"On–Off" Thermocontrol of Solute Transport. II. Solute Release from Thermosensitive Hydrogels

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Poly(*N*-isopropylacrylamide) (NIPAAm)/polytetramethylene ether glycol (PTMEG) interpenetrating polymer networks (IPNs) were synthesized and their feasibility as thermosensitive hydrogels for drug release was investigated. The release of indomethacin incorporated into these matrices showed pulsatile patterns in response to temperature changes and was sensitive to a few degrees of temperature fluctuation. The temperature inducing on–off release deviated from the gel collapse temperature of unloaded gel, possibly because of solute effects on network properties. The lag time and release profile of indomethacin in the low-temperature region (on process) of each temperature cycle were affected by the gel composition and applied temperature. The results of this study demonstrate that solute release can be regulated by rapid deswelling of the surface of the gels in response to temperature.

KEY WORDS: thermocontrol; on–off release; thermosensitive hydrogels; interpenetrating polymer networks; *N*-isopropylacrylamide; polytetramethylene ether glycol.

INTRODUCTION

Many recent and interesting methodologies to control the release rate of drugs have been explored in order to obtain zero- or first-order release kinetics, as reviewed by Kim *et al.* (1). The main emphasis of this research has been to utilize polymeric matrices or membranes for diffusion controlled drug release.

Another type of drug delivery system, where environmental conditions or signals, such as pH, electric field, certain chemicals, and temperature, can modulate drug release, termed stimuli-sensitive release, has been developed to supply bioactive agents on demand or to overcome the shortcomings of fixed release kinetics. This type of release system may be applied to two categories: self-regulating and externally modulated drug delivery systems (2).

Stimuli-sensitive hydrogels have been investigated as potential drug carriers, rate barriers, or sensors in both self-regulating systems and externally modulated drug delivery systems. A stimuli-sensitive polymer may change its structure and physical properties in response to a corresponding external stimuli and would subsequently effect drug release from the drug reservoir.

Temperature is one possible external stimulus for modulating drug delivery. Several polymers show dramatic changes in physical properties in response to temperature. The thermal collapse of poly(*N*-isopropylacrylamide) [poly(NIPAAm)] and its copolymers has been studied (3–6) and applied to a separation process as extraction solvents (7), temperature-modulated drug delivery (8,9), and others (10,11). Other examples of temperature-modulated solute release systems include porous nylon capsule membranes with grafted poly(NIPAAm) (12) or coated with a dialkyl surfactant (13), the thermal transition of vesicle to micelle of lipids (14), and the crystal–nematic liquid crystal transition (15). Some of these approaches have utilized complex membrane systems or reservoir-type devices with complicated fabrication procedures to achieve on–off release. An on–off release control of solute from simple monolithic devices by changing environmental conditions is a novel concept.

We reported, in paper I in this series (16), the temperature dependence of equilibrium swelling and the deswelling behavior of NIPAAm networks modified with hydrophobic components. The swelling properties of these gels were affected by modification methods and gel composition and were observed to form a dense surface layer when the temperature increased past the gel collapse point. This phenomenon retarded water efflux and thereby resulted in water pockets at the membrane surface (6,16).

In this paper, the temperature-modulated on–off release of indomethacin, as a model solute, from those gels is reported.

EXPERIMENTAL

Polymer Matrices

The polymer matrices used in this experiment were poly(*N*-isopropylacrylamide) [poly(NIPAAm)]/polytetramethylene ether glycol (PTMEG) (MW 2000) interpenetrating polymer networks (IPNs). The feed composition of the IPN system was varied from 0 to 50 wt% of PTMEG and the polymerization products were denoted IPN(wt% poly(NIPAAm)/wt% PTMEG), such as IPN(50/50). The detailed synthetic conditions and feed compositions were described in the previous paper (16). The synthesized membranes (about 1-mm thickness) were cut into disks with a cork borer (12-mm diameter). Unreacted compounds and solvents were extracted by soaking the disks in water/methanol (50/50, v/v%) for 1 week.

Drug Loading

Dried IPN disks were equilibrated with a saturated solution of indomethacin (a model drug) in a t-butanol/ethanol/water (60/20/20, v/v/v%) mixture for 3 days. The swollen gels were vacuum dried by gradually increasing the temperature from −23 to 23°C for 6 hr and keeping them at 23°C for more than 1 week to evaporate the residual t-butanol. The dried, yellow-colored disks had dimensions of 10 to 11 mm in diameter and 1.0 to 1.1 mm in thickness.

Drug Release

Indomethacin release experiments were conducted in externally stirred, constant-temperature PBS solutions (pH 7.4, 1 liter) equipped with an external stirrer. The sample was held in the release medium by using a sample holder.

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The concentration of released drug was monitored by taking 3-ml aliquots of the medium 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). The release experiments were also conducted by fluctuating the water bath temperature between two specified temperatures.

To study detailed on–off release behavior, a monitoring system for drug release rate using a flow cell was devised. In this system, the monolith was kept in a flow cell held in a water bath. The flow cell (volume, 4 ml) was consisted of a polycarbonate chamber frame positioned between two silicone rubber gaskets and pressure plates to provide a uniform flow. The release medium was pumped from the bottom to the top of the cell at a flow rate of 2.32 ml/min. The outstream was directly connected to a UV flow cell for continuous measurement of drug concentration. The lag time of the system was 1.4 min. This was determined by the time at which a maximum peak of output function was reached after injection of tracer (1 ml) for 10 sec into the bottom of the flow cell. The lag time was counted from the starting point of input injection.

RESULTS AND DISCUSSION

Indomethacin was loaded into polymer matrices by a solvent sorption method. Problems associated with this method, including drug migration onto the surface and poor recovery to original shape after drying, were avoided using a cold drying technique (17). Solvent formulations and low temperatures (below −15°C) in the initial drying step, as described under Experimental, resulted in device shape recovery and an absence of drug migration. These results may be due to slow solvent evaporation, reduced drug solubility, sol-like solvent properties by frozen water (high viscosity), and low drug diffusivity at low temperatures. No noticeable heterogeneities were found by visual observation of the final dried disks, which appeared to be uniformly drug dispersed monolithic devices. The loading content of indomethacin was determined by the total amount of released indomethacin, as summarized in Table I.

As discussed in paper I in this series (16), complete gel deswelling of all the IPN copolymers was observed between 30 and 32°C. Thus, an attempt was made to simulate on–off release of indomethacin by changing the external temperature of the drug/IPN system between 30 and 35°C. There were, however, no significant differences in the indomethacin release rate at these two temperatures, regardless of the IPN compositions, as seen in Fig. 1. IPN(95/5) and IPN(90/10) showed negligible drug release at these temperatures. At 25°C, indomethacin release was greatly enhanced and fractional release rate was not affected much by gel composition and loading content (Fig. 2). The fractional release rate of indomethacin at higher temperatures increased as PTMEG content increased. This, along with the evidence of phase separation and the swelling characteristics of the homopolymers, given in paper I (16), indicates that indomethacin permeability in the poly(NIPAAm) phase of the IPN is negligible at 30 and 35°C when compared with 25°C. On the other hand, the PTMEG phase had a higher permeability, even though this phase is not swollen, resulting in enhanced release rates with an increased PTMEG content. In the cases of IPN(95/5) and IPN(90/10), the PTMEG phase may be a completely isolated "island" in a poly(NIPAAm) phase "sea" resulting in negligible release rate.

Table I. Indomethacin Loading Content

Matrices	Loading content (wt %) (n = 4)
IPN(95/5)	24.0 ± 0.3
IPN(90/10)	26.0 ± 0.5
IPN(75/25)	21.6 ± 0.5
IPN(50/50)	11.2 ± 0.2

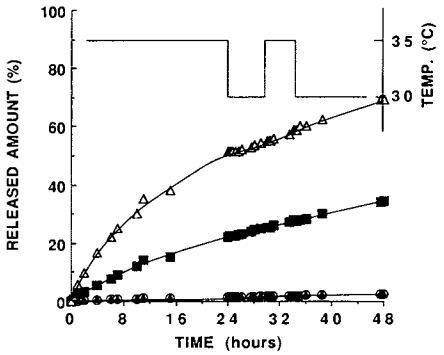

Fig. 1. Fractional release of indomethacin as a function of time from IPN matrices at 30/35°C: open triangles, IPN(50/50); filled squares, IPN(75/25); filled triangles, IPN(90/10); open circles, IPN(95/5).

After release experiments were conducted at higher temperatures (30 and 35°C), the temperature was fluctuated between 25 and 35°C or between 25 and 30°C. The total amounts of indomethacin released during high- and low-temperature periods in each temperature cycle are summarized in Table II. The on–off release of indomethacin was obtained from matrices of IPN(95/5) and IPN(90/10). IPN(75/25) and IPN(50/50) showed high release rates in the high-temperature period during the first cycle, but the release rates in high-temperature periods during subsequent cycles were remarkably reduced. The release profiles of indomethacin from IPN(90/10) at 25°C during each temperature cycle are illustrated as an example in Fig. 3. There are lag

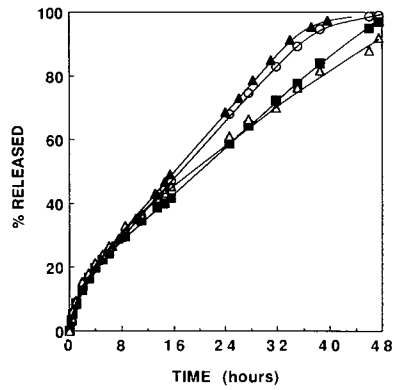

Fig. 2. Fractional release of indomethacin as a function of time from IPN matrices at 25°C: open circles, IPN(95/5); filled triangles, IPN(90/10); filled squares, IPN(75/25); open triangles, IPN(50/50).

Table II. Total Released Amount of Indomethacin from Poly(NIPAAm)/PTMEG IPNs in Each Temperature Cycle

Sample	High-temperature period			Low-temperature period		
	Period (hr)	Temp. (°C)	Amount (mg)	Period (hr)	Temp. (°C)	Amount (mg)
1st cycle						
IPN(95/5)	48	30/35	1.5	7	25	13.6
IPN(90/10)	48	30/35	1.6	7	25	12.8
IPN(75/25)	48	30/35	7.4	7	25	3.9
2nd cycle						
IPN(95/5)	17	35	0	7	25	5.5
IPN(90/10)	17	35	0	7	25	7.3
IPN(75/25)	17	35	1.0	7	25	2.6
3rd cycle						
IPN(95/5)	20	30	0	9	25	5.7
IPN(90/10)	20	30	0	9	25	6.0
IPN(75/25)	20	30	0.3	9	25	2.4
4th cycle						
IPN(95/5)	15.5	30	1.2	10.5	25	4.9
IPN(90/10)	15.5	30	0.9	10.5	25	6.0
IPN(75/25)	15.5	30	0.7	10.5	25	2.4

times in the third and fourth cycle, which may be caused by depletion of indomethacin in the outer region of the monolithic device.

As mentioned before, the on–off switching temperature was not consistent with the gel collapse temperature observed during swelling studies. A study was performed to estimate on–off temperature of a real device, as well as the influence of drug release near the on–off temperature. With an IPN(90/10) device, the short-term drug release profile was obtained at several fixed temperatures to approach the temperature inducing on–off drug release. Here, after keeping the initially dried device in buffer solution at 30°C for 4 hr, the temperature was decreased stepwise. The accuracy of the thermostat was 0.1° and the temperature was readable up to 0.01°. After keeping the device at a given temperature for 20 min, the release profile for 1 hr was obtained by continuous monitoring of the drug concentration in 1 liter of release medium. The bath temperature was readjusted to the next lower temperature and the indomethacin release for 1 hr was monitored after 20 min. These procedures were repeated at each temperature and relative initial slopes (slope at 25°C = 1) were plotted as a function of temperature, as shown in Fig. 4. As can be seen, no release was detected above 28.9°C. At 28.7°C, a low indomethacin release rate was detected and there was a sudden increase in release rate at 28.6°C. Below this temperature, the initial slope increased gradually with decreasing temperature. These slopes were obtained within the release of 20% of loaded drug in the same device. This result suggests that the on–off release occurs at a temperature between 28 and 29°C. The on–off release of indomethacin from IPN(90/10) matrix occurred a few degrees below the gel shrinking temperature of the unloaded matrix. This is probably caused by the interaction of the polymer matrix with indomethacin, which could alter NIPAAm chain properties, such as hydrophobicity of the polymer chain. A detailed study of solute effects on the lower critical solution temperatures of water-soluble polymer was reported by Taylor and Cerankowski (18).

There were difficulties in detecting the detailed behavior of indomethacin release in the transition state during tem-

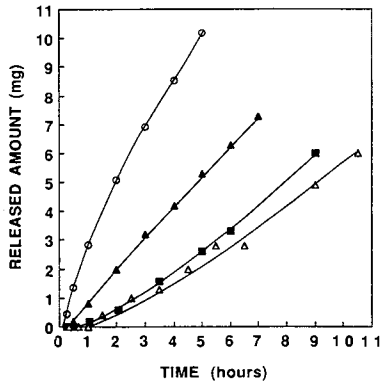

Fig. 3. Indomethacin release profile from IPN(90/10) at 25°C in each cycle: open circles, first cycle; filled triangles, second cycle; filled squares, third cycle; open triangles, fourth cycle.

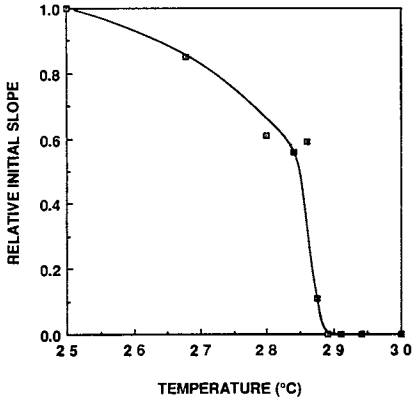

Fig. 4. Relative initial slope vs temperature. The relative initial slopes were obtained from indomethacin release for 1 hr from IPN(90/10) after keeping the device for 20 min at each temperature.

Table III. Temperatures and Time Period for Short-Term On–Off Release of Indomethacin from IPN(90/10)

	Temp (°C)	Period (hr)	
On	30	2	Cycle 1
Off	25	4	
On	30	7.66	Cycle 2
Off	25	4	
	37	36	
On	30	4	Cycle 3
Off	25	2	
On	30	3	Cycle 4
Off	25	4	
On	30	8	Cycle 5
Off	25	4	
On	35	5	Cycle 6
	25	1.5	

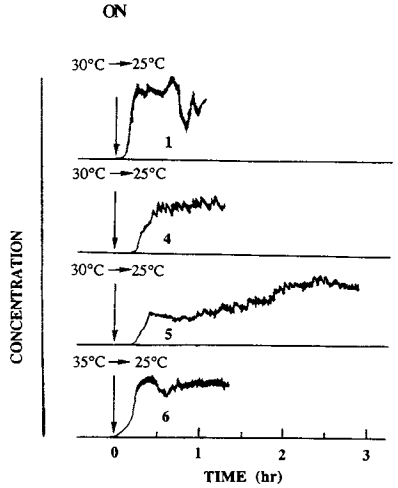

Fig. 6. Indomethacin release rates from IPN(90/10) in the on process. The arrows indicate the time point at which the temperature was changed.

perature changes by monitoring the cumulative released amount of indomethacin, namely, dilution effects and errors in detecting a small amount of indomethacin released for a short transition period of on–off process in a total of 1 liter of release medium. Thus, release rates were directly measured in a flow system, especially at the transition state for on–off release. The applied temperature, period, and cycle number are summarized in Table III. The temperature cycles (high → low → high temperature) were repeated in relatively short times as a comparison with previous experiments. In addition, changes from one temperature to another were completed within 3 min during each cycle. The off process during release is demonstrated in Fig. 5 with indicated cycle numbers and temperature changes. When the temperature was increased from 25 to 30°C, there were sharp double peaks within 20 min and a diminished concentration profile within 1 hr. Figure 5 suggests that the off process at 30°C, for the IPN(90/10) matrix, involves a "burst" of drug release. Dissolved drug existing in the outer layer of the device may be expelled quickly, followed by shrinking of the outer membrane and blocking of drug release by a rigid surface layer. At 35°C, the burst effect was significantly reduced with a shorter lag time.

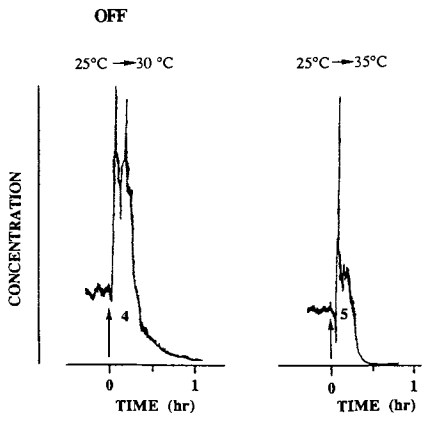

Fig. 5. Indomethacin release rates from IPN(90/10) in the off process. The figures indicate cycle number (e.g., 4 = four cycle). The duration of the on step in each cycle was about 4 hr. The arrows indicate the time point at which the temperature was changed.

The significance of the double peaks in the off process is not clear at this time. However, higher temperatures may more effectively block the drug release, with a reduced burst effect and shorter lag time. The on process was also affected by the applied temperature in the previous off process as seen in Fig. 6. When indomethacin release was not initiated at 25°C by decreasing the temperature from 30°C, the initial release rate decreased and the lag time increased in subsequent cycles. This may be caused from the gradual depletion of drug from the outer layer after each cycle and consistent with our previous results (Fig. 3). But the on process from 35°C showed a short lag time and an enhanced initial release rate, which may result from the rapid blocking effect during the previous off process.

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