An Electrically Modulated Drug Delivery Device. II. Effect of Ionic Strength, Drug Concentration, and Temperature

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The effects of various physicochemical parameters on the changes in drug delivery rate produced by an electrophoretic current are examined using a model system. It was shown that ionic strength has an inverse relationship with the change in delivery rate produced by a given current. Small changes in pH were measured during electrophoresis experiments which were considered to be insignificant. Drug reservoir concentration selection is critical in the design of an electrophoretic device and is based on achieving a balance between providing a suitable reservoir and allowing adequate electrophoretic control. Electrophoretic control is affected by temperature in a manner which can be predicted using the Arrhenius relationship. The low power requirements of the model system demonstrate the feasibility of using the principle of electrophoresis to control drug delivery rates in a therapeutic system.

KEY WORDS: electrophoresis; electrically modulated drug delivery device; chronotherapeutics; ionic strength; drug concentration; temperature.

INTRODUCTION

The application of the principle of electrophoresis to the development of a controlled drug delivery system has been previously described (1). Predictable and reproducible control over the transport of a model cation, propranolol HCl (PHC), through crosslinked poly(2-hydroxyethyl methacrylate) (PHEMA) has demonstrated the potential of this type of delivery system. The device would allow complete control over the release of a drug ranging from a basal level controlled by diffusion to a higher level which would be determined primarily by the magnitude of current between the electrodes and polymer composition. The need for such a device with flexible control over release rates is becoming more apparent as demonstrated by the continually expanding disciplines of chronopharmacology and chronotherapeutics (2,3). In addition, the therapeutic effectiveness of the new generation of peptide-based drugs (4,5) may be improved by complex delivery patterns not attainable with conventional delivery systems but which should be possible using electrophoretic control. In the present study the effects of various physicochemical parameters on the performance of an electrophoretic device are examined. In particular, the effects of varying ionic strength, reservoir drug concentration, and temperature are examined. The changes in pH that occur during electrophoresis are also examined. The power consumption of the model system is considered. As demonstrated below, these parameters are important considerations in the design of a device in order to obtain optimal modulation of drug delivery rates by an electric field.

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MATERIALS AND METHODS

Materials

Materials used in this study have been described previously (1).

Electrophoresis Studies

The assembly of the electrophoretic cell and the methodology used in electrophoresis studies have been described previously (1). The PHEMA disks used in the study, crosslinked with 1% ethylene glycol dimethacrylate, were prepared by chemical initiation as previously described (1). The disks used in the present study were 4 cm in diameter with a thickness of approximately 0.09 cm.

Effect of Ionic Strength

The effect of ionic strength on the electrophoretic delivery of PHC through crosslinked PHEMA was determined in the present study. Acetate buffer with a range of ionic strengths from 0.039 to 0.2 was examined. This range of ionic strengths was of interest as it encompassed the expected ionic strength of plasma, which can be approximated from the concentration of the principal plasma ions (6). The interest in the effect of ionic strength stems from one of the envisaged applications of an electrophoretic delivery device as an implant system, where the ionic strength of the environment may have an effect on the device. The electrophoretic cell was assembled as described previously (1). Once a constant delivery rate due to diffusion had been established, a constant current of 2.4 mA was applied by the power supply for a period of 4 hr. The experiment was repeated with a range of buffer ionic strengths, with the buffer ionic strength kept the same in both the reservoir and the receptor compartments for each experiment. The initial concentration of PHC in the reservoir compartment was 14 m*M* in this study. A range of ionic strengths of the acetate buffer was prepared by adding a known quantity of previously dried sodium chloride to the buffer. The effect of ionic strength on the pH of the buffer was estimated by taking into account activity effects; the calculated change in pH caused by increasing the ionic strength of the buffer to 0.2 is approximately 0.06 pH unit. A uv scan of the 0.039 and 0.20 ionic strength buffers was performed between the wavelengths of 200 and 400 nm (550S, Perkin Elmer Ltd., Slough, U.K.) in order to examine whether the addition of sodium chloride affected the uv absorbance of the acetate buffer: no significant difference was found. In order that the addition of the stock solution of PHC at the start of experiments did not change the ionic strength of the buffer, a series of stock solutions of PHC was prepared, with the ionic strength of the buffer appropriately adjusted.

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As well as examining the effects of ionic strength on electrophoresis, the changes in pH that occurred during electrophoresis were also examined in each experiment. A combination electrode, 0.7 cm in diameter and 10 cm long (Russell CTWL/B14, Russell pH Ltd., Fife, UK), was used in this study. The electrode was inserted periodically into both the reservoir and the receptor compartments of the electrophoresis cell during experiments to measure the pH (Radiometer PHM64 research pH meter, V. A. Howe and Co. Ltd., London, UK).

Effect of Reservoir Propranolol HCl Concentration

The effect of varying the concentration of PHC in the reservoir compartment on the drug delivery rate produced by a constant electrophoretic current of 1 mA was examined in the present study. Varying the reservoir concentration would be expected to alter the delivery rate across the PHEMA film as a result of diffusion effects as well as effects on electrophoretic control. Previous studies using this model system have been based on the addition of 20 ml of stock PHC added to the reservoir compartment at the start of an experiment to give a final reservoir concentration of approximately 14 m*M* (1). However, in the present study, the volume of buffer placed in the reservoir compartment was varied so that, on addition of an appropriate volume of stock PHC solution necessary to make the volume up to 220 ml, a range of reservoir PHC concentrations could be obtained from 1 to 55 m*M*. The final concentration of the reservoir was determined as previously described by removing a 10-ml sample from the reservoir for assay by uv spectrophotometry at 288 nm (550S, Perkin Elmer Ltd., Slough, UK). Once the delivery rate due to diffusion had become constant, a constant current of 1 mA was produced by the power supply for a period of 4 hr. The experiment was repeated for a range of reservoir concentrations.

Effect of Temperature

The effect of temperature on the electrophoretic transport of PHC through crosslinked PHEMA was examined. The electrophoretic cell was assembled as described previously (1), with an initial reservoir concentration of 14 m*M* PHC. Once the delivery rate due to diffusion had become constant, a constant current was applied by the power supply for a period of 4 hr. The experiment was repeated for a range of currents from 0 to 2.5 mA, and changes in the delivery rate of PHC were determined. This series of experiments was repeated at 25, 31, and 37°C. The power requirements of the model electrophoretic system were calculated at each of these temperatures by measuring the voltage across the platinum electrodes using a voltmeter (Weston 6100, supplied by RS Components Ltd., Corby, UK). The voltage was measured 10 min after the start of electrophoresis and was used as an estimate of the voltage during an experiment since it has been shown that the voltage remains constant during experiments (i.e., constant power conditions) (1). The power requirements of the model system could then be calculated to give an indication of the power requirements of a therapeutic electrophoretic device.

RESULTS AND DISCUSSION

Effect of Ionic Strength

As expected, the addition of sodium chloride resulted in a decrease in buffer pH of 0.1 unit, the experimentally measured pH of the 0.2 ionic strength buffer being 4.38. This change was thought to be insignificant as far as the effect of electrophoresis is concerned since the pK_a of PHC is 9.5 (7).

Figure 1 is typical of the relationship found between PHC receptor compartment concentration and time, showing the effect that an electric current of 2.4 mA has on the delivery rate with a buffer ionic strength of 0.039. Samples were taken at hourly intervals, except during electrophoresis, when samples were taken every 20 min. As in previous work (1), the delivery rate during electrophoretic control was found to be linear, allowing the calculation of delivery rates under electrophoretic control. The effect of ionic strength on the delivery rate of PHC during electrophoretic delivery is shown in Fig. 2. At a constant current of 2.4 mA, the delivery rate was found to decrease with an increase in ionic strength, tending toward a value for delivery rate which was produced by diffusion alone. Figure 2 also compares the effect of ionic strength on the delivery rate of PHC prior to electrophoretic control with that during electrophoretic control. The results indicate that an increase in ionic strength caused a slight decrease in the delivery rate produced by diffusion alone, this decrease probably being due to activity effects. A similar effect of ionic strength based on polyacrylamide electrophoresis has recently been reported with a study on the effects of an electric current on the delivery rate of bovine serum albumin (8).

The effect of ionic strength on the delivery rate may be explained by two main effects that are occurring as ionic strength is changed. The first and least significant effect in this particular model occurs as a result of the changes in the conductance of propranolol cations arising from electrophoretic and relaxation phenomena, which are the result of concentration dependent interactions between ions in solution (9). The Onsager equation, which relates ionic strength to the changes in conductance that result from these effects,

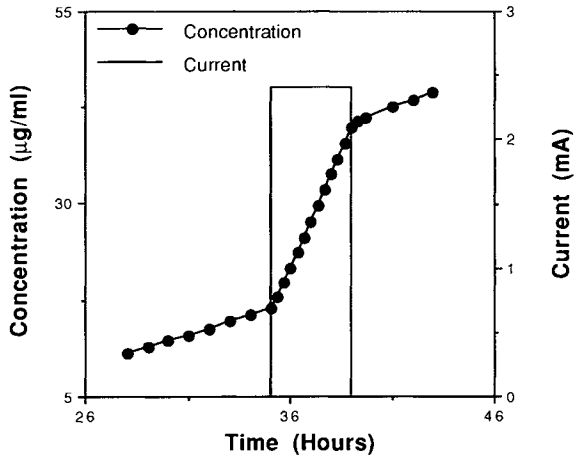

Fig. 1. Effect of a current of 2.4 mA on the transport of PHC into the receptor compartment of the electrophoresis cell with an ionic strength of 0.039.

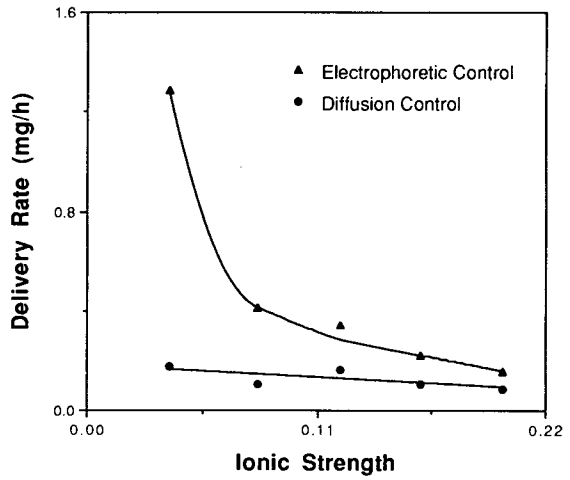

Fig. 2. Effect of ionic strength on diffusional and electrophoretic transport of PHC through 1% crosslinked PHEMA film using a constant current of 2.4 mA.

suggests an inverse relationship between increasing ionic strength and molar conductivity. This relationship is significant in the present work because it predicts that, for a fixed concentration of PHC, an increase in ionic strength would be expected to decrease the conductivity of PHC. The second and more significant reason for the decrease in drug delivery rate is related to the total concentration of ions in solution and the fact that electrophoresis was carried out under constant-current conditions. Electric current is a measure of the rate at which electric charge is transported and, thus, the rate at which ions are transported into the receptor. Since in this study the effect of constant current was being investigated, irrespective of the ionic strength of the buffer, the same quantity of charge will be transported over a given period. As ionic strength was increased, the proportion of propranolol cations to the total number of ions in solution was found to decrease; thus it might be expected that the amount of PHC transported during electrophoresis would decrease as ionic strength was increased due to competition from buffer species. The results show that ionic strength has a significant effect on the electrophoretic control of the transport of PHC, higher ionic strengths decreasing the delivery rate produced by a given electrophoretic current.

The changes in pH that occurred during the study of ionic strength effects on drug delivery rates are shown in Table I. The values shown are the difference between the pH measured after electrophoresis and the pH before electrophoresis. The results show that as a result of electrophoresis, there is a slight decrease in pH in the reservoir (anolytic) compartment and a slight increase in the receptor (catholytic) compartment pH. These changes may be the result of low-level electrolysis of water and are not considered to be significant.

Table I. Relationship Between Changes in pH and Changes in Ionic Strength Which Occurred as the Result of Electrophoresis

	Change in	
Ionic strength	Reservoir pH	Receptor pH
0.039	−0.03	0.00
0.080	−0.04	0.01
0.120	−0.03	0.00
0.160	−0.04	0.02
0.200	−0.05	0.01

Effect of Reservoir Propranolol HCl Concentration

The effect of varying the reservoir concentration of PHC on the delivery rate produced by an electrophoretic current of 1 mA is shown in Fig. 3. At lower reservoir concentrations, small increases in concentration were found to produce a rapid increase in the drug delivery rate during electrophoresis. However, the gradient of the delivery rate versus concentration curve decreased as the reservoir concentration was increased. Further, as the electrophoresis-induced delivery rate increased, so did the delivery rate by diffusion prior to electrophoresis. Figure 4 shows the ratio of the delivery rate during electrophoresis to that prior to electrophoresis. Thus, as the concentration of PHC in the reservoir compartment increases, the change in drug delivery rate produced by an electrophoretic current of 1 mA decreases, tending toward a limiting value corresponding to that produced by diffusion alone. These results seem to indicate that the choice of reservoir concentration is critical: too high a concentration making electrophoretic control ineffective, too low a concentration being unsuitable for practical use as a drug reservoir. The actual mechanism by which concentration affects electrophoretic drug delivery rate is not clear. As well as increasing the contribution of diffusion, increasing the reservoir concentration will also decrease the conductance of the propranolol cation because of electrophoretic and relaxation phenomena (9). However, this effect would not explain the decreasing effectiveness of electrophoretic control as PHC concentration was increased. The results show that increasing the reservoir PHC concentration results in a greater influence on molecular transport by passive diffusion than transport by electrophoresis. A previous study on constant voltage electrophoresis reported a complex relationship between concentration and electrophoretic mobility (10), however, this may have been due to the

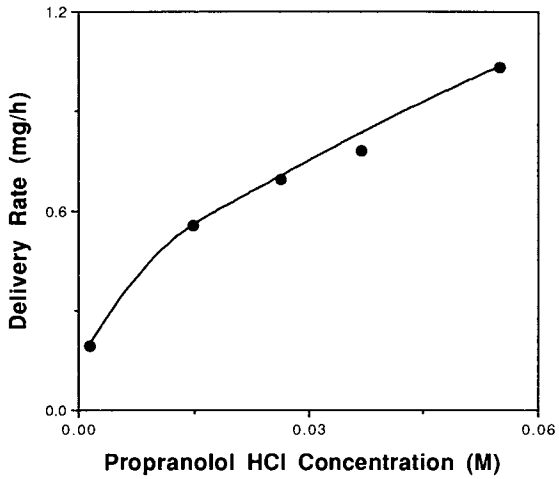

Fig. 3. Effect of PHC reservoir concentration on electrophoretic drug delivery rate at a current of 1 mA.

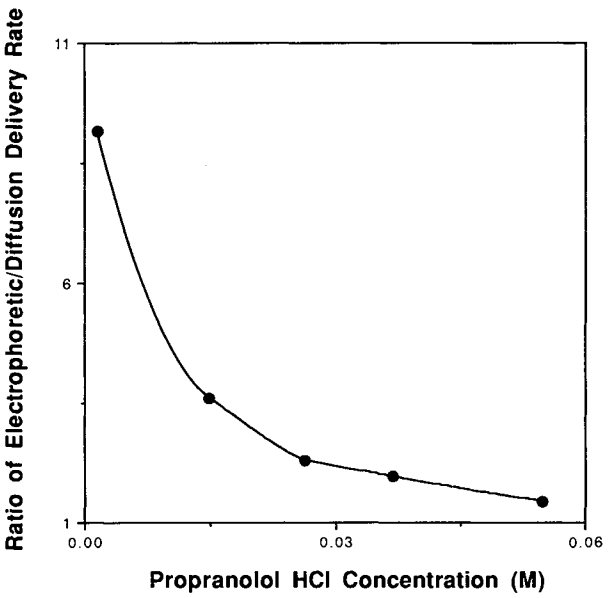

Fig. 4. Effect of PHC reservoir concentration on the change in drug delivery rate produced by a current of 1 mA.

fact that experiments were performed during the lag period of diffusion, which has been discussed previously (1).

Effect of Temperature

Figure 5 shows the effect of current on the electrophoretic delivery of PHC through PHEMA films at different temperatures. For any given current it can be seen that as the temperature is increased, so is the drug delivery rate. In addition, the rate of change of delivery rate with current increases as the temperature is increased. Figure 6 shows the relationship between the logarithm of the delivery rate per unit current and the reciprocal of absolute temperature. The results suggest that the effect of temperature on the relationship between drug delivery rate and current may be described by the Arrhenius equation. The effect of increasing temperature may be explained by an associated increase in free diffusion and ionic mobility, together with a decrease in the viscosity of the electrophoresis medium (11).

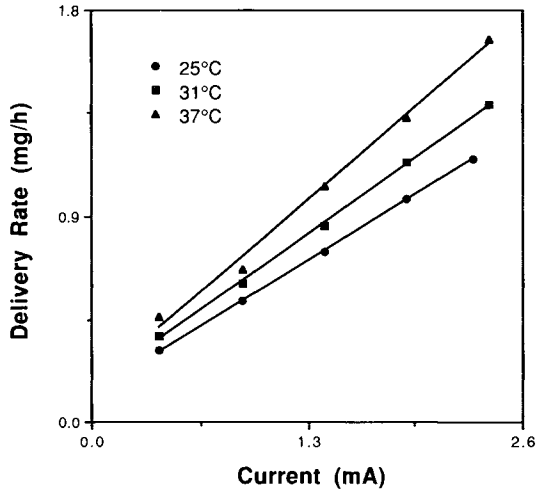

Fig. 5. Effect of current on the electrophoretic delivery of PHC through 1% crosslinked PHEMA film at 25, 31, and 37°C.

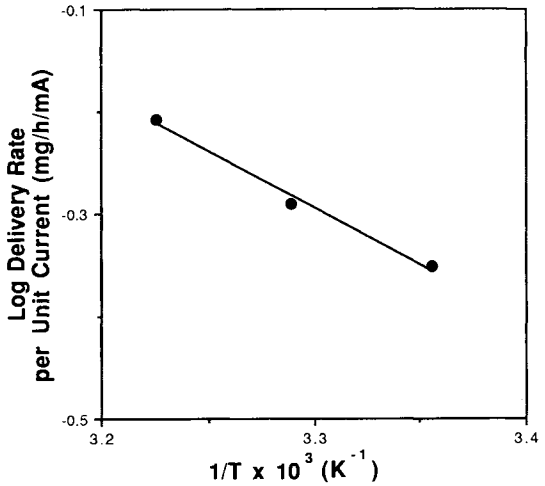

Fig. 6. An Arrhenius plot of the log delivery rate per unit current versus the reciprocal of the absolute temperature.

The power requirements of the model system at a current of 2 mA were calculated as 3.3 mW (25°C), 2.9 mW (31°C), and 2.5 mW (37°C). As expected, the power requirements decrease with increasing temperature. These values have significant implications with respect to the use of a low-power electrophoresis drug delivery device for clinical use. Such a device could be powered by batteries, for example, a typical button-type lithium cell is capable of supplying 200 mAh at a constant 3 V (RS Components Ltd., Corby, UK), which is approximately equivalent to 200 operating hr at a power consumption of 2.5 mW. The model system thus demonstrates that power requirements are relatively low, thus demonstrating the feasibility of an electrophoretic device.

CONCLUSIONS

Several parameters were found to be important to the design of an electrophoretic device. Ionic strength has a significant effect on electrophoretic control and determined the magnitude of the change in transport of PHC produced by a given current. Small changes in pH were found to occur during electrophoresis. Drug reservoir concentration is important and selection must be based on a balance between providing a suitable reservoir and allowing adequate electrophoretic control. Delivery rates can be related to temperature changes by the Arrhenius equation. The low power requirements and control over drug transport demonstrate the feasibility of an electrophoretically modulated drug delivery system.

ACKNOWLEDGMENT

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