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Some chemically modified poloxamer hydrogels: preparation, morphology and swelling properties

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Summary

Polymerizable diacryloyl derivatives of a series of commercial poly(oxyethylene)–poly(oxypropylene)–poly(oxyethylene) block copolymeric surfactants have been prepared and polymerized to form cross-linked hydrogels whose properties can be varied by controlling the proportions of hydrophilic and hydrophobic monomers (e.g. Pluronic F68, poloxamer 188 and Pluronic L61, poloxamer 181). Morphology and spherulite formation of the hydrogels prepared from pure monomer and mixtures of the modified monomers were studied using optical and scanning electron microscopy.

Spherulite formation in these mixtures was used as a probe of mixing compatibility and the imbibition of water, acting as a selective solvent, revealed different states of heterogeneity in the various cross-linked gels.

Swelling of the gels in aqueous media increased in a non-linear fashion with increasing proportion of the modified, more hydrophilic, poloxamer 188 in the gel.

Introduction

Cross-linked hydrogels derived from poly(oxyethylene)–poly(oxypropylene)–poly(oxyethylene) (PEO-PPO-PEO) poloxamer[1] surfactants have previously been made in our laboratory and their swelling and drug release properties studied

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[1] Poloxamer is the generic name for PEO-PPO-PEO block copolymers sold under the trade name (BASF, Wyandotte Corporation) 'Pluronic'.

(Al-Saden et al., 1980, 1981). These hydrogels were formed by random inter-molecular cross-linking induced by high energy γ-irradiation.

In this paper is described an alternative route to gel-forming systems based on a series of chemically modified, polymerizable poloxamer surfactant monomers. The modified poloxamer surfactants carry an acryloyl group at each end of the molecule; with two polymerizable groups on one single molecule, those compounds and mixtures of different homologues provide opportunities for determining the nature of the resultant cross-linked material both in terms of structural features and drug releasing properties.

The colloidal properties of block and graft copolymers have been investigated in both the solid state and solution form (Molau 1968; Riess, 1975). The parameters which determine the formation of a heterophase in a copolymeric material include the composition of the mixture, the molecular weight and structure of the macromolecules, and the environmental conditions. On mixing two different polymers, the Gibbs' free energy of the process:

$$\Delta G_m = \Delta H_m - T\Delta S_m$$

has to be negative if the components are mutually compatible. The entropy of mixing, ΔS_m, is generally small in mixtures of polymers and the process is endothermic in most cases (Flory, 1953). So, for a mixture of chemically dissimilar polymers there is normally phase separation. These aspects of pattern, domain, size and the molecular mixing at the interface between phases as well as within one phase depend on factors such as configuration of the components and their relative proportion, as well as the interactions between them. A study of poly(ethylene oxide)–polyisoprene–poly(ethylene oxide) (PEO-PI-PEO) block copolymers (Hirata, 1975) showed the need for the presence of a long PEO fraction in developing a spherulite crystalline texture; increased content of PI in the copolymer system induced a less perfect formation of spherulite texture.

In these polymer systems, hydrogen bonding between the PEO chains, and water molecules dominate the hydrophilicity of these non-ionic surfactants. The cross-linked network which is formed, could be classified as a multicomponent cross-linked structure following the terminology of Bamford and Eastwood (1975). Thus the morphology of the cross-linked material blended from two members of the modified surfactant series could be attributed to both the compatibility between them and the colloidal properties of individual molecules. Water would then become a selective solvent for this particular system.

Here we describe the preparation, morphology and swelling of such systems in aqueous media; the release of solutes from the gels will be discussed in a later paper.

Materials and Methods

Poly(oxyethylene)–poly(oxypropylene)–poly(oxyethylene) poloxamer (Pluronic) surfactants were obtained from Serva Feinbiochemica, Heidelberg. Poloxamer 188

(Pluronic F68), av. mol. wt.: 8350, HLB (25 °C) 29; poloxamer 181 (Pluronic L61), av. mol. wt.: 2000, HLB (25°C) 3. Acryloyl chloride was purchased from Aldrich Chemicals, Dorset, U.K.; triethylamine and azobisisobutyronitrile (AIBN) from BDH, Poole, U.K., used without further purification. Toluene for the surfactant modification was dried in the presence of sodium wire. All organic reagents used were Analar grade (BDH).

Preparation of polymerizable non-ionic surfactants

The general procedure to prepare the di-acryloyl surfactant molecules was as follows.

Pluronic F68 (20.25 g) was dissolved in dried toluene (60 ml) in a 250 ml flask to which triethylamine (1.4 ml) was added at 45 °C with constant stirring. Acryloyl chloride (0.8 ml) was added dropwise into the flask, followed by a further 0.5 ml triethylamine with 5 ml dried toluene. The reaction mixture was held at 45 °C for 90 min and the contents cooled and filtered. The solvent and residual volatile components were then removed under vacuum at 25 °C. The recovered compound in flake form was dissolved in toluene and reprecipitated from a large (e.g. 500 ml) volume of *n*-heptane with stirring. The recovered product was then redissolved in a minimum amount of toluene, and chromatographed through a 40 × 1.8 cm alumina column with a mobile phase of toluene/methanol (4 : 1). Solvent was removed under vacuum from the eluted compound at room temperature, and was then redissolved in minimum amount of toluene. Reprecipitation of the product was once again carried out from a large volume (500 ml) of well stirred *n*-heptane and the recovered product dried at room temperature under vacuum for 48 h. The final compound was characterized by UV (λ_{max}, 215 nm for acryloyl groups), IR (the stretching vibration of carbonyl groups at 1730 cm^{-1}, and of vinyl groups at 1640 cm^{-1}, whilst the absorption at 3500 cm^{-1} for the hydroxyl groups had disappeared), and TLC (Merck, Silica Gel GF_{254} type 60, 7% v/v methanol in chloroform, $R_f = 0.70$). The yield was found in general to be about 80%.

For poloxamers in liquid form, purification was carried out with a further step involving extracting the toluene solution of the sample with saturated sodium chloride in HCl solution 3 times and repeatedly extracting with distilled water. This was carried out before the column chromatography; the reprecipitation step was omitted.

Formation of cross-linked poloxamer gels

A 'Teflon' mould was used and disc form samples were polymerized in the mould at 85 °C for 90 min. Sample weight was controlled between 1.3 and 1.5 g. The mixing of two different poloxamer surfactants was carried out in diethyl ether and the solvent later removed under vacuum. 0.5% (w/w) AIBN was used as initiator of the cross-linking reaction which was carried out in the absence of oxygen in the reactor.

Morphology

Slices of the swollen samples were obtained with the ultra-microtome technique with the samples in the frozen state. The micrographs were obtained by using a Polyvar microscope, supplied by Reichert-Jung (U.K.), with the aid of a dark-field condenser.

Cubes of the swollen samples frozen in distilled water were prepared by a freeze-fracture technique followed by freeze-drying of the fractured sample and coated with a layer of gold in a Sputter Coater S150A apparatus. The samples were examined in a Philips PSEM-500 scanning electron microscope.

Spherulite formation

A solvent casting technique was used to prepare the mixtures, and the spherulite structures were grown at room temperature from the melt state on a glass slide. The samples were then observed under a microscope equipped with cross-polarizer.

Swelling study

The degree of swelling of the gels was measured via the weight of dried and swollen sample and calculated as the Gel Swelling Index (GSI) where:

$$\text{G.S.I.} = \left(\frac{(W_t)}{W} - 1 \right) \times 100\%$$

where W_t is the weight of the sample at time t and W is the initial dry weight of the sample.

The experiments were carried out at 37 °C in a Sørensen's modified phosphate buffer at pH 7.2, consisting of 3.1 g/l $NaP_2PO_4 \cdot 2H_2O$ and 16.7 g/l $Na_2HPO_4 \cdot 12H_2O$.

Abbreviations used

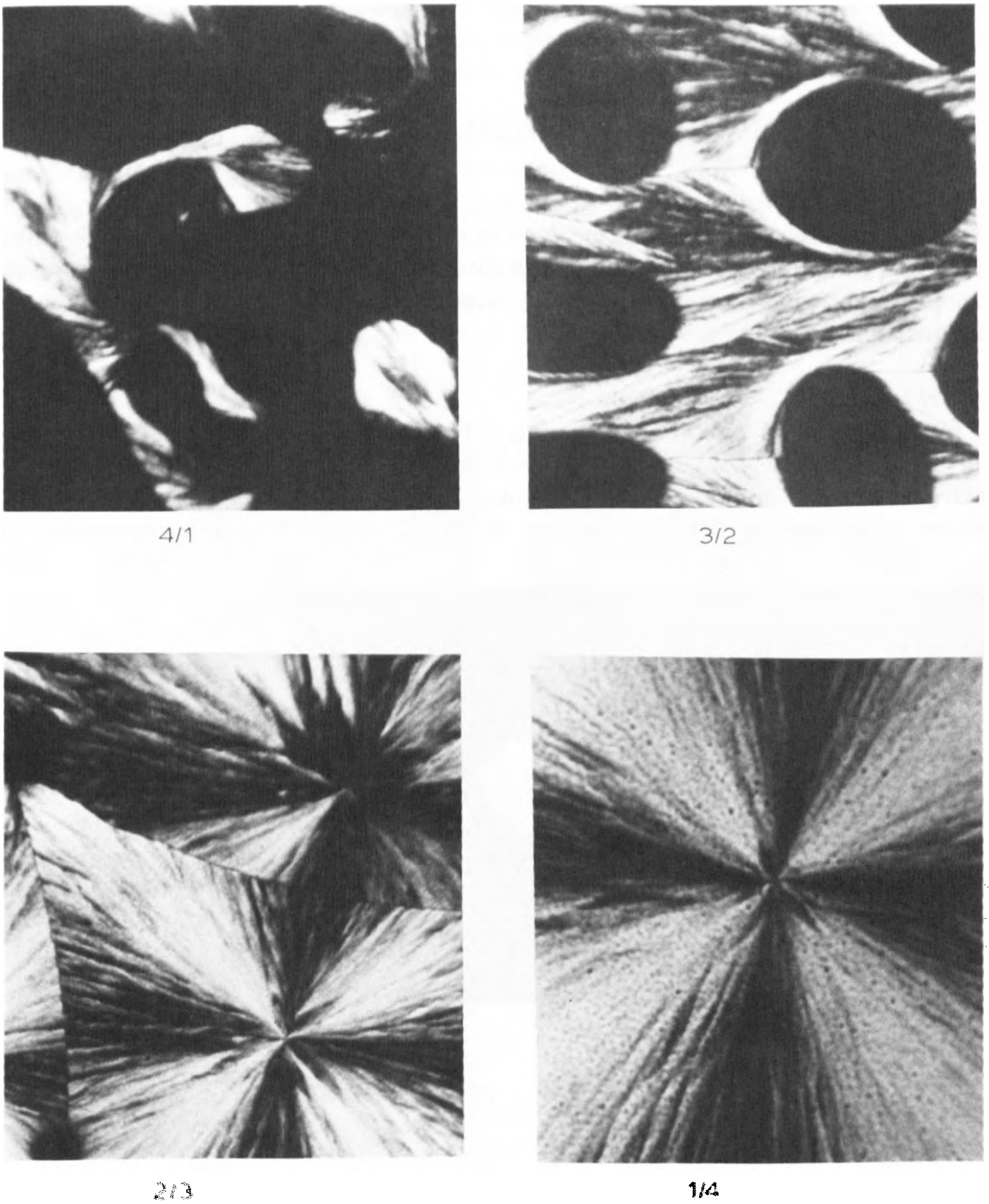
The diacryloyl derivatives of the poloxamer (Pluronic) surfactants are given the prefix (V) in the original notation coded from its location on the 'Pluronic Grid', e.g. VL61 for L61; and VF68 for F68.

The VL61/VF68 networks made in this study were prepared with weight ratios varying between 4 : 1 to 1 : 4; the samples would then be given a two-number code which describes the ratio between VL61 and VF68, e.g. sample 3/2 contain 3 parts of VL61 and 2 parts of VF68.

Results and Discussion

(a) Spherulite growth of blended samples

Fig. 1 shows photomicrographs of the mixed samples of modified poloxamers taken under a cross-polarizer; a changing pattern of spherulite formation can be observed. Well defined and complete Maltese Crosses can be seen in sample 1/4, and sample 2/3 shows some domains of defect in the spherulite texture being formed. The pure VL61 sample remained as liquid and did not have any spherulite features under similar conditions. As the VL61 proportion increased in the blends, (1/4 → 2/3 → 3/2 → 4/1) spherulite texture becomes more fragmented and, eventually only isolated 'islands' of spherulite texture can be seen as in sample 4/1. The inability of pure VL61 to form any crystalline texture is attributed to its short PEO chain. It is interesting to note that sample 1/4 showed a complete spherulite texture and it may suggest a rather compatible mixing in the sample. The two components

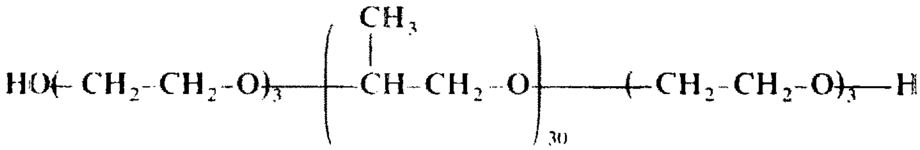


4/1 3/2

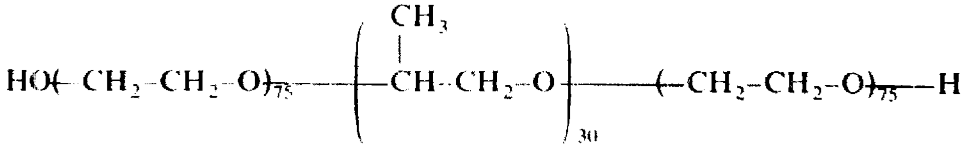
2/3 1/4

Fig. 1. Cross-polarized photomicrographs of blends of modified poloxamers VL61 and VF68. The codes are explained in the text.

of the blends, VL61 and VF68 originate from a homologous series of poloxamers with a similar central PPO block and different length PEO block.

L61 

$$HO\!\left(CH_2\text{-}CH_2\text{-}O\right)_3\!\!-\!\!\left[\begin{array}{c}CH_3\\|\\CH\text{-}CH_2\text{-}O\end{array}\right]_{30}\!\!-\!\!\left(CH_2\text{-}CH_2\text{-}O\right)_3\!-\!H$$

F68 

$$HO\!\left(CH_2\text{-}CH_2\text{-}O\right)_{75}\!\!-\!\!\left[\begin{array}{c}CH_3\\|\\CH\text{-}CH_2\text{-}O\end{array}\right]_{30}\!\!-\!\!\left(CH_2\text{-}CH_2\text{-}O\right)_{75}\!-\!H$$

The formation of spherulites takes place in a layer of the mixture on a glass slide; the gels in this study were cross-linked in disc form from the melted state. However, the spherulite features could be a useful probe in understanding the morphology of the cross-linked gels.

(b) Gel structure

The VL61/VF68 cross-linked materials form a 3-dimensional cross-linked network. When the cross-linked materials were brought to a swollen state in an aqueous environment, the imbibition of water into the gels caused a whitening effect to various extents in the different samples, as Fig. 2 shows. The swollen specimens of

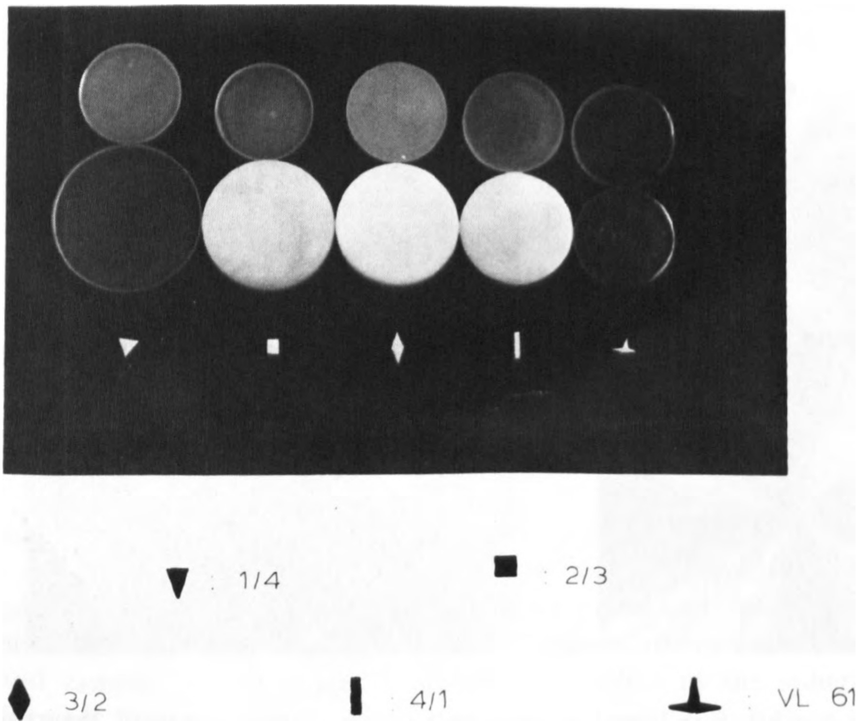


Fig. 2 Dried (upper) and aqueous swollen (lower) gels of blends of modified poloxamers VL61 and VF68.

the 4/1, 3/2 and 2/3 samples are opaque but with an increase in the VF68 content the swollen gels tend to be less opaque and the swollen sample of 1/4 appears transparent as does the pure VF68 cross-linked gel.

The photomicrographs of the swollen gels sliced into thin sections and immersed in water were taken with the assistance of a dark-field condenser, and showed clear phase separation in the opaque swollen gels, samples 3/2 and 4/1 (Fig. 3A and B). The swollen transparent 1/4 sample showed no phase separation. The boundary in the 3/2 and 4/1 systems separate an unswollen region from the water-imbibed gel domain. The pure VL61 cross-linked material was found not to absorb any measurable amount of water.

The transparent appearance of swollen sample 1/4 could be interpreted in parallel with the spherulite study of the same sample in terms of homogeneous mixing with no long range phase separation occurring. The imbibed water would be uniformly absorbed through the swollen network and no macrophase separation effect would be observed. The pure VL61 monomer with a short oxyethylene chain was not soluble in water and neither was its cross-linked network able to take up any water. The oxyethylene regions are linked through a polyacrylate chain (Scheme I)

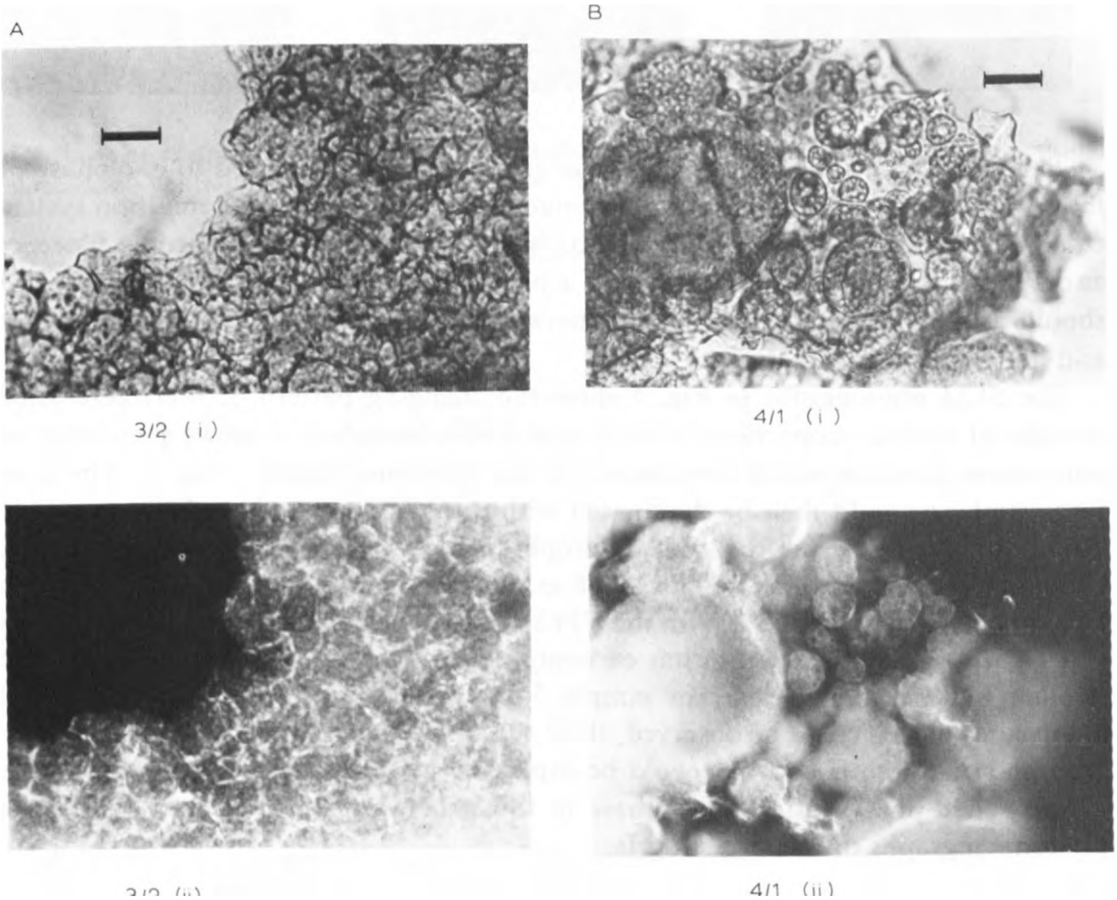
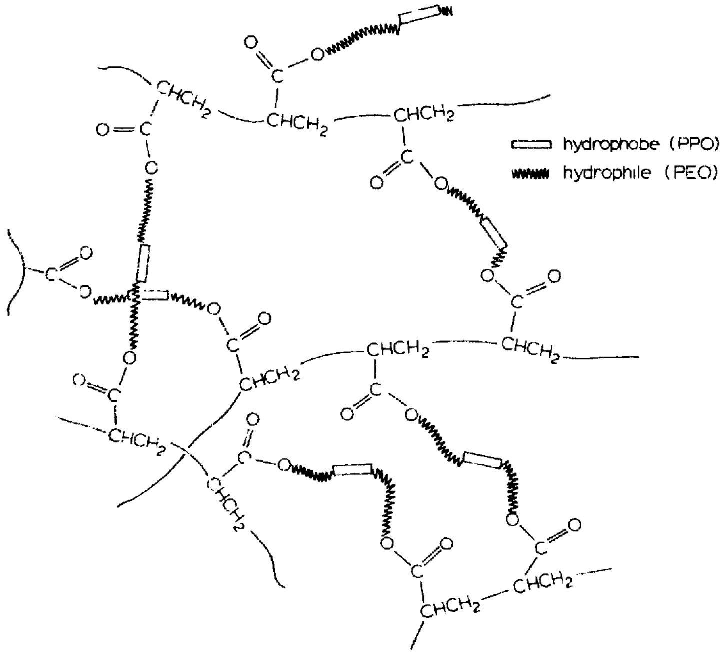


Fig. 3 Photomicrographs of cross-linked aqueous swollen poloxamer gels. A: Sample 3/2; B: Sample 4/1. (i) Normal bright-field; (ii) dark background. Scale marker = 20 μm.

and it is probable that this hydrocarbon backbone reduces the hydrophilic character of the cross-linked structure. The swelling properties of these blends will be discussed later.



Scheme 1

The imbibition of water in the opaque gels is probably confined to one phase of the system, either continuous or discontinuous, and a swollen solid emulsion system could be imagined. A similar phenomenon has previously been described by Florence and Whitehill (1982) whilst developing a polymerized multiple emulsion system. It should be noted that these cross-linked networks swell in ethanol to different extents and all appeared transparent.

The SEM photographs in Fig. 4 show the changing pattern of the freeze-dried samples of various proportions of VL61 and VF68. Sample 4/1 shows some isolated amorphous domains which correspond to the photomicrograph (Fig. 1). The continuous phase would then be dominated with the VL61 network and this probably did not imbibe any water due to its hydrophobicity. Even the dispersed domains are likely to be a mixture of VL61 and VF68 as the dark-field micrograph of the swollen 4/1 sample shows (Fig. 3B). With the VF68 content increasing the SEM micrograph (Fig. 4) shows that the definition of continuous phase or dispersed phase in the swollen gels became unclear. In sample 3/2, linkage between the dispersed and amorphous phases could be observed; the 2/3 sample showed only a more 'solid-like' amorphous structure, and this could be explained by the more random co-existence of unswollen phase and swollen phase in the structure. This is also shown in the photomicrographs of the swollen gels.

(c) Swelling study

The swelling studies of the cross-linked gels were carried out with and without incorporated solutes. The presence of embedded solute in the dried gel did not have any effect on the eventual uptake of water. Only in the presence of VF68 could the cross-linked network absorb water and swell; this phenomenon could be followed

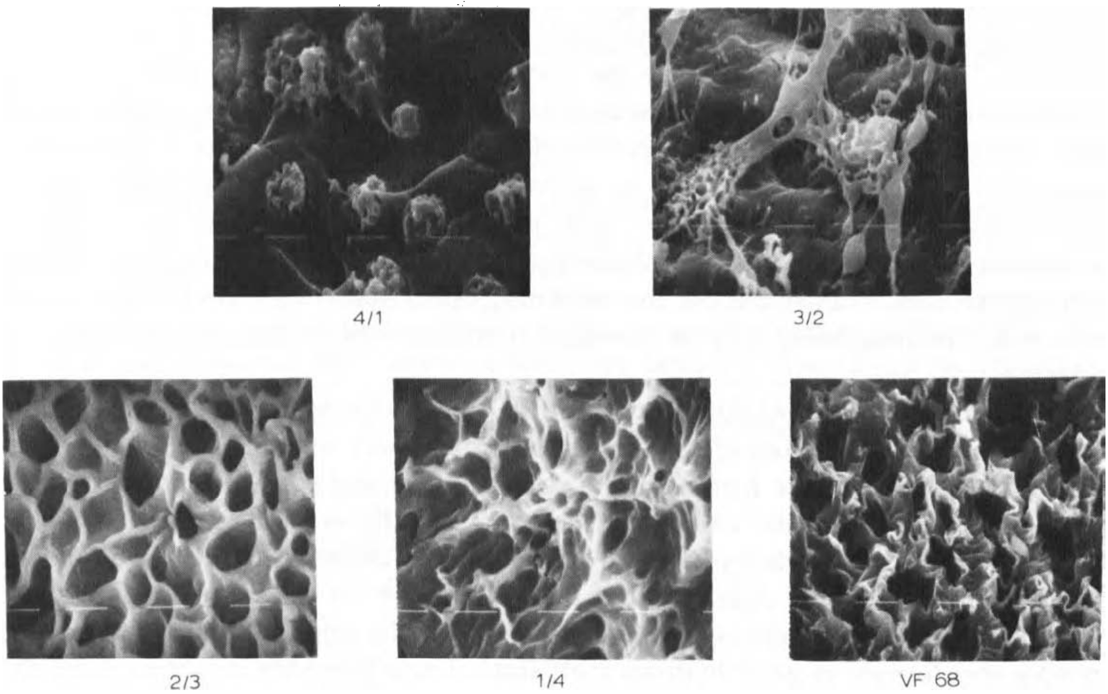

4/1
3/2
2/3
1/4
VF 68

Fig. 4. Scanning electron micrographs of cross-linked poloxamer gels prepared by freeze-fracture method. Scale marker = 10 μm.

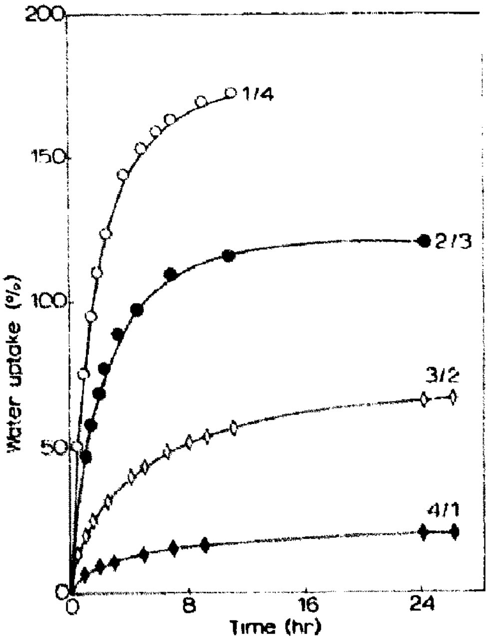


Fig. 5. Rate of water uptake by the dried cross-linked poloxamer gels at 37 °C in phosphate buffer (6.65×10^{-2} mol·dm^{-3}; pH 7.2).

with the appearance of amorphous domains in the SEM photographs. Fig. 5 shows the rates of water imbibition into the mixed networks. Tortuous structures of the network have been shown to reduce the rate of absorption of water in the poorly swelling blends, e.g. sample 4/1. Fig. 6 shows the non-linear increase in GSI with increasing amounts of VF68 in the gels. This non-linearity may show that the presence of VL61 tends to suppress the hydrophilicity of the VF68 portions in the gels, perhaps due to a limited compatability between the two components, which leads to reduced hydrophilic interaction in the resultant mixture. The miscible domains of VL61/VF68 could then be more amorphous than the pure VL61 region; but less hydrophilic in comparison with pure VF68 regions. With an increased proportion of VL61 beyond the miscibility limit with VF68 a heterophase would then appear. This is supported by the whitening effect observed upon the swelling of some gels. The miscibility may be provided by the structural similarity between the molecules.

In previous studies (Al-Saden et al., 1980) on poloxamer hydrogels, random intermolecular cross-linking of the long-chain copolymers were initiated by γ-irradiation. These systems were formed in aqueous solution and could form gels capable of absorbing water up to 1300% of their dry weight in 400 min. With higher concentrations of the surfactant, the gels had a lower capacity for hydration due to their higher cross-linking density and a tighter network. In the present systems, the average cross-linking density depends on the size of the original monomer, and the network was formed in an anhydrous melt state. These gels take longer to reach the equilibrium due to the tortuosity implied by the corss-linking reaction and the formation of a hydrophobic polyacrylate skeleton.

The implication of gel morphology and swelling studies on the release rates of solutes will be reported as part of a programme to utilize these novel hydrogels as drug delivery systems.

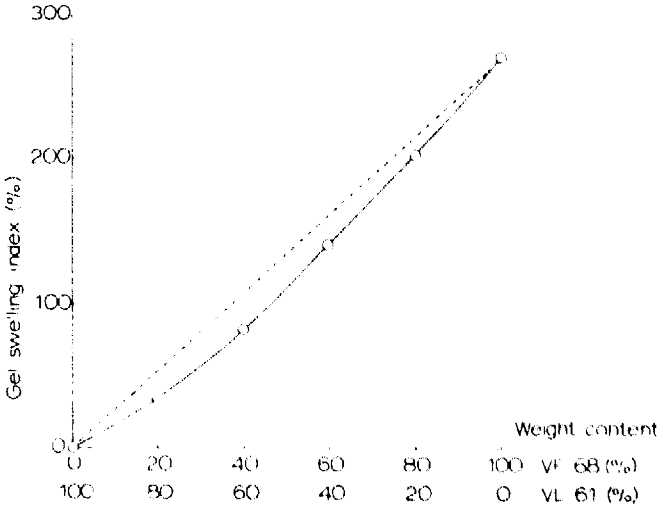


Fig. 6. Variation of gel swelling index (GSI) with VF68 content of cross-linked gels.

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