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William F. Blatt[a]; Lita Nelsen[a]; Eliseo M. Zipilivan[a]; Mark C. Porter[a]
[a] SCIENTIFIC SYSTEMS DIVISION, AMICON CORPORATION, LEXINGTON, MASSACHUSETTS

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Rapid Salt Exchange by Coupled Ultrafiltration and Dialysis in Anisotropic Hollow Fibers

WILLIAM F. BLATT, LITA NELSEN,
ELISEO M. ZIPILIVAN, and MARK C. PORTER

SCIENTIFIC SYSTEMS DIVISION
AMICON CORPORATION
LEXINGTON, MASSACHUSETTS 02173

Summary

Anisotropic hollow fibers allow construction of a dialyzing system that provides extremely large membrane surface in a small laboratory-sized system. Possessing the added property of high ultrafiltration flux, these fibers reduce salt exchange times from days to hours. In this system the exchange of salt by dialytic transport is largely unaffected by recirculation rate, solute type, or content, but is strongly affected by those variables which affect molecular diffusion, such as microsolute size and temperature. In contrast, diafiltration (convective salt removal by ultrafiltration), which primarily relates to solvent transport through the membrane, can be changed by operating pressure, *polarizability* of the macrosolute, as well as those conditions which tend to influence this latter phenomenon.

INTRODUCTION

Conventional dialytic methods for removing salt from macrosolute solutions are inconveniently slow and the protracted times may lead to denaturant changes. Augmenting the rate of salt removal by dialysis has customarily involved two approaches: increasing the dialysis membrane area available, and stirring or recirculating the fluid adjacent to the membrane in order to sustain the exchange gradient. A major

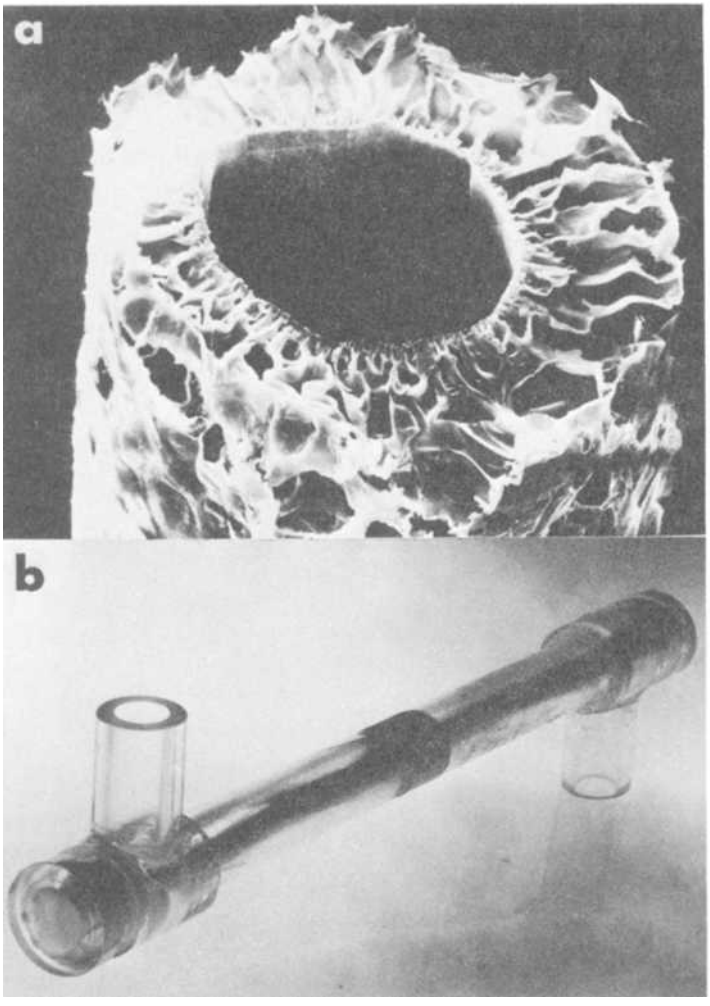


FIG. 1. (a) Scanning electron microphotograph of an anisotropic hollow fiber membrane. Magnification, 230×. (b) Assembly into a 200-fiber cartridge. Individual fiber lengths, 18 cm; fiber inner diameter, 200 μ.

innovation to afford high surface areas and good control of fluid boundary layers has been the use of hollow fiber dialysis membranes In these systems the solution to be dialyzed is recirculated through the interior of the fibers at modest pressures under conditions of laminar flow; dialysis fluid is simultaneously circulated outside the fiber bundle.

Because the thin channels and relatively high fluid shear conditions allow good control of the fluid boundary layers adjacent to the membrane, salt exchange rates are rapid and well controlled.

Despite the attractiveness of this design, such devices have thus far found wide application only as artificial kidneys, where their small size and high efficiency are beginning to make major improvements in the management of the anephric patient (*1–3*). The fibers in these systems have been primarily cellophane—a material which has undesirably slow dialysis and ultrafiltration rates for most laboratory applications.

In this work we examine a new class of high flux anisotropic ("skinned") fibers for the high-speed removal of salt. These fibers are capable of operating in both dialysis (i.e., diffusive removal of microsolutes) and ultrafiltrative (i.e., convective removal of solvent and salt under pressure) modes. In order to achieve high salt removal rates, we have found it advantageous to operate with dialysis and ultrafiltration proceeding simultaneously; a fluid reconstitution system has been devised to continuously replace the solvent lost by ultrafiltration, thus maintaining the original sample volume. (The process of continuous ultrafiltration and reconstitution has been given the name "diafiltration.") The net result of this dual system is microsolute exchange times 5 to 10 times shorter than conventional cellophane dialysis procedures.

Membrane and Fiber Cartridge Properties

Anisotropic, protein-retentive membranes have found wide use in the last 5 years for the concentration and desalting of protein solutions

TABLE 1

Ultrafiltration and Dialysis in Hollow Fibers

Fiber type	Ultrafiltrate flux (ml/min m² mmHg)	Dialysis transport coefficient for salt or urea (cm/min)
Amicon polyolefin (present study)	0.9–1.5	0.022–0.048
Dow deacetylated cellulose triacetate	0.019–0.033	0.013–0.036
Abcor deacetylated cellulose acetate	0.033	0.014–0.033

(*4–6*) and for salt exchange by constant volume diafiltration (*6*). Formation of similar membranes into fine hollow fibers for use in an ultrafiltrative artificial kidney has recently been reported (*7*).

An electron microphotograph of a typical cross section of a fiber is shown in Fig. 1a. The very thin (ca. 0.1 μ) skin of the membrane, shown on the interior of the fiber in Fig. 1a, leads to an exceptionally high water filtration rate under pressure (see Table 1). As might also be anticipated, the dialysis rates for microsolutes through this thin skin are also high, as shown by the salt and urea transport coefficients listed in the same table. For comparative purposes, data has also been given for unskinned cellulosic fibers Coupled dialysis and diafiltration allows one to take advantage of both the high filtration and high dialysis rates demonstrated by the Amicon fibers.

MATERIALS AND METHODS

Fibers used in this study had an internal diameter of approximately 200 μ, with an outside diameter of 350 μ. The fiber length was 18 cm, providing a membrane exchange area of approximately 1.1 cm^2/fiber. The fibers were assembled in bundles with the ends potted to provide an entry to the interiors of the fibers as well as separation from the dialysate compartment (see Fig. 1b). Sample solutions were circulated through the interior of the internally "skinned" fibers; dialysis fluid circulated through the cartridge casing around the exterior surface of the fibers. The fibers were unsupported along their length except at the potted ends of the cartridge. While the studies reported herein are concerned with bundle sizes of 200 and 500 fibers, cartridges encompassing 15,000 fibers have been prepared.

The system used is schematically illustrated in Fig. 2. A dual-headed peristaltic pump provided cocurrent recirculation of both sample and dialysate streams. (Although counter-current flow is more efficient when the dialysis rate is high compared to the recirculation rate, the recirculation rate was sufficiently high in the present study to make the extra complexity of counter-current flow unnecessary). In these studies, sample and dialysate flow rates were equal.

The dialysate reservoir was open to the atmosphere, and either a fixed volume of dialysate was employed or, in some studies, fresh dialysate was constantly added to the system in single-pass fashion to sustain the exchange gradient in the latter stages of salt removal.

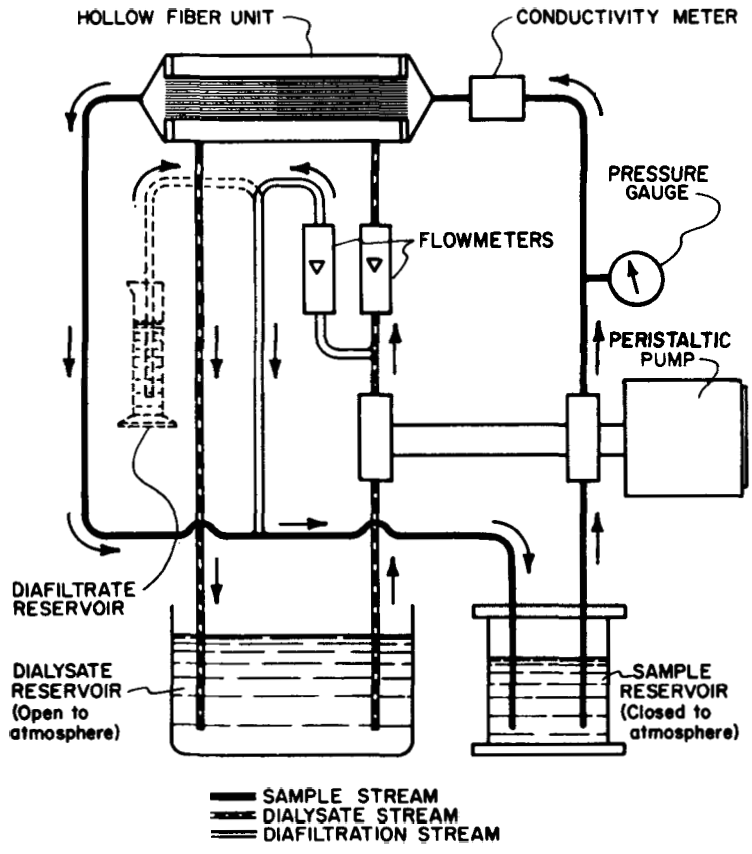


FIG. 2. Schematic of the flow and detector systems for evaluating combined dialysis and ultrafiltration in constant volume salt exchange.

Diafiltration replacement fluid was added continuously to the closed (constant volume) sample chamber, either from a graduated diafiltration reservoir (see dotted area), or alternately, via a shunt line from the dialysate inlet side to the return line of the sample vessel with a flowmeter inserted for determination of the diafiltration rate. With either fluid make-up system, the sample volume remained constant during the course of the experiments. The exchange of salt was monitored by an in-line conductivity meter (Radiometer, Copenhagen) placed as shown in Fig. 2.

The variables examined in this study were salt type and concentration,

macrosolute type and concentration, and recirculation rate. The separate effects of these variables on dialysis and on diafiltration were examined.

THEORY

Basically, the reasons for distinguishing dialysis from diafiltration in evaluating these parameters are as follows: Diafiltration (and therefore the rate of salt removal by diafiltration) will not be affected by the molecular weight of the diffusable solute. Conversely, dialysis will be a strong function of the molecular weight of the membrane-permeating species. While dialysis will not be strongly (if at all) affected by the type or concentration of macrosolute in the solution, the diafiltration rate is dependent on these variables (*8*). In this flow region, dialysis will not be altered by flow parameters, while diafiltration varies directly with the recirculation rate and with pressures below about 25 psi. As a consequence of the divergent effects produced by system parameters on each of the modes of salt exchange, mathematical modeling is warranted to define the contribution of each.

The equation governing the mass balance of simultaneous constant-volume ultrafiltration and dialysis is

$$V_0 \frac{dC}{dt} + (C_{exit} - C_D)F + Q_B(C - C_{exit}) = 0 \qquad (1)$$

where V_0 is the sample volume in the reservoir, ml (V_0 = constant); C is the concentration of dialyzable solute (salt) in the reservoir, g/ml; t is the total elapsed time, min; F is the filtration rate, ml/min; Q_B is the flow rate of sample solution through the fiber bundle, ml/min; and C_{exit} is the concentration of dialyzable solute in the solution exiting from the fiber unit, g/ml.

We can also express C_{exit} in terms of C by using

$$Q_B(C - C_{exit}) = D_B(C - C_D) \qquad (2)$$

where D_B is the dialysance (D_B is defined as the over-all solute transport rate by diffusion across the membrane, divided by the concentration gradient of dialyzable solute across the membrane). Thus D_B has the dimensions of ml/min; D_B/Q_B is a measure of how closely the concentration of the sample stream exiting from the unit approaches the theoretical equilibrium value; and C_D is the concentration of dialyzable solute in the dialysate bath at any time, t.

For a recirculating dialysate, C_D is related to C by

$$(C_D - C_{D_0}) = (C_0 - C)(V_0/V_D) \tag{3}$$

where C_0 is the initial sample concentration, g/ml; C_{D_0} is the initial dialysate concentration, g/ml; and V_D is the total dialysate volume, ml.

After the above substitution, if we assume that the filtration rate F is a constant, the solution to Eq. (1) becomes

$$C = \left[\frac{V_D}{V_D + V_0}\right]\left[C_{D_0} + \frac{V_0}{V_D} C_0 + (C_0 - C_{D_0}) \times \exp\left(-\frac{V_D + V_0}{V_D V_0}\{F[1 - (D_B/Q_B)] + D_B\}t\right)\right] \tag{4}$$

When $V_D \gg V_0$, Eq. (4) simplifies to

$$\frac{C - C_{D_0}}{C_0 - C_D} = \exp\left[-\frac{F[1 - (D_B/Q_B)] + D_B}{V_0} t\right] \tag{5}$$

This is also the expression for single-pass dialysis (where C_D enters always at C_{D_0}) and for the early stages of all dialysis processes when C_D is still essentially unchanged. Under any of these conditions, the slope of a semilog plot of $C - C_{D_0}$ vs. t is equal to

$$\text{slope} = \frac{d \ln (C - C_{D_0})}{dt} = -\frac{F[1 - (D_B/Q_B)] + D_B}{V_0} \tag{6}$$

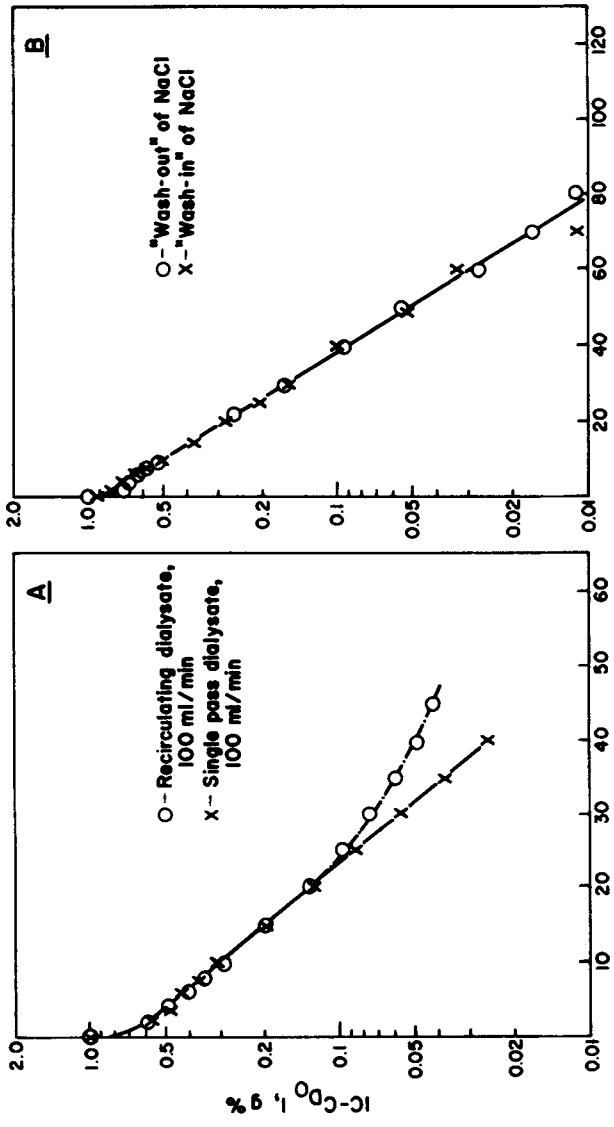
from which D_B may be determined if F is known. D_B is, in turn, related to the over-all dialysis coefficient K (cm/min) by Eq. (7) (for cocurrent dialysis) (*9*):

$$D_B = Q_B\left(\frac{1}{1 + Z}\right)\left\{1 - \exp\left[\frac{KA}{Q_B}(1 + Z)\right]\right\} \tag{7}$$

where Z is the ratio of sample flow to dialysate flow through the dialyzer, and A is the total wall area of the fibers, cm².

RESULTS

The graphic results, showing exponential washout of salt according to Eq. (5), are basically similar for all studies; just a few typical experiments are therefore presented to illustrate the salient points. Figure 3A



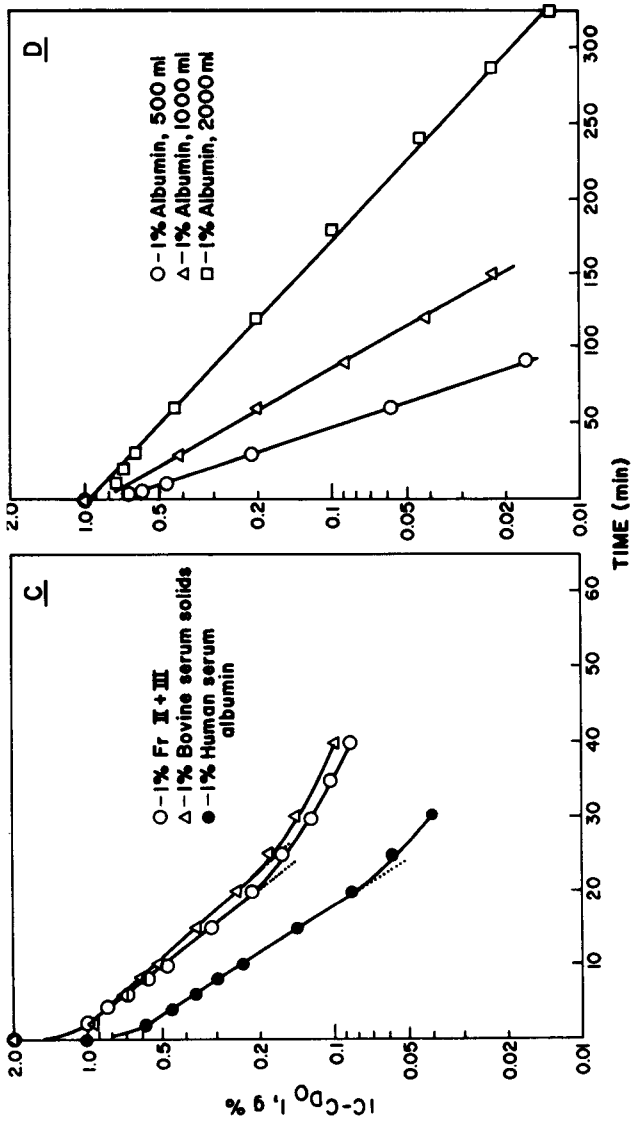


FIG. 3. The washout and/or washin of NaCl (as indicated by change in absolute concentration) from solutions of macrosolute in combined dialytic-ultrafiltrative transport. (A) Washin of 1% NaCl from 1% human serum albumin in a 200-fiber cartridge in recirculating and single-pass dialysate flow. Sample size, 100 ml; recirculation rate, 100 ml/min. (B) Washin and washout of 1% NaCl from 1% human serum albumin in a 200-fiber cartridge in single-pass dialysate flow. Sample size, 250 ml; recirculation rate, 200 ml/min. (C) Washout of salt (2% NaCl from 1% human plasma fraction II and III and from 1% bovine serum solids; 1% NaCl from 1% human serum albumin) in a 200-fiber cartridge in recirculating dialysate flow (ratio of dialysate to sample, 20:1). Sample size, 100 ml; recirculating rate, 200 ml/min. (D) Washout of 1% NaCl from varying volumes of 1% human serum albumin in a 500-fiber cartridge in single-pass dialysate flow. Recirculation rate, 400 ml/min.

TABLE 2

Salt Removal by Coupled Ultrafiltration and Dialysis in a Hollow Fiber System[a]

Solvent	Solute	Recirculation rate (ml/min)	P_{inlet} (psi)	F (ml/min)	D_B (ml/min)	K (cm/min)
	A. Varying Salt Content					
1% NaCl	—	64	—	3.1	5.0	0.022
2% NaCl	—	64	—	3.3	4.0	0.021
4% NaCl	—	64	—	3.6	4.6	0.020
1% NaCl	—	200	8.7	5.2	4.4	0.020
2% NaCl	—	200	8.9	4.8	4.8	0.022
4% NaCl	—	200	8.9	4.4	4.5	0.020
2.5% NaCl	—	200	10.0	5.0	5.2	0.024
5.0% NaCl	—	200	10.0	5.0	5.0	0.023
10.0% NaCl	—	200	11.0	4.8	5.2	0.024
20.0% NaCl	—	200	12.5	4.6	5.4	0.025
	B. Varying Recirculation Rate					
1% NaCl	—	50	2.5	1.8	5.3	0.023
1% NaCl	—	100	4.5	3.1	5.7	0.026
1% NaCl	—	150	6.3	4.2	4.7	0.021
1% NaCl	—	200	8.5	5.0	4.5	0.020
1% NaCl	1% Albumin	50	2.5	2.5	5.0	0.022
1% NaCl	1% Albumin	100	4.7	4.3	4.2	0.018
1% NaCl	1% Albumin	150	6.9	4.8	4.5	0.020
1% NaCl	1% Albumin	200	9.0	4.8	5.6	0.025
1% Mixed salts	6% Cheese whey solids	50	3.3	1.8	3.4	0.015
1% Mixed salts	6% Cheese whey solids	100	5.0	2.4	4.6	0.021
1% Mixed salts	6% Cheese whey solids	150	7.5	2.3	4.2	0.019
1% Mixed salts	6% Cheese whey solids	200	10.0	2.6	4.6	0.021
	C. Varying Solute Content					
1% NaCl	1% Albumin	200	9.0	5.5	5.7	0.026
2% NaCl	1% Bovine serum solids	200	13.2	1.8	5.9	0.027
2% NaCl	1% Fr. II & III	200	11.0	4.4	4.3	0.020
1% Mixed salts	6% Cheese whey solids	200	10.0	2.6	4.6	0.021

(*continued*)

TABLE 2 continued

Solvent	Solute	Recirculation rate (ml/min)	P_{inlet} (psi)	F (ml/min)	D_B (ml/min)	K (cm/min)
	D. Varying Solute Concentration					
1% NaCl	1% Albumin	100	4.6	4.4	4.0	0.017
1% NaCl	10% Albumin	100	6.8	2.4	5.1	0.023
1% NaCl	1% Albumin	200	10.0	4.7	6.3	0.029
1% NaCl	2% Albumin	200	9.4	5.2	5.8	0.026
1% NaCl	5% Albumin	200	10.5	5.0	6.0	0.027

[a] Sample volume, 100 ml; 200 fiber cartridge; membrane area, 220 cm².

contrasts the washout of NaCl from a solution of 1% human serum albumin using a fixed recirculating dialysate volume (ratio of dialysate to sample, 20:1) and an infinite dialysate volume (single-pass system). Predictably, washout of salt in the latter study is linear to extremely low microsolute content. However, at a fixed recirculating dialysate volume of 20 times the sample volume, deviation from the linear portion occurs at about 90% washout. This is the result of salt concentration of the dialysate approaching that of the sample solution.

The ability of the fibers to permit transfer of microsolute in both directions through the fiber walls (validating their use in exchange dialysis) is shown in Fig. 3B where, following washout of salt in an

TABLE 3

Effect of Varying Salts on Dialysis Washout Rate

Salt solution	D_B (ml/min)	K (cm/min)
1% NaCl	4.5	2.0×10^{-2}
0.22% $CaCl_2$	2.3	1.0×10^{-2}
10% $(NH4)_2SO_4$	3.6	1.6×10^{-2}
0.1 M Phosphate buffer[a]	2.0	0.90×10^{-2}

[a] 5 parts 0.1 M Na_2HPO_4 to 1 part 0.1 M KH_2PO_4 (final pH 7.5).

TABLE 4

Effects of Reduced Temperature on Dialytic Transport Rate

Solution	25°C		4°C		$K_{4°C}$ / $K_{25°C}$
	D_B (ml/min)	K (cm/min)	D_B (ml/min)	K (cm/min)	
1% NaCl	4.5	2.0×10^{-2}	2.8	1.2×10^{-2}	0.63
10% $(NH_4)_2SO_4$	3.6	1.6×10^{-2}	2.5	1.1×10^{-2}	0.69
0.1 *M* Phosphate buffer	2.0	0.90×10^{-2}	1.2	0.52×10^{-2}	0.60

infinite dialysate stream, the dialysate vessel was filled with solvent of the original NaCl content (1%) and the study repeated. Salt transfer rates were identical in both directions.

The effect of varying the impermeable solute is shown in Fig. 3C.

The examples above have illustrated the over-all salt exchange process. Detailed evaluation of the relative effect of each parameter studied on both dialysis and diafiltration is given in Table 2.

Table 3 presents data obtained with a variety of permeable salts. The salt types and concentrations were chosen to represent typical solvents encountered in the laboratory.

Table 4 presents data showing the effects of reduced temperature on dialytic transport rates.

In anticipation of scaling up the system, a 500-fiber cartridge was evaluated with substantially larger volumes, i.e., 500, 1000, and 2000 ml, using infinite dialysate volume; these results are shown in Fig. 3d. This latter study was included primarily to demonstrate the rapid rate of exchange possible with larger volumes in this system, e.g., the washout of 98% salt within 6 hr from a 2-liter sample.

DISCUSSION

As shown by Eq. (4), the rate of salt removal is the result of a complex interaction between dialysis transport and ultrafiltration; the controlling parameters, F and K, vary independently. The data of Table 2A indicates that both dialysis (D_B or K) diafiltration (F) were insensitive to varying salt concentration—as would be expected since the ultrafiltration membranes employed in the fiber cartridges are unaffected by

salt, and the diffusion coefficient of the salt in solution is constant. Recirculation rate or pressure (which varies together) did not appear to significantly influence the dialysis rates in either the absence or the presence of proteins. In this region of recirculation rates, K is essentially theoretically independent of recirculation rate, while low pressures affect neither salt diffusion nor membrane permeation by salt. The ultrafiltration rate, however, was a function of fiber recirculation rate and transmembrane pressure. In the absence of protein the filtration rate F is directly proportional to pressure; however, with protein present, there is a complex interaction between pressure, recirculation rate, and ultrafiltration flux. This phenomenon has been reviewed in detail in a previous publication (*8*). In general, the ultrafiltration rate for protein solutions increases with pressure to a "plateau" level, above which the flux remains relatively constant and only mildly affected by changes in the recirculation rate. This plateau pressure varies with protein species and concentration. For example, it would appear (Table 2B) that this occurs at lower pressure for the defatted cheese whey preparation as contrasted with 1% human serum albumin.

At fixed recirculation rate, and equivalent pressures, the ultrafiltration rate is dependent upon the "polarizability" of the nondiffusible species, which is a function of its molecular weight, concentration, tendency to aggregate, etc. The concept of "polarizability" is discussed in detail in the publications cited earlier (*8*). In brief, however, under ultrafiltration conditions, high molecular weight species will tend to layer out on the membrane surface and retard filtration rates. The higher in molecular weight (or the greater the tendency of the species to aggregate) and the higher the concentration, the lower the flux. High fluid velocities across the plane of the membrane surface help to minimize the polarization layer and serve to maintain high ultrafiltration fluxes.

Part C of Table 2 indicates that fractions containing higher molecular weight species, (e.g., bovine serum) or those which form aggregates (e.g., bovine cheese whey) display lower ultrafiltration rates. However, as expected, the salt dialysis (D_B or K) is not affected in any consistent manner by the nature of the nondiffusible solute. As the concentration of a particular protein in solution is increased (Part D), the salt dialysis rate appears unchanged. The effect of increasing solute content on the reduction of filtrate flow F is only apparent at the 10% albumin level.

As shown in Table 3, the type of permeable solute (salt) has a significant effect on the dialytic contribution to the salt washout rate (K or D_B). Since dialysis is a diffusion-controlled process, the larger the

diffusing ion, the slower will be the transfer across the membrane and out of the solution.

The reduction of dialytic transport of salt with decreased temperature shown in Table 4 corresponds to an average activation energy for dialytic transport of approximately 4000 cal/g-mole—closely in accord with the value of 3750 cal/g-mole (i.e., the viscous activation energy for water) encountered for the variation with temperature of salt diffusivity in water solution. The correspondence of dialytic transport with diffusivity would be expected since dialysis is a diffusion-controlled process.

In summary, unique, high flux fibers can be used for extremely rapid macrosolute exchange utilizing both dialytic and convective salt transport. In that these are independent processes, conditions can be established to maximize each function and optimize system design.

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