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HYDROGELS AS ULTRAFILTRATION DEVICES

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Abstract

Hydrogels in solutions can reversibly swell and collapse with small changes in the process conditions. In this paper we focus on using this characteristic as a purification device. The gels prove to be effective and gentle substitutes for ultrafiltration membranes for the purification of sensitive products such as biomaterials.

Introduction

Conventional separation techniques such as extraction and evaporation are unwieldy and expensive for separation problems involving dilute aqueous solutions, especially of organic or biological materials.[1] Examples include the removal of small solutes like water and lactose from cheese whey and the concentration of antibiotics in fermentation broths. In this paper we

examine a promising separation method for these systems: the use of hydrogels as extraction solvents.

Hydrogels are effective extraction solvents because they absorb low molecular weight solutes but not high molecular weight components. Also, they can be regenerated easily with relatively small changes in process conditions. Typical conditions include temperature[2,3], pH[4,5], electric field[6], mixed solvent[5,7], ionic strength[2,8] and pressure.[9] Other potential applications for these systems are the controlled release of macromolecules[10–12] and mechanomechanical manipulation in biomedical applications.[13,14]

The concentration of macromolecular solutions with gels was first suggested in 1960.[15] While specific applications developed sporadically since,[16,17] the techniques were of limited application because an efficient method for gel regeneration was lacking. Tanaka's 1978 report[18] of discrete changes of the gel volume with an infinitesimal change in solvent composition sparked interest in gel regeneration. Cussler *et al.*[19] used such a gel to demonstrate the feasibility of gel extraction.

The manner in which the gels are used in an extraction, shown in Figure 1, starts by adding a collapsed gel to a dilute solution. The gel swells, absorbing the low molecular weight solvent (and other small solutes) but excluding high molecular weight solutes (or counter ions in the case of charged gels). The concentrate, with an increased solute concentration, is separated from the swollen gel by filtration or centrifugation. A small change to the process condition to which the gel is sensitive (pH, temperature, etc.) causes the gel to collapse and desorb the solvent. The collapsed gel is again separated from the solvent and the conditions restored to the initial one, enabling the gel to swell when added to a fresh solution.

Solution Behavior of Hydrogels

The success of this type of separation is based on the unusual properties of these gels. To understand their behavior, we must first consider their

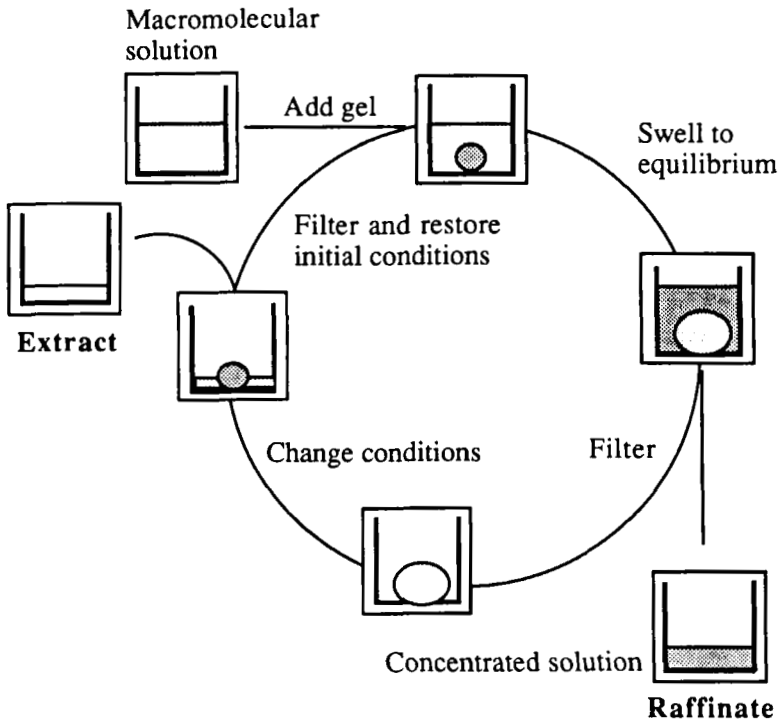

FIGURE 1

A Generalized Separation Scheme Using Near-Critical Gels

characteristics. Because the gels used are largely based on chemically crosslinked, substituted acrylamides, they are related to the gels used in gel permeation chromatography. However, the gels employed as extraction solvents require a strong dependence of their swelling volume with process conditions. In contrast, the gels used in chromatography are chosen to have a weak dependence of swelling volume on process conditions[20].

The gels swell in water because they are hydrophilic; the swelling is constrained because of the chemical crosslinks present between the polymer chains. Therefore, while the gels can retain a significant amount of solvent within their structure, they are unable to completely dissolve in the solvent. Swelling occurs for the same reason that a solvent completely dissolves the

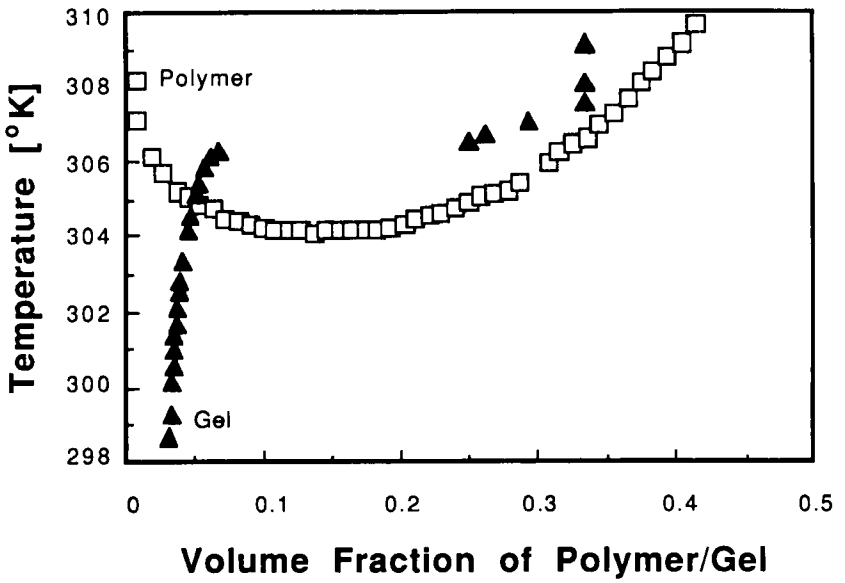

FIGURE 2

Isobaric Phase Diagrams for the Temperature Sensitive Poly(isopropylacrylamide) Polymer/Gel-Water Systems

uncrosslinked polymer chains to form an ordinary solution. In fact, the swollen gel is a solution, in spite of its elastic properties.[21] In this sense, the gels are normal.

However, gel swelling is a violent function of process conditions. The violent changes in swelling occur because of the proximity of a consolute point in the phase behavior of the homologous uncrosslinked polymer. The experimental phase diagram shown in Figure 2 illustrates these ideas for the temperature sensitive poly(isopropylacrylamide) — water system. The uncrosslinked polymer is shown as squares[22], and the gel as triangles[2]. The region above the squares is a two phase region, consisting of a polymer-rich phase in equilibrium with a water-rich phase. Below 304° K, the polymer and water are completely miscible; above this temperature they become only partially so. The minimum on this curve is a *lower consolute point* or *lower critical solution temperature.*[23]

The phase behavior of the crosslinked gel above 306° K is similar to that of the uncrosslinked polymer, forming a pure water phase in equilibrium with a gel-rich phase. The pure water phase contains no gel because the presence of crosslinks does not allow the complete dissolution of the gel. The behavior below 306° K is very different to that of the polymer: the gel may exist as a highly swollen gel phase in equilibrium with excess water. Still, near the lower consolute point, the volume fraction of polymer changes abruptly with temperature. Phrased in other terms, gel swelling changes abruptly with temperature.

As a result, the sudden change in gel swelling occurs because of the proximity of a critical point, in this case, a lower consulute point. In this sense, these gels are like supercritical solvents which can be held in the palm of the hand[24,25]. Similar ideas explain the behavior of pH, pressure, ionic strength, mixed solvents, and electric field dependence of the swelling behavior of gels.[24–28]

The degree of crosslinking will determine the ability of the gel to show a continuous or discrete volume change near the critical region. If the crosslink density of the poly(isopropylacrylamide) gel shown in Figure 2 is increased, the maximum swelling will occur at higher gel volume fractions, or smaller gel volumes. Further increases of the crosslink density will produce a continuous phase envelope, and obscure the discrete phase transition shown in the figure. Gel extraction can succeed with either type of volume transition, so long as large volume changes can be induced with a small change in process conditions.

Gel Selectivity

The selectivity of the gel separation process depends on what the gel excludes and what it absorbs. The selectivity has often been reported as a separation efficiency η, defined as the measured increase in raffinate concentration divided by the increase that would be observed if the solute were to be completely excluded from the gel. Therefore, an efficiency of

100% means that the gel does not absorb any solute. An efficiency of 0% means that the solute concentration absorbed into the gel is equal to the feed concentration.

The separation efficiency may also reflect an incomplete mechanical separation of the swollen gel and the raffinate due to the entrainment of raffinate between the gel particles.[29-31] The losses can be particularly significant if concentration polarization occurs. In this situation, the solute concentration nearest to the gel surface is higher than that in the bulk raffinate. This concentrated solution can be removed by washing the swollen gel once it has been separated from the raffinate.[29]

The mechanism by which the gels separate remains unclear. The most obvious variable is solute size, examined in Table I. The gels clearly separate large solutes like proteins from small solutes like urea. However, the gels will not normally separate solutes of similar size, for example, solutes whose molecular weights are within 50%.

The size exclusion effect can be best rationalized by imagining the gel as an expanded mesh. Small molecules can easily penetrate the pores in the mesh, but large solutes cannot enter. If the pore size of the gel is reduced by more crosslinks, the gel extraction characteristics are also changed, as shown in Figure 3. Poly(isopropylacrylamide) gels with higher nominal crosslink densities than 1% (shown in Table I) were used to concentrate a 3,400 dalton glycol and vitamin B_{12}. The efficiencies for separating both the glycol and B_{12} double as the nominal crosslink density increases from 1% to 6%.[29]

The similar results for the molecularly compact vitamin B_{12} and the extended poly(ethylene glycol) seem to discourage the idea that gel separation could also be shape sensitive.[30] However, Gehrke *et al.*[29] found that poly(ethylene glycol) linear chains of different molecular weights were extracted with a hydrolyzed commercial acrylamide gel (polyelectrolyte) (cf. Figure 4). The separation efficiencies for the linear glycols are compared to those of the molecularly compact urea and sucrose using the same gel. The

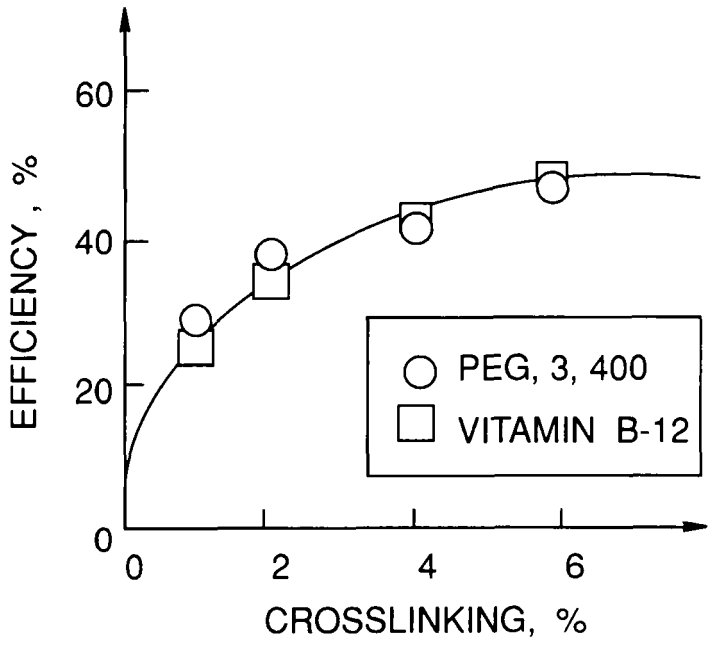

FIGURE 3

Separation Efficiency as a Function of the Nominal Crosslink Density. The solutes are a 3,400 poly(ethylene glycol) and Vitamin B_{12} extracted with a poly(isopropylacrylamide) gel[2]
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results in this case suggest that linear solutes can be separated more efficiently than compact ones. These results are inconsistent with others for similar solutes using other gels, as shown in Table I. More experiments are required to settle this issue.

Polyelectrolyte hydrogels can also separate by solute charge, as also illustrated in Table I. For example, the separation efficiency of sodium pentachlorophenolate is much higher with a diethylacrylamide: sodium methacrylate copolymer than with the non-ionic poly(isopropylacrylamide) (51% *vs.* 18%) . These results can be understood with Donnan equilibrium:

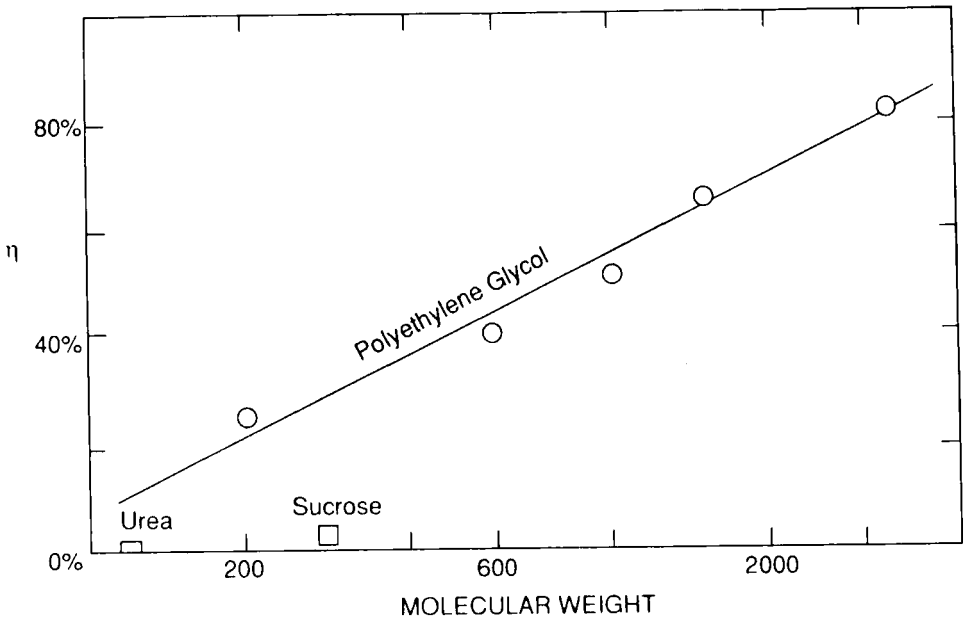

FIGURE 4

Dependence of Separation Efficiency on Solute Shape.
A hydrolyzed acrylamide was used to separate the solutes.
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small ions are unequally distributed on the two sides of a semi-permeable (gel) barrier.[29] The negatively charged copolymer matrix makes the gel behave as a membrane impermeable to anions.

Gehrke[29,30] studied these effects extensively, as shown in Table II. He showed that the selectivity of the gel could be successfully estimated from expressions of Donnan equilibrium. For example, 10^{-4} M divalent congo red is more efficiently separated than 10^{-4} M monovalent sodium pentachlorophenolate. However, the separation efficiency of congo red is reduced by two thirds in the presence of 0.9 M NaCl. The efficiencies drop steadily as the ionic strength of the solution is increased. This indicates

TABLE I

Separation Efficiencies for Different Solute-Hydrogel Pairs. The number in parenthesis indicates the nominal crosslinking density of the gel[2,29]

Solute	Molecular Weight [dalton]	η [%] Isopropyl-acrylamide (1%)	Diethylacrylamide: Sodium Methacrylate (4%)
Urea	60	2	3
Sodium penta-chlorophenolate	267	18	51
Poly(ethylene glycol)	400	10	5
Vitamin B_{12}	1,355	32	15
Poly(ethylene glycol)	3,400	30	19
Poly(ethylene glycol)	8,000	56	35
Poly(ethylene glycol)	18,500	80	61
Ovalbumin	45,000	97	84
Monoclonal Antibody	160,000	88	-
Poly(ethylene oxide)	600,000	95	89
Blue Dextran	2,000,000	97	99

that an osmotic force in a nonpolyelectrolyte gel can also affect its selectivity, at least at high solute concentrations. It is important to stress that the separation efficiencies are equilibrium values and therefore unaffected by dynamic effects.[32–33]

Separation mechanisms beyond solute size and gel charge have not been carefully studied. These mechanisms probably include polar repulsion and hydrogen bonding. A good starting point for their investigation is probably the wealth of studies on two phase aqueous partitioning[34,35] In any case, we expect that the simplest gels to employ as extraction solvents are the temperature sensitive gels. Gel regeneration requires only a small

TABLE II

Separation of Charged Solutes with a Partially Hydrolyzed Poly(acrylamide) Gel[29,30]

Solute	Solute Concentration [M]	Molecular Mass [dalton]	Charge	NaCl Concentration [M]	η [%] Experimental	η [%] Predicted
Methyl orange	$9 \cdot 10^{-5}$	327	-1	0	97	>99
Methyl orange	$9 \cdot 10^{-5}$	327	-1	0.1	55	48
Methyl orange	$9 \cdot 10^{-5}$	327	-1	0.9	14	18
Sodium pentachlorophenol	$2 \cdot 10^{-4}$	288	-1	$3 \cdot 10^{-3}$	65	69
Congo red	$1 \cdot 10^{-4}$	697	-2	0	97	>99
Congo red	$1 \cdot 10^{-4}$	697	-2	0.1	71	79
Congo red	$1 \cdot 10^{-4}$	697	-2	0.9	34	36
Trypan blue	$1 \cdot 10^{-4}$	961	-4	0	96	>99
Trypan blue	$1 \cdot 10^{-4}$	961	-4	0.1	73	97
Trypan blue	$1 \cdot 10^{-4}$	961	-4	0.3	52	89

temperature change to collapse the gel and a subsequent restoration of the initial conditions to reuse it. The application of one such gel is the focus of the next section of this paper: the concentration of soy protein using a poly(isopropylacrylamide) gel.

Soy Protein Isolation using a Temperature Sensitive Gel

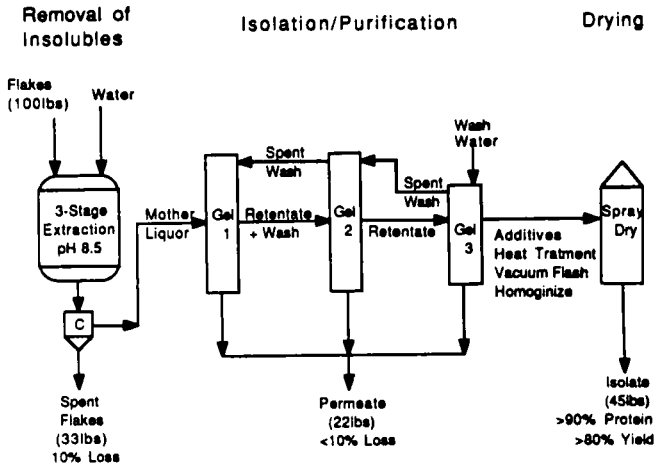
Trank *et al.*[36–37] have developed a gel based process for the manufacture of soy protein isolate. The isolate is made from the protein solution (the "mother liquor") obtained by cracking, dehulling and

extracting soybeans. Traditionally, the mother liquor is mixed with acid to precipitate the protein; the resulting curd washed with water and redispersed at pH 7. The final solution (13-18% protein) is spray dried to produce an isolate of 90% purity, containing about 65% of the total protein originally present in the mother liquor. The remaining protein, including valuable albumins, is lost in solution as unprecipitated solute.

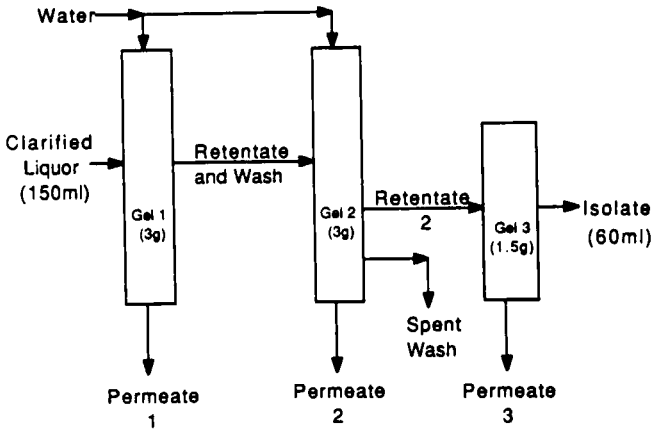
The target of the gel process is the recovery of virtually all the protein present in the mother liquor. The process employs poly(isopropylacrylamide) in place of the acid precipitation using the extraction scheme presented in Figure 1. First, the mother liquor is added to the collapsed gel. The gel swells and absorbs water but excludes the protein. The swollen gel and raffinate (retentate) are separated in a basket centrifuge. The retentate can be subjected to further gel extractions to reach the desired protein concentration and purity. The final retentate, a concentrated protein solution, is spray dried as in the conventional process.[37]

Figure 5(a) shows the process in greater detail. Protein moves from left to right during the three gel extraction stages. Each stage uses a cycle similar to the one shown in Figure 1, plus a gel washing step. The washing is required to avoid protein losses due to concentration polarization. The wash liquor, pure water in the third stage, moves from right to left to stages 2 and 1, respectively.

In practice, the first stage yields a 50% reduction in the content of non-protein solutes without significant increase in the protein concentration. The swelling is carried out at 5° C, while the collapsing is done at 40° C. The second stage doubles the protein concentration, while the non-protein solutes are is reduced to a quarter of the initial value. The third stage is half the size of the other two in order to absorb half the volume of the retentate obtained in the second stage. The protein concentration is again doubled and the non-protein solutes are reduced to one eighth of their initial value. Therefore, the protein concentration in the final isolate is four times larger than in the mother liquor.[36,37]



(a)



(b)

FIGURE 5

Soy Protein Isolate Production Using temperature Sensitive Gels
(a) Proposed industrial process. (b) Laboratory scale process.
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TABLE III

Laboratory Scale Production of Soy Protein Isolate[26]

	Mother Liquor	Retentate 2	Permeate 2	Spent Wash	Isolate
Protein (wt%)	8	i3	<1	1	17
Yield (wt%)	100	86	4	7	79
Purity (wt%)	67	88	28	47	96

The process was tested in the laboratory following the scheme presented in Figure 5(a) with some modifications shown in Figure 5(b). Pure water was used to wash the gel instead of the recycled wash water from the subsequent stages in stages 1 and 2. The retentate and wash were fed to the second stage, from which a spent wash and a retentate were obtained. The third step was carried out without wash. While these changes increase the protein recovery in the first stage, they decrease the recovery in the subsequent stages.[37]

A mother liquor containing 7% protein and 68% purity, representative of commercial liquors, yielded an isolate solution containing 18% protein and a purity greater than 95%.[36] These results are in the upper range of commercial soy protein concentration and purity. Furthermore, the overall yield based on the protein originally present in the mother liquor is 80%, 15% higher than in the precipitation process. This improved yield is due to the retention of the soluble proteins normally lost in the precipitation step. Table III shows the results obtained using the extraction scheme shown in Figure 5(b).

The gel separation process may also have some additional advantages over the traditional one. The protein separation is carried out at 5° C, a

temperature that may reduce the risk of microbial growth. Also, the system does not require the use of expensive high speed centrifuges, nor does it require the use of alkali and acid. The warming and cooling involves modest temperatures, well within reach of waste heat in, for example, boiler effluent.

However, if the gels are to be used commercially for making edible products several questions requiring further research must be addressed. These involve gel toxicity, gel production costs, and the life-time of the gel under process conditions. Only some preliminary work has been done regarding the last question. Cussler *et al.*[19] showed that similar gels lasted for at least 100 extraction cycles. In spite of these questions, the potential for using gels as extraction solvents remains.

Concluding Remarks

The gentle nature of gel extraction makes this process potentially superior for the separation of macromolecular solutes highly sensitive to process conditions. Examples center on proteins and other biological materials which are particularly sensitive to temperature, shear and pH. Thus, gels can become the important separations for these specialty products.

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