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Some excursions in the world of stimuli-responsive polymeric gels*

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Abstract

Stimuli-responsive polymeric gels are attracting increasing attention due to their great potential as smart materials. Some of the recent work in the area of science and applications of these materials, including from our own school at NCL, is described. The quantitative basis for volume transition in the gels is first presented. Our recent findings on deformation-dependent swelling as well as certain aspects of microdynamics in gels studied through NMR have been highlighted. Specific applications based on this fundamental understanding have been described. These include the development of a macromolecular separation technique based on swelling/collapsing gels. The basis for diffusion modulation of gels to switch from Fickian to non-Fickian diffusion has been presented. A practical application of such diffusion modulation in sustained-release systems is described. Diverse applications exploiting the stimuli-responsive ability of gels in areas such as sensors, soft actuators, artificial muscles, intelligent sponges, etc., are finally presented.

Key words: Stimuli-responsive polymeric gels, macromolecular separation.

1. Introduction

Gels are swollen polymeric networks. They possess the cohesive properties of solids and the diffusive transport properties of liquids. The combination of elastic properties and osmotic reactivity make them very special. In Japan, gels are being looked at as the most exciting materials of the 21st Century. Among other things, this is certainly due to the 'smartness' or 'intelligence' that these gels demonstrate.

We have been involved in the study of these materials both with respect to their microscopic structure as well as some interesting macroscopic phenomena that they exhibit. We wish to highlight some of these studies. To start with, we will explain the quantitative basis for the swelling of gels. We will then bring out the special features of volume phase transitions that these materials undergo. These transitions

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are reversible and can be both continuous or discontinuous. We will then explain the imaginative way in which such phenomena can be exploited in diverse areas. We will then do some 'crystal glazing' about the future of these smart materials.

2. Thermodynamics of swelling gels

The theory of swelling of non-ionic crosslinked polymeric networks was first proposed by Flory[1], who subsequently modified it to take into account the effect of ionic substituents. Flory proposed an analogy between the swelling equilibrium and the osmotic equilibrium. The total osmotic pressure (π) acting on the gel comprises the forces arising from polymer–polymer affinity and rubber elasticity. It can be given as,

$$\pi = \mu_1 - \mu_1^0 = RT\left\{ ln(1-V_2) + V_2 + \chi V_2^2 + V_1\left(\frac{V_e}{V_0}\right)\left(V_2^{1/3} - \frac{V_2}{2}\right)\right\} \qquad (1)$$

Here, μ_1 and μ_1^0 are chemical potentials of solvent within the gel and outside the gel, respectively. V_2 is the volume fraction of the network, χ, the interaction parameter between the polymer and the solvent, R, the gas constant, T, the absolute temperature, V_1, the molar volume of the solvent and the term $\left(\frac{V_e}{V_0}\right)$, the deformation factor, which arises due to the elasticity of the network. At equilibrium swelling, we have $\pi = 0$. With some rearrangement, eqn (1) can be written as,

$$-[ln(1 - V_2) + V_2 + \chi V_2^2] = \left(\frac{V_1}{\bar{v}M_c}\right)[1 - 2M_c]\left(V_2^{1/3} - \frac{V_2}{2}\right). \qquad (2)$$

Here, M_c is the molecular weight between crosslinks and M_n, the number average molecular weight. The term $(1–2\ M_c/M_n)$ in the above equation is the correction factor for network imperfections resulting from the chain ends.

With suitable approximations, eqn (2) can be simplified to

$$q^{5/3} = \left(\frac{\bar{v}M_c}{V_1}\right)(1 - 2M_c/M_n)\ (1/2 - \chi). \qquad (3)$$

This relationship shows how the swelling ratio (q), which is the volume of the swollen gel divided by the volume of the unswollen gel, changes as a function of the extent of crosslinking and also the thermodynamic quality of the solvent. This equation has been experimentally confirmed for a number of systems.

The extent of swelling attainable in ordinary network systems is rather limited and the swelling ratios usually approach about 10. Some superswelling gels, which are essentially ionic networks, attain q values of 100 to 1000. This is because in the case

of networks containing ionisable groups, the swelling forces may be greatly increased as a result of the localisation of the charges on the polymer chains. Electrostatic repulsions between like groups set up considerable expansion of the networks. The equilibrium between the swollen ionic gel and its surroundings can be considered by recognising that the osmotic pressure will arise from a difference in mobile ion concentrations. Using suitable approximations, two asymptotic limits can be calculated. The first one relates to the case when the electrolyte concentration outside the gel is negligible. We then have,

$$q^{5/3} = [iq/V_m\rho_p + (0{\cdot}5 - \chi)/\rho_p V_1]M_c/(1 - 2M_c/M_n) \tag{4}$$

whereas in the presence of significant electrolyte concentration on the outside, the expression reduces to

$$q^{5/3} = [i^2/4V_m^2 I_0 + (0{\cdot}5 - \chi)/\rho_p V_1]M_c/(1 - 2M_c/M_n). \tag{5}$$

Here i is the degree of ionisation, I_0, the ionic strength of the solvent present outside, V_m, the molar volume of the structural repeat unit of the network and ρ_p, the density of the polymeric network.

Badiger *et al*[2] have validated eqn (4) and shown that it is capable of quantitatively predicting the extent of swelling in ionic networks. Figure 1 shows some experimental data for specially tailored sulfonated polystyrene (divinyl benzene crosslinked) gels at rather low degrees of crosslinking and the influence of electrolyte (sodium chloride) concentration on the extent of swelling. As we see, the agreement between the experimental data and the theory is rather good.

3. Volume transitions in gels

The validation provided in Fig. 1 shows a continuous decrease in swelling due to an increase in the electrolyte concentration. However, a wide range of ionic, non-ionic, synthetic as well as natural polymers can exhibit either continuous or discontinuous volume phase transitions. Further, the transitions could be induced by changes in temperature, solvent composition, pH, salt concentration and electric field. A quantitative approach to elucidate the volume phase transitions in polymers has been given by Tanaka[3,4]. This is based on a reformulated equation of state of gels, arising out of an extension of Flory's theory of swelling, and was summarised in the foregoing.

For an ionic gel, Tanaka[4] has recast the equation as

$$\tau = \left(1 - \frac{\Delta F}{kT}\right) = \frac{\nu_1 \nu}{N\phi^3}[(2f + 1)(\phi/\phi_0) - 2(\phi/\phi_0)^{1/3}] + 1 + 2/\phi + \frac{2ln(1-\phi)}{\phi^2}. \tag{6}$$

Here τ denotes the reduced temperature, f, the number of dissociated hydrogen ions per effective chain, ν_1, the specific volume of the solvent molecule, ν, the specific

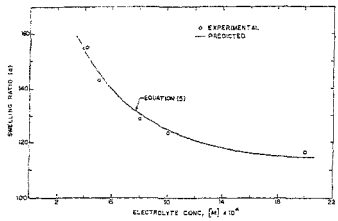

FIG. 1. Validation of eqn (5) for predicting swelling equilibria in ionic gels by using a sulphonated *poly(styrene divinyl benzene) gel.* For *details of* characteristics of gel, see Badiger *et al*[2].

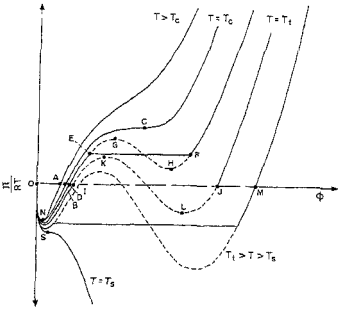

FIG. 2. Osmotic prame-volume isotherms for gels at various temperatures.

volume of the polymer segment, ϕ, the volume concentration of the network and ϕ_0, the volume concentration of the network in the absence of polymer segments. Through its dependence on ΔF and T, τ changes with temperature and composition. A plot of reduced temperature *vs* swelling ratio for some gels, *e.g.*, for a partially hydrolysed polyacrylamide gel, which has various degrees of hydrolysis shows that for certain values of the reduced temperature, the equation is satisfied by three values corresponding to two minima and one maximum of the free energy (Fig. 2). The values of ϕ corresponding to the lower minimum represents the equilibrium value. When two free energy minima have the same value, a discrete volume phase transition is observed.

The expansion of the term $ln\ (1 - \phi)$ results in

$$t = S(\rho^{-5/3} - \rho/2) - \rho/3 \tag{7}$$

where

$$t = (1 - \Delta F/kT)(2f + 1)^{3/2} \tag{8}$$

with

$$\rho = (\phi/\phi_0)(2f + 1)^{3/2}, \tag{9}$$

and

$$S = S_0(2f + 1)^4. \tag{10}$$

For the unionized polymer, we have $S = S_0$.

The value of the parameter S governs the magnitude of collapse. S increases rapidly with the degree of ionisation. For a reduced temperature greater than $-$ 0·338, (ϕ/ϕ_0) increases continuously with f, while below this value the swelling ratio changes

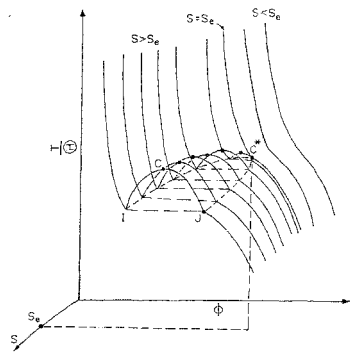

FIG. 3. Phase diagrams for gels illustrating continuous and discontinuous transition.

discretely (see Fig. 3). It is thus clear that whether the polymer would undergo a continuous or a discrete volume phase transition would depend upon the relative contribution of rubber elasticity and the free energy of mixing to the osmotic pressure. Higher degree of ionisation and stiffer chains will increase the possibility of discontinuous volume phase transition.

4. Generalisation of volume transitions in polymeric gels

Interactions between macromolecules fall into four categories: ionic, hydrophobic, van der Waals and hydrogen bonding. The recent work by Ilmain *et al*[5] made it possible to classify all the gel phase transitions in terms of these four biologically relevant intermolecular forces, each of which may independently be responsible for a discontinuous volume transition in polymer gels.

Figure 4 shows the gel volume phase transitions induced by four types of intermolecular forces. Figure 4a shows how the van der Waals interaction causes phase transitions in hydrophilic gels in a mixed solvent, such as an acrylamide gel in an acetone–water mixture. A non-polar solvent is needed to decrease the dielectric constant of the solvent. Figure 4b shows the phenomena for hydrophobic gels, such as *N*-isopropylacrylamide undergoing a phase transition in pure water, from a swollen state at low temperatures to a collapsed state at high temperatures. Figure 4c shows the gels influenced by cooperative hydrogen bonding. An interpenetrating polymer network (IPN) of acrylic acid/acrylamide gel undergoes phase transitions in pure water (the swollen state is the high-temperature state). The repulsive ionic interaction determines the transition temperature and the volume change at the transition. In

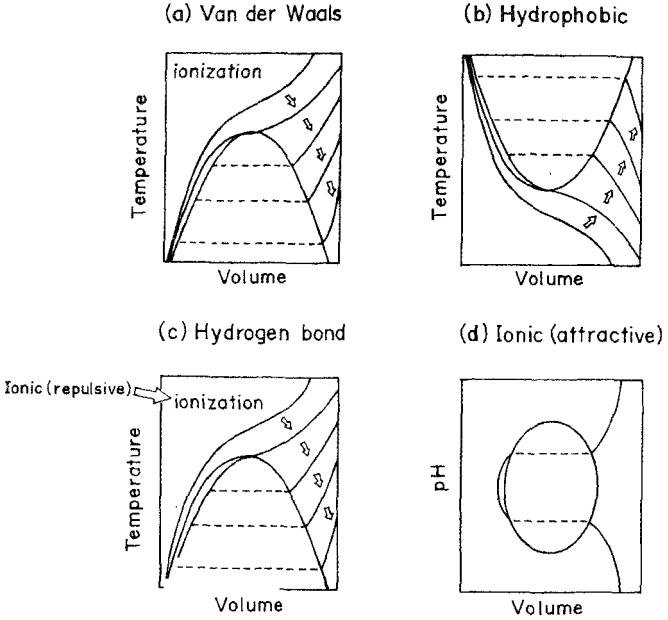

FIG. 4. Generation of volume phase transitions in gels.

Figure 4d, the role of attractive ionic interaction is shown for pH-driven phase transitions. A typical example is that of acrylamide–sodium acrylate/methacrylamidopropyltrimethylammonium chloride gels.

5. Some recent studies from NCL

We will now focus on some recent studies from NCL, which have added to our understanding of such gels, both at the microscopic and the macroscopic level. Some of the results given below have not been published before.

5.1. *Deformation-dependent swelling*

The capacity of swelling polymers to absorb and retain solvents is influenced very

strongly by the elasticity of the network, which in turn is determined by the crosslinking of the network. The crosslinking can be induced chemically by covalent bonds by using certain bifunctional monomers as crosslinking agents. In some cases, networks can be formed by physical crosslinking by weak forces such as hydrogen bonding, van der Waals forces, ionic interactions, as we have discussed in the foregoing.

We postulate that physical crosslinking, which is of a semipermanent nature, can be altered by subjecting the swollen gel to certain deformation or a stress. We know that physical crosslinking should contribute to the elasticity of the network and therefore to the elastic retractive force. It follows that due to a decrease in the extent of physical crosslinking, the absorption and retention capacity of the swollen polymer should be increased. Surprisingly, there was no study in the literature so far, which has addressed this issue. We undertook direct experimental studies to prove this postulate. We also supported the ensuing macroscopic observations by measurements performed at a molecular level by using NMR[6].

We synthesized two polymeric networks, namely, HSPAN (hydrolysed starch-g-polyacrylonitrile) and HPAM (hydrolysed polyacrylamide). These were synthesized in our laboratory and isolated in the form of a dry powder with about 80 mesh particle size. The equilibrium water absorption capacities were 178·0 and 175·0 millilitres of water per gram of polymer at 25°C for HSPAN and HPAM, respectively. HSPAN did not have a chemical crosslinking agent, whereas HPAM was chemically crosslinked.

All the NMR experiments were carried out on an FT-NMR spectrometer (Bruker MSL-300) operating at 7·1 Tesla. The ^{13}C spectra were recorded at 75·5 MHz by employing a 45° flip angle pulse (2μs), followed by acquisition. During acquisition, the proton were decoupled by using a $\simeq$ 30 kHz R.F. field. Quadrature phase cycling was used throughout to eliminate artifacts in the final spectra. Number of accumulations were typically of the order of 2000–4000 and were chosen to give spectra with a good signal to noise (S/N) ratio. Proton MASS spectra were recorded on a MASS probe, which gave negligible proton background signal. The proton FID was recorded following a $\pi/2$ pulse and then Fourier transformed. The number of accumulations was forty. ^{13}C and ^{1}H spectra are referred to TMS. All the NMR measurements were carried out at ambient probe temperature (25°C).

The equilibrium swollen polymers (HSPAN and HPAM) were sheared in a high-speed device for 0–5 minutes at an approximate shear rate of 2800 s^{-1}. It can be seen from Fig. 5 that the initial absorption capacities of HSPAN and HPAM increased substantially, when the samples were sheared for 4 minutes. After 4 minutes we observed a slight decrease in the absorption capacity and a lower mechanical stability of these polymeric gels.

It is important to note that before examining the sheared samples for absorption capacities, they were precipitated in ethanol and dried in oven. In order to find the effect of solvent treatment on absorption, we subjected both the sheared and the unsheared samples to identical treatment of precipitation and isolation. From the

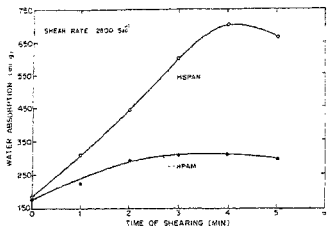

FIG 5 Influence of shearing on water absorption in swelling gels.

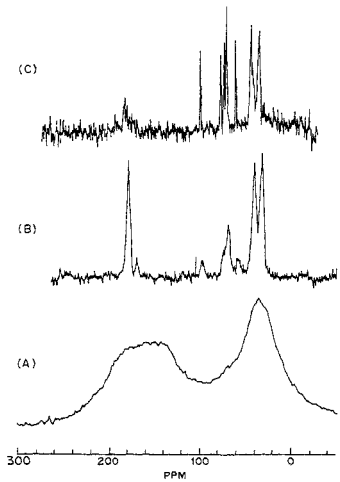

FIG. 6. ^{13}C Spectra of HSPAN polymer at different (%) saturations. (A) 0·08%, (B) 0·25%, and (C) 2·0%.

analysis, we found that the absorption capacity of the sheared and precipitated samples increased from 178·0 ml/g to 700·0 ml/g, whereas in the case of unsheared and precipitated sample, only a marginal enhancement was observed.

It is interesting to see that in the case of HSPAN (a largely physically crosslinked network) there was a considerable increase in superabsorption, whereas in the case of a chemically crosslinked polymer (HPAM), there was only a marginal increase. Breakdown of temporary crosslinks, therefore, appears to be crucial in enhancing the degree of swelling.

We used NMR spectroscopy to provide a support to our hypothesis of deformation-dependent absorption on a molecular basis. We believe that the breakdown of the physical entanglements due to the application of a shear force is reflected in the enhancement of macromolecular mobility of the chains. In a network polymer, the addition of a solvent enhances the local motion. Fully relaxed Bloch decay ^{13}C spectra taken with dipolar decoupling are shown in Fig. 6. Even at low saturation the ^{13}C spectrum has a sufficiently high resolution, emphasising near-complete averaging of chemical shielding (carbon–proton couplings are removed by dipolar decoupling).

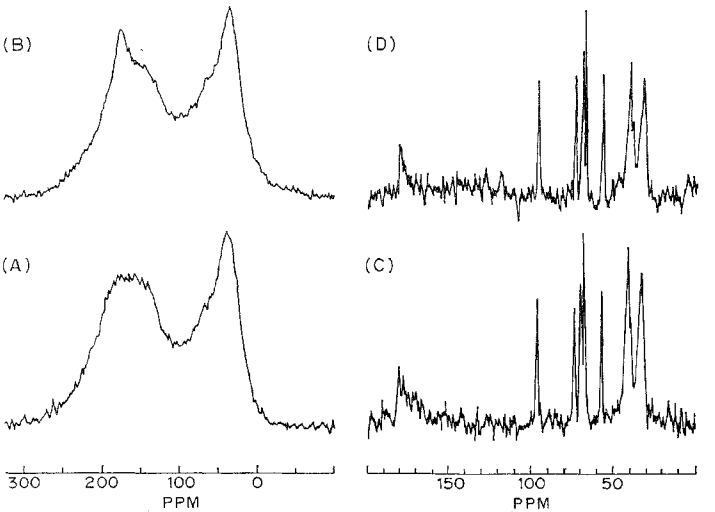

FIG. 7 ^{13}C Spectra of HSPAN polymer (A) unsheared and (B) sheared at low % saturation. (C) Unsheared and (D) sheared at high % saturation

Figure 7 shows the dipolar decoupled ^{13}C spectra of an unsheared and sheared polymer. The spectrum for unsheared sample has overlapping ^{13}C resonances from the carbonyl, glucose and aliphatic regions. Upon shearing, the spectrum shows narrowing of the peak, especially in the low-field region (see Figs 7a and b). In these spectra, since the carbon–proton dipolar coupling is removed by dipolar decoupling, the observed narrowing of the line is attributed to a better averaging of the chemical shielding anisotropy (CSA), which is expected to be more pronounced for the carbonyl and amide carbons. This was, in fact, observed. It may be noted that no differences can be discerned from the carbon – 13 spectrum obtained for unsheared and sheared samples having a high per cent saturation as shown in Figs 7c and d.

We also obtained the Magic Angle Sample Spinning (MASS) proton NMR spectra of the same samples and the results are summarized in Figs 8a and b. The corresponding static proton spectra are shown in Figs 8c and d. Pronounced side band pattern is seen, which originates from inhomogeneously broadened proton–proton dipolar interactions due to lack of spin diffusion among protons. The envelope of spinning side bands maps the so-called super-Lorentzian proton line shape. The degree of super-Lorentzian character strongly depends upon the mobility of the polymer chains. In the sheared sample, the side band manifold extends twice the spectral range as compared to the unsheared sample.

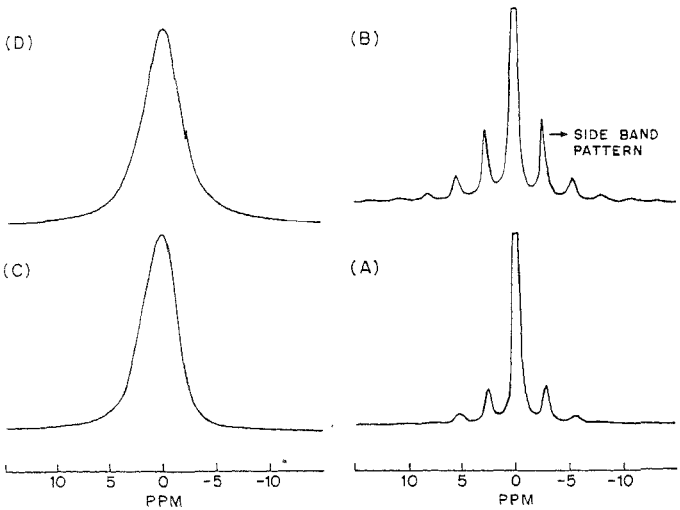

FIG. 8. ^1H Spectra of HSPAN polymer (A) unsheared and (B) sheared at low % saturation. (C) Unsheared and (D) sheared (static spectra).

Based on the above results, it is apparent that subjecting the polymeric gels to deformation through shearing does enhance the extent of absorption. The phenomenon of enhanced superabsorption through shearing polymeric gels, which are largely physically crosslinked, has a number of overtones in practical terms, and it can have fundamental implications also. The fact that one could subject a polymeric gel to a mechanical stress and increase its absorption capacity has a pragmatic importance in the manufacture of superabsorbers. More fundamentally, all the previous theories of swelling have been based on consideration of equilibrium thermodynamics. New non-equilibrium frameworks to interpret these new observations will have to be built. The subject of free energy changes in temporary polymeric networks due to the imposition of a stress field has been addressed recently by Raviprakash and Mashelkar[7]. The metastability of the networks with pseudo-crosslinks due to stress also raises some interesting new issues about the theories describing the thermodynamics and kinetics of swelling of these gels. These do not seem to have been addressed so far.

6.2. *Microdynamics in gels probed through NMR*

The NCL school has also contributed to the studies on the dynamics of hydration at a microscopic level in these gels by doing extensive NMR studies. For example, the

aspects of preferential hydration in swelling gels was probed by Ganapathy *et al*[8] and Rajamohanan *et al*[9] by doing solid-state ^{13}C NMR studies. Similarly, the dynamics of hydration-induced motion in swelling gels was probed through $^{13}C-^{1}H$ Nuclear Overhauser Enhancements by Ganapathy *et al*[10]. Recently, even two-dimensional exchange spectroscopy was used by Ganapathy *et al*[11] to probe the dynamics of hydration in such gels.

The volume transitions in polymeric gels had been explored so far at the macroscopic level. However, Badiger *et al*[12] were the first ones to probe the microscopic events that take place at the point of volume transition by examining thermo-reversible hydrogels. More such studies are now beginning to appear in literature. For instance, recently, Katayama *et al*[13] have done electron paramagnetic resonance studies to probe the behaviour of gels at volume phase transition.

6.3. *Concentration of macromolecules by using a swellex process*

After enumerating some of the fundamental contributions from the NCL group to the structure and microdynamics in polymeric gels, we will turn to the question of exploitation of these volume transitions.

The large swelling capacity of the polymeric gels can be utilised for concentrating aqueous solutions of macromolecules, such as proteins. Two special features of the gels can be exploited. The fact that the gels are crosslinked materials implies that there is a finite mesh size and, therefore, molecules greater than a particular size cannot pass through the network. Secondly, the peculiar differences between the diffusion of small solutes (such as salt or water) and that of the polymer network (required for swelling through the participation of the cooperative diffusion of the entire network) can be elegantly exploited for devising unique separation strategies.

We recently reported the use of lightly crosslinked, sulphonated poly(styrene divinyl benzene) gels for the concentration of macromolecular solutions[2]. The gels had much higher swelling capacity (100–200 g/g) than the conventional ion-exchange resins (0·1–1·0 g/g) used in water treatment. This process, which makes use of the highly swellable ion-exchange resins was named as 'swellex process'. The term 'swellex' signified the absorption of the solvent by a polymer which undergoes swelling and excludes the macromolecular solutes depending upon their molecular size and mesh size of the polymer. For conventional processes, such as solvent extraction, the capacities are high but selectivities are low. For membrane separations or adsorptive separations, the capacities are low but the selectivities are high. The swellex process, on the other hand, can successfully exploit the most desirable features of the solvent extraction and membrane separation/adsorption processes, *viz.*, high capacity and high selectivity.

The principle of the process and the regeneration strategy are shown in Fig. 9. The basis for the regeneration strategy needs to be discussed first. It is apparent that the swellex gel can be regenerated by collapsing it in an electrolyte solution (see data in

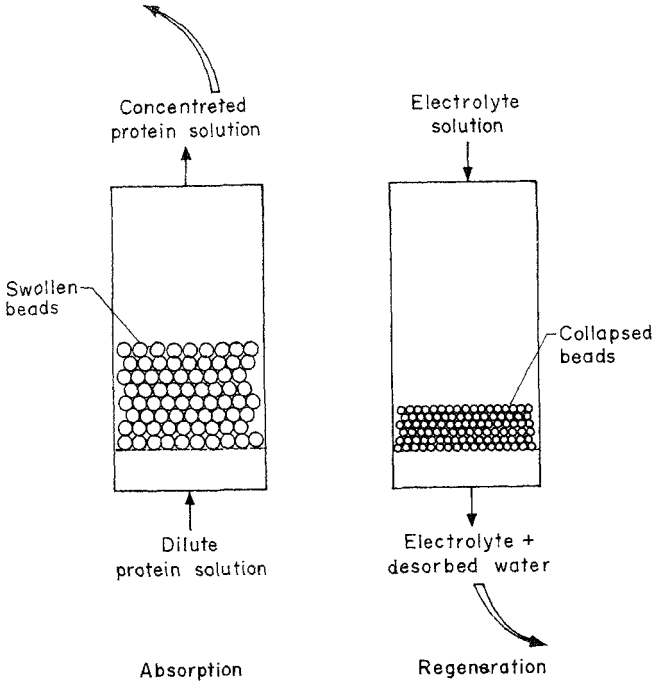

FIG. 9. The regeneration strategy in the swellex process.

Fig. 1) and draining the desorbed fluid. During the process, the salt is washed off and the gel is ready for the next cycle. Figure 10 shows the influence of regeneration on the ability of the gel beads to regain their absorption characteristics. Up to 75% of the original absorption capacity can be regained by such cycling. The loss of 25% capacity is presumably due to the retention of small amounts of electrolyte.

Badiger *et al*[2] devised an interesting strategy for preventing the loss of capacity. The electrolyte could be removed provided one was able to elute it with water. On the other hand, on coming in contact with water, the polymeric network will swell again appreciably and thereby reduce the column capacity. The time required for the

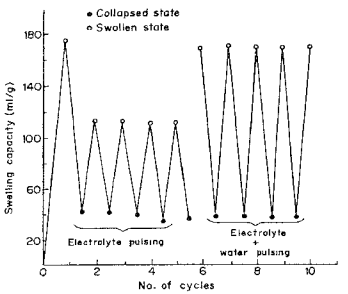

FIG. 10. Influence of electrolyte pulsing *vs* electrolyte plus water pulsing on regeneration.

elution of the adsorbed electrolytes by the water (t_{elu}) should be compared to the rate of absorption of water in the gel (t_{abs}). The solute could be leached out without appreciable swelling, provided $t_{elu}/t_{abs} \ll 1$.

These time scales can be estimated as follows. The time required for the elution of the electrolyte in the vicinity of the surface can be calculated if the external mass transfer coefficient (k_s) in the bed is known. t_{elu} can be estimated to be the order of D/k_s^2, where D is the diffusivity of the electrolyte in water (10^{-5} cm^2/s). we obtain $t_{elu} = 10{\cdot}0$s. On the other hand, t_{abs} depends on the cooperative diffusion coefficient of the polymeric network. Experimentally, it was estimated to be of the order of 2000 s. We thus have, $t_{elu}/t_{abs} = 10^2$. It is, therefore, clear that the time of electrolyte solution pulsing could be suitably chosen to ensure an elegant regeneration facility.

The selectivity in the gels can be manipulated by controlling the mesh size of the network. The mesh size of the network can be approximated by the formula[2]

$$\xi = \phi^{-1/3}\ \gamma_0 \tag{11}$$

where γ_0 denotes the end-to-end distance in the unperturbed state and is given as $\gamma_0 = C_n\gamma_f^2$.

Here,

$$\gamma_f = l\sqrt{N} \tag{12}$$

and

$$N = \lambda M_c/M_r. \tag{13}$$

In the above equations, γ_f is the end-to-end distance in the freely jointed chain. l

Table I
Macromolecular separation by the swellex process

Macromolecule	*Molecular weight*	*Concentration factor*	*Recovery*[+] *(%)*	*Flux (g/cm² min atm)*
Casein	115,000	4·8	94·6	0·048
Dextran	71,500	1·7	96·8	0·024
Bovine serum albumin (HSA)	68,000	4·6	98·6	0·048
Egg albumin	45,000	4·4	98·5	0·050
Poly(ethylene glycol (PEG))	9,000	4·0	80·8	0·032
Insulin	6,000	1·9	60·8	0·016

[+]Recovery (%) = 1000 measured increase in concentration/increase in concentration expected due to volume change.

is the carbon–carbon bond length (1·54 Å), C_n, the characteristic ratio (for polystyrene, $C_n = 10$), λ, the number of links per repeat unit ($\lambda = 2$ in our case), M_r, the molecular weight of the structural repeat unit (for polystyrene sulphonic acid, $M_r = 184$) and M_c, the molecular weight between crosslinks. The mesh sizes could be estimated from the above equation.

The efficacy of the separation of macromolecules by the swellex process can be seen from Table I. The effect of the mesh size is clear from the fact that the recoveries for low molecular weight systems are low but they increase as the molecular weight goes up.

It needs to be emphasised that many elegant strategies for separation of macromolecules by using the solvent absorption capabilities of polymeric gels have been developed in the past by Vartak *et al*[14], Freitas and Cussler *et al*[15], Gehrke *et al*[16], and so on. However, the strategy for a semi-continuous operation presented here, with an easy regeneration cycle, is rather unique and does offer a special advantage as a potentially attractive separation technology for macromolecular solutions.

6.4. *Diffusion modulation through gels*

The foregoing example shows a unique way in which we can exploit the solvent absorption capacity of polymeric gels, the size selectivity (afforded through the creation of controlled mesh size brought out through crosslinking), and also the reversible collapse *and expansion processes that these gels* undergo. The relative difference in rates of diffusion of small molecules and the entire network were also imaginatively exploited for developing a regeneration strategy. We now illustrate a further case of diffusion modulation through such networks.

Using the pH sensitivity of the hydrogels, we have recently proposed[17] a new approach to attaining time-invariant diffusional flux through bilayered membranes with collapsible barriers. Such systems can be designed on the basis of an understanding

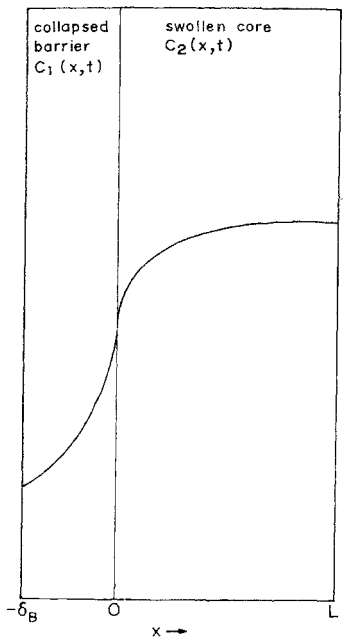

FIG. 11. A schematic diagram showing diffusional transfer across a bilayer membrane.

of the kinetics of swelling and deswelling of pH-sensitive hydrogels. The novelty of the approach is that the bilayers can be formed *in situ* and the diffusional behaviour can be manipulated at will depending on the external stimuli.

It needs to be recalled that diffusion of a low molecular weight solute through a rubbery polymer is generally Fickian. As a result, the diffusional flux decreases with time. Yet, there are situations, especially in the area of drug delivery systems, where it is desirable to ensure that the diffusional flux does not change with time. We show how such smart diffusers can be designed on a quantitative basis.

6.5. *The basis of diffusion modulation in gels*

Consider the problem of diffusion of a solute through a bilayered membrane depicted

schematically in Fig. 11. Here, a polymer core of half length L is surrounded by a barrier of thickness δ_B. The concentration of the solute in the core at a distance x and time t is $C_2(x,t)$, whereas that in the barrier layer is $C_1(x,t)$. The diffusivity of the solute in the polymer core (D_2) is different than that in the barrier layer (D_1). The appropriate balance equations then follow as

$$\frac{\delta C_i}{\delta t} = D_i \frac{\delta^2 C_i}{\delta x^2} \cdot \tag{14}$$

The details of the appropriate boundary conditions arrived at on the basis of physical considerations have been provided by Kulkarni *et al*[17]. They also provide an analytical solution to the attendant diffusion problem. In a more tractable form, they have provided two limiting cases that are interesting. They show that for

$$t \gg \frac{D_2 \delta_B^2}{D_1^2 K^2} \tag{15}$$

one obtains

$$\frac{M_t}{M_\infty} \sim \left(\frac{2}{L}\right) \sqrt{\frac{D_2}{\pi}} \left(\sqrt{t} - (\sqrt{D_2 \pi}) \frac{\delta_B}{2 D_1 K}\right) \tag{16}$$

whereas for

$$\frac{D_2 \delta_B^2}{20 D_1^2} < t < \frac{D_2 \delta_B^2}{7 D_1^2 K^2} \tag{17}$$

one obtains

$$\frac{M_t}{M_\infty} \sim \left(\frac{K D_1}{\delta_B L}\right) t. \tag{18}$$

Here, M_t is the amount of solute released at any time t whereas M_∞ is the total solute released. M_t/M_∞ thus represents the fractional release. K is the partition coefficient.

Equation (16) shows that M_t/M_∞ varies as square root of time, whereas eqn (18) shows that under certain conditions, M_t/M_∞ can be made to vary linearly with time. Thus, by manipulating the conditions, one can obtain a release rate that is independent of time. This is precisely the feature that the practical sustained-release delivery systems should be designed for.

Kulkarni *et al*[17] devised an interesting strategy to exploit these phenomena. They focussed their attention on hydrogels, which have been variously explored in the

literature[18]. If these hydrogels are made pH sensitive, then this sensitivity could be exploited to create barrier layers. On immersing a hydrogel in an acidic medium, collapse of the surface layer can take place. The thickness of this collapsed layer, which now forms the barrier layer, can be controlled by controlling the time of immersion. If the pH is again changed to the alkaline range, this barrier layer will swell. A mechanism for creating reversible barriers, where the thickness δ_B (shown in Fig. 11) can be controlled at will, is now available. For designing specific systems, we consider hydrogels made of 2-hydroxy propyl methacrylate (HPMA), which undergo swelling in water. To form a reversible barrier, we must incorporate monomers that interact with the medium. A suitable system to consider is the copolymer of HPMA with 4-methyl-7-hydroxy methyl coumarine methacrylate (MOCM). The basis for the choice of this copolymer needs an explanation.

Coumarines undergo ring opening in the presence of sodium hydroxide to yield sodium coumarinate. Acidification leads to relactonization to yield coumarine and not coumarinic acid[19]. Thus, when a polymer containing coumarine in the pendant chain, namely, P(HPMA-MOCM) is immersed in the alkaline medium, coumarine ring opens up to produce COO^- and OH^- ioins which leads to the enhanced swelling of the polymer. When the swollen polymer is brought in contact with the acidic medium for a limited time period, the surface layer undergoes relactonization and collapses to form the barrier layer.

Having controlled δ_B through such chemical means, it is readily seen that with the manipulation of diffusion coefficients in the swollen core (D_2) and in the barrier layer (D_1), we could use eqns (17) and (18) to design systems, where the diffusional flux is invariant with time.

Kulkarni *et al*[17] demonstrated the validity of the concepts enumerated above by conducting experiments on release of theophylline from such pH-sensitive hydrogels. The release of theophylline from the equilibrium swollen P(HPMA-MOCM) hydrogel having degree of hydration of 74% is shown in Fig. 12a. We see that M_t varies as $\sqrt{t}$ and the release follows Fickian diffusion. The release of theophylline from the hydrogel, which has undergone complete deswelling (Fig. 12b) in the acidic medium also follows Fickian diffusion. Obviously, the release rate of theophylline from the deswollen matrix of lower degree of hydration (namely 16%) is considerably lower.

When the swollen hydrogel is immersed in 0·5 N sulphuric acid for a short time period (2 h), the hydrogel in the surface layer undergoes volume phase transition to form a barrier layer on the surface. The hydrogel now consists of a core having a degree of hydration of 74% and a barrier layer of degree of hydration of 16%. We see from Fig. 12c that M_t varies as t now and the rate of diffusion of theophylline from such a system is indeed constant.

We have thus shown qualitatively that either Fickian diffusion or a diffusion rate, which is invariant with time, can be obtained by designing the bilayer systems. A limitation of the system P(HPMA-MOCM) is that the coumarine undergoes ring

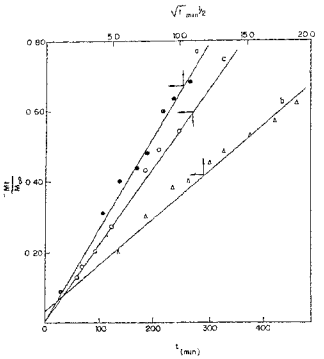

FIG. 12. Diffusional release from P(HPMA-MOCM). Curve a—fully swollen hydrogel, hydration, 74%, curve b—completely deswollen hydrogel, hydration 16%, curve c—acid-treated polymer with bilayer.

opening at pH ~ 10. Instead, the polymer could be so designed as to undergo swelling/deswelling under physiological conditions. Such systems could find applications in the design of drug delivery systems in the gastrointestinal tract. It would be further desirable to quantify the release rates from such systems using the physico-chemical properties of the bilayered systems based on the theoretical considerations presented earlier. Kulkarni *et al*[17] have not only devised alternative systems, which can meet these criteria, but have also validated the theoretical framework presented in the foregoing by a quantitative comparison with experimental data obtained on diverse systems. There is thus a quantitative basis for diffusion modulation in gels now, based on which Fickian or non-Fickian diffusion can be obtained at will.

6.5. *Exploitation of the transition phenomena in gels*

As we have seen, gels consist of a solvent, usually water, held in place by a hydrophilic lattice of long-chain molecules. The fragile balance between the electrostatic repulsion of the adjacent polymer strands and the osmotic pressure exerted by the ions in the solvent holds the key to the behaviour of gels. As emphasised before, disrupting a gel's charge distribution by altering its environment can trigger it to swell or shrink. With an improved and quantitative understanding of the behaviour of gels, it is now possible to conceive of several applications.

All living organisms move by the isothermal conversion of chemical energy into

mechanical work as exemplified by muscular, flagellar and ciliary movement. Such highly efficient energy conversion systems can now be realized in synthetic polymer gels, which expand and contract upon changing their solubility and/or degree of ionization according to an external stimulus supplied in the form of thermal, chemical and electrical energy.

Many artificial chemomechanical systems made of externally responsive polymer gels are being developed for sensor/actuator systems such as controllable membrane separation systems and electronically regulated drug delivery systems. A sophisticated application of such intelligent gels was reported by Kwon *et al*[20]. In their system, a mixed poly(acrylic acid)/poly(ethyloxazoline) gel was shown to be dissolved when a current was passed through it. The authors proposed to make this the basis of a long-period, controlled release device that could, for example, furnish insulin for diabetics.

Several studies have been appearing recently, where the temperature responsiveness of gels for devising sustained release systems is being exploited. For instance, Bae *et al*[21] showed how the insulin permeation could be modulated through thermo-sensitive hydrogels. Bae *et al*[22] have shown how thermo-sensitive polymers could be used as on-off switches for drug release. Okahata *et al*[23] demonstrated the thermo-selective permeation from a polymer-grafted capsule membrane. Hoffman *et al*[24] and Hoffman[18] have shown yet another interesting way of delivery through thermally reversible hydrogels. It is expected that great advances will take place in this area in years to come.

Osada *et al*[25] have shown as to how a polymeric gel can be induced to have electrically driven motility. They show that a gel bar made of polyelectrolytic material can bend backwards and forwards by the application of an alternating electrical field. Here, water and ions migrate towards the electrode bearing a charge opposite in sign to the net charge in the gel, and this coupling of electro-osmosis and electrophoresis is thought to be responsible for the observed chemomechanical behaviour. A gel bar prepared from poly(vinylalcohol) and poly(acrylic acid) bends towards the anode under a static electric field. Osada and coworkers have described the behaviour of a hydrogel that can move through a bath of an electrolyte solution. The system consists of a poly(2-acryl-amido-2-methyl propane sulphonic acid) gel doped with n-dodecyl pyridinium chloride surfactant. A ratchet-type 'gel looper' can 'crawl' along a bar when a 20 V voltage is supplied.

Since gels can exert a force when they swell, they even have the potential to act as actuators of artificial muscles for robots or prostheses. Toshio Kurauchi and his colleagues at the Toyota Central Research and Development Labs in Japan, for example, have already made a mechanical hand composed of four smart polymer 'fingers' that can pick up and hold a quail egg. An artificial 'fish' that swims with the help of the flapping action of its tail made by an electrically responsive polymer has also been made. The conceptual design, kinematics and dynamics of swimming robotic structures using ionic polymeric gel muscles is elegantly summarised by

Shahinopoor[26]. The theory and application of electrically controlled polymeric gels have been recently described by Segalman *et al*[27]. The emerging strategies on macromolecular smart materials and structures have also been enumerated by Reneker *et al*[28].

Gels that would react to specific molecules are also being developed. Kokufata *et al*[29,30] demonstrated the existence of sachharide-sensitive phase transition of a lectin-loaded gel. This type of work may eventually pave the way for intelligent sponges that would mop up specific pollutants. One could also conceive biomedical devices that react to specific markers of disease. Smart reactive gels that show enzyme-like catalytic activity have also been developed recently by Kulkarni *et al*[31].

The greatest interest in smart gels is shown by the Japanese today. Society of Polymer Science of Japan held a meeting recently in the science city of Tsukuba. A number of demonstrations of intelligent gels were shown. Examples included a polymer gel finger that works in air rather than in solution, which is considered to be a significant advance. Also shown was a gel beetle that can crawl up an incline; a gel-powered rotational micromotor, a flapping gel wing, etc.

Many interesting clues may yet again lie in nature and might eventually show the way. For instance, hidden in the secretory mechanism of many cells are natural polymer matrices that can change shape when exposed to certain ions. Recently, Nanavati and Fernandez[32] have shown that some natural gels in secretory granules exhibit dramatic and unexpected responses to changes in electrical voltages. These findings might pave the way for use of similar matrices as biocompatible electrical diodes for implantable mechanisms, driving gears in micromachines, etc.

The field of smart polymeric gels is still in its infacy. Many scientific and technological barriers will have to be crossed before such stimuli-responsive gels can be successfully exploited. One limitation is that the gels respond rather slowly, typically over timescales of minutes. The time required for a spherical gel to shrink is proportional to the square of its radius. Sufficient speed of response could be obtained by miniaturization. Gel microfibres are already being conceived. These may one day lead to the construction of devices, which can be inserted into muscle to emulate a nerve response! The possibilities for application of stimuli-responsive gels are indeed tremendous. The Japanese vision of gels becoming the most exciting materials of the twenty-first century may well be right.

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