The Structure of Crosslinked Poly(glyceryl methacrylate) Hydrogel Networks

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SYNOPSIS

Poly(glyceryl methacrylate) hydrogels with different degrees of hydration (75–98% H) and cross-linking densities (X = 0.005–0.05 mol tetraethylene glycol dimethacrylate/mol glyceryl methacrylate) have been prepared by solution polymerization. Cross-linking densities of the fully swollen hydrogels were analyzed using a modified Flory equation. Poly(glyceryl methacrylate) gels polymerized with no added cross-linker were found to be highly cross-linked, the degree of cross-linking depending upon monomer dilution at polymerization. Modeling studies indicated that entanglement of polymer chains explained the highly cross-linked nature of these materials. Gels polymerized with tetraethylene glycol dimethacrylate exhibited higher cross-link densities than did gels polymerized with no added cross-linker. However, for gels polymerized with cross-linker, but at different initial dilutions, cross-linking densities varied depending upon initial concentration, indicating that entanglement contributed appreciably to cross-linking. These hydrogels may be regarded as highly swollen entangled networks, contrary to previous views. Correlation of these findings with those from earlier studies on the ultrafiltration behavior of the poly(glyceryl methacrylate) hydrogels suggested that the packing density of polymer fibers in the matrix may be more predictive of ultrafiltration behavior than is mesh size.

INTRODUCTION

Thin films prepared from poly(glyceryl methacrylate) (Pgma) act as ultrafiltration barriers[1-3] closely mimicking the behavior of the renal glomerular basement membrane (GBM), which serves to ultrafilter blood in the kidneys.[4] Both materials exhibit high void volumes (fractional water volumes, ϵ) of 0.9 and their permeation behavior can be modeled as matrices of randomly arranged fibers.[5-7] According to this model, permeation behavior is defined by the fiber radius, r_f, and by the density of packing of the fibers in space, l_f (the fiber length per unit volume); these parameters determine the void volume of the material. The permeation behavior of the films is affected by compression during ultrafiltration.[1,8] Applied hydraulic pressure extrudes water from the matrix, causing l_f to increase, though this is offset by a decrease in the thickness of the film. The overall consequence is that compression increases rejection and decreases the hydraulic permeability coefficient.

The fiber packing density is primarily defined by the degree of cross-linking of the matrix including both covalent cross-linking and fiber entanglements. Indeed, the ultrafiltration behavior of Pgma (Ref. 2) and of GBM (Refs. 8–10) can be altered by cross-linking, though the effects are different. Pgma films become less permeable with cross-linking,[2] whereas GBM may become more permeable.[10] Since there is little information on the degree of cross-linking of highly hydrated Pgma gels, the cross-linking frequency has been measured using equilibrium swelling methods.[11-13] These procedures report covalent cross-linking as well as entanglements. One advantage in studying synthetic hydrogels is the ease with which structure and composition can be readily changed by choosing appropriate polymerization formulations and conditions. Additionally, gels can be cast in shapes and sizes appropriate for physical and mechanical study. In contrast, the naturally oc-

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curring material, GBM, is isolated as irregular tiny fragments[14] that cannot be studied easily by conventional methods. Thus, study of Pgma hydrogels may yield insights relevant in understanding GBM.

EXPERIMENTAL

Materials and Methods

The glyceryl methacrylate monomer was prepared from glycidyl methacrylate by acid hydrolysis.[15] Hydrogels of different hydrations were prepared by diluting GMA with water, in the range 1:1–1:6 v/v monomer:water prior to polymerization. Hydrogels with nominal cross-linking ratios of $X = 0.005$, 0.01, 0.02, 0.03, 0.04, and 0.05 mol tetraethylene glycol dimethacrylate (TEGDMA) per mol GMA were prepared by admixing TEGDMA (Ventron-Alfa, Coventry, U.K.) with GMA and diluting 1:3 v/v with water before polymerization. In addition, gels with a fixed amount of cross-linker ($X = 0.05$ mol) but of different initial dilutions were also prepared. Polymerization was initiated by adding 6% ammonium persulfate (w/v) and 12% sodium metabisulfite (w/v) each in the ratio 1:10 (v/v) to monomer. Reaction mixtures were allowed to polymerize at 60°C for 1 h between glass plates to form sheets 0.15 cm in thickness. The resulting homogeneous gels were cut into buttons 1.5 cm in diameter before swelling. Measurements were made on six buttons from each gel sample and weighings showed a standard deviation of ±0.05%. Wider variations were found between different gel batches where hydration values were found to show a standard deviation ±0.5%.

Analysis of the Structure of Cross-linked PGMA

Swelling experiments were performed by weighing each hydrogel button in air, $w_{a,r}$, and in n-heptane, $w_{h,r}$, immediately after simultaneous polymerization and cross-linking but before swelling (relaxed state), then again in air, $w_{a,e}$, and in heptane, $w_{h,e}$, after swelling (equilibrium state) in water at 20°C. The gel buttons were then dried to constant weight, $w_{a,d}$:

$$V_{g,r} = (w_{a,r} - w_{h,r})/\rho_h \quad (1)$$

$$V_{g,e} = (w_{a,e} - w_{h,e})/\rho_h \quad (2)$$

$$V_p = w_{a,d}/\rho_p \quad (3)$$

$V_{g,r}$ and $V_{g,e}$ are the volumes of the gel before and after swelling, respectively; V_p, the volume of the dry polymer; and ρ_h and ρ_p, the density of n-heptane and Pgma, respectively. Swelling experiments gave values of the polymer volume fractions:

$$\nu_{2,r} = V_p/V_{g,r} \quad (4)$$

$$\nu_{2,e} = V_p/V_{g,e} \quad (5)$$

$$\nu_{e,r} = \nu_{2,e}/\nu_{2,r} \quad (6)$$

Two equations[16] were used to predict the molecular weight between cross-links, M_c, depending upon whether the distribution of chain lengths may [eq. (7)] or may not [eq. (8)] be judged to be Gaussian:

$$M_c^{-1} = 2/M_n - \frac{[\upsilon/V_1][\ln(1-\nu_{2,e}) + \nu_{2,e} + \chi\nu_{2,e}^2]}{\nu_{2,r}[\nu_{e,r}^{1/3} - 0.5\nu_{e,r}]} \quad (7)$$

$$M_c^{-1} = 2/M_n - \frac{[\upsilon/V_1][\ln(1-\nu_{2,e}) + \nu_{2,e} + \chi\nu_{2,e}^2][1 - N^{-1}\nu_{e,r}^{2/3}]^3}{\nu_{2,r}[\nu_{e,r}^{1/3} - 0.5\nu_{e,r}]\cdot[1 + N^{-1}\nu_{e,r}^{1/3}]^2} \quad (8)$$

where M_n is the number-average molecular weight of the primary polymer; υ, the partial specific volume of Pgma (0.722 $cm^3\ g^{-1}$)[17]; and V_1, the molar volume of water (18 $cm^3\ mol^{-1}$). $N = \lambda M_c/M_r$ represents the number of (C—C) links, where λ is the number of (C—C) links per repeating unit (for vinyl polymers its value is 2) and M_r is the molecular weight of the GMA repeating unit. χ is the Flory thermodynamic interaction parameter; values have been previously determined for Pgma with $\nu_{2,e}$ of 0.1–0.4 ($\epsilon = 0.6$–0.9)[18] and are obtained here using the relationship

$$\chi = 0.42 + 0.67\nu_{2,e} \quad (9)$$

The cross-linking density ρ_x of the network may be determined from M_c as follows:

$$\rho_x = (\upsilon M_c)^{-1} \quad (10)$$

In addition, the theoretical cross-linking density $\rho_{x\,\mathrm{theory}}$ can also be calculated (from the theoretical intercross-link molecular weight, $M_{c\,\mathrm{theory}} = M_r/2X$) by assuming the vinyl groups in the cross-linking agent react quantitatively; this value assumes no cross-linking by impurities or entanglements.

RESULTS

The composition of the hydrogel samples and results obtained for the equilibrium swelling measurements are shown in Table I. Gels with no added cross-link-

Table I The Composition of Hydrogel Samples with Different Degrees of Hydration, Crosslinking Densities, and Parameters Calculated from Swelling Experiments

Membrane	Cross-link Ratio $X \times 10^3$ (mol/mol)	% H	Vol Fraction Relaxed ($v_{2,r}$)	Vol Fraction Swollen ($v_{2,e}$)	Interaction Parameter (χ)	M_c [eq. (7)] (g/mol)	M_c [eq. (8)] (g/mol)	Monomer Units (M_c/M_r)	Cross-link Density $\times 10^4$ (mol/cm^3)	ξ (nm)
Pgma-1	—	79.6	0.330	0.157	0.525	4780	4950	31	2.8	5.9
Pgma-2	—	87.0	0.215	0.098	0.486	5420	5570	35	2.49	7.3
Pgma-3	—	91.7	0.160	0.062	0.461	7790	7920	50	1.75	10.2
Pgma-4	—	94.7	0.122	0.039	0.446	11830	12000	75	1.15	14.6
Pgma-5	—	98.6	0.075	0.011	0.427	33100	33200	207	0.42	37.5
Pgma-3×0	0.00	91.1	0.157	0.067	0.465	6930	7070	44	1.96	9.4
Pgma-3×1	4.85	89.6	0.159	0.077	0.472	5740	5890	37	2.35	8.1
Pgma-3×2	9.62	88.5	0.161	0.086	0.478	4970	5130	32	2.70	7.3
Pgma-3×3	18.60	86.9	0.161	0.098	0.485	4210	4380	27	3.16	6.5
Pgma-3×4	28.99	85.4	0.161	0.108	0.493	3660	3840	24	3.61	5.9
Pgma-3×5	39.04	83.6	0.165	0.122	0.501	3220	3410	21	4.06	5.3
Pgma-3×6	50.54	82.7	0.163	0.128	0.506	2890	3180	20	4.36	5.1
Pgma-2×6	53.38	74.9	0.224	0.189	0.546	2880	3080	19	4.50	4.4
Pgma-3×6	48.87	82.3	0.166	0.131	0.508	2940	3130	20	4.43	5.0
Pgma-4×6	53.36	87.9	0.134	0.090	0.480	3950	4120	26	3.36	6.5

Pgma-1–Pgma-5 indicates gels polymerized at increasing initial dilution of the monomer. Pgma-3×1–Pgma-3×6 indicates gels polymerized at constant initial dilution but with increasing quantities of cross-linker. Pgma-2×6–Pgma-4×6 indicates gels polymerized with constant cross-linking but at increasing initial dilution. Details are described in the text. % H is the percentage hydration determined by weighing. ξ, the distance between adjacent cross-links, was calculated using eq. (14).

ing agent were polymerized at increasing initial dilutions (Pgma-1:5) and are referred to as E-gels. Gels with added covalent cross-linking agent were polymerized with increasing levels of TEGDMA and at a constant initial dilution (Pgma-3×0:6) and are referred to as C-gels. Gels with added covalent cross-linking agent were polymerized with a constant ratio of TEGDMA but at different dilutions (Pgma-2:4×6) and are referred to as EC-gels. For E-gels, void volumes increased as cross-linking decreased (judged by the M_c values) with increasing dilution prior to polymerization. C-gels exhibited reducing M_c with increasing addition of TEGDMA, and in EC-gels, cross-linking declined with increasing dilution.

For the calculation of M_c, two theoretical analyses [eqs. (7) and (8)] may be employed.[16] Equation (7) assumes a Gaussian distribution where the number of repeating units between cross-links is large: $N > 100$. Values of M_c as calculated from eq. (7) for the series of hydrogels (Table I) ranged from 2900 to 33,100, corresponding to $N = 36$ to 414, indicating that except for highly hydrated samples a Gaussian distribution of the actual chain lengths cannot be assumed. Equation (8) was therefore used to calculate M_c based on an assumption of a non-Gaussian distribution, where $N < 100$. Since the polymerization of GMA occurred simultaneously with cross-linking even in the absence of added cross-linking agent, it was not possible to measure the number-average molecular weight of the primary chain, M_n. The calculation of M_c was relatively insensitive to values of $M_n > 100{,}000$ and this value was used.

The correlations between gel hydrations and mesh sizes are illustrated in Figure 1. The mesh sizes of cross-linked C-gels are close to those of the E-gels of lower hydrations. However, differences are more readily seen when cross-linking densities are compared in Figure 2. From $M_{c\,\text{theory}}$, values of $\rho_{x\,\text{theory}}$ are calculated, and these are compared with the experimentally determined values of ρ_x shown in Figure 3. The relationship between the cross-linker concentration (cross-linking ratio, X) and $v_{2,e}$ is illustrated in Figure 4.

DISCUSSION

The results in Table I (Pgma-3×0:6; C-gels) illustrate the expected effect that increasing the cross-linker concentration in the polymerization solution gave gels with decreasing M_c values, reflecting increased covalent cross-linking. More surprisingly,

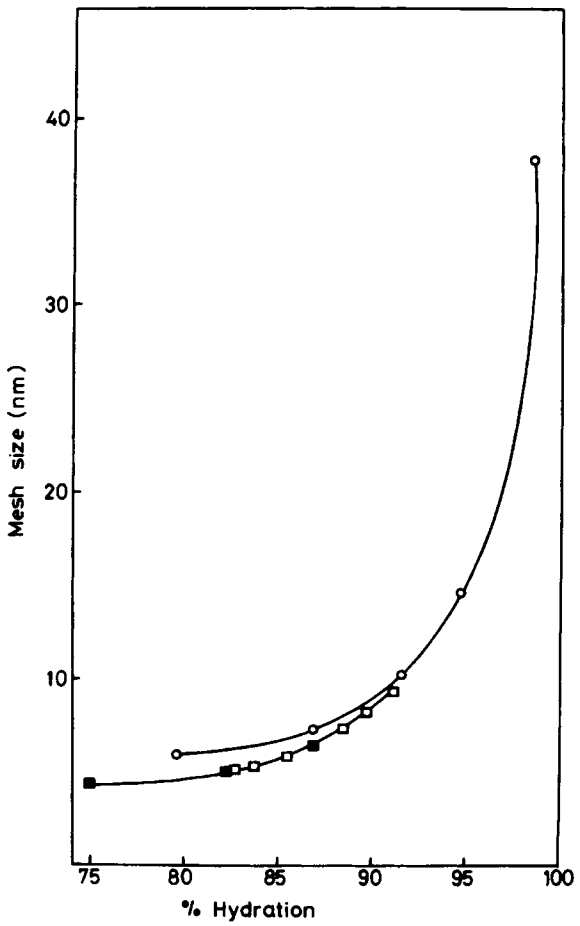

Figure 1 Correlation between gel hydrations and mesh sizes for (○) E-gels, (□) C-gels, and (■) EC-gels. Mesh size was calculated using eq. (14).

gels with no added cross-linker (Table I, Pgma-1:5; E-gels) also showed marked cross-linking, approaching the levels of cross-linking seen in the C-gels. This has been noted by others and has been attributed to contamination of the monomer by cross-linkers derived from disproportionation reactions[15] or to chain transfer reactions during polymerization.[16] Impurities seem to provide an insufficient explanation for gel formation since highly purified acrylamide forms gels when polymerized at a sufficiently high concentration (> 5% w/v), as does GMA.[15,18] Although chain transfer reactions may explain the formation of gels, an alternative reason may be entanglement of the polymer chains during polymerization; the equilibrium swelling method measures both entanglements and covalent cross-links.[19] Entanglement would be more likely to occur when gels are polymerized from increasingly concentrated solutions and would explain the dependence of the degree of cross-linking of the E-gels on initial polymerization concentration (Fig. 2). The degree of cross-linking when cross-linker is added should be less markedly affected by dilution of the initial polymerization solution. This idea was examined using the EC-gel series. These gels showed much higher cross-linking densities than did the E-gels, indicating marked covalent cross-linking. However, the level of cross-linking varied with monomer concentration during polymerization, suggesting that entanglement cross-links were also important in the gel structure (Fig. 2).

Some insight into the structure of E-gels can be gained by assuming that each cross-link is a quadripartite nexus, a crossover (*X*-link), which differs from the tripartite nexus (*Y*-link) in C-gels, in that the two component polymer chains retain mobility with respect to each other. At equilibrium swelling, when the gel is expanded, the structure will resemble

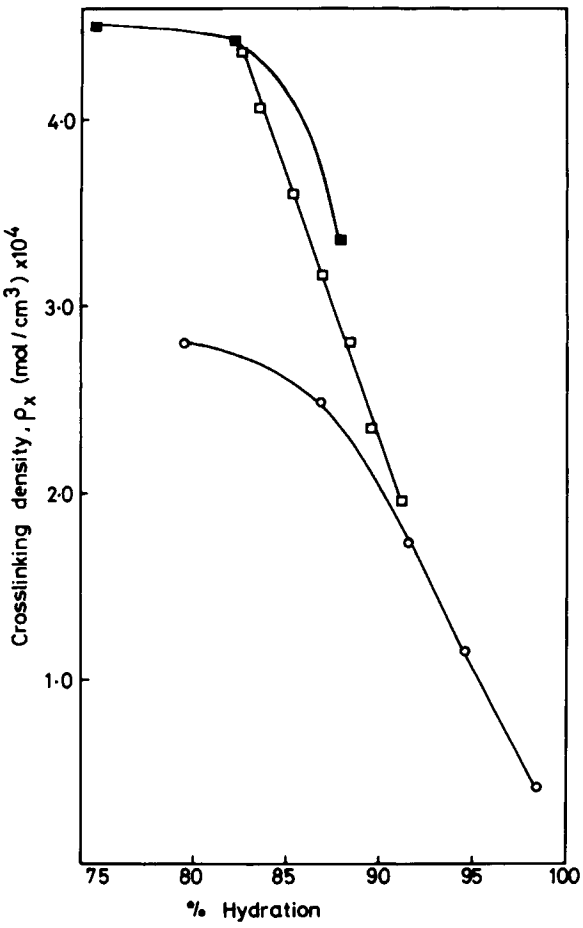

Figure 2 Correlation between gel hydrations and cross-linking densities for (○) E-gels, (□) C-gels, and (■) EC-gels.

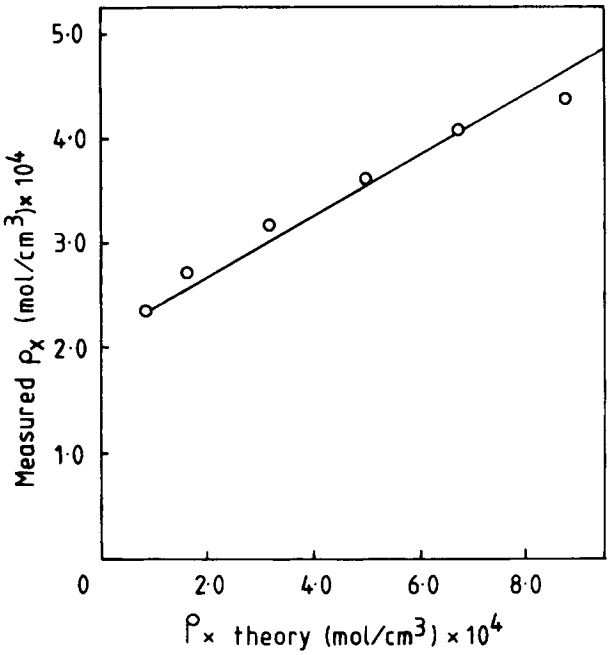

Figure 3 Comparison between measured (ρ_x) and calculated ($\rho_{x\,\text{theory}}$) cross-linking densities.

an equilateral three-dimensional network. The volume (V_t) occupied by the unit cell will be

$$V_t = 22.5L^3 \tag{11}$$

while the volume of the polymer chains (V_c) will be

$$V_c = 28L\pi r_f^2 \tag{12}$$

leading to calculation of the void volume (ϵ):

$$\epsilon = 1 - (V_c/V_t) \tag{13}$$

L for the extended polymer chain can be calculated from M_c (Table I) using the usual lengths and angles for a polyethylene chain; r_f was taken as 0.8 nm (Refs. 1–3), allowing calculated values of ϵ be compared with measured values (Table II). The agreement is poor unless a shorter effective intercross-link length is used, where $L_e = 0.65L$ (Table II). This suggests that the E-gels might be portrayed as a partially collapsed three-dimensional network, a view that accords with the conclusions from permeation studies[1-3] that the gels behave as randomly arranged, rather than as ordered, networks.

Peppas et al.[16] proposed that the permeability properties of hydrogels are related to the mesh size, which is defined as the space between macromolecular chains in a cross-linked structure, i.e., the distance between two adjacent cross-links, ξ:

$$\xi = \alpha(C_nNl^2)^{1/2} \tag{14}$$

where α ($= \nu_{2,e}^{-1/3}$) is the chain extension or linear deformation coefficient, C_nNl^2 represents the end-to-end distance of the polymer chains in the unperturbed state; C_n is the Flory characteristic ratio (6.9 ± 0.5),[16] and l (= 0.154 nm) is the C—C bond length.

The results for ξ are shown in Table I for comparison with values of L_e for the series of E-gels found in Table II. The values for L_e are somewhat lower than values for ξ, but, overall, the agreement is reasonable, suggesting that the geometric model for the polymer is not unrealistic.

Applying the geometric model to the C-gels and EC-gels does not provide a consistent correlation between L and ϵ; this might be expected since Y-links interrupt the symmetry of packing assumed by the model. Packing with Y-links rather than X-links is likely to be less dense since fewer chains are clustered at each nexus. This explains the puzzling observations that E-gels tended to show lower hy-

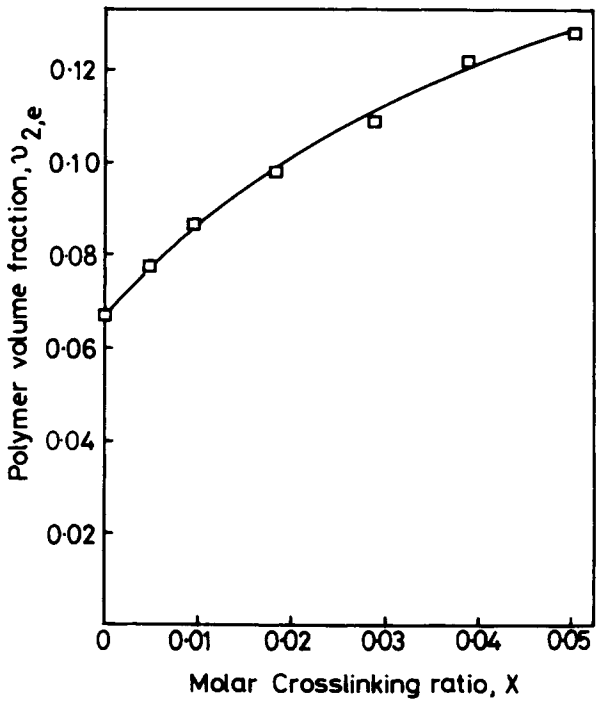

Figure 4 Relationship between cross-linking ratios and volume fractions of fully swollen cross-linked hydrogel samples.

Table II Comparison of Void Volumes for E-gels Measured from Swelling Experiments and Calculated Assuming a Crumpled Tetrahedral Configuration

	L (nm)	L_e (nm)	ϵ Calculated	ϵ Measured	ζ (nm)
Pgma-1	7.7	5.0	0.849	0.843	8.2
Pgma-2	8.7	5.7	0.882	0.902	9.3
Pgma-3	12.5	8.1	0.942	0.938	13.3
Pgma-4	18.7	12.1	0.974	0.961	19.9
Pgma-5	51.7	33.6	0.997	0.989	55.0

drations than did C-gels even when M_c values were comparable (cf. Pgma-1 and Pgma-3×2).

The modeling suggests that entanglement is likely to be the predominant form of cross-link, rather than cross-links due to impurities or chain-transfer reactions, in the absence of added cross-linker. The relative importance of entanglement was observed in the EC-gels (Pgma-2:4×6) where the degree of cross-linking was appreciably influenced by the initial dilution of the monomer solution notwithstanding a molar ratio of 1:20 cross-linker to monomer (Fig. 2).

Peppas et al.[16] concluded that PHEMA gels show high levels of entanglement based on extrapolation of the linear relationship between theoretical and experimentally measured cross-linking densities for covalently cross-linked gels. Such a plot is shown in Figure 3 for the C-gels having an intercept corresponding to $M_c = 6500$, which represents the molecular weight between entanglements for a non-covalently cross-linked gel. The value measured for the equivalent E-gel (Pgma-3×0, Table I) was 7070, in reasonable agreement with the predicted value. Comparing Pgma-3 and Pgma-3×0 shows that for these two comparable gels the M_c values were 7920 and 7070, indicating that the degree of cross-linking does vary between gels. This may reflect statistical variation in the probability of entanglement.

The proposal that E-gels are entangled rather than covalently cross-linked may be further explored by measuring the mechanical behavior of the gels since elasticity measurements would provide a measure of covalent cross-linking. The friable nature of these materials makes mechanical testing difficult; nevertheless, unilateral compression measurements of Pgma gels have been attempted.[17] Unfortunately, no measurements were performed on gels polymerized without added cross-linker, but the results reported for cross-linked gels indicated that compression modulus increased as the monomer concentration prior to polymerization was decreased. This finding was attributed to hydrophobic interactions influencing the mechanical behavior of the gel.

Refojo and Leong[20] demonstrated that penetration of macromolecules into hydrogels depended upon the degree of hydration of the gels. Reinhart et al.[21] subsequently proposed that the mesh (ξ) of the cross-linked matrix governed diffusion of macromolecules in hydrogels. If the geometry of the network is that of a three-dimensional netting, then the mesh space that governs permeation is the distance between adjacent parallel fiber segments, ζ, given by:

$$\zeta = 2(\cos \phi L_e) \tag{15}$$

where $\phi = 35.25°$ for a tetrahedral framework.

However, the crumpled conformation of the fibers will cause these to obtrude into the framework space and the matrix will be more restrictive than indicated by the values given for ζ found in Table II. For example, using a hydrogel film with a composition equivalent to Pgma-3 to ultrafilter myoglobin (diameter ~ 4 nm), rejection values of 0.6–0.9 were obtained,[1-3] but the mesh size calculated for the swollen Pgma-3 gel of ~ 10 nm (and ζ of ~ 13 nm) might be judged as unlikely severely to restrict permeation by this protein. Previously, we have demonstrated that the ultrafiltration behavior of hydrogels was modified by the compression of the gels under operating conditions[1-3]; compression resulted in extrusion of water from the matrix with a consequent increase in the packing density of the fibers. Hence, knowledge of the mesh size is of little value in predicting ultrafiltration behavior under such conditions.

Analysis of ultrafiltration behavior using the fiber-matrix hypothesis[5-7] has shown that the length of the fiber per unit volume of the network (i.e., the packing density, l_f) is a determinant of permeation behavior, and this parameter is useful in explaining ultrafiltration properties. The equilibrium l_f varies proportionally with $\nu_{2,e}$ as shown in eq. (16), which, in turn, depends upon the cross-linking density (Fig. 2):

$$\epsilon = 1 - \nu_{2,e} = 1 - \pi r_f^2 l_f \tag{16}$$

Thus, cross-linking will influence l_f and, hence, ultrafiltration behavior. Additionally, cross-linking will affect the compression modulus of the material and this will also affect ultrafiltration behavior. These relationships are currently being studied. Optimistically, it should be possible to prepare hy-

drogel films with predetermined ultrafiltration characteristics by controlling the degree of cross-linking during polymerization.

The glomerular basement membrane shows very similar ultrafiltration properties[8,9] to the Pgma hydrogels.[1-3] GBM is primarily composed of type IV collagen,[22] which, *in vitro,* forms a three-dimensional network of fibers with an equivalent L of 400 nm.[23] It seems unlikely that a material with such a large L value should show parallel behavior to the Pgma hydrogels with much lower L values. For instance, the most hydrated sample Pgma-5 has an L of 52 nm only, assuming the chain to be fully extended. Hence, it would seem that the structure of GBM is probably either much more heavily cross-linked or entangled than has previously been recognized,[24] so as to form the compact structure necessary to account for its ultrafiltration behavior. Indeed, recent studies[25-27] on collagen IV have identified potential intra- and intermolecular lateral cross-linking sites along the triple helical collagen chains. Therefore, the view that basement membrane is a rather loosely composed network needs to be modified to accommodate a highly complex three-dimensional cross-linked meshwork consisting of highly entangled structures. Thus, studies with hydrogels are providing insights toward our understanding of the biological material.

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GLOSSARY

- C_n Flory characteristic ratio
- L length of extended polymer chain between cross-links
- L_e effective chain length between cross-links
- l C—C bond length
- l_f fiber length per unit volume of gel
- M_c molecular weight of the polymer segments between cross-links
- M_n number-average molecular weight of the primary polymer
- M_r molecular weight of the poly(glyceryl methacrylate) repeating unit
- N number of C—C links
- r_f polymer fiber radius
- V_c volume of polymer chain in unit cell
- $V_{g,e}$ volume of the gel after swelling
- $V_{g,r}$ volume of the gel before swelling
- V_p volume of the dry polymer
- V_l molar volume of water
- V_t volume of unit cell
- υ partial specific volume of poly(glyceryl methacrylate)
- $w_{a,d}$ weight of dried gel in air
- $w_{a,e}$ weight of swollen gel in air
- $w_{a,r}$ weight of relaxed gel in air
- $w_{h,e}$ weight of swollen gel in n-heptane
- $w_{h,r}$ weight of relaxed gel in n-heptane
- X nominal cross-linking ratio
- α chain extension coefficient
- ϵ fractional water volume (void volume)
- ζ distance between adjacent parallel fiber segments
- λ number of C—C links per repeating unit
- $\nu_{2,e}$ fractional polymer volume of swollen gel
- $\nu_{2,r}$ fractional polymer volume of relaxed gel
- $\nu_{e,r}$ fractional volume ratio
- ξ distance between adjacent cross-links calculated by eq. (14)
- π pi
- ρ_h density of n-heptane
- ρ_p density of poly(glyceryl methacrylate)
- ρ_x cross-linking density
- χ Flory thermodynamic interaction parameter

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