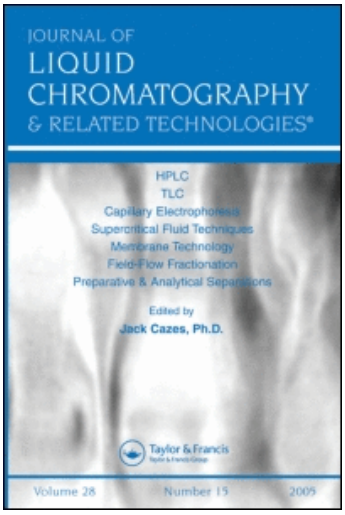

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STRONG CATION AND ANION EXCHANGE MEMBRANES AND BEADS FOR PROTEIN ISOLATION FROM WHEY

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ABSTRACT

Protein sorption from raw rennet whey at pH 3.0 onto S-type (strong acid), and at pH 7.2 onto Q-type (strong base), ion exchange beads and membranes was measured. The data were used to analyze protein binding capacities, percentage recoveries, production rates, and design parameters for a commercial-scale process. Performance of S-type beads was superior to Q-type beads, but Q-type and S-type membranes performed comparably, except that the S-type membranes lost capacity during repeated cycling without cleaning, while the Q-type membranes did not. Performance of the S-type membranes was increased by microfiltration of the whey before loading, but this was partially offset by the lower protein content of the microfiltered whey. Increasing the flow rate through the cartridge increased productivity, but the percentage protein recovery decreased. This

was attributed to the pore size of the membrane, which may have been too large for protein to reach the pore wall by diffusion before it passed through the membrane. A smaller pore size may increase the capture of protein and the binding capacity, but at the expense of plugging if the pores are too small.

INTRODUCTION

Commercial ion exchange processes for whey protein separation utilize stirred tanks containing porous beads onto which an ion exchange ligand is immobilized.[1-4] First, whey is stirred with regenerated-cellulose ion exchange beads in a large stainless steel tank, where the proteins adsorb onto the beads. Second, deproteinized whey is drained from the tank. Third, the beads are washed with water to leach out entrained fat, lactose, and ash. Fourth, whey proteins are desorbed from the beads using either an acidic or basic water solution, or a strong salt solution (1 M NaCl). The bead size is chosen to balance slow liquid percolation rates for small beads against slow intra-bead diffusion rates for large beads. Increasing the rate for adsorption of the proteins to the beads is of great practical importance because it maximizes the throughput of the process.

Ion exchange membranes are a new technology, designed to overcome the limitations encountered in conventional commercial processes using beads.[5,6] For beads, the rate of adsorption is controlled by external diffusion of protein to the bead surface (film diffusion), or internal diffusion of protein (intra-bead diffusion) to the adsorption site. Beads can be made smaller to increase diffusion rates, but this increases resistance to flow. For ion exchange membranes, whey flows by convection through the micron-sized pores of the membrane. Therefore, protein is transported into the membrane structure by convection, which is faster than intra-bead diffusion. Flow limitations are negligible if the membranes are made thin. Consequently, properly designed and operated ion exchange membrane separations may outdo bead-based separations in the isolation of proteins from whey and other biological fluids.

The feasibility of using ion exchange membranes for isolation of proteins from microfiltered whey has been demonstrated previously using membranes with a pore size of either 1.2 μm or 50-300 μm.[6] Microfiltration was necessary to prevent plugging of the smaller pore size membrane. Microfiltration decreased the protein content of the whey by 30%, and involved an extra processing step.

There has not been a comparison of the isolation of proteins from whey by ion exchange membranes and ion exchange beads. The requisite fundamental sorption properties of proteins in raw (not microfiltered or demineralized) whey with ion exchange membranes and beads are absent from the literature. A few data points are available for isolation of proteins from raw whey at pH 3.0 using S-type beads,[1,2] but Q-type beads were not evaluated, nor were membranes. The performance of S-type ion exchange membranes for isolation of proteins from microfiltered whey at pH 3.0 was evaluated,[6] but raw whey was not used, nor were beads or Q-type membranes.

In this work, new experimental data for protein sorption from raw whey with S-type and Q-type ion exchange membranes were collected along with similar data for ion exchange beads. These data were used to analyze the protein binding capacities, percentage recoveries, production rates, and design parameters for membranes and beads in a commercial-scale process. The primary focus was on characterization of the newer membrane technology rather than the conventional bead technology. Consequently, fewer experiments were performed with beads.

MATERIALS AND METHODS

Separated (partially defatted by centrifugation) Cheddar cheese whey at pH 6.2, obtained from Associated Milk Producers, Inc. (Arena, WI), was adjusted to either pH 3.0 using 0.375 M HCl, or to pH 7.2 using 1 M NaOH, and stored at 4°C. S Sepharose Fast Flow beads (S-1264, 45-165 μm wet-diameter cross-linked 6% agarose beads, $4x10^6$ Da exclusion limit, Sigma Chemical Co., St. Louis, MO) were repeatedly washed with 0.1 M citric acid/sodium citrate pH 3.0, followed by vacuum filtration to remove residual buffer.

Q Sepharose Fast Flow beads (Q-1126, Sigma) were washed with deionized water, vacuum filtered, washed with 1 M NaCl, vacuum filtered, washed with deionized water, and again vacuum filtered. The wet vacuum-filtered beads had a packed volume of 1.35 mL/g. The initial bulk concentration of water in the vacuum-filtered beads was determined by oven drying at 70°C to be 0.84 g/g for the Q-type beads, and 0.82 g/g for the S-type beads. In 50 mL centrifuge tubes, whey solution and beads were equilibrated with agitation for 24 h at 4°C, and then centrifuged to remove the beads.

The supernatant solutions were analyzed for Kjeldahl total nitrogen (TN) and non-protein nitrogen (NPN) using prior methods.[6] Supernatant pH did not change after equilibration.

Two commercially-available membrane cartridges (Productiv S model PSC10-SP, and Productiv QM model PSC10-QM, BPS Separations, Ltd., Spennymoor, County Durham, U.K.) were evaluated. The protein recovery cycle consisted of equilibration, loading, washing, and elution. Equilibration consisted of pumping 100 mL elution buffer (E buffer), followed by 100 mL loading/washing buffer (L/W buffer) through the cartridge. During loading, whey solution was pumped through the cartridge. Then, L/W buffer was pumped through the unit until the absorbance returned to baseline.

The cycle was completed by pumping E buffer through the unit until baseline absorbance was attained, followed by 0.2 M NaOH until baseline absorbance was reestablished. The cartridge was then disconnected and cleaned. The L/W buffer was 50 mM citric acid/sodium citrate pH 3.0 for the PSC10-SP, and deionized water for the PSC10-QM. For both cartridges, the E buffer was 1 M NaCl in L/W buffer. All buffers were vacuum degassed just prior to use. The flow rate was 10 mL/min, equal to one bed volume (BV) per min.

Cleaning followed a standard procedure,[6] wherein the sealed cartridge containing 0.2 M NaOH was submerged in a 60°C water bath for 1 h. It was then removed from the water bath, reconnected, and backflushed with deionized water, 0.2 M HCl, and deionized water, all in sequence.

An orange color accumulated on the Q-type adsorbents after contacting with whey, increasing in intensity with increasing extent of contact. This was attributed to norbixin, an anatto-derived pigment added during cheesemaking (American Cheese Color, code 41001, Sanofi Bio-Industries, Waukesha, WI). This divalent anion probably bound to the positively-charged adsorbent. It could be removed with acetone, but its concentration in milk (7 μM) was negligible compared to the charge density of the beads (0.18-0.25 M), and probably also of the membranes.

RESULTS

Protein Recovery from Whey by Ion Exchange Beads

Whey protein adsorption to ion exchange beads was determined by measuring the decrease in protein content in the whey solution in contact with the beads. Equating the amount of protein removed from the whey to that adsorbed by the ion exchange beads yields:

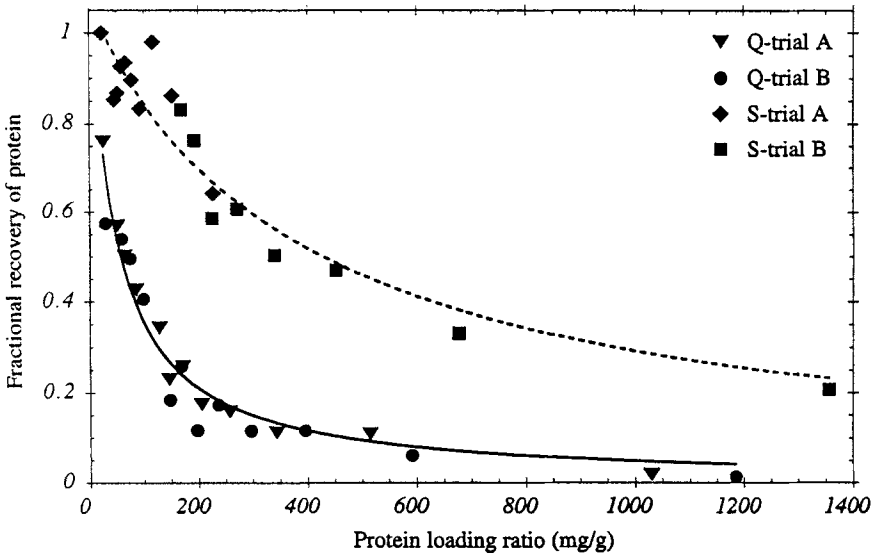

Figure 1. Fraction of protein removed ($y = q_1 m/wc_0$) from whey at pH 3.0 by S-type beads, and from whey at pH 7.2 by Q-type beads, versus the ratio of the mass of protein initially in the whey to the mass of beads ($x = wc_0/m$).

$$w\, c_o - (w + c_w m)\, c_1 = q_1 m \qquad (1)$$

where w is the mass of whey (45 g), c_O is the initial bulk concentration of protein in the whey (mg/g), c_W is the initial bulk concentration of water in the beads (g/g), m is the mass of the wet beads (g), c_1 is the bulk concentration of protein after equilibration (mg/g), and q_1 is the average concentration of protein in an equilibrated bead (mg/g).

As shown in Figure 1, as the protein loading ratio wc_o/m increased, the fraction of protein removed from the whey $q_1 m/wc_o$ steadily decreased. The data were fit by least-squares regression to $y = a/(b + x)$, where $y = q_1\, m/wc_o$, and $x = wc_0/m$. Using this equation, the fitted parameters carry a specific meaning. At very large protein loading ratios, the maximum capacity of the beads is simply equal to a. The capacity of the beads is half the maximum value when the protein loading ratio is equal to b. For S-type beads, $a = 400 \pm 50$ mg/g, and $b = 380 \pm 60$ mg/g. For Q-type beads, $a = 52 \pm 4$ mg/g, and b

= 45 ± 8 mg/g. The capacity of the beads is the product of x and y. Thus, as the protein loading ratio wc_o/m increases (more whey, fewer beads), the recovery of protein decreases, and the bead capacity increases.

The capacity and protein recovery for S-type beads was always greater than for Q-type beads under the conditions studied. For example, at wc_o/m = 150 mg/g, q_1 = 110 mg/g and $q_1 m/wc_o$ = 0.75 for S-type beads, compared to q_1 = 40 mg/g and $q_1 m/wc_o$ = 0.27 for Q-type beads. In other words, the capacity (or, equivalently, the fractional recovery) is 275% greater for the S-type beads than for the Q-type beads under these conditions.

Recovery and Binding Capacity of Protein from Whey by Ion Exchange Membranes

Whey protein adsorption to ion exchange membranes was analyzed in a similar manner. Equating the amount of protein removed from the whey to that adsorbed by the ion exchange cartridge yields

$$wc_o - ec_e = Q_1 v \qquad (2)$$

where e is the volume of the effluent (mL), which includes the whey loaded and the wash buffer, c_e is the concentration of protein in the effluent (mg/mL), Q_1 is the average concentration of protein in the cartridge (mg/mL), and v is the volume of the membranes in the cartridge (mL). The membrane volume was defined as the total bed volume (10 mL).

As shown in Figure 2, as the protein loading ratio $x = wc_o/v$ increased, the fraction of protein removed from the whey $y = Q_1 v/wc_o$ steadily decreased. The recovery data were fit by least-squares regression to $y = a/(b + x)$. For the PSC10-SP cartridge, a = 26±7 mg/mL, and b = 24±9 mg/mL. For the PSC10-QM cartridge, a = 30±20 mg/mL, and b = 60±40 mg/mL. Under the conditions studied, the capacity and protein recovery for the PSC10-SP cartridge did not differ significantly from the PSC10-QM cartridge.

As with ion exchange beads, the capacity of the cartridge is the product of x and y. Thus, as the protein loading ratio wc_o/v increases (more whey), the recovery of protein decreases, and the cartridge capacity increases.

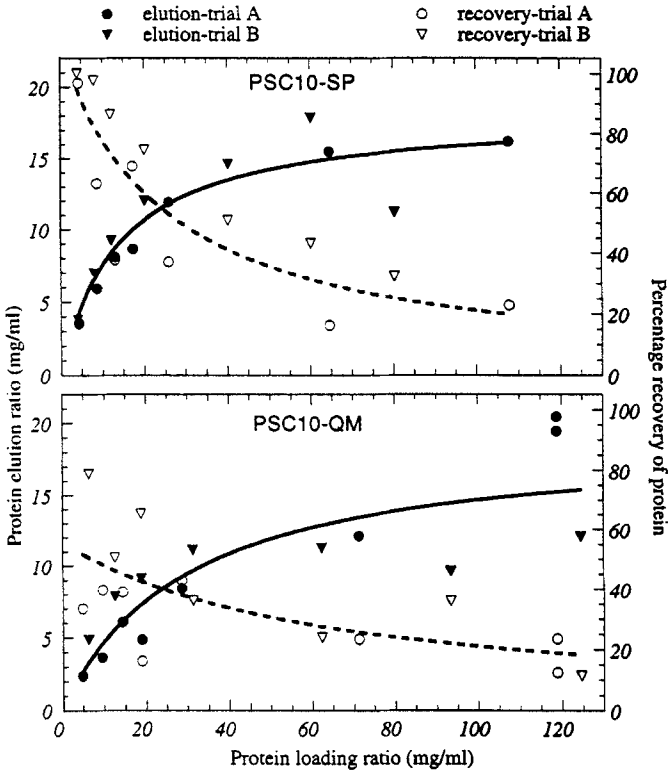

Figure 2 . Ratio of the amount of protein recovered in the elution peak to the volume of the membrane cartridge (left ordinate = pc_p/v), and percentage of protein removed from the whey (right ordinate = $100xQ_1v/wc_0$) by the PSC10-SP at pH 3.0 (top), and by the PSC10-QM at pH 7.2 (bottom), versus the ratio of the amount of protein initially in the whey to the volume of membrane ($x = wc_0/v$). By definition, p is the volume of the elution peak (mL), and c_p is the concentration of protein in the elution peak (mg/mL).

Elution Peak Composition vs. Protein Loading Ratio for Ion Exchange Membranes

The amount of protein in the elution peak was determined after loading from 10 to 250 mL of whey solution into the ion exchange membrane cartridges with cleaning between cycles (Figure 2). The total amount of protein in the elution peak generally increased with increased loading of protein for

Table 1

Percentage of Protein Bound and Recovered. Whey (50 ml, pH 7.2) was Loaded at Different Flow Rates into a PSC10-QM Cartridge. The Wash Buffer was D.I. Water, and the Elution Buffer was 1 M NaCl.

Flow Rate (mL/min)	Protein Bound (%)	Protein Recovered (%)
1.0	53.2±0.7*	50±10
2.0	52±9	40±20
5.0	33	39
10.0	33±7	31±9
18.5±0.2	20±10	28±5

* mean±S.D., n=2

both the PSC10-SP and PSC10-QM. The data were fit to $z = ax/(b + x)$. The parameters in this equation have the same conceptual meaning as before, but this form of the equation is for capacity rather than fractional recovery. For the PSC10-SP cartridge, a = 18±1 mg/mL, and b = 14±3 mg/mL. For the PSC10-QM cartridge, a = 19±3 mg/mL, and b = 30±10 mg/mL. The maximum amount of protein eluted was not significantly different between the two cartridges.

The fraction of protein bound to the membrane that eluted (pc_p/Q_1v) can be computed from the fitted parameters, and is equal to $z \div xy$. It was not significantly different from 100%, indicating complete recovery of protein within the deviation of the fitted parameters. However, only the first portion of the elution peak was collected in order to avoid dilution of the peak due to tailing. A small amount of the protein desorbed from the membrane was lost in the portion of the elution peak which was not collected. Therefore, strictly speaking, not all the protein which bound to the cartridges was present in the elution peak fraction.

Effect of Flow Rate on Protein Recovery from the PSC10-QM Cartridge

In order to determine if the results depended on flow rate, the loading, washing, and eluting cycle, with cleaning between cycles, was repeated at five different flow rates using a fixed loading volume (Table 1). The percentage of protein loaded which bound decreased significantly as the flow rate increased, as did the percentage of protein loaded which was present in the elution peak.

Stability of Cartridge Performance

In a commercial process, the ion-exchange cartridge is repeatedly cycled through the sequential steps of loading, washing and eluting in a semi-continuous manner without cleaning between cycles. To simulate this, ten cycles were repeated under identical conditions to measure any decreases in membrane performance.

For the PSC10-SP membrane cartridge, there was a significant decrease in the amount of protein recovered in the elution peak during repeated cycling without cleaning (Table 2). The mass of protein recovered per cycle decreased by an average of 5-6% per cycle. The elution peak volume was 48.8±0.6 mL. For this protein loading ratio ($wc_o/v = 20$), 106 mg of protein eluted in a single cycle followed by cleaning as calculated from Figure 2. This falls within the range of the early cycling data. The protein production rate of the semi-continuous process was 40 mg protein per h per mL of membrane volume.

For the PSC10-QM cartridge, there was not a significant change in the amount of protein recovered in the elution peak during repeated cycling without cleaning (Table 3). The amount of protein recovered per cycle was 90±10 mg (mean±S.D.) in an elution peak volume of 49.1±0.8 mL. This compares closely to 97 mg of protein eluted for this protein loading ($wc_o/v = 31$) in a single cycle followed by cleaning as calculated from Figure 2. The protein production rate of the semi-continuous process was 40 mg protein per h per mL membrane volume.

For minerals, the amounts recovered for the PSC10-SP cartridge were: K = 2.4±0.2 mg, Ca = 3.3±0.3, Mg = 0.45±0.05, P = 0.23±0.04, and S = 0.9±0.2. For the PSC10-QM cartridge the amounts were: K = 0.44±0.06 mg, Ca = 2.28±0.08, Mg = 0.25±0.01, P = 6.2±0.2, and S = 1.98±0.07. There was a significant decrease in Ca and S with cycling of the PSC10-SP cartridge, paralleling decreases in protein recovery, but there were no decreases in K, Mg, or P. There was no decrease in the amount of minerals recovered with cycling of the PSC10-QM cartridge.

Because whey proteins bind Ca and contain S,[7] these minerals can bind along with the protein or as individual ions. Cations (K, Ca, Mg) bound more to the PSC10-SP cartridge compared to the PSC10-QM cartridge. Anions (S as SO_4 and P as PO_4) bound more to the PSC10-QM cartridge. The minerals contents of the elution peaks were much lower than that of the whey on a concentration basis, and relative to the protein content. Therefore, protein was preferentially adsorbed compared to minerals.

Table 2

Contents of Elution Peaks for the PSC10-SP Cartridge. Each Cycle Consisted of 50 mL of Whey, pH 3.0 (Load), 15 mL of 50 mM Sodium Citrate, pH 3.0 (Wash), 50 mL of 50 mM Sodium Citrate 1 M NaCl, pH 3.0 (Elute), and 15 mL Of 50 mM Sodium Citrate, pH 3.0 (Wash). A Flow Rate of 10 mL/Min was Used.

Cycle	Protein (mg)	K (mg)	Ca (mg)	Mg (mg)	P (mg)	S (mg)
1	126	2.1	3.7	0.5	0.1	1.3
2	115	2.5	3.6	0.5	0.2	1.1
3	112	2.8	3.6	0.5	0.3	1.1
4	101	2.4	3.4	0.5	0.2	0.9
5	97	2.6	3.4	0.5	0.3	0.9
6	90	2.5	3.2	0.4	0.3	0.9
7	84	2.3	3.1	0.4	0.2	0.8
8	30	2.2	2.9	0.4	0.3	0.7
9	78	2.2	3.0	0.4	0.2	0.8
10	70	2.2	2.8	0.4	0.3	0.7
whey*	201	46.3	15.7	2.4	19.0	3.5

* composition of the feed solution

DISCUSSION

The capacity and protein recovery of S-type beads was superior to Q-type beads. This difference may have resulted from the pH of the whey solution in each experiment. At pH 3, all the proteins in whey have a positive net charge, and are able to bind to S-type beads.[4] However, at pH 7.2 some of the proteins in whey, such as the immunoglobulins, have a net positive charge and cannot bind to Q-type beads. At pH > 9, all the proteins in whey have a negative net charge.

Using an elevated pH may increase the performance of the Q-type beads, but it also may promote undesirable alkaline protein denaturation. Protein recovery was comparable for the PSC10-SP and the PSC10-QM for a single cycle followed by cleaning. However, the PSC10-SP lost capacity rapidly during repeated cycling without cleaning, while the PSC10-QM did not.

Table 3

Contents of Elution Peaks for the PSC10-QM Cartridge. Each Cycle Consisted of 50 mL of Whey, pH 7.2 (Load), 15 mL of Water (Wash), 50 mL of 1 M NaCl (Elute), and 15 mL of Water (Wash). A Flow Rate of 10 mL/Min Was Used.

Cycle	Protein (mg)	K (mg)	Ca (mg)	Mg (mg)	P (mg)	S (mg)
1	110	0.5	2.3	0.2	6.5	1.9
2	94	0.4	2.2	0.2	6.3	2.0
3	97	0.5	2.3	0.3	6.5	2.0
4	83	0.4	2.4	0.3	6.3	2.0
5	85	0.4	2.4	0.3	6.4	2.1
6	98	0.5	2.4	0.3	6.3	2.0
7	96	0.4	2.3	0.3	6.3	2.0
8	83	0.4	2.2	0.3	6.1	2.0
9	60	0.3	2.2	0.2	5.9	1.9
10	95	0.5	2.2	0.2	5.9	1.9
whey*	312	49.7	14.0	2.1	20.8	3.7

* composition of the feed solution

The recovery data reported here form a technical basis for comparing beads and membrane cartridges for isolation of proteins from whey. The volume of the membrane cartridge, or the mass of the beads, required to process a commercial-scale quantity of whey were calculated and compared.

For comparison purposes, the whey throughput (T) of each membrane cartridge and of each tank was set equal to the commercial-scale value (220 L/min). The protein content of the whey (c_o) was set at 6 mg/mL.

The commercial process utilizes two stirred tanks of approximately 40,000 L each filled with ion-exchange beads to recover protein from 550,000 L/d of whey.[3,4] Each tank has a cycle time (t_C) of three hours. The superficial residence time in each membrane cartridge (t_R) was fixed at the experimental value (1 min).

Table 4

Comparison of Beads to Membrane Cartridges. Values for X were Calculated from the Fractional Protein Recovery and Figures 1 and 2. Other Values Were: c_0 = 6 mg/mL, T_r = 1 min, and T = 220 L/min.

	Protein Recovered from Whey											
	40%				60%				80%			
Adsorbent	x mg/g	t_c min	w m^3	m,v kg.L	x mg/g	t_c min	w m^3	m,v kg, L	x mg/g	t_c min	w m^3	m,v kg, L
S-Beads	620	180	40	390	290	180	40	840	120	180	40	2000
Q-Beads	85	180	40	2800	42	180	40	5800	20	180	40	12000
PSC10-SP	41	15	3.3	480	19	11	2.5	770	8.5	9.4	2.1	1500
PSC10-SP*	140	41	9.1	270	66	24	5.2	330	29	15	3.3	470
PSC10-QM	15	11	2.3	920	NA**	NA	NA	NA	NA	NA	NA	NA

* 0.45 μm microfiltered whey, c_0 = 4.2 mg/ml

** target protein recovery cannot be attained

The cycle time for the membrane cartridge is the sum of the time required to load whey, wash away contaminants, elute bound protein using salt, and rinse out salt. By definition, the bed volumes (BV) of whey loaded (= w/v) is equal to the protein loading ratio divided by the whey concentration (x/c_0). In data reported here, 8 BV were required to wash, elute, and rinse the cartridge after loading. Therefore, the cycle time for each cartridge is $t_C = t_R(x/c_0 + 8)$. The product of t_C and T is the volume of whey loaded per cycle *i.e.* $w = t_C T$. The volume of each cartridge is $v = wc_0/x$. The mass of beads per tank is $m = wc_0/x$. The known parameters are: c_0, t_R, T, and the fractional protein recovery ($q_1 m/wc_0$ or $Q_1 v/wc_0$).

Performance data for S-type beads, Q-type beads, the PSC10-SP cartridge, and the PSC10-QM cartridge were used for comparison (Table 4). Six to seven times more adsorbent mass is required for Q-type beads than for S-type beads to achieve either 40, 60 or 80% protein recovery. Two times more adsorbent volume would be required for a scaled-up PSC10-QM cartridge than for a scaled-up PSC10-SP cartridge to achieve 40% protein recovery. It was not possible to achieve 60% or 80% recovery for the PSC10-QM cartridge under the conditions studied.

The extrapolated maximum capacity of S-type beads was 15 times greater than the capacity of the PSC10-SP membrane cartridge. However, the time for

loading, washing, and regeneration of the beads in a stirred-tank adsorption process was 3 h, compared to 9 min for the membrane cartridge. Consequently, the membrane process would require a similar amount of adsorbent compared to the tank process. At 60% and 80% recovery, the S-type membrane process requires less adsorbent than the S-bead process, but the opposite is true at 40% recovery. At all recoveries, the membrane process occupies less space than the tanks process because both 40,000 L tanks could be eliminated.

Protein recovery from microfiltered whey using a PSC10-SP cartridge was included in the comparison using prior results.[6] Compared to unfiltered whey, the membrane volume required to process microfiltered whey is 40-70% smaller, but the process throughput is 30% smaller because of the lower protein content of the whey (c_o = 4.2 mg/mL).

If the residence time (t_R) could be decreased in the membrane process, then the required membrane volume would decrease proportionately, and the capital cost of the membrane process would decrease. However, increasing the flow rate through the cartridge decreased the percentage protein recovery (Table 1), although it did increase productivity.

Recovery may have decreased because the pore size of the PSC10 cartridge was too large to capture the protein. In order for protein to diffuse to the wall of the pore and bind before it passes through the membrane, t_R must greatly exceed the time scale for boundary-layer mass transfer to the pore wall (t_{BLMT}). As an order-of-magnitude approximation,[8] $t_{BLMT} = (d_p)^2/4D$, where d_p is the membrane pore size (50-300 μm), and D is the diffusion coefficient of the whey protein *e.g.* $D = 6.7 \times 10^{-7}$ cm^2/s for bovine serum albumin. For these experiments, t_R was 1 min, and t_{BLMT} was 0.2-6 min. Consequently, the percentage protein recovery may have decreased as t_R decreased, as shown in Table 1, because the membrane pore size was too large.

A smaller membrane pore size would be desirable to eliminate boundary-layer mass transfer effects. It would increase the internal surface area of the membrane, increasing capacity. However, prior microfiltration of the whey would be needed to prevent plugging if the pore size was too small (< 5 μm). Conceivably, a pore size of 5-50 μm would provide a more suitable balance between capacity and plugging than did the PSC10 cartridges.

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