Drug Delivery via Ion Exchange Across a Micromembrane

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The exchange of pharmaceutically significant amounts of dopamine across a micromembrane is reported, establishing the practical basis for such a drug delivery system. Drug release was accomplished with a commercially available device initially intended for use as a postcolumn reactor in ion chromatography. Release of other ionic drugs (e.g., methyldopate and piperacillin) was also achieved but with a lesser efficiency than was dopamine, presumably because of a size effect. The effect of releasing ion identification and concentration, the flow rate of the delivery solution and concentration of drug in the device reservoir on the drug release efficiency was examined. Under optimal conditions the efficiency approaches 80%, and 1 mg of drug is released/ml of delivery solution. Alternatively, operating conditions can be changed so that magnitude of release is optimized but absolute efficiency is sacrificed. Under such conditions the magnitude of dopamine release approaches 2 mg/ml but exchange efficiency is approximately 25%.

KEY WORDS: drug delivery; ion exchange; micromembrane; dopamine hydrochloride.

INTRODUCTION

Postcolumn reactors utilizing ion exchange across a membrane to modify the mobile phase have been used extensively in liquid and especially in ion chromatography (1). In these reactors, two solutions, flowing countercurrent to one another, are separated by an ion-permeable membrane which mediates exchange between the two solutions. Pharmaceutically significant ions (e.g., drugs and amino acids) have the ability to participate in the exchange reaction (2) and thus the exchange process can be exploited for drug delivery. Previous research, performed with commercially available fiber membranes, demonstrated the validity of the concept by documenting the release of dopamine hydrochloride under both static and continuous-flow conditions (3); however, the efficiency of the process was limited by the intrinsic exchange efficiency of the fiber membranes used. Additionally, the utilization of hollow fibers as a means of facilitating drug delivery has been reported by several research groups (e.g., Refs. 4 and 5). Since the completion of our original research, the exchange capacity of commercially available ion-exchange reactors (specifically ion chromatography suppressors) has been improved via the development of micromembrane technology (6). Thus we have revisited membrane drug delivery by examining the operating characteristics of the micromembrane design and expanding our consideration to additional drugs.

DISCUSSION OF THE EXCHANGE MECHANISM

The micromembrane suppressor facilitates the exchange of similarly charged species between two counterflowing solutions. It contains alternating ion-exchange screens and membranes which define the solution flow paths. The eluent (delivery solution) enters the reactor, flows lengthwise through the weave of the screen, and exits at the other end. Regenerant (reservoir) solution flows through the reactor in a countercurrent direction. Ions of the appropriate charge are directed by the screens toward the membranes where ion exchange between the two solutions occur. The screens direct the ions toward the membrane via both mechanical and chemical (ion exchange) means. The membrane possesses a surface charge, and only ions of a certain charge type are exchanged (ions of charge similar to the membrane are repelled).

A drug delivery system based on the membrane is shown for a cationic drug (Fig. 1). The two solutions used are a reservoir solution, which initially contains the drug, and a delivery solution, which is ultimately directed to the patient and into which the drug must migrate. In the reservoir solution, the drug exists in an appropriate ionic form (the D^+ cation). The delivery solution contains a species of similar charge (e.g., Na^+); as the two solutions flow past each other in the reactor, ion exchange occurs. The drug is released into the delivery solution and ultimately dispensed to the patient. The releasing ion can be added to the delivery solution as a discrete event, resulting in the release of a discrete amount of drug, or it may be present in the delivery solution at a constant concentration, in which case the drug will be released continuously until the reservoir is depleted.

Dopamine hydrochloride is amenable to the exchange process. At neutral to acidic pH, dopamine is positively charged (Fig. 2) and can participate in exchange. Dopamine thus is an appropriate model for most compounds which contain an ionizable amine.

A similar situation exists for anionic drugs wherein the micromembrane surface is positively charged and only anions cross the membrane. Piperacillin sodium is an appropriate example of drug compounds that possess an ionizable acid group and thus can participate in anion-mediated exchange (Fig. 2).

MATERIALS AND METHODS

Materials

Dopamine hydrochloride was obtained from Knoll Fine Chemicals (New York), methyldopate hydrochloride was obtained from AKZO Dionsynth (Holland), and piperacillin sodium was obtained from Lederle Piperacillin, Inc. (Puerto Rico). Reagents used to prepare the various solution phases were all reagent grade and distilled, deionized water was used in all preparations.

The micromembrane reactors used were commercially available ion chromatography suppressors. Units used were

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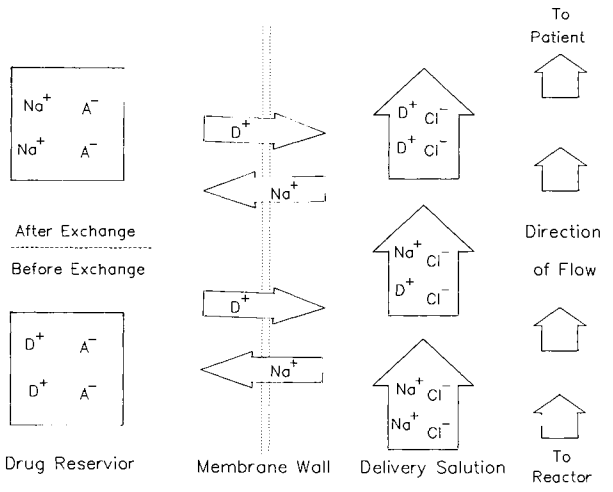

Fig. 1. Schematic diagram of the drug delivery process. D represents the drug species and A represents the drug's counter-ion.

Models AMMS-1 (for anion analysis, allows for migration of cations) and CMMS-1 (for cation analysis, allows for migration of anions) from the Dionex Corporation (Sunnyvale, CA). These devices were used per the vender guidelines; however, in this application the IC eluent was actually the drug delivery solution, while the regenerant solution was the drug reservoir solution. Since the suppressor's contact chamber volume is small, an external reservoir chamber was prepared to contain the drug. The reservoir solution was recirculated through the micromembrane device via a peristaltic pump.

Analytical Apparatus

The system used to monitor drug release is shown in Fig. 3. An HPLC pump circulates the drug delivery solution through the micromembrane and into UV detector 1, which monitors the instantaneous in-line drug concentration. The detector effluent flows through a flow-through pH probe (Lazar Research Labs, Los Angeles, CA) and to a collection vessel containing a known amount of a continuously stirred solution. The collection solution is recirculated via HPLC pump 2 through the second UV detector, which monitors the instantaneous collection solution drug concentration (which is multiplied by the vessel's volume to determine the cumulative amount of drug released). The outputs of both UV detectors and the pH probe were directed to strip-chart recorders and laboratory integrators for data collection and analysis. HPLC components from various vendors were used. Tubing lengths were minimized so as to eliminate dead volume and the flow rate of the second HPLC pump was 3 ml/min to minimize any variable time lags.

Discrete Release Experiments

A Rheodyne Model 7010 injection valve was placed between pump 1 and the delivery device. Aliquots of a releasing solution were injected into a flowing delivery solution (water) and the release of drug was followed using UV detector 1 (set at 250 nm) and the pH probe. The effluent from the pH probe was not collected. Variables examined included drug identity, identity of the releasing ion and delivery solution flow rate.

Continuous Release Experiments

These experiments were performed with the apparatus as shown in Fig. 3. Delivery solutions contained various amounts of sodium chloride and hydrochloric acid and their flow rate was varied throughout the study. In experiment A, the dopamine concentration in the reservoir was 0.3 *M*, the relative flow rate was 0.4 and the NaCl concentration in the delivery solution was varied. In experiment B, the dopamine concentration was varied, while the NaCl concentration was 0.9% and the same relative flow rate was used. In experi-

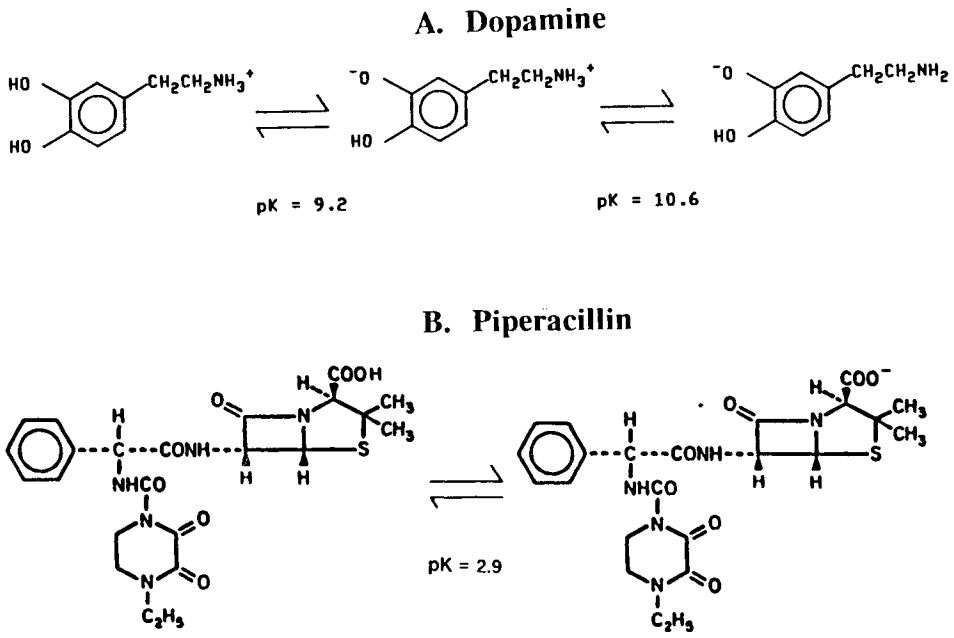

Fig. 2. Acid/base chemistry of the drugs studied.

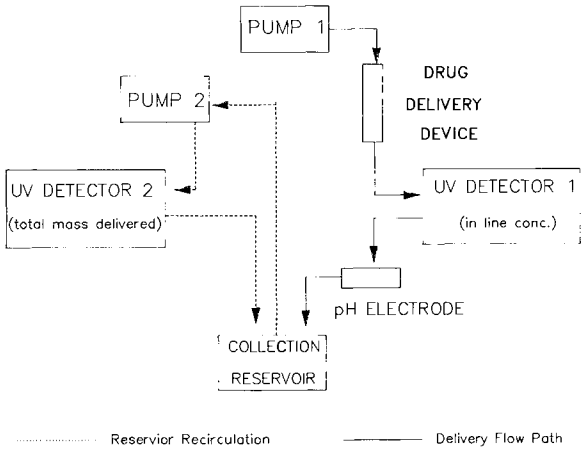

Fig. 3. Schematic diagram of the drug release monitoring apparatus, highlighting the analytical apparatus. The entire apparatus used in this study included a drug reservoir and a third pump which connected the drug reservoir and the drug delivery device.

ment C, relative flow rate was varied with a dopamine concentration of 0.3 *M* and a NaCl concentration of 0.9%. The drug reservoir volume was 50 ml; however, the concentration of drug in the reservoir as well as the flow rate of the reservoir solution was varied throughout the study. The drug reservoir solution contained no active antioxidants; its pH was sufficiently low that no significant dopamine degradation was expected over the course of the experiments performed. The collection reservoir contained either 500 or 1000 ml of 1% (v/v) acetic acid; both the drug and the collection reservoirs were constantly stirred. Continuous-release experiments were initiated by flushing all solution transport tubing and the micromembrane with water. The micromembrane was equilibrated with the drug reservoir solution (with water still in the delivery side of the membrane). Drug delivery was initiated by switching from the water flush solution to the delivery solution and directing the pH probe effluent to the collection reservoir. The two UV detectors and the pH probe were continuously monitored throughout the experiment; detection wavelengths used were optimized for each detector and each drug. The response of all detectors was calibrated by pumping standards through each and noting the equilibrium signal. Calibration curves, equating the equilibrium signal with analyte concentration in the standards, were used to determine the instantaneous analyte delivery concentration. For these experiments, detection wavelengths of 250 nm (a local minimum in the dopamine absorption spectrum) and 280 nm (a local maximum) were used in detectors 1 and 2, respectively.

RESULTS AND DISCUSSION

Discrete Release Experiments

A discrete amount of drug is released from the micromembrane reservoir when a releasing ion is injected into an otherwise nonionic diluent. The amount of drug released is related to (i) the amount of releasing ion injected, (ii) the exchange reaction stoichiometry, and (iii) the exchange efficiency. The exchange or release efficiency (the ratio of mass of drug released per unit mass of releasing ion that passes through the reactor) is a manifestation of the interaction kinetics; that is, the relationship between the rates at which drug and releasing ion move through the membrane, the rate at which these two species move to and away from the membrane surface, and the residence time of an individual solute in the reactor. Qualitatively, one expects that the magnitude of drug released will be impacted by operational variables such as the identity and concentration of the releasing ion and the flow rates of the delivery and reservoir solutions. Consistent with previously reported research (3), no change in release efficiency as a function of amount of releasing ion injected was observed for dopamine release over a 10-fold range of releasing ion (sodium) concentration (10 to 100 μg injected). However, changing the identity of the releasing ion to calcium increased mass efficiency by approximately 10%, since calcium has a smaller normal weight than sodium. Changing the identity of the drug to be released to methyldopate decreased efficiency dramatically; under similar operating conditions the relative release rate for methyldopate was approximately 20% of that for dopamine. One hypothesizes that the difference in behavior between dopamine and methyldopate represents a difference in size consistent with their molecular weights of 153.2 and 239.2 grams per mole, respectively. Additionally, release efficiency was impacted by delivery solution flow rate (at constant reservoir solution flow rate). Relative release efficiencies of 1, 0.94, and 0.62 were observed at delivery flow rates of 0.25, 0.5, and 1 ml/min, respectively. These data suggest that the release system is limited by the rate at which the releasing ion is incorporated into the membrane. That is, at the higher flow rates the releasing ion is "washed out" of the reactor before it can participate in exchange across the membrane.

Discrete release of piperacillin via use of the micromembrane reactor was also observed; in the case of this species, chloride represents the releasing ion. The release of this drug under the conditions used herein was inefficient (typically less than 10% of the theoretical release was observed), which again is probably an indication that the membrane's pore size is sufficiently small that piperacillin diffusion through the membrane used is constrained.

Continuous Release Experiments

To obtain a continuous release of drug from the micromembrane reactor, the delivery solution must provide a constant source of releasing ion. As with discrete release, the efficiency of the continuous release process will be impacted primarily by the relative kinetics of the exchange process. Uptake of the releasing and drug ion and exchange of these two species across the membrane must occur within the time the ions are in the reactor. If the releasing or delivery (drug) species is flushed out of the reactor before exchange occurs, the release efficiency is reduced. The flow rates of the delivery and reservoir solutions and the concentrations of both drug and releasing ion in the reservoir and delivery solution will all impact the apparent release efficiency. The effect of these operational variables on the release of dopamine from the reactor was examined. From experiment A, we observe that the release efficiency decreases as the concentration of releasing ion in the delivery solution increases. That is, at higher concentrations the re-

leasing ion moves out of the reactor before it can participate in the exchange for the drug. At NaCl concentrations in the delivery solution of 0.1, 0.3, and 0.9%, the measured release efficiency was 100, 69, and 42%, respectively. Clearly the micromembrane is being swamped with releasing ion as the releasing ion's concentration increases.

Increasing the drug concentration in the reservoir solution provides a thermodynamic and kinetic means of increasing the release efficiency. Thermodynamically, the increased drug concentration in the reservoir results in a more favorable "driving force" for the exchange (that is, the change in Gibb's free energy for the exchange process is increased when the concentration of drug in the reservoir is increased). Kinetically, diffusion of the drug to the membrane surface, as well as the diffusion of the drug through the membrane, should be enhanced as the concentration of the drug in the reservoir solution increases. At dopamine concentrations in the reservoir of 0.025, 0.1, and 0.3 *M* (experiment B), the measured release efficiency was 15, 28, and 42%, respectively.

The flow rates of the delivery and reservoir solutions have a significant impact on the release efficiency by controlling the residence time of the drug and releasing ion in the reactor. If the membrane's ion uptake rate and/or the ion's diffusion through the membrane is fast relative to the flow rates (no residence time concerns), then efficiency and flow rate should be independent. In a system where a residence time constraint exists, the efficiency of release will be strongly influenced by the flow rates. If the system is residence time constrained, the residence time of the releasing ion in the reactor increases as the flow rate of the delivery solution decreases and thus efficiency should increase. Additionally, increasing the flow rate of the reservoir solution should increase the rate at which the drug is replenished to the membrane surface and thus efficiency should be increased. Thus, as the ratio of the flow rate of the delivery solution to that of the reservoir solution decreases, release efficiency should increase. At relative flow rates of 0.06, 0.12, and 0.4 (delivery to reservoir flow rate, experiment C), the release efficiency was 91, 52, and 42%, respectively. The dramatic increase in efficiency at the low flow rate illustrates a situation wherein the kinetic constraint is most pronounced. After a certain critical relative flow rate is reached, any further gain in efficiency is minimized.

The pH probe revealed an additional constraint on release efficiency, the presence of competing exchange interactions. When profiles were generated with sodium as the releasing ion, the release efficiency was lower than when hydrogen ion was the releasing ion. During the sodium exchange experiments, the pH of the delivery solution was observed to decrease with time (one expects essentially no pH change to occur when dopamine and sodium participate in exchange across the membrane). Apparently hydrogen ions in the reservoir solution are preferentially exchanging with sodium (which is not surprising given the relative size of the dopamine and hydrogen ions) and thus the efficiency of dopamine release was decreased. One expects and experimentally observes that when sodium (or any other releasing ion other than hydrogen) is used, the pH of the reservoir solution impacts efficiency not only by impacting the speciation of the drug but also by providing a competitive exchange mechanism. However, when hydrogen ions are used as the releasing ion, the reservoir pH becomes unimportant in terms of possible exchange competition.

The greatest practical efficiency for dopamine release (≈76%) was achieved under the following conditions: delivery solution, 0.05 *N* HCl; flow rate, 0.4 ml/min; reservoir solution, 1 g/50 ml; and flow rate, 3.3 ml/min. Thirty-seven milligrams of dopamine was delivered in a solution volume of approximately 32 ml over 80 min. When the experiment was continued to 225 min, efficiency decreased somewhat to 66.4% and 92 mg of drug was released in 90 ml.

The conditions producing maximum efficiency do not maximize the amount of drug released per unit time. While higher concentrations of sodium in the delivery solution, higher delivery solution flow rate, and higher initial drug concentration in the reservoir all adversely impact the efficiency with which the drug reservoir is depleted of drug, one can improve absolute delivery somewhat by increasing these quantities. The maximum drug release obtained was 1.9 mg dopamine/ml solution and was achieved using 0.3% NaCl as the delivery solution at a flow rate of 0.4 ml/min (efficiency approximately 25%).

Concentration versus time plots obtained from both UV detectors are release rate profiles providing essentially complementary information. The in-line release profile is the derivative of the cumulative mass release profile obtained from the second UV detector (one notes that the concentration versus time plot obtained from the second detector is equivalent to mass released versus time if the volume of the collection reservoir does not change significantly over the experiment). Both types of plots provide an insight into the mechanisms impacting the exchange-mediated release. Specifically, Figs. 4 and 5 illustrate typical concentration and cumulative mass release profiles. When the micromembrane device is first activated, a large amount of drug is released. This release is essentially 100% efficient as drug initially loaded onto the micromembrane is removed. The duration of this burst release is short-lived as the in-line concentration approaches the kinetically controlled efficiency limit (i.e., a period of steady-state release). During this steady-state period, the in-line concentration is essentially constant and the mass release curve is characterized by a linear region. As the device operation continues, the thermodynamic driving

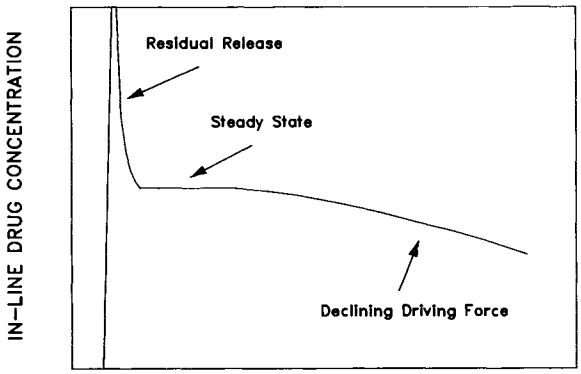

Fig. 4. Release rate profile, in-line concentration of drug (dopamine) as a function of device use time.

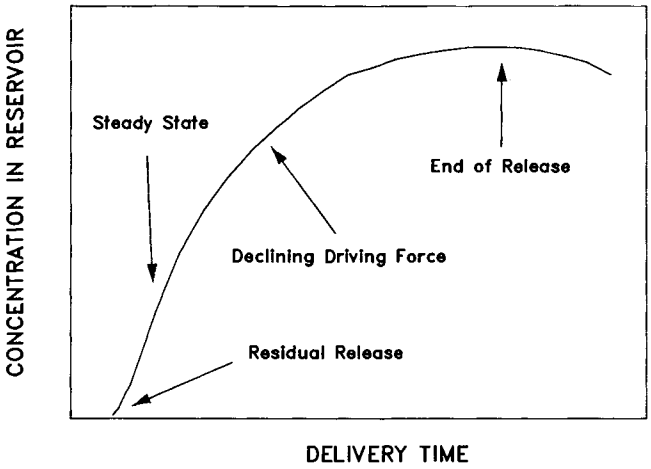

Fig. 5. Release rate profile, concentration of drug (dopamine) in the collection reservoir as a function of device use time.

force decreases as the reservoir becomes more concentrated with respect to the releasing ion and depleted with respect to the drug. As the thermodynamic driving force decreases, so does the in-line drug concentration, producing a decreasing slope in the mass release profile. Ultimately, the thermodynamic driving force is zero and the release of drug stops. Residual drug in the reservoir line is flushed out and the in-line drug concentration drops to zero, producing a plateau in the cumulative mass release curve. Continued operation of the device after end of release produces a dilution effect in the collection reservoir and thus the mass released profile begins to slope back toward zero. Both the steady state in-line concentration and the total mass released provide estimates of the operational efficiency of the exchange release.

The thermodynamic driving force for drug release can be understood in the context of the Gibb's free energy involved with the exchange process. Specifically, the release process can be expressed via the following reaction:

$$n(D\text{-R}) + mI^{n+}(\text{aq}) \leftrightarrow m(I\text{-R}) + nD^{m+}(\text{aq})$$

where "-*R*" refers to a species in the reservoir, (aq) refers to a species in the delivery solution, *I* is the releasing ion of charge *n*, and *D* is the released drug of charge *m*. The thermodynamic driving force for drug release is the change in Gibb's free energy associated with the exchange process,

$$\Delta G = RT\ln K_{op} - RT\ln K_{eq}$$

where K_{eq} is the equilibrium constant for the exchange reaction and K_{op} is the operational ion product, which takes the form

$$K_{op} = [D^{m+}]^n[I\text{-R}]^m/[D\text{-R}]^n[I^{n+}]^m$$

For reaction 1 to proceed to the right (for drug to be released), ΔG must be negative and thus K_{op} must be less than K_{eq}. During the initial stages of release, [*D*-R] is at its maximum and [*I*-R] is essentially zero and the thermodynamic driving force is large. As drug release proceeds, [*D*-R] decreases and [*I*-R] increases until the operational ion product equals K_{eq}, the thermodynamic driving force is zero, and drug release will cease.

The release of pharmaceutically significant quantities of dopamine could not be achieved with the micromembrane device used in this research because this apparatus is poorly suited for pharmaceutical applications. The rather poor efficiency observed for the larger drugs evaluated (methyldopate and piperacillin) indicates that the membrane pore size is too small for effective drug release. Additionally, the contact area between the solution phases and the micromembrane surface is relatively small (approximately 25 cm^2), while the void volume associated with the device used is 50 μl or less (7). While such a feature is necessary in the analytical applications for which the device is designed (where extracolumn band dispersion must be minimized), the small contact area/volume essentially lessens the efficiency in the drug delivery application. Finally, in an apparatus specifically designed for drug delivery the reservoir chamber would need to be sufficiently large so that it could contain the entire reservoir solution, thus eliminating the need for a circulating pump when the micromembrane is used. Future research will be directed toward generating a prototype device more suitable for pharmaceutical applications.

REFERENCES

1. T. S. Stevens, J. C. Davis, and H. Small. Hollow fiber ion exchange suppressor for ion chromatography. *Anal. Chem.* 53:1488–1492 (1981).
2. D. Brown, R. Payton, and D. Jenke. Elimination of matrix related interferences in indirect photometric chromatography. *Anal. Chem.* 57:2264–2267 (1985).
3. D. R. Jenke. Drug delivery via ion exchange across a fiber membrane. *Pharm. Res.* 6:96–99 (1989).
4. D. Tores, B. Seijo, G. Garcia-Encina, M. Alonso, and J. Vila-Jato. Microencapsulation of ion exchange resins by interfacial nylon polymerization. *Int. J. Pharm* 59:9–17 (1990).
5. M. A. Hussian, R. C. DiLuccio, E. Shefter, and A. R. Hurwitz. Hollow fibers as an oral sustained release delivery system using propranolol hydrochloride. *Pharm. Res.* 6:1052–1055 (1989).
6. G. O. Franklin. Development and applications of ion chromatography. *Am. Lab.* 17(6):65–80 (1985).
7. J. Stillian. An improved suppressor for ion chromatography. *LC* 3(9):802–812 (1985).