The physico-chemical characterization of poly (2-hydroxyethyl methacrylate-co-methacrylic acid: 2. Effect of water, PEG 400 and PEG 6000 on the glass transition temperature

J. Verhoeven, R. Schaeffer, J. A. Bouwstra* and H. E. Junginger
Centre for Bio-Pharmaceutical Sciences, Division of Pharmaceutical Technology, PO Box 9502, 2300 RA Leiden, The Netherlands
(Received 27 July 1988; revised 11 January 1989; accepted 20 February 1989)

Today, attention in the design of new drug delivery systems is focused on the application of so-called hydrogels. These hydrogels have the attractive property of swelling in water without dissolving. One of the important parameters which affects the diffusion of solvents and solutes in these swellable systems is the glass transition temperature (T_g). When the T_g is exceeded the hydrogel transforms from a glassy to a rubbery state, thereby potentially triggering the diffusion of drugs which are incorporated in these polymers. A range of copolymers of 2-hydroxyethyl methacrylate and methacrylic acid was prepared as a first step in the design of a transdermal drug delivery system. When on the human skin, these systems will meet changing humidity and pH conditions. Therefore, the T_g values of both the dry co-polymers and the effect on the T_g of water, PEG 400 and PEG 6000 were measured, as well as the effect of the pH. Both water and PEG 400 are excellent plasticizers, whereas the effect of the pH of the medium appears to be of minor importance. In addition, the structure of water in the hydrogels was studied by differential thermal analysis (d.t.a.), indicating an amount of 'non-freezing' water. It was concluded that this phenomenon results from non-equilibrium experimental conditions.

(Keywords: poly-(2-hydroxyethyl methacrylate-co-methacrylic acid); glass transition temperature; plasticizer; water; PEG 400; differential thermal analysis)

INTRODUCTION

In the design and development of new transdermal drug delivery systems, much attention is focused on the class of hydrogels. Hydrogels are hydrophilic polymers which have the attractive property of swelling in water without dissolving. Due to the strong solvating effect of water on these hydrophilic macromolecules, water is an excellent plasticizer, having a strong relaxing effect on the polymeric chains. The resulting increase in chain mobility can lead to the transformation of the polymer from its glassy state into the rubbery state. Moreover, water leads, on a macroscopic level, to swelling of the hydrogel. During this process a large amount of water is absorbed into the gel. The polymer then transforms from the glassy state into the rubbery state and the polymeric system 'opens up' to absorb extra water into its structure. When the rate of penetration of water is of about the same order of magnitude as the relaxation process of the polymer, the penetration is accompanied by a clearly visible moving front which separates the swollen rubbery region from the glassy region. Thus the rate of penetration of water into the hydrogel depends to a large extent on the glass transition temperature (T_g) of the hydrogel. This emphasizes the importance of studying the relationship between the T_g of the hydrogel and the amount of water which penetrates the hydrogel.

The properties of swelling and water sorption were recognized by many to be of potential use in the design of new drug delivery systems. By incorporating drugs into a hydrogel and subsequently controlling the rate of swelling and water sorption, it might be possible to control the diffusion rate and thus the rate of drug delivery. The most important property to determine this process seems to be a combination of the hydrophilicity/hydrophobicity of the polymer and the degree of crosslinking[1].

In a previous paper[2] we reported the tacticities and reactivity ratios of a range of crosslinked poly-(HEMA-co-MAA) hydrogels. Both parameters strongly affect the T_g of the copolymers. However, once the copolymers have been prepared their composition and tacticity are fixed and as a result, the T_g of the copolymers is also fixed. Only processes like thermal annealing and quenching might still change the physico-chemical behaviour of the hydrogel. It is our intention in this paper to study these 'fixed' T_g values in relation to plasticizers such as water, PEG 400 and PEG 6000 and to check to what extent they are related. Potential pH effects of the swelling medium on the T_g of the copolymers were also studied.

The reason for looking at these relationships originates from the potential application of these hydrogels on the human skin as transdermal drug delivery systems. On the skin we encounter conditions such as high humidity and decreasing pH (from about 6 to about 5) incurred by the occlusive effects of these systems. In order to find out whether these *in vivo* conditions can trigger the

* To whom correspondence should be addressed

0032-3861/89/101946-05$03.00

release of drugs and to what extent they affect the rate of release of drugs, we tried to map the effects of humidity and pH on the T_g values of these hydrogels.

EXPERIMENTAL

2-Hydroxyethyl methacrylate (HEMA) (Serva p.a.), methacrylic acid (MAA) (Fluka, purum) and ethylene glycol–dimethacrylate (EGDMA) (Serva p.a.) were used as the basic components of the copolymer. Azoisobutyronitrile was used as radical initiator. Demineralized water was added (35% m/m) as solvent to prevent vitrification during the polymerization process. The HEMA contained several impurities, such as MAA, EGDMA, ethyleneglycol, water and inhibitor. It was purified over an activated basic alumina column to contain no more than 0.1 mol% MAA and 0.25 mol% EGDMA. The inhibitor was removed by column elution over Amberlyst A_{26} (Serva). PEG 400 and PEG 6000 were of pharmacopoeia grade (DAB IX). All other chemicals used were of analytical grade.

The monomer mixtures used to prepare the copolymers had the composition listed in *Table 1*. In addition, EGMDA 0.3% mol, AIBN 0.03% mol were used in a 65 vol% in water. When PEG 400 or PEG 6000 were added to this mixture we used 75% m/m of the above mixture and 25% m/m PEG. The mixture was carefully degassed before use. The polymerization reaction was performed in small stoppered glass tubes. The temperature programme for the polymerization was: from 298 K to 343 K in 1 h (0.75 K/min) followed by a 24 h isothermal period at 343 K ($t_{\frac{1}{2}}$ AIBN $\approx$ 3.5 h at 343 K). The polymers were rinsed at room temperature for two weeks in demineralized water which was refreshed daily. They were cut in small pieces and dried under vacuum over phosphorus pentoxide for one week.

Differential thermal analysis (d.t.a.) of the dry copolymers was performed with a Mettler DSC 3000. The temperature scan was performed from 293 K to 453 K at 10 K/min. Glass transition temperatures, T_g, were measured from these scans.

The effect of water (T_g = 135 K (refs. 9, 10)) and both PEG 400 (T_g = 198 K) and PEG 6000 (T_g = 259 K) on the T_g was monitored by d.t.a. scans cooling from 292 K to 192 K followed by an immediate increase back to 373 K. Both scans were carried out at 10 K/min.

The composition of the buffers was: pH 4.15 (citric acid · 1 H_2O 2.577 g/l; $Na_2HPO_4 \cdot 2H_2O$, 2.737 g/l); pH 7.15 (citric acid · 1 H_2O 0.742 g/l; $Na_2HPO_4 \cdot 2H_2O$ 5.935 g/l); pH 9.05 (boric acid 0.183 g/l, borax · 10 H_2O 17.954 g/l).

Table 1 Experimental and calculated T_g data (according to equation 1) for different dry poly-(HEMA-co-MAA) polymers

MAA (mol%)	$T_{g_{exp}}$ (K)	$T_{g_{calc}}$ (K)
0	363.5	363.5
10.1	363.4	365.7
20.1	366.7	368.2
30.2	374.2	371.1
40.2	377.0	374.6
50.2	378.2	378.7
60.2	384.9	383.6
70.2	389.2	389.8
80.1	395.7	397.5
90.1	407.5	407.9
100.0	422.7	421.9

Table 2 Calculated parameters from equation (2) for three different polymer systems (*p*-HEMA, 50/50 *p*-(HEMA-co-MAA) and *p*-MAA), at three different pH-values (4.05; 7.15; 9.05)

Sample	K[a]	T_g (K)	SS_{res}[b]	n[c]	r[d]
p-HEMA					
4	2.854	369.6	132.4	13	0.9883
7	2.799	371.2	216.6	13	0.9819
9	2.760	368.9	98.6	10	0.9921
4+7+9	2.806	369.9	465.6	36	0.9878
co-pol					
4	2.309	386.1	1468.6	15	0.9123
7	3.115	406.3	441.2	19	0.9547
9	2.440	416.8	1559.3	17	0.9398
4+7+9	2.265	400.9	8739.5	51	0.8665
p-MAA					
4	2.336	447.0	983.5	11	0.9430
7	2.854	449.8	636.4	11	0.9747
9	1.838	445.9	378.0	9	0.9417
4+7+9	2.420	448.6	2853.5	31	0.9430

[a] K = constant
[b] SS_{res} = residual sum of squares
[c] n = number of data points
[d] r = correlation coefficient

The T_g of the copolymers was fitted to equation (1):

$$M_A\left(\frac{\alpha_A}{W_A}\right)(T_g - T_{gA}) + M_B\left(\frac{\alpha_B}{W_B}\right)(T_g - T_{gB}) = 0 \qquad (1)$$

where M_A and M_B are the weight fractions of the monomers; α_A and α_B are the number of flexible bonds per monomer unit and W_A and W_B are the molecular weights of the monomers. T_{gA}, T_{gB} and T_g are the experimental T_g values of the homopolymers and the copolymer, respectively. The flexible bonds (α) were defined as the number of rotatable bonds of the monomeric unit, which can change the shape of the homopolymer on rotation. The number of flexible bonds in (*p*-)HEMA is 5 and in (*p*-)MMA is 2, giving a theoretical value for the quotient of 0.4. By fitting this equation for a number of compositions, we could predict the T_g of other compositions of the same monomers. This was important both in the design and manufacturing of the hydrogels for drug delivery systems.

The relationship between the plasticizer concentration and the T_g can be described by

$$T_g = Kw_1T_{g_1} + w_2T_{g_2}/Kw_1 + w_2 \qquad (2)$$

T_{g_1} and T_{g_2} are the T_g values of the solvent and the polymer, respectively; w_1 and w_2 are the weight fractions ($w_1 + w_2 = 1$) and

$$K = (\alpha_r - \alpha_g)_2/(\alpha_r - \alpha_g)_1$$

where α_r and α_g are the expansion coefficients in the rubbery state and glassy state for the solvent (1) and the polymer (2) respectively.

The effect of water and pH on T_g

The results of the glass transition measurements are presented in *Table 1*. The data were fitted by equation (1) with Fletcher's variable metric method resulting in a glass transition temperature of 363.5 K for HEMA and

421.9 K for MAA. In comparison, data for 'conventional' (i.e. syndiotactic) p-HEMA in the literature range from 347 to 373 K (ref. 11). The calculated value for $\alpha_{MAA}/\alpha_{HEMA}$ was 0.347 (the residual sum of squares, $SS_{res} = 29.2$) which is close to the theoretical value of 0.4. Both the experimental points as well as the calculated fit are presented in *Figure 1*.

The effect of water on the T_g is presented in *Figure 2* for *p*-HEMA (*Figure 2a*) and *p*-MAA (*Figure 2b*). *Figure 3* shows the effect of water on a 50/50 copolymer in the presence of buffers with pH values of 4.15, 7.15 and 9.05. Some differences were observed in that for both homopolymers, no effect of the pH was seen. However, for the 50/50 copolymer there was a tendency towards an increase in the solvent effect (see *Figure 3a, b* and *c*) on the T_g at the lower pH. The fit according to equation (2) was poor especially at a pH of 4, and there was a much steeper initial slope (*Figure 3a*). Perhaps the presence of dimers between carboxylic groups within the copolymer plays an important role here, which effect is neutralized by the water. However, one might expect a similar effect with *p*-MAA (*Figure 2b*).

It may be doubted whether ions are capable of penetrating the swollen hydrogels[8]. However, the degree of swelling increased at the higher pH, and this is undoubtedly an effect of the ionization.

It should be noted that the T_g values of the dry (co)polymers in these experiments were higher than similar data presented in *Table 1*. This was due to a difference in the drying procedure. The polymers used in the last experiment were dried under vacuum at 323 K for two weeks in contrast to the polymers dried over phosphorus pentoxide at room temperature.

The effect of PEG 400 and PEG 6000 on the T_g

The effect of both PEG 400 and PEG 6000 on the T_g are presented in *Figure 4* for *p*-HEMA and a 50/50 copolymer. The data could not be fitted to equation (2). In accordance with the expected plasticizing capacity both compounds decrease the T_g. About 25% m/m PEG 400 does decrease the T_g below 273 K whereas at 50% m/m phase separation between the polymeric system and PEG 400 was observed. PEG 400 was selected as the plasticizer of choice for our transdermal systems because PEG 400 did not penetrate into the skin *in vivo*[12] and it is an excellent co-solvent for hydrophobic drugs in water.

Water distribution in hydrogels

D.t.a. experiments were performed around 273 K at increasing water concentrations on these hydrogels, in order to get an idea about the distribution of water in these hydrogels. In these experiments (see *Figure 5*) a large amount of 'non-freezing' water was observed. The data therefore suggest that the 'non-freezing' water might be classified as bound water and the freezing water might be the extra water that is absorbed in the hydrogel once the T_g is exceeded. Data similar to that presented in *Figure 5* were used to make plots of the enthalpies of fusion (ΔH) against the water fraction. The amount of 'non-freezing' water was then determined by extrapolating the curve to $\Delta H = 0$. For a 25 mol% MAA/75 mol% HEMA copolymer this extrapolation results in 21% m/m 'non-freezing' water and for a 75 mol% MAA/25 mol% HEMA copolymer an amount of 'non-freezing' water of 29% m/m is obtained.

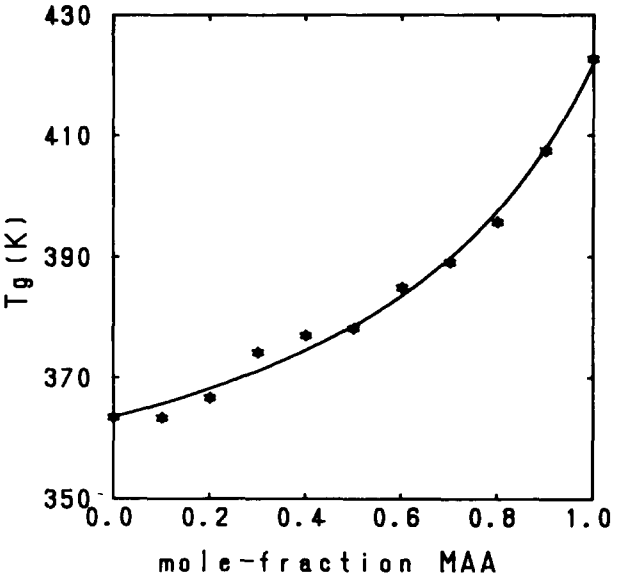

Figure 1 The experimental T_g vs. the composition of *p*-(HEMA-co-MAA). The dots represent the experimental data. The solid line represents the curve fitted according to equation (1)

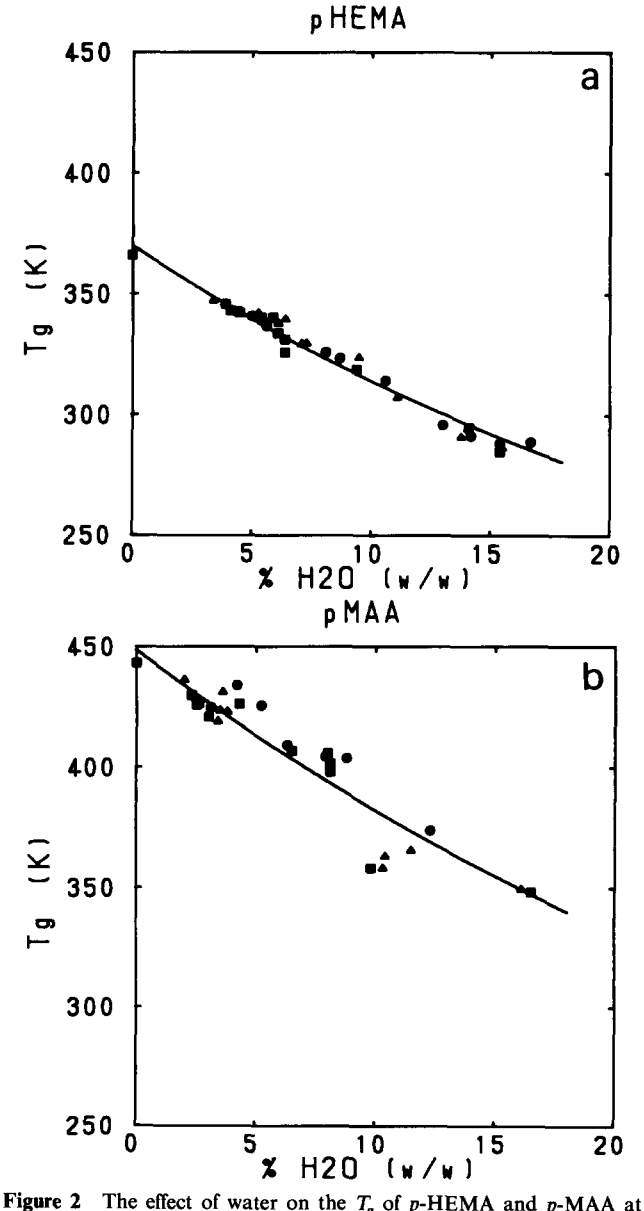

Figure 2 The effect of water on the T_g of *p*-HEMA and *p*-MAA at (■), pH = 4; (▲), pH = 7; and (●), pH = 9. The solid line represents the calculated curve according to equation (2)

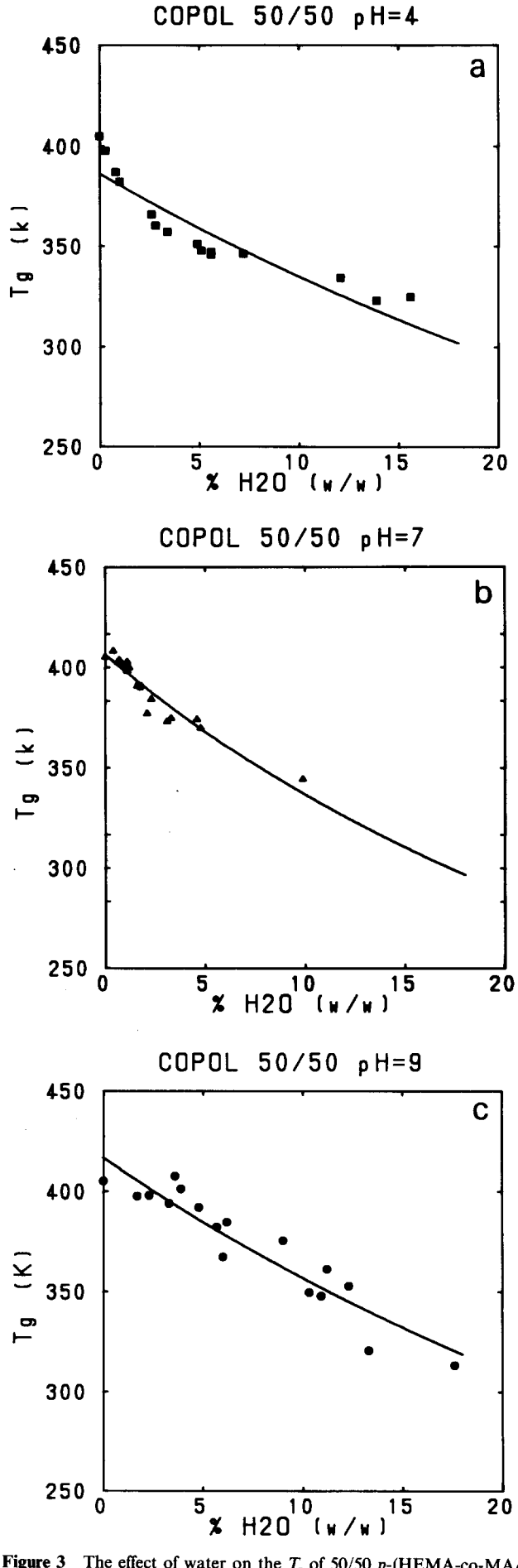

Figure 3 The effect of water on the T_g of 50/50 *p*-(HEMA-co-MAA) at (■), pH = 4; (▲), pH = 7 and (●), pH = 9. The solid line represents the calculated curve according to equation (2)

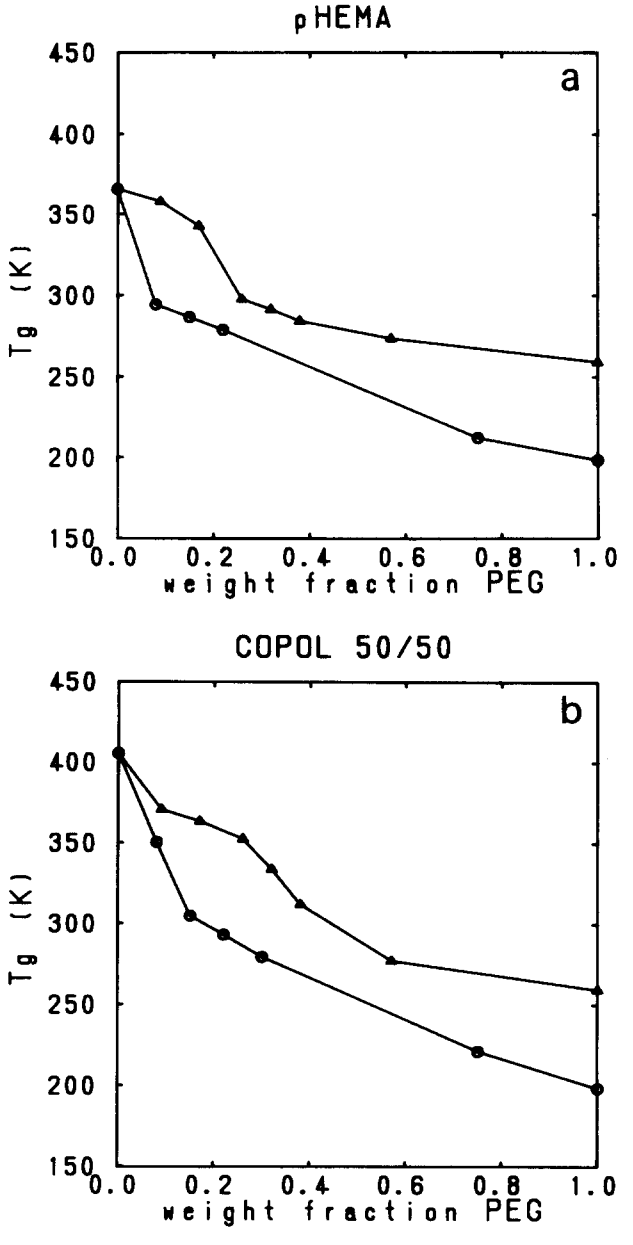

Figure 4 The effect of PEG 400 (○) and PEG 6000 (▲) on *p*-HEMA and 50/50 *p*-(HEMA-co-MAA). Because PEG 400 and PEG 6000 are hygroscopic excipients, some of these effects will be due to water

However, the freezing of water in these hydrogels seems to be a diffusion controlled process[5]. The T_g experiments mentioned above clearly show that at low water concentrations the polymer will be in a glassy state at these low temperatures, thus limiting a fast diffusion of water. Furthermore, the crystallization of water will immediately withdraw water which plasticizes the polymer, and results in an increase in the T_g. A similar suggestion was recently made by Roorda[5,13] for *p*-HEMA. It was therefore expected that long term equilibration below 0°C will result in an increase in the melt enthalpy.

Roorda showed that at least one molecule of water interacts with one monomeric HEMA unit. The diffusion of water might thus also be hampered by the interaction between water and the polymer itself. It is therefore interesting to see whether the ionization of the polymer affected the interaction between water and the hydrogel. The data in the literature are contradictory rather

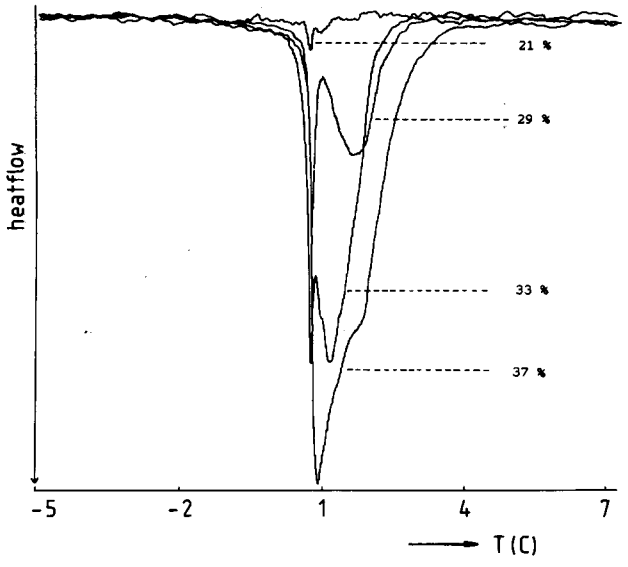

Figure 5 D.t.a. scans of a 25 mol% MAA/75 mol% HEMA co-polymer at a water concentration of 0 to 37% m/m. Temperature programme: cooling from 293 K to 193 K at 10 K/min. The enthalpy, calculated by the area under the curve, can be plotted against the water fraction thus resulting in the amount of non-freezing water

controversial[14,15]. Ilavsky *et al.*[16] calculated the Flory–Huggins parameter (χ) for these copolymers and showed that χ was dependent on the volume fraction of water in the gel, but was independent on the degree of ionization. This aspect needs further attention and will be the subject of further investigations.

CONCLUSIONS

When hydrogels are used as a transdermal drug delivery system, in contact with human skin they will immediately start to absorb water. However, substantial amounts of water are required to decrease the T_g to skin temperature in order to trigger the diffusion and release of drugs from these systems to the skin. For this reason PEG 400 was selected as a safe and suitable plasticizer for these hydrogels.

The pH of the skin under such a system will decrease from about 6 to about 5, for which reason potential pH effects were also studied. It was shown that there was hardly any effect of the pH on the decrease of the T_g by water. The presence of non-freezing water in d.t.a. experiments was attributed to non-equilibrium conditions. These *p*-(HEMA-co-MAA) copolymers will be further explored in the design of laminated transdermal drug delivery systems.

REFERENCES

1 Klier, J. and Peppas, N. A. *J. Control. Rel.* 1986, **7**, 61
2 Verhoeven, J., Peschier, L. J. C., van Det, M. A. and Junginger, H. E. *Polymer* 1989, **30**
3 Janacek, J. and Kolarik, J. *Int. J. Polym. Mater.* 1976, **5**, 71
4 Kolarik, J. and Janacek, J. *J. Polym. Sci.* 1972, **A2**, 10, 11
5 Roorda, W. E., Bouwstra, J. A., de Vries, M. A. and Junginger, H. E. *J. Control. Rel.* 1988, **5**, 722
6 Lee, H. B., Jhon, M. S. and Andrade, J. D. *J. Colloid. Interf. Sci.* 1975, **51**, 225
7 Wisniewski, S. and Kim, S. W. *J. Membr. Sci.* 1980, **6**, 309
8 Roorda, W. E., Bouwstra, J. A., de Vries, M. A., Kosho, C. and Junginger, H. E. *Thermochim. Acta* 1987, **112**, 111
9 Franks, F., ed. 'Water, A Comprehensive Treatise' Plenum Press, New York (1972)
10 Sugisaki, M., Suga, H. and Seki, S. *Bull. Chem. Soc. Jpn.* 1968, **41**, 2591
11 Sung, Y. K., Gregonis, D. E., Russel, G. A. and Andrade, J. D. *Polymer* 1978, **19**, 1362
12 Hoelgaard, A. and Mollgaard, B. *J. Control. Rel.* 1985, **2**, 111
13 Roorda, W. E., Bouwstra, J. A., de Vries, M. A. and Junginger, H. E. *Biomaterials* 1988, **9**, 494
14 Glasel, J. A. *J. Am. Chem. Soc.* 1970, **92**, 375
15 Molyneux, P. In: 'Water, A Comprehensive Treatise', Vol. 4 (Ed. F. Franks), Plenum Press, New York (1975)
16 Ilavski, M., Dusek, K., Vacik, J. and Kopecek, J. *J. Appl. Polym. Sci.* 1979, **23**, 2073