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### Poly(Urethane)-Crosslinked Poly(HEMA) Hydrogels

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## **POLY(URETHANE)-CROSSLINKED POLY(HEMA) HYDROGELS**

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### **ABSTRACT**

Hydrogels have been prepared from 2-hydroxyethyl methacrylate polymerized in the presence of isocyanate-terminated poly(ethylene glycol) (PEG) crosslinking agents. PEGs of molecular weights 200, 400, and 1000 were investigated. The crosslinked nature of the hydrogels was demonstrated by their insolubility in solvents which normally dissolve poly(HEMA). Hexamethylene diisocyanate (HDI) was mainly used as the isocyanate. The molecular weight of the PEG and the crosslinker content significantly influenced the equilibrium water sorption and mechanical properties of the saturated networks. It was observed that as the molecular weight of the PEG increased, the water sorption increased and the nominal modulus decreased. However, for higher levels of crosslinker, water sorption decreased and modulus increased at low molecular weight PEG; for PEG 1000, water absorption increased as crosslinker content increased. These results are explained by the competing effects of flexibility, crosslink density, and hydrophobicity contributed by the various constituents of the hydrogels.

### **INTRODUCTION**

Hydrogels are polymeric systems designed to contain a significant amount of water. They are used in various ways in the biomedical field, including soft contact lenses [1], drug delivery systems [2, 3], and burn dressings [4]. High water content,

a soft and rubbery nature, and good transport properties contribute to their acceptance as biomaterials. The most thoroughly investigated hydrogels are based on polymers of 2-hydroxy-ethyl methacrylate (HEMA). These polymers are generally crosslinked in order to provide dimensional stability and improve the mechanical properties; low concentrations of multifunctional methacrylates are typically used as crosslinking agents. Crosslinking with these materials, though, usually results in a decrease in the equilibrium water content and diffusion coefficient [2, 5, 6]. Certain hydrophilic monomers (such as *N*-vinyl-2-pyrrolidone) do promote high equilibrium water contents [5, 7].

One factor which has hindered the clinical use of hydrogels is the poor mechanical response of the hydrated network [1, 8] and the stiff and brittle nature of the dry polymer. The purpose of our work was to flexibilize the P(HEMA) network, both in the dry and hydrated states, without sacrificing water absorption properties, by introducing crosslinkers based on isocyanate-terminated poly(ethylene glycol) (PEG) chains of various molecular weights (200, 400, 1000). Polyurethanes have been recognized as possessing relatively good biocompatibility, while PEG contributes hydrophilicity, flexibility, and biocompatibility [9]. Isocyanate-terminated PEG trimers were prepared by reacting diisocyanate and PEG in a 2:1 mole ratio. The NCO-terminated trimers were then reacted with the OH pendant groups of HEMA, at the desired concentration, while HEMA polymerized in the presence of azo-bis-isobutyronitrile, following the conventional free radical mechanism. This process of simultaneous polymerization and crosslinking resulted in hydrogels of controllable hydrophilic and mechanical properties, depending upon the nature of the poly(urethane) (PU) trimer. The molecular weight (MW) of the PEG segment, type of isocyanate, and crosslinker content were all observed to be important factors.

## EXPERIMENTAL

### Materials

The hydrogels were prepared from HEMA monomer (Hydro Med Sciences), 99.6% pure, which was used as received. The monomer contained less than 0.02% ethylene glycol dimethacrylate. PEGs of molecular weights 200, 400, and 1000 were purchased from Aldrich. Two isocyanates were investigated: aliphatic hexamethylene diisocyanate (HDI) and aromatic diphenylmethane diisocyanate (MDI). The isocyanates were purchased from Sigma. The isocyanate-PEG reaction was catalyzed with dibutyl tin dilaurate (Fluka), whereas the HEMA polymerization was initiated with azo-bis-isobutyronitrile (AIBN) (Merck). Analytical grade solvents (Frutarom, Israel) were used as received.

### Preparation of PU Crosslinking Agents

Two methods were investigated for the preparation of the PU crosslinking agents, or trimers as they will be referred to. (It is realized that additional oligomers, besides trimers, could have been formed.) The first method involved conducting the reaction in bulk, and the second method in solution. For the bulk method, 0.1 mol PEG, 0.205 mol HDI, and 0.05 cm<sup>3</sup> dibutyl tin dilaurate were mixed thoroughly in

an atmosphere of dry nitrogen. The reaction was carried out at room temperature (RT) in a closed container with constant shaking for 4 h. For the solution preparation, 0.205 mol HDI and 0.05 cm<sup>3</sup> of the catalyst were dissolved in 25 cm<sup>3</sup> THF in a reaction vessel in an inert atmosphere. A solution of 0.1 mol PEG in 75 cm<sup>3</sup> THF was added dropwise over a period of 30 min, and then the reaction was conducted at 80°C for 1.5 h. However, difficulty in purifying the trimer from the solvent led to bulk synthesis being selected as the method of choice.

### Preparation of Crosslinked Hydrogels

HEMA was crosslinked either with diisocyanate alone or with an isocyanate-terminated trimer. As a control, HEMA was polymerized without crosslinker, following the same procedure as described in the following, except for the addition of the crosslinker. The crosslinking agent was dissolved in HEMA according to the desired mole ratio in a polypropylene (PP) vial, followed by addition of 0.05 wt% of AIBN (based on the weight of the HEMA monomer). The reactants were mixed well under dry nitrogen, the container was sealed, and then placed in an oven at 60°C. The reaction was continued for 30 h.

### Monitoring of Reactions

Two methods were used for monitoring the progress of the trimer formation and the reaction of a model system representing the polymerization-crosslinking reaction. Both methods were based on the disappearance of isocyanate groups. In the first method, FTIR (Analect model FX-6260) was used to monitor the decrease of the characteristic isocyanate band at 2274 cm<sup>-1</sup>. Measurements were taken on liquid samples placed between two NaCl plates. The second method involved a standard titration procedure used for determining the amount of NCO groups by reacting the sample with butylamine. Free isocyanate groups react with the amine to yield ureas. The excess nonreacted amine was titrated with HCl. A blank amine titration was run, and the difference in the amount titrated was the amount of isocyanate remaining in the sample [10].

### Sorption Experiments

In order to determine the rate and equilibrium amount of water sorption of the various materials, as well as the associated dimensional changes, disks were cut from the bulk polymer removed from the PP containers. The sample size was 3.06 cm diameter by 0.5 cm height. These dimensions approximate one-dimensional diffusion, although a higher aspect ratio would have been preferred. Each sample was placed in 100 cm<sup>3</sup> of distilled water at 37°C. Weights were recorded periodically during a period of 10 days in order to insure the attainment of equilibrium. Generally, 120 h was sufficient, after which time no further changes in weight were observed. The equilibrium weight gains of water reported here refer to the weight of water/weight of dry polymer. Changes in dimensions at equilibrium were recorded with a micrometer to a precision of 0.01 mm; the changes in dimensions were used to calculate the volume change on swelling.

## Mechanical Properties

Samples which had reached saturation were tested in compression in an Instron tensile tester (Model 1114). Four samples of each polymer were tested to determine the nominal compression modulus, which was taken from the load-crosshead displacement chart.

## RESULTS AND DISCUSSION

### Progress of Trimer Reaction

The results of both the titration and FTIR indicated that the number of NCO groups decreased rapidly to approximately one-half the starting amount after 15 min, and thereafter remained constant. These data were used as evidence that isocyanate-capped trimers were formed.

### Progress of Polymerization/Crosslinking Reaction

Due to the difficulty of quantitatively following the crosslinking reaction, and in order to verify that the isocyanate groups did react with the OH groups of HEMA, a model system was investigated. The model consisted of HDI or trimer dissolved in HEMA at a mole ratio of 1:10, but without the addition of the AIBN. In other words, the polymerization of HEMA was suppressed, but the "crosslinking" reaction was allowed to proceed. The reaction was conducted as described above: the reactants were mixed under nitrogen for 10 min, then the PP vials were sealed and placed in an oven at 60°C. The material was removed after various times, and FTIR and titration were performed. There was good agreement between the two methods. As an example, Fig. 1(a) shows the reaction mixture (HEMA and HDI) at time zero, where the NCO peak at 2274  $\text{cm}^{-1}$  is clear. After about 2 h at 60°C, no NCO peak is evident (Fig. 1b).

The time in the model system for completion of the isocyanate-hydroxyl reaction was dependent on concentration and type of crosslinker. Higher concentrations of HEMA and lower concentrations of crosslinker led to shorter reaction times. Also, as expected, the aromatic isocyanate (MDI) reacted faster than its aliphatic counterpart.

Whereas no quantitative analyses were conducted on the crosslinked and polymerized P(HEMA) systems, in terms of disappearance of NCO groups, the resulting polymers swelled but remained insoluble in solvents, such as DMF and ethylene glycol, which normally dissolve uncrosslinked P(HEMA). This insolubility confirmed the crosslinked nature of the polymer.

### Equilibrium Sorption Results

The effect of the concentration of HDI crosslinker on the equilibrium water absorption of P(HEMA) is summarized in Fig. 2. As expected, as the concentration of HDI is increased, the equilibrium water absorption decreases, which is the normally observed effect of increasing levels of crosslinker. In addition to the increase in crosslink density, there is a concomitant decrease in the polarity of the system,

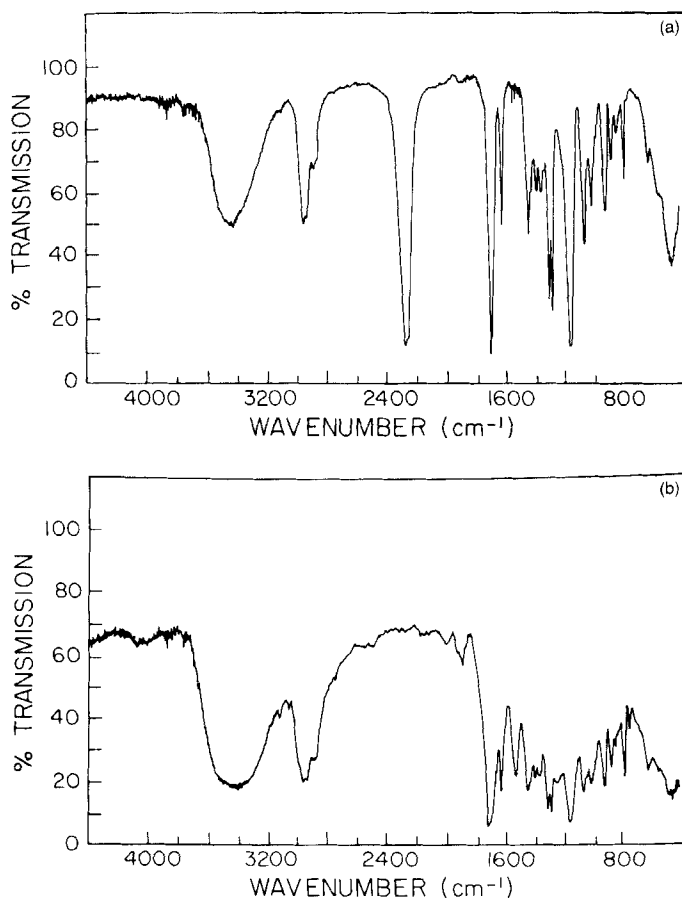


FIG. 1. Infrared spectrum of HEMA and HDI mixture (10:1 mole ratio): (a) beginning of reaction; (b) after 2 h at 60°C.

since HEMA hydroxyl groups are exchanged for less polar urethane groups, and hydrophobic methylene groups of HDI are introduced. All these factors explain the rather severe decrease in water absorption as the level of HDI is increased.

The equilibrium water absorption of the crosslinked P(HEMA) as a function of the trimer MW and concentration is shown in Fig. 3. Two trends are evident from these data. First of all, as the MW of the PEG segment increases, the absorption of water increases, which can be understood by the increased number of polar ethylene oxide (EO) groups per molecule of crosslinking agent. The more open structure of the resulting network, as the length of the crosslinker increases, should also contribute to the increase in sorption. (This point will be discussed later in connection with mechanical properties.) Second, as the concentration of crosslinker increases, water absorption decreases for the low MW trimers (PEG 200 and 400) and increases for the high MW crosslinker (PEG 1000). This can be explained by the dominant effects of the hydrophobic HDI methylene groups and the disappearance of OH groups at low PEG molecular weight, whereas with PEG 1000, the increased length, flexibil-

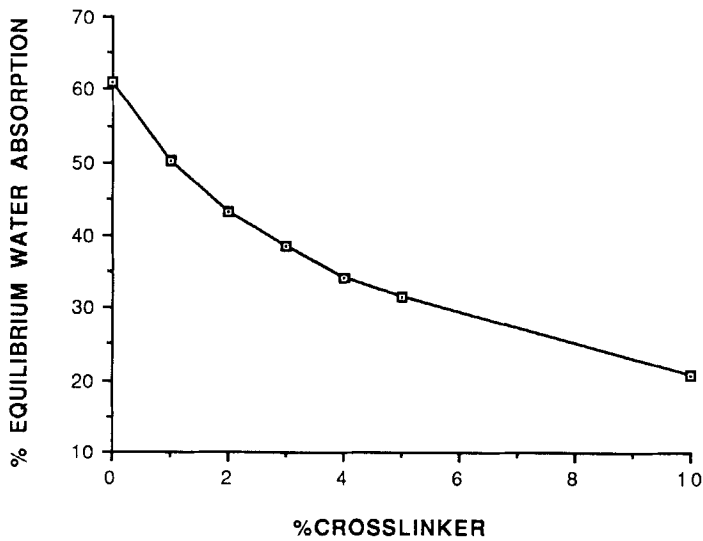


FIG. 2. Percent equilibrium water absorption as a function of HDI crosslinker content.

ity, and number of hydrophilic groups balance these two negative factors. This second trend also indicates that only the PEG-1000 trimer is able to enhance the matrix hydrophilicity and equilibrium water content with increasing levels of crosslinker. Thus, P(HEMA) hydrogels with desired sorption properties should be attainable by the proper selection of hydrophilic crosslinking agents.

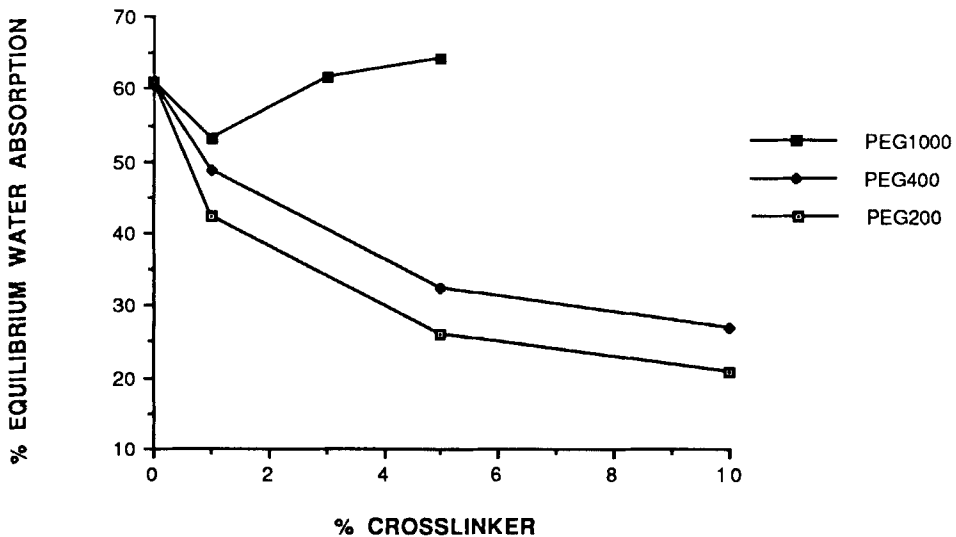


FIG. 3. Percent equilibrium water absorption as a function of crosslinker content for different HDI-terminated trimers.

Finally, the lack of success of PEG 200 and PEG 400 (except for 10% crosslinker) in exceeding the sorption properties of HDI-crosslinked P(HEMA) can be attributed to the fact that each PEG molecule has two HDI molecules associated with it. Also, with the method used in this work, it was not possible to dissolve more than 5% of the PEG-1000 trimer in HEMA. We are currently investigating systems crosslinked in solution in which much higher levels of hydrophilic trimers were introduced into the system, thereby greatly increasing the equilibrium water absorption.

Although it was assumed that the flexibility of the network also contributes to the overall water sorption, this point was investigated further by comparing P(HEMA) crosslinked with 5% HDI as opposed to 5% MDI. MDI is aromatic and therefore considerably stiffer than HDI; MDI is also not as hydrophobic as HDI. The equilibrium values of water absorption are as follows: P(HEMA)/HDI, 31.6%; P(HEMA)/MDI, 24.4%. If the same number of hydroxyl groups was consumed by each crosslinker, then we are led to the conclusion that the stiffness of the matrix can also significantly affect the amount of water absorbed by the hydrogel, independent of the crosslinking density.

At the end of the sorption experiments, the changes in diameter and height were recorded for each sample, and the volume change due to swelling was calculated. The results were used to determine the volume fraction of polymer in the swollen hydrogel; the volume fraction was in turn used to calculate the diffusion coefficient (see next section).

The data from Figs. 2 and 3 can be replotted as % equilibrium water absorption vs the molecular weight of the PEG segment of the crosslinker for different levels of crosslinking (Fig. 4). HDI, without PEG, is shown on the figure as having

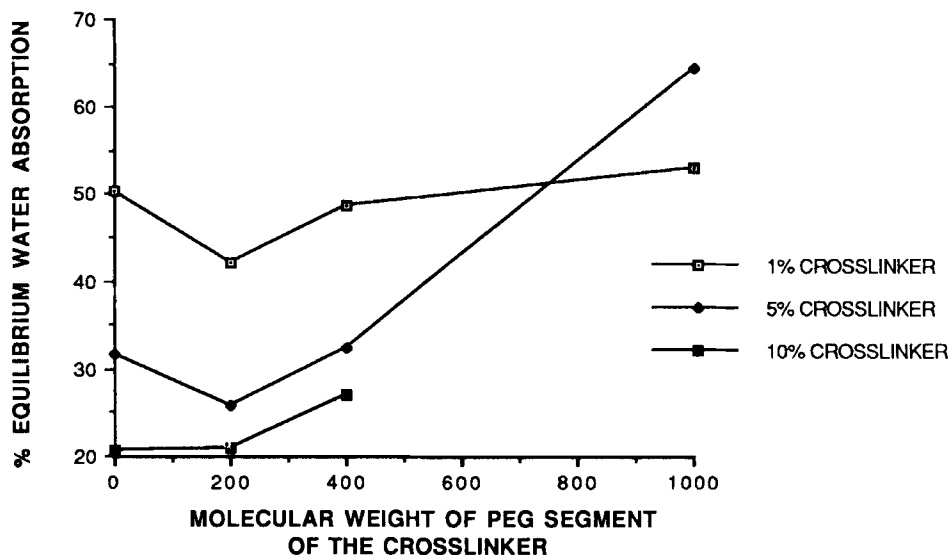


FIG. 4. Percent equilibrium water absorption as a function of the molecular weight of the PEG segment of the crosslinker for different amounts of crosslinker (note that 0 molecular weight refers to the HDI crosslinker without PEG).



zero molecular weight. This plot gives a different perspective on the data, and shows that at 1% crosslinker none of the trimers is effective in increasing the water absorption above the value of HDI. At the higher levels of crosslinker, only the PEG-1000 trimer dramatically improves the sorption characteristics of the hydrogels.

### Kinetics of Sorption

Various models have been presented for the kinetics of penetrant sorption in glassy polymers [3]. For polymers which only absorb small amounts of penetrant, with little or no swelling, Fickian absorption is generally observed (i.e., weight gain is initially proportional to  $\text{time}^{1/2}$ ). However, for systems which swell significantly in the solvent, such as the effect of water on hydrogels, then deviations from Fickian behavior have been observed. The data are commonly plotted as  $M_t = Kt^n$ , and various values of  $n$  are used for the linear portion of the data [6, 11]. The results for the materials reported in this work are shown in Figs. 5 and 6, where % water absorption ( $M_t$ ) is plotted against  $\text{time}^{1/2}$ . It can be seen that linearity is observed for all the systems studied, both HDI-crosslinked (Fig. 5) and trimer-crosslinked (Fig. 6), seemingly indicating Fickian behavior. However, from a study of a number of models extant in the literature, it appears that sample size is an important factor in influencing the observed behavior [12–14]. In this work a rather large sample dimension was used (5 mm), which may have masked any anomalous effects which were occurring. The large sample size does contribute to accuracy in the measurements, since removal of the samples for weighing should not introduce much error.

From the data presented in Figs. 5 and 6, along with the equilibrium sorption values, it is possible to extract a nominal diffusion coefficient by using the equation

$$M_t = 4M_{\text{eq}}t^{1/2}(D/L^2)^{1/2}\pi^{-1/2} = Kt^{1/2} \quad (1)$$

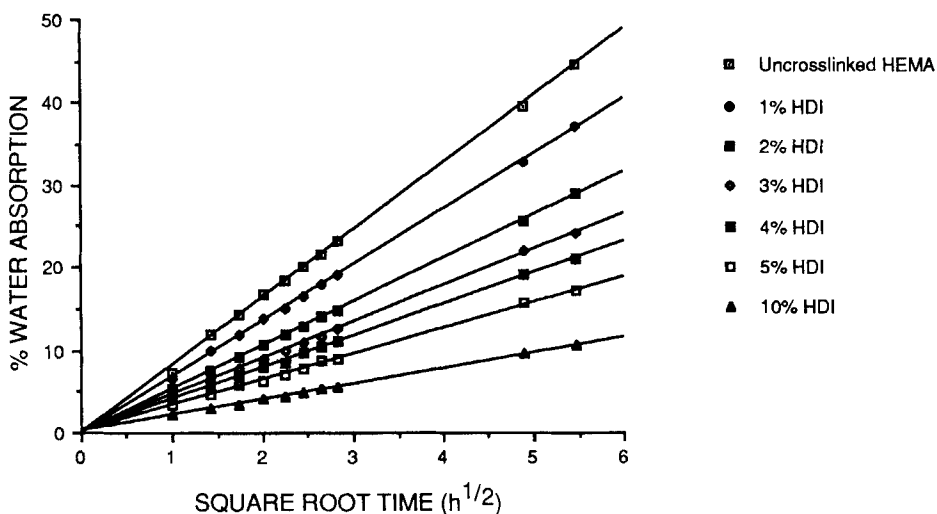


FIG. 5. Percent water absorption as a function of  $\text{time}^{1/2}$  ( $h^{1/2}$ ) for different levels of HDI crosslinker.

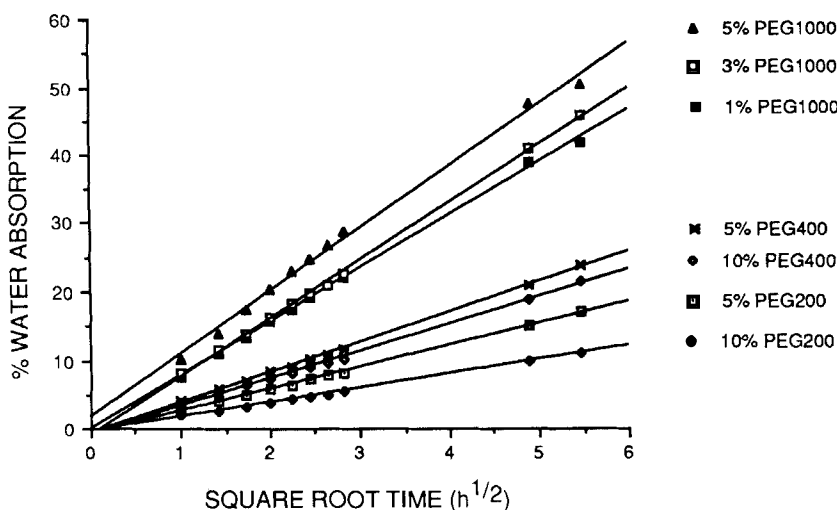


FIG. 6. Percent water absorption as a function of  $\text{time}^{1/2}$  ( $\text{h}^{1/2}$ ) for crosslinking with HDI-terminated trimers at different levels.

where  $M_{\text{eq}}$  = equilibrium water absorption,  $L$  = sample thickness, and  $D$  = diffusion coefficient. Since the dimensions are not constant due to the extensive swelling, a correction must be introduced, as discussed by Crank [15]. The correction factor is given as

$$D_s = D/V_p^2 \quad (2)$$

where  $D_s$  = diffusion coefficient in the swollen sheet and  $V_p$  = volume fraction of the polymer. The results for the different crosslinking agents are shown in Fig. 7., which can be compared with Figs. 2 and 3 for the effects of crosslinking on equilibrium sorption. For HDI, the decrease in diffusion coefficient with increasing amounts of crosslinker parallels the effect on water saturation level. For the trimers, the same general behavior is observed in that increasing MW leads to an increase in rate of diffusion. At higher levels of crosslinking for the trimers, the diffusion coefficient is greater than that of HDI, and even increases for PEG 400 and PEG 1000, which may indicate some level of increased flexibility of the network.

### Mechanical Properties

The effect of the trimers in flexibilizing the network was determined by measuring the equilibrated hydrogels in compression. A nominal modulus,  $E'$ , was calculated, and the results for HDI and PEG 200 and 400 crosslinked networks are reported in Table 1. These results show that for each of the materials tested, as % crosslinker increases, the flexibility decreases. This is consistent with the decrease in water absorption observed for these networks at the higher levels of crosslinking. In addition, the trimers yield more flexible networks, the flexibility increasing as MW increases. These data are not completely consistent with those of the water

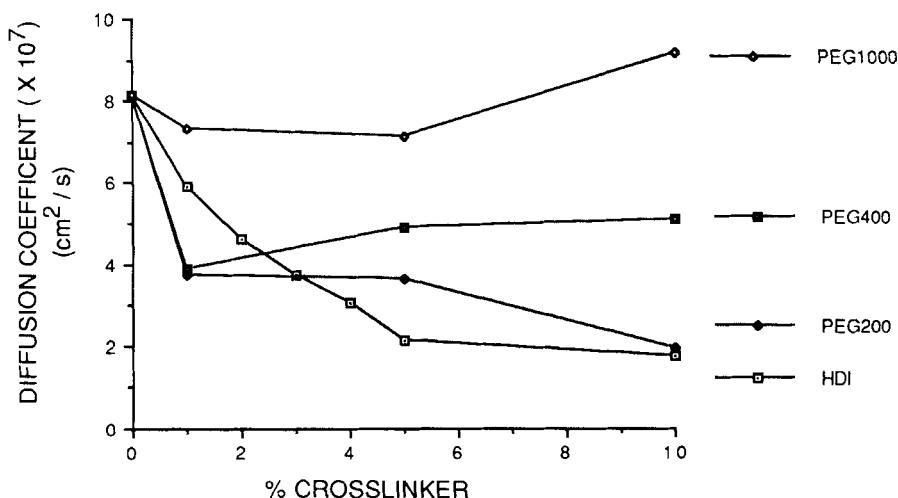


FIG. 7. Diffusion coefficient ( $\times 10^7$  cm<sup>2</sup>/s) as a function of crosslinker content for HDI and HDI-terminated trimers.

absorption, as can be seen by a comparison with Fig. 4. For example, at 5% crosslinker content, the PEG-200 trimer crosslinked hydrogel absorbs less water than with HDI alone, but is nevertheless slightly more flexible. At 10% crosslinker, the PEG-200 trimer yields a considerably more flexible network than the one crosslinked with HDI, but the water absorption is practically identical.

These observations lend support to the idea that water absorption is controlled by two, sometimes competing, factors: the chain stiffness or flexibility and the polarity of the system. For PEG 200, the short PEG chains do not impart enough hydrophilicity to the system to overcome the hydrophobic HDI groups and the decrease of OH entities. For PEG 400, only higher concentrations contribute enough flexibility and hydrophilicity to compensate for the HDI. For PEG 1000, it appears that low concentrations are effective in rendering the polymeric network flexible and hydrophilic enough to absorb large amounts of water.

TABLE 1. Effect of Crosslinker Type and Concentration on Nominal Modulus of Saturated Networks

Type of crosslinker	% Crosslinker	$E'$ , MPa
HDI	5	3.9
HDI	10	5.0
PEG-200 trimer	5	3.7
PEG-200 trimer	10	4.3
PEG-400 trimer	5	3.2
PEG-400 trimer	10	3.7

## CONCLUSIONS

Hydrogels are generally crosslinked by materials which lead to decreases in the water absorption and flexibility of the network. The purpose of this work was to introduce trimeric crosslinking agents, polyurethane in nature, which would flexibilize the networks without reducing the hydrophilicity. The PU crosslinking agents were composed of isocyanate(HDI)-terminated PEGs of various molecular weights: 200, 400, and 1000. At a given level of crosslinking, water absorption increased as the PEG molecular weight increased due to the enhanced polarity and flexibility of the network. However, only the PEG-1000 trimer resulted in higher levels of water absorption at increasing levels of crosslinking. The overall water absorption is influenced by the system polarity and flexibility. At low PEG molecular weight, the contributions to the polarity and flexibility are not enough to overcome the hydrophobic methylene groups of the HDI and the decrease in OH moieties as more crosslinker is introduced. PEG 1000 is long enough to contribute sufficient flexibility and polarity to compensate for the negative influences of the hydrophobic HDI and disappearance of OH groups. Thus, hydrogels of controlled properties should be obtainable with the proper selection of trimeric crosslinkers as described in this work.

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