An Electrically Modulated Drug Delivery Device. III. Factors Affecting Drug Stability During Electrophoresis

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A number of factors affecting the stability of propranolol HCl during electrophoretic control were investigated. It was found that significant degradation of propranolol HCl and hydrolysis of water occurred when a current of 15 mA was used with platinized electrodes. This degradation was thought to be due to decomposition of propranolol HCl at the electrodes. Degradation could be significantly reduced by using uncoated platinum electrodes and currents in the range of 0 to 2.5 mA, while still allowing control of drug delivery rates. Electrode reaction processes were found at high ionic strengths and high drug concentrations but were not thought to be associated with drug decomposition.

KEY WORDS: controlled drug delivery system; chronotherapeutics; electrically modulated; electrophoresis; degradation of propranolol hydrochloride; stability.

INTRODUCTION

The development of a drug delivery system based on the principles of electrophoresis has been described (1). Control over the delivery rate of ionic drugs using low constant currents has been demonstrated with propranolol HCl (PHC) as a model drug and crosslinked poly(2-hydroxyethyl methacrylate) (PHEMA) as a model polymer. It has been shown how the basal zero-order delivery rate due to diffusion from a reservoir device may be modulated in a positive manner, the increase in delivery rate having been shown to be a linear function of current in the range of 0 to 2.5 mA. The effect was also found to be highly reproducible.

Despite the recent interest in the development of electrophoretically controlled drug delivery systems (1–3), no attention has been given to any potential degradation of active drug in the electrophoretic system, due to either electrode processes or local heating effects in the polymer. A previous study commented on suspected drug degradation, but no detailed investigation was made (2). This is an important aspect of an electrophoretic drug delivery device, as degradation could lead to drug inactivation, or the production of irritant or toxic products. In the present study the stability of PHC during electrophoresis is investigated. The effect of current magnitude is considered and related to the degradation of PHC. The effect of using platinized electrodes is also examined.

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MATERIALS AND METHODS

Materials

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

Chromatography

The degradation of PHC was assessed by HPLC. The instrumentation used for this work consisted of a SP8100 liquid chromatograph solvent pump and autosampler (Spectra-Physics Ltd., St. Albans, U.K.) and a SP8400 uv detector (Spectra-Physics Ltd.) set to a wavelength of 288 nm. Data were analyzed using a SP4200 computing integrator (Spectra-Physics Ltd.). Quantitation was carried out using the external standard method. The chromatographic separations were performed at 37°C on a stainless-steel column (150 × 5-mm I.D.) packed with 5-mm ODS reversed-phase packing material (Hypersil, Shandon Southern Products, Runcorn, U.K.). An isocratic system was used, with the mobile phase flow rate maintained at 1.2 ml/min. The mobile phase composition was 25 ml of 40% (w/v) tetrabutylammonium hydroxide, 8 ml of 85% (w/v) phosphoric acid, 450 ml of methanol, and water to 1000 ml. The mobile phase was filtered and degassed before use.

External Standard Solutions

Five standard solutions were prepared from a stock solution. The standards contained PHC in the concentration range 5 to 41 μg/ml. The solutions were prepared in pH 4.48 Walpole buffer (4). Each standard was injected in duplicate and a calibration curve constructed.

Preparation of PHEMA Films

PHEMA disks crosslinked by the addition of 1% ethylene glycol dimethacrylate (EGDMA) were prepared as previously described (1). The disks were 4 cm in diameter with a thickness of approximately 0.09 cm.

Preparation of Platinized Electrodes

In order to reduce polarization at platinum electrodes, a thin layer of platinum black is usually coated onto platinum electrode surfaces (5). The platinizing of electrodes was achieved by electrodeposition from a solution consisting of 2 g chloroplatinic acid and 0.02 g lead acetate in 100 ml of distilled water. The electrodes to be coated were placed in the solution and a 12-V power supply (E30/1 Farnell Instruments Ltd, Wetherby, U.K.) connected across the electrodes, the polarity of the electrodes being reversed every 30 sec; this was repeated for 10 min. The electrodes were then placed in dilute sulphuric acid and the 12-V power supply was again connected for 10 min, the polarity being reversed every minute. The purpose of this was to remove traces of platinizing solution, which are liable to adsorb onto the electrodes. The electrodes were then rinsed in warm distilled water several times, followed by double-distilled water. The electrodes were subsequently stored in double-distilled water prior to use.

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Effect of Current in the Range 0 to 25 mA

Our previously reported electrophoretic studies were based on the use of electric currents in the range 0 to 2.5 mA (1), however, preliminary studies were based on the use of currents in the range of 0 to 25 mA. A schematic diagram of the model system used in these studies together with the assembly of the electrophoretic cell and the methodology used in electrophoresis studies has been described previously (1). In the present studies PHEMA films crosslinked with the addition of 1% EGDMA were used, and a PHC reservoir concentration of approximately 1.8 mg/ml was used. The electrodes used in the present study were platinized. Once the delivery rate of PHC into the receptor compartment had become constant, the power supply was turned on to a current of 15 mA for a period of 7 min. After approximately 17 hr the power supply was again turned on for a further 7 min. The effect on the delivery rate of PHC into the receptor compartment was examined.

The temperature changes within the PHEMA film during electrophoresis were examined to determine whether any localized heating occurred. PHEMA films crosslinked with the addition of 1% EGDMA were prepared as described previously (1); however, a Type K nickel-chromium/nickel-aluminium thermocouple wire (RS Components Ltd., Corby, U.K.) was also placed into the polymerizing solution between the glass molds, ensuring that the thermocouple tip did not protrude from the hydrogel and was firmly embedded as the film polymerized. A disk of 4 cm was then cut around the thermocouple tip using a scalpel. The electrophoresis cell was then assembled, with the thermocouple wire being fed through the electrode arm in the reservoir compartment and connected to a digital temperature indicator (RS Components Ltd., Corby, U.K.). In the present study the initial reservoir concentration of PHC was 1.8 mg/ml. Once the delivery rate, due to diffusion, had become constant, the power supply was switched on to provide a current of 15 mA for 2 hr, and the temperature noted.

Effect of Current in the Range 0 to 2.5 mA

The effects of currents in the range 0 to 2.5 mA were also investigated. The electrophoresis cell was assembled using platinized electrodes and 1% crosslinked PHEMA film, with a PHC reservoir concentration of approximately 1.8 mg/ml. Once the delivery rate due to diffusion had become constant, the power supply was switched on to provide a current of 1 mA for 1 hr; then after approximately 19 hr the power supply output was increased to provide a current of 2 mA for a further hour, and the effect on the delivery rate of PHC into the receptor compartment examined.

Traditionally, electrophoresis studies using platinum electrodes have involved the use of platinized electrodes in order to reduce electrode polarization (5). The effect of platinizing the electrodes with a layer of platinum black is to increase the effective electrode surface area and alter the electrode potential. In order to investigate whether the platinizing of electrodes affected the stability of PHC during electrophoresis, experiments using uncoated electrodes were performed. The electrophoresis cell was assembled using 1% crosslinked PHEMA and an initial reservoir concentration of 1.8 mg/ml PHC. Once the delivery rate due to diffusion had become constant, a current of 1 mA was passed for 4 hr. The effect on PHC degradation was examined, together with the effect on the voltage required to maintain a constant current of 1 mA. The experiment was performed in duplicate.

RESULTS AND DISCUSSION

Chromatography

The retention time of PHC was found to be approximately 3.6 min; an example of the type of chromatogram obtained is shown in Fig. 1, which also shows the presence of the decomposition product obtained in these studies. The external standard solutions produced only one peak. A calibration curve was obtained by plotting peak areas of the PHC peak against concentration. A linear correlation was found over the concentration range examined (r^2 = 0.9997).

Effect of Current in the Range 0 to 25 mA

Application of a constant current of 15 mA produced a near-instantaneous and very marked increase in the delivery rate of PHC into the receptor compartment compared with that due to diffusion pre- and postelectrophoresis (Fig. 2). However, during electrophoresis electrolysis of water appeared to occur, with bubbles being evolved at the electrodes; the gases were assumed to be hydrogen at the cathode and oxygen at the anode. At the end of the experiment, the solutions in both reservoir and donor compartments were colored brown. A control experiment showed no discoloration in the absence of PHC from the reservoir compartment. This suggests that the discoloration was not caused by material coming off the electrodes or being leached from the polymer, but more likely due to electro-

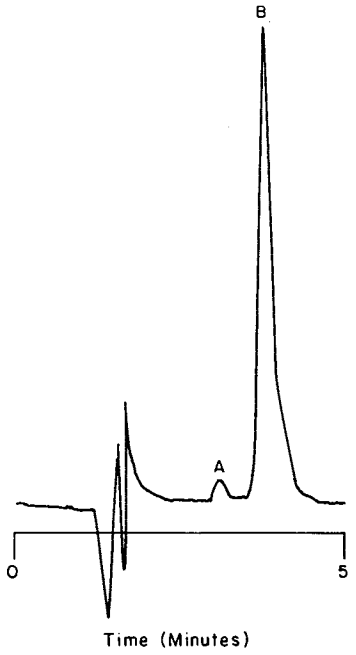

Fig. 1. HPLC chromatogram of a degrading sample of propranolol HCl showing a degradation product peak (A) and a propranolol HCl peak (B).

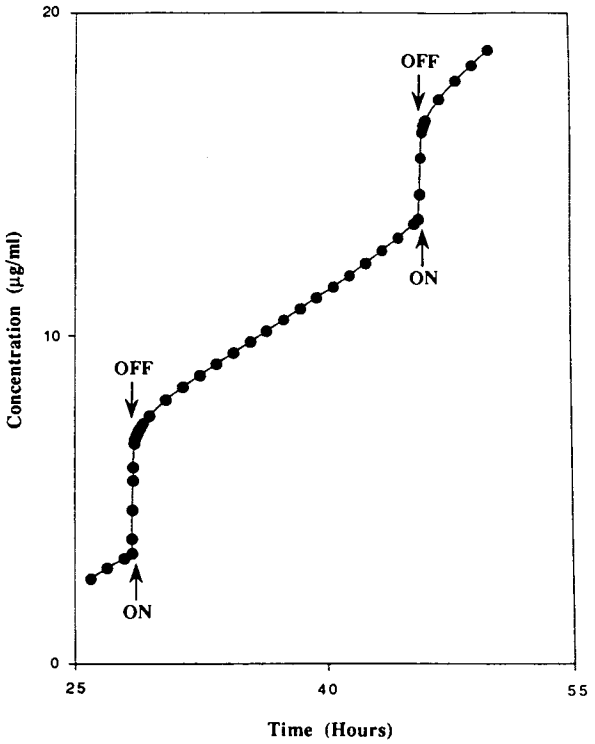

Fig. 2. Effect of applying an electrophoretic current of 15 mA using platinized electrodes on two separate occasions on the transport of propranolol HCl through crosslinked PHEMA film.

chemical degradation of PHC. Samples of the reservoir and receptor compartments were taken at the end of the experiment and analyzed for degradation of PHC using uv spectrophotometry at 288 nm (550S, Perkin Elmer Ltd., Slough, U.K.) and HPLC. The HPLC chromatogram showed the appearance of two peaks, one characteristic of PHC and the second showing a degradation product (Fig. 1). Ultraviolet spectrophotometry of the discolored solution, however, did not distinguish between the peaks and showed a concentration of PHC higher than that from HPLC studies. In the development of our HPLC assay method, we performed a study on a solution of PHC maintained at pH 10 under ambient conditions and exposed to light, which is known to cause instability (6). Measurement of PHC by uv spectrophotometry did not indicate a change in concentration even though discoloration of the solution occurred. HPLC, however, showed that the concentration of PHC decreased with time, with a corresponding increase in the size of the degradation product peak, though the nature of this degradation peak was not determined. Thus by using uv spectrophotometry and HPLC, the amount of PHC degradation could be estimated. Assay of samples from the reservoir and receptor compartments in the electrophoresis experiment showed that although only 5.0% degradation of PHC had occurred in the reservoir, 45.6% of the delivered PHC had degraded in the receptor. Thus even though a constant current of 15 mA had a significant effect on the drug delivery rate, a significant level of drug degradation had also occurred, thus making the use of such a high current unsuitable for modulating the delivery rate of PHC.

A thermocouple embedded in PHEMA films did not reveal any significant heating effects during electrophoresis; the digital temperature indicator was found to remain constant at 25°C throughout the application of an electric current. Visible gas evolution occurred from the electrodes and visible darkening of the solutions occurred in this period. It was considered that the reason that no localized heating effects were found in the present study was due to the very low currents used, perhaps combined with efficient heat transfer. It was therefore concluded that heating effects were probably not involved in the degradation of PHC found during electrophoresis in the system under investigation, and which was therefore thought to be a result of a reaction of PHC at the electrodes. This conclusion was supported by the difference in degradation found between coated and uncoated platinum electrodes (see below).

Effect of Current in the Range 0 to 2.5 mA

The effect on the delivery rate of PHC into the receptor compartment using lower currents (Fig. 3) was significant but not as great as that produced by a current of 15 mA (Fig. 2). The delivery rate produced by the 2-mA current was greater than that produced by the 1-mA current, which was in turn greater than the passive delivery rate produced by diffusion alone. A slight brown discoloration after electrophoresis was still present, though not as intense as that found with a current of 15 mA. Samples of the reservoir and receptor compartments were removed at the end of the experiment and analyzed for degradation of PHC using HPLC and uv spectrophotometry. The assay showed a 1.2% deg-

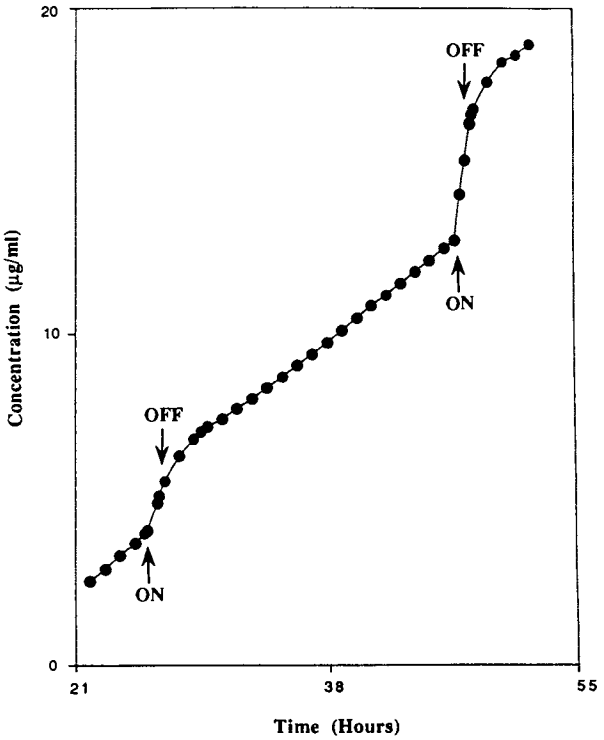

Fig. 3. Effect of applying an electrophoretic current of 1 mA for a period of 1 hr, followed by application of a current of 2 mA for 1 hr using platinized electrodes, on the transport of propranolol HCl through crosslinked PHEMA film.

radation of PHC in the reservoir, and 7.8% of the delivered PHC had degraded in the receptor. Thus, using the lower currents a significant effect on the drug delivery rate can still be produced, with drug degradation much less of a problem, though still present.

A significant effect on the delivery rate of PHC into the receptor compartment was still found when using uncoated platinum electrodes; an example of the effect found is shown in Fig. 4. However, the voltage required to provide the current increased by approximately 1 V in comparison to that required in the system using platinized electrodes. The voltages and power requirements found in these experiments have been reported previously (7). No brown discoloration was found after electrophoresis. Samples of the reservoir and receptor compartments were taken at the end of both experiments and analyzed for degradation of PHC. The assay showed that no detectable degradation had occurred after a constant current of 1 mA had been flowing for 4 hr. Thus, the layer of platinum black on the electrodes plays an important role in the degradation of PHC, possibly acting as a catalyst for an electrode reaction. Degradation may still be occurring, but at a much less significant level. Thus degradation of PHC can be avoided during constant-current electrophoresis provided that uncoated platinum electrodes are used. Several routine checks for degradation were performed on subsequent electrophoresis experiments using a range of currents from 0 to 2.5 mA, with no detectable degradation found.

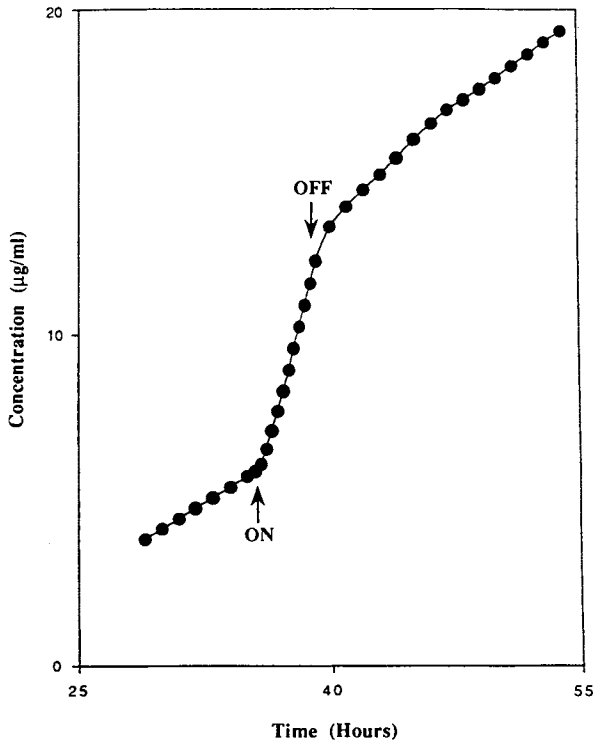

Fig. 4. Effect of an applied current of 1 mA for 4 hr on the transport of propranolol HCl through crosslinked PHEMA film.

It was observed that during experiments examining the effect of ionic strength in the range of 0.039 to 0.2 (8), at ionic strengths of 0.12 and above, the anode was found to have a fine mauve-colored film at the end of electrophoresis experiments which increased in color intensity as the ionic strength was increased. It was found that the film was easily removed with concentrated sulphuric acid, the resulting solution having a green coloration. A similar effect was found in studies on the effect of reservoir PHC concentration in the range of 1 to 55 m*M* (8). At a PHC concentration of 54.9 m*M* the anode was found to have a fine mauve film after electrophoresis. Since this phenomenon was seen only at the anode, it was not thought to be related to drug decomposition. It was considered that this film may have been due to an accumulation of chloride ions, although the nature of the electrode reaction is not understood and requires further investigation.

Conclusions

In the model electrophoretic system, significant degradation of PHC occurred with platinized electrodes when using a current of 15 mA, even when applied for a very short time. This degradation was thought to be due to decomposition of PHC at the electrodes. Using lower currents in the range of 0 to 2.5 mA, degradation was found to be significantly less using platinized electrodes and could be eliminated by using uncoated electrodes. The use of even lower currents, while preventing drug decomposition, still allows significant control over drug delivery rates.

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