Pharmaceutical Research, Vol. 6, No. 1, 1989

Technical Note

Drug Delivery via Ion Exchange Across a Fiber Membrane

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Received May 5, 1988; accepted August 15, 1988
KEY WORDS: drug delivery; ion exchange; dopamine; fiber membrane.

INTRODUCTION

Post column reactors based on ion exchange across a hollow fiber membrane have been used extensively in liquid chromatography, especially in the technique termed 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. Pharmaceutically significant ions (e.g., drugs and amino acids) have the ability to participate in this exchange (2), thus providing the conceptual basis for a drug delivery system involving such a technology. A scheme for such a delivery system based on the membrane exchange is shown in Fig. 1. The membrane reactor, enclosed within a solid support, consists of the membrane fiber, a delivery solution which flows through the fiber, and a quiescent drug reservoir solution which surrounds the fiber. The chemistry of the reservoir solution is such that the drug exists in an appropriate ionic form, in the case of cationic exchange, as D^+. The delivery solution contains a species of similar charge (e.g., Na^+); thus as this solution flows through the reactor, ion exchange occurs. The net result is that the drug is mobilized into the delivery solution (and ultimately is dispensed to the patient). The mobilizing ion can be added to the delivery solution as a distinct event, resulting in a discrete release of the drug, or it may be present in the delivery solution at a constant concentration, in which case a continuous release of drug can be obtained. It is the purpose of this paper to demonstrate the potential utility of the membrane exchange process for drug delivery by characterizing a system constructed from commercially available materials.

MATERIALS AND METHODS

Materials

Dopamine hydrochloride was obtained from Knoll Fine Chemicals (New York). Sodium chloride and any acids used were reagent grade and all solutions used were prepared from research-grade distilled and deionized water.

The fiber membrane used was obtained from an AFS-1 anion suppressor manufactured by Dionex, Inc. (Sunnyvale, Calif.). The membrane is a Nafion-type fiber manufactured by a proprietary process; the particular fiber used herein had a total length of 90 cm, of which approximately 80 cm was immersed in the drug reservoir and thus participated in the exchange process. The fiber had an internal diameter of approximately 0.5 mm and contained small beads in the fiber passageway (as received from the manufacturer), which serve to promote effective exchange between the two solutions. The fiber was immersed in a 150-ml beaker which served as the drug reservoir. The delivery solution, as identified later, was pumped through the fiber with a peristaltic pump. All experiments were performed at ambient temperature.

Discrete-Release Experiments

In these experiments, a Rheodyne (Berkley, Calif.) Model 7125 injector was placed between the peristaltic pump and the fiber and the effluent from the membrane was directed into a Kratos (Ramsey, N.J.) 757 HPLC UV detector. The delivery solution used was either water or 5% dextrose injection and was pumped at a rate of 1 ml/min through the system. The drug reservoir solution contained 500 mg/l dopamine hydrochloride at pH 4 (with hydrochloric acid). Stock solutions containing varying amounts of sodium chloride or dopamine hydrochloride were injected into the delivery solution and the detector response was monitored at 280 nm and measured as the peak area.

Continuous-Release Experiments

No injector was required in these experiments and the effluent from the membrane reactor was directed into a collection reservoir. The delivery solution used contained various amounts of sodium chloride and was delivered at a rate of 0.5 ml/min. The drug reservoir contained 125 ml of a solution with 500 mg/l dopamine hydrochloride at pH 4. The collection reservoir initially contained 950 ml of 1% acetic acid. Both the drug reservoir and the collection reservoir solutions were stirred during the experiment. The experiment was initiated by immersing the fiber in the drug reservoir and flushing the fiber with water (bypassing the collection reservoir). Drug delivery was initiated by switching from the water flush to the delivery solution and directing the effluent of the reactor to the collection reservoir. Samples of the drug and collection reservoir solutions were ob-

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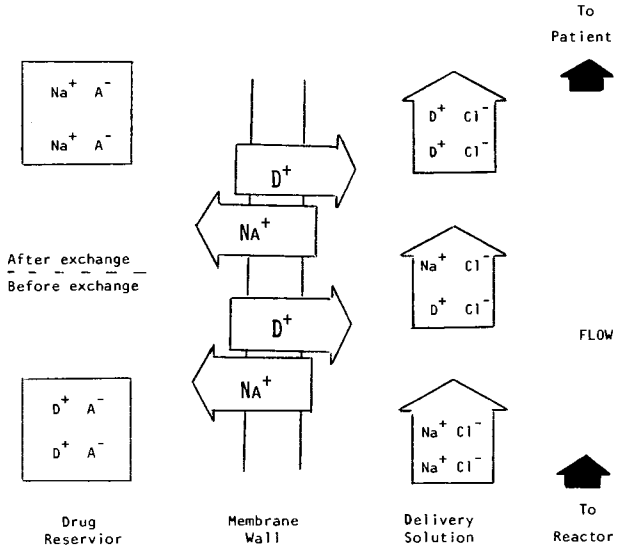

Fig. 1. Schematic diagram of the membrane exchange process. D represents the drug species and A represents the drug's counter ion.

tained just prior to the initiation of drug release. At timed intervals during the release experiment, a 1-ml sample was removed from the collection reservoir. After 300 min of operation, the flow of the delivery solution was stopped, the drug and collection reservoir solutions were sampled, and the total volume of the collection solution was measured. All samples were analyzed for dopamine content using a stability-indicating HPLC method (3).

Chromatographic Analysis

The chromatographic system consisted of the 757 UV detector, the Rheodyne 7125 injector, a Kratos SF400 pump, a Perkin Elmer (Norwalk, Conn.) HS-3 C18 column, and a computer integrator. The mobile phase was 9% acetonitrile, 1% acetic acid, 0.09% sodium octylsulfonate, and 0.004% EDTA in water. Operating conditions included detection at 280 nm, a sample size of 20 µl, and a mobile-phase flow rate of 0.7 ml/min. Dopamine concentrations were calculated from a calibration curve obtained from the analysis of independently prepared standards. The method precision was roughly 1.5% RSD over the concentration range studied.

RESULTS AND DISCUSSION

Dopamine was chosen as the cationic test drug for use in this study since it is able to cross the membrane (2). In order to produce a discrete release of drug from the reservoir solution, an injection of releasing ion (in this case Na^+) is made directly into the flowing diluent. The effect of injecting varying amounts of sodium ion into the diluent on the amount of dopamine released is shown in Fig. 2. The dopamine released appears as a peak in the detector response and the amount obtained is linearly related to the amount of sodium injected. The slope of the plot of sodium injected versus dopamine released (0.119) is effectively equivalent to the ratio of the equivalent weights of the exchanging species (0.121), indicating that stoichiometric exchange is occurring. While eventually stoichiometry will be violated as the amount of sodium injected becomes large enough that exchange kinetics are slow compared to the residence time in the reactor, such behavior was not observed in this study. The fact that drug release is exchange mediated is also indicated by the lack of drug release observed when nonionic diluent flowed through the reactor for long periods of time or when injections of nonionic solutions were made into the diluent. Other releasing ions (e.g., K^+, Ca^{2+}, and Mg^{2+}) were also observed to participate in stoichiometric exchange with dopamine across the fiber. The drug release was extremely reproducible; 15 injections of 50 mg of Na^+ released a quan-

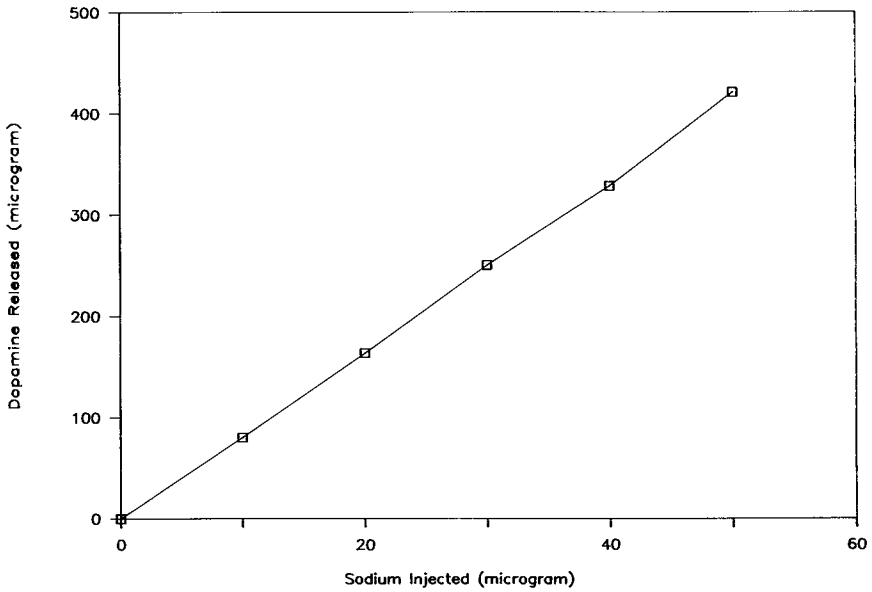

Fig. 2. "Calibration" curve relating the amount of sodium injected into a flowing diluent and the amount of dopamine released from the reactor. Linear regression curve-fit parameters include a slope of 0.119, an intercept of 0.2, and a correlation coefficient of 0.999.

tity of drug (6 mg) which varied by less than 1.1% RSD, which is roughly the precision of the injection process itself.

Generating a diluent containing a constant amount of drug over extended periods of time requires that the diluent contain a constant amount of releasing ion and that the concentration gradient across the membrane be maintained for both species. Water diluents containing varying amounts of sodium as the releasing ion were passed through the reactor, which contained a known quantity of dopamine, and the amount of dopamine released per unit time was determined as described previously. The results of one such experiment, which were quite reproducible in terms of amount and rate of dopamine release, are shown in Fig. 3. In this experiment, the diluent contained 1000 mg/l Na^+. Release of the drug follows a smooth asymptotic curve; after 220 min of operation, 90% of the drug originally contained in the reservoir has been delivered; 50% release occurs at 60 min. It is clear from Fig. 4, the release rate profile or derivative plot of Fig. 3, that an initial rapid and constant rate of release is maintained for roughly 40 min. Thereafter, the rate slows asymptotically to one representing little drug release.

The shape of the rate profile is interpreted via a thermodynamic analysis of the exchange process. To wit, the exchange process can be expressed via the following reaction:

$$m(D - R) + I^{n+}\,(\text{aq}) \leftrightarrow I - R_m + nD^{m+}\,(\text{aq}) \quad (1)$$

where "$-R$" refers to a species in the reservoir, (aq) refers to a species in the delivery solution, I is a releasing ion of charge n, and D is the released drug of charge m. The operational equilibrium expression for this reaction can be written as

$$K_{op} = [D^{m+}]^n\,[I - R_m]/[D - R]^m\,[I^{n+}] \quad (2)$$

The change in Gibbs free energy associated with the exchange process (the thermodynamic driving force) is written as

$$\hat{}G = -RT\ln K_{eq} + RT\ln K_{op} \quad (3)$$

where K_{eq} is the equilibrium constant for the exchange. In order for exchange to occur as written in Eq. (1), $\hat{}G$ must be negative and thus K_{op} must be less than K_{eq}. In the first 40 min of device operation, $[D - R]$ is at its maximum and $[I - R_m]$ approaches zero, and thus the thermodynamic driving force is large and the reaction is constrained by the kinetics of ion diffusion across the membrane. As the drug release proceeds, $[I - R_m]$ becomes large, $[D - R]$ becomes smaller, and the thermodynamic driving force decreases. Eventually, $K_{op} = K_{eq}$ and the exchange process will cease, although such a scenario was not observed in this research.

Practically, it is useful to keep the thermodynamic driving force large (and thereby maximize the efficiency of the delivery process). Equation (2) indicates that the driving force is maximized when $[D - R]$ is large and $[I - R_m]$ is small. Maximizing the driving force by keeping $[D - R]$ large is a poor strategy since it essentially requires that the reactor contains more drug than one intends to deliver. To keep $[I - R_m]$ small, the chemistry of the reservoir must be such that the releasing ion is immobilized therein. For example, if calcium were used as the releasing ion and the reservoir contained sulfate, calcium sulfate precipitation would occur as the exchange process proceeded. In this case $[\text{Ca} - R_m]$ would remain small and the driving force would be maintained throughout the delivery process.

The efficiency of the exchange process can be expressed in terms of the ratio of drug released to the amount of releasing ion passing through the reactor. Even over the period of the most rapid drug release, the efficiency of the release process is poor. At 40 min of operation, the reactor has released only 30 mg of drug, while the stoichiometric equivalent to the amount of sodium which was passed through the reactor is approximately 120 mg. Clearly the exchange kinetics in the reactor are sufficiently slow (when coupled with the residence time in the reactor) that equilibrium between the flowing delivery solution and the drug reservoir solution is not achieved. No attempt was made in this

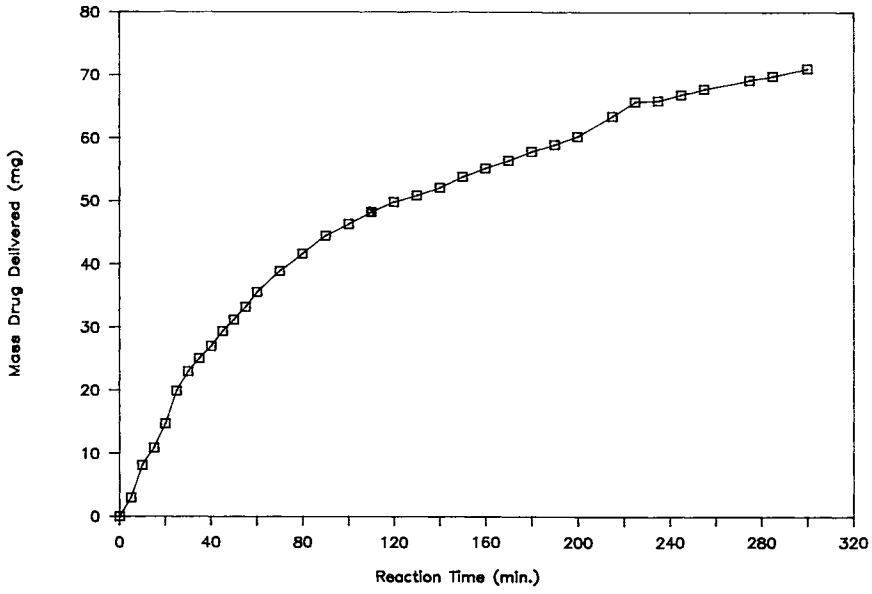

Fig. 3. Release profile indicating the amount of drug delivered as a function of the amount of time a delivery solution containing 1000 mg/liter sodium flows through the reactor.

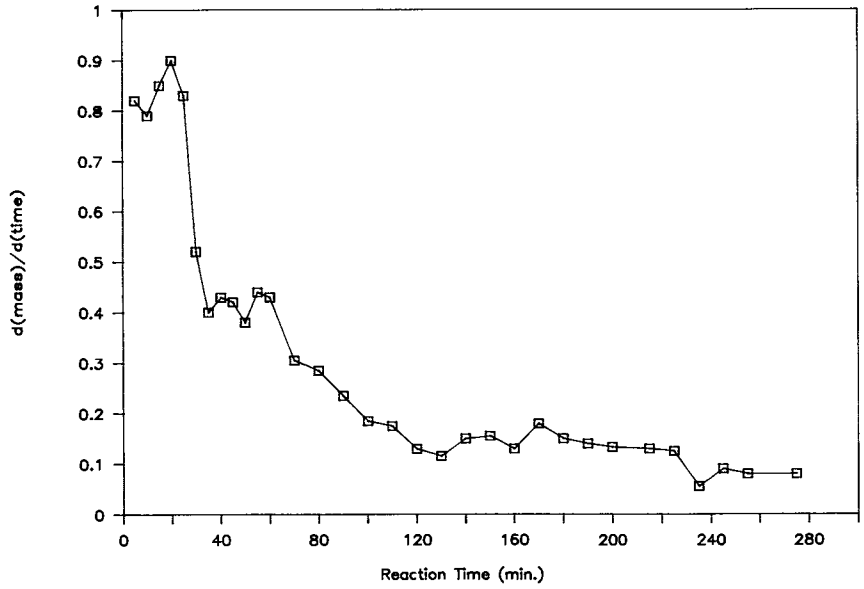

Fig. 4. Release rate profile: derivative plot of the data presented in Fig. 3.

study to optimize the efficiency of the release of drug in a dynamic situation, although it is noted that efficiency could be influenced somewhat by changing the operating conditions. A variety of factors, including the nature of the fiber (chemical and physical), flow rate, composition of the delivery and drug reservoir solutions, and temperature, controls the exchange process to some extent and thus can be varied to produce an optimized release system.

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