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Rapid Communication

Photo-responsive hydrogels for potential responsive release applications

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Summary

Two *N*-isopropylacrylamide hydrogels that include photoreactive azobenzene groups were prepared, one copolymerized with monomer with an azobenzene pendant group (4-methacryloylaminoazobenzene) and the other formed with the crosslinker (4,4′-di(methacryloylamino)azobenzene. Azobenzene is known to isomerize and to change its dimensions on UV irradiation. Release of two model solutes (caffeine and poly(styrene sulfonic acid)) from the hydrogels was measured upon UV irradiation. The results show that UV irradiation of hydrogels with azobenzene pendant groups increases the extent of release from the matrix, while irradiation of hydrogels with an azobenzene crosslinker results in a decrease.

We report on preliminary research to obtain a photo-responsive drug delivery system in which irradiation via a fibre optic will release a drug from a reservoir. *N*-Isopropylacrylamide (NiPAAm) hydrogels containing azobenzene pendant or crosslinking groups were chosen as the delivery matrix; these hydrogels have negative thermosensitivity, at room temperature being highly water swollen in water, while on increasing the temperature a slow deswelling that becomes rapid as the temperature approaches the lower critical solution temperature (LCST) take place. When the LCST is reached, the gel collapses, losing its water content (Taylor and Cerankowski, 1975). Due to the negative thermosensitivity these gels are suitable matrices for drug delivery, since the drug can be loaded at lower temperatures (by swelling the gel in an aqueous solution of the drug) and then released at a higher temperature (Okano et al., 1990). There are three factors that affect the release profile of solutes from the NiPAAm hydrogels to an aqueous solution: the temperature, the degree of crosslinking and solute size (Hoffman et al., 1986). Co-polymerizing different molecules with NiPAAm changes the thermosensitivity of the hydrogel (Okano et al., 1990), and therefore results in different release kinetics of the drug at given temperatures.

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Two photoresponsive molecules, 4-methacryloylaminoazobenzene (MAAB) and 4,4′-di(methacryloylamino)azobenzene (DMAAB), the former as a co-monomer (with azobenzene as a pendant group) and the latter as a crosslinker (with azobenzene in the crosslinking unit) were incorporated into the polymer. The azobenzene group exists as the *trans* isomer and is known to isomerize to the *cis* isomer upon UV irradiation (300 nm $< \lambda <$ 360 nm). This process is slowly reversible in the dark, the reverse isomerization being enhanced by visual light ($\lambda > 420$ nm) (Kumar and Neckers, 1989). The light induced *cis* → *trans* isomerization changes the dimensions of the azobenzene group from 9 Å (*trans*) to 5.5 Å (*cis*) (Fig. 1) (Hampson and Robertson, 1941).

The materials used were *N*-isopropylacrylamide (Eastman Kodak), azoisobutyronitrile (Fluka), methylenebisacrylamide, methyl sulfoxide, phenylazoaniline, methacryloyl chloride, caffeine (Aldrich), poly(styrene sulfonic acid) (PSSA, average Mol. Wt 7000, Polysciences), 4,4′-azodianiline (Pfaltz & Bauer). 4-Methacryloylaminoazobenzene was synthesized as described by Eisenbach (1978). 4,4′-Di(methacryloylamino)-azobenzene was synthesized by the same method from 4,4′-azodianiline and methacryloyl chloride (molar ratio 1 : 2).

The hydrogels were prepared using free radical polymerization by dissolving the monomers, the crosslinker and the initiator (AIBN) in methyl sulfoxide. The solution was injected to 1.5 mm tubing and polymerization carried out at 60°C for 4 h. Cylindrical gels (2–3 mm length) were removed from the tubing and immersed in distilled

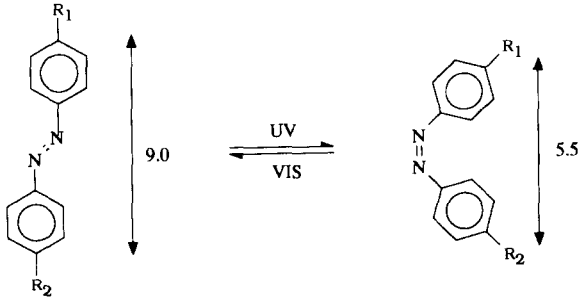

Fig. 1. Change in dimensions of the aromatic azo chromophore upon irradiation.

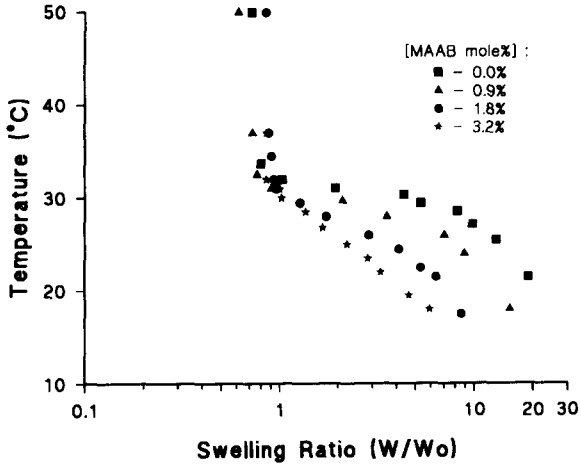

Fig. 2. The weight swelling ratio of NiPAAm/MAAB hydrogels with different concentrations of MAAB and 0.076 mol% crosslinker, in water as a function of temperature.

water for 7 days. Model drugs were loaded into the polymer by transferring the hydrogels to aqueous solutions of the drug (15 mg/ml) for 3 days. The hydrogels were taken out from the solution, the surface of the hydrogels was dried on a filter paper and the gel transferred to an aqueous solution in a silica cuvette. The temperature was controlled to ±0.2°C. Concentration was determined using a Shimadzu spectrophotometer (MPS-2000) at 273 nm for caffeine and 224 nm for PSSA. Fig. 2 shows the difference in the swelling profile (swelling ratio vs temperature, swelling ratio = $(W_{polymer} + W_{water})/W_{polymer}$) when different concentrations of a highly hydrophobic co-monomer, 4-methacryloylaminoazobenzene (MAAB) are incorporated into the hydrogel. Higher concentrations of MAAB increasing the hydrophobic interactions within the gel and reduce the swelling capacity, resulting in lower LCSTs as the concentration of MAAB increases. Therefore, increasing hydrophobic interactions control the thermosensitivity of the hydrogel and affect the release kinetics of the drug at a given temperature. We have induced a chance in the dimensions and interactions in the gel by UV irradiation, which results in changes in the solute release profile.

To test the functioning of azopolymer constructs we incorporated caffeine and PSSA into

modified hydrogels, irradiated them with a 200 W mercury-xenon lamp for 3 h and measured drug release at constant intervals.

Incorporating azobenzene pendant groups in the polymeric chain can result in two – opposite – effects as was previously reported (Lovrien, 1967; Matejika and Dusek, 1981) from viscosity measurements. In some structures the *trans* isomer increases the internal hydrophobic forces supporting a compact arrangement, while the formation of the *cis* isomer reduces those forces and allows the polymer chains to expand, while other structures show the opposite effect. Therefore, in some cases, UV irradiation can expand the polymer (Lovrien, 1967) and in others the opposite effect can be observed (Matejka and Dusek, 1981).

Fig. 3 shows release data of caffeine from copolymerized hydrogels of NiPAAm and MAAB (2.9 mol%) with 0.8 mol% methylenebisacrylamide (crosslinker) at 30°C, upon UV irradiation. Gels irradiated by visual light were used as controls. UV irradiation increased the release of caffeine by 8% after 3 h. This suggested that in this case, the UV-induced *cis* isomer reduces the hydrophobic forces inside the hydrogel, and allows it to expand at the micro level to increase diffusion rate from the network.

Fig. 4 shows the release profile of PSSA from poly(NiPAAm) hydrogels crosslinked with 0.36 mol% of DMAAB at 30°C. The release upon UV irradiation was reduced by 10% after 3 h. The response of an azobenzene derivative used as a crosslinker has one most likely mechanism. Changing the *trans* isomer to *cis* by UV irradiation reduces the crosslink length and therefore should reduce the free volume inside the network, causing a lower diffusion rate from the hydrogel.

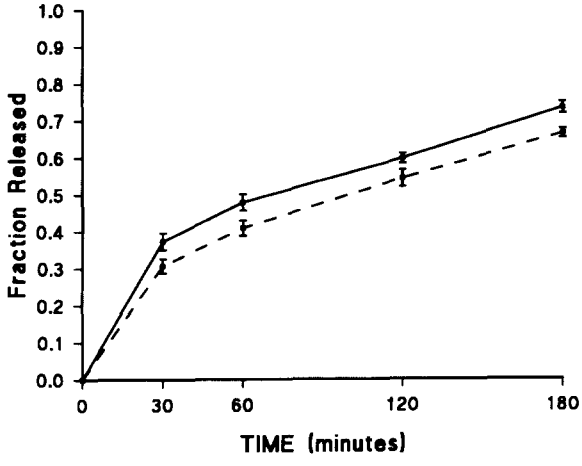

Fig. 3. Fraction of caffeine released upon UV irradiation (solid line) and visual light (dashed line); $n = 3$.

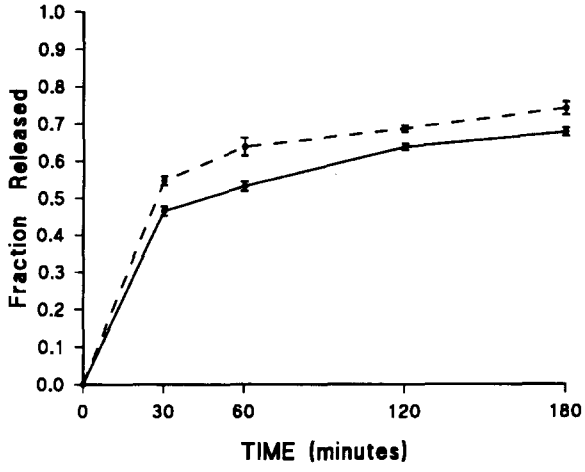

Fig. 4. Fraction of PSSA released upon UV irradiation (solid line) and visual light (dashed line); $n = 3$.

Although the extent of the change in the release rate in each case was not great, the results show that given the optimum concentration of polymer, photoresponsive molecule and crosslinker, controllable polymer systems of drug delivery can be fabricated. When MAAB is used as co-monomer, UV irradiation increases release from the network, while when DMAAB is used as crosslinker, release is reduced upon UV irradiation. Our results emphasize the potential in using photoirradiation as a trigger for responsive and pulsatile drug release.

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