Synthetic hydrogels: 2. Copolymers of carboxyl-, lactam- and amide-containing monomers—structure/property relationships

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The use of nitrogen- and carboxyl-containing monomers in conjunction with hydroxyalkyl acrylates and methacrylates enables hydrogels having equilibrium water contents in the range 30–90% to be obtained. Although such systems are described in the patent literature, the effect of structural variation on properties is not well recognized. In this paper, the effect of copolymer composition on equilibrium water content is discussed, together with the way in which water structure within the polymer varies. Although weakly interacting monomer pairs, such as hydroxyethyl methacrylate and vinylpyrrolidone, produce steady and predictable changes in polymer properties as a function of compositional variation, the same is not true of monomers that possess appreciable hydrogen-bonding capability. In such cases, typified by acrylamide–methacrylic acid and acrylamide–acrylic acid, hydrogen bonding between the constituent monomers produces the most marked structural effects at around equimolar feed ratios. The resultant interaction is reflected in equilibrium water content, mechanical properties and surface properties. The effect of composition on these properties (as measured by micropenetrometry and surface energy analyses) is discussed together with the results of more structure-specific biological probe experiments.

(Keywords: hydrogel; protein deposition; acrylamide; N-vinylpyrrolidone; surface properties)

INTRODUCTION

In an earlier paper in this series, we have discussed the way in which hydroxyalkyl acrylates and methacrylates can be used to obtain a range of synthetic hydrogels having varied water binding, mechanical and transport properties[1]. A great deal of additional interest has centred around the synthesis of hydrogels that have higher equilibrium water contents (*EWCs*) than that attainable by hydroxyalkyl acrylates alone. One of the major driving forces has been the desire to produce contact lens materials based on hydrogels that have sufficiently high oxygen permeability to enable the criteria for extended, or overnight, wear to be met. The correlation of oxygen permeability with *EWC* has been clearly demonstrated, and over 100 patent specifications have described hydrogels for contact lens use, many of them claiming oxygen permeabilities of a sufficiently high level for extended wear. We have previously reviewed the hydrogel chemistry disclosed in these patent specifications and given an overview of the compositions currently used in commercial contact lens materials[2].

One feature that is apparent both in the compositions disclosed and also in the compositions of the currently available high-water-content contact lenses is the dependence on vinylpyrrolidone. Thus, it is predominantly by the use of this hydrophilic monomer that these high *EWC*s are obtained. Unfortunately, such reference as there is in patent specifications to alternative monomers of high hydrophilicity is rarely accompanied by any discussion of the detailed chemistry or characterization of the resultant materials. In this paper we describe the use of a variety of hydrophilic nitrogen-containing monomers, together with the way in which these interact with each other and with monomers that contain hydroxyl and carboxyl groups.

EXPERIMENTAL

Monomers

Optical grade 2-hydroxyethyl methacrylate was supplied by Ubichem Ltd. Acrylic acid (Koch-Light), methacrylic acid (Koch-Light), 2-hydroxypropyl methacrylate (BDH), *N*-vinylpyrrolidone (BDH) and methyl methacrylate (BDH) monomers were purified by reduced-pressure distillation as described in the literature[3] and their purity monitored by g.l.c. Acrylamide (Koch-Light), methacrylamide (Aldrich), diacetone acrylamide (Polysciences) and methylene bis-acrylamide (Cambrian) monomers were purified by recrystallization from ethyl acetate. Ethylene glycol dimethacrylate (BDH) and azo-bis-isobutyronitrile (Aldrich) were used as supplied.

Membrane preparation

Membranes were prepared by copolymerizing the monomers *in situ* between two glass plates separated by a gasket as previously described[1]. Unless otherwise stated, compositions contained 1% of ethylene glycol dimethacrylate as a crosslinking agent.

Equilibrium water content

The *EWC* was calculated by weight difference as described in the first paper of this series. Small samples

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were cut from a hydrated sheet of the hydrogel and, after the surface water had been removed, the samples were weighed, then dehydrated overnight in a vacuum oven to constant weight. For each determination an appropriate number of samples were chosen, according to the expected water content, to produce a difference between hydrated and dehydrated weights of at least 0.1 g. The *EWC* (weight of water in the gel/total weight of hydrated gel) was calculated and the final value is an average of at least three determinations. Some comments on the precision and accuracy of this method have been presented previously[1].

Differential scanning calorimetry

Thermograms were obtained using a Perkin–Elmer DSC2 differential scanning calorimeter fitted with a liquid-nitrogen subambient accessory[1]. This involves cooling small weighed samples (~ 2 mg) in sealed aluminium sample pans to 223 K to ensure the freezing of any supercooled water. A heating rate of $5\,\mathrm{K\,min^{-1}}$ produced well separated endothermic peaks in the region of the melting point of water. Using a calibration graph, produced from samples of pure water, the area under the endothermic peaks was converted to the weight of freezing water in the sample.

Oxygen permeability

The dissolved oxygen permeability coefficients were determined using the apparatus and experimental techniques described in a previous paper[4].

Protein adsorption

For protein adsorption studies, the following reagents were used: human serum albumin (fraction V; 96–99% pure, remainder mainly globulins) (Sigma), human fibrinogen (fraction 1; >90% of protein clottable) (Sigma), iodinated (^{125}I) human albumin injection (specific activity = 2.5 mCi/mg albumin) (Amersham International), iodinated (^{125}I) human fibrinogen injection (specific activity > 100 mCi/mg fibrinogen) (Amersham International) and tris(hydroxymethyl)aminoethane (Sigma). All protein solutions were made up in physiological Krebs solution, pH 7.4.

The protein adsorption of the samples under test was investigated using a static technique to minimize consumption of radiolabelled protein solution. A gentle 'rocking' agitation of a sealed vial (which contained the sample) was employed to maintain steady movement of the solutions over the polymer interface. This technique enabled a statistically significant number of samples, of a large number of copolymers, to be examined over a series of (12) time intervals. The apparatus used in these studies was of relatively simple design and construction, enabling multiple simultaneous analyses.

The samples were placed in 20 ml vials and 2 ml of Krebs solution, followed by 2 ml of radiolabelled protein solution, were added to each sample; the times were noted and at this point 3 × 100 ml aliquots were taken from the radiolabelled protein 'stock' solution to be used as internal counting standards. The vials were sealed and stored in the dark until the prescribed time had elapsed, whereupon the radiolabelled solution in each vial was displaced from the samples by a volume displacement method using 500 ml of Krebs solution, at room temperature, and at a flow rate of $100\,\mathrm{ml\,min^{-1}}$. It had been established that this flow rate was effective in eliminating all the radiolabelled solutions from the vials, leaving the samples suspended in Krebs solution. The efficiency of the 'washing' procedure was monitored by taking 1 ml aliquots of this latter suspending Krebs solution. The samples were then carefully transferred to counting vials and sealed, in preparation for γ counting. The use of this technique to establish protein adsorption vs. time profiles is described in a subsequent paper[5]. The values quoted here (*Figures 12–14*) all relate to measurements after 72 h, by which time equilibrium or 'plateau' values had been reached.

All samples ready for counting were loaded into the γ counter (Nuclear Enterprises, type 8312), together with the internal standards and a requisite number of blanks for the estimation of background radiation and to act as experimental controls. Machine counting efficiency was determined for the ^{125}I isotope by the conventional procedures, from which the optimum operating conditions were obtained. Each sample was counted for 2×10^5 counts or 600 seconds (whichever elapsed first). As ^{125}I has a half-life of 60 days, for the typical total counting time of 6 h for 60 samples, the decay during this period is insignificant. The mean adsorbed protein was then calculated using internal standards, after correcting for background radiation.

Surface properties

The surface properties were investigated using the Hamilton (water/octane), captive air bubble and conventional sessile drop techniques[5]. Sessile drop measurements were made using water and methylene iodide. The results thus obtained were converted into polar, γ^{p}, and dispersive, γ^{d}, components of the surface free energy, γ^{t}.

Mechanical properties

The deformation properties of the hydrogels were investigated using a modified version of the REL pneumatic microindentation apparatus. A detailed account of its use is given in a subsequent part of this series[5] but, in principle, it allows the measurement of equilibrium deformation h of a polymer surface, when a spherical indentor of radius r is loaded with a mass m. These parameters have been related to the rigidity modulus G and Young's modulus E of a sample of thickness t and Poisson's ratio v by the mathematical treatment of Hertz[6], Taylor and Kragh[7] and others, using equations of the form:

$$\frac{E}{1-v^2}=\frac{3}{4}\frac{mg}{r^{0.5}h^{1.5}} \tag{1}$$

$$G=0.36\frac{mg}{r^2}\left(\frac{t-h}{h}\right)^{1.5} \tag{2}$$

RESULTS AND DISCUSSION

Effect of monomer–comonomer structure on equilibrium water content and its stability

The effect of incorporation of vinylpyrrolidone (VP) as a comonomer on the *EWC* of hydroxyalkyl methacrylate copolymers is illustrated in *Figure 1*. This figure contrasts the effect of copolymerizing 2-hydroxyethyl methacrylate

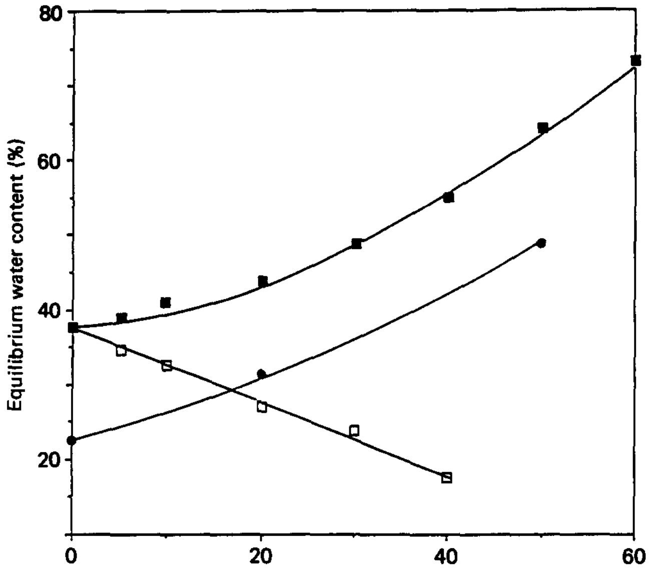

Figure 1 Comparison of the *EWC* of HEMA–VP (■), HEMA–MMA (□) and HPMA–VP (●) copolymers at 22°C

(HEMA) with both methyl methacrylate (MMA) and VP. Vinylpyrrolidone incorporation offers an easy way of producing homogeneous hydrated copolymer systems that have increased *EWC*s relative to that of HEMA. The 60:40 (VP–HEMA) copolymer, which is seen to have an *EWC* in excess of 70%, is commonly used as a material for the manufacture of so-called high-water-content extended-wear contact lenses[2].

One important difference between the HEMA–MMA copolymers and the HEMA–VP copolymers lies in the relative radical reactivity ratios of the two monomer pairs. The reactivity ratios for the HEMA–MMA system have been reported as 1.06 and 0.30 respectively[8]. Al-Issa *et al.*[9] have reported values for the reactivity ratios of the HEMA–VP system of 3.12 and 0.05, while Reddy *et al.*[10] report values of 4.4 and 0.04. The information in *Figure 1* and ensuing figures is based on feed ratios. Some comment on the effect of reactivity ratios on copolymer composition, together with the results of elemental analysis, will be presented in the characterization section (*Table 2*). In principle, it is sufficient at this point to note that there will be some disparity between feed ratio and copolymer composition, especially in the VP copolymers. The residual monomer is, however, very water soluble and readily extracted in the membrane hydration process. The amounts of residual monomers have not been observed to produce abnormal porosity in these families of hydrogels.

Despite differences in reactivity ratios, VP copolymers form the basis of a useful group of materials that are relatively insensitive to pH and tonicity. This feature is very important in contact lenses, and in some other biomedical applications. The copolymers do, however, show a degree of sensitivity to temperature variation. This point is illustrated in *Figure 2*, which shows the *EWC* vs. temperature profile for poly(vinylpyrrolidone) for VP–hydroxypropyl methacrylate (HPMA) copolymers of differing crosslink densities. Further information is contained in *Figure 3*, which shows the effect of temperature on HEMA–VP copolymers at a nominal crosslink density of 1%. The relative similarity in reactivity ratios of ethylene glycol dimethacrylate (EGDM) and HEMA, and the contrasting disparity in reactivity ratios of EGDM and VP produces differences in crosslink density distribution. Therefore, VP homopolymers are apparently less sensitive (in terms of water content decrease) to small amounts of EGDM crosslinking agent than those VP copolymers that contain substantial proportions of hydroxyalkyl acrylates or methacrylates. Despite this, as a general rule, hydrogels of higher *EWC* (such as those based on VP) show a greater sensitivity to substantial increases in crosslink density than do lower-water-content polymers, such as poly(HEMA) and copolymers of HEMA with less hydrophilic monomers. The relative mismatch of reactivity ratios of VP and EGDM is reflected in the large

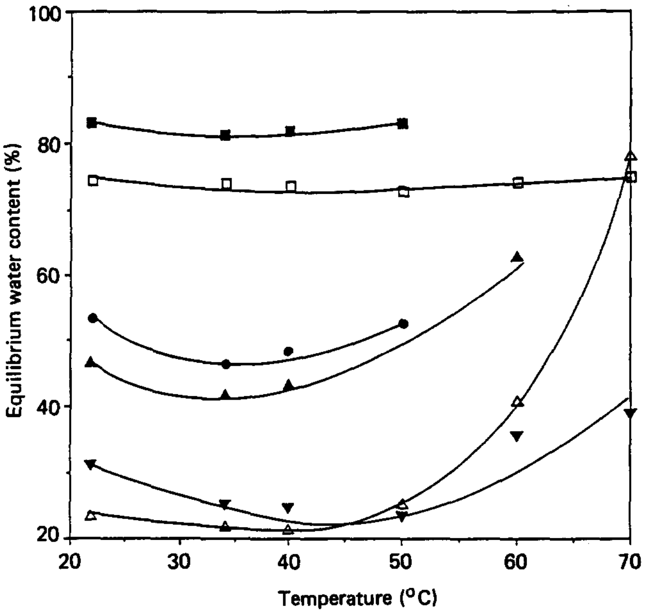

Figure 2 Variation in *EWC* with temperature for poly(VP) with 5% (■) and 10% (□) ethylene glycol dimethacrylate (EGDM) crosslinking agent, for HPMA–VP (50:50) containing 0.6% (●) and 1.2% (▲) EGDM crosslinking agent, and for HPMA–VP (80:20) (▼) and poly(HPMA) (△)

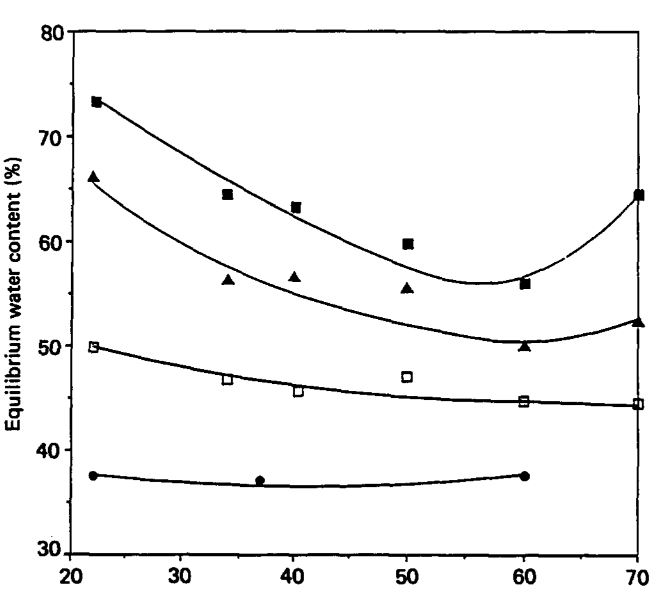

Figure 3 Effect of temperature on the *EWC* of HEMA–VP (40:60) (■), HEMA–VP (50:50) (▲), HEMA–VP (70:30) (□) and poly(HEMA) (●)

number of patents dealing with 'novel' crosslinking agents for VP. These are claimed to be more efficiently and uniformly incorporated[2].

The question of water binding in these polymers is interesting, and the double extrapolation of MMA–HEMA and VP–HEMA copolymers on the same graph (cf. *Figure 1*) is valuable in this respect. Thus, *Figure 4* shows the corresponding change in freezing water content as a function of copolymer composition for these two families. This provides a useful confirmation of the freezing water content (13.2%) of poly(HEMA) at 1% crosslink density, a figure that has been open to some dispute in the past. The concept of the ratio of moles of bound water per mole of polymer (or moles of bound water per mole of repeat unit for copolymers) gives an indication of the water binding potential of a single monomer unit. In lower-water-content gels the water binding properties of a given repeat unit are limited by steric exclusion factors. The binding ratio does, however, reach a limiting value in highly swollen systems, and becomes independent of the amount of water present. Thus, poly(HEMA) binds 2.80 moles of water per mole of polymer, while in the 50:50 HEMA–VP copolymer, the value has increased to 3.33 moles of bound water per repeat unit. It is difficult to determine an accurate figure for the ratio of moles of bound water per mole of vinylpyrrolidone because of the low volume fraction of polymer in high-water-content gels. However, our work suggests that a value in excess of 7 moles of bound water per mole of polymer is a not unreasonable estimate of this ratio.

Interesting changes from the uniform increase and decrease in *EWC* with copolymer composition, exhibited in *Figure 1*, are encountered when comonomers having stronger hydrogen bonding acceptor–donor properties are used. This point is illustrated in *Figure 5*, which shows the effect of composition on *EWC* for copolymers of acrylic acid (AA) with HEMA, with VP and with acrylamide (ACM). The increase in donor–acceptor interactions along the series is reflected in increasing deviation from linearity in the *EWC* vs. composition curves. A similar, but more pronounced, deviation is shown in the copolymers of methacrylic acid (MAA) with HEMA, with VP and with ACM (*Figure 6*). An additional feature demonstrated in this figure is the pH sensitivity of the carboxyl group. The conversion of carboxyl group to carboxylate anion is brought about in moving from acidic to alkaline hydration conditions, and is accompanied by a marked increase in water content, associated with the greater hydrophilicity of the carboxylate anion. *Figure 6* strikingly illustrates the difference in water content between HEMA–MAA copolymers hydrated in distilled water (pH$\leqslant$7) and in Krebs solution. Krebs solution is based on sodium, potassium, magnesium and calcium chlorides, together with glucose, sodium dihydrogenphosphate and sodium bicarbonate, buffered at pH 7.4.

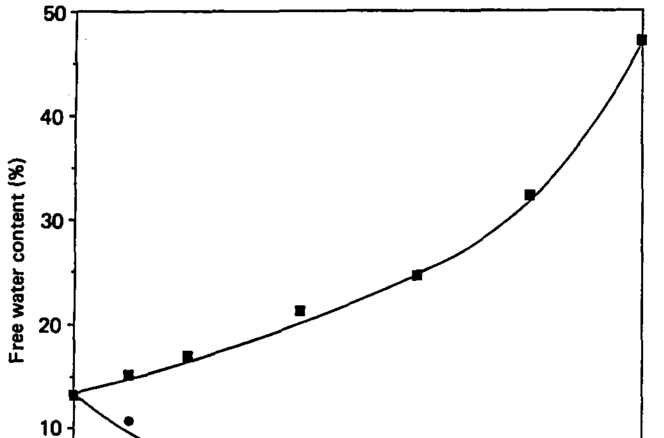

Figure 4 Variation in free water content, at 22°C, with composition for copolymers of HEMA with VP (■) and MMA (●)

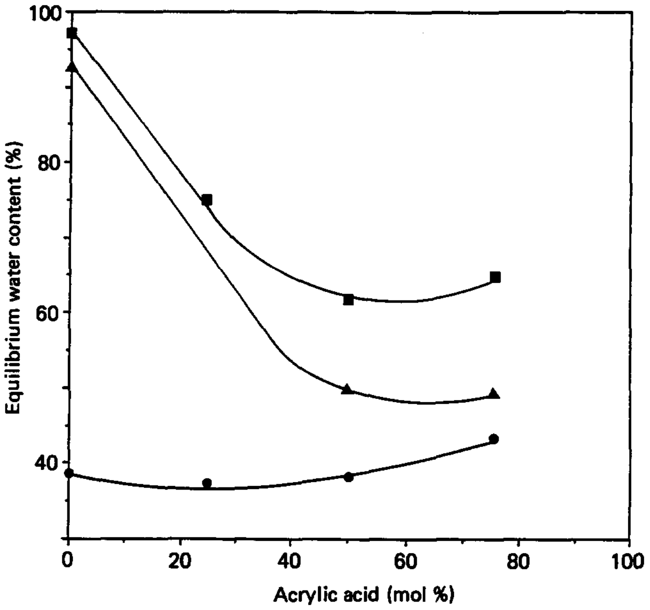

Figure 5 Effect of composition on *EWC*, at 22°C, for copolymers of acrylic acid with VP, (■), ACM (▲) and HEMA (●)

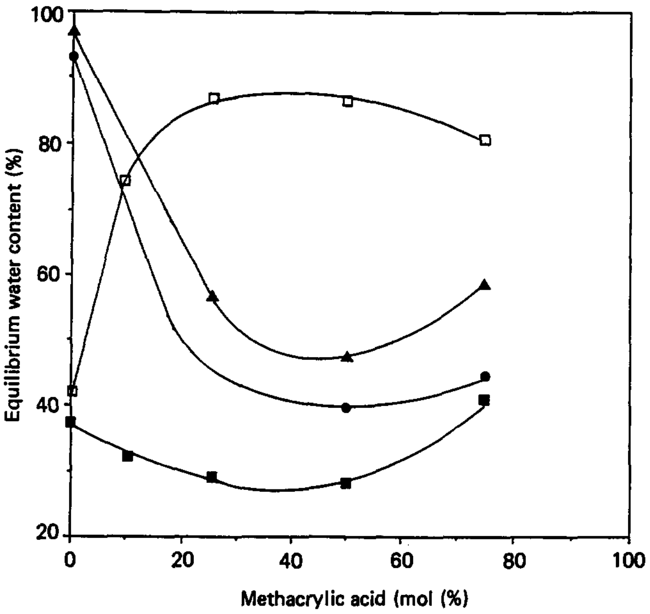

Figure 6 Variation in *EWC*, at 22°C, with composition for copolymers of methacrylic acid with ACM (▲), VP (●) and HEMA (■) in distilled water and MAA–HEMA (□) in Krebs solution

The high hydrophilicity of the carboxylate anion is well known and has been utilized in some contact lens materials, although not with great success. Incorporation of small amounts of MAA in HEMA produces materials which, if treated in sodium bicarbonate, undergo a marked increase in water content. The dramatic sensitivity of these materials in the region of pH 7 (illustrated in *Figure 6*) produces dimensional instability. This is generally found to be unsatisfactory for contact lens use, particularly where wear protocols require removal from the eye, and transferral to cleaning and storage solutions.

Having indicated the major single disadvantage of carboxyl-containing monomers, such as MAA, it is appropriate to indicate, in contrast, the advantages that they bring to systems of the type described here. In the first place, they show very marked hydrogen bonding behaviour, especially with nitrogen-containing monomers. As a result they produce systems in which the competitive interactions between the different groups in the polymer backbone, and between those groups and water, have interesting consequences in terms of surface, mechanical and transport properties. Some aspects of this behaviour will be subsequently discussed. The second valuable feature of MAA stems from that mentioned above, and is its ability to dissolve appreciable quantities of ACM and the substituted acrylamides.

The use of a solid monomer such as acrylamide does present some problems in the synthesis and characterization of extended copolymer composition ranges based on this monomer. In the first place, both the *EWC* and physical properties of poly(ACM) homopolymer are affected by the conditions used to dissolve and polymerize the monomer in membrane form. Thus, values associated with ACM homopolymer in these figures and tables must be regarded as subject to some variation. In the copolymers of the solid amides, the presence of a monomer with good solvent properties, such as MAA, is an obvious advantage. On the other hand, its pH sensitivity suggests that amide–hydroxyalkyl acrylate or methacrylate copolymers might be more useful materials. Unfortunately, because of solubility limitations, it is not possible to investigate complete molar ranges in this case. Although water can be used as a solvent to extend these ranges, for the reason previously mentioned, this has only been done as a means of locating relative *EWC* values for the ACM homopolymer in *Figures 5* and *6*.

Table 1 summarizes the variation in *EWC* for copolymers of hydroxypropyl acrylate (HPA) and HEMA with ACM, with methacrylamide (MACM) and with diacetone acrylamide (DAACM) or *N*-(1,1-dimethyl-3-oxybutyl) acrylamide. Several points can usefully be made in relation to these materials, and to the *EWC* values shown in the table. First, they provide an interesting range of moderately high-water-content materials that show good stability to pH, temperature and tonicity changes. In this respect they show some advantages over VP copolymers, not least in the fact that the reactivity ratios appear to be better matched. For these reasons, we have previously described their potential as contact lens materials, and indeed, an extended-wear contact lens material based on these comonomers has achieved commercial significance[11–14]. The relative hydrophilicities of the amide monomers fall as expected, in the sequence ACM > MACM > DAACM.

Table 1 Equilibrium water contents for copolymers of HEMA and HPA with acrylamide and acrylamide derivatives

Weight % acrylamide derivative	Composition					
	Acrylamide		Methacrylamide		Diacetone acrylamide	
	HEMA	HPA	HEMA	HPA	HEMA	HPA
0	37.8	51.0	37.8	51.0	37.8	51.0
25	56.0	61.7	36.2	48.5	28.8	30.8
33	59.3	67.0	39.6	55.7	26.4	25.8
40	63.7		56.5			
50	63.0		47.8		27.5	22.2

Table 2 Comparison of initial feed ratio with true molar ratio of some vinyl pyrrolidone, acrylamide and HEMA copolymers

Copolymer	Initial feed ratio (mol%)	True molar ratio from C, H, N analysis
VP–MAA	75:25	47:53
	50:50	17.5:82.5
	25:75	2.6:94.7
VP–AA	75:25	47:53
	50:50	15:85
	25:75	3:97
VP–HPMA	50:50	39:61
	30:70	15:85
ACM–MAA	50:50	40:60
ACM–AA	50:50	49.5:50.5
HEMA–St	70:30	77:23

Closer inspection of the *EWC* vs. copolymer composition results (*Table 1*) indicates that the greatest deviation from linearity occurs in the DAACM–HEMA and DAACM–HPA copolymers, possibly a manifestation of the greater basicity of DAACM. Perhaps the greatest interest in these polymers lies in the effect of comonomer structure on physical properties (described in a subsequent section) rather than on *EWC*. For this reason a combination of the features associated with styrene (St) incorporation, and described in a previous paper[1], can be usefully extended to the copolymers described here. Indeed two distinct families based on St–MAA–ACM, on the one hand, and St–VP–HPA, on the other, show considerable potential for specific applications and will be described in later papers.

Hydrogel characterization

In summary, the copolymer families described above provide a range of hydrogels that, for the most part, are optically clear and show good stability of water binding properties to changes in temperature, pH and tonicity. Exceptions to these generalizations are some of the HPMA–VP copolymers which, at high HPMA contents, become translucent at temperatures in excess of 60°C. The AA- and MAA-containing copolymers are also unusual in that they show marked sensitivity to pH changes in the region of pH 7. The low solubility of some of the solid monomers (particularly MACM) in some copolymer compositions, together with the low reactivity of VP, present problems or limitations in the use of these particular monomers. In this respect, it is appropriate to compare feed ratios with actual matrix-incorporated ratios in a range of the hydrogel systems examined. Some of these results are summarized in *Table 2*.

Oxygen permeability

The oxygen permeability of a series of membranes, having *EWC*s between 60% and 80%, based on copolymer compositions described in this paper, were studied at 25°C. Permeation cell characteristics, including the effects of stirring rate, membrane thickness and temperature, have been previously described[4]. The results may be presented in different ways, but the form shown in *Figure 7*, in which log permeability is plotted as a function of *EWC*, is most satisfactory. The value for the transport of oxygen through bulk water is included for comparison. The empirical relationship shown in the figure may be represented by the equation:

$$P_{\mathrm{d}\,25^\circ\mathrm{C}} = 17.4\times10^{-10}\exp(0.0397w) \quad \mathrm{cm^3(STP)\,mm\,cm^{-2}\,s^{-1}\,(cmHg)^{-1}} \tag{3}$$

where $w = EWC$ and in which the constants 17.4×10^{-10} and 0.0397, obtained by least-mean-squares analysis, compare favourably with the values of 14×10^{-10} and 0.0418 obtained for hydroxyalkyl acrylate and methacrylate copolymers ranging from 30% to 80% *EWC*[15].

Mechanical properties

The mechanical properties of hydrogel membranes may conveniently be investigated using a microindentation technique based on the use of a spherical indentor. The results are converted to Young's and rigidity moduli by the mathematical treatment described in the experimental section. The primary form of the experimental results is shown in *Figure 8*, in which the indentation behaviour as a function of time of one of the VP–HPMA (50:50) copolymers contained in *Figure 2* is shown. The indentation height (or better, recovery) from the graph is then plotted in the form of load *versus* indentation, in one of the two alternative forms described in the experimental section. *Figure 9* illustrates a direct load vs. indentation plot for poly(ACM), together with poly(AA) and the 50:50 ACM–AA copolymer contained in *Figure 5*. Lines that are displaced to the left on graphs of this type correspond to lower indentation at a given load, or increased load for a given indentation, and thus to higher values of both Young's and rigidity moduli. In *Figure 9* it is apparent that the 50:50 ACM–AA copolymer has a higher rigidity modulus than either of the homopolymers.

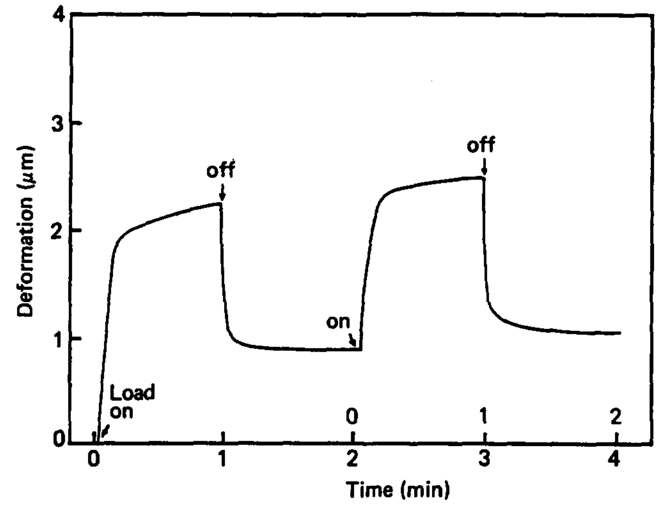

Figure 8 Deformation properties of HPMA–VP (50:50) copolymer containing 1.2% ethylene glycol dimethacrylate (EGDM) crosslinking agent under eyelid pressure. Some settling of the sample is apparent after the first cycle

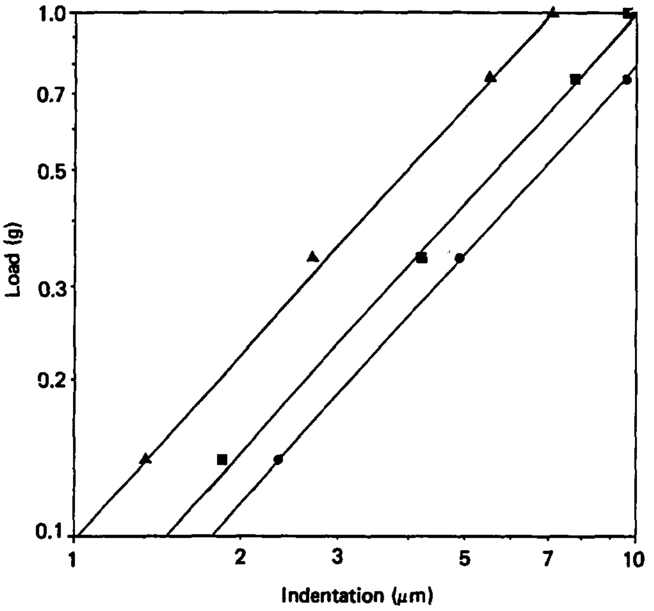

Figure 9 A plot of load *versus* indentation for poly(ACM) (●), poly(AA) (■) and an ACM–AA (50:50) copolymer (▲)

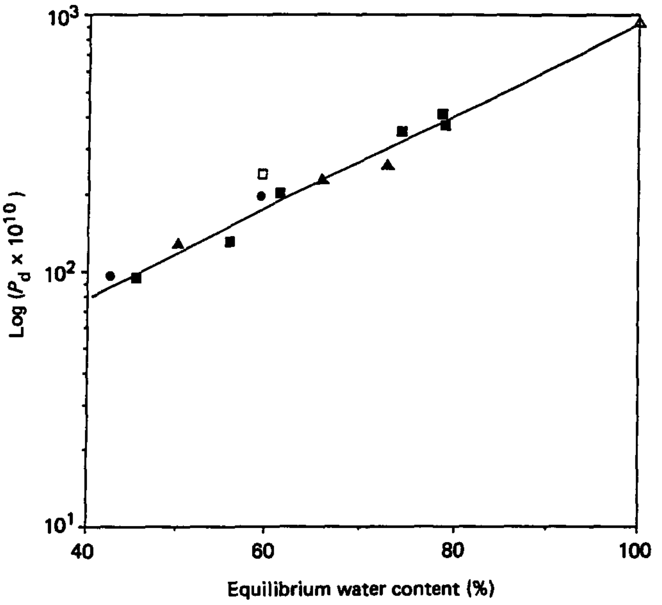

Figure 7 Plot of log oxygen permeability *versus EWC* for HPA–VP–St copolymers (■), HEMA–VP copolymers (▲), HEMA–VP–St copolymers (●), an ACM–HPA–EA terpolymer (□) and water (△) at 22°C (units of P_d as in equation (3))

Table 3 lists the rigidity moduli and water contents of some representative members of the copolymer series described here. These figures illustrate the fact that the mechanical properties of these copolymers, unlike their oxygen permeabilities, are not solely related to *EWC*. The ACM–AA (50:50) copolymer shown in *Figure 9*, for example, has both a higher water content and a higher rigidity modulus than does poly(HEMA). One broad generalization that can be made here is that freezing water has a far greater plasticizing effect on the hydrogel than does non-freezing water[1].

Table 3 Rigidity moduli with variation in *EWC* for a series of homopolymers and copolymers at a nominal crosslink density of 1%

EWC (%)	Composition (wt%)	Rigidity modulus ($\times 10^{-7}$ mN m^{-2})
92.0	ACM	3.5
73.5	MAA	2.4
73.0	AA	4.5
58.5	VP–MAA (25:75)	4.2
56.5	VP–MAA (75:25)	5.5
51.0	HPA	4.7
50.5	AM–AA (50:50)	6.7
50.0	VP–MAA (50:50)	>10.0
40.0	ACM–MAA (50:50)	4.7

Surface properties

The surface properties of poly(HEMA), and of various HEMA-based copolymers, in both dehydrated and hydrated states, is discussed in detail in a separate paper[5]. The hydrogels described in this paper are for the most part of high water content and extremely hydrophilic, even in the dehydrated state. This produces problems in the accurate measurement of surface energies of the dehydrated materials, because of both rapid hydration in air and rapid interaction with water, when this is used as a liquid in sessile drop measurements. In principle, the most successful method of overcoming the problems associated with surface energy measurements on hydrogels is to use the inverted octane droplet method due to Hamilton[16], in conjunction with the captive air bubble method. Andrade[17] has successfully combined these techniques to produce estimates of the polar and dispersive components of surface energy of HEMA–MMA copolymers, for example. Although these inverted droplet methods solve the problem of dealing with hydrated materials in principle, they are not without shortcomings in practice. Thus, interfacial angles are difficult to measure with precision, deformation of the air bubble leads to variation in values produced by different workers, and the whole principle of the technique produces the suspicion that interfacial adsorbed water layers dominate the measurements that are made. We compare here measurements on a wide range of materials, using both inverted droplet and sessile drop in air methods, in conjunction with predictive techniques and direct measurements made on dehydrated samples.

An initial assessment of surface energy values for the dehydrated materials (sometimes called xerogels) was made and the results are collected in *Table 4*. This table summarizes total surface energy obtained both by predictive techniques (based on group contribution methods using the parachor and cohesive energy density (*CED*)), together with direct determination using the principles contained in the method of Owens and Wendt[18]. The details of these procedures have been described in a separate paper[5] dealing primarily with hydroxyalkyl acrylate and methacrylate copolymers. Whereas, in the systems where the primary hydrophilic centre is a simple hydroxyl group, good agreement is obtained between predictive and experimental techniques for dehydrated surfaces, that is not the case here. Two contributing factors are responsible for this. The first is the lack of reliable constants for the parachor and cohesive energy density for carboxyl-containing monomers. The values for the carboxyl group are derived from the values for the carbonyl and hydroxyl groups, which is clearly unsatisfactory. The second reason, in the event less important because of the poor predictive constants, is the fact that strongly hydrogen-bonding comonomers tend to produce abnormalities in surface behaviour (as with mechanical properties and *EWC*). This is reflected in the surface properties of such compositions in the hydrated state.

In addition to the general decrease in surface energy (particularly of the polar component) associated with the removal of water, two points are worthy of note. The first is that the cohesive energy density, being dominated by the dispersive component, tends to give lower predicted surface energies than does the parachor. The second is that the predictive method suggests a linear variation in surface energy with composition, whereas the experimentally determined surface energies of the dehydrated surfaces show, in some cases, pronounced minima. This is presumably due to intermolecular attraction of the type described and discussed in relation to *EWC* variation (*Figures 5* and *6*). Because such minima are associated with a decrease in water content, surface energy variations are smoothed when presented as a function of *EWC*. Thus, the Hamilton contact angle of the hydrated surfaces demonstrates the familiar deviations associated with strongly hydrogen-bonding comonomers, examples of which are listed in *Table 5*. These figures, which reflect the polar component of surface energy, parallel in an interesting way both the deviations from linearity in the *EWC* vs. composition curves (*Figures 5* and *6*, *Table 1*) and the compositional independence of mechanical properties (*Figure 9*, *Table 3*) on water content. Even when the Hamilton contact angle is shown as a function of *EWC*, as in *Figure 10*, the

Table 4 Comparison of predicted and experimentally determined surface energies

Composition	Parachor predicted surface energy (mN m^{-1}) γ^t	Surface energy calculated from Owens and Wendt[18] equations (mN m^{-1}) γ^t	γ^p	γ^d	*CED* predicted surface energy (mN m^{-1}) γ^d
HEMA–MAA					
100:0	50.5	51.6	20.2	31.4	39.1
75:25	48.1	52.6	15.9	36.7	38.6
50:50	45.6	55.4	20.1	35.3	38.0
25:75	42.8	56.4	21.5	35.0	37.5
0:100	39.6	57.0	23.6	33.4	36.9
HEMA–AA					
75:25	50.8	51.9	14.4	37.5	40.6
50:50	50.2	51.8	15.4	36.4	42.2
25:75	48.0	52.1	16.3	35.8	43.7
0:100	43.5	50.9	13.1	37.8	45.2
VP–MAA					
100:0	51.1	48.6	11.0	37.6	39.7
75:25	49.1	49.4	9.9	39.5	39.0
50:50	46.5	47.9	11.3	36.6	38.3
25:75	43.3	53.0	14.5	38.5	37.6
VP–AA					
75:25	52.2	47.9	1.9	46.9	41.1
50:50	51.7	45.0	3.8	41.2	42.5
25:75	48.9	48.2	2.0	46.2	43.8
HEMA–VP					
90:10	50.4	45.5	6.2	39.3	39.2
70:30	50.4	43.4	3.4	40.0	39.3
50:50	50.5	43.9	4.1	39.8	39.4

Table 5 Hamilton contact angles for a selection of the copolymer compositions shown in *Figure 10*

Monomer ratio	Hamilton contact angle (deg)					
	HEMA–St	HEMA–MAA	HEMA–AA	HEMA–VP	ACM–MAA	ACM–AA
100:0	148	148	148	148	–	–
75:25	126	140	140	154	–	–
50:50	108	135	131	130	117	136
25:75	93	146	136	–	154	146
0:100	55	151	141	157	151	141

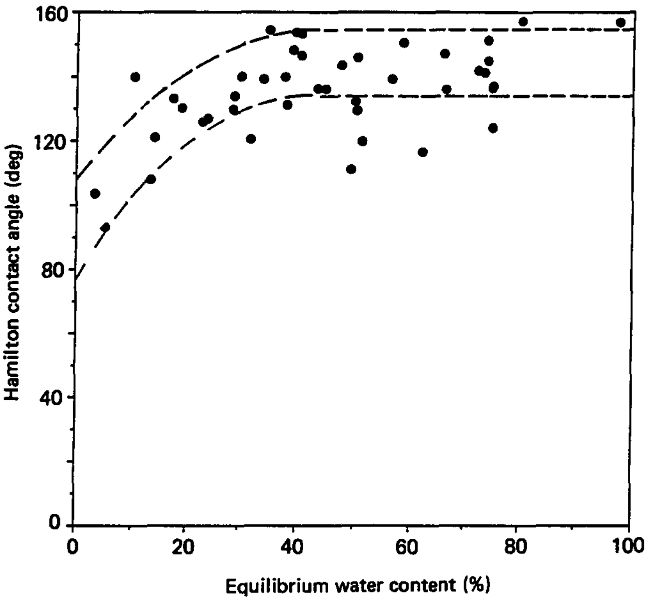

Figure 10 Variation in the polar component of surface free energy (as reflected by the Hamilton contact angle) for hydrogels of various compositions and equilibrium water contents. The general trend in behaviour is reflected by the 10° error band

dependence on *EWC* is overridden by variations in polymer structure that do produce effective differences in surface properties at a given water content. This is shown by the points that lie outside the 10° band, which illustrates the reasonable limits of experimental error in *Figure 10*. This figure contains the copolymers listed in *Table 5*, together with an extended range of hydrogels based on hydroxyalkyl acrylates, substituted acrylamides, vinyl lactams, alkyl acrylates and styrene. The less hydrophilic gels at a given composition are in general copolymers of methacrylic (but not acrylic) acid with comonomers possessing appreciable hydrogen bonding ability and vinylpyrrolidone copolymers. At lower water contents, hydroxyalkyl methacrylate copolymers with styrene have noticeably less hydrophilic surfaces than their hydroxyalkyl acrylate counterparts, at similar water contents. A more detailed analysis of simple lactam-, amide- and carboxyl-containing copolymers based on octane and air droplet measurements is presented in *Figure 11* in which both the polar and dispersive components of surface energy are displayed for copolymers of HEMA with MAA, with ACM and with VP. The fact that surface measurements of this type, although valuable, do not reflect events at a molecular level is illustrated, for example, by protein adsorption measurements.

Figure 12 shows the variation in human serum albumin (HSA) and human fibrinogen (HFb) absorption on copolymers of HEMA with the amide-containing

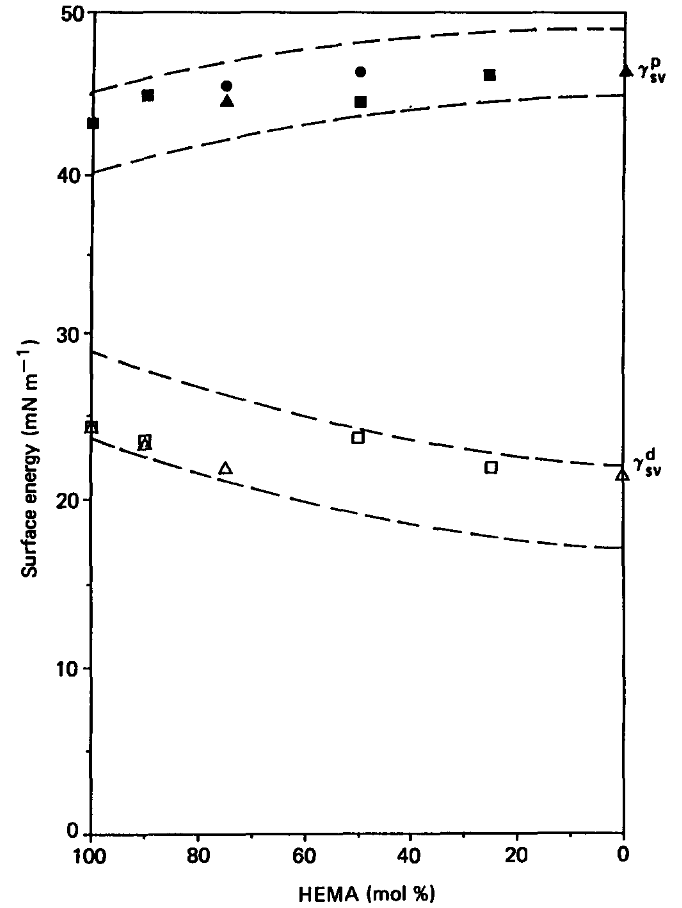

Figure 11 Components of surface free energy γ^{p}_{sv} and g^{d}_{sv} for hydrophilic HEMA–MAA (■), HEMA–ACM (▲) and HEMA–VP (●) copolymers; γ^{d}_{sv} for HEMA–MAA (□) and HEMA–ACM (△) copolymers

monomers. It is clear that, even in the regions where conventional surface energy probes detect little difference between polymers, protein adsorption shows considerable selectivity. It appears that, in terms of fibrinogen adsorption, the two monomers with unsubstituted amide groups (MACM, ACM) are more markedly different from HEMA than is the heavily substituted DAACM. Albumin adsorption is more comparable in the case of MACM and HEMA than in either of the copolymers of ACM and DAACM with HEMA. This may be a reflection of the effect of the α-methyl group on the backbone of MACM- and HEMA-based polymers. Although the water content of the polymers provides a limited correlation with adsorption behaviour, the exceptions are too many and too marked for this to provide a satisfactory basis for interpreting these results. The general, although oversimplified, principle that albumin adsorption takes place preferentially at more hydrophobic sites, and fibrinogen adsorption at more

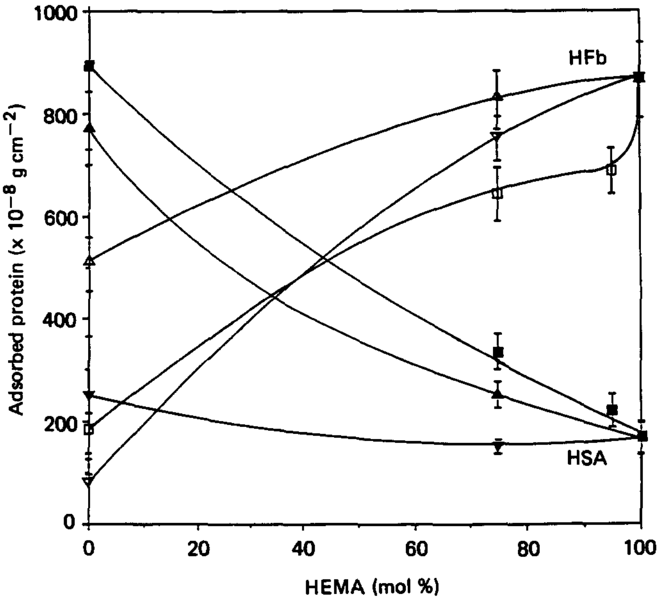

Figure 12 Adsorption of HSA (75 mg%) and HFb (10 mg%) on copolymers of HEMA and ACM derivatives: adsorption of HSA on HEMA-ACM (■), HEMA-DAACM (▲) and HEMA-MACM (▼) copolymers; and adsorption of HFb on HEMA-ACM (□), HEMA-DAACM (△) and HEMA-MACM (▽) copolymers

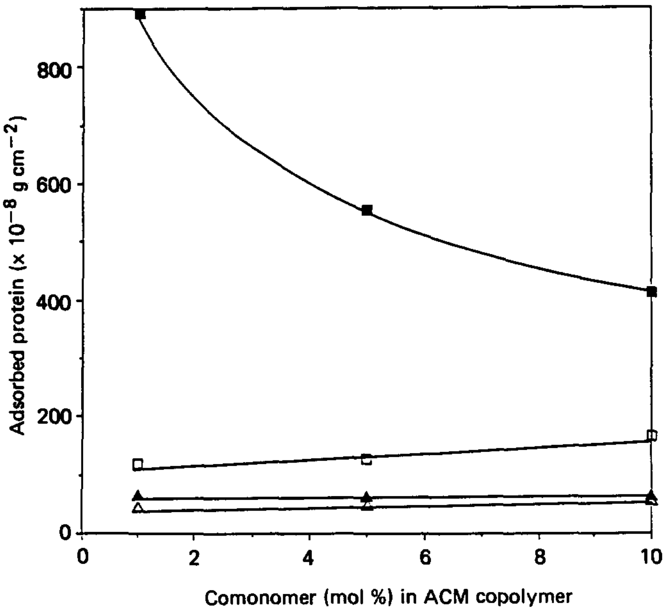

Figure 13 Influence of MBACM incorporation on the adsorption of HSA (■) (75 mg%) and HFb (□) (10 mg%) in ACM copolymers; and influence of MAA incorporation on the adsorption of HSA (▲) (75 mg%) and HFb (△) (10 mg%) in ACM copolymers

hydrophilic sites, has been well recognized elsewhere[19-22]. This selectivity, together with the dramatic effect of surface charge changes (consequent upon incorporation of the carboxylate anion and quite undetected by the techniques used to obtain the data of *Figure 11*), is seen again in *Figure 13*, which shows the effect of small amounts of comonomer on protein adsorption at ACM surfaces. The first comonomer illustrated is methylene bisacrylamide (MBACM) whose incorporation produces a marked decrease in albumin adsorption, coupled with a relatively small, but statistically significant, increase in fibrinogen adsorption. In contrast, incorporation of even 1% of MAA (present in the form of the carboxylate anion at the pH used for protein deposition studies) causes a dramatic decrease in the adsorption of both proteins to a level that does not change with increasing MAA concentration in the range shown. A parallel effect was observed when MAA was progressively incorporated into HEMA membranes[5]. It is only at very low levels of MAA incorporation (<1%) that a dramatic convergence of the comonomer adsorption profiles occurs, producing adsorption levels shown for the ACM homopolymer in *Figure 12*. Although conventional surface property measurements do not detect significant differences between the substrates shown in this figure, water binding studies do show significant changes and, interestingly, reflect the protein adsorption results. Thus, *Figure 14* shows the *EWC*, together with the freezing and non-freezing water contents, for the MBACM compositions shown in *Figure 13*. The non-freezing and freezing water contents parallel quite remarkably the albumin and fibrinogen adsorption results.

A useful biological probe technique, which reflects changing surface properties in hydrogels with water contents between 40% and 80%, involves the use of anchorage-dependent fibroblast cells. We have carried out cell adhesion and growth studies on a variety of synthetic polymer substrates, as a means of investigating the interfacial conversion process that occurs when synthetic materials are placed in contact with a biological environment[23-26]. Interestingly, poly(HEMA) hydrogel itself is not cell adhesive. As the water content of hydrogel copolymers increases above the level of this material (~40%), the region of cell non-adhesion is followed by a steady increase in cell adhesion. The relationship of cell adhesion to water content is much more sigmoidal than linear and, again, reflects the fact that interesting surface changes are occurring in this region. There is, however, a current lack of direct physicochemical techniques whereby they may be monitored.

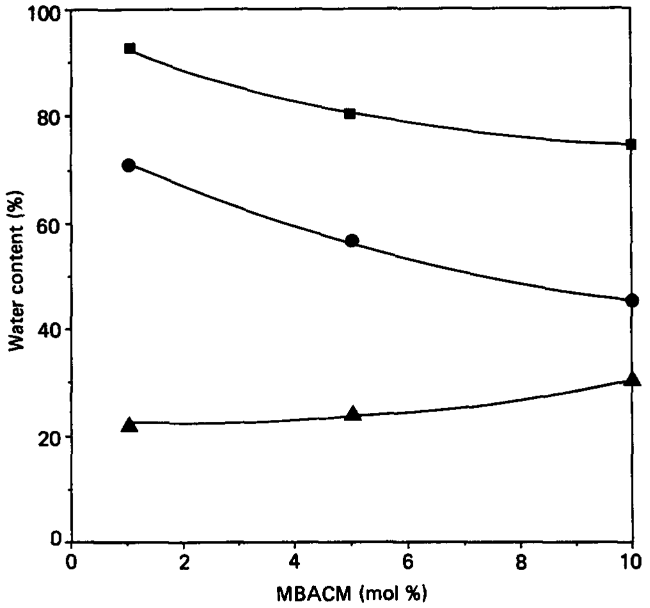

Figure 14 Effect of incorporation of MBACM on the equilibrium (■), freezing (●) and non-freezing (▲) water contents of ACM–MBACM copolymers at 22°C

CONCLUSIONS

The range of copolymers described in this paper show interesting differences in hydrogen bonding capability (and thus interchain attraction), which results in differences in water binding, mechanical and surface properties. The behaviour described illustrates the impracticability of constructing a simple 'hydrophilicity series' of functional monomers for use in hydrogel synthesis, since the competitive processes involved override, in many cases, the individual hydrophilicities of the groups involved.

The incorporation of a hydrophobic monomer such as styrene offers the potential to modulate water binding further in these copolymers and thus to increase strength. It is important to note, as shown in *Figure 7*, that, in the case of water contents between 40% and 80%, this can be done without adversely influencing the permeability of the polymers to oxygen or to other small molecules (a property that is still controlled by *EWC*). Such materials are useful in those biomedical applications that require a combination of strength, permeability and dimensional stability, such as contact lenses. On the other hand, incorporation of hydrophobic monomers into copolymers that have strong hydrogen bonding capability enables materials having high strength, moderate water content and very low freezing content to be obtained[12]. Such materials have shown unusual permselectivity behaviour and are of interest in membrane and sensor applications. The design of hydrogels with properties appropriate to these specific applications will be discussed in subsequent papers.

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