An Electrically Modulated Drug Delivery Device: I

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A controlled drug delivery device based on the principle of electrophoresis is described. A model system using propranolol HCl and PHEMA films was used to demonstrate how control over the release of a model drug may be achieved using low constant electric currents. It was found that a linear relationship existed between electric current and drug delivery rate. Additionally, two main effects of applying an electric current during the lag period of delivery from the system were identified. First, the drug delivery rate was less when a current was applied before the lag period had expired, and second, the voltage–time profiles were found to be significantly different. The model shows the feasibility of using an electrophoretically controlled drug delivery device to provide truly controllable and predictable release rates.

KEY WORDS: controlled drug delivery system; electrically modulated; electrophoresis; poly(2-hydroxyethyl methacrylate) (PHEMA); propranolol hydrochloride.

INTRODUCTION

There has been a growing awareness in recent years of the potential therapeutic importance of achieving true controlled drug delivery where the rate of drug output may be modulated in a precisely controlled manner (1). This desirable property is not currently achievable using conventional dosage forms, many of which can provide only zero-order release, and although advantageous, is still not the ideal delivery rate for many drugs. Controlled delivery systems are desirable for therapeutic peptides which may require delivery to the body in a manner similar to physiological release profiles (2). The aim of this work is to demonstrate the feasibility of using the principles of electrophoresis to develop such a drug delivery system and to examine some of the factors that may be important in the design of such a system. Electrophoresis encompasses the migration of charged particles in an electric field, though the term is usually associated with the analytical technique, typically involving the application of up to several hundred volts. In this study, however, control over the migration of a model ionic drug is demonstrated using low voltages and currents.

Other approaches aimed at controlled or feedback delivery include the use of mechanical pumps (3), polymeric systems responsive to an oscillating magnetic field (4), temperature-sensitive polymers (5), polymers responsive to externally applied ultrasound (6), and chemically sensitive polymers (7).

A schematic diagram of the proposed electrophoretically controlled device is shown in Fig. 1. It consists of a polymer reservoir device with the addition of a pair of electrodes placed across the rate-limiting membrane. In the absence of an electric field, a basal level of drug release will occur which may be modulated in a controlled and predictable manner by altering the magnitude of the electric field between the electrodes. A similar system based on controlled-voltage polyacrylamide electrophoresis demonstrated that effective control over the release of molecules such as insulin and hyoscine methyl chloride could be achieved using low voltages; however, problems were encountered because of changes in electrical resistance during experiments (8). In the present study a model system based on constant current electrophoresis was examined using cross-linked poly(2-hydroxyethyl methacrylate) (PHEMA) as the rate-limiting membrane and propranolol hydrochloride (PHC) as a model drug.

MATERIALS AND METHODS

Materials

Propranolol hydrochloride (Lot No. 3327) was received as a gift from Forum Chemicals Ltd. (Redhill, UK). 2-Hydroxyethyl methacrylate (stated purity >97%) and ethylene glycol dimethacrylate (stated purity >96%) were obtained from Fluorochem Ltd. (Glossop, UK). Ammonium persulfate (electrophoresis grade) was obtained from FSA Laboratories Supplies (Loughborough, UK). Platinum foil (0.025-mm thickness) and wire (0.5-mm diameter) were obtained from FSA Laboratories Supplies (Loughborough, UK). All water used in these studies was freshly distilled. All other chemicals used were of analytical reagent purity.

Preparation of PHEMA Films

Homogeneous PHEMA films cross-linked with ethylene glycol dimethacrylate (EGDMA) were prepared by chemical initiation (9). Films were produced by polymerizing in a mold which consisted of two thin glass plates separated by a spacer. In the present study, PHEMA cross-linked by the addition of 1% EGDMA was prepared according to the following formulation: EGDMA, 0.2 ml; HEMA, 19.8 ml; distilled water, 8.0 ml; and 4% ammonium persulfate, 4.0 ml. The solution was degassed thoroughly with helium prior to the addition of the ammonium persulfate. The polymerization was allowed to proceed for 18 hr at 60°C, after which the glass plates were separated and the polymerized PHEMA film was peeled away. The films were stored in distilled water at 4°C, the distilled water being changed daily for 21 days. The purpose of this was to leach out any ammonium persulfate or unreacted monomers and to allow the polymer to swell to its equilibrium volume. The polymer was then cut into disk form and immersed in pH 4.48 Walpole acetate buffer and stored at 4°C until ready for use. The hydrogel film thickness was measured by placing it between two glass plates of known thickness and measuring the total thickness with a precision digital micrometer (Mitutoyo, supplied by RS Components Ltd., Corby, UK), using the torque control

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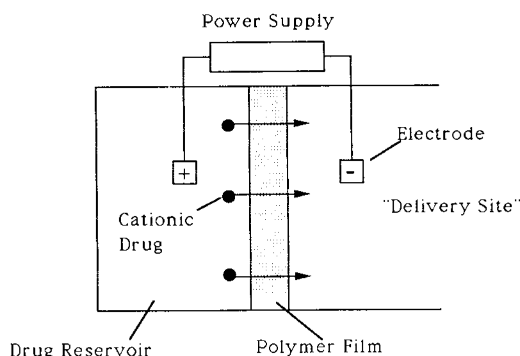

Fig. 1. Diagrammatic representation of an electrophoretically modulated drug delivery device.

so as not to overcompress the hydrogel. The disks used in the present study were approximately 0.09 cm in thickness and 4 cm in diameter.

Electrophoresis Studies

Cross-linked PHEMA discs were mounted in a glass electrophoresis cell (Fig. 2), composed of two equal-volume compartments of approximately 220 ml, with a contact area of 6.16 cm^2. The interfacial glass joints of the cell were smeared with a thin layer of vacuum grease (Apiezon N, Apiezon Products Ltd., London, UK). An annular sheet of polytetrafluoroethylene (PTFE) with a thickness of 0.08 cm and internal diameter of 4 cm was used to provide a liquid tight gasket. The PTFE gasket also ensured that the polymer disc was not placed under excessive strain when the cell was clamped together. The electrodes were fabricated from 1-cm^2 uncoated platinum foil, suspended on platinum wire. The separation of the two electrodes was maintained constant throughout all the experiments at a distance of 8.5 cm. In the present study the reservoir-compartment electrode was the cathode. The drug reservoir compartment contained 200 ml of pH 4.48 buffer (I = 0.039); the receptor compartment contained 210 ml of pH 4.48 buffer. The whole cell was mounted in a specially constructed Perspex stand and immersed in a water bath maintained at 25°C. The compartments were stirred continuously using Perspex stirrers driven by 12-V motors at 330 rev min^{-1} (RS Components Ltd., Corby, UK), which were powered by a constant-voltage power supply (E30/1 Farnell Instruments Ltd., Wetherby, UK). The cell was allowed to equilibrate for 30 min, after which 20 ml of a stock PHC solution in acetate buffer was added to the reservoir compartment to give a final concentration of approximately 14 m*M* (4.3 mg/ml) PHC. Timing was then started, and after 15 sec a 10-ml sample was withdrawn from the reservoir compartment to give a measurement of the initial reservoir PHC concentration. This sample was analyzed by uv spectrophotometry. The receptor-cell solution was pumped at a rate of 0.5 ml min^{-1} (Gilson Minipuls 2, Anachem, Luton, UK) into a flowthrough uv detector (Gilson 116, Anachem, Luton, UK), and the outflow returned to the receptor cell. The uv detector, set to a wavelength of 288 nm, was connected to a microcomputer (BBC Master, Acorn Computers Ltd., Cambridge, UK), which collected the data at preprogrammed time intervals, usually of 1 hr. The computer was calibrated by passing a number of solutions of known concentration through the uv detector. The computer was used to record the variation of receptor concentration with time as well as to control the electrophoretic power supply. Data were graphically displayed on a monitor and continuously updated. The constant-current power supply, which was specially designed and constructed (School of Electrical Engineering, University of Bath), was interfaced with the computer via the 1-MHz bus. The power supply could be controlled either manually or, as in this study, via the computer. Software was written which enabled data points from the uv detector to be collected at any desired time interval. In addition, the software was used to control the constant-current power supply, allowing control of the polarity and magnitude of the current between 0 and 2.5 mA. The current and voltage across the electrodes were also recorded. The power supply could be preprogrammed to turn on and off to a desired current at desired time intervals. At the end of any given experiment the data were stored onto floppy disks and analyzed using a statistics package (INSTAT, University of Reading, UK), which enabled the effects of electrophoresis on the transport of PHC through cross-linked PHEMA films to be examined, as well as allowing the calculation of various parameters such as drug delivery rate. At the end of each experiment the hydrogel thickness was measured. A control experiment was performed where no PHC was added to the drug reservoir, and the power supply turned on for several periods of 4 hr using a current of 15 mA. No significant baseline drift was found over a period of 5 days.

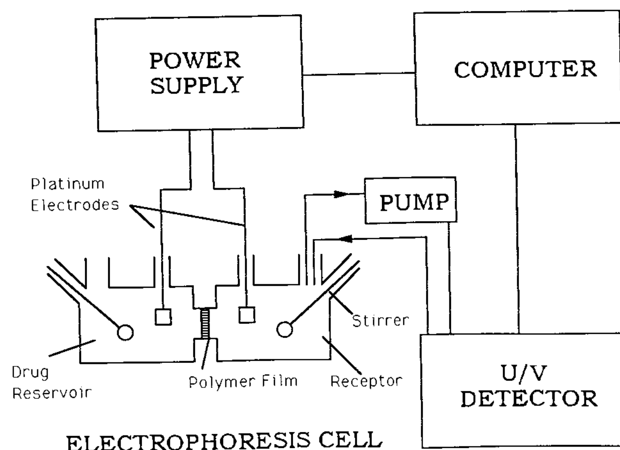

Fig. 2. Schematic diagram of the apparatus used in electrophoresis studies.

RESULTS AND DISCUSSION

Effect of Electric Current

The effect of using electric currents on the transport of PHC was not examined until transport as a result of diffusion had become constant, which could be estimated from a plot of receptor PHC concentration against time. A constant current was then produced by the power supply for a period of 4 hr, then turned off again. The experiment was repeated for a range of currents from 0 to 2.5 mA. Each experiment at a given current was performed in triplicate. Figure 3 shows the

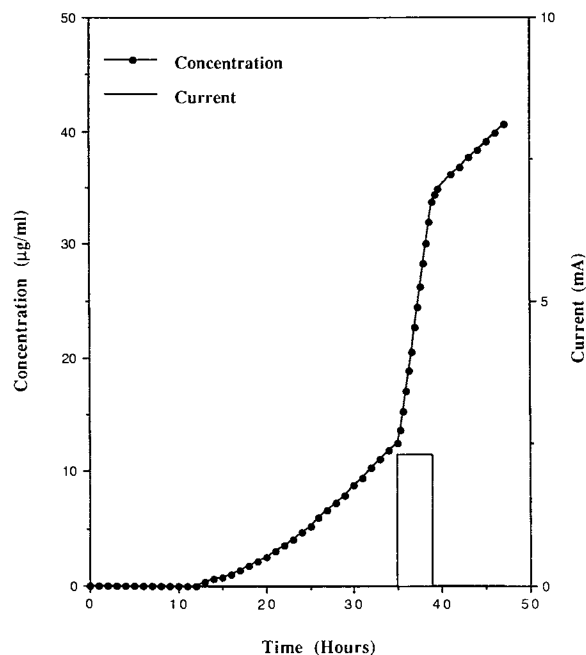

Fig. 3. Effect of current on the transport of PHC into the receptor of the electrophoresis cell.

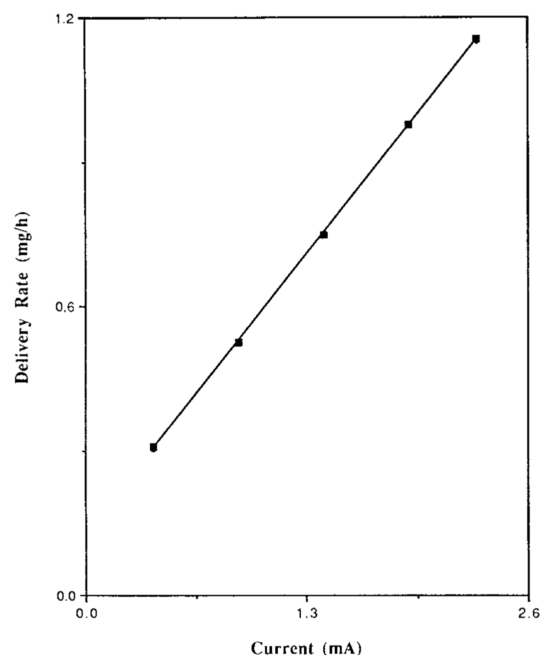

Fig. 4. Effect of applied current on the delivery rate of PHC into the receptor compartment of the electrophoresis cell.

relationship between PHC receptor compartment concentration and time using 1% cross-linked PHEMA film, showing the effect that an electric current of 2.3 mA has on the delivery rate of PHC into the receptor when applied for 4 hr. This type of profile is representative of those obtained with all the currents examined in the range 0 to 2.5 mA; the magnitude of the change in drug delivery rate was found to vary with current. Samples were taken at hourly intervals, except during electrophoresis when samples were taken every 20 min. Application of a current had an almost immediate effect, increasing the drug delivery rate into the receptor compartment significantly over that produced by diffusion alone. On removal of the current, the drug delivery rate dropped significantly. The data for each experiment were analyzed to check for linearity of the drug delivery rate during electrophoresis.

All drug delivery rates during electrophoresis were found to be linear (zero order) for all values of current examined; the magnitude of the delivery rate of PHC into the receptor compartment for a given current was determined from the change in concentration that occurred with time during electrophoresis. The relationship between PHC delivery rate and current was found to be linear; Fig. 4 shows this relationship (standard error bars were too small to be shown). Linear regression analysis of the line yielded the following statistics: number of points = 5, correlation coefficient (r^2) = 0.9999, slope (SD) = 0.4448 (0.0024), and intercept (SD) = 0.1297 (0.0037). The intercept of the line in Fig. 4 with the ordinate represents the approximate delivery rate of PHC under diffusion control, without any electrophoretic contribution. Previous studies on electrophoretic drug delivery devices have shown a similar linear relationship when insulin was investigated using constant voltages (8) and bovine serum albumin using constant currents (10); both these studies used polyacrylamide as the membrane material. It was observed in the present study that the delivery rate of PHC due to diffusion prior to electrophoresis varied slightly in each experiment because of slight differences in film thickness and initial reservoir concentration. These differences, however, were not reflected in changes in delivery rate produced during electrophoresis, the delivery rate for any given current showing little variability between the replicates. On cessation of electrophoresis, the drug delivery rate decreased significantly in less than 20 min and quickly approached the preelectrophoresis level. However, the instantaneous value of the postelectrophoresis delivery rate was up to 30% greater than the delivery rate preelectrophoresis, although this delivery rate usually decreased to a value within 5% of the initial level about 6 to 10 hr following cessation of electrophoresis. A possible explanation for this effect is that during electrophoresis the PHEMA disc is loaded with a higher level of PHC than would normally be present as a result of diffusion, so that on removal of the current, this "extra" PHC was released before the concentration eventually returned to its "normal" level. Future experiments are planned to compare the PHC concentration within PHEMA membranes in diffusion and electrophoresis experiments. The recorded changes in voltage that occurred during electrophoresis were similar in shape for all currents examined. A typical relationship between measured voltage across the electrodes and time (Fig. 5) shows that the voltage rises rapidly and then plateaus to give a near-constant value during the remaining period of electrophoresis. It can therefore be assumed that most of the electrophoretic delivery was carried out under near-constant power conditions. Different results were found when the changes in voltage during constant current polyacrylamide electrophoresis were examined (10); an initial voltage was measured, which after a lag time of about 1 hr (corresponding to the lag time of bovine serum albumin release) reached a maximum value, then de-

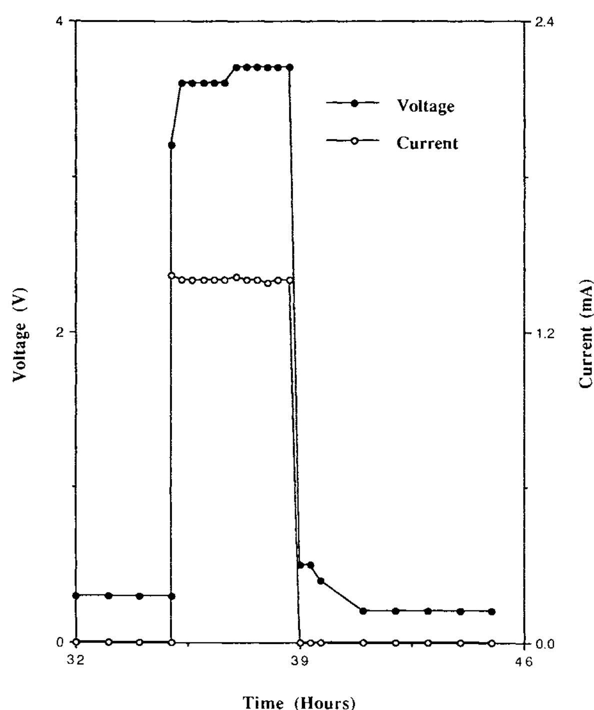

Fig. 5. Changes in voltage measured during electrophoresis at a constant current of 1.4 mA.

cayed slowly to a value obtained during the lag time so that electrophoresis was carried out under conditions of decreasing power. This effect may be due to the fact that diffusion of the bovine serum albumin had not attained steady state before electrophoresis was commenced (see below).

Previous studies on electrophoretic drug control using polyacrylamide have indicated that measurable drug delivery occurs only during periods of electrophoresis (8,10). This type of control over drug delivery rate would be highly desirable, however, these models may not be realistic. In the case of Lescure *et al.* (10), no details of the concentrations of drugs used or polymer thickness are given. However, in work reported by Kumar (8), the absence of drug delivery due to diffusion may be accounted for by two factors. The first and most important concerns the lag period of diffusion. In permeability studies it was found that with a polyacrylamide disk of 1.5-mm thickness, taking hyoscine methyl chloride as an example, a lag time of approximately 2 hr was found (8). In the electrophoresis studies which were over a period of approximately 90 hr, the polyacrylamide disks used were of a thickness of 10 mm. If diffusion was the only process occurring, then it could be expected that a lag period of approximately 88 hr would exist, since lag time is proportional to the square of polymer thickness (11); therefore these studies were performed in the lag period of diffusion. Drug delivery can be produced by electrophoresis during the calculated diffusion lag time (see below), the lag time apparently resuming after cessation of electrophoresis. Examining electrophoretic effects during this lag time may lead to misleading interpretation of results since there will be concomitant changes in concentration occurring during the diffusion lag time. A second and probably less important factor is the depletion of the reservoir compartment in the reported study (8) during electrophoresis (leading to a significant buildup in the receptor). Diffusion-controlled drug delivery is dependent on the maintenance of a concentration gradient (11); however, if this concentration gradient decreases, there will be a continual decrease in the amount of drug being delivered by diffusion. In the present study, high concentrations of PHC were used in the reservoir and sink conditions prevailed throughout the experimental time (the receptor concentration never exceeded 2% of the reservoir concentration during experiments); also, electrophoresis studies were commenced only after the delivery rate due to diffusion had become constant. This model was thought to be more realistic of an electrophoretically controlled drug delivery device where a drug loaded reservoir would be used. The maintenance of sink conditions explains why low-level diffusion-controlled drug delivery was found in this study, as would be expected from diffusion theory. The lag time before which an applied current had a significant effect on the drug delivery rate was found to be less than 5 min. Only one previous study on electrophoretic drug delivery devices commented on the magnitude of this lag time (10). Using cross-linked polyacrylamide discs a lag time of approximately 1 hr occurred before any noticeable effect on the drug delivery rate was produced. The work was carried out using a constant-current power supply to control the delivery of bovine serum albumin. No details of the polyacrylamide gel thickness were given, however, this long lag time would suggest that the polymer thickness was considerably greater than that examined in the present study.

Effect on Diffusion Lag Time

In the experiments described above to investigate drug transport through cross-linked PHEMA films using constant currents, electrophoresis was commenced only after the diffusional delivery rate had become constant. However, a lag time greater than 24 hr was necessary before any studies could be performed. Previous studies on the use of electrophoretic drug delivery devices (8,10) have not considered any possible differences between the effects of electrophoresis before and the effects after steady-state diffusion has been attained. In these previous studies the effects of electrophoresis appear to have been examined prior to steady-state diffusion being attained as discussed earlier. The aim of this part of the study was to examine the significance of attainment of steady state diffusion on electrophoretically controlled drug delivery. An electrophoretic current of 2 mA was applied for a period of 8 hr starting approximately 20 sec after initiation of the experiment, and the effect of the electrophoretic current on drug delivery was examined (Fig. 6). The results show a lag time of approximately 1.2 hr before a change in PHC concentration occurred, which was much greater than the time taken for an electrophoretic current to produce a change in delivery rate during steady-state diffusion. After the lag time, zero-order delivery of PHC was found to occur at a rate of 0.75 mg/hr. This value is less than that which would be expected if electrophoresis at 2 mA was performed after steady-state diffusion had been attained (1.02 mg/hr). The voltage–time profile obtained also differed from that obtained when electrophoresis was effected during steady-state diffusion. The voltage reached a peak corre-

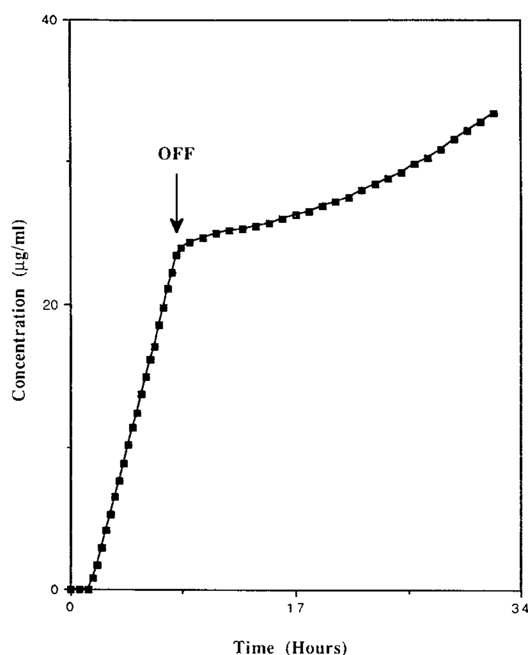

Fig. 6. Effect of application of an electrophoretic current of 2 mA on the transport of PHC into the receptor of the electrophoresis cell during diffusion lag time.

sponding to the lag time for drug appearance and then decreased gradually (Fig. 7). The measured voltages in this study were also higher than expected (4.5 V) if electrophoresis had been effected during steady state diffusion, peaking at 6.4 V. These findings suggest a greater resistance to passage of an electrophoretic current prior to steady-state diffusion. This effect is not fully understood, however, it may be related to the PHEMA not having attained equilibrium

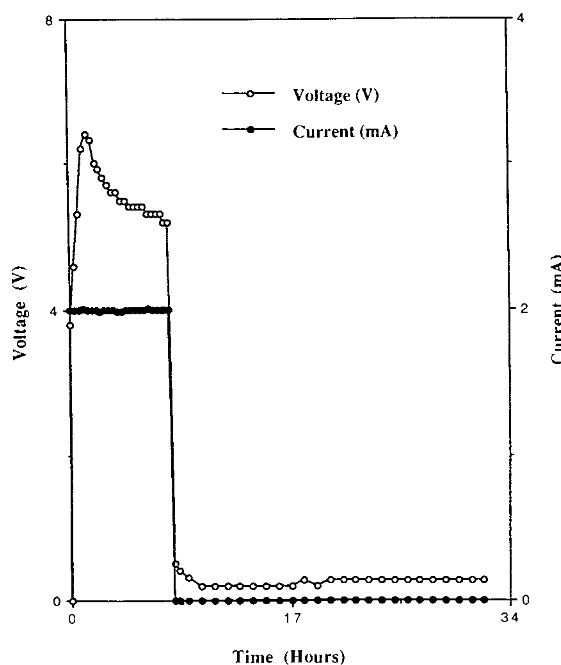

Fig. 7. Changes in voltage measured during electrophoresis at a constant current of 2 mA applied during the diffusion lag time.

with PHC; on application of an electrophoretic current there is an additional retarding force imposed by the affinity of drug for the polymer. This effect may not be important at later times when the polymer is loaded with drug. On removal of the electrophoretic current, the buildup of PHC in the receptor appears to carry on as if the lag period had merely been interrupted by the electrophoretic current, the delivery rate decreasing slightly from that which would be expected during the lag time. From previous experiments on the diffusion of PHC through 1% cross-linked PHEMA, during the lag phase, between 8 and 32 hr, the increase in PHC mass in the receptor was found to be approximately 2.94 mg, while in the present study it was 2.07 mg. The results in this study indicate that a significant difference between drug delivery rates is produced by application of an electrophoretic current before and after steady-state diffusion has been attained. The voltage–time profile produced in this study follows a pattern similar to that reported in the work of Lescure *et al.* (10), where a constant current was applied from the start of experiments (without waiting for a lag time), and a peak voltage corresponding to the lag time of bovine serum albumin appearance was found. The results in this study may also explain some of the findings of Kumar (8), where the drug delivery rate appeared to be virtually zero during periods of no electrophoresis in the lag phase of diffusion. Further, different measured rates of drug delivery can be accounted for when a constant voltage was applied at different stages of an experiment.

CONCLUSIONS

The results obtained showed that constant-current electrophoresis in the range 0 to 2.5 mA had a significant effect on the delivery rate of PHC through 1% cross-linked PHEMA films. The effects are rapid and reversible. The results also indicated that the delivery rate of PHC during electrophoresis can be predicted using currents in the range examined. Application of an electrophoretic current during the diffusion lag time period was found to produce a different effect to that found when electrophoresis was carried out during steady-state diffusion. The results indicate the feasibility of a controlled drug delivery device based on electrophoretic control.

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