

## THERMALLY ON–OFF SWITCHING POLYMERS FOR DRUG PERMEATION AND RELEASE\*

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**Key words:** swelling; thermosensitive hydrogels; modulated drug delivery; poly(*N*-isopropylacrylamide); interpenetrating polymer networks

*The swelling of crosslinked poly(N,N'-alkyl substituted acrylamides) in water was studied in relation to changes in external temperature. The significant swelling changes of the polymer in water in response to temperature can be attributed to the delicate hydrophilic/hydrophobic balance of the polymer chain, and was affected by the size, configuration and mobility of the alkyl side chains on the substituted acrylamides. Sharp swelling transitions may occur at an optimum hydrophilic/hydrophobic balance and was found only in N-isopropylacrylamide network, among the tested networks.*

*Copolymers including crosslinked poly(N-isopropylacrylamide (IPAAm)-co-butylmethacrylate (BMA)) and interpenetrating polymer networks (IPNs) of poly(IPAAm) and polytetramethylene ether glycol (PTMEG) were also synthesized and investigated as modified IPAAm networks.*

*The gel shrinking behavior for a disk-shaped geometry (10 mm diameter, 0.7 mm thickness) with increasing temperature was affected by the gel composition and fabrication techniques. An important observation in these studies was that the initial shrinkage of the gel occurred on the surface of the membrane. The consequence of this phenomenon was that the outer surface (skin) formed a denser structure, as compared to the bulk of the membrane, which regulated water and subsequently solute transport.*

*To evaluate the controlled release aspects of these "thermosensitive" networks, indomethacin (a model drug) was solution loaded into the devices. The release of indomethacin from the gels correlated with the observed swelling properties. At low temperature, indomethacin followed pseudo-zero-order or first-order release kinetics, depending on the matrices, while at elevated temperatures indomethacin failed to diffuse out of the gels. This "on-off" release in response to temperature was restricted to a narrow temperature range. The lag time and release profile in the low temperature region of each temperature cycle was influenced by the composition of the copolymer or IPNs. In addition, the permeation of insulin and glucose through the same membrane demonstrated a similar on-off mechanism in response to temperature.*

## INTRODUCTION

The design of zero-order and modulated drug

releasing polymers has been an important subject in current pharmaceutical science research. Central to this research is the polymer science involved in the fabrication of the devices to achieve zero-order [1,2] or modulated drug release [3]. Approaches such as swelling-controlled, bioerodible, and stimuli-sensitive polymers have received much attention. Stim-

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uli-sensitive polymers respond to external signals, such as temperature, electric current, photoelectric, magnetic, and specific chemical or pH changes, in such a way as to modify conformation or interchain interactions. Ideally, a stimulus-sensitive polymer can sense the signal (outer stimulus) and release drug according to the strength of the signal. This type of response can be used in a self-regulating [4,5] or auto-feedback system, in which the released drug itself can effect a decrease of the signal.

There are many hydrogels which can modulate swelling in response to external stimuli such as pH [6–8], chemicals [9,10], photo irradiation [11], electric field [12,13], and so on. These polymers contain specific functional groups in their networks that are sensitive to the given stimuli. A gel collapse phenomenon (gel volume transition) by environmental changes has been predicted by Dušek and Patterson [14] and was intensively investigated by Tanaka and his coworkers in recent years [15–19].

A polymer network in an organic or aqueous solvent may have an intrinsic temperature dependence of swelling on the specific heat of mixing of the polymer chain and solvent. Most polymer networks show increased swelling in organic solvents with increased temperature, due to the enhanced compatibility of the chains and solvent, as predicted by conventional polymer solution theory [20]. However, the temperature dependence of hydrogel swelling may demonstrate a different pattern and is closely related to the chemical properties of the main chain and pendent groups. Aqueous solutions of some water-soluble polymers show phase separation on cooling; the maximum temperature for phase separation is termed the upper critical solution temperature (UCST). However, other polymers demonstrate demixing when the temperature is raised until a lower critical solution temperature (LCST) occurs [21].

Polymers which have an LCST in aqueous solutions can be utilized for specific swelling and drug release properties in response to temperature. Among water-soluble polymers, poly(*N*-

isopropylacrylamide) shows an LCST around 32–35°C [22,23] and its network demonstrated unique thermal volume transitions (gel shrinking) near its LCST. Poly(*N*-isopropylacrylamide) and its copolymers have been applied to several fields such as extraction [24], controlled release [25,26], and enzyme activity control [27,28].

This paper is a summary of our recent work with thermosensitive hydrogels [26,29–33]. Specifically, the alkyl side chain effects on thermosensitivity in swelling and the applications of modified *N*-isopropylacrylamide networks to the thermocontrol of solute transport will be discussed.

## EXPERIMENTAL

### Synthesis

The feed compositions for the networks of *N,N'*-alkyl-substituted acrylamides, IPAAm-co-BMA, and poly(IPAAm)/PTMEG IPNs are listed in Table 1.

### Crosslinked poly(*N,N'*-alkyl substituted acrylamides) [29]

All monomers were purified by distillation under nitrogen at reduced pressure. *N,N,N',N'*-tetramethylethylene diamine (TEMED) was used as a redox initiator, along with ammonium persulfate (AP) (coinitiator). *N,N'*-methylene-bisacrylamide (MBAAm) was used as a crosslinking agent and distilled-deionized water was used as a diluent. The polymerization mixtures were vigorously shaken for 15 seconds prior to injection into glass molds separated by a rubber gasket. After polymerization, the polymeric gels were separated from the glass molds and washed with distilled-deionized water to extract unreacted compounds.

### Crosslinked poly(IPAAm-co-BMA) [30,31]

A series of crosslinked *N*-isopropylacrylamide (IPAAm)/butylmethacrylate (BMA) co-

TABLE 1

The feed compositions for the polymer networks used in this work

a. For poly(*N,N'*-alkyl substituted acrylamides)

	AAM	DMAAM	EAM	APy	DEAM	IPAM
Monomer (g)	2.00	2.00	2.00	2.00	2.00	2.00
(mol)	0.0294	0.0202	0.0202	0.0160	0.0157	0.0177
MBAAM (g) <sup>a</sup>	0.0434	0.0311	0.0311	0.0246	0.0242	0.0272
AP (mg)	4	4	4	4	4	4
TEMED ( $\mu$ l)	40	40	40	40	40	40
Water	added to make a total 10 ml					
Temp. ( $^{\circ}$ C)	23	23	23	23	23	4
Time (h)	1	3	5	2	4	12

b. For crosslinked poly(NIPAAm-*co*-BMA)

Component	Sample code				
	R(100/0)	R(97.5/2.5)	R(95/5)	R(92.5/7.5)	R(90/10)
NIPAAm (g)	4.00	4.00	4.00	4.00	4.00
(mol)	$3.53 \times 10^{-2}$	$3.53 \times 10^{-2}$	$3.53 \times 10^{-2}$	$3.53 \times 10^{-2}$	$3.53 \times 10^{-2}$
BMA (g)	0.00	0.142	0.266	0.408	0.559
(mol)	0.00	$1.00 \times 10^{-3}$	$1.87 \times 10^{-3}$	$2.87 \times 10^{-3}$	$3.93 \times 10^{-3}$
EGDMA (ml)	0.070	0.072	0.074	0.076	0.078
(mol)	$3.71 \times 10^{-4}$	$3.82 \times 10^{-4}$	$3.92 \times 10^{-4}$	$4.03 \times 10^{-4}$	$4.14 \times 10^{-4}$
BPO (ml)	0.012	0.012	0.012	0.012	0.012
(mol)	$4.97 \times 10^{-5}$	$4.97 \times 10^{-5}$	$4.97 \times 10^{-5}$	$4.97 \times 10^{-5}$	$4.97 \times 10^{-5}$
1,4-Dioxane (ml)	4.00	4.13	4.27	4.41	4.56

c. For poly(NIPAAm)/PTMEG IPNs

Component	Sample code				
	IPN(100/0)	IPN(95/5)	IPN(90/10)	IPN(75/25)	IPN(50/50)
NIPAAm (g)	5.00	4.75	4.50	3.75	2.50
(mol)	$4.42 \times 10^{-2}$	$4.20 \times 10^{-2}$	$3.98 \times 10^{-2}$	$3.31 \times 10^{-2}$	$2.21 \times 10^{-2}$
EGDMA (ml)	0.083	0.079	0.075	0.063	0.042
(mol)	$4.40 \times 10^{-4}$	$4.19 \times 10^{-4}$	$3.98 \times 10^{-4}$	$3.34 \times 10^{-4}$	$2.23 \times 10^{-4}$
BPO (ml)	0.015	0.015	0.015	0.015	0.015
(mol)	$6.21 \times 10^{-5}$	$6.21 \times 10^{-5}$	$6.21 \times 10^{-5}$	$6.21 \times 10^{-5}$	$6.21 \times 10^{-5}$
PTMEG (g)	0.00	0.25	0.5	1.25	2.5
(mol)	0.00	$1.25 \times 10^{-4}$	$2.5 \times 10^{-4}$	$6.25 \times 10^{-4}$	$12.5 \times 10^{-4}$
Tri-NCO (g)	0.00	0.054	0.108	0.269	0.539
(mol)	0.00	$8.40 \times 10^{-5}$	$1.68 \times 10^{-4}$	$4.19 \times 10^{-4}$	$8.39 \times 10^{-4}$
DMSO (ml)	5.00	5.00	5.00	5.00	5.00

<sup>a</sup>1 mole% of monomer.

polymers were synthesized using ethyleneglycol dimethacrylate (EGDMA) as a crosslinker, t-butylperoxyoctanoate (BPO) as an initiator, and distilled 1,4-dioxane as a diluent. The solutions were bubbled with dried nitrogen for 20 min and injected between two Mylar<sup>®</sup> sheets separated by a rubber gasket and backed by glass plates. Polymerizations were performed at 80°C (constant temperature oven) for 40 hours. After cooling to room temperature, the membrane was separated from the Mylar sheets and immersed in 100% methanol to remove all unreacted water-insoluble compounds. The methanol solution was changed daily for two weeks, then soaked in 75/25 v/v% and 50/50 v/v% methanol/distilled water mixtures for one day each. The final washing was pure water for one day.

#### **Poly(IPAAm)/PTMEG IPNs [31,32]**

Simultaneous interpenetrating networks of poly(IPAAm) and polytetramethylene ether glycol (PTMEG) were synthesized. The reaction involved the free radical polymerization of NIPAAm to form a network and a condensation reaction between PTMEG and a triisocyanate to form the second network.

IPAAm, EGDMA, BPO, PTMEG and 1,1,1-tris[*N*-(4'-methyl-3'-isocyanatophenyl) carbamoyloxymethyl]propane (triisocyanate) were warmed with hot water to assure a clear solution in dimethyl sulfoxide (DMSO) and injected between siliconized glass plates separated by a rubber gasket. Polymerization and crosslinking reactions for both networks were conducted at 80°C for three days. DMSO and the unreacted compounds were extracted by soaking in water/methanol mixtures (50/50 v/v%) for one week.

#### **Swelling**

Different-size samples ( $n=3$ ) (3–10 mm diameter disks) of each polymer were dried at room temperature for one day and then vacuum dried at 50°C for three days. After immersing

in water at a desired temperature (the initial temperature was 60°C), the polymer samples were removed from the water and tapped with filter paper to remove excess water on the sample surface. The polymer samples were weighed at given time intervals at a fixed temperature ( $\pm 0.1^\circ\text{C}$ ) until the weight change was less than 0.5%. After equilibration at one temperature, samples were re-equilibrated at a lower temperature. The weight swelling ratio,  $(W_s + W_p)/W_p$ , was used, where  $W_s$  is the absorbed water weight and  $W_p$  is the dried polymer weight.

#### **Permeation experiments**

Insulin and glucose permeation experiments were conducted using a two-chamber diffusion cell separated by the swollen membrane equilibrated in PBS (pH 7.4) at the desired temperature. Each cell had a volume of 1.5 ml and an effective diffusional area of 0.55 cm<sup>2</sup>. Stirring was achieved by a small Teflon propeller driven by a 150 rpm constant-speed motor. Permeability measurements of <sup>14</sup>C-labelled insulin and glucose were carried out at 20°C and 30°C by step-wise temperature changes of the water bath during the experiments at predetermined times. The step-wise temperature change was obtained by moving the diffusion cells between two water baths maintained at 20°C and 30°C, respectively. The initial concentration of insulin in the donor chamber was 2 µg/ml. This concentration was low enough to avoid considerable insulin aggregation during the experimental period [34].

#### **Drug loading**

Dried poly(IPAAm-co-BMA) disks were equilibrated for three days in a saturated solution of indomethacin in ethanol/water (80/20 v/v%) at room temperature. IPNs composed of poly(IPAAm) and PTMEG were equilibrated in a saturated indomethacin solution in t-butanol/ethanol/water (60/20/20 v/v/v%) for

three days. The water/ethanol mixture required vacuum drying of the swollen disks for one day at  $-15^{\circ}\text{C}$  and three days at  $23^{\circ}\text{C}$  to prevent drug migration to the surface [35]. In the case of the butanol/ethanol/water mixture, the swollen gels were vacuum dried by gradually increasing the temperature from  $-23^{\circ}\text{C}$  to  $23^{\circ}\text{C}$  during six hours, and maintaining them at  $23^{\circ}\text{C}$  for more than one week to evaporate the residual *t*-butanol.

### Drug release

Indomethacin release experiments were conducted in a constant-temperature PBS solution (pH 7.4, 1 l) equipped with an external stirrer. The concentration of released drug was monitored by taking 3 ml aliquots of the media at specific time points, replacing the solution with fresh PBS and determining the drug concentration at 265.9 nm on a UV spectrophotometer (Perkin Elmer Lambda 7).

## RESULTS AND DISCUSSION

### Thermo-sensitive polymeric hydrogels

The LCST phenomenon has been characterized by negative enthalpy of mixing and negative entropy of mixing [36,37]. In an aqueous system, these conditions are associated with hydrogen bonding or hydrophobic interactions. Taylor and Cerankowsky [38] reported several examples concerning LCST formulation in an aqueous system by copolymerization of hydrophilic and hydrophobic monomers or changing side group hydrophilicity in repeat unit. Recently, Priest et al. [22] also showed LCST changes with *N*-isopropylacrylamide copolymers by varying comonomer composition.

The relation between alkyl group and aqueous swelling for crosslinked poly(*N,N'*-alkyl substituted acrylamides) (poly(ASAAM)) were

studied in relation to temperature changes, as shown in Fig. 1. Each swelling curve in this figure represents a specific poly(ASAAM) as described in the legend. Poly(acrylamide) (poly(AAm)) shows a slight increase in water swelling with increased temperatures. This "thermosensitivity" is characteristic of strongly hydrogen-bonded polymers, such as poly(acrylic acid). The decreased swelling of poly(AAm) at low temperature, as compared to the other alkyl-substituted acrylamide gels, can be explained by a different degree of crosslinking density or enhanced intramolecular hydrogen bonding at low temperatures. The increased swelling at elevated temperatures may be attributed to the weakened hydrogen bonding interactions among side groups. The equilibrium swelling of all the other polymer networks decreased with increased temperature.

The temperature dependence, i.e., a more pronounced deswelling or gel collapse with increased temperature, followed the trend: poly(*N,N'*-dimethylacrylamide) < poly(*N*-ethylacrylamide) < poly(*N*-acryloylpyrrolidine) < poly(*N,N'*-diethylacrylamide) and <

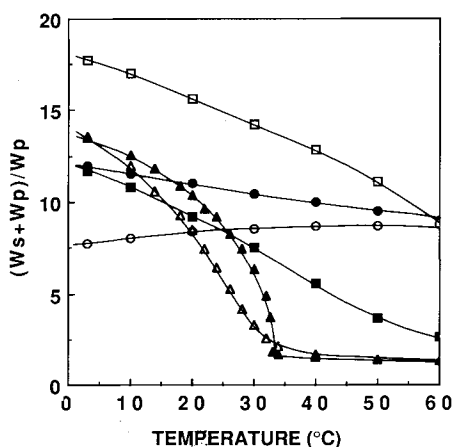


Fig. 1. The weight swelling ratio,  $(W_s + W_p)/W_p$ , of cross-linked poly(*N,N'*-alkyl substituted acrylamides) in water as a function of temperature: (□) crosslinked poly(EAAM); (●) crosslinked poly(DMAAm); (○) crosslinked poly(AAm); (■) crosslinked poly(APy); (▲) crosslinked poly(IPAAM); (△) crosslinked poly(DEAAM).

poly(*N,N'*-isopropylacrylamide). In the case of poly(*N*-isopropylacrylamide) (poly(IPAAm)), the thermosensitivity is close to that of poly(DEAAm) (below 30°C) and it demonstrates a sharper swelling transition at 33°C.

Considering these results and monomer

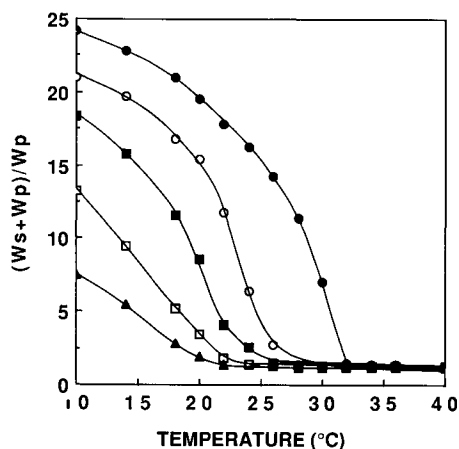


Fig. 2. The weight swelling ratio of crosslinked poly(IPAAm-co-BMA) in water as a function of temperature: (●) 0 mole% BMA; (○) 2.5 mole% BMA; (■) 5 mole% BMA; (□) 7.5 mole% BMA; (▲) 10 mole% BMA.

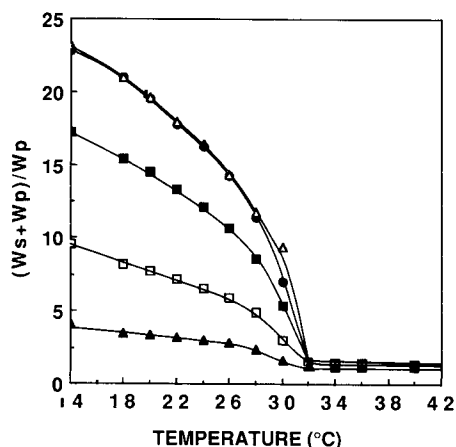


Fig. 3. The weight swelling ratio of poly(IPAAm)/PTMEG IPNs in water as a function of temperature: (●) 0 wt% PTMEG; (△) 5 wt% PTMEG; (■) 10 wt% PTMEG; (□) 25 wt% PTMEG; (▲) 50 wt% PTMEG.

structures, that is, unsubstituted (AAm), monosubstituted (EAAM, IPAAM), disubstituted (DMAAM, DEAAm, APy (five-membered ring)) monomers, it was suggested that the size and stereospecific configuration of the alkyl group on the backbone may affect the thermosensitivity more than the total hydrophobicity. In addition, the mobility of the side chain may contribute the hydrophobicity or thermosensitivity [29].

The copolymerization of IPAAM with butyl-methacrylate (BMA) and the synthesis of interpenetrating polymer networks (IPNs) of poly(IPAAm) with poly(tetramethylene ether glycol) (PTMEG) are two methods to modify the temperature dependence of swelling and the gel shrinkage of poly(IPAAm) hydrogel.

The effect of copolymerization of IPAAM with BMA and IPNs of poly(IPAAm) with PTMEG on the thermosensitivity of aqueous swelling are shown in Figs. 2 and 3, respectively [31]. The copolymer system revealed that gel shrinking occurred at lower temperature regions with a gradual deswelling. This was a function of increased BMA content in the copolymer. In the case of IPNs, the gel shrinkages of all the polymers occurred near the same temperature, regardless of the composition, as shown in Fig. 3. The PTMEG network in the IPNs may not affect the intrinsic property of poly(NIPAAm), yet it may affect the overall hydrophobicity of the system, resulting in less swelling and reduced thermosensitivity with an increased PTMEG content. If copolymer networks and IPNs are combined, the required thermosensitivity and gel shrinking behavior for specific applications could easily be designed.

### Surface skin layer mediated swelling change

An interesting consequence of this gel shrinkage was observed for both copolymers and IPN matrices. When the temperature increased pass the gel shrinking temperature, the

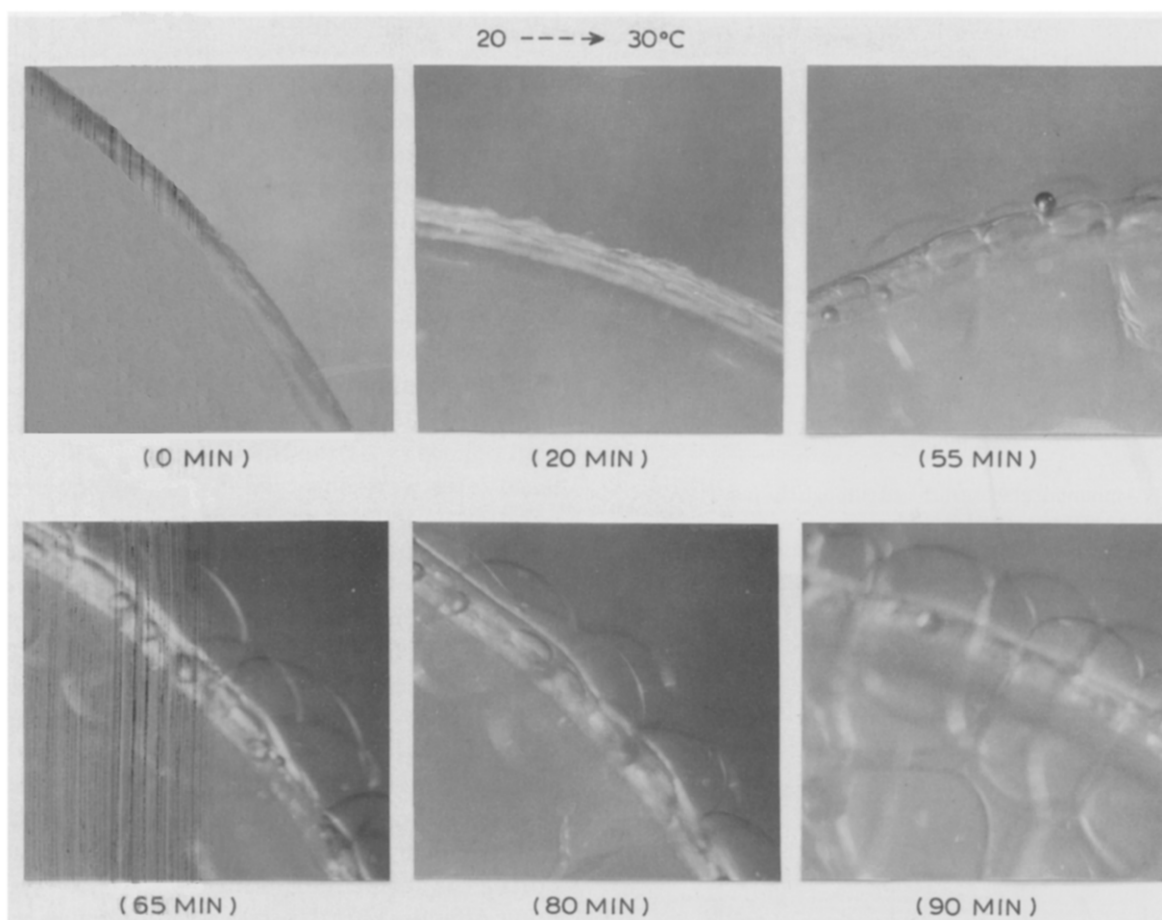


Fig. 4. Photographs of deswelling process of poly(IPAAm-co-BMA) (97.5/2.5) when the temperature is raised from 20°C to 30°C.

outer surface was the first area to be affected, and was found to be denser than the bulk matrix. This layer on the surface of the gels was dense enough to retard the flux of water out of the membranes. This resulted in irregular deswelling in the gels with the formation of bubbles at the surface; the size of these bubbles increased with time. Equilibrium deswelling at the higher temperature took more than one month. An example of the process of deswelling of poly(IPAAm-co-BMA) when the temperature was changed from 20°C to 30°C is shown in Fig. 4.

#### On-off permeability control

The permeability of glucose and insulin, Figs. 5 and 6 respectively, across the poly(IPAAm-co-BMA) membrane consisting of 5 mole% BMA in response to step-wise temperature fluctuations between 20°C and 30°C were studied. In the case of glucose, a constant permeation rate was observed during the first four-hour period at 20°C. When the temperature increased to 30°C, the permeation of glucose ceased for 20 hours. The insulin permeation experiment showed similar results, except that there was a small lag time during the initial 20°C and second 20°C period. Upon the sud-

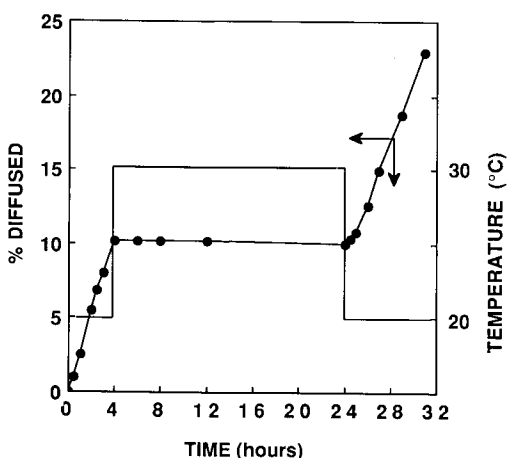


Fig. 5. Amount of glucose diffused through the poly (IPAAm-co-BMA) (95/5) membrane in response to step-wise temperature change between 20°C and 30°C in PBS (7.4).

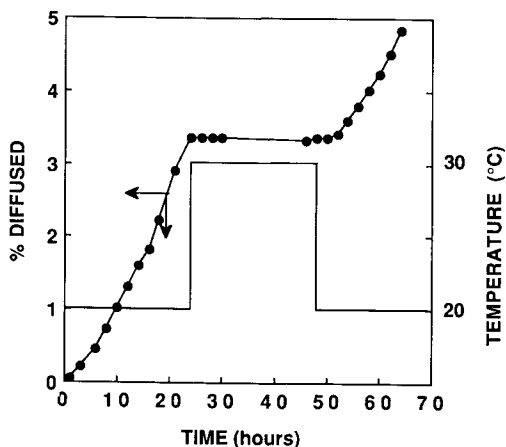


Fig. 6. Amount of insulin diffused through the poly (IPAAm-co-BMA) (95/5) membrane in response to step-wise temperature change between 20°C and 30°C in PBS (7.4).

den temperature change from 20°C to 30°C, insulin permeation was completely blocked without any time lag, as was the case for glucose permeation.

This rapid on-off permeation control in response to temperature fluctuations can be explained by the surface response (dense and rapid surface layer formation in deswelling) to temperature rather than bulk swelling change.

### On-off release control

The loading content of indomethacin was determined by the total amount of released indomethacin until no drug release was detected by UV, and was determined to be 26 wt% for poly(IPAAm)/PTMEG IPNs (90/10 weight ratio) and 21.4 wt% for poly(IPAAm-co-BMA) (95/5 mole ratio).

Using these monolithic devices, indomethacin release was investigated by step-wise temperature changes between 25°C and 35°C or 25°C and 30°C. Figure 7 shows the indomethacin release rate from the IPN matrix. High release rates were observed during the low temperature period and no release rate was observed during high temperature period. Again, an "on-off" pattern of drug release was confirmed, even though lag times were observed during the initial periods at different temperatures.

A possible mechanism for on-off drug release is schematically represented in Fig. 8. During the "off" process (increased temperature), the surface of polymer may shrink before the bulk material. This action may cause the drug partitioned near the surface to be squeezed out during the surface shrinking to show the initial burst effects. This dense surface structure will then slow or prevent further drug release. During the "on" process (low temperature), the shrunken surface layer starts to reswell and can allow drug release after a certain period, depending on the time for minimum reswelling of the surface. Another possible aspect affecting the drug release pattern during the "on" period may be drug solubility at different temperatures and a redistribution of drug and water concentration profiles during the "off" period.

The temperature which triggers drug release in a dynamic situation with this system was estimated to be around 28.5°C–30°C [32]. The "on-off" temperature for the IPNs/indomethacin device is a few degrees lower than the swelling transition of the unloaded matrix. This may be due to indomethacin interacting with the polymer matrix to alter the hydrophobicity



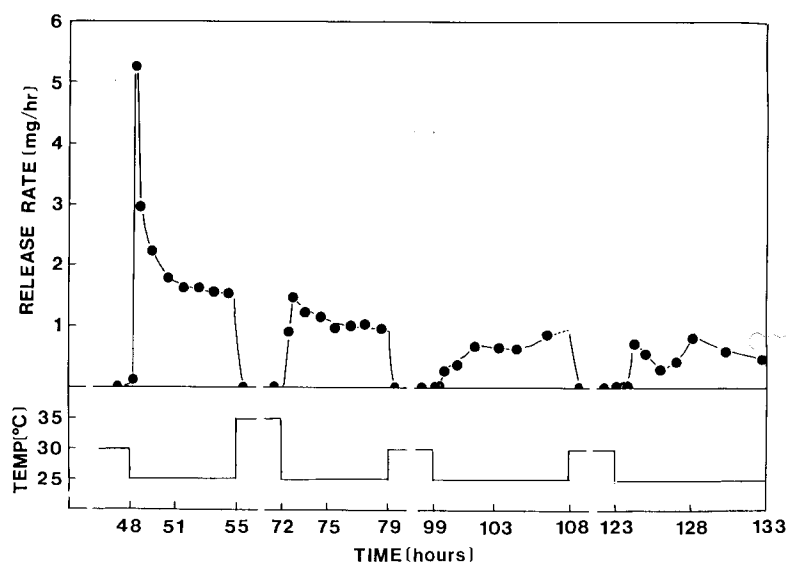


Fig. 7. Pulsatile release rate of indomethacin from poly(IPAAm)/PTMEG IPNs (90/10) in response to step-wise temperature change in PBS (pH 7.4).

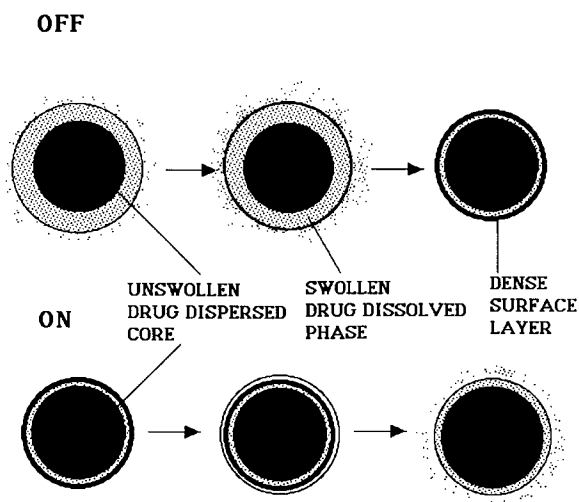


Fig. 8. Schematic illustration of on-off drug release in response to temperature fluctuation through the swelling transition temperature.

of the poly(IPAAm) chain, which is similar to the solute effects on LCST [38].

Another clear “on-off” release of indomethacin from poly(IPAAm-co-BMA) (95/5 mole ratio) in response to a step-wise temperature change between 20°C and 30°C was reported by Bae et al. [26]. In this case, enhanced burst

effects and minimal lag times were observed. This observation is different from the case of the poly(IPAAm)/PTMEG IPNs and may have resulted from a more rapid response of the gel surface to the temperature, compared to the IPN system.

## SUMMARY

The “negative thermosensitivity” (decreased swelling at increased temperature) of the studied crosslinked poly(*N,N'*-alkyl substituted acrylamides) was determined to be a function of the specific hydrophilic/hydrophobic balance effects and the configuration/mobility of pendent side chains of the polymers.

Among the tested *N,N'*-alkyl substituted acrylamide networks, only poly(IPAAm) demonstrated a sudden swelling transition at a specific temperature. This temperature and swelling transition behavior is sensitive to the comonomers which are directly incorporated into the IPAAm network. The incorporation of a hydrophobic component, as an independent

network in an IPN device, did not influence the swelling transition temperature.

A significant observation in this study was the formation of a dense surface layer during rapid surface deswelling, which was shown to affect subsequent drug release.

“On-off” solute release and permeation through modified IPAAm networks were regulated by the swelling/deswelling aspects of the surface, rather than the bulk matrix. An “on-off” temperature regulation of solute release was demonstrated in this experiment, and the drug release pattern may be affected by the specific chemical and physical properties of the polymer and the applied temperature.

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