monomer and crosslinking comonomer are distributed between the suspended phase and the suspension medium, the feather-like species possibly arising from polymerization of monomers dissolved in the aqueous phase. Unfortunately time does not allow our own research efforts to pursue this matter further. However, the ability to generate such structures may have important consequences in the fields of colloid stability and polymer compatibility, and other groups may wish to examine this phenomenon in more detail.

Suspension copolymerization[2] was carried out as follows. *N,N*-methylenebisacrylamide (0.875 g) and *N,N*-di-n-propylacrylamide[3] (7.50 g) in toluene (10 ml) was suspended by rapid stirring (~800 rpm) in a previously prepared solution of poly(vinyl pyrrolidone) (1 g) in water (400 ml). After addition of the initiator, azobisisobutyronitrile (0.1 g), the reaction flask was flushed for 10 min with nitrogen gas and then stirred at 80°C for 3.5 h. Part of the product was retained in suspension for examination as described above, the remainder was collected by suction filtration and was washed consecutively with acetone, 50% aqueous acetone and finally water before being left to dry in air. The final product is a translucent amorphous solid.

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References

1 'Solid Phase Synthesis', (Eds E. C. Blossey and D. C. Neckers), Dowden, Hutchinson and Ross, Stroudsburg, 1975
2 Greig, J. A. and Sherrington, D. C. *Polymer* 1978, **19**, 163
3 Butler, K., Thomas, P. R. and Tyler, G. J. *J. Polym. Sci.* 1960, **48**, 357

Novel macroporous hydrogel adsorbents for artificial liver support haemoperfusion systems

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The clinical use of haemoperfusion in blood detoxification and in the treatment of uraemia is now well established. Problems still exist, however, particularly in the wider use of the technique as the basis of artificial liver support systems for the treatment of acture liver failure[1]. Many of these problems are associated with the nature of the adsorbent and the need exists for a range of biocompatible adsorbents showing some degree of specificity for various blood toxins. Although activated carbons have a high adsorbation capacity for many such toxins, especially those that are water soluble, the need to improve its blood compatibility and prevent the detachment of carbon microparticles entails its impregnation or encapsulation in a polymeric coating such as poly(2-hydroxyethyl methacrylate). One major disadvantage of homogeneous hydrogels of this type is that they effectively behave as a membrane, restricting the rate of adsorption and to some extent the size of species that are adsorbed. Thus a compromise between compatibility and adsorption properties must be accepted. An alternative group of materials are the macroreticular cross-linked polystyrene or acrylic resins used in ion exchange. These are effective in the removal of certain toxins (particularly the bile acids) but are of limited value because of their poor blood compatibility.

We have investigated the possibility of employing the principle of polymerization on a crystalline matrix (used by Krauch and Sanner[2] and extended by Halden and Lee[3] to the polymerization of 2-hydroxyethyl methacrylate) to provide a macroporous hydrogel bead having strength, blood compatibility and adsorption properties appropriate to use in haemoperfusion systems[4]. Since ice forms a convenient matrix for these systems, phase diagrams were constructed to establish solubility limits for mixtures of appropriate monomers and cross-linking agents in water and water–ethylene glycol mixtures. Rapid cooling of the homogeneous solutions, photopolymerization (in the presence of, for example, benzoin or uranyl nitrate) and subsequent hydration produced macroporous polymer gels. Initial work showed that variation in solvent: monomer ratio, the nature of the monomer and cross-linking agent and the cross-link density produced membranes having a range of equilibrium water contents. The properties of these membranes are different from their homogeneous counterparts in respect of strength, opacity, water binding properties (as measured for example by differential scanning calorimetry) and porosity (having mean pore diameters in the range 0.2–2.0 microns). The relevance of these differences is illustrated in the Figure which shows the variation in permeability of a series of macroporous membranes to bromosulphophthalein (BSP, a useful model compound in this work), as a function of water content. In contrast the permeability of homogeneous hydrogel membranes of similar water contents is seen to be vanishingly small; measureable permeabilities being shown only by membranes with high water contents (and consequently with low cross-link densities and strength). The blood clotting times of the hydrated macroporous membranes were found to be in the range 30–40 min and only slightly worse than that of hydrated poly-2-hydroxyethyl methacrylate which had a blood clotting time of around 45–50 min measured under the same conditions.

Macroporous beads were prepared by a modification of the foregoing technique involving the introduction of a stream of monomer solution (either dropwise or with a motorised syringe) into a stirred bath of non-solvent (e.g. heptane) cooled to −70°C by the addition of solid carbon dioxide. Variation in the rate of injection from 0.2 to

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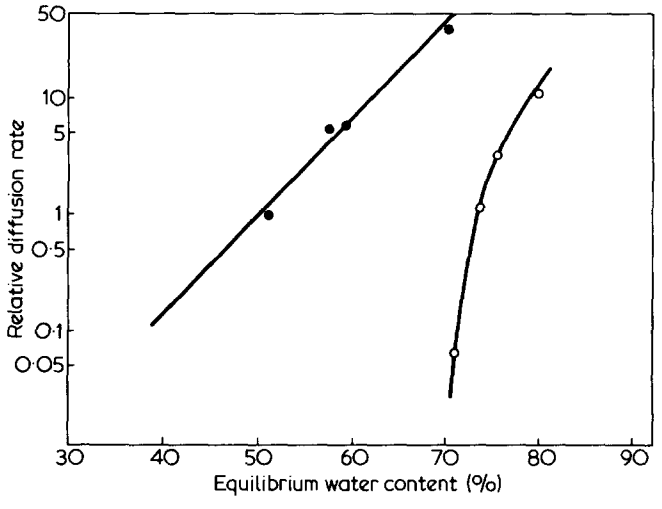
Table 1 Properties of macroporous beads (monomer injection rate 0.5 ml sec^{-1})

Principal monomers (mole %)	EDM content (mole % of principal monomers)	Solvent ratio (EG:H_2O)	Equilibrium water content (%)	Blood clotting times (mins)	Mean hydrated radius (mm)	Mean hydrated density (g cm^{-3})
HEMA	1.0	(1:4)	52.0 ± 0.5	27	1.7	1.13
HEMA	2.0	(1:4)	53.5 ± 0.5	27	1.6	1.13
HEMA	4.0	(1:4)	51.0 ± 0.5	27	1.5	1.13
HEMA	9.8	(1:4)	55.0 ± 0.5	21	1.5	1.14
HEMA (75) MAA (25)	8.5	(1:2)	42.0 ± 0.5	21	1.7	1.16
HEMA (75) AA (25)	8.5	(1:4)	56.0 ± 0.5	25	1.6	1.15
AA	8.5	(1:4)	55.0 ± 0.5	18	1.5	1.09

Key: HEMA: 2-hydroxyethyl methacrylate; AA: acrylic acid; EMD: ethyleneglycol dimethacrylate; EG: ethylene glycol



Relative diffusion rates of BSP across macroporous (●) and homogeneous (○) hydrogel membranes as a function of equilibrium water content

5 ml sec^{-1} caused a decrease in the mean diameter of the beads produced from 3 mm to 0.1 mm. The frozen beads were either photopolymerized in 'in situ' or could be removed, stored in cold non-solvent and polymerized subsequently. Scanning electron microscopy and surface area measurements on the dehydrated beads showed in the best cases a uniform and inter-connected pore structure extending throughout the beads and internal surface areas several thousand times greater than that of their superficial external surfaces. *Table 1* summarises some properties of typical macroporous beads obtained at a fixed (50:50) monomer: solvent ratio. Variation in this ratio produces a range of beads of different equilibrium water contents. Under comparable conditions the blood clotting times of commercially coated (4% polyHEMA) charcoal, Amberlite XAD-7, Dowex X-4 and similar resins were found to be in the region of 12 min.

Some indication of the way in which the adsorption properties of the macroporous beads can be modified by changes in monomer structure is illustrated in *Table 2* which compares the capacity of three adsorbents of this type for bilirubin removal from plasma, with that of other adsorbants used in the artificial liver support field. Bilirubin, a water insoluble breakdown product of haemoglobin, is a protein-bound toxin and its removal from plasma presents a severe test for synthetic adsorbents.

Table 2 Billrubin adsorption capacities of various materials (expressed as mg bilirubin per gram dry resin weight; solution (a) contained 20 mg bilirubin per 100 ml plasma; solution (b) contained 8.5 mg bilirubin per 100 ml plasma). All macroporous hydrogels have a crosslink density (EDM) of 10%

Material (mole %)	Mean radius (mm)	Adsorption from solution (a) (mg g^{-1})	Adsorption from solution (b) (mg m^{-1})
HEMA	1.5	0.55	0.20
HEMA (75) AA (25)	1.5	1.10	0.40
HEMA (50) AA (50)	1.5	1.70	0.60
Dowex X-4	≅0.5	1.55	0.45
Amberlite XAD-7	≅0.2	1.45	0.45
Coated charcoal (4% HEMA)	1–2 (irregular)	1.10	0.35

Adsorption capacities were carried out to equilibrium (50 h) using 0.5 g dehydrated resin in 5 ml plasma

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References

1 Dunlop, E. H., Weston, M. J., Gazzard, B. G., Langley, P. G., Mellon, P. J. and Williams, R. *Biomed. Eng.* (1975) **10**, 213
2 Krauch, C. H. and Sanner, A. *Naturwissenschaften* (1968), **55**, 539
3 Haldon, R. A. and Lee, B. E. *Br. Polym. J.* (1972) **4**, 491
4 Tighe, B. J. and Skelly, P. J. 'Materials for Haemoperfusion', Brit. Pat. Prov. Spec., 7703/78 (27.02.78)