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RESEARCH PAPER

In Vitro Iontophoretic Release of Lithium Chloride and Lidocaine Hydrochloride from Polymer Electrolytes

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ABSTRACT

Ionically conducting polymers, frequently known as polymer electrolytes, *are potential candidates as hosts for drugs to be delivered iontophoretically. The iontophoretic delivery of lithium or lidocaine from polymer electrolyte films through a cellophane membrane was examined using different delivery current regimes. Thin, mechanically strong, polymer electrolyte films were fabricated from poly(ethylene oxide) (PEO) with lithium chloride or lidocaine hydrochloride. Experiments showed that iontophoretic transport of both lithium chloride and lidocaine hydrochloride might be achieved from these PEO-based films. Cation transport number determinations give values for PEO-based films of about 0.4 for lithium chloride systems and 0.12 for lidocaine hydrochloride systems. The mechanism of transport from these PEO-based polymer electrolyte films allows the delivery of ionic salts such as lithium chloride and lidocaine hydrochloride to be controlled solely by current, thus providing a system that can deliver precise amounts of drug.*

Key Words: *Drug delivery; Iontophoresis; Poly(ethylene oxide); Polymer electrolytes; Transport number.*

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INTRODUCTION

Although the principle of iontophoresis has been known for about 90 years (1), it has been the subject of considerable recent research activity because of the interest in the delivery of ionic drugs, peptides, and oligonucleotides (2–6). A typical iontophoretic device consists of two electrodes in contact with electrolyte solutions that are placed on different sites on the skin. These electrodes usually are connected to an external power supply such as a battery, which induces a potential difference across the skin; it is the resulting electric field component of the electrochemical potential that is the predominant driving force in iontophoretic drug delivery. Hence, positively charged ions are driven across the skin by means of electrostatic repulsion from the anode, and negatively charged ions are driven from the cathode. This type of drug delivery has numerous potential advantages over other methods of administration, such as control of delivery rate, prolonged administration, and increased patient compliance (2–7).

Ionically conducting polymers, frequently known as *polymer electrolytes*, are potential candidates as hosts for drugs to be delivered iontophoretically. Polymer electrolytes are solidlike, ionically conducting polymers that are essentially solutions of ionic salts in heteropolymers such as poly(ethylene oxide) (PEO) in which the polymer is the immobile solvent. They therefore differ from gel electrolytes, for which the polymer acts as an inert supporting matrix for the salt solution. PEO-based polymer electrolytes are formed by complexing PEO with salts of various monovalent cations (e.g., Li^+, Na^+, Ag^+, K^+), as well as divalent and transition metal ion salts (e.g., Ca^{2+}, Mg^{2+}, Co^{2+}, Ni^{2+}), and they have been used as electrolytes in devices such as lithium batteries, sensors, and supercapacitors (8–10). These PEO-salt complexes can be formed as soft, flexible films with thicknesses that can vary from a few micrometers to, more typically, about 100 μm. Some other important attributes that must be considered in the design of a transdermal delivery device include minimal adverse reactions in the skin (which could include skin irritation or sensitization), as well as a sufficient capacity for the drug dose. The low molecular weight analogs of PEO, the poly(ethylene glycol)s, have widespread acceptability in many dosage forms (11), so PEO should also be a suitable host material into which ionic drugs may be incorporated to form polymer electrolytes. However, their use as a chemically and mechanically stable matrix from which iontophoretic drug delivery can be achieved is an application that has still to be developed.

In polymer electrolytes, ion transport is facilitated by chain segmental motion of flexible and disordered polymer chains in a matrix that constrains the ions against long-range migration (8–10,12). Polymer-salt complex formation is made possible by strong ion-solvent interactions that overcome the lattice energy of the salt. As PEO has the same repeat unit as a crown ether (i.e., CH_2CH_2–O), solvation of cations by association with the ether oxygen of the polymer chain may be expected. PEO, which is the most widely studied host polymer used in polymer electrolytes, can incorporate large concentrations (~4 M) of salt, making it eminently suitable as a matrix into which highly potent drugs may be incorporated. Polymer electrolytes are complicated systems because of their mixed morphology, i.e. they are semicrystalline, with both amorphous and crystalline polymer-salt complex phases, sometimes together with crystalline PEO. The conduction pathway for ions, however, is through the amorphous phase of the polymer-salt complex (13).

Earlier studies on the characterization of polymer electrolytes as matrices for iontophoretic drug delivery have been reported elsewhere by us (14,15). These studies were concerned with the incorporation of water-soluble salts such as lidocaine hydrochloride, ampicillin sodium, thiamine hydrochloride, lithium citrate, lithium chloride, and lithium triflate (a well-characterized salt in polymer electrolyte systems) into PEO to form polymer electrolyte films of various compositions. Differential scanning calorimetry, variable temperature polarizing microscopy, and AC impedance studies of these polymer-salt complexes have shown that PEO-based polymer electrolyte films of lithium chloride and lidocaine hydrochloride may have suitable characteristics to act as drug matrices (15).

Results for the delivery of lithium and lidocaine from PEO-based polymer electrolyte films cast from water through a synthetic membrane such as cellophane are reported in this paper.

MATERIALS AND METHODS

Preparation of Polymer Electrolyte Films

All materials were procured from the Aldrich Chemical Company (Milwaukee, WI), except lidocaine hydrochloride, which was supplied by the Sigma Chemical Company (St. Louis, MO); materials were used as received. The preparation of polymer electrolyte films has been described extensively previously (14,15). Briefly, all polymer electrolyte films were prepared using a standard solution casting technique and were of stoichiomet-

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ric ratio PEO*n*-salt, where $n = 10$ (15). This represents the molar ratio of the ethylene oxide (EO) repeat unit to the salt; thus, a composition of PEO_{10}:salt represents 1 molecule of salt associated with 10 EO units. For each preparation, 1 g of PEO (RMM 4,000,000 daltons) was used, and the mass of salt (lithium chloride or lidocaine hydrochloride) to be used was calculated by dividing the molecular mass of the salt by the molar ratio of 10 and the molecular mass of the EO repeat unit (i.e., 44).

The calculated mass of salt was then added to the 1 g of PEO in 50 ml of distilled water and stirred until complete dissolution. The mixture, which was a viscous solution, was then cast into polystyrene petri dishes (9 cm diameter). These solutions were covered, and the water was allowed to evaporate at a constant temperature of 20°C. The film was then peeled from the petri dish and stored in a sealed plastic bag over silica gel in a desiccator.

In Vitro Delivery and Membrane Permeation Studies

The cellophane membrane (UCB Films Ltd., Somerset, UK; thickness 100 μm) was retained in a custom-made glass side-by-side diffusion cell, which was maintained at 37°C by a thermostated water jacket. The surface area of membrane exposed for permeation was 7.1 cm^2. For all studies, the receptor compartment had a volume of 71 ml and contained 0.1 M NaCl solution, which was kept homogeneous by a magnetic stirrer. A silver foil anode (50 mm × 50 mm × 1 mm) was placed in direct contact with the polymer electrolyte film. Silver chloride rods were used as the cathode; they were made by placing the silver rod (diameter 3.2 mm) in a solution of ferric chloride in concentrated hydrochloric acid for 12 hr and then were washed with acetone and distilled water prior to use.

The iontophoretic delivery current was provided from a power source (Thurlby, RS Components), with the potential difference maintained at 12 V. The power supply was connected in series with a resistance box, multimeter, and the test cell. The function of the resistance box in this arrangement was to provide the necessary load resistance so the desired delivery current for each experiment could be selected and maintained. Once the delivery current was selected, it was maintained for the full duration of the experiment. Manually altering the resistance via the resistance box ensured that a constant current source, which was monitored via the multimeter, was maintained. Finally, the positive terminal of the power source was connected to the anode and the negative terminal to the cathode.

The duration of all experiments was 6 hr. In all experiments, 5-ml samples were withdrawn from the receptor compartment at hourly intervals, and the receptor compartment was replenished each time with 5 ml of fresh 0.1 M NaCl. All experiments were performed in triplicate, and a correction was made for the dilution caused when the sample volume was replaced with fresh 0.1 M NaCl.

Analytical Techniques

Lithium ion concentrations were determined by atomic absorption spectrophotometry using an IL 357 spectrophotometer, and each sample was analyzed by the standard additions technique. Lidocaine hydrochloride concentrations were determined by UV/Vis spectroscopy (UNICAM-UV2 spectrometer) operating at a fixed wavelength of 263 nm.

RESULTS AND DISCUSSION

In Vitro Delivery from Poly(Ethylene Oxide) Films

Before proceeding with the iontophoretic delivery of lithium and lidocaine, control experiments were performed to monitor passive diffusion. In both cases, the amount of ions permeating through the membrane was found to be negligible. For both PEO-based films of lithium chloride and lidocaine hydrochloride, there was no detectable ''leaching'' of the salts into the receptor compartment. As polymer electrolyte formation relies on the solvation of the salt by the host polymer (PEO), it is not surprising that no ions resulting from passive diffusion were detected in the receptor compartment as the salt is coordinated strongly to the polymer. As no lithium or lidocaine were detected by atomic absorption and UV/Vis spectroscopy, respectively, no correction was necessary for passive diffusion in the iontophoretic experiments.

The results from initial experiments, shown in Figs. 1 and 2, were for films of composition PEO_{10}-LiCl and PEO_{10}–lidocaine HCl. As shown by others (2,3), Fig. 1 demonstrates that the concentration of lithium transported through the membrane was directly proportional to the delivery current when currents of 1.0 and 1.5 mA were used. A similar relationship can also be seen in Fig. 2 for lidocaine hydrochloride transported from a PEO-based film using delivery currents of 0.6 mA and 1.5 mA.

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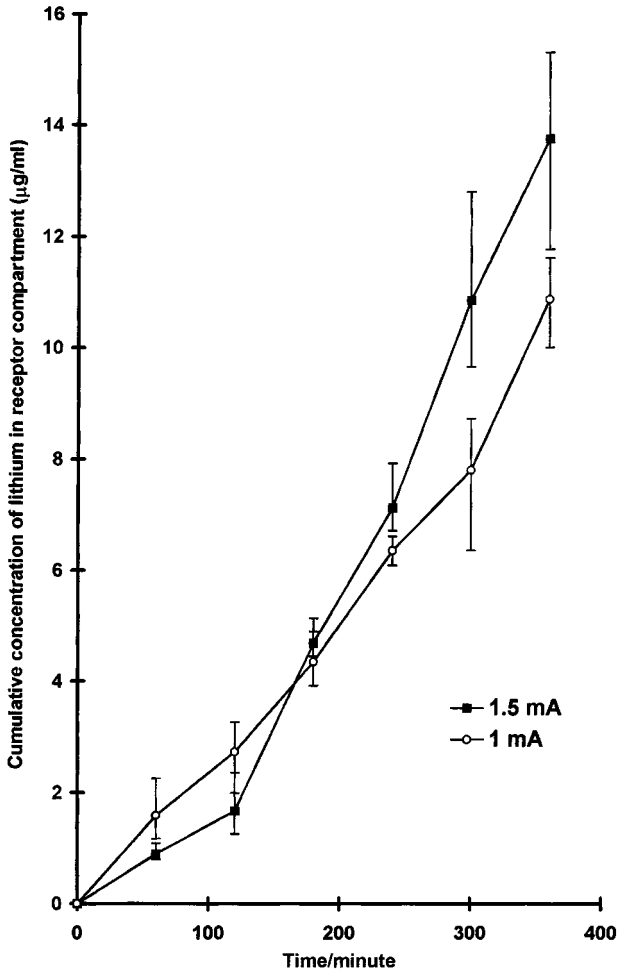

Figure 1. Delivery of lithium from a $(PEO)_{10}$-LiCl film using currents of 1.0 and 1.5 mA (receptor volume 71 ml, area 7.1 cm^2, mean ± SD, $n = 3$).

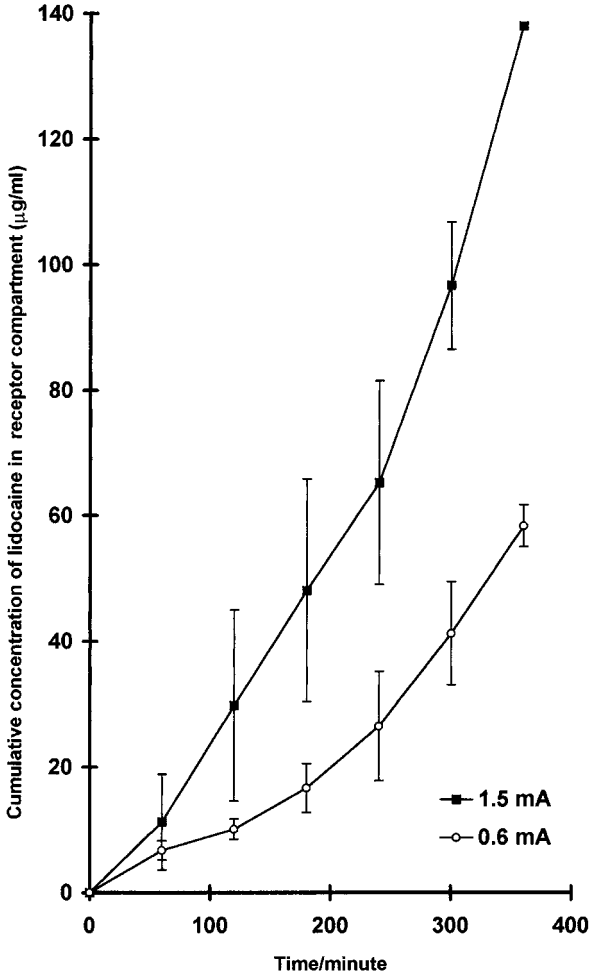

Figure 2. Delivery of lidocaine from a $(PEO)_{10}$–lidocaine hydrochloride film using currents of 1.5 and 0.6 mA (receptor volume 71 ml, area 7.1 cm^2, mean ± SD, $n = 3$).

Further studies carried out using a PEO_{10}-LiCl film as the drug matrix and a higher delivery current of 4.5 mA yielded interesting results over a 6-hr experimental period. Figure 3 shows how the concentration of lithium transported varies with time using this delivery current. In this experiment, a current of 4.5 mA could not be maintained for longer than 1 hr even by adjusting the resistance of the circuit via the resistance box. It should be noted, however, that constant delivery currents were maintained for the experiments described in Figs. 1 and 2 by adjustment of the resistance of the circuit. After 6 hr, about 24 μg/ml of lithium ions were transported from the donor film into the receptor compartment; this corresponds to about 95% of the lithium initially incorporated into the film. However, from Fig. 3, it can be seen that the concentration of lithium in the receptor compartment begins to become constant after 4 hr.

The main reason for this behavior can be associated with the decay in current (from 4.5 mA for the first hour, the current fell to 1 mA after 4 hr and thereafter remained constant), suggesting that further effective transport cannot take place at such a low current. This behavior is not surprising because, over time, the number of charge carriers (i.e., the lithium ions in the film) decreases and the bulk resistance of the polymer electrolyte film increases, causing a drop in the current passing through the system. However, the use of a higher initial delivery current provides evidence that the majority of drug ions in a PEO-based film can be delivered across a membrane over a reasonable period of time.

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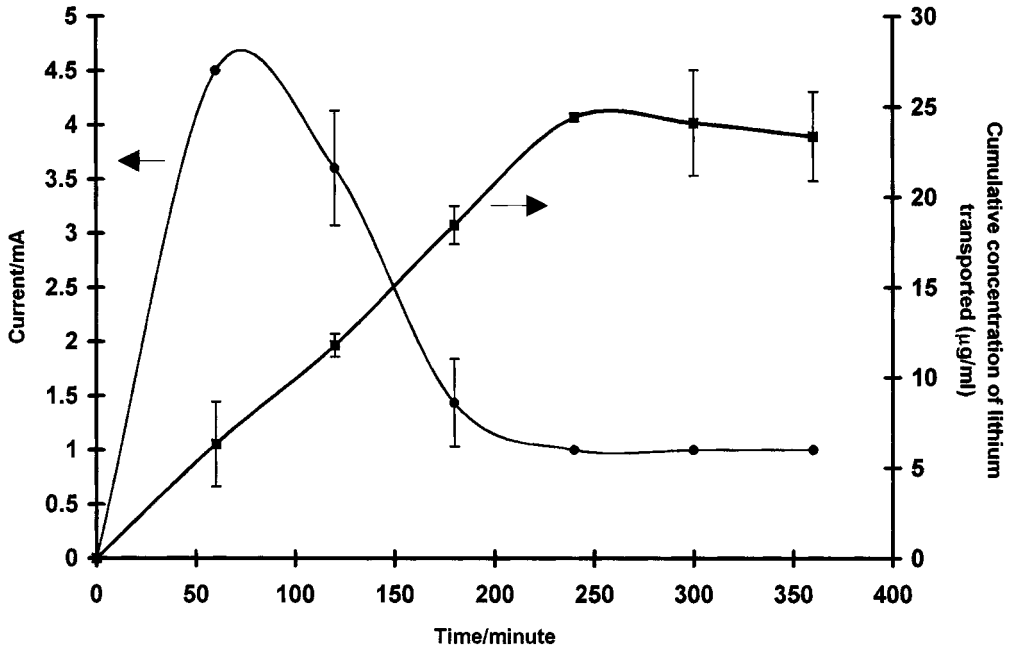

Figure 3. Delivery of lithium from a $(PEO)_{10}$-LiCl film using a current of 4.5 mA (receptor volume 71 ml, area 7.1 cm^2, mean ± SD, $n = 3$).

The delivery of about 95% of the lithium ions after 4 hr also suggests that all the lithium ions from the PEO_{10}-LiCl film that are available for transport have been removed, as indicated by the plateau in the fifth and sixth hour of the experiment. As polymer electrolytes are mixed-morphology systems, it is inevitable that there will be some crystalline polymer-salt complex material present that will retain some of the lithium (15). It can be assumed, therefore, that, after 4 hr using a delivery current of 4.5 mA, all the available lithium (i.e., lithium ions present in the mobile amorphous phase) have been delivered. The plateau that occurs after this time has elapsed suggests that transport of the lithium ions from the PEO_{10}-LiCl film is complete, and further removal of lithium ions from the crystalline polymer-salt complex material is difficult.

Transport Number Determination

The transport numbers of both lithium and lidocaine have been determined from these experiments according to the method of Banga and Chein (2) and are shown in Table 1. The amount of drug delivered iontophoretically can be predicted by Faraday's law as described in the following equation:

$$Q = \frac{t_j i t}{|z|F}$$

where i is the current in amperes, t is the duration of the experiment in seconds, t_j is the transport number that reflects the percentage of current carried by the charged drug molecules, $|z|$ is the absolute valence of the drug ion, and F is the Faraday constant.

As discussed previously, when no potential difference was applied to both polymer electrolyte systems, passive diffusion of lithium and lidocaine was negligible. However, when an electric field was applied to the polymer

Table 1

Transport Numbers of Lithium and Lidocaine in the Receptor Compartment After 6 Hours

Film	i (mA)	Mass (mg)	t_j
	1.0	0.77	0.49
PEO_{10}-LiCl	1.5	0.96	0.42
	4.5	1.71	0.36[a]
PEO_{10}–lidocaine HCl	0.6	3.55	0.12
	1.5	9.73	0.12

[a] t_j was calculated after a run time of 4 h because of the concentration in the receptor plateaus.

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electrolyte systems, both lithium and lidocaine were transported across the cellophane membrane.

Ion transport in polymer electrolytes takes place through the amorphous phase of polymer-salt complexes and at temperatures above their glass transition. As is the case with these PEO-based films (13), high molecular weight amorphous polymers exhibit mechanical properties similar to those of a true solid. This is because of transient cross-linking between the polymer chains caused by the ions becoming attached to more than one chain and also by chain entanglement. Ion transport takes place by a combination of motion within the polymer segments and inter- and intrapolymer ion transitions between suitable coordinating sites. As the polymer chains undergo segmental motion, ions migrate from sites in which the linkages have been broken to new sites that appear further down the chain, the direction of ionic motion being dictated by the applied field. Therefore, the release of the mobile species from the polymer electrolyte is controlled only by this mechanism of ion transport. From Table 1, it can be seen that, for studies on PEO-based films, the transport numbers lie between zero and unity, as expected; also, in the case of lidocaine hydrochloride, they appear not to depend on the current. It can also be seen that the transport number of lithium (~0.42, average of three experiments) from a PEO_{10}-LiCl film is in close agreement to that of Phipps et al. (16), who found the transport number of lithium from a 1 M lithium chloride solution through a polyvinyl alcohol membrane to be about 0.4. The transport number for lidocaine is also smaller than for lithium in these systems; this can be attributed to the difference in the size of the mobile species (2,3).

CONCLUSIONS

From these initial experiments, it can be seen that the iontophoretic delivery of lithium and lidocaine from solidlike PEO-based films is possible. The mechanism of transport from these polymer electrolyte films allows the delivery to be controlled by current, thus providing a system that can deliver precise amounts of drug.

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