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Separation of Proteins Via Semicontinuous *p*H Parametric Pumping

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A semicontinuous *p*H parametric pump for separating proteins was experimentally investigated using the model system haemoglobin and albumin on a Sephadex ion exchanger. The pump considered had a center feed between an enriching column and a stripping column and was operated batchwise during upflow and continuously during downflow. Various factors affecting separations were examined. It was shown that parametric pumping is capable of separating proteins with high separation factors.

SCOPE

Parametric pumping is a cyclic separation process which involves reciprocating flow of a fluid phase over a solid phase in a packed bed and at the same time synchronous periodic variation of an intensive variable, such as temperature, pressure, or *p*H. The fluid phase contains the mixture to be separated, components of which distribute between the two phases. Change of the intensive variable displaces the equilibrium distribution of these components between phases and, in combination with the reciprocating flow, causes preferential movement of the distributing components toward one end of the bed, leading, under certain conditions, to complete removal of these components from the other end of the apparatus.

The name parametric pumping was applied to the separation process in 1966 by the inventor of the batch pump, the late R. H. Wilhelm of Princeton University. Since the time of that invention, much experimental and theoretical work has been done on thermal and heatless (or pressure cycling) parametric pumps. Included are the studies of Wilhelm et al. (1966, 1968), Jenczewski and Meyers (1968, 1970), Wilhelm and Sweed (1968), Pigford et al. (1969), Rolke and Wilhelm (1969), Aris (1969), Horn and Lin (1969), Gregory and Sweed (1970, 1971, 1972), Turnock and Kadlec (1971), Butts et al. (1972, 1973), Kowler and Kadlec (1972), Shendalman and Mitchell (1972), Weaver and Hamrin (1974), Sweed and Rigaudeau (1975), Camero and Sweed (1976), Grevillot and Tondeur (1976), and Chen et al. (1971, 1972, 1973, 1974*a*, 1974*b*, 1974*c*, 1975, 1976*a*, 1976*b*). By contrast, very little work has been done on *p*H parametric pumping. Sabadell and Sweed (1970) used *p*H changes to concentrate aqueous solutions of K^+ and Na^+ using ion exchange resins. Shaffer and Hamrin (1975) studied trypsin concentration by affinity chromatography and parametric pumping.

In the present work, it was desired to determine the feasibility of *p*H driven parametric pumping separation of a two-component protein mixture. The solid phase was an ion exchange medium, and *p*H levels were to be selected so that one protein was selectively removed from the mixture while not affecting the other.

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CONCLUSIONS AND SIGNIFICANCE

Separation of haemoglobin and albumin has been obtained using a semicontinuous *p*H parametric pumping system. The separation was inverse to expectations based on equilibrium theory, and slow interphase mass transfer was suggested as the cause. Factors found to be important in determining pump performance were buffer concentration, *p*H levels, reservoir displacement, and product flow rate relative to reservoir displacement.

Many proteins are often processed batchwise. Parametric pumping as described here offers the possibility of semicontinuous processing, thereby tending to minimize both processing time and degradation. Also, no regeneration chemicals are needed, and therefore no regenerant can contaminate the product. Finally, the semicontinuous process can be operated with high separation factors.

Parametric pumping is a separation process which involves reciprocating flow of the mixture to be separated through a fixed bed and, simultaneously, synchronous cyclic variation of an intensive variable, such as gas pressure, solution temperature, or solution *p*H. Theoretical and experimental investigations have shown that operation of the cyclic process causes movement of sorbable components of the mixture toward one end of contacting apparatus. Very high separation factors are sometimes obtained as a result of the movement. This feature is a special characteristic of the parametric pumping process.

Intensive variables which have most often been used to motivate parametric pumping have been temperature and pressure. Less often has *p*H been used. Parametric pumping via *p*H variation usually involves the so-called recuperative mode of operation of the process. In this mode, two levels of *p*H are set in the streams entering either end of the parametric pumping column. As the entering streams penetrate the column, the *p*H change in the column occurs. This is as opposed to the direct mode in which the intensive variable is changed over the entire length of column at once. Cyclic pressure variation is brought about using the direct mode, whereas cyclic temperature variation may be induced by either mode. Thus, temperature may be changed by changing the temperature of a liquid in a jacketed column (direct mode) or by using a heat exchanger to change the temperature of liquid entering a bare column (recuperative mode). Small displacement volumes have been shown to lead to high separation factors in the direct mode (Gregory and Sweed, 1970; Chen and Hill, 1971), whereas in the recuperative mode small displacement can lead to so-called inverse separation (Sweed and Rigaudeau, 1975).

In the present paper, *p*H parametric pumping is applied to the processing of a mixture of two proteins, haemoglobin and albumin. A form of apparatus is described which led to inverse separations.

EXPERIMENTAL

System Selection

Proteins carry both positively and negatively charged groups and can be bound to anionic or cationic ion exchange media. The net charge on a protein is dependent on *p*H. At low *p*H, the net charge is positive, and the protein will be taken up by a cationic exchanger; at high *p*H, it is negative, whereupon it will be taken up by an anionic exchanger. The intermediate *p*H at which there is zero net charge is called the isoelectric point. These facts can serve as the basis for a parametric pumping separation of a multicomponent protein mixture.

Consider a mixture of n proteins ordered according to their isoelectric point I_i. Choose two *p*H values P_1 and P_2, such that

$$I_1 < I_2 < \cdots < I_m < P_2 < I_{m+1} < \cdots < I_{n-1} < I_n < P_1$$

Regardless of *p*H level, the first m components will always bear a negative charge, whereas the remainder will bear a negative charge at P_1 and a positive charge at P_2. Thus, the latter group will be taken up by a suitable cationic exchanger at P_2 and released at P_1. The first m components will be unaffected. Therefore, a parametric pump operating with levels of P_1 and P_2 should be capable of removing components $m + 1, \cdots, n$ from one product stream and concentrating them in the other product stream.

A two-component protein mixture was selected to examine experimentally the feasibility of this parametric pumping separation scheme:

Component	Protein	Molecular Weight	Isoelectric Point
A	Haemoglobin	63 000	6.7
B	Albumin	69 000	4.7

Worthington human haemoglobin and human serum albumin were used. The levels of *p*H used are shown in Table

Table 1. Experimental Parameters

Run	Feed weight, % Haemoglobin	Feed weight, % Albumin	Buffer conc. molarity, M	*p*H High *p*H reservoir	*p*H Bottom product, P_1	*p*H Low *p*H reservoir	*p*H Top product, P_2	$Q\left(\frac{\pi}{\omega}\right)$, cm³	$\frac{\pi}{\omega}$, s	ϕ_T
1	0.0080	0.0552	0.2	8.9	7.9	6	6	20	2 400	0.2
2	0.0107	0.0485	0.035	8.9	8.2	6	6.2	20	2 400	0.2
4	0.0097	0.0554	0.035	8.9	8.1	6	6.1	24	2 880	0.2
5	0.0099	0.0652	0.035	8.9	7.9	6	6.2	18	2 160	0.2
7	0.0090	0.0488	0.2	8.9	7.4	6	6.2	20	2 400	0.075
9	0.0071	0.0414	0.15	8.9	7.8	4.9	5.5	20	2 400	0.2
10	0.0082	0.0608	0.15	8	7.6	6	6	20	2 400	0.2

For all runs $\phi_T + \phi_B = 0.4$. Packing height for either column A or B (Figure 3) was 0.08 m.

1. Note that for all runs, pH levels chosen bracketed the isoelectric point of haemoglobin, leading to the expectation that this component would be removed from one product stream and concentrated in the other.

For the solid phase one of the Sephadex (Registered Trademark) ion exchange media manufactured by Pharmacia Fine Chemicals was chosen. The exchanger chosen was SP-Sephadex (C-50). This is the sodium form of a relatively high porosity, strongly acidic, cation exchanger. The porosity is suitable for the molecular weight range 30 000 to 200 000. The particle size range is from 40 to 120 μm. The ion exchange capacity of this material is high at high ionic strength and is relatively insensitive to pH over the range $p\text{H} = 3$ to 11. It is thus suitable for protein separations, since the low ionic strength where aggregation and protein instability may occur is avoided. (Pharmacia Fine Chemicals, 1975).

Apparatus and Procedure

The experimental apparatus is shown schematically in Figure 1. The column actually was made up of two sections, one for stripping and the other for enriching, and consisted of two jacketed chromatographic columns (0.016m inside diameter and 0.4m length, manufactured by Pharmacia Fine Chemicals). The column were packed with SP Sephadex (C-50). The column were maintained at a constant temperature of 288°K by the use of a refrigeration unit which circulated cooling water in the jacket. Reservoirs each having a dead volume of 6 cm^3 were located at the two opposite ends of the columns and consisted of two 50 cm^3 glass syringes. Reciprocating flow within the columns was obtained by coupling the syringe plungers to a dual infusion-withdrawal pump manufactured by Harvard Apparatus Company. The feed was introduced between the stripping and enriching columns by a second such pump with a 50 cm^3 syringe. After every six cycles, operation was interrupted and the feed syringe refilled. To insure perfect mixing in the reservoirs, small magnetic stirrers were placed in the reservoir syringes. The product take-off valves were micrometer capillary valves used both to regulate flow and impose a small back pressure on the system.

The two pH levels were produced by two Bio-Fiber Beakers manufactured by Bio-Rad Laboratory. One was for high pH and the other for low pH. Both were magnetically stirred in order to assure perfect mixing. The protein solution was allowed to pass through the tube bundles of these beakers, while the buffers (high and low pH) were circulated around the tubes by a BioFber pump module. The buffers were mixtures of monobasic and dibasic sodium phosphate (Colowick and Kaplan, 1955).

The apparatus was operated batchwise during upflow and continuously during downflow as shown in Figure 2. As indicated in the figure, high pH liquid enters the bottom of the column during upflow, and low pH liquid enters the top during downflow. The reservoir displacement flow rate is Q cm^3/s, the half-cycle time is π/ω s, and the displacement volume is $Q(\pi/\omega)$cm^3. Dead volumes associated with the top and bottom reservoirs are V_T and V_B cm^3, respectively. The flow rate within the column during upflow is identical to the reservoir displacement rate Q, corresponding to batch operation. In downflow, both feed and product streams flow steadily into and out of the column. The top and bottom product flow rates are $\phi_T Q$ and $\phi_B Q$ cm^3/s, respectively, so that the feed flow rate is $(\phi_T + \phi_B)Q$ cm^3/s. Material balances show that during downflow the flow rate is $(1 - \phi_T)Q$ in the stripping section and $(1 + \phi_B)Q$ in the enriching section.

The evolution of this mode of operation occurred as follows. Preliminary experiments were conducted with feed

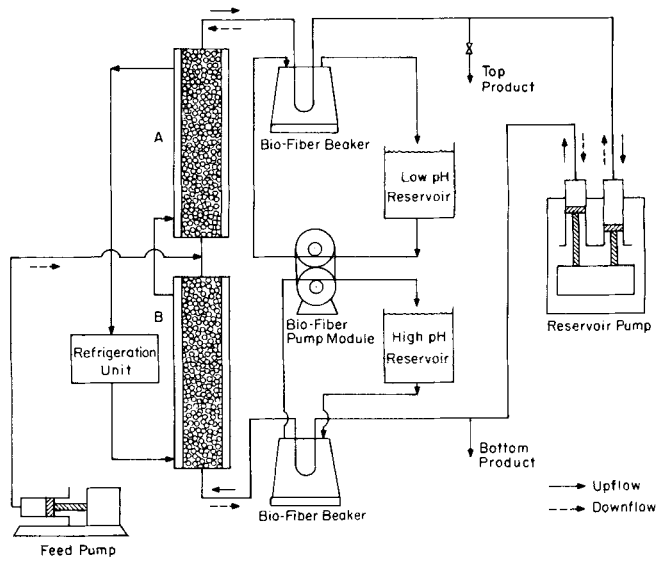

Fig. 1. Experimental apparatus for semicontinuous pH parametric pumping.

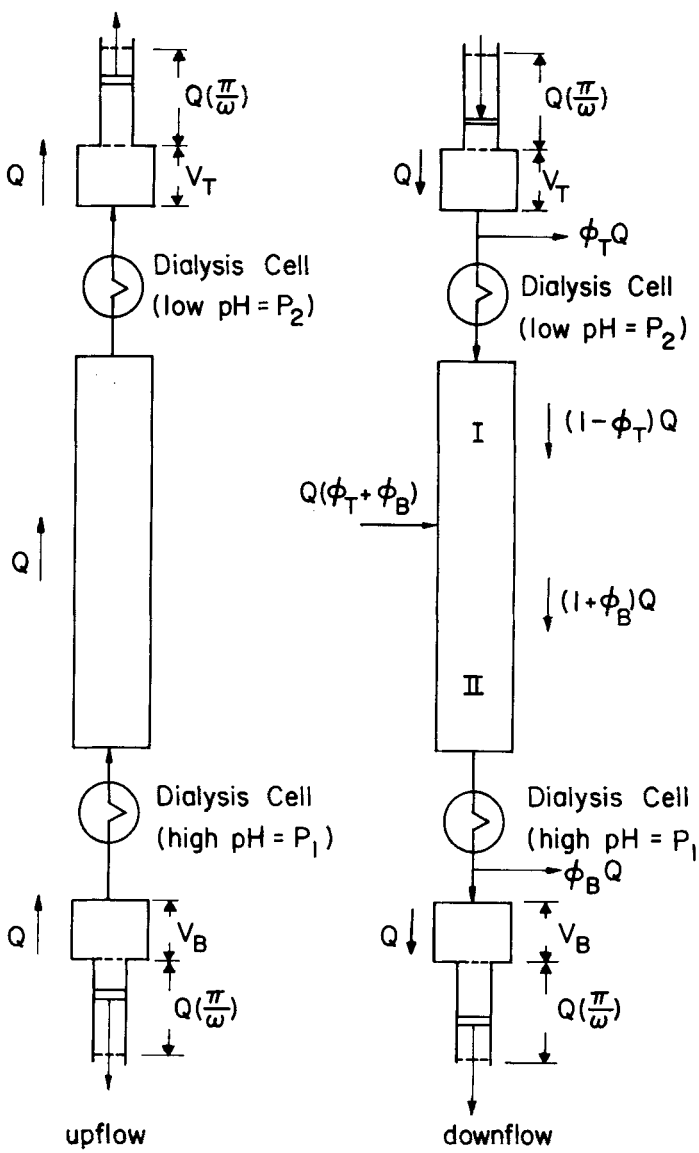

Fig. 2. Column diagram for semicontinuous pH parametric pumping.

introduction at the top of a single column. A buffer concentration of 0.035 M was used, leading to very large capacity of the column for haemoglobin. Introduction of this feed stream into the top of the column led, during the

early cycles of operation, to the accumulation in the uppermost layers of packing of substantially all of the haemoglobin. The resulting layer persisted in later cycles, as determined visually, and led eventually to excessive pressure drop and inability to pump bottom reservoir liquid into the column. In this arrangement of parametric pumping, the linear velocity in downflow was greater than that in upflow. Hence, the liquid from the bottom reservoir, for which the pH was high (or P_1), never reached the topmost layers of the column, and, therefore, the haemoglobin was never caused to transfer back into the liquid phase where it would be accessible for further downward movement. (Note that it was established in separate experiments that hydrogen ion did not exchange for sodium ion and that therefore there was no lag of the pH wave velocity behind the linear liquid velocity.) Because of this excessive immobilization of haemoglobin in the top of the column, no further experiments with feed at the top were conducted. Instead, a center feed was used.

With a center feed, continuous pump operation with a consistent rationale would require a synchronous cyclic variation in feed pH between two levels maintained in the upper and lower reservoirs, so that when high pH fluid was entering the enriching section from the lower reservoir, feed at the same pH would pass from the feed point into the stripping section, and vice versa. For experimental convenience, cyclic pH variation in the feed was not used. Instead, the feed was always introduced at the lower pH value, and semicontinuous operation was adapted. Thus, low pH feed is introduced into the enriching section when low pH fluid enters the top of the stripping section. No feed was introduced when high pH liquid introduces the bottom of the enriching section. With this arrangement of a center feed and semicontinuous operation, liquid from the lower reservoir with high pH did flow to and in fact passed the feed point, and the haemoglobin immobilization problem did not occur. Also, the liquid entering the enriching section in downflow broke through into the lower reservoir, thus assuring that the entire enriching section was active. Note that this was not true of the stripping section. Thus, the high pH liquid from the bottom reservoir penetrated the enriching section completely but only partially penetrated the stripping section. The result was that the haemoglobin initially present in the top of the stripping section above the point of high pH liquid penetration was permanently immobilized there.

Prior to each run, a quantity of Sephadex ion exchanger was mixed with 60 cm^3 of pH = 6 buffer solution and swollen for 1 day. Then, the swollen ion exchanger was mixed with 32 cm^3 of the starting feed solution, and equal amounts of the resulting mixture were poured into both column A and B (Figure 1). The height of each column was adjusted to 0.08 m according to the instruction given by Pharmacia Fine Chemicals (1975). Note that the amount of ion exchanger used depends on the concentration of the buffer, that is, 0.85, 0.70, and 0.65 g of exchanger, respectively, per 60 cm^3 of buffer solution for the buffer concentrations of 0.2, 0.15, and 0.10 M. During the first half cycle, the fluid in the bottom reservoir was pumped through the high pH beaker and into the bottom of column B. At the same time, solution that emerged from column A flowed through the low pH beaker and filled the top reservoir. On the next half cycle, the solution in the top reservoir flowed back through the low pH beaker, passed through columns A and B, and then the high pH beaker to the bottom reservoir. Simultaneously, the feed pump was activated and the product take-off valves were opened and adjusted for the desired product flow rates. This procedure was repeated for each cycle.

Samples for analysis were taken from the product

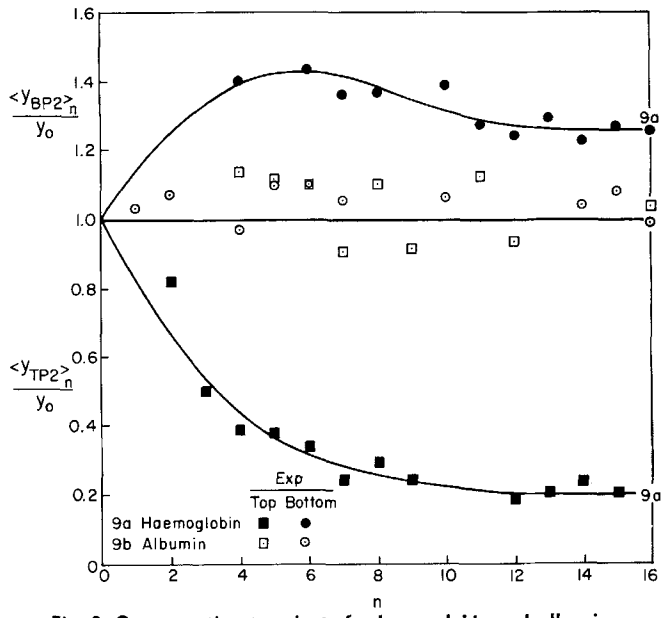

Fig. 3. Concentration transients for haemoglobin and albumin.

streams at the end of each cycle and analyzed spectrophotometically. A differential method of analysis was necessary, since both components exhibit absorbances at 280 μm whereas haemoglobin absorbs as well at 403 μm.

RESULTS AND DISCUSSION

All experiments were carried out in the apparatus depicted in Figure 1. Table 1 summarizes the experimental conditions for selected experiments. In all cases, the reservoir displacement rate Q was 0.5 cm^3/s. Typical concentration and separation factor transients following the start of pump operation are presented in Figures 3 to 8.

The most striking result of the experiments indicated in all of the figures showing concentration and separation transients is the fact that haemoglobin concentrated in the lower reservoir, that is, that inverse separation occurred. The usual view of pump operation, as expressed by the equilibrium theory, would predict haemoglobin concentrated in the top reservoir. In terms of this theory, haemoglobin would be released to the high pH upward flowing liquid entering the bottom of the column and retained on the solid in the presence of the downward flow-

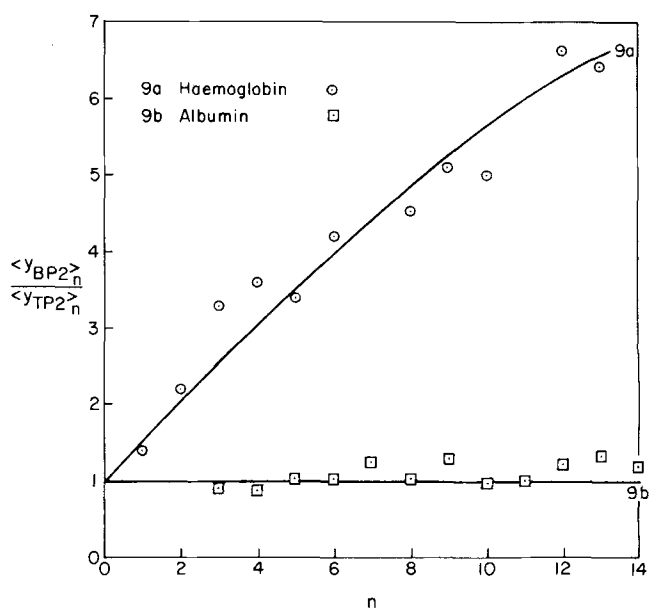

Fig. 4. Separation factors vs. number of cycles.

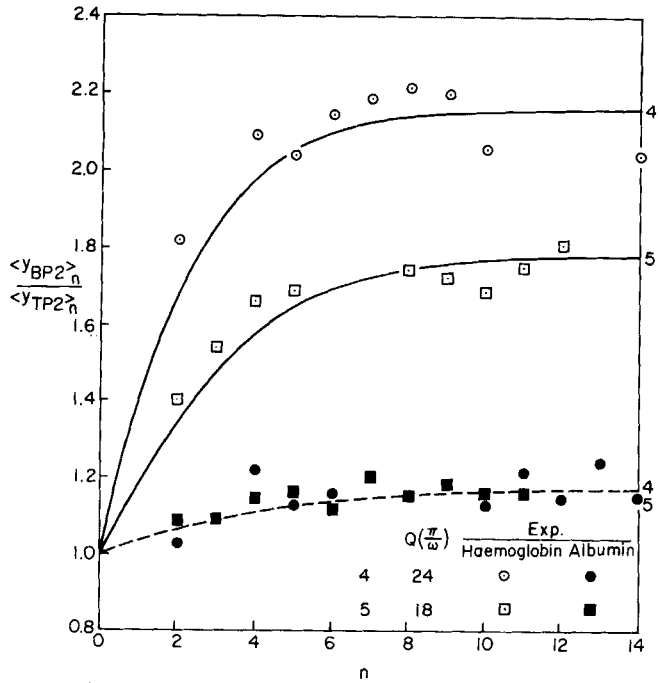

Fig. 5. Effect of reservoir displacement on separation.

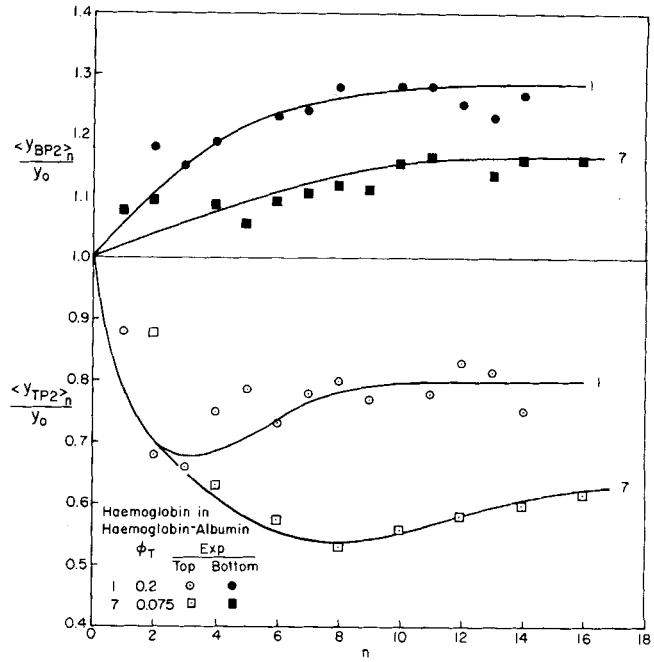

Fig. 7. Effect of top product flow rate on separation.

ing low *p*H liquid supplied to the top of the column. This view assumes interphase mass transfer to be very fast with, in the extreme, instantaneous establishment of equilibrium between phases anywhere in the column. The present results seem consistent with the view that interphase mass transfer is slow so that in effect interphase transfer occurs after reservoir displacement. In this case, upflow is followed by desorption and downflow by adsorption, with net movement of haemoglobin occurring toward the bottom of the column. Sweed and Rigaudeau (1975) have encountered the phenomenon of inverse separation in calculations of recuperative mode parametric pumping with slow mass transfer and reservoir displacement volumes less than twice column void volume. In the present experiments, the displacement volumes considered are 18, 20, and 24 cm^3, respectively, corresponding to approximately 1.5, 1.67, and 2.0 times the void volume of the enriching section.

Inverse separations have been found before at small displacements, but not recognized as such. Wilhelm et al. (1966, 1968) reported what turns out to be small inverse separations in the sodium chloride-water ion exchange resin system using thermal parapumping in the recuperative mode. Likewise, the separations reported by Shaffer and Hamrin (1975) of trypsin using an affinity chromatography column appear to be an inverse separation.

Beyond the fact that the separations reported in the present paper were inverse to the normal equilibrium theory expectations, the characteristics of the separations are qualitatively consistent with the equilibrium theory

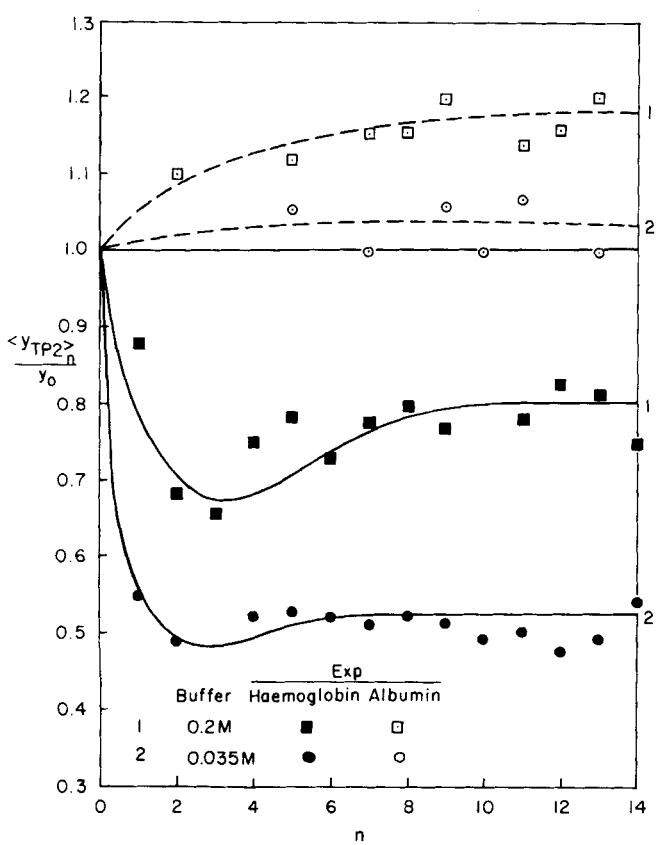

Fig. 6. Dependence of separation on ionic strength.

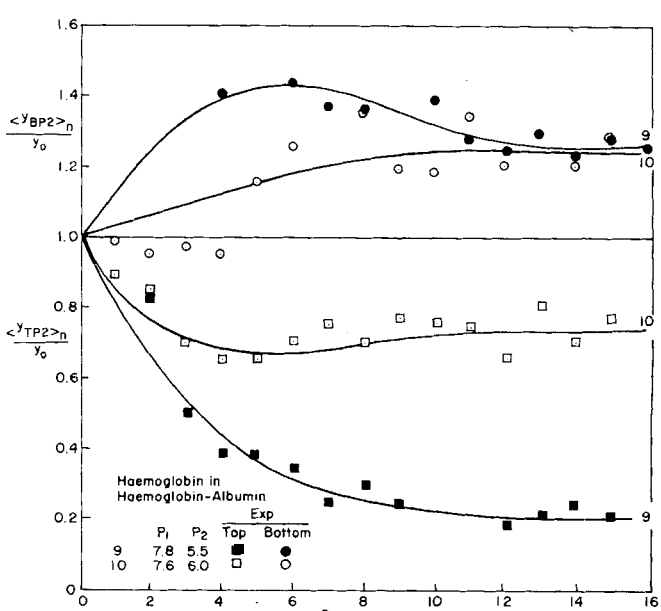

Fig. 8. Effect of *p*H level on separation.

predictions as indicated in the following discussion. The albumin concentration is unaffected by the pumping operation as shown in Figure 3 for run 9. In both top and bottom product streams, it remains essentially at the feed concentration. The haemoglobin concentration falls in the top product stream with increasing number of cycles of operation and rises in the bottom product stream. After a characteristic overshoot in the latter stream, the concentrations in both streams level off to steady values.

The separation factor ($<y_{BP2}>_n/<y_{TP2}>_n$) for run 9 is plotted vs. n, the number of cycles of operation, in Figure 4. The separation factor is defined as the quotient of the bottom and top concentrations. The separation factor for haemoglobin increases with n, whereas that for albumin remains at unity. At larger values of n than shown in Figure 4, the separation factor for haemoglobin approaches a limiting value.

The effect of displacement volume is shown in Figure 5. The separation factor for haemoglobin is higher at higher displacement volumes, while that for albumin is unaffected. The separation could thus be improved by increasing the displacement volume, although at the point at which breakthrough from one reservoir to the other occurs the separation would decline or become nonexistent.

The dependence of separation on ionic strength is demonstrated in Figure 6, which shows the concentration transients for runs 1 and 2. An increase in the buffer concentration and, hence, in sodium ion (counter ion) concentration results in a shifting of the position of equilibrium involving the ion exchanger. This results in less uptake of haemoglobin and high concentration of the substance in the top product stream. For albumin there is no significant difference between run 2 and those shown in Figures 3 and 5, where the product concentration is essentially equal to the feed concentration. But for run 1, $<y_{TP2}>_n/y_o$ is somewhat larger than expected. Further study on this point is underway.

Figure 7 shows the effect of ϕ_T, top product volumetric flow rate/reservoir displacement rate, on the concentration transients. A decrease in ϕ_T produced a decrease in steady state top product concentration, and at the same time the transient time for depletion of the solute (haemoglobin) from the top reservoir or the top product stream became longer.

The net charge on an amphoteric molecule is pH dependent. Change of pH towards the isoelectric point of the substance renders it neutral and thus reduces interaction with the ion exchanger. As shown in Figure 8, less separation is found at a smaller spread of pH values.

No attempt was made in this work to optimize the separation process. Theoretical analysis and process optimization will be discussed in subsequent papers.

ACKNOWLEDGMENT

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NOTATION

I_i = isoelectric point for component i
n = number of cycles of pump
Q = reservoir displacement rate, cm^3/s
P_1 = pH in the bottom product
P_2 = pH in the top product
V_T = top reservoir dead volume, cm^3
V_B = bottom reservoir dead volume, cm^3
y_o = concentration of solute in the feed, kg moles/cm^3
$<y_{BP2}>_n$ = average concentration of solute in the bottom product during downflow at n^{th} cycle, kg moles/cm^3
$<y_{TP2}>_n$ = average concentration of solute in the top product during downflow at n^{th} cycle, kg moles/cm^3
ϕ_B = bottom product volumetric flow rate/reservoir displacement rate, dimensionless
ϕ_T = top product volumetric flow rate/reservoir displacement rate, dimensionless
π/ω = duration of half cycle, s

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Dispersed Phase Mass Transfer During Drop Formation Under Jetting Conditions

A recent design procedure for perforated plate extraction columns requires extension to include jetting conditions at each perforation. For this purpose, correlations are obtained for jet length, jet contraction, drop size, and mass transfer coefficients in disperse phase controlled liquid-liquid systems. Experimental variables include nozzle size, flow velocity, and physical properties.

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SCOPE

A rate approach to the complete design of perforated plate extraction columns was recently published by Skelland and Conger (1973). This provisional procedure uses rate equations describing mass transfer during droplet formation, rise, and coalescence and incorporates relevant hydrodynamics to locate a pseudoequilibrium curve. This curve is used in place of the true equilibrium relationship when stepping off the necessary number of actual stages between the pseudoequilibrium and operating curves on the x-y diagram. The provisional procedure was written in Fortran IV computer language, by W. L. Conger, and his complete computer program is given by Skelland (1974). The print-out gives the number of real plates required for a prescribed separation, the number of perforations per plate, the column diameter, and the cross-sectional area of the downcomers. Substantial agreement was found between predictions and all appropriate data in the published literature.

The design procedure just described is limited to operations in which drops form and detach at the perforations on each plate. Mayfield and Church (1952), however, have shown that plate efficiency increases substantially (in some cases 2½ fold) when drops are formed at the ends of liquid jets issuing from the perforations. Column throughput rates are also much higher under such conditions.

This study was accordingly undertaken to extend the above design procedure to columns operating with the benefits of drop formation under jetting conditions. Correlations were sought for jet length, jet contraction, drop size, and mass transfer coefficients in disperse phase controlled liquid-liquid systems. Variables included nozzle size, flow velocity, and physical properties, and photographic techniques were used to determine drop and jet characteristics.

CONCLUSIONS AND SIGNIFICANCE

The length of a liquid jet issuing from a hole or nozzle on a perforated plate in extraction under jetting conditions has been correlated in Equation (27) of the present paper. The expression is confined to flow rates up to the maximum jet length and to systems with high interfacial tension. The contraction at breakup of a liquid jet undergoing mass transfer to another liquid agrees quite well with that for a jet without mass transfer; the jet diameter at breakup is correlated here in Equation (28). Equation (29) correlates the size of drops formed from jet breakup in the presence of mass transfer to the surrounding liquid.

The mass transfer aspects of this work have shown that correlations of coefficients for mass transfer during drop formation, free fall, and coalescence obtained under nonjetting conditions can be extended to the jetting region with success. The assumption of cone-parabolic flow in the liquid jet gave slightly better predictions of mass transfer rate than did the penetration theory. Good agreement