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RESEARCH PAPER

Physical Characterization of Polymer Electrolytes as Novel Iontophoretic Drug Delivery Devices

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ABSTRACT

Polymer electrolytes are solidlike materials formed by dispersing a salt at the molecular level in a high molecular weight polymer such as poly(ethylene oxide) (PEO). They have been extensively studied for use in electrochemical applications such as batteries and display devices. This paper considers a novel application of polymer electrolytes as the basis of iontophoretic drug delivery systems. Polymer electrolyte films were cast from solutions of PEO and various drug salts using either water or an acetonitrile/ethanol mixture as the solvent. These films were characterized by variable-temperature polarizing microscopy (VTPM), differential scanning calorimetry (DSC), and alternating current (AC) impedance analysis. The films were around 100-μm thick and mechanically strong; the optical and thermal methods provided evidence that the polymer electrolytes had crystalline and amorphous phases, although some drugs may exist in films as nanodispersions. The amorphous phase is important as ions have greater mobility in this phase and therefore allow a current to be passed when the material is incorporated into a device such as one suitable for drug delivery by iontophoresis. The AC impedance analysis showed that the conductivity of the films varied between 10^{-6} and 10^{-3} S cm^{-1}, depending on the salt, casting solvent, and temperature. Two drugs in particular were shown to be promising candidates in these systems: lidocaine hydrochloride and lithium chloride.

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INTRODUCTION

Conventional dosage forms such as tablets may not allow the optimum therapeutic response to drugs. This can be for various reasons, including low or variable absorption of the drug, the need for intermittent dosing, or poor patient compliance. The result is often a plasma concentration of the drug that varies markedly with time, so that on some occasions it is too low to be of therapeutic use and on others it is so high that toxic effects might follow. Considerable effort has therefore been made to develop drug delivery systems that use different routes of administration and new technologies to minimize these problems.

The skin has been investigated for several decades as a route of drug administration, and many commercial products have resulted. The benefits of this route include patient compliance and convenience of use, the ability to deliver drugs for a relatively long time at a constant rate, and the safety afforded by being able to stop the delivery of drug immediately by removing the device from the skin. A major drawback of transdermal administration, however, is that it is difficult for many drugs to cross the skin. This situation can be improved if the drug is ionic by using the technique of iontophoresis, which increases the passage of drugs across the skin by means of an electric current.

A typical iontophoretic device consists of a store of drug, two electrodes, and an external electric cell (Fig. 1). If the drug is negatively charged, then its formulation is placed between the negative electrode (cathode) and the skin, and the drug ion is then attracted through the skin toward the positive electrode (anode) by the electromotive force provided by the cell; the electrode polarities would be reversed for a positively charged drug (1–3). Once the drug has passed through the outer, barrier layer of the skin, it is rapidly removed into the circulation and hence to its site of action, and the electrical circuit is completed by movement of counterions from within the skin. Although this method is simple in principle, there are considerable technical challenges in translating it into an actual drug delivery system.

Transdermal drug delivery systems generally fall into one of two categories. The first is a reservoir system in which a liquid or semisolid formulation of the drug is retained by a permeable membrane in direct contact with the skin. The second is a matrix system in which the drug is uniformly dispersed through a solid material, dispensing with the need for a membrane. The latter type of system is intrinsically safer than a reservoir system as puncture of a membrane can lead to rapid loss of drug followed by uncontrolled absorption. Matrix systems are better candidates for iontophoretic devices providing the matrix can be successfully amalgamated with the device's electrical components and is sufficiently permeable to ions to allow a current to flow.

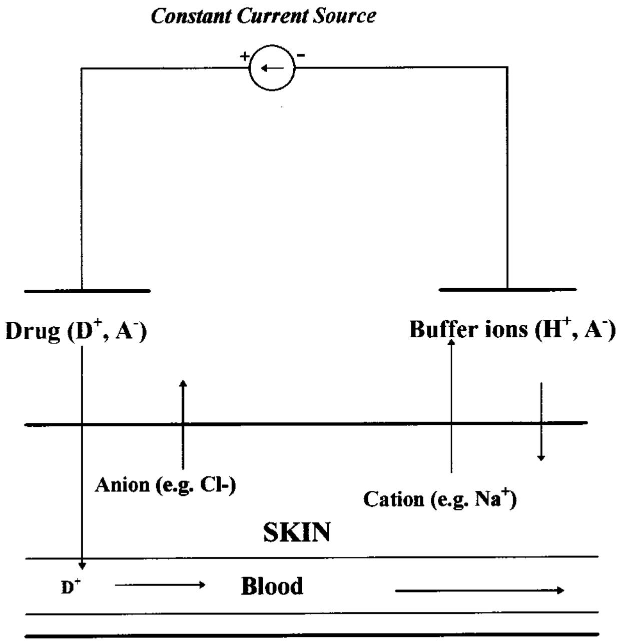

Figure 1. A typical anodal iontophoretic system; D^+ is the positively charged drug, with A^- as its counterion under the anode, while H^+ and A^{--} are ions under the cathode. Na^+ and Cl^- are primary ionic components of extracellular fluid underneath skin.

In this paper, we propose that polymer electrolytes could provide a suitable drug matrix for iontophoretic devices. Polymer electrolytes consist of an ionic compound dispersed in an uncharged high molecular weight polymer, often as a solid solution, and because of their electrical properties, mechanical strength and chemical stability have received considerable attention in such electrochemical devices as batteries and sensors (4–6). A polymer that is commonly studied is poly(ethylene oxide) (PEO), which forms a solid matrix, unlike its low molecular weight analog poly(ethylene glycol), which tends to form liquids or semisolids. Under normal ambient conditions, PEO is a semicrystalline solid with a high proportion of crystalline regions distributed in a continuous amorphous phase; the melting point of pure PEO is about 65°C, and its glass transition temperature is approximately −60°C (7). These two properties are important as they mean that PEO is a solid at room temperature (thus, it has structural integrity), but the PEO chains in the amorphous regions have a sufficient degree of segmental mobility (being at a temperature well above the glass transition temperature), permitting ion transport.

The amount and state of amorphous material in the polymer is therefore crucial to its functioning as a polymer electrolyte, and the amorphous material can be altered by many factors, including the type and amount of the added ions and the method by which the polymer electrolyte is formed (7). In this paper, we investigate the effect of various model cationic and anionic compounds on the properties of PEO films cast from different solvent systems. The compounds selected consisted of the following drug salts: lidocaine hydrochloride, chlorpromazine hydrochloride, thiamine hydrochloride, lithium chloride, lithium citrate, and ampicillin sodium. A further lithium salt (lithium triflate, $LiCF_3SO_3$) was chosen because it has been well characterized as part of PEO polymer electrolytes used in battery technologies. The solvents used for casting were either a mixture of acetonitrile and ethanol (this mixture is commonly used for polymer electrolyte films, but is otherwise too toxic for pharmaceutical use) or water, which is more acceptable.

The most important property of the polymer electrolyte film for iontophoresis is its ability to deliver drug ions, and this was assessed by measuring the conductivity of PEO-salt films by an alternating current (AC) impedance method. This was supported by information on the morphology of the films derived from thermal and visual methods: differential scanning calorimetry (DSC) and variable-temperature polarizing microscopy (VTPM).

MATERIALS AND METHODS

All films were prepared using high molecular weight PEO (RMM 4,000,000; Aldrich Chemical Company). The salts were all used as received and were obtained from the Aldrich Chemical Company, except for lidocaine hydrochloride, which was supplied by Sigma Chemicals.

Films of PEO-salt mixtures were prepared by the standard solvent casting technique used for the preparation of polymer electrolyte films (8), and compositions were expressed in the form PEO_n : salt (where $n = 10$ or 20). This represents the molar ratio of the ethylene oxide (EO) repeat unit to the salt; thus, PEO_{10} : salt represents 1 molecule of salt associated with 10 EO units (and a higher salt concentration than PEO_{20} : salt). For each preparation, 1g of PEO was used, and the mass of salt to be used was calculated by dividing the molecular mass of the salt by the molar ratio (10 or 20) and the molecular mass of the EO repeat unit (i.e., 44).

The appropriate amount of salt and 1 g PEO were added to 100 ml solvent, which was either water or a 3 : 1 v/v mixture of acetonitrile and ethanol, and the resulting dispersion was stirred until solution was complete. The solutions were then cast in glass rings (9-cm diameter) placed on silicone paper, and the solvent was allowed to evaporate at a constant temperature of 20°C. After casting, the water-based films were placed in polyethylene bags and stored in a desiccator over silica gel. Acetonitrile/ethanol-based films were placed in a vacuum oven at 50°C for 24 hr for further drying immediately after initial solvent evaporation, to remove any residual solvent, and were subsequently placed in polyethylene bags and stored in a desiccator over silica gel.

The VTPM studies were conducted using an Olympus BHS polarizing microscope with an automatic photographing system and hot stage, allowing heating of the samples to 150°C. For these experiments, water-based polymer-salt samples were prepared by inserting a glass microscope slide into the 1% solution of the appropriate PEO-salt solution until completely covered and then leaving them to dry in a fume cupboard. For acetonitrile/ethanol-based polymer-salt solutions, the slides were prepared in exactly the same way except they were dried in a vacuum oven at 50°C for 24 hr and then placed in a polyethylene bag to prevent moisture absorption.

The conductivity of the films was determined by impedance measurements carried out over a frequency range of 10 Hz–10 MHz using a Hewlett Packard 4192A impedance analyzer with stainless steel blocking electrodes at temperatures between 25°C and 205°C.

The DSC studies were carried out over the temperature range 25°C–300°C at a heating rate of 10°C min^{-1} using a Perkin-Elmer DSC-4 system.

RESULTS AND DISCUSSION

Variable Temperature Polarizing Microscopy

Pure PEO is a semicrystalline polymer that consists of a continuous amorphous phase that contains regions of closely packed crystalline polymer radiating from central points. These crystalline regions are known as spherulites and are visible in thin films using light microscopy, although they do not form perfect spheres as crystal growth stops when they touch a neighboring spherulite. Films made from PEO and salts are also semicrystalline, but complexation between PEO and the salt can lead to a second type of spherulite, which may not be distinguishable by light microscopy from pure PEO spherulites. The

Table 1

Melting Points of Drugs

Drug	Melting Point (°C)
Lidocaine HCl	74–79
Ampicillin sodium salt	205
Chlorpromazine HCl	195
Thiamine HCl	248
Lithium citrate	112

thermal methods (VTPM and DSC) help to distinguish between these different types of crystalline material; the amorphous phase, however, is most important for polymer electrolytes as it is in this phase that ions are most mobile, facilitating the passage of an electric current (7).

The melting points for the drugs included in this study are shown in Table 1. Table 2 illustrates the data from the VTPM experiments. For each of the polymer-salt complexes (whether cast in acetonitrile/ethanol or water), the onset of spherulite melting is seen with VTPM at approximately 65°C (Table 2), and this is associated normally with the melting of pure crystalline PEO-like material. A melting transition at this temperature is also usually observed on DSC scans for most PEO-based polymer electrolytes (shown as peak T_{m_1} in Table 3). Table 3 also shows that, for all the films, there are one or more peaks present (T_{m_2}) at higher temperatures that may be associated with the melting of crystalline polymer-salt complex material.

For the VTPM experiments, all the films, with the exception of water-based films incorporating chlorpromazine hydrochloride, lithium chloride, and lithium triflate, spherulites of crystalline material appear to melt at around the temperature of pure crystalline PEO, and there is no evidence for the presence of spherulites of high-melting polymer-salt complexes. This should be compared with the DSC results in Table 3, which show

Table 2

Melting Characteristics of Spherulites in the Various Polymer-Salt Complexes

	Water-Cast Films		Acetonitrile/Ethanol-Cast Films	
PEO_{10}-Salt	Onset of Melting (°C)	Completely Melted (°C)	Onset of Melting (°C)	Completely Melted (°C)
Chlorpromazine HCl	62	104	65	>150
Ampicillin sodium	63	63	67	70
Lithium citrate	65	73	64	70
Lidocaine HCl	63	63	64	70
Lithium chloride	67	>150	66	>150
Thiamine HCl	65	73.5	66	71
Lithium triflate	65	145	65	70
PEO (control)	63	67	64	67

Table 3

Comparison of Main Features from DSC Traces for Polymer-Salt Complexes Cast from Water and Acetonitrile/Ethanol

	Water-Cast Films		Films Cast from Acetonitrile/ Ethanol (3:1)	
PEO_{10}-Salt	T_{m_1} (°C)	T_{m_2} (°C)	T_{m_1} (°C)	T_{m_2} (°C)
Lithium triflate	66	160–180	65	—
Lidocaine HCl	65	235–290	67	220–300
Ampicillin sodium	61	230–300[a]	67	220–300
Lithium citrate	67	180–210[a]	—	—
Chlorpromazine HCl	65	140[a] and 195	65	190
Thiamine HCl	63	255	67	250, 270–300
Lithium chloride	67	190–210	65	70–150, 200–220
PEO (control)	65	—	66	—

[a] Exothermic peaks.

that, in addition to the expected peak associated with the melting of pure PEO-like material, there is an additional melting phenomenon at higher temperatures outside the operating temperature of the microscope.

The DSC results for the chlorpromazine hydrochloride, lithium chloride, and lithium triflate films, however, show the melting peaks of the crystalline polymer-salt material at temperatures that are within the range of the VTPM. It is generally the case that, when pure PEO-like material and high-melting polymer-salt complex material are both present in a polymer electrolyte, there are two separate and clearly defined melting processes. However, as the appearance of a melting peak for the crystalline polymer salt complex for water-based films of lithium chloride and lithium triflate films appears to occur just over the operating temperature of the VTPM, there may be an overlap in the melting point of the two crystalline phases of complexed and uncomplexed PEO that may account for the resistance to the normal melting of the spherulites at approximately 65°C.

For chlorpromazine hydrochloride, the DSC results show a broad exothermic transition with a maximum at 140°C, which may be attributed to the reordering of the crystalline polymer-salt complex (the peak at 190°C is the melting of uncomplexed chlorpromazine hydrochloride; see Table 1). When this was compared with the melting of the spherulites seen on the VTPM, it becomes apparent that the broad exothermic peak seen in the DSC at 140°C influences the disappearance of the spherulites at a temperature associated with the melting of PEO-like material (~65°C), and this leads to complete melting of spherulites at a higher temperature of 104°C.

When films of these three salts are cast using acetonitrile/ethanol, only chlorpromazine hydrochloride and lithium chloride exhibit a resistance to complete melting within the temperature range of the experiments. For lithium chloride systems, DSC studies show the presence of a broad peak between 70°C and 150°C, which can be attributed to the presence of small amounts of crystalline PEO-complex. For chlorpromazine hydrochloride films, the peak that was observed for the water-cast film at around 140°C has disappeared, but a peak at 190°C associated with undissolved, possibly nanodispersed, crystalline chlorpromazine hydrochloride may prevent the film from melting at around 65°C.

Conductivity

The polymer-salt complexes examined were composed of PEO_{10} and were cast using water as the solvent. The conductivities of the polymer-salt complexes were compared with the well-characterized lithium triflate system. The PEO_{10}-lithium triflate film cast from water was found to be too ‘‘sticky’’ for use in these experiments, and a PEO_{20}-lithium triflate film was used. Figure 2 shows how the conductivity of these polymer-salt complexes varies within a given temperature range (25°C–205°C), and the results have been compared with the PEO_{20}-lithium triflate reference system.

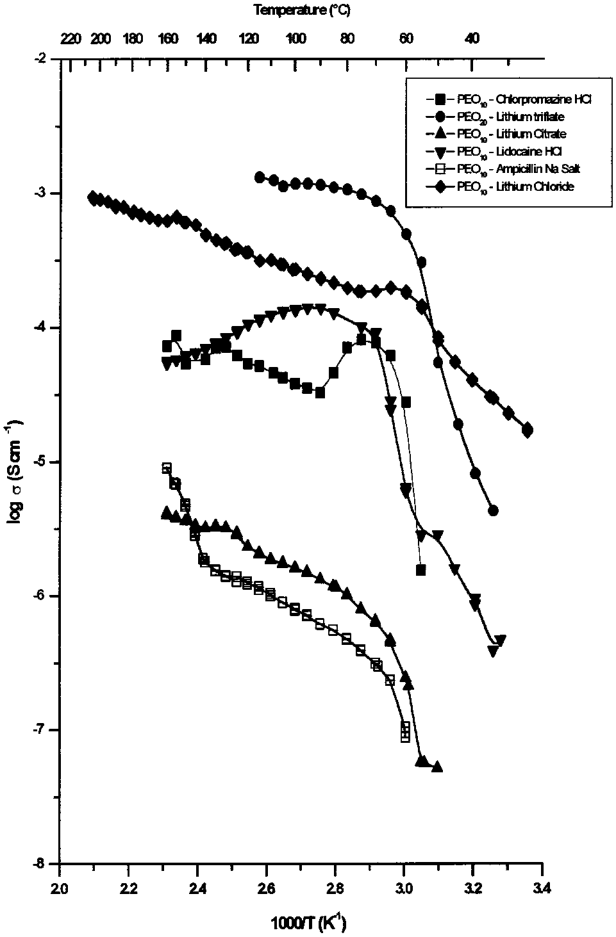

Figure 2. Comparison of conductivity of various PEO_{10}-salt complexes and PEO_{20}-lithium triflate (all cast from water).

From Fig. 2, it can be seen that, between 25°C and about 65°C, there is an initial rapid increase in conductivity. However, above 65°C when all the crystalline PEO-like material within the polymer electrolyte film has melted, the changes in conductivity are less pronounced; this is characteristic of the behavior associated with the amorphous region within PEO-based polymer electrolytes.

Of the polymer-salt complexes examined in this study, the three that show behavior similar to the lithium triflate system (i.e., conductivities on the order of 10^{-4} S cm^{-1} or higher) are films based on lithium chloride, lidocaine hydrochloride, and chlorpromazine hydrochloride. The behavior of lidocaine hydrochloride films is very similar to that of lithium triflate films, the only difference being lower conductivity throughout the temperature range used. In the PEO–chlorpromazine hydrochloride system, there seems to be an unusual feature at about 100°C that may be attributed to the crystalline high-melting polymer-salt complex discussed above.

In comparison, the conductivities of films based on lithium citrate and ampicillin sodium are much lower. This may be due to the presence of large, bulky anions that destabilize the system when interaction between the ether oxygen and metal ion occurs. The conductivity of thiamine hydrochloride films was also measured over the chosen temperature range, but these types of films were found to be very poor conductors.

However, with the exception of these last systems, the conductivity results indicate that the mobility of the ionic drugs within these films is sufficiently high to make polymer electrolytes useful as the basis of an iontophoretic delivery device. This potential use is further emphasized when the conductivities of the water-cast polymer-salt films are compared with their acetonitrile/ethanol-cast counterparts. Figure 3 shows conductivities of some of the polymer-salt complexes over the same temperature range when cast from the two different solvents. In the polymer-salt films involving the three most-promising salts (lithium chloride, lidocaine hydrochloride, and chlorpromazine hydrochloride), the conductivity of the acetonitrile/ethanol-cast films is lower than for the water-cast films until a temperature greater than 100°C is reached. At this temperature, the conductivity begins to rise above that seen in the water-cast films. Up to about 100°C, the water-cast films may still contain some residual water, which can act as a plasticizer, and as this evaporates, the films become less conductive.

The PEO_{10}-chlorpromazine hydrochloride films display an interesting feature in that, when the films are cast from either of the two solvents, there is a sharp fall in the conductivity at around 100°C, which in the discussion above was attributed to the crystalline PEO-salt complex. However, when another sample of the same film was reexamined for conductivity after a period of 12 weeks, this feature not only disappears, but the conductivity also increases. This behavior is shown in Fig. 3 for water-cast films of chlorpromazine hydrochloride. One possible reason for this unusual behavior could be that the PEO-salt complex does not reach its final configuration for some time after casting: it is well known that the formation of films containing PEO and simple salts is controlled by kinetic, rather than thermodynamic, factors (6).

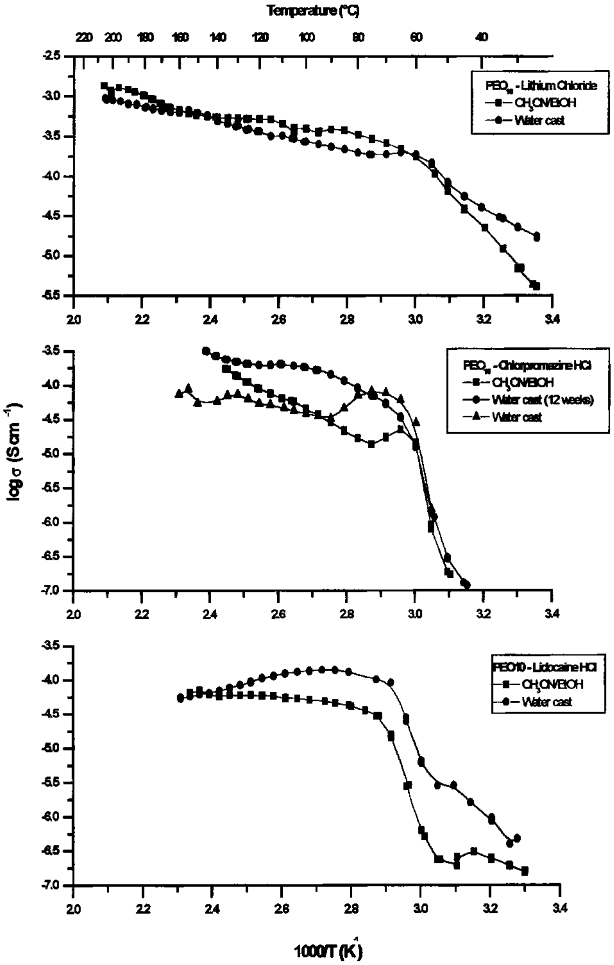

Figure 3. Comparison of conductivity over a temperature range 25°C to 205°C of films cast from acetonitrile/ethanol and water.

CONCLUSIONS

To be useful for drug delivery, a dosage form needs to satisfy a number of general requirements. Chief among these are safety, the ability to carry a useful dose of drug, and the ability to deliver the drug at a suitable rate. There is enough evidence from this paper to justify further investigation of polymer electrolytes as part of an iontophoretic delivery system. PEOs are generally regarded as having low toxicity, as demonstrated by their widespread use as a pharmaceutical excipient. The films studied here typically contained around 40% w/w of drug, so they are likely to be able to carry a suitable therapeutic dose.

It is more difficult to estimate drug delivery rates from conductivity data. However, it is possible to estimate the current that the films would deliver, and this is an indirect indication of drug delivery. A film of an area of 1 cm^2 that has a conductivity of 10^{-4} S cm^{-1} and a thickness of 100 μm would have an internal resistance of 100 Ω. For typical iontophoretic devices, the applied voltage used is 9 V, thus (from Ohm's law) providing a current density of 90 mA cm^{-2}. This compares favorably with Phipps, Padmanabhan, and Lattin (9), who were able to deliver lithium through pig skin in vitro using a current density of 0.33 mA cm^{-2}. Singh et al. (10) have also shown transdermal iontophoresis of model compounds such as salicylate, phenylethylamine, and mannitol using a similar current density of 0.3 mA cm^{-2} through an excised human skin model.

From the initial results presented in this paper, it can be seen that PEO-drug films are potential candidates for iontophoretic drug delivery. These studies have shown that PEO-salt films incorporating lidocaine hydrochloride, lithium chloride, and chlorpromazine hydrochloride are the most-promising candidates. Further investigations are being carried out to establish the rate at which these films can deliver drug across skin.

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