the hydrogel), that is, over 3 weeks (Figure 7). This kind of release behavior pattern in the hydrogels and PLGA particles limits their application as drug-delivery systems. We hypothesized that a complex system based on NPs entrapped into hydrogels would show a totally new and different pattern.

In this study, a new thermosensitive drug-delivery system based on a combination of drug-loaded PLGA NPs and PNIPAAm hydrogels was prepared. During the synthesis of the neat hydrogel and PLGA/PNIPAAm composite, some samples were taken from the washing liquids and tested by UV–vis spectrometry for possible traces of the drug. In the case of the neat hydrogel, when the drug was loaded directly into the hydrogel, a small amount of drug (<2%) was released during each washing sequence. However, when the drug was loaded into the NPs and then embedded in the hydrogel, no detectable amount of drug was released.

To achieve gelation in the system that contained NPs, a higher percentage of crosslinker was needed. At first, PLGA-loaded hydrogels with strengths similar to those of the plain hydrogels were prepared. Their drug-release behaviors were investigated with the same method used for the drug-loaded hydrogels. However, no drug release from the complex system took place in the first days. This was probably due to the large size of the drug molecules and the tight network structure of the hydrogels. To achieve drug release from the composite system, the preparation procedure was repeated with a lower amount of crosslinker. In this case, hydrogels with a looser structure were obtained. FITC–albumin release from these composite systems is shown in Figure 7. As shown, this drug-delivery system showed no initial burst behavior, and drug release continued for 20 days.

When the drug was loaded into the PLGA NPs, which were embedded within PNIPAAm hydrogels, the drug passed through two barriers (after the FITC–albumin released from the NPs in the hydrogel composite, it needed to diffuse further through the hydrogel matrix) to diffuse into the bulk media. This, consequently, resulted in a lower initial burst effect and the NP loaded hydrogel showed an approximately linear profile, releasing 55–65% of the FITC–albumin within 20 days (Figure 7). The elimination or reduction of the amount of drug that was initially released suggested that the hydrogel acted as a reservoir, encapsulating the particles, retarding diffusion of the FITC–albumin, and also restricting the contact of NPs with the released medium.[26]

To identify the *in vitro* release characteristics, a linear trend line was fitted to the release data (Figure 7) and analyzed with a zero-order kinetics equation, and regression analysis was performed on this fitted curve. The fitted line showed that the drug release from the composite system was approximately linear, as indicated by its high R^2 value of 0.96.

The release characteristic of the developed PLGA/PNIPAAm composite systems showed a great potential to use these materials as novel drug-delivery vehicles with sustained release behavior.

CONCLUSIONS

In this research, PEGDA crosslinked PNIPAAm hydrogels were prepared by free-radical polymerization. The FTIR results confirm the formation of the polymer and crosslinked hydrogel. The LCSTs of the PNIPAAm hydrogels were investigated by DSC and the evaluation of their swelling behavior, and a distinctive shift from swollen to shrunken hydrogel was observed in the temperature range 31–34°C.

The other components of the complex system were PLGA NPs, which were successfully prepared by a w/o/w double-emulsion solvent-evaporation method and were characterized by SEM. The results show a mean size of 87 nm for the prepared PLGA particles.

The composite systems were fabricated, and the SEM images exhibited a homogeneous dispersion of PLGA particles in the PNIPAAm hydrogels. Studies on the LCSTs of the neat hydrogel and composite system investigated by DSC revealed that the addition of PLGA NPs to the PNIPAAm hydrogels did not change the LCSTs or the thermosensitive behavior of the system significantly.

FITC–albumin as a model protein drug was loaded into the PNIPAAm and PLGA NPs, and its release pattern was studied. An initial burst release followed by a constant slow release occurred in both the drug-loaded hydrogels and polymer NPs with a difference in the release duration. However, when the composite system based on the PNIPAAm hydrogel containing drug-loaded PLGA NPs was used, no significant immediate release was observed, and FITC–albumin was released in a sustained manner for 3 weeks. This change and the improvement in the release behavior was probably due to the existence of both particles and hydrogel barriers, which retarded the diffusion of the drug molecules and resulted in the reduction or omission of the initial burst release.

In conclusion, this study suggests a new approach to the control of drug (especially proteins) release behavior through a combination of PNIPAAm hydrogels and PLGA particles that could be useful in many delivery and biomedical applications.

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