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Heparin release from thermosensitive hydrogels

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Thermosensitive hydrogels (TSH) were synthesized and investigated as heparin releasing polymers for the prevention of surface induced thrombosis. TSH were synthesized with N-isopropyl acrylamide (NiPAAm) copolymerized with butyl methacrylate (BMA) (hydrophobic) or acrylic acid (AAc) (hydrophilic) comonomers. The incorporation of hydrophobic and hydrophilic comonomers strongly influences the swelling/shrinking behavior of TSH. Upon deswelling, gels containing the hydrophobic comonomer formed a skin-type layer, which acted as a rate controlling membrane, while the hydrophilic comonomer greatly increased gel swelling, relative to NiPAAm. Equilibrium swelling in isotonic PBS and deswelling kinetics of the synthesized gels were examined at various temperatures. The loading of heparin into the different gels was studied as a function of temperature, solution concentration, and gel composition. The release kinetics of heparin was found to be influenced by gel composition and loading temperature; the release correlated with the gel deswelling kinetics. In the case of NiPAAm/BMA gel, the release profile of heparin was affected by temperature dependent properties of the skin-type diffusional barrier formed on the gel surface.

Key words: Thermosensitive hydrogels; Heparin releasing polymers; Poly(N-isopropylacrylamide)

Introduction

Thermosensitive hydrogels (TSH) exhibit temperature dependent swelling in water due to the fact that their polymer-polymer and polymer-water interactions are strongly influenced by temperature. Hydrogels based on N-isopropyl acrylamide (NiPAAm) demonstrate a negative thermosensitivity i.e., they are highly swollen at low temperatures and deswell significantly with increasing temperature [1]. An abrupt change in swelling is observed around 32°C, the temperature corresponding to the lower critical solution

temperature (LCST) of poly(NiPAAm) [2]. At this temperature the entropy driven release of water molecules, structured around the hydrophobic isopropyl side chains, leads to the gel deswelling.

Recently, thermally reversible polymers and hydrogels applied in therapeutics and diagnostics were reviewed by Hoffman [3]. Okano et al. [4] discussed the application of temperature responsive membranes for controlled drug delivery. Utilization of TSH gels in molecular separations [5,6] enzyme activity controlling systems [7], and as a tissue culture substrates [8] have also been described. Okano et al. [9] and Bae et al. [10,11] demonstrated an "on-off" release profile in response to a stepwise tempera-

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ture change with NiPAAm based TSH modified with hydrophobic components. The “on-off” release profile was explained by the formation of a dense, less permeable surface layer of gel, described as a skin-type barrier. Formation of the skin was confirmed by the presence of water pockets on the disk surface, shown by optical microscopy. Surface skin layer formed upon a sudden temperature change, through gel shrinking temperature, because the gel surface deswelled and collapsed faster than the interior.

We propose the use of TSH as heparin releasing polymers for the prevention of surface induced thrombosis. Surface induced thrombosis occurs when a polymer surface contacts blood, stimulating the intrinsic clotting pathway [12]. One method to improve the properties of a blood contacting surface is the application of heparin releasing polymers [13,14]. Heparin, a well known anticoagulant, prevents fibrin formation by catalyzing the inactivation of thrombin by ATIII. Systemic administration of heparin, however, may cause serious side effects, such as thrombocytopenia and prolonged bleeding. Controlled release of heparin from the surface of a blood contacting device is advantageous over systemic administration because optimum anticoagulant activity is achieved at the blood-polymer interface with much smaller doses of drug, thereby decreasing side effects.

Heparin releasing polymers, studied so far, may be divided into two main types, ionically bound heparin polymers and polymers containing physically dispersed heparin. The first class of materials involves polymers with surface bound cationic groups [15–17]. Heparin is released from these polymers via an ion exchange mechanism with the ions circulating in blood. It has been shown, however, that positively charged surfaces exposed to blood may cause adverse reactions with platelets [18]. Therefore, to maintain the antithrombogenic properties of the polymeric surface, these materials require a relatively high heparin release rate, nearly $2.4 \mu\text{g}/\text{h}/\text{cm}^2$, as determined by Tanzawa et al. [17].

Materials containing heparin physically dispersed within the matrix exhibit antithrombo-

genic properties with a lower heparin release rate from the polymer. Silicone rubber containing physically dispersed heparin was examined by Hufnagel [19]. Ebert et al. [20] synthesized poly-(hydroxyethyl methacrylate) (p-HEMA) with dispersed heparin and prostaglandin. Their results showed that drug release from the gel matrix continued for 10 h, and 25% of heparin remained entrapped within the network. Lin et al. [21] dispersed heparin within a polyurethane network, and demonstrated patency of a rabbit arterio-arterio shunt for 5 h with a minimum heparin release rate of $0.24 \mu\text{g}/\text{h}/\text{cm}^2$.

The rationale of this manuscript is based on the properties of TSH offering unique flexibility as to the amount and kind of anticoagulant drug(s) which can be loaded into the gel. A TSH, exhibiting negative thermosensitivity, when immersed into a heparin loading solution at low temperature would swell and absorb the drug. At higher (body) temperature, the swollen gel would collapse and release heparin (Fig. 1). An initial rapid release of heparin, due to the squeezing effect of the collapsing polymer, is expected to be followed by a slow release of drug controlled by solute diffusion within the collapsed network.

Our gels are design to prevent surface induced thrombosis for short term applications (few days of contact with blood). The initial events occurring on the blood contacting surface are very important in controlling surface induced thrombosis. These events include almost immediate adsorption of the protein layer (within 5 min) and the subsequent activation of the intrinsic clotting pathway. If not prevented, thrombosis

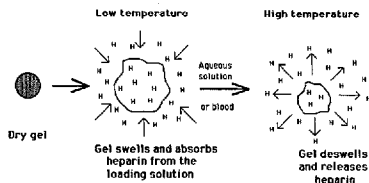


Fig. 1. Schematic representation of heparin loading and release from thermosensitive hydrogels.

occurs within minutes upon the contact of blood with a polymer surface. Initial local high concentrations of heparin at the blood contacting surface could be essential for deactivation of clotting factors. The subsequent slow release rate of heparin is expected to prevent surface induced thrombosis for up to 6 days. Future *in vivo* experiments will determine how long the heparin releasing system is bioactive.

Heparin releasing TSH, based on NiPAAm copolymers with butyl methacrylate (BMA) or acrylic acid (AAc) were designed. BMA comonomer, a hydrophobic component, was incorporated to study the influence of the skin-type diffusional barrier on the heparin release kinetics. AAc comonomer, a hydrophilic component, was added to increase gel swelling levels at physiological temperature. The following properties of synthesized gels were investigated: equilibrium swelling, deswelling kinetics, loading and release characteristics. Loading and release studies were conducted using commercial polydisperse heparin. The influence of the loading temperature on heparin release kinetics from gels containing BMA and AAc comonomers was also described.

Materials and Methods

Materials

N-isopropylacrylamide (NiPAAm), obtained from Eastman Kodak Company, was recrystallized from hexane. Acrylic acid (AAc), obtained from Aldrich, was purified by distillation under reduced pressure; fractions collected at 42–44°C/13 mmHg were used. Butylmethacrylate (BMA) was obtained from Polysciences, Inc. (Warrington, PA) and purified by distillation under nitrogen, the fraction at 57°C/17mmHg was collected. Ethyleneglycol dimethacrylate (EC₂MA) was obtained from Polysciences and used as received. 2,2'-Azobis-isobutyronitrile (AIBN) was obtained from Eastman Kodak Company, and recrystallized from methanol. Dioxane, HPLC grade, was obtained from Aldrich and used as received. Polydisperse heparin

sodium salt (mol. wt. 5,000–20,000), from porcine intestinal mucosa, was obtained from Diosynth, INC., and used as received. Isotonic phosphate buffer saline (PBS), pH=7.4, was used as a release medium and to prepare loading solutions.

Gel synthesis

Poly(NiPAAm) gels were synthesized with 5 mole% BMA (NiPAAm/BMA) or 2 mole% AAc (NiPAAm/AAc) comonomers in 50 wt% dioxane solution. EGDMA (1 mole%) was used as a crosslinking agent, and AIBN (7.4 mmol/l) was used as a free radical initiator. Reaction mixtures were bubbled with dry nitrogen for 20 min and then injected between two Teflon plates separated by a 1 mm thick rubber gasket. Polymerization was carried out at 65°C for 24 h. Gels, obtained in the form of films, were immersed in distilled water at room temperature and cut into disk shape samples. Disks were then Soxhlet extracted in ethanol for 48 h, and dried under vacuum before use. Obtained dried disks were 6 mm in diameter and 0.4 mm thick.

Swelling measurements

Equilibrium swelling properties of NiPAAm/BMA and NiPAAm/AAc gels were studied over a temperature range of 10–40°C in isotonic PBS. Disks were equilibrated for 3 days at each temperature to a constant equilibrium weight. Equilibrium swelling ratio, $S_{(eq)}$ was calculated from the following equation:

$$S_{(eq)} = (W_s - W_d) / W_d$$

where W_s denotes the weight of a swollen polymer, and W_d denotes the weight of a dry polymer.

For deswelling kinetic studies, gels were equilibrated in isotonic PBS at 1, 15, and 20°C to constant weight. Swollen disks were immersed directly in PBS pre-equilibrated at 37°C. The disks were removed from the 37°C buffer at predetermined times, the weight recorded, and the swelling ratio at time t , S_t , was calculated based on:

$$S_t = (W_t - W_d) / W_d$$

where W_t denotes the weight of a swollen polymer at time t .

Heparin loading

Heparin was loaded into NiPAAm/BMA and NiPAAm/AAC gels using solution sorption method. Heparin solutions (1.25–10.0 wt%) were prepared in isotonic PBS (pH=7.4). Heparin was loaded into the gels at 1, 15, and 20°C for 3 days. Before the immersion in the release medium, the disks were briefly rinsed with PBS (same temperature as the loading solution), and the surface blotted with a damp filter paper. Total loading was determined after extensive extraction in 1°C buffer solution. Loading percent was calculated as:

$$\text{Load\%} = \{W_{\text{drug}} / (W_{\text{polymer}} + W_{\text{drug}})\} \times 100$$

Heparin release

Heparin release from disk shaped samples was conducted at 37°C in PBS at pH=7.4. No drying procedure was applied to the loaded disks. Swollen disks were taken out of the loading solution, briefly rinsed with PBS (temperature of the loading solution), and immersed directly in the release medium. To maintain sink conditions, discs were transferred into 10 ml fresh PBS, preequilibrated at 37°C, at predetermined times.

The amount of released heparin was measured by the Azure II colorimetric assay [22]. In this assay the absorption of heparin-Azure II complex is measured at 500 nm. Samples (0.5 ml) of the release medium were added to 4.5 ml of 0.01 mg/ml Azure II solution in water and vigorously mixed on the Vortex mixer. Absorption of the solution was measured after 1 min, with water used as a reference.

Release profiles are presented as a fractional release of drug, and only the points corresponding to the release rates higher than 0.24 $\mu\text{g}/\text{cm}^2/\text{hr}$ are reported. Calculations of the release rates per surface area of the disk were based on disks dimensions at 37°C. After each release experi-

ment at 37°C the amount of drug that remained entrapped in the collapsed network was determined by extensive extraction of the disks at 1°C in PBS.

Results and Discussion

Equilibrium swelling properties

The results of equilibrium swelling of NiPAAm, NiPAAm/BMA and NiPAAm/AAC gels between 10–40°C in isotonic PBS are presented in Fig. 2. Gel composed of crosslinked NiPAAm deswells abruptly around 32°C, i.e. at the LCST of poly(NiPAAm), due to the entropy driven release of water molecules structured around the hydrophobic isopropyl side chains. This temperature, at which the gel collapse is observed, might be defined as a gel collapse temperature (GCT). Above the GCT only very small changes in the equilibrium swelling ratio occur with increasing temperature. It is possible to modify the GCT of a gel by copolymerization with more hydrophobic (HPB) or more hydrophilic (HPL) comonomers. HPB comonomer decreases the GCT, whereas the HPL comonomer increases the GCT.

As seen in Fig. 2, copolymerization of NiPAAm with BMA resulted in a lower GCT, as compared to the pure NiPAAm gel, and copolymerization with AAC, resulted in an increased

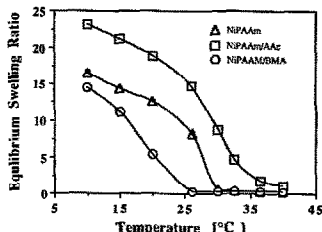


Fig. 2. Equilibrium swelling of NiPAAm, NiPAAm/BMA and NiPAAm/AAC in isotonic PBS. Error bars represent the standard deviation for $n=4$. For some data points error bars are smaller than the plot symbols.

GCT. NiPAAm/AAC gel showed the highest equilibrium swelling at each temperature studied, due to the hydrophilic contribution of AAC. Based on the equilibrium swelling curve (Fig. 2), the NiPAAm/AAC gel at 37°C contained 52% water, while the NiPAAm and NiPPAm/BMA gels contained 20% and 18% water, respectively. This is a significant difference from the point of view of the diffusion of hydrophilic macromolecules, such as heparin, at physiological temperatures.

Deswelling kinetics

In the proposed application of NiPAAm based gels, heparin loading takes place at low temperatures (high swelling levels), and the release occurs at 37°C (low swelling levels). Upon the immersion of the loaded, swollen gel in the release medium at 37°C, a significant volume change of the gel occurs due to deswelling. Hence, deswelling kinetics will greatly influence release profiles.

Fig. 3 presents the deswelling kinetics for NiPAAm/BMA gel preequilibrated at three different temperatures, 1, 15, and 20°C, and subsequently immersed at 37°C. Disks swollen initially at 1°C collapsed to their equilibrium state

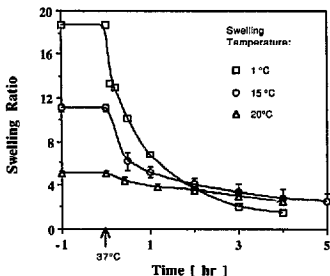


Fig. 3. Deswelling kinetics of NiPAAm/BMA gel equilibrated at three different temperatures (1, 15 and 20°C) and immersed at 37°C at time "0". Error bars represent the standard deviation for $n=4$. For some data points error bars are smaller than the plot symbols.

within 3 h, whereas disks swollen initially at 15 and 20°C remain swollen above their equilibrium water content for 24 h and 7 days, respectively. These data suggest that, in the case of NiPAAm/BMA gel, the rate of the deswelling process depends on the temperature of the initial equilibration.

As described by Okano et al. [9] and E.S. Matsuo [23], the sudden temperature change from 20 to 30°C leads to the formation of a dense, less permeable surface layer of NiPAAm/BMA gel, described as a skin-type barrier. Formation of the skin was confirmed by the presence of water pockets on the disk surface, shown by optical microscopy. A possible explanation for the surface skin layer formation is that upon a sudden temperature change, through GCT, the gel surface collapses faster than the bulk matrix.

In the present study, swollen NiPAAm/BMA gel was exposed to even larger temperature changes, from 1 to 37°C and from 15 to 37°C (Fig. 3). These results suggest that the properties of the skin-type barrier are influenced by the temperature difference between the initial and final medium. This temperature difference, in turn, determines the difference between the initial and final equilibrium swelling degrees (ΔS_{eq}). In cases where ΔS_{eq} is large, a significant hydrostatic pressure will build within the swollen disk. The high hydrostatic pressure of the entrapped water expands the water pockets, and only a thin and permeable skin will form on the surface. This temperature dependence of skin permeability lead to an observation that the release rate from swollen NiPAAm/BMA gels can be controlled by optimizing the initial loading temperature.

Fig. 4 shows the results of the deswelling kinetic studies of NiPAAm/AAC gel. Here, the deswelling profiles are independent of the initial temperature. NiPAAm/AAC gel showed the same rate of deswelling at 37°C, after equilibration at 1, 15 or 20°C. It can be concluded that free water efflux occurred in this case, and that a skin-type barrier did not form on the surface of a gel containing hydrophilic comonomer.

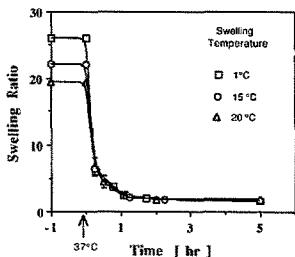


Fig. 4. Deswelling kinetics of NiPAAm/AAC gel equilibrated at three different temperatures (1, 15 and 20°C) and immersed at 37°C at time "0". Error bars represent the standard deviation for $n=4$. For some data points error bars are smaller than the plot symbols.

Loading studies

The following factors controlling heparin loading into NiPAAm based gels were examined: loading solution concentration, loading temperature, and the effect of comonomers. Fig. 5 illustrates the effect of the loading solution concentration on the loading percent of polydisperse heparin. NiPAAm/AAC gel was loaded with heparin at 15°C in isotonic PBS solutions containing 1.25–10 wt% heparin. A nonlinear loading profile at increasing concentration was observed, with the highest loading percent corresponding to 4–6 wt% heparin. Nonlinear loading can be explained by the corresponding swelling curve of NiPAAm/AAC gel in heparin loading solutions (Fig. 6), which shows that swelling of the gel decreases with increasing heparin concentration. Decreased swelling of gel with increasing solute concentration is due to the osmotic deswelling caused by decreased water activity in the solution. Hence, as the concentration of heparin increases, the gel is less swollen, and the free volume available for the diffusion of macromolecules is smaller. Heparin molecules with the highest molecular weight are probably excluded from gel and are the reason for an additional osmotic deswelling. A similar phenomenon was observed by Bastide et al. [24], who

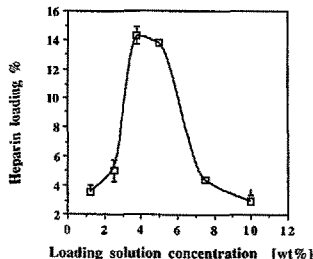


Fig. 5. Heparin loading into NiPAAm/AAC gel at 15°C. The effect of loading solution concentration on the loading percent of drug. Error bars represent the standard deviation for $n=3$.

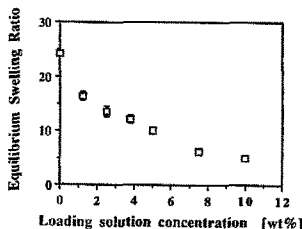


Fig. 6. Equilibrium swelling of NiPAAm/AAC gel in loading solutions of heparin. Error bars represent the standard deviation for $n=3$. For some data points error bars are smaller than the plot symbols.

described an osmotic deswelling of polymeric gels in solutions of macromolecules.

The effect of comonomers (AAC vs. BMA) and the loading temperature on heparin content in NiPAAm based gels is illustrated in Fig. 7. As shown, NiPAAm/AAC gel gave higher heparin loading percents at each temperature, compared to NiPAAm/BMA. Heparin content decreased significantly with increasing temperature for both gels. These results suggest that heparin loading depends on the gel equilibrium swelling. Since heparin and the NiPAAm/AAC gel are negatively charged, the loading is expected to be af-

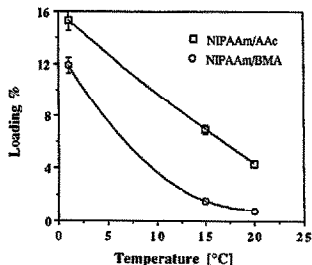


Fig. 7. Heparin loading into NiPAAm/BMA and NiPAAm/AAC gels. Loading temperature and comonomer effect. (5 wt% heparin loading solution in PBS was used).

ected by the ionic (repulsive) solute-matrix interactions. However, these experiments were conducted in isotonic PBS, and the concentration of ions is sufficient to screen the effect of charges. Therefore, based on the results presented in Fig. 7 it was assumed that in both NiPAAm/AAC and NiPAAm/BMA gels, heparin loading was controlled by the equilibrium swelling of gels.

In order to check whether heparin was actually diffusing into the core of the disks, loading experiments were performed with disks with different thicknesses. The results showed that comparable loading percentages ($\pm 2\%$) were obtained with disks having the same radius, but differing by a factor of two in thickness. Therefore, it can be concluded that disks are loaded homogeneously.

Release studies

Heparin release from NiPAAm thermosensitive hydrogels was studied as a function of loading temperature (1, 15, and 20°C) and a comonomer effect (BMA vs AAc). The release profiles presented in Figs. 8 and 9, show an initial high heparin release rate, followed by a significantly slower rate at later times. This suggests that initially, due to the dynamic squeezing of the collapsing polymer network, drug release was a result of a convective flow of heparin and water.

Later, at low swelling levels of gel, release was controlled by the diffusion of heparin from the collapsed network.

The effect of loading temperature was studied to verify the hypothesis suggested by the deswelling kinetics studies. That is, the release rate can be controlled by the temperature dependent skin-type barrier which forms on the surface of the NiPAAm/BMA gel. Fig. 8 illustrates the effect of the loading temperature on the heparin release rate from the NiPAAm/BMA gel. Disks loaded with heparin at 1, 15 or 20°C were immersed in the 37°C release medium. Obtained release profiles are the following: disks loaded at 1°C released 98% of heparin within 8 h, disks loaded at 15°C showed a more gradual release profile and released 95% of drug within 18 h, disks loaded at 20°C showed no heparin release at 37°C. In each case, all of the drug, which remained entrapped in the NiPAAm/BMA network at 37°C was released at 1°C. The various heparin release profiles obtained after loading at different temperatures can be explained by considering the equilibrium swelling ratio of a gel in the loading solution and the percent loading of drug, as summarized in Table 1. A comparison of these values with the release profiles presented in Fig. 8, leads to the conclusion that a higher initial equilibrium swelling combined with a higher loading

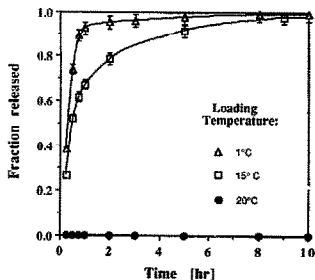


Fig. 8. Heparin release from NiPAAm/BMA gel at 37°C after loading at three different temperatures (1, 15 and 20°C). Effect of the loading temperature on the heparin release kinetics. (Error bars represent the standard deviation for $n=3$).

TABLE 1

Loading of heparin into NiPAAm/BMA gel. Heparin loading percentages and the corresponding equilibrium swelling ratios of gel in 5 wt% heparin loading solution at 1, 15 and 20°C.

Temperature	Heparin loading (%)	Swelling ratio in heparin loading solution
1°C	11.9 ± 0.2	9.7 ± 0.4
15°C	1.5 ± 0.3	5.3 ± 0.1
20°C	0.6 ± 0.2	1.8 ± 0.1

percent leads to the faster release rate. This conclusion correlates well with the results of the deswelling kinetics studies, where the higher initial equilibrium swelling resulted in a faster deswelling of NiPAAm/BMA gel (Fig. 3).

In the case of heparin release, however, the effect of the hydrophilic drug on the properties of the skin-type barrier should be also considered. Heparin attracts water and provides a more hydrophilic environment within the disk. It is thus possible that the properties of the rate controlling barrier are influenced by both the temperature gradient between the loading and release medium and by the content of a hydrophilic drug within the disk. Therefore, after loading at 1°C, (the highest equilibrium swelling and the highest heparin load percent) the thinnest and the most permeable skin is formed on the disk surface at 37°C, and as a consequence the fastest release is observed. Loading at 15°C results in a lower equilibrium swelling of the gel and also lower heparin content than those at 1°C. Hence, after loading at 15°C, a less permeable skin formed on the disk surface at 37°C, and a more gradual release profile of heparin was observed. These results show that in the case of NiPAAm/BMA gel, loading temperature can be used as a variable to control the heparin release rate.

After loading at 20°C, NiPAAm/BMA gel showed no release of heparin at 37°C, suggesting the presence of a dense skin on the disk surface. These results are consistent with the results obtained by Ibae et al. [10], who showed that by changing the temperature of the release medium from 20 to 30°C the release of drug stopped, due

to the formation of a skin-type barrier on the surface.

Heparin release profiles from NiPAAm/AAC gel loaded at 1, 15 and 20°C are presented in the Fig. 9. Loading percentages and the corresponding equilibrium swelling ratios in loading solutions are summarized in Table 2. All release profiles show similar kinetics, an initial rapid release due to the gel squeezing effect and a subsequent slow release of heparin controlled by the rate of solute diffusion through the collapsed network. Slightly higher release rates were obtained from disks loaded at 1 and 15°C due to the higher loading percentages of heparin at these temperatures. It could also be noted that the initial rapid

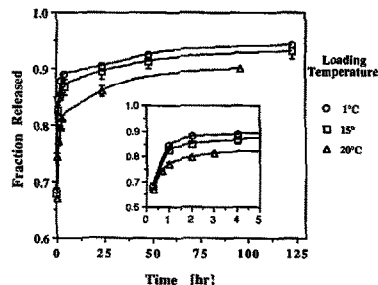


Fig. 9. Heparin release from NiPAAm/AAC gel at 37°C after loading at three different temperatures (1, 15 and 20°C). Effect of the loading temperature on the heparin release kinetics. The small inserted figure shows early times of the release, 0 to 5 h. (Error bars represent the standard deviation for $n=3$).

TABLE 2

Loading of heparin into NiPAAm/AAC gel. Heparin loading percentages and the corresponding equilibrium swelling ratios of gel in 5 wt% heparin loading solution at 1, 15 and 20°C

Temperature	Heparin loading (%)	Swelling ratio in heparin loading solution
1°C	15.3 ± 0.2	13.2 ± 0.1
15°C	6.9 ± 0.3	9.3 ± 0.1
20°C	4.3 ± 0.2	7.9 ± 0.1

release, which lasted for about 1 h, corresponded to the initial rapid deswelling of NiPAAm/AAC gel (Fig. 4). As was discussed, deswelling profiles of the NiPAAm/AAC gel equilibrated at 1, 15 and 20°C overlapped and did not show temperature dependence. Correlation between the deswelling curves and the heparin release profiles is in agreement with our hypothesis that the NiPAAm/AAC gel does not form a skin-type barrier on the surface, due to the presence of the hydrophilic comonomer.

A direct evaluation of the comonomer effect on the heparin release kinetics is illustrated by comparing the heparin release profiles of NiPAAm/BMA and NiPAAm/AAC gels loaded at the same temperature. Heparin release profile from NiPAAm/BMA gel loaded at 15°C is presented in Fig. 8, and the corresponding profile for NiPAAm/AAC gel in Fig. 9. After the initial squeezing, NiPAAm/BMA gel continued to release heparin for 15 h, whereas the NiPAAm/AAC gel showed a prolonged slow release of heparin for 124 h. This difference is related to the higher GCT of NiPAAm/AAC gel and higher swelling levels at 37°C. Equilibrium water content of NiPAAm/AAC gel at 37°C (52%) allows for diffusion of heparin macromolecules which remained in the gel network after the initial squeezing. NiPAAm/BMA gel contained only 20% water after 15 h at 37°C and also a dense skin was present on the disk surface, therefore, no further heparin release was observed.

The shape of the obtained release profiles is consistent with the behavior of swollen thermosensitive gels above their GCT. Upon a sudden temperature change, the collapsing polymer network squeezes the drug, and an initial rapid release is observed. This initial rapid release is followed by a slow release, where the drug release rate is controlled by the diffusion of solute within the collapsed network (NiPAAm/AAC gel), and/or by the presence of the skin-type rate controlling barrier (NiPAAm/BMA gel).

Conclusions

NiPAAm based thermosensitive hydrogels containing HPB or HPL comonomers were ob-

tained, and their application as heparin releasing polymers were examined.

Equilibrium swelling studies showed that incorporation of BMA (HPB comonomer) resulted in a lowering of the GCT of NiPAAm gels, and incorporation of AAC (HPL comonomer) resulted in the increase of the GCT.

Deswelling kinetics studies revealed that in the case of NiPAAm/BMA gel, the rate of deswelling depended on the temperature of the initial equilibration. This was due to the formation of a skin-type rate controlling barrier on the gel surface. NiPAAm/AAC gel showed the same rate of deswelling, independent of the temperature of the initial equilibration. It was concluded that a skin-type barrier does not form on the surface of NiPAAm gel containing a hydrophilic comonomer.

Loading studies showed that the amount of heparin loaded into NiPAAm/BMA and NiPAAm/AAC was controlled by the equilibrium swelling ratio of gels in the drug solution. Non-linear loading with increasing solution concentration was observed, with maximum loading corresponding to a 4–6 wt% heparin solution.

Studies of the heparin release from swollen NiPAAm/BMA and NiPAAm/AAC gels revealed that release profiles correlated with deswelling kinetics of gels. The release profiles showed two distinct kinetics controlled by different mechanisms: an initial rapid release due to the network collapse (squeezing effect) and the subsequent slow release controlled by the rate of solute diffusion within the collapsed matrix, and /or by the presence of a rate controlling barrier.

NiPAAm/AAC gels were obtained which released heparin with a rate greater than 0.24 $\mu\text{g}/\text{cm}^2/\text{hr}$ for 124 h. In the case of NiPAAm/BMA gel, the release rate was controlled by the temperature dependent properties of the skin-type rate controlling barrier which formed on the gel surface. This allowed for control of the release rate by changing loading temperature only, without polymer modification.

The results demonstrate loading and release of heparin using NiPAAm based TSH. These gels

may be applied as a polymeric coatings on the surface of a blood contacting devices for prevention of the surface induced thrombosis.

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