Polymer Journal, Vol. 22, No. 3, pp 250—265 (1990)

# A Thermo-Sensitive Hydrogel: Poly(ethylene oxide-dimethyl siloxane-ethylene oxide)/Poly(*N*-isopropyl acrylamide) Interpenetrating Polymer Networks II. On-Off Regulation of Solute Release from Thermo-Sensitive Hydrogel

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(Received September 7, 1989)

ABSTRACT: Interpenetrating polymer networks (IPNs) of poly(ethylene oxide-dimethyl siloxane-ethylene oxide) (PEO-PDMS-PEO) ABA triblock copolymer and poly(*N*-isopropyl acrylamide) (PIPAAm) has been synthesized as thermosensitive gels. Indomethacin and ketoprofen were selected as model drugs and incorporated into thermosensitive gel. Pulsatile drug release produced from these thermosensitive gels was strongly influenced by the swelling–deswelling kinetic properties of thermosensitive gels solubility dependence of drug as a function of temperature, and the temperature applied. However, the release behavior of indomethacin and ketoprofen at several fixed temperatures from the thermosensitive gel showed similar patterns. The exact initiation temperatures for drug release of both drugs were similar and slightly below the swelling transition temperature of an unloaded gel.

KEY WORDS Indomethacin / Ketoprofen / Pulsatile Drug Release / Solubility Dependence / Swelling Transition Temperature / Phase Continuity / Morphology / Swelling–Deswelling Kinetic /

It is important to control drug release from delivery devices in order to produce a zero order release rate of sustained release. Therapeutically, the advantages of controlled release are ability to maintain drug levels constantly within an effective blood concentration range, to administer less drug to produce effective therapy and less frequent administration than with conventional dosage forms.

Many efforts have been made to create new controlled release methods that sometimes emphasize the use of polymer.[1-3]

On the other hand, new types of drug delivery systems which can control drug output in response to a physiological condition or a stimuli signal, such as pH,[4,5] temperature,[6-9] magnetism,[10] and chemical[11] have created much interest. Heller[12] recently reviewed the progress in this field. In the future, activities using these drug delivery concepts may create an auto-feedback drug delivery system that will provide better therapy than conventional dosage forms or precisely controlled zero-order release devices.

Recently, the transport control of solute or ion from polymeric devices by changing en-

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vironmental conditions has gained much attention and emphasized the reversibility of transport. These phenomena and concepts were recognized as an important trigger in creating a new effect.

Crosslinked poly(*N*-isopropyl acylamide) (PIPAAm) gel shows a sharp swelling transition temperature around its lower critical solution temperature of its aqueous solution.[13] Recently, the swelling transition behavior was utilized as a molecular size selective adsorbent[14,15] and for control of enzyme activity.[16] However, its weak mechanical strength limits its use.

The properties of crosslinked PIPAAm can be manipulated by copolymerization[17,18] with hydrophobic (HPB) or hydrophilic (HPL) monomer or interpenetrating polymer network (IPN) polymerization.[19] One can control the degree of swelling and swelling transition temperature in a gel made by the copolymerization method. On the other hand, one can control the degree of swelling, but not the swelling transition temperature in a gel made by IPN polymerization.

We previously reported that thermosensitive gels which were modified by copolymerization or IPN polymerization could be utilized as a thermal on-off switch for pulsatile drug release in a system using indomethacin.[17,20]

In this paper, poly(ethylene oxide-dimethyl siloxane-ethylene oxide) (PEO-PDMS-PEO)–poly(*N*-isopropyl acrylamide) (PIPAAm) IPNs were used as thermal on-off switches using indomethacin and ketoprofen. The pulsatile drug release patterns for two drugs from initially dried thermosensitive gels are discussed in respect to gel swelling-deswelling behavior, temperature dependency of drug solubility and the temperatures applied. In addition, the release behavior of two drugs at several fixed temperatures were also examined and are discussed.

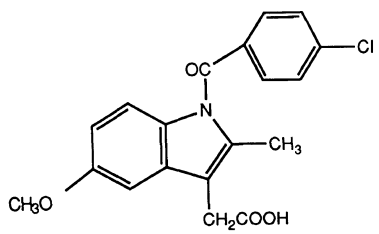
## EXPERIMENTAL

Indomethacin and ketoprofen were obtained by Sigma Chemical Co. Their chemical structures are listed in Figure 1.

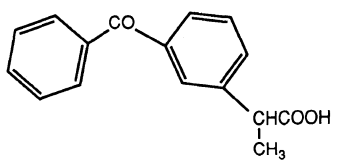
The thermosensitive gels used in this paper were poly(*N*-isopropyl acrylamide) (PIPAAm)/poly(ethylene oxide-dimethyl siloxane-ethylene oxide) (PEO-PDMS-PEO) IPNs and crosslinked poly(*N*-isopropyl acrylamide) (PIPAAm). The feed composition of the IPN system was 80 wt% IPAAm. We denote this IPNs as 80/20 IPNs. A simultaneous reaction using stepwise and free radical polymerization was used to synthesize the 80/20 IPNs. The materials used and detailed synthesis conditions were described previously.[21]

### *Drug Loading*

The dried polymer disks were equilibrated




indomethacin




ketoprofen

**Figure 1.** Structures of indomethacin and ketoprofen.

**Table I.** Drug loading content for pulsatile release studies

| Sample | Drug | Temperature cycle T1(°C)—T2(°C) | Drug loading content | | Diameter | Thickness |
|---|---|---|---|---|---|---|
| | | | wt% | mg/disk | mm | μm |
| 80/20 IPNs | Indomethacin | 25—40 | 29 | 10 | 7.2 | 780 |
| 80/20 IPNs | Indomethacin | 25—33 | 29 | 10 | 7.2 | 780 |
| Crosslinked PIPAAm | Indomethacin | 25—40 | 29 | 9 | 6.1 | 830 |
| Crosslinked PIPAAm | Indomethacin | 25—33 | 30 | 9.4 | 7.0 | 800 |
| 80/20 IPNs | Ketoprofen | 25—40 | 30 | 11 | 7.5 | 850 |
| 80/20 IPNs | Ketoprofen | 25—33 | 30 | 10.5 | 7.3 | 860 |
| Crosslinked PIPAAm | Ketoprofen | 25—40 | 31 | 10 | 7.5 | 800 |
| Crosslinked PIPAAm | Ketoprofen | 25—33 | 31 | 10 | 7.2 | 800 |

**Table II.** Drug loading content for release studies

| Sample | Drug | Drug loading content | | Diameter | Thickness |
|---|---|---|---|---|---|
| | | wt% | mg/disk | mm | μm |
| 80/20 IPNs | Indomethacin | 30 | 11 | 7.5 | 850 |
| Crosslinked PIPAAm | Indomethacin | 31 | 11 | 7.5 | 850 |
| 80/20 IPNs | Ketoprofen | 30 | 11 | 7.5 | 850 |
| Crosslinked PIPAAm | Ketoprofen | 31 | 11 | 7.5 | 850 |

for three days in 1.8% indomethacin or 2.0% ketoprofen in *t*-butanol–ethanol–water (60:20:20 in volume ratio). After the swollen disks were blotted with a paper towel, the disks were frozen on a recrystalizing dish, set in a dry-ice/acetone mixture (−78°C) and vacuum-dried for one hour at −15°C. The temperature was gradually increased over six hours from −15 to 25°C, then maintained at 25°C for three days and 60°C for six days to remove the residual *t*-butanol. The drug loading content, diameter and thickness of the disks used in the pulsatile drug release experiments are listed in Table I. Drug loading content was determined as the weight of loaded drug (mg) per mass (mg) of dried polymer. The weight of loaded drug (mg) was obtained by subtracting the weight of unloaded polymer (mg) from the weight of drug loaded polymer (mg).

Table II also lists the drug loading contents, diameter and thickness of disks used in other release experiments. Here, the size of 80/20 IPNs and crosslinked PIPAAM was adjusted to compare release behavior between 80/20 IPNs and crosslinked PIPAAm.

*Drug Solubility Measurement*

Excess amounts of indomethacin and ketoprofen were separately put in disposable vials filled with PBS buffer pH 7.4. The vials were kept in a temperature controlled water bath at temperatures ranging from 15 to 45°C. After one day, the solution was filtered through a disposable filter (Gelman Sciences ACRO

LC3S filter, pore size = 0.45 $\mu$m, Ann Arbor, MI, U.S.A.), and content measured at the wavelength of 265.9 nm for indomethacin and 259.2 nm for ketoprofen on a UV spectrophotometer (Perkin Elmer Lamba 7, Norwalk, Conn., U.S.A.).

*Drug Release Study*

The pulsatile dlrug-release experiments were conducted in PBS pH 7.4 buffer solution and kept in a constant temperature water bath. The dried drug loaded device was held in a basket made by nickel-chrome wire and immersed in the release media. The drug concentration was monitored by taking 3 ml aliquots of the media at specific time points, replacing the aliquot with fresh PBS buffer and concentration determined by UV absorption. After a certain period at one temperature, the samples were moved to a new release media kept at another temperature. Pulsatile drug release for indomethacin and ketoprofen was conducted at 25, 33, or 40°C.

The release experiments at 25, 33, and 40°C were also conducted in a constant temperature buffer solution (PBS pH 7.4 1 l). The sample was held in the same way. The released drug concentration was also determined in a same procedure.

Another set of release experiments was conducted by gradually decreasing the water bath temperature from a higher temperature above the swelling transition temperature. The system is shown in Figure 2. A peristaltic pump (model P-1), single path UV monitor (254 nm, model UV-1), composed of an optical unit and a control unit, and recorder (model REC-482) were obtained from Pharmacia Fine Chemicals (Uppsala, Sweden) and used to record the initial temperature inducing drug release when the temperature was decreased from high temperature above swelling transition temperature. Here, the sample was immersed in PBS pH 7.4 at 40°C by the same way as pulsatile release studies for 10 h to get a constant release rate. Drug concentration monitored at a each fixed temperature, decreased in stepwise procedure after leaving for 20 min, and a 1 h release profile was obtained. Relative slopes (slope at 25°C = 1) of release rate were plotted as a function of temperature.

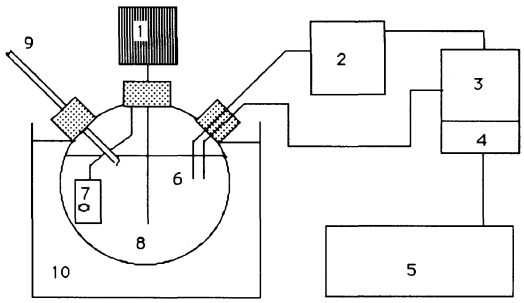



**Figure 2.** Schematic diagram of the continuous monitoring system for drug release rate experiment: 1, motor; 2, peristaric pump; 3, UV monitor optical unit; 4, UV monitor control unit; 5, recorder; 6, buffer solution; 7, sample; 8, stirer; 9, thermometer; 10, water bath.

## RESULTS AND DISCUSSION

In a previous paper,[21] we synthesized interpenetrating polymer networks (IPNs) composed of poly(ethylene oxide-dimethyl siloxane-ethylene oxide) (PEO-PDMS-PEO) and poly(*N*-isopropyl acrylamide) (PIPAAm). These IPNs were denoted as 50/50 IPNs and 80/20 IPNs (the feed compositions were 50 and 80% IPAAm, respectively). The bulk morphology was determined with differential scanning calorimetric (DSC) studies and transmission electron microscopic (TEM) studies. Swelling–deswelling kinetics with temperature modulation at 25, 33, or 40°C were affected by gel composition and temperatures applied.

In this paper, the pulsatile release of indomethacin and ketoprofen was conducted with temperature modulation at 25, 33, or 40°C. Here, we regarded the beginning stage of release where the sample initially was kept in release media at higher temperature as the prestage process. In subsequent temperature cycles, the low temperature period was regarded as the first, second or third on-process.

The higher temperature period was regarded as the first, second or third off process. Bae[18,22] proposed a plausible model for the explanation of the observation of indomethacin release behavior from another thermosensitive gel. In his model, two cases of a sudden temperature increase from low temperature and a sudden temperature decrease from high temperature past a swelling transition temperature for the swollen phase of a drug loaded sample are considered. In the first case, when the temperature was suddenly increased past the swelling transition temperature, the swollen phase deswells and squeezes out dissolved drug from the surface layer and/or blocks drug release. By deswelling, the water content of the swollen phase decreases and the deswollen or shrunken surface layer thickens while the drug solubility in the swollen phase increases due to increased temperature. In the second case, the gel starts to reswell at the surface of deswollen/or shrunken surface layer when temperature was suddenly decreased past a swelling transition temperature. The drug was released with an initial high rate attributed to a drug solubility change profile and a water content profile change in the deswollen phase at the previous off process at high temperature followed by drug release due to the swelling release mechanism of the next off process. Therefore, the first objective of this research was to interpret the fluctuation of pulsatile drug release using the temperature dependency of drug solubility and the swelling-deswelling kinetic properties of thermosensitive gel. We assumed that the swelling-deswelling kinetics of unloaded thermosensitive gel are correlated to the swollen phase behavior of drug loaded thermosensitive gel with modulated temperatures. The other objectives are to examine drug release from IPNs used in pulsatile drug release studies. Two kinds of release experiments were conducted to learn the release mechanism of two drugs from IPNs. The first release experiment was conducted with both drug release from IPNs at several fixed temperatures. The second release experiment was conducted by monitoring a drug solution while gradually decreasing the temperature of the release media from a temperature higher than the gel swelling transition temperature. Drug solubility was measured as a function of temperature for indomethacin and ktoprofen. All release experiments with IPNs were compared

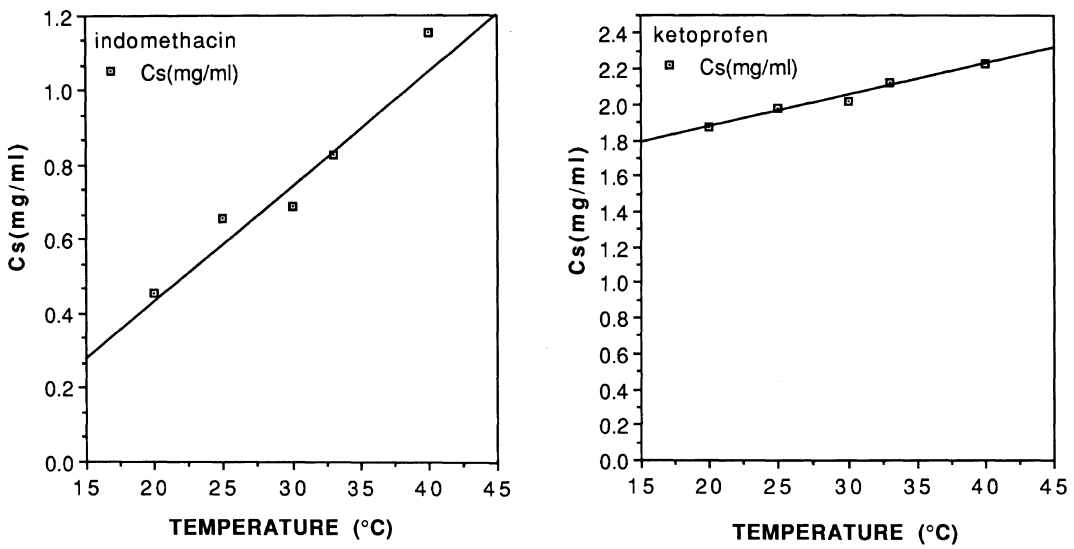



**Figure 3.** Solubility properties of indomethacin and ketoprofen in PBS (pH 7.4).

with those using crosslinked PIPAAm.

*Drug Solubility Measurements*

Figure 3 shows drug solubilities in PBS pH 7.4 for the temperature range of 15 to 45°C. The measured solubility of indomethacin showed a more temperature dependence than ketoprofen, although ketoprofen has higher solubility over the tested temperature range. We assumed that the solubility profile change of drug in the swollen phase in off process was correlated with the reference of saturated solubility profile in PBS pH 7.4.

*Pulsatile drug release studies*

The pulsatile release of indomethacin from 80/20 IPNs and crosslinked PIPAAm between 25 and 40°C are shown in Figures 4 and 5. The pulsatile release of ketoprofen from the sample matrices between 25 and 40°C is shown in Figures 6 and 7. Total released amounts of indomethacin and ketoprofen from the sample matrices are summarized in Table III for indomethacin and in Table IV for ketoprofen. The 50/50 IPNs, used in the previous study,[21] were neglected due to their drug release behavior in the off process. This phenomenon may have been caused by the PEO-PDMS-PEO pathway when the bulk morphology of loaded 50/50 IPNs showed the same bulk morphology as unloaded 50/50 IPNs.

The complete on-off regulation of drug re-

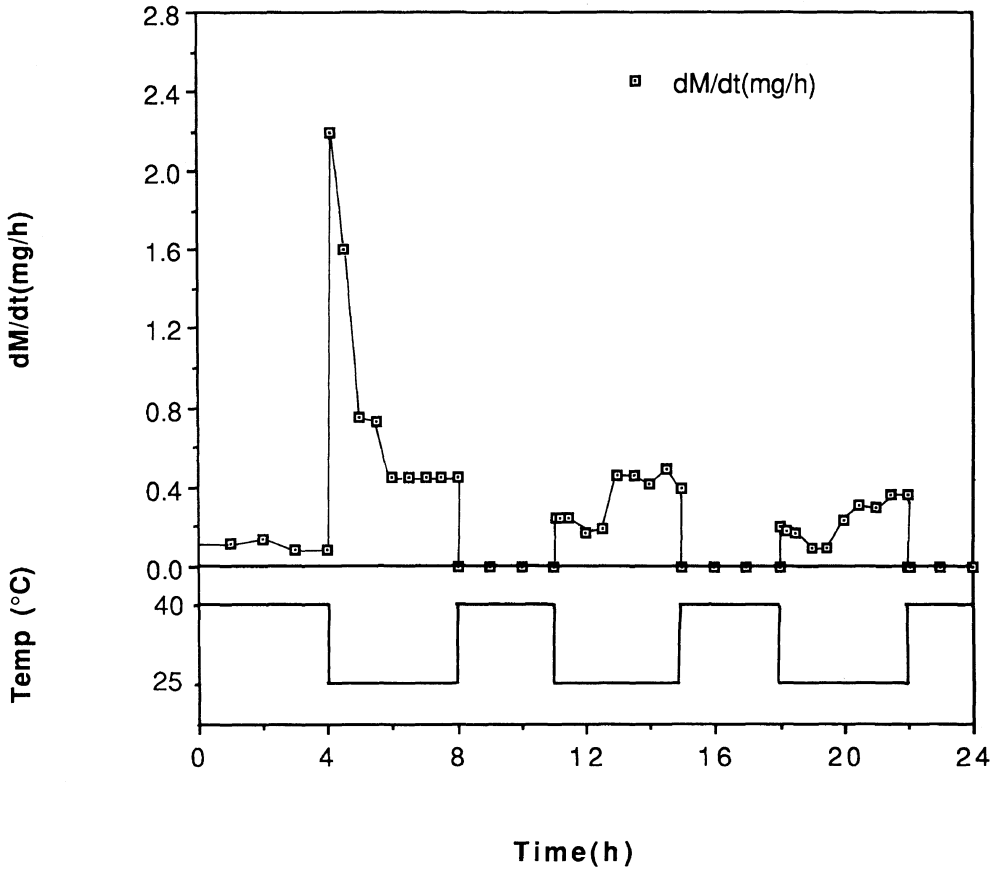



**Figure 4.** Pulsatile indomethacin release rate from 80/20 IPNs in response to a step-wise temperature change between 25 and 40°C in PBS (pH 7.4). The drug loading content was 29% (10 mg/disk). $\phi = 7.2$ mm; $d = 780\ \mu$m.

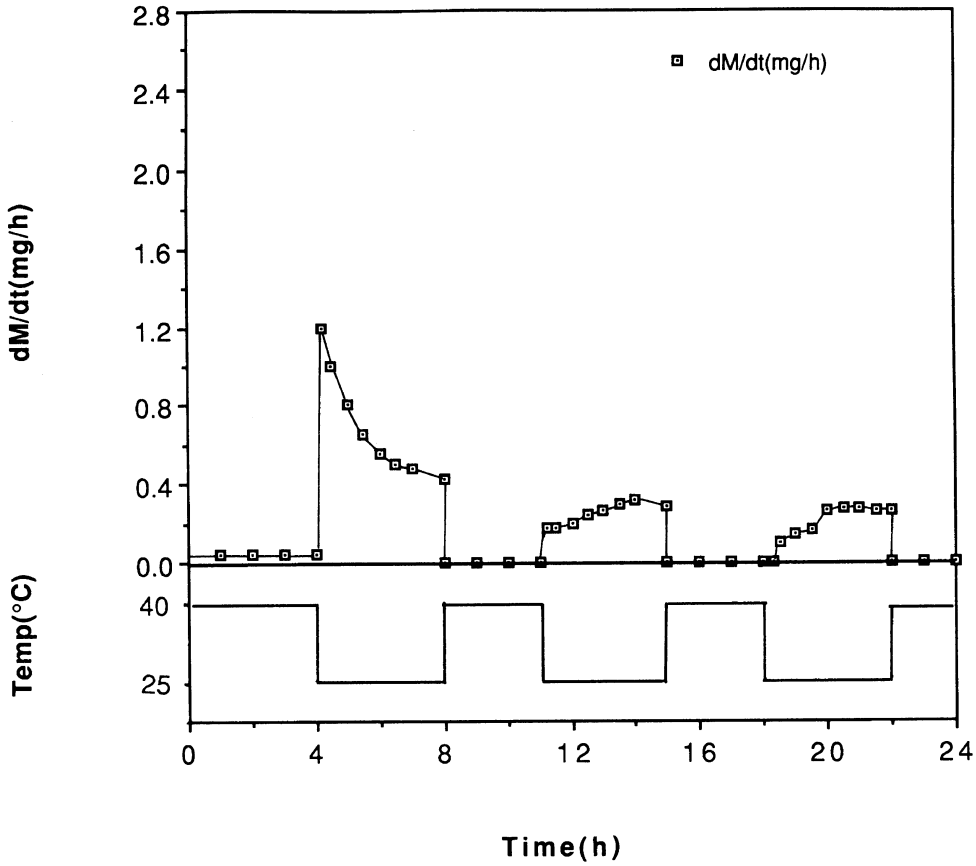



**Figure 5.** Pulsatile indomethacin release rate from crosslinked PIPAAm in response to a step-wise temperature change between 25 and 40°C in PBS (pH 7.4). The drug loading content was 29% (9 mg/disk). $\phi = 6.1$ mm; $d = 830\ \mu$m.

**Table III.** Total released amount of indomethacin at each cycle temperature

| Cycle | 80/20 IPNs (25—40°C) | 80/20 IPNs (25—33°C) | PIPAAm (25—40°C) | PIPAAm (25—33°C) |
|---|---|---|---|---|
| | mg | mg | mg | mg |
| Prestage | 0.33 | 0.32 | 0.20 | 0.20 |
| 1st on | 2.87 | 2.75 | 2.4 | 2.45 |
| 1st off | 0.0 | 0.13 | 0.0 | 0.1 |
| 2nd on | 1.42 | 1.34 | 1.03 | 1.07 |
| 2nd off | 0.0 | 0.08 | 0.0 | 0.09 |
| 3rd on | 0.96 | 0.95 | 0.83 | 0.83 |
| 3rd off | 0.0 | 0.08 | 0.0 | 0.10 |

lease was observed with temperature modulation between 25 and 40°C regardless of gel composition and drug structure. However, complicated fluctuations of drug release in each on process have also been observed, as shown in Figures 4, 5, 6, and 7.

**Table IV.** Total released amount of ketoprofen at each cycle temperature

| Cycle | 80/20 IPNs (25—40°C) | 80/20 IPNs (25—33°C) | PIPAAm (25—40°C) | PIPAAm (25—33°C) |
|---|---|---|---|---|
| | mg | mg | mg | mg |
| Prestage | 0.38 | 0.35 | 0.19 | 0.20 |
| 1st on | 2.27 | 2.20 | 2.11 | 2.21 |
| 1st off | 0.0 | 0.1 | 0.0 | 0.1 |
| 2nd on | 1.67 | 1.37 | 1.13 | 1.48 |
| 2nd off | 0.0 | 0.1 | 0.0 | 0.05 |
| 3rd on | 1.07 | 0.82 | 0.88 | 0.83 |
| 3rd off | 0.0 | 0.05 | 0.0 | 0.05 |

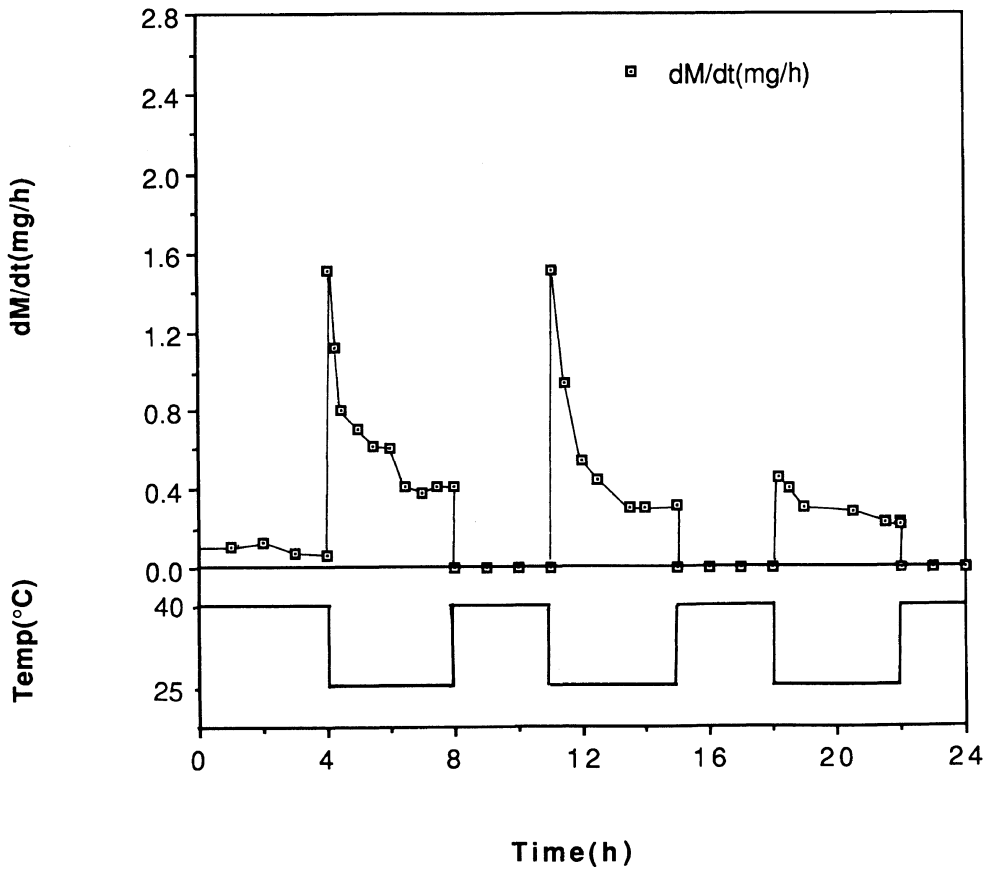



**Figure 6.** Pulsatile ketoprofen release rate from 80/20 IPNs in response to a step-wise temperature change between 25 and 40°C in PBS (pH 7.4). The drug loading content was 30% (11 mg/disk). $\phi = 7.5$ mm; $d = 850$ $\mu$m.

In the previous study,[21] the swelling–deswelling kinetics of unloaded 80/20 IPNs and crosslinked PIPAAm were affected by gel composition and temperature applied. In this study, the interpretation of pulsatile drug release by temperature modulation between 25

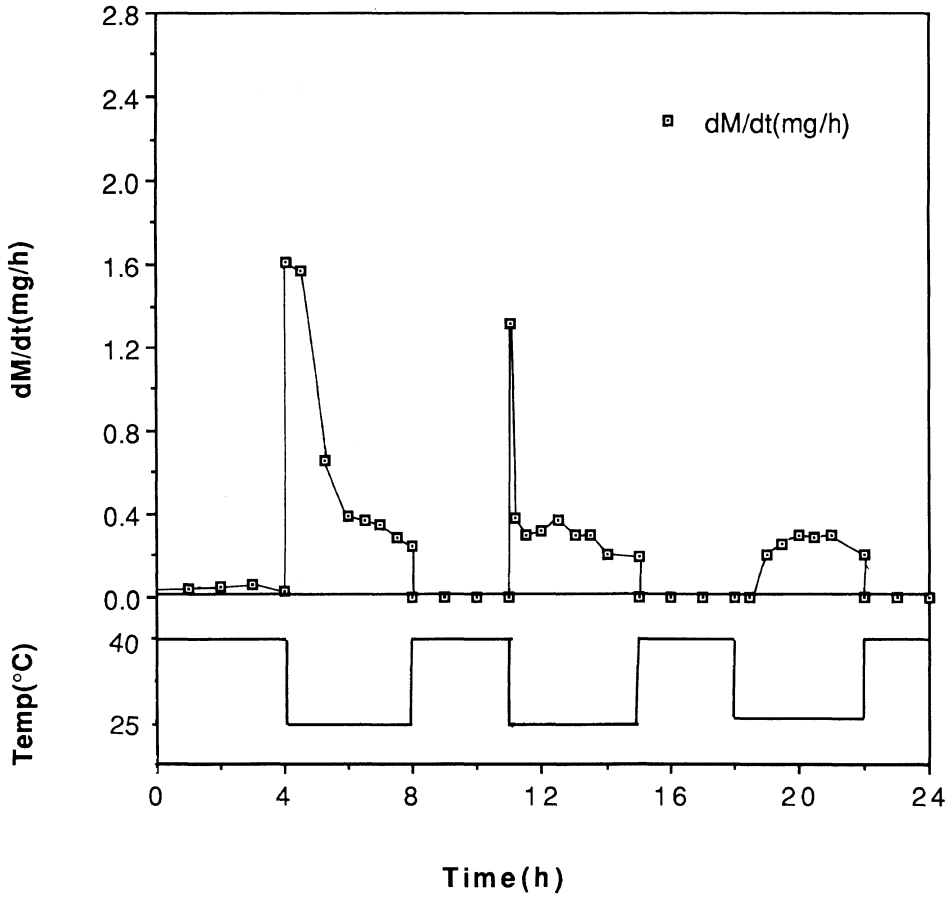



**Figure 7.** Pulsatile ketoprofen release rate from crosslinked PIPAAm in response to a step-wise temperature change between 25 and 40°C in PBS (pH 7.4). The drug loading content was 31% (10 mg/disk). $\phi = 7.5$ mm; $d = 800\,\mu$m.

and 40°C in Figures 4, 5, 6, and 7 can be discussed with consideration of the swelling-deswelling kinetics of the thermosensitive gel and temperature dependence of drug solubility.

In the first on process, a kind of burst effect of drug release was observed followed by a gradual decrease in release.

In the subsequent temperature cycles, the indomethacin release rate in the second on process of 80/20 IPNs (Figure 4) showed a slightly high release rate followed by a gradual decreasing and finally the release rate slightly recovering. This phenomenon may have been caused by a release of concentrated drug solution enclosed in the gel layer by the previous slower deswelling off process.

On the other hand, the indomethacin release rate fo crosslinked PIPAAm in the second on process (Figure 5) showed a low release rate without the early second on process high release behavior observed with 80/20 IPNs. This phenomenon may have been also caused by the release of small amounts of concentrated drug solution enclosed in the shrunken gel layer by fast deswelling in the previous off process.

The indomethacin release rate of 80/20 IPNs in the third on process was similar to the second on process. The indomethacin release

rate in the third on process of crosslinked PIPAAm showed a lag time. This phenomenon suggests that a fast deswelling process of the swollen gel layer may have created a thicker shrunken gel layer at the end of the second off process producing a lag time when the gel reswells in the third on process.

Pulsatile release of ketoprofen from 80/20 IPNs (Figure 6) showed a higher release rate at the early stage of the second and third on processes than indomethacin. This observation may be attributed to a release of the drug solution enclosed in the deswollen phase due to the slow deswelling kinetics of the previous off process and the higher solubility of ketoprofen over a wider temperature range.

The second on process in crosslinked PIPAAm (Figure 7) shows a higher release rate for ketoprofen followed by a more rapid decrease in the beginning stage than from 80/20 IPNs. This phenomenon was also created by the same effect seen in 80/20 IPNs. The lag time for the third on process of crosslinked PIPAAm was observed and may also be attributed to the same reasons for the lag time with indomethacin.

As seen in Tables III and IV, drug leakage during each off process was observed with temperature modulated between 25 and 33°C. These patterns indicate that dense structure

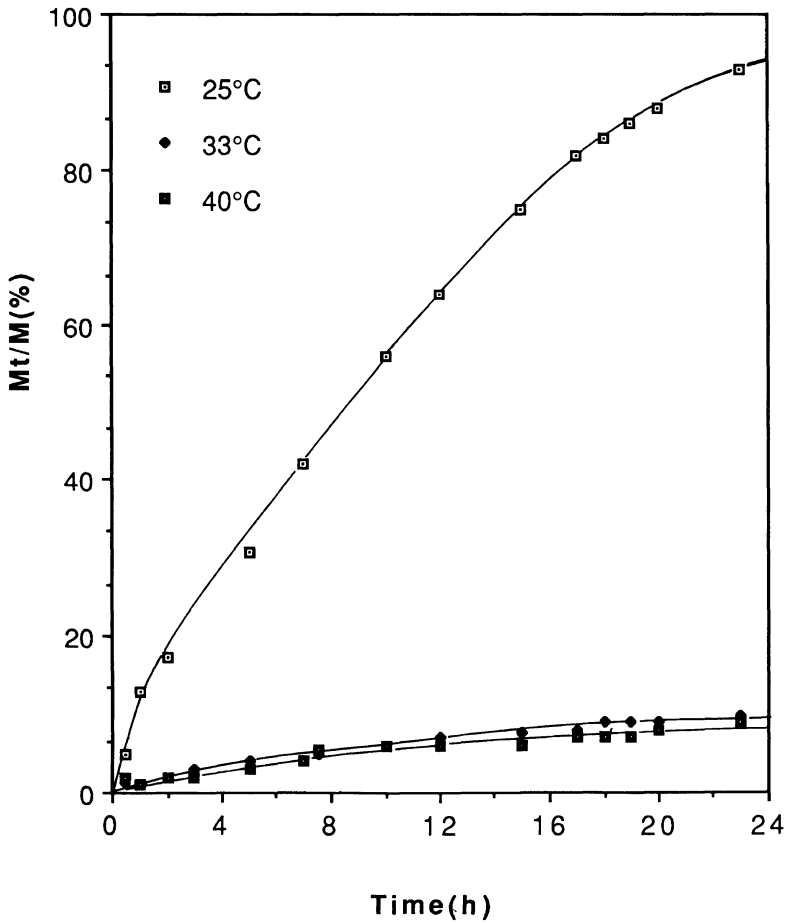



**Figure 8.** Release of indomethacin from 80/20 IPNs at 25°C (□), 33°C (◆), and 40°C (■) in PBS (pH 7.4). The drug loading content was 30% (11 mg/disk). $\phi = 7.5$ mm; $d = 850$ μm.

formation in the gels for the deswelling stage at 33°C was not strong enough to block drug release and squeeze out a drug solution when temperature was modulated from 25 to 33°C, although 33°C was above the swelling transition temperature. On the other hand, the off process in the pulsatile release studies between 25 and 40°C did not created any drug release. These observations demonstrated that dense structure formation during the swollen phase of 80/20 IPNs and the deswelling stage of crosslinked PIPAAm at 40°C occurred and prevented or blocked drug release regardless of the gel composition.

Therefore, these release patterns for pulsatile drug release study could be reasonably interpreted by considering Bae's model, solubility of indomethacin and ketoprofen, and the swelling-deswelling kinetics of unloaded 80/20 IPNs and crosslinked PIPAAm.

*Release Experiment*

Release experiments at 25, 33, and 40°C were also conducted with dried drug loaded 80/20 IPNs and crosslinked PIPAAm. The release profiles of indomethacin are presented in Figures 8 and 9. The release profiles of ketoprofen are presented in Figures 10 and 11.

Release at 25°C were analogous patterns and similar pseudo-zero order release behavior independent of drug properties. The release

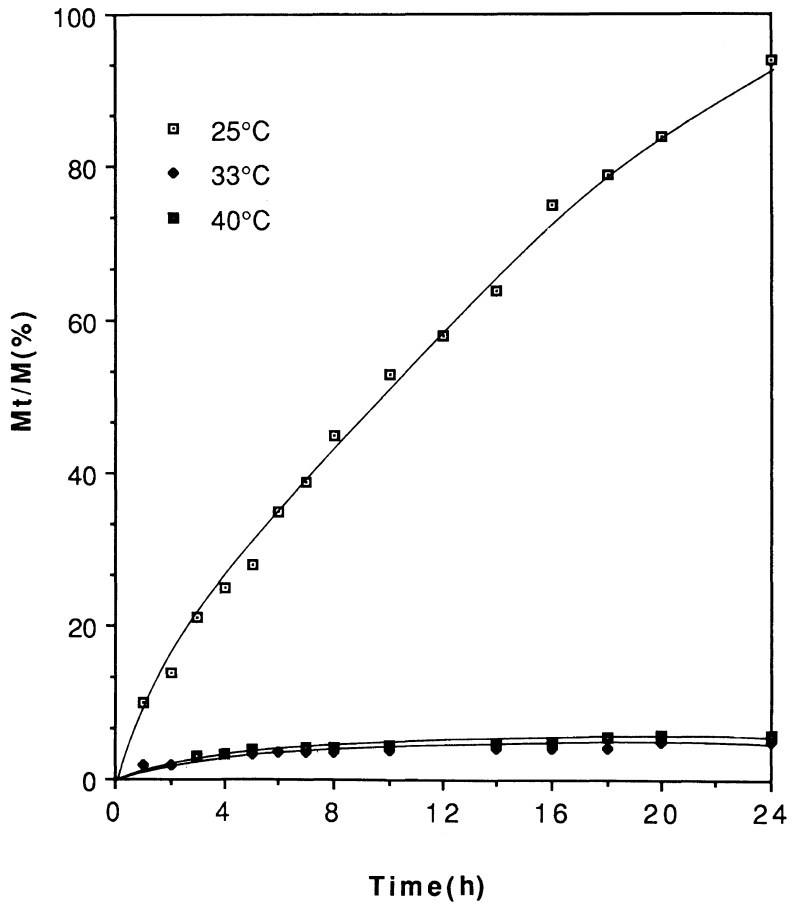



**Figure 9.** Release of indomethacin from crosslinked PIPAAm at 25°C (□), 33°C (◆), and 40°C (■) in PBS (pH 7.4). The drug loading content was 29% (11 mg/disk). $\phi = 7.5$ mm; $d = 850$ μm.

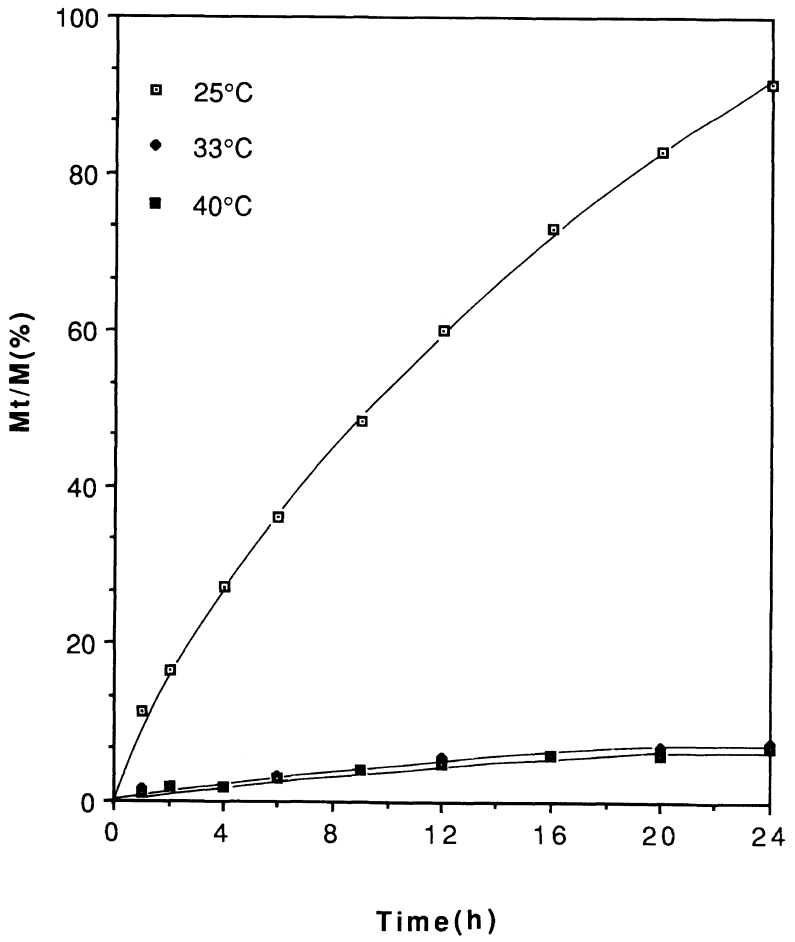



**Figure 10.** Release of ketoprofen from 80/20 IPNs at 25°C (□), 33°C (◆), and 40°C (■) in PBS (pH 7.4). The drug loading content was 30% (11 mg/disk). $\phi = 7.5$ mm; $d = 850$ $\mu$m.

from 80/20 IPNs of indomethacin and ketoprofen at 33 and 40°C showed a slightly higher release pattern than with crosslinked PIPAAm. The release of both drugs from crosslinked PIPAAm at 33 and 40°C was quite negligible after 10 h. However, the difference of cumulative amount of drug released between 80/20 IPNs and crosslinked PIPAAm at 33 or 40°C till 24 h was 3—4% for both drugs.

Therefore, the effect of the PEO-PDMS-PEO pathway for drug release from 80/20 IPNs at 33 or 40°C may be negligible. In the previous study,[21] we observed PIPAAm phase continuity and PEO-PDMS-PEO domain in bulk 80/20 IPNs morphology study and concluded that the swelling–deswelling kinetics of 80/20 IPNs were similar to those of crosslinked PIPAAm. Similar conclusions can be drawn here to understand the release phenomena from 80/20 IPNs when compared to crosslinked PIPAAm. Namely, if drug loaded dried 80/20 IPNs and crosslinked PIPAAm have the same bulk morphology as unloaded 80/20 IPNs and crosslinked PIPAAm, the release behavior above the swelling transition temperature should show negligible drug release from drug loaded 80/20 IPNs and crosslinked PIPAAm due to the PIPAAm phase con-

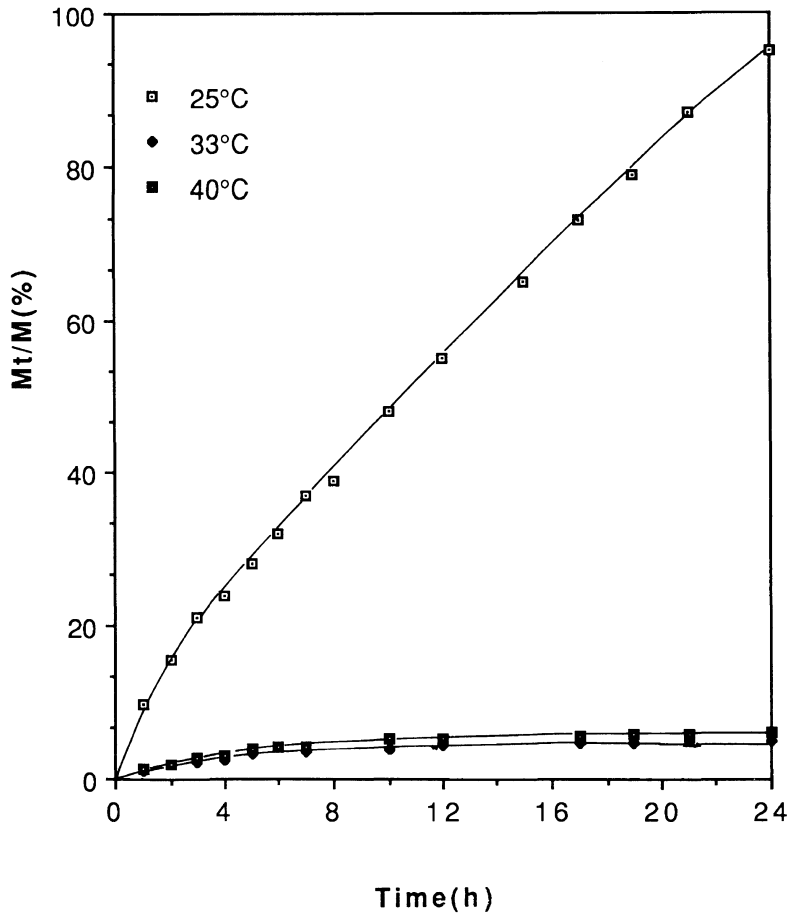



**Figure 11.** Release of ketoprofen from crosskinked PIPAAm at 25°C (⊡), 33°C (◆), and 40°C (■) in PBS (pH 7.4). The drug loading content was 31% (11 mg/disk). $\phi = 7.5$ mm; $d = 850$ $\mu$m.

tinuity. Also, release behavior below the swelling transition temperature may show similar drug release patterns for the above same reasons when drug is released by a swelling process.

Another release experiment was conducted to examine the effects and differences of the interaction of polymer matrix with indomethacin or ketoprofen when drug release was initiated from the thermosensitive gel.

Figure 12 shows a relative slope of indomethacin release and Figure 13 shows the relative slope of ketoprofen release from 80/20 IPNs and crosslinked PIPAAm.

In the previous paper,[21] the swelling transition temperature range of crosslinked PIPAAm was 31—33°C. The initiation temperature of drug release from crosslinked PIPAAm for both drugs was analogous and about 29.2—29.5°C. This difference between the swelling transition temperature and initiation temperature may be due to interactions between polymer molecules and the hydrophobic drug or character of PIPAAm phase itself when PIPAAm phase swells. However, this hypothesis needs further clarification through research.

On the other hand, the relative slope curves of 80/20 IPNs for both drugs indicate that a slightly lower degree of drug release in the

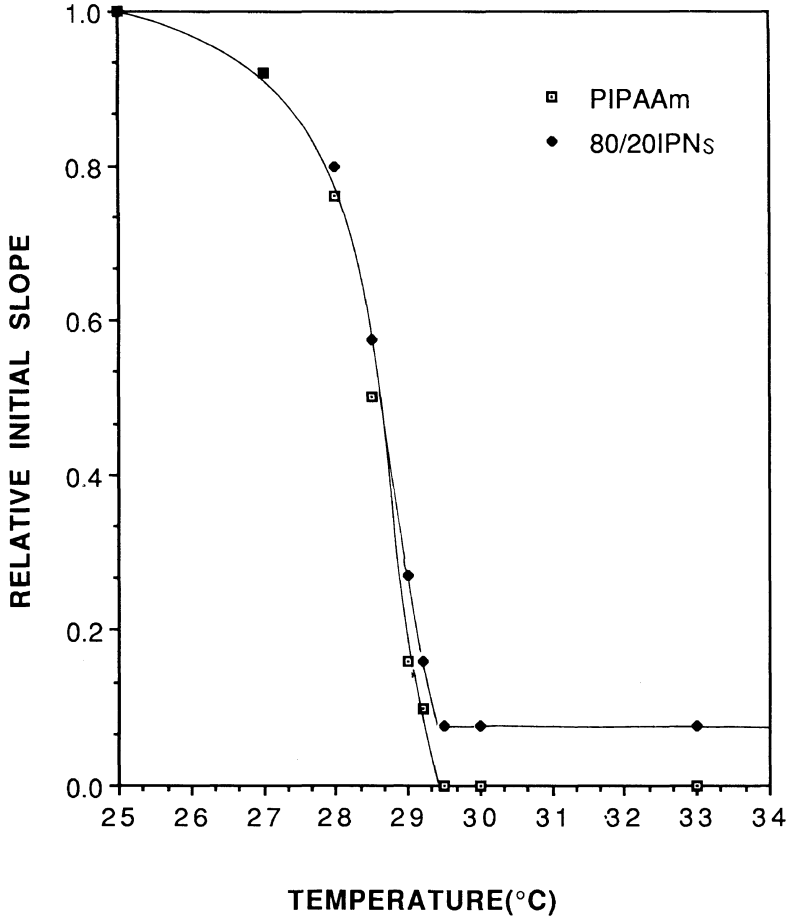



**Figure 12.** Relative indomethacin release rate as a function of temperature from 80/20 IPNs (◆) and crosslinked PIPAAm (⊡). the relative slopes were obtained from indomethacin release for 1 h from each thermosensitive gel. 80/20 IPNs: The drug loading content was 29% (11 mg/disk). $\phi = 7.5$ mm; $d = 850$ μm. Crosslinked PIPAAm: The drug loading content was 29% (11 mg/disk). $\phi = 7.5$ mm; $d = 850$ μm.

range of temperature above the initiation temperature for drug release from crosslinked PIPAAm as temperature decreased.

These observations indicate that ketoprofen and indomethacin release from 80/20 IPNs devices has two pathways. However, the effect for drug release from PEO-PDMS-PEO network in 80/20 IPNs may be negligible, which is also consistant with release experiments for both drugs at 25, 33, and 40°C. Overall drug release from 80/20 IPNs was initiated by the PIPAAm phase relaxation process regardless of PEO-PDMS-PEO component. Namely, the release from 80/20 IPNs was controlled by the IPAAm phase, whose structure may be expected from its bulk unloaded morphology. The initiation process was similar for both indomethacin and ketoprofen.

## CONCLUSIONS

In conclusion, the pulsatile drug release from these thermosensitive gels was strongly influenced by the swelling-deswelling properties of thermosensitive gel, temperature dependency of drug solubility and temperature

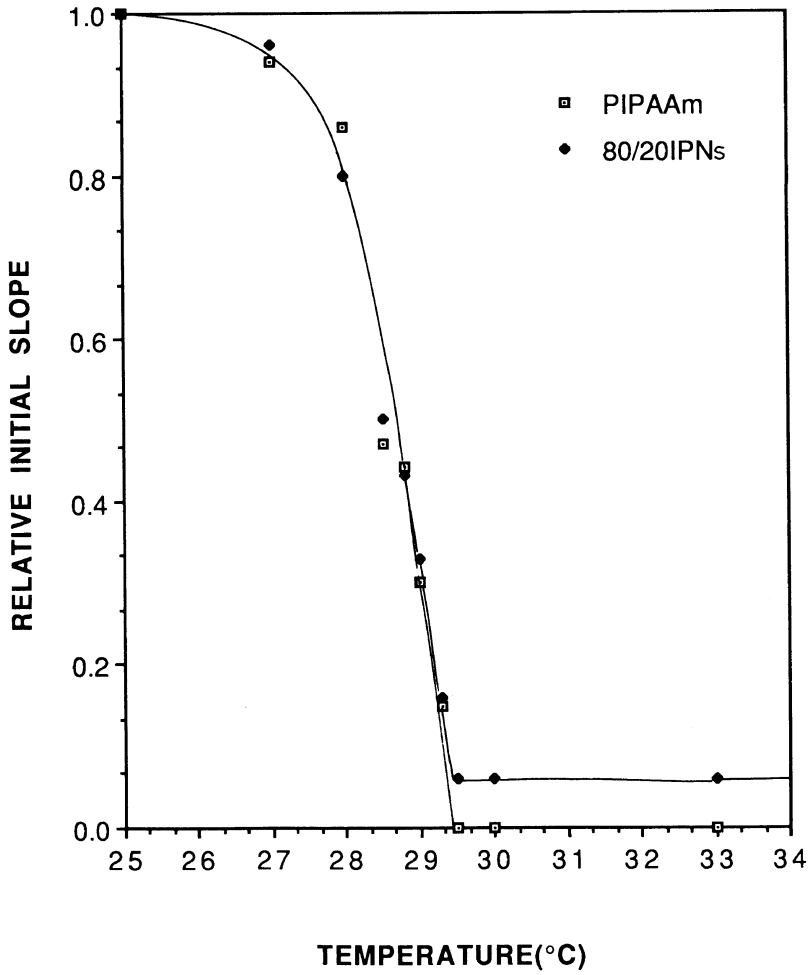



**Figure 13.** Relative ketoprofen release rate as a function of temperature from 80/20 IPNs (◆) and crosslinked PIPAAm (□). The relative slopes were obtained from ketoprofen release for 1 h from each thermosensitive gel. 80/20 IPNs: The drug loading content was 30% (11 mg/disk). $\phi = 7.5$ mm; $d = 850$ μm. Crosslinked PIPAAm: The drug loading content was 31% (11 mg/disk). $\phi = 7.5$ mm; $d = 850$ μm.

applied. These phenomena may be applied to create an optimum release of drugs in a non-continuous fashion.

On the other hand, release studies for both indomethacin and ketoprofen from 80/20 IPNs at several fixed temperatures did not show significantly different behavior than release from crosslinked PIPAAm. These observations demonstrate that the pathway through PEO-PDMS-PEO in 80/20 IPNs for drug release is negligible above the swelling transition temperature and that both drugs are released by a similar mechanism below the swelling transition temperature. The exact initiation temperatures for drug release of drug release of both drug were similar and slightly below the swelling transition temperature of unloaded gel.

*Acknowledgement.* The authors wish to thank Drs. Harvey Jacobs and Eric Mack (University of Utah) for their valuable com-

ments.

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