Determinants of the Modulated Release of Antiarrhythmic Drugs by Iontophoresis through Polymer Membranes

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ABSTRACT: For the purpose of preventing progressive ventricular arrhythmias, iontophoretic delivery of several antiarrhythmic drugs (classes I–IV) and a model cationic drug, (±)-phenylpropanolamine (PPA), through polymer membranes was investigated. Rate-limiting membranes were prepared by mixing simple cation-exchange resin into silicone rubber matrices. Transport of the drug cations was evaluated at 37 °C as a function of drug size and external salt concentration by using diffusion cells, a constant current source, a digital multimeter, and Ag/AgCl electrodes. Release of the antiarrhythmic agents *d*-sotalol and lidocaine through the above membranes was modulated over 2.5- and 6-fold ranges as a function of input current at doses and response times that were consistent with prior investigations of therapeutic epicardial drug delivery in dogs. The application of a negative current (opposing the movement of drug) reduced the delivery rate of PPA relative to the zero-current rate, and a 13-fold range of release rates was observed for this species over the entire current interval (−20 to +80 μA). The reduced drug conductance (γ_D), a measure of the relative membrane permeability for the drug to Na^+, was found to decrease with increasing molecular mass with a particularly sharp decline between (±)-acebutolol (MM = 327 amu, and $\gamma_{ABL} = 0.011 \pm 0.002$) and (±)-verapamil (MM = 456 amu, and $\gamma_{VPL} = 0.0006 \pm 0.0002$). Increasing external salt concentration from 0.01 M NaCl to Sörensen buffer pH 7.3, increased membrane conductance ($\kappa_{Na^+} = 1.04 \pm 0.08$ to 12 ± 1 kΩ^{-1}) but only marginally reduced membrane water content and membrane permselectivity for Na^+. The release of lidocaine was controlled at clinically relevant doses (0.8 to 5.0 mg/h) and response times (~30–60 min) under rigorous conditions (0.15 M LDN hydrochloride into Sörensen buffer, pH 7.3). Hence, iontophoresis through these membranes may be a valuable approach for the development of clinically useful modulated epicardial release implants.

Introduction

The clinical benefits of controlling drug delivery from polymer implants for extended periods (months to years) are now being realized.[1-4] Various techniques to expand this simple concept by modulating the release rate following administration have also been reported.[5-8] Controlling the movement of drugs (usually ions) by externally modulating the electrical driving force across the rate-limiting medium of the transported drug (iontophoretic drug delivery) is one such method, which has been investigated recently in our laboratory.[9] In this previous study, a model bi-ionic system comprising the transport of (±)-phenylpropanolamine (PPA) and Na^+ through heterogeneous cation-exchange membranes (HCMs) was evaluated as a function of the degree of cross-linkage of the cation-exchanger beads. In addition, a simple transport model was developed to predict the steady-state drug delivery rate and other transport phenomena as a function of current and observed electrical resistances of the membrane. Since we are interested in local controlled release for prevention and conversion of cardiac arrhythmias,[10] we have let this model serve as our guide for the design of membranes for the control of delivery of antiarrhythmic drugs.

The goal of drug release from an iontophoretic implant for a specific application dictates requirements such as therapeutic release rates and response times. Furthermore, the concentration of salt in extracellular fluid (or any other body fluid), which would be in contact with any implant, is significantly greater than the salt concentration that was used in the previous model bi-ionic system (0.01 M),[9] and most antiarrhythmic cations are somewhat larger in molecular mass than our previous model compound, PPA. For the present study, we have chosen for iontophoretic transport a series of antiarrhythmic compounds of a broad range of molecular mass and therapeutic potential.[11]

The present study sought to address the following: (1) modulation of the release of antiarrhythmic cations by iontophoresis at therapeutically relevant doses, which have been established previously in dogs,[1,2] (2) evaluation of the conductance of the HCMs in the presence of Na^+ and a series of antiarrhythmic agents of increasing molecular size, (3) examination of the effects of external salt concentration on the permselectivity and rate-limiting properties of the membranes, and (4) optimization of the range and response of release rates by utilizing negative currents and simple current schedules.

Experimental Section

Materials. Unless otherwise stated, all chemicals were used as received. NaCl, (±)-phenylpropanolamine hydrochloride (PPA), (±)-acebutolol hydrochloride (ABL), and (±)-verapamil hydrochloride (VPL) were obtained from Sigma (St. Louis, MO). Lidocaine hydrochloride (LDN) was generously provided by Abbott Laboratories (Chicago, IL) and *d*-sotalol hydrochloride (STL) was donated by Bristol Meyers Squibb (Wallingford, CT). All aqueous solutions were prepared with distilled and deionized water (>16 MΩ cm, Millipore Co., Bedford, MA). For membrane preparation, Silastic Q7-4840 and Q7-4865 medical grade silicone rubbers were generously supplied by Dow Corning (Midland, MI), and Dowex 50W cation-exchange resin (2X, H^+ form, 200–400 mesh) was obtained from Sigma. Silver wire (0.405-mm diameter, 99.9% purity) and hydrochloric acid (Mallinckrodt, Paris, KY) were required for making Ag/AgCl electrodes. For preparation of salt bridges, agar (purified grade) and KCl were purchased from Fisher Scientific (Fairlawn, NJ) and Mallinckrodt. High performance liquid chromatography (HPLC) grade methanol and acetonitrile (Mallinckrodt), glacial acetic acid

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(Baker Chemical, Phillipsburg, NJ), 1-heptanesulfonic acid (Sigma or Aldrich, Milwaukee, WI), and sodium phosphate (monobasic, Sigma) were used for HPLC. For the STL assay, procainamide hydrochloride (Sigma) was used as an internal standard.

Potentiometry and iontophoresis were performed in side-by-side diffusion cells (3.4 mL/half-cell), Crown Glass Co. (Somerville, NJ). The temperature of the cells was maintained at 37 ± 1 °C by a Lauda thermostat (type K2-D), Messgerate-Werk Lauda, Inc. (Postfache, Germany). Current was supplied by a 10-channel galvanostat (current range: 0.67 to >1000 μA, 35-V maximum), which was built by the Chemistry Electronics Shop at the University of Michigan. The current source supplied the desired current (1–800 μA) to within ±5%. Membrane potential was monitored with a digital multimeter, Fluke Mfg. Co. (Everett, WA) Model 8062A. For anodization of silver wire, platinum foil was required as a nonerodible electrode material and a power source (Bio Rad Laboratories, Model 500, Melville, NJ) supplied the current. The resin beads were lyophilized with a Virtis Freezemobile (1SL, Gardiner, NY), and membrane thickness was measured with a caliper (Mitutoyo, No. 193-11, Japan).

For analysis of PPA and LDN, the HPLC system consisted of a Waters pump (Model M6000A) and WISP autoinjector (Model 712) (Millipore Corp., Milford, MA), a 15-cm μ Bondapak C_{18} column (Waters), a Kratos variable UV detector (No. 783, Ramsey, NJ), and a Hewlett-Packard 3390A integrator (Avondale, PA). For the separation of STL, a Waters HPLC system was used and contained a pump (Model 501), a WISP autoinjector (Model 712), a 30-cm μ Bondapak C_{18} column, a scanning fluorescence detector (Model 470), and a Data Module 740 recorder.

Methods. Dowex 50W cation-exchange resin (2% cross-linkage, H^+ form) was conditioned and converted to the Na^+ form, as described previously.[9] The resin was freeze dried over night and sieved to either 53–74- or 74–89-μm particle size distributions. For iontophoretic delivery of PPA, the above resin (53–74 μm) was levigated (42% w/w) into silicone rubber (Silastic Q7-4840) and compression molded[9] into films (350 ± 10 μm thickness). For the remainder of the investigations, resin (74–89 μm) was mixed, 52% by weight, with high durometer silicone rubber (Silastic Q7-4865) to form films (550 ± 50 μm). The high resin content (52%) and high durometer silicone (Q7-4865) were chosen in an attempt to maximize the cation permselectivity of the membrane and to reduce membrane aging, which has been observed previously in the presence of dilute salt solutions.[12] For measurement of equilibrium membrane water content, disks were cut from the films (0.40 cm^2) and placed in either 0.01 M NaCl or Sörensen buffer, pH 7.3[13] (0.195 M in Na^+), for 2 days at 37 °C. The fractional water content was deduced from dry and wet disk weights.

For transport studies, disks of the same size (0.40 cm^2) were cut from both types of resin–rubber suspensions and partially covered (0.27/0.40 of each surface) with Teflon Overlay, Cole Parmer (Chicago, IL). The exposed surfaces (disk edges) were covalently bound to Silastic Q7-4840 as previously described.[9] The resulting membranes contained a pure silicone rubber surface to make contact with diffusion cells and a rubber–resin surface (0.27-cm^2 dry surface area) to make contact with solutions. Before use, the membranes were swollen in either 0.01 M NaCl or Sörensen buffer, pH 7.3, for 2 days (37 °C) and current conditioned for 12 h in the presence of the same medium at 40 μA to help remove salts deposited during silicone rubber vulcanization. Ag/AgCl electrodes for current passage and Ag/AgCl reference electrodes were prepared by anodization of silver wire.[9]

After current conditioning, the membrane potential in the presence of Na^+ was measured at either 0, ±20, ±40, ±60, and ±80 μA (for NaCl) or 0, ±200, ±400, ±600, and ±800 μA (for Sörensen buffer, pH 7.3). HCM Na^+ conductance (κ_{Na^+}) was determined from least squares regression of current versus membrane potential data ($r^2 > 0.99$). For measurement of reduced drug conductance (γ_D), the HCMs were converted into the drug form by placing either the 0.01 or 0.15 M hydrochloride salts in cells and initiating a current (40 μA for 0.01 M and 400 μA for 0.15 M salt) with frequent reservoir replacement until the membrane potential had stabilized for some time. The membrane potential was measured with varied current in the same manner as with Na^+, and γ_D was determined from the ratio of drug conductance (κ_D) to κ_{Na^+}. The reduced drug conductance was determined for PPA and four antiarrhythmics (LDN, STL, ABL, and VPL). All compounds were completely soluble at 0.15 M, although verapamil hydrochloride had to be warmed for complete dissolution. Furthermore, the permeability of the membranes was so low in the presence of VPL that the membrane potential was monitored at 0, ±1, ±3, ±5, and ±10 μA for the 0.15 M salt and the conductance for the 0.01 M salt could only be estimated (0, ±1 μA) since nonlinear and asymmetric membrane potential response was observed in this case.

Potentiometric evaluation of the permselectivity for cations was carried out following preswelling in either 0.01 M NaCl or Sörensen buffer. The membrane potential was measured as a function of Na^+ activity in one half-cell for a concentration range 0.003–0.3 M NaCl with preswelling solutions used as reference. This procedure is described elsewhere.[9]

Iontophoretic delivery of PPA and STL hydrochloride was carried out from the 0.01 M hydrochloride salts into 0.01 M NaCl at 37 °C. The experimental configuration was similar to those reported by Burnette[14] and Srinivasan.[15] It consisted of diffusion cells, a constant-current source, a voltmeter, and four electrodes as previously described.[9] In all release studies the membranes were converted to the drug form prior to the experiment since the time to steady-state release rate has been shown to be brief in this instance (relative to the Na^+ form).[16] The time scale and currents were chosen on the basis of the drug and membrane properties. At each time point, the receiver solutions (containing the cathode for positive current) were sampled and both half-cells were emptied, rinsed with distilled water, and refilled with the appropriate solution as the experiment continued. The sampling time was ~1 min/diffusion cell pair (n = 3). The membrane potential was monitored directly following sampling since the Cl^- activity was the same in both the donor and receiver solutions at this time (and the electrode potentials virtually canceled).

LDN was delivered during iontophoresis from 0.15 M LDN hydrochloride into Sörensen buffer, pH 7.3, at 37 °C. This buffer solution was chosen because of its equivalent pH and osmotic pressure with blood and its strong buffer capacity, and since Na^+ is the only concentrated cation in solution. Replacement sampling (as described above) was performed, although the donor solution was allowed to remain for the duration of the experiment to be more consistent with an actual iontophoretic device.

PPA, LDN, and STL were assayed by HPLC and conditions for PPA analysis were as previously described.[9] LDN was detected at 260 nm from a mobile phase consisting of 20% (v/v) acetonitrile and 80% 0.1 M sodium phosphate buffer (monobasic adjusted to pH 3 with HCl) at 2 mL/min. The fluorescence detector for the STL assay was set to 235-nm (excitation) and 325-nm (emission) wavelengths. The flow rate was 1.5 mL/min, and the mobile phase consisted of 35% (v/v) methanol, 64% water, 1% glacial acetic acid, and 0.005 M heptanesulfonic acid as an ion pairing agent. Dilutions of STL were prepared with procainamide hydrochloride as an internal standard.

Data Analysis. By integration of the steady-state Nernst–Planck equations with the charge neutrality constraint, a transport model was developed previously to predict iontophoretic delivery of a cationic drug into a Na^+-containing release medium (i.e., PPA hydrochloride into NaCl).[9] The reduced drug flux (j_D^*) at steady state was shown to be related to the reduced constant current (I^*) by the parameter s (reduced electric field, defined below), as follows:

$$I^*(s) = s(\gamma_D e^s - 1)/(e^s - 1) \quad (1)$$

$$j_D^*(s) = \gamma_D s e^s/(e^s - 1) \quad (2)$$

where the reduced variables, j_D^*, I^*, and γ_D (reduced drug conductance), are related to their dimensional components (I, j_D, and κ_D, respectively) by

$$I^* \equiv I/(\kappa_{Na} RT/F) \quad (3)$$

$$j_D^* \equiv (j_D A)/(\kappa_{Na} RT/F^2) \quad (4)$$

$$\gamma_D \equiv \kappa_D/\kappa_{Na^+} \quad (5)$$

Here, A and κ_{Na^+} are the membrane surface area and conductance in the presence of Na^+, respectively; R, T, and F are the gas constant, absolute temperature, and Faraday's constant.

In order to predict the drug release rate from constant current at steady state, I^* was calculated from I, κ_{Na^+} (mean of observed values), and (3), s was determined from measured γ_D and (1) by using a root-finding method, j_D^* was determined from the resulting s and (2), and then $j_D A$ (release rate) was deduced from (4).

The reduced drug concentration in the membrane (c_D^*) may be related to s and reduced position coordinate (ξ) by

$$c_D^*(s,\xi) = (e^s - e^{s\xi})/(e^s - 1) \quad (6)$$

where c_D^* and ξ are defined in terms of the dimensional equivalents (c_D and x) by division by the membrane fixed charge concentration (X) and membrane thickness (L), respectively, as follows:

$$c_D^* \equiv c_D/X \quad (7)$$

$$\xi \equiv x/L \quad (8)$$

Values of $c_D^*(s,\xi)$ were predicted from s, which was calculated in the same manner as above (for prediction of j_D) over the entire membrane cross-section ($0 \le \xi \le 1$).

The reduced membrane potential (η_m) is the sum of s ($\equiv -d\eta/d\xi$) and the reduced boundary potential (η_b):

$$\eta_m(s) = s + \eta_b \quad (9)$$

where η_b, the difference of the two interfacial Donnan potentials, is related to the drug–Na^+ selectivity coefficient (assumed constant independent of s) and η is the reduced electric potential in the membrane. The reduced membrane potential η_m is related to its dimensional component (ϕ_m) by

$$\eta_m \equiv \phi_m/(RT/F) \quad (10)$$

In the presence of dilute salt solution, membrane conductance has been observed to be nonlinear,[9] although it has been found that the reduced drug conductance can be approximated by the empirical relationship:

$$\gamma_D(s) = \begin{cases} A \sinh^{-1}(s/B)/s & \text{for } s > 0 \\ A/B & \text{for } s \le 0 \end{cases} \quad (11)$$

where A and B are empirical parameters, which were determined elsewhere for HCMs with 2% resin cross-linkage.[9]

For determination of ϕ_m, s was produced by inserting the nonlinear expression for $\gamma_D(s)$, (11), into (1) and carrying out the root-finding procedure from the resulting expression and input I^*. The steady-state membrane potential, ϕ_m, was evaluated from s, (9), (10), and the previously determined value for η_b (for HCMs with 2% cross-linkage).[9]

Results

Iontophoretic Delivery of PPA. Over a 48-h interval, the release rate of phenylpropanolamine (PPA) was modulated over a 5-fold range for two on/off cycles at 37 °C (Figure 1). Prior to the experiment, the 42% (w/w) resin-loaded HCMs were preswollen in the release medium for 48 h and then coverted into the PPA form. The initial release rate of PPA at 40-μA constant current (0.27-cm^2 dry membrane surface area) from 0.01 M PPA hydrochloride into 0.01 M NaCl decreased over the first few hours to its steady-state value (1.39 μmol/h, transference number of PPA (t_{PPA}) = 0.93), which was slightly lower than the predicted value of 1.49 μmol/h. At 6 h, the current was shut off and the release rate declined to a new steady-state rate just above the predicted values based on HCM mean Na^+ conductance (κ_{Na^+}) and reduced PPA conductance data (γ_{PPA})[17] reported previously.[9] Once again, the current was adjusted to 40 μA at the 24-h point and the rate of accumulation of PPA in the receiver reservoir slowly approached the steady-state rate which it had attained during the previous 6-h on phase. Finally, at 30 h, the current was shut off a second time and the PPA release rate responded in the same manner as the first 18-h off phase.

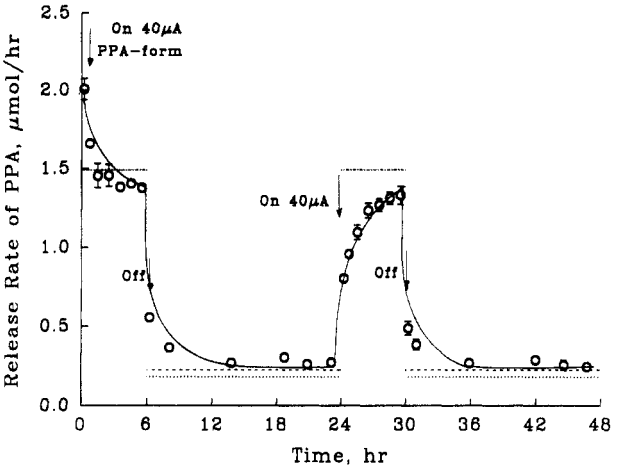

Figure 1. Modulation of delivery of PPA with iontophoresis for two on/off cycles. PPA was delivered from 0.01 M PPA hydrochloride into 0.01 M NaCl between 40 and 0 μA at 37 °C. Data represent the mean (n = 3) ± sem, [– – –] represents the theoretical release rate ($j_{PPA}A$) for γ_{PPA} = 0.43, and [– – –] represents the same for γ_{PPA} = 0.30. The mean κ_{Na^+} was 0.44 $k\Omega^{-1}$, and error bars were not shown when smaller than the symbols.

The release of PPA into NaCl was slowed to 0.19 μmol/h when the direction of the current was reversed (opposing the movement of the drug), resulting in controlled release over a 13-fold range. In Figure 2, the release of PPA was carried out over 12 h for two on/off cycles. The concentration of reservoirs and the membrane type were the same as in Figure 1. The initial release from HCMs (originally in PPA form) at 40 μA (Figure 2A) declined over 3 h, and the current was turned off. At 6 h, the current was set to 80 μA and the release rate approached a higher steady-state value than during the first on phase. At 9 h, the current was reversed to –20 μA, which decreased the rate of PPA delivery to a greater extent than during the zero-current phase.

The corresponding observed membrane potential during iontophoretic delivery of PPA (Figure 2B) responded faster than the release rate (Figure 2A) to the input current. As expected, the membrane potential was found to increase nonlinearly as the current was increased from 0 to 80 μA, as reported previously.[9] The predicted steady-state membrane potential values, which were determined as described in the Data Analysis from reduced boundary potential (η_b) and empirical parameters obtained previously,[9] are also plotted in the figure and were in fair agreement with the experimental values.

As expected, the composition of PPA in the membrane was predicted to increase with increasing constant current (Figure 3). The theoretical reduced concentration of PPA in the membrane, c_{PPA}^* (concentration of PPA normalized for membrane fixed charge concentration), is plotted in the figure as a function of reduced position, ξ (position normalized for membrane thickness), and input current. The fraction of fixed charge sites in the cation exchanger that is neutralized by PPA cations at steady-state (Γ_{PPA}^{SS}) is equivalent to the area under each curve at the input current. Likewise, this area subtracted from 1 corresponds to the fraction of sites neutralized by Na^+. Therefore, when the HCMs were converted into PPA form prior to the beginning of the experiments described in Figures 1 and 2, theory suggests that $c_{PPA}^* = 1$ for all ξ and the membrane composition of PPA must decrease for any

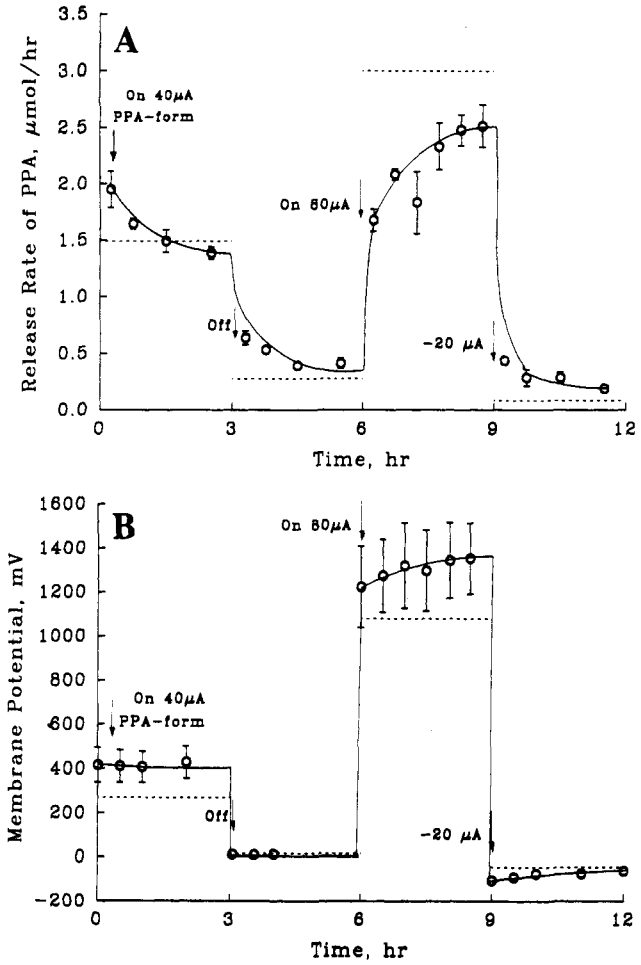

Figure 2. Illustration of halting the release rate when the current is reversed (opposing movement of the drug) during two different on/off cycles of iontophoretic delivery. The PPA flux (A) and membrane potential (B) are plotted versus time during the release of 0.01 M PPA hydrochloride into 0.01 M NaCl. Symbols represent the mean (n = 3) ± sem, and [- - -] represents the predicted steady-state values based reduced boundary potential (η_b = −0.23), empirical parameters (A = 2.6, B = 6.0), and γ_{PPA} = 0.43 determined previously.[9] The mean κ_{Na^+} was 0.35 kΩ^{-1}, and error bars were not shown when smaller than the symbols.

initial current upon exposure to the Na^+-containing receiver solution. Another interesting case is at zero current, where the fractional composition of PPA in the membranes was predicted to be greater than 0.5 due to the smaller diffusion coefficient of PPA relative to Na^+. The predicted c_{PPA}* values were calculated as described in the Data Analysis from the same parameters (γ_{PPA}, κ_{Na^+}) that were used for prediction of PPA release rate in Figure 2.

Reduced Membrane Conductance in the Presence of Therapeutic Cations. Cations of a broad range of molecular size and therapeutic potential were evaluated. In Figure 4, the structures and molecular masses of four different classes[11] of antiarrhythmic drugs are displayed with the model compound, PPA. There was 100–300-fold variation in reduced drug conductance over the entire range of drugs studied (PPA (154 amu) to VPL (456 amu)), as shown in Figure 5. After preswelling the HCMs for 2 days in either 0.01 M NaCl or Sörensen buffer, pH 7.3, the conductance of the HCMs was measured in the presence of dilute and concentrated chloride salts of Na^+, PPA, LDN, STL, ABL, and VPL. The reduced drug conductance ($\gamma_D \equiv \kappa_D/\kappa_{Na^+}$) declined sharply as molecular mass was increased, except for LDN and STL, where the trend

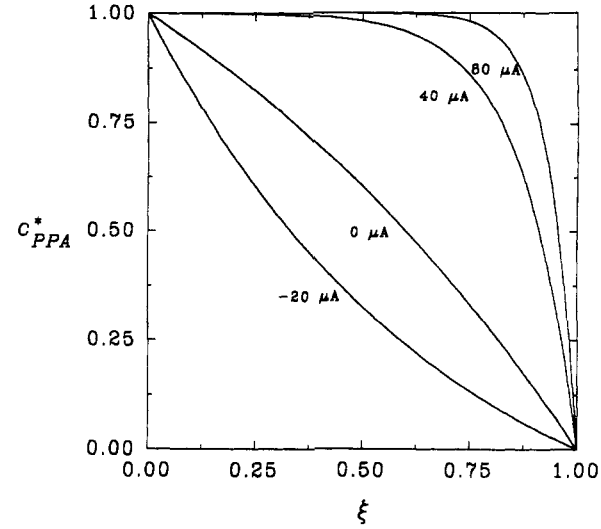

Figure 3. Reduced concentration profile of PPA at steady state as a function of input current for the membrane type in Figure 2. The predicted reduced concentration of PPA in the membrane, c_{PPA}* (normalized for fixed charge concentration), is plotted against the reduced position coordinate, ξ (normalized for membrane thickness), as described in the *Data Analysis*. γ_{PPA} (0.43) was determined as previously,[9] and the mean κ_{Na^+} was 0.35 kΩ^{-1}. The area under each curve corresponds to the expected fractional PPA content in the membrane at steady state (Γ_{PPA}^{ss}).

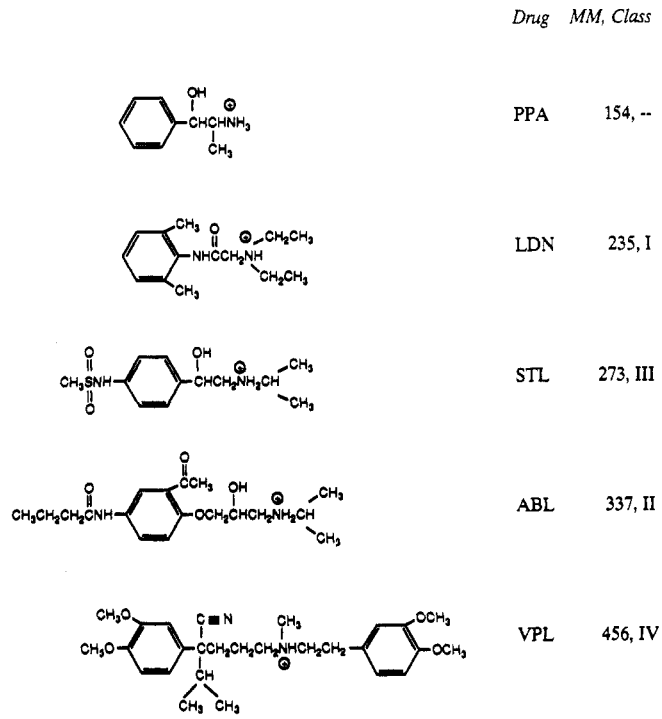

Figure 4. Structures and molecular masses of cationic drugs transported by iontophoresis. A model compound, (±)-phenylpropanolamine (PPA), and four different classes of antiarrhythmic agents are shown in order of increasing molecular mass. Lidocaine (LDN), the smallest antiarrhythmic is class I by the Vaughan Williams convention,[11] followed by sotalol (STL, class III for *d* isomer), (±)-acebutolol (ABL, class II), and (±)-verapamil (VPL, class IV).

was reversed, suggesting that other factors are playing a significant role in the transport of these compounds.

External Salt Concentration. The HCM Na^+ conductance increased more than 1 order of magnitude as the concentration of salt was increased from 0.01 M NaCl to Sörensen buffer, pH 7.3 (Figure 6A). The water content was also found to decrease with increasing external salt concentration, which is the normal trend for cation

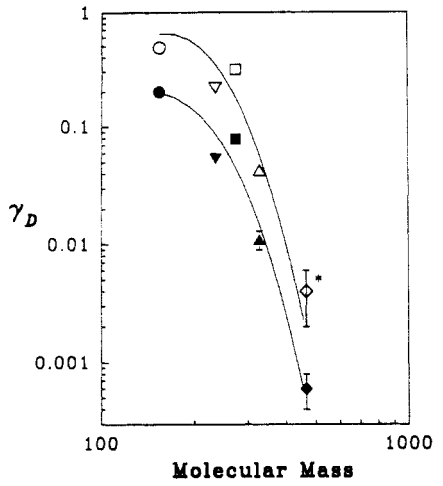

Figure 5. Dependence of reduced drug conductance on molecular size. The reduced conductance of the membrane (log scale) in the presence of 0.01 M (open symbols) and 0.15 M hydrochloride salts (closed symbols) of PPA (○, ●), LDN (▽, ▼), STL (□, ■), ABL (△, ▲), and VPL (◇, ◆) are plotted against the molecular mass (log scale). The reference conductances were measured in the presence of 0.01 M NaCl and Sörensen buffer, pH 7.3, preswelling solutions. Symbols represent the mean (n = 3) ± sem, error bars are not shown when smaller than the symbols, and lines are drawn through the data points. *The value for VPL in the presence of the 0.01 M hydrochloride salt could only be estimated.

exchangers.[18] The reduced conductance ratio ($\gamma_D^{0.15M}/\gamma_D^{0.01M}$) was the same value for LDN, STL, and ABL (Figure 6B). The ratio was determined from the values in Figure 5 and was found to be somewhat greater for PPA (0.41) than for the lower molecular mass antiarrhythmic drugs (~0.25). The estimated value for VPL was even lower (0.14) further separating its transport behavior from the other antiarrhythmics.

Potentiometric Evaluation of HCM Permselectivity to Na^+. The zero-current membrane potential responded to the logarithm of Na^+ activity with a transference number of Na^+ greater than 0.93 following preswelling of the membranes in 0.01 M NaCl or Sörensen buffer, pH 7.3 (in Figure 7). Ideal Donnan equilibrium would be indicated by a slope of 61.5 mV/decade at 37 °C, according to the Nernst equation.[19] Slopes of 60 ± 1 (t_{Na^+} = 0.99) and 52.8 ± 0.2 mV/decade (t_{Na^+} = 0.93) were recorded for the HCMs in the presence of 0.01 M NaCl and Sörensen buffer, respectively. The lower transference number of Na^+ as the external salt concentration was increased is consistent with increased Cl^- sorption in the cation-exchanger beads as the Donnan potential is reduced.[20]

Iontophoretic Delivery of Antiarrhythmic Drugs. The released *d*-sotalol (STL) was modulated sharply between ~1000 and 400 μg/h for two on/off cycles. In Figure 8, the release rate of STL during iontophoretic delivery from 0.01 M STL hydrochloride into 0.01 M NaCl is plotted as a function of time for a 4-h period. The 45-min on (120 μA) and off (0 μA) phases were preceded by 15-min phases that were designed to remove the kind of lag effects that were observed in Figures 1 and 2. When a burst of the drug was expected at 0-, 1-, and 3-h periods, lower current setpoints (+90, −120, and −120 μA) than the on or off phase currents (120, 0, and 0 μA) were initiated. Similarly, when a lag was anticipated at the 2-h point, a higher input current (240 μA) than the on phase current (120 μA) was applied. The apparent transference number of STL, t_{STL}, at 120 μA was ~0.72, indicating a reduced charge carrying ability of the larger STL relative to PPA, as depicted in Figures 1 and 2. In addition, the steady-

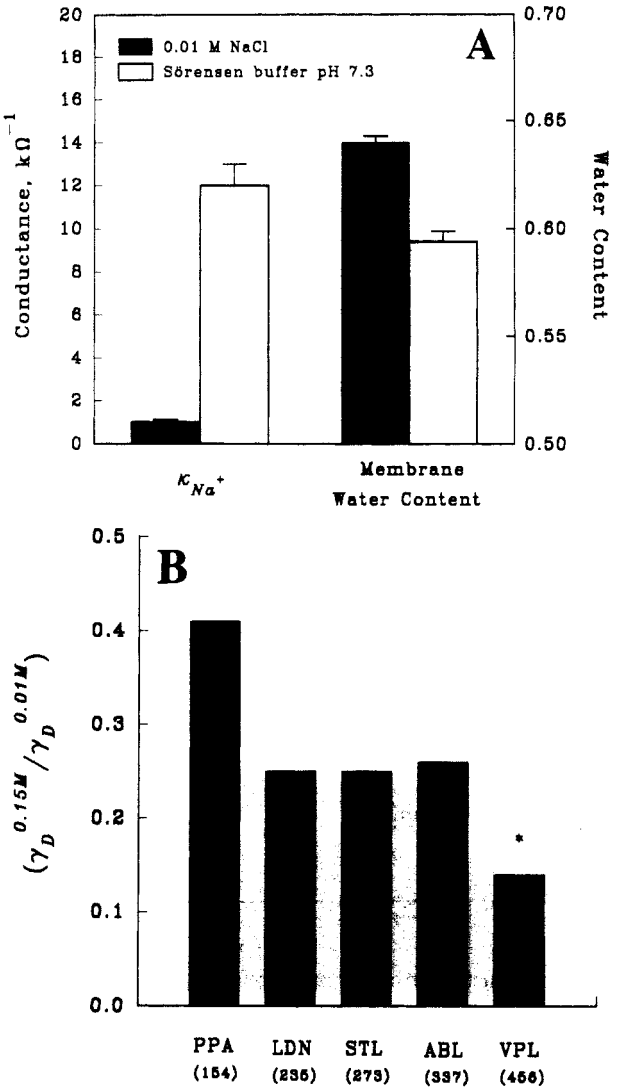

Figure 6. Effect of external salt concentration on HCM sodium conductance and water content (A) and reduced drug conductance ratio (B). The membrane sodium conductance and water content were measured in the presence of 0.01 M NaCl and Sörensen buffer, pH 7.3, preswelling (or release vehicle) solutions. The reduced drug conductance is taken from the mean values plotted in Figure 5. *The value for VPL could only be estimated.

state STL release rate at zero current was much higher than expected by the model (described by the horizontal solid lines), further contributing to reduced iontophoretic enhancement of drug release. However, the steady-state membrane potential during the on phase was 330 ± 4 mV (data not shown), suggesting that a much higher delivery rate could have been obtained if a higher constant current had been applied. The HCMs for the delivery of the antiarrhythmic drugs were loaded with 52% (w/w) resin in high durometer silicone rubber (Silastic Q7-4865).

Lidocaine (LDN) was released between 0.8 and 5 mg/h from a 0.15 M LDN hydrochloride solution into Sörensen buffer, pH 7.3, for two on/off cycles. The current schedule was chosen, as in Figure 8, to reduce the lag effects associated with drug content changes in the membrane. During the release experiment, the donor solution was not replaced and the receiver solution was sampled and replaced at each time point. LDN was released during the 600- and 200-μA on phases with corresponding apparent LDN transference numbers of ~0.80 and 0.76, respectively, indicating an apparent decrease in efficiency of LDN transference with time. Release rates during the off phases were much higher than the model predicted,

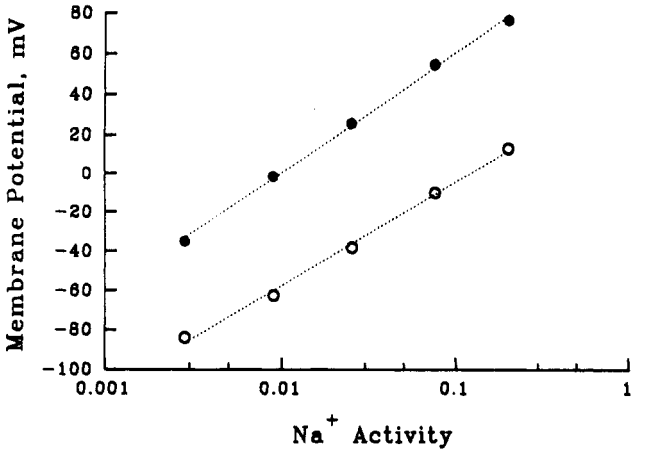

Figure 7. Evidence supporting membrane integrity. The membrane potential is plotted versus log Na^+ activity for 0.01 M NaCl (●) and Sörensen buffer, pH 7.3 (○), reference solutions. A slope of 61.5 mV/decade log counterion activity corresponds to negligible transference of Cl^- in the membrane. Slopes of 60 ± 1 and 52.8 ± 0.2 mV/decade were observed in the presence of dilute and concentrated reference solutions, respectively. HCMs had 0.52 fractional resin content. Symbols represent the mean (n = 3), and standard error bars were smaller than the symbols.

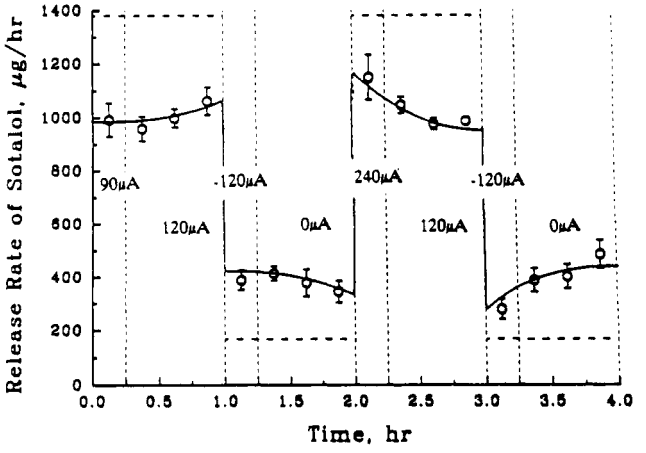

Figure 8. Illustration of the reduction in the burst and lag effects by utilizing simple current schedules. Modulation of the release of *d*-sotalol (STL) for two on/off cycles from 0.01 M STL hydrochloride into 0.01 M NaCl was carried out through HCMs originally in the STL form at 37 °C. The current schedule was designed to reduce the burst and lag effects which accompany drug content transients in the membrane. Symbols represent the mean (n = 3) ± sem, and [– – –] (horizontal) represents the predicted steady-state values (for 120 and 0 μA) based on the mean of the measured parameters (κ_{Na^+} = 1.0 $k\Omega^{-1}$, γ_{STL} = 0.31). Error bars are not shown when smaller than the symbols.

although as with the 200-μA on phase, it was unclear whether the system had fully attained a steady state in these instances. Following the 4-h release of LDN, the donor reservoir was sampled and contained ~95% of its original LDN concentration (0.15 M). The release of VPL and ABL was not measured due to the size exclusion of VPL (Figure 5) and to the fact that the class II antiarrhythmics (similar to ABL) have been shown previously to be ineffective in converting ventricular tachycardia in dogs by epicardial administration.[21]

Discussion

Modulating Drug Release by Iontophoresis. The ranges of delivery rates observed during release of LDN (0.8–5.0 mg/h) and STL (0.4–1 mg/h) through HCMs (0.27-cm^2 dry area) are consistent with previously reported therapeutic doses by epicardial administration to dogs (0.52 (mg/kg)/4 h or ~1.8 mg/h for LDN[1] and 1.2 (mg/kg)/2 h or ~8 mg/h for STL[2]) and with an implant fabricated with reasonable surface area (0.25–4 cm^2). Furthermore, the response times (time to steady-state flux) following changes in input current were generally from 15 to 60 min, which is most desirable from a clinical standpoint. In addition, during LDN delivery the HCMs separated (virtually) isotonic solutions of high ionic strength and yet the transport was reproducible and consistent with results previously reported for PPA through HCMs with 8% resin cross-linkage (smaller pore size) under very different experimental conditions (Table I).[9] In the table, the observed to predicted flux (j_D^{exp}/j_D^{theo}) during on (200–600 μA) and off (0 μA) phases of LDN release was extremely close to those previously reported during on (4–8 μA) and off phases of PPA release (for virtually identical γ_D and I^*). For the above reasons, we are currently assembling iontophoretic implants incorporating these types of membranes to be evaluated for epicardial administration in dogs.

The release of PPA through membranes with 2% resin cross-linkage (Figures 1 and 2) is indicative of nearly ideal behavior where the transference number of the drug is generally >0.9 (9 mol of drug transferred across the membrane for every 10 total mol of charge transferred) and the zero-current flux at steady-state (Figure 1 only) is close to the predicted values (10–40% error depending on the method[17] of determining γ_{PPA}). The small PPA molecule (MM = 154) would appear to be easily accommodated by the pores in the resin beads. LDN and STL on the other hand only transferred 70–80% of the charge and displayed much higher than predicted zero-current flux. The latter phenomenon for LDN was characteristic of constrained transport observed previously[9] (Table I). However, the mean reduced membrane conductance to STL transport under conditions during its release (0.01 M, Figure 8) was 0.31 (Figure 5), which was close to that for PPA (γ_D = 0.49). This apparent discrepancy is difficult to evaluate without more experience with this membrane type (i.e., HCMs prepared with high durometer silicone rubber). The (apparent) decrease in efficiency of LDN release during the second on phase (t_{LDN} ~ 0.76) following the first on phase (t_{LDN} ~ 0.80) brings up the potential difficulty following transport of Na^+ into the donor reservoir (the LDN reservoir was not changed during the experiment). Since the transference number of Na^+ would be much higher than LDN, any small amount of Na^+ present in the donor solution (or donor side of the membrane) would reduce substantially the efficiency of LDN release. This suggests that ways of scavenging (or removing) the Na^+ in the donor reservoir may be an important consideration for the implementation of this technology.

Influence of Drug Size. Three of the four classes of antiarrhythmic agents (LDN, STL, and ABL) exhibited normal transport behavior during iontophoresis, implying a capability of this technique for releasing this set of therapeutic compounds. Furthermore, from the reduced conductance (γ_D) and membrane Na^+ conductance (κ_{Na^+}), a useful estimate of zero-current flux can be obtained (Figures 1, 2, 8, and 9 and Table I). The effect of increasing the molecular mass of the drug (Figure 5) would appear to be similar to decreasing the resin pore size (by increasing resin cross-linkage[9]). Aside from the secondary effect of the increased friction with increasing molecular size, two factors may be primarily responsible for the sharp decline in γ_D observed in Figure 5.

Exclusion of large organic cations from the aqueous pores in sulfonated polystyrene cation-exchanger beads has been

Table I
Constrained Transport and Deviations from Ideal Behavior

drug transported	HCM params		transference conditions (on)			zero current (off)
	γ_D	κ_{Na^+} ($k\Omega^{-1}$)	I^*	I (μA)	j_D^{exp}/j_D^{theo}	j_D^{exp}/j_D^{theo}
LDN	0.054[a,b]	12	0.62–1.9	200–600	0.76–0.80[c]	1.9
PPA (Schwendeman et al.[9])	0.030[d]	0.14	1.1–2.2	4–8	0.68–0.81	2.2

[a] HCM parameters represent the mean of measured values. [b] 0.15 M LDN released into Sörensen buffer, pH 7.3. HCM type is listed in the Methods. [c] Theoretical drug flux (j_D^{theo}) was determined as described in the Data Analysis. [d] 0.01 M PPA released into 0.01 M NaCl. HCMs were 42% fractional resin content and 8% resin cross-linkage.

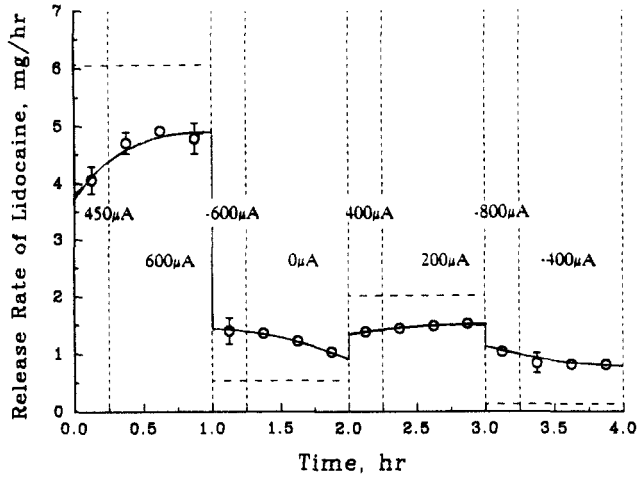

Figure 9. Modulation of the release of lidocaine (LDN) under rigorous conditions for two different on/off cycles. Iontophoretic delivery of lidocaine (LDN) from 0.15 M LDN hydrochloride into Sörensen buffer, pH 7.3, was carried out through HCMs originally in the LDN form at 37 °C. The current schedule was designed to reduce the burst and lag effects which accompany drug content transients in the membrane. Symbols represent the mean (n = 3) ± sem, and [- - -] (horizontal) represents the predicted steady-state values (for 600, 0, 200, and −400 μA) based on the mean of the measured parameters (κ_{Na^+} = 12 $k\Omega^{-1}$, γ_{LDN} = 0.054). Error bars are not shown when smaller than the symbols.

reported to increase with increased molecular size or decrease with increased resin cross-linkage.[22] Exclusion from a small population of pores would severely restrict transference across the membrane by blocking channels for transport. Another factor is the decrease in free-water content (nonhydrated water) in the exchanger, which is expected to occur when the membrane is converted from the Na^+ to drug form[18] (in some cases a decrease in membrane volume was visible). A water decrease could cause a large decrease in diffusion coefficient of the drug as the resin pore size is reduced. Both of these factors would invalidate the assumption of independence of the counterion form used in deriving the transport model,[9] which may explain the deviations of the observed from predicted flux in Figures 8 and 9. The decrease in free-water content would also explain the consistently high estimates under zero-current conditions (Table I). The membrane water content during counterdiffusion of the cationic drug and Na^+ must lie somewhere between the water contents existing in either the Na^+ or drug form and thereby increase the drug diffusion coefficient (the effect of Na^+ is not so predictable)[9] over that during the reduced drug conductance measurement. This argument suggests that by incorporation of a small extraneous counterion into the donor reservoir (e.g., Na^+), the drug transference number would decrease but the drug diffusion coefficient should increase (because of the increase of water in the membrane), resulting in increased drug flux per unit energy exhausted by the system. In addition, we are presently evaluating a resin with 1% cross-linkage to increase the pore size and water content relative to the membranes in this study. With a resin of reduced cross-linkage, it may be possible to extend the use of these membranes for larger drugs (like VPL) by making the sharp decline in γ_D (Figure 5) more modest. However, there is a point where the increase in pore size may decrease cation permselectivity since the Donnan exclusion is reduced with decreased fixed charge concentration.

The higher observed γ_D in the presence of LDN than STL (~47%) was unexpected, since LDN has a lower molecular mass (235 amu) than STL (273 amu). Since there are three side chains on the benzene ring of LDN, the two methyl groups may cause an increased steric hindrance relative to STL, which has only two side chains on its benzene ring. Another potential cause for this reversal may be related to differing free-water contents in the exchanger between the STL and LDN forms. Upon conversion of the resin to a more polar counterion form (e.g., from the LDN to STL form), the entropy of water in the exchanger is expected to increase, which in turn may cause an increase in resin water content (and likewise an increase in counterion diffusion coefficient).

Effects of External Salt Concentration. Although some of the effects of concentration are complex, the transport of LDN in the presence of concentrated media was quite comparable to previous work with PPA in dilute solutions (Table I). This shows the advantage of preparing cation-exchange membranes over membranes which contain no fixed charge groups. Since the distribution of cations into the HCMs is almost indifferent to external concentration (between 0.003 and 0.3 M), as in Figure 7, the behavior depicted in Table I was strikingly comparable. In addition, the high zero-current permselectivity of the HCMs to Na^+ suggests that the membranes are intact and have no appreciable defects.

The most important effect of increasing salt concentration was the increase in observed conductance of the membrane (Figure 6A). The fact that the increase was greater for Na^+ (12-fold)[23] than for the low molecular mass antiarrhythmics (3-fold) may have contributed to the slower response of LDN release to changes in current (Figure 9, see Optimization of Iontophoretic Response) as compared with STL release (Figure 8). When the external salt concentration is increased, some water leaves the membrane (Figure 6A) as the osmotic pressure difference is reduced. Likewise, as the Donnan potential is reduced (membrane is negative with respect to external solutions), more Cl^- can distribute into the membrane (Figure 7) and act as mobile charge sites.[24,25] The reduced water content not only increases the activity of the counterion in the membrane but reduces the site (fixed charge group) to site distance. Each of these effects may have added to the increased membrane permeability. Examination of the underlying causes of the difference between changes in Na^+ permeability with that found with the antiarrhythmics may establish individual contributions of each of the above factors.

The constant ratio of reduced conductance ($\gamma_D^{0.15M}/\gamma_D^{0.01M}$) for LDN, STL, and ABL shown in Figure 6B

suggests that external concentration affects the transport of these drugs in the same way. Thus, we would expect the results with STL and ABL in concentrated media to be similar to those observed with LDN (Figure 9). In addition, problems that we have encountered with membrane aging in the past[12] have thus far not been observed in the presence of concentrated salt solutions (0.15 M). Our hypothesis for the cause of the aging involves the presence of water movement due to electroosmosis,[25] which may be altering the silicone rubber/cation-exchange resin interface and is favored by decreased external ionic strength.[26]

Optimization of Iontophoretic Response. For an application where drug is required rapidly, it is desirable to reach a target delivery rate as quickly as possible. In previous studies,[9] up to 2 days were required to reach a steady state (even under transference conditions). In Figure 8, the response time to reach target STL delivery was ~15–30 min. The time for the drug content changes that are expected to take place (Figure 3) with changes of input current was reduced by simple current schedules, as in Figures 8 and 9. This strategy was more successful for STL delivery in dilute solution than for LDN in concentrated solutions, which is unexpected since the HCM permeability is increased in the latter instance. The small reduced conductance of LDN ($\gamma_{LDN} = 0.054$) may be a cause of the slow response, since the transference number of LDN in the membranes of mixed (Na^+/LDN) form would be expected to be low. In addition, since the electric field is absent for a short time during sampling (~1.5 min for the LDN experiment), it is conceivable that LDN could exchange with the Na^+ at sites present near the receiver surface side of the membrane, which would cause drug dumping upon replacement of the buffer solution.

The greater or smaller than steady-state release rate when the current is adjusted to a new setpoint, as in Figure 2, can be explained by the dependence of steady-state fractional PPA composition in the membrane (Γ_{PPA}^{SS}) with current (Figure 3). At the beginning of the release experiment, Γ_{PPA} is predicted to be 1 (all the sites are occupied by PPA). When the current is adjusted to 40 μA, the release rate is initially greater than at steady state, since some of the PPA released is due to Na^+–PPA exchange (and Γ_{PPA} becomes <1). When the current is turned off, Γ_{PPA} must decrease again so another burst of PPA is observed. Only when the current is set to 80 μA is a smaller than steady-state release rate initially observed, since more PPA must accumulate in the membrane.

The application of a negative current (current opposing movement of the drug) reduced the drug flux relative to the zero-current flux (Figures 2 and 9), although this effect was not substantial in the case of LDN. The less than predicted reduction in the negative-current LDN release could have been either due to dumping following sampling as discussed above or from artificially low observed reduced conductance values because of membrane water content differences between counterion forms.

Iontophoresis for Prevention and Conversion of Cardiac Arrhythmias. Recently, implantable defibrillator systems have become available to high-risk heart attack patients.[27] While this detection/response technology has been useful for extending life, much more could be done to help patients if the ventricular arrhythmias that often cause the heart attack, could be converted (or avoided) prior to the life-threatening event via a drug delivery implant. We have chosen iontophoresis as a modulated release strategy because of implant size and power requirement considerations.[9]

Controlled release of antiarrhythmics from drug-loaded polymer matrices has been effective in converting ventricular arrhythmias in many different artificially induced disease states.[1,2,28] Furthermore, by placing the drug delivery device on the epicardium of the heart, unusually low systemic blood levels have been observed relative to those following normal intravenous administration, thereby reducing the risk of toxicity often observed with these compounds. A major factor in selecting a modulated release implant over a drug-loaded matrix, which releases drug at a predetermined rate, is that antiarrhythmic agents may become proarrhythmic.[29] In these instances where the drug increases the incidence of arrhythmias, drug release should be able to be terminated, which could only be accomplished with an on/off system.

Avitall et al. have reported iontophoretic delivery of procainamide (class I antiarrhythmic) directly to the epicardium of dogs.[30] In this study, a pulsed current was passed through the heart of dogs between two defibrillator electrodes; the anode was converted into a drug reservoir by sealing the electrode with a dialysis membrane (40 nm). The authors found that ventricular tachycardia (a dangerous arrhythmia) was suppressed relative to the control following iontophoretic delivery of procainamide to an infarcted zone (dying or dead tissue), although normal physiological indicators (effective refractory period and diastolic threshold) were only marginally altered. Imposition of an electrolytic current across the tissue, similar to transdermal iontophoresis, brings up the important consideration of the rate-limiting medium for transport.

Ionic drugs do not easily diffuse across skin without current passage,[15] so the additional electrical driving force across the tissue (stratum corneum) is essential for transport. However, Levy et al.[2] have shown that the epicardium poses no such rate limit at therapeutic dosing rates (using lidocaine) from the equivalence of the release from drug-loaded matrices in buffer in vitro and the release to the epicardium in vivo. Therefore, at therapeutic release rates, the delivery device must limit the rate of release and it should not be necessary for the current to be passed across the cardiac tissue for the drug to reach the local blood circulation. In fact, our future investigations are focused on an iontophoretic system which releases the therapeutic cations in a controlled manner to a low-resistant gel, which will be attached directly to the epicardium. Finally, in the above study with procainamide, no in vitro or in vivo release studies were performed to suggest any kind of control over delivery rate with the iontophoretic system that was used. Other systems[31,32] have been suggested for iontophoretic controlled release such as release of propranolol through poly(ethylhydroxymethacrylate),[30] although the membranes in these studies provide no permselectivity for the drug over extraneous ions (such as Cl^-).

Conclusions

The factors controlling the release of antiarrhythmic drugs by iontophoresis through cation-exchange membranes were investigated. The delivery of the antiarrhythmic drugs sotalol and lidocaine can be modulated at delivery rates and response times consistent with therapeutic objectives. The application of a negative current can be used to reduce the drug release rate, but not without rapidly increasing the extraneous cation content (e.g., Na^+) in the drug reservoir. In addition, simple adjustments in the input current can reduce the response time of delivery rate, which suggests a future use of current regulation in

a control feedback loop with cardiac monitoring devices. The reduced drug conductance, which may be used (with Na^+ conductance) to calculate the zero-current release rate, exhibits a pronounced size-exclusion property of the membranes and indicates which cationic drugs are easily (i.e., sotalol, lidocaine, and acebutolol) or poorly (i.e., verapamil) transported by iontophoresis through these membranes. Increasing salt concentration from 0.01 M to isotonic conditions increases membrane permeability but does not affect the HCM permselectivity for cations over Cl^- by any appreciable extent. In summary, these results suggest that these HCMs may be appropriate for use in iontophoretic drug delivery implants.

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