Enhancement of Iontophoretic Transport of Diphenhydramine Hydrochloride Thermosensitive Gel by Optimization of pH, Polymer Concentration, Electrode Design, and Pulse Rate

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ABSTRACT

The purpose of the present study was to explore the passive and electrically assisted transdermal transport of diphenhydramine hydrochloride (DPH) by iontophoresis. For better bioavailability, better patient compliance, and enhanced delivery of DPH, an iontophoretic drug delivery system of a thermosensitive DPH gel was formulated using Lutrol F-127. The study was conducted using silver–silver chloride electrodes across hairless pig skin. The effects of pH, polymer concentration, electrode design, and pulse rate on the DPH permeation were investigated. The relationship between temperature, viscosity, and conductance of DPH was correlated using conductometry. Iontophoretic transport of DPH was found to increase with a decrease in the pH of the medium and an increase in the surface area of the electrode. Viscosity measurements and flux calculations indicated the suitability of the Lutrol gel for transdermal iontophoretic delivery of DPH. Anodal pulsed iontophoresis with disc electrode significantly increased the DPH skin permeation as compared with the passive controls.

KEYWORDS: Pig skin, thermosensitive gel, conductance, viscosity, permeation, pulsed current.

INTRODUCTION

Diphenhydramine hydrochloride (DPH) is 2-diphenylmethoxy-N,N-dimethylethanamine hydrochloride.[1] The free base has a molecular weight of 255.4 and a pK_a of 9.12. The hydrochloride salt is freely soluble in water, and its molecular weight is 291.8.

DPH, being anticholinergic, is used to control parkinsonism in the elderly with doses of 25 to 50 mg administered 3 to 4 times a day.[2,3] DPH undergoes extensive (50%) presystemic metabolism through the liver, and therefore its bioavailability is only 40% to 60%. Dose adjustment depends on the degree of symptom alleviation and the occurrence of dose-limiting side effects. This dose adjustment/individualization of dose can be done effectively by iontophoresis. Moreover, iontophoresis avoids the inconvenience of the intravenous route.

Iontophoresis is a technique that facilitates movement of ions of soluble salts across a membrane under an externally applied potential difference that is induced across the skin by a low-voltage electric current.[4] The application of constant current is controlled by an electronic device that adjusts the voltage in response to the changes in skin electrical resistance. Charged drug as well as other ions are carried across the skin as a component of induced ion flow. Iontophoresis effectively delivers a large variety of compounds across the skin.[5] Numerous factors affect iontophoretic delivery.[5,6] Some important considerations include flux proportionality with respect to applied current density and the presence of ions other than drug (these decrease the efficiency of iontophoretic transport of the drug). Current up to 0.5 mA/cm^2 is believed to be tolerable for patients. The onset of action with iontophoretic treatment is rapid, in contrast to hours for passive transdermal delivery.[7] Since drug delivery is proportional to applied current, significant advantages of iontophoresis include the possibility of preprogramming the drug delivery, dose tailoring on an individual basis, or time tailoring in a constant or pulsatile fashion.[5]

Because of the complex nature of the drug delivery, most of the studies related to transdermal iontophoresis are focused on aqueous solutions.[8] Gels are considered to be the most suitable delivery vehicles for iontophoresis, as they can be easily amalgamated with the iontophoretic delivery system and match the contours of the skin. Gels also have other advantages over liquids, such as ease of fabrication into the device, suitability with the electrode design, deformability into skin contours, better occlusion, and better stability. Moreover, the high proportion of water employed in gel formulations can in turn provide an advantageous electroconductive base for clinical use.[9] Lutrol is a polyoxypropylene-polyoxyethylene, non-ionic, surface-active block copolymer composed of ~70% ethylene oxide and 30% propylene oxide with an average molecular weight of 115 000 Da.[10] The fact that poloxamer solution (20%-30% wt/vol in water) forms a reversible gel above 4°C (ie, solution at low temperature and gel at higher temperature) offers an unique advantage of ease in handling

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and application. The reversible sol-gel property allows the cool solution to flow onto the skin and spread across it during its transformation to a nonocclusive gel at body temperature.[11] Furthermore, because of the poloxamer solution's ability to form a hydrogel, it can show good electrical conductivity. In addition, this property can be exploited for refillable unit dose iontophoretic drug delivery systems.

The present study was undertaken to assess the feasibility of delivering DPH using Lutrol F-127 as a vehicle for the iontophoretic transdermal delivery. The approach involved checking the drug permeability by passive and iontophoretic transport using an ex vivo hairless pig skin model. The effects of pH, electrode design, and pulsed current on the DPH permeation were examined. The relation between temperature and viscosity of Lutrol gel and conductance of DPH was also investigated.

Materials and Methods

Chemicals

DPH (Banner Pharma Pvt Ltd, Mumbai, India) and Lutrol F-127 (BASF, Ludwigshafen, Germany) were obtained as gift samples. Silver wire (1 mm diameter, 99.9% pure) was purchased from Loba Chime (Mumbai, India). Distilled water having a resistivity of more than 18 MΩ was used to prepare aqueous solutions. Other chemicals used in the study were of analytical grade and were purchased from Loba Chime.

Preparation of Electrodes

Silver–silver chloride electrodes were used for their stability and reversibility.[12] The rod-shaped electrode that is used as cathode was prepared by dipping the silver wire into the molten silver chloride.

Preparation of Skin

The density of the hair on human skin and pig skin is similar.[13] Hence, pig skin was chosen for the permeation studies. Pig skin from a 3-day-old pig that was killed by cervical dislocation was obtained from a local slaughterhouse. Muscles, fat layer, and tissue remains were removed, hair was cut short, and skin pieces were examined for pin holes. The skin was then cut into pieces of appropriate size and was used within 2 hours.

Ex Vivo Permeation Study for Optimizing the pH of Donor Medium

The hairless pig skin was mounted on vertical diffusion cells that were maintained at 37°C ± 1°C using a hot water circulator. The skin was mounted on the diffusion cell with the stratum corneum facing the donor compartment. DPH in a concentration of 25 mg/mL was dissolved in prefiltered buffer solutions (prepared as per US Pharmacopeia) of pH values 4.2, 5.5, 6.4, and 7.4. Exactly 2 mL of each DPH solution was placed in the donor compartment. The receiver solution for permeation studies was pH 7.4 saline phosphate buffer solution. A constant direct current of 0.5 mA was applied for iontophoresis using silver–silver chloride electrodes. They prevent electrolysis of water, which may result in pH shifts. Silver wire of 1.5 cm was used as the anode and silver–silver chloride wire of 4.0 cm was used as the cathode. The anode was dipped in the donor solution and the cathode in the receptor solution, which was stirred using a Teflon-coated magnetic stirrer (Whirlmatic motorless magnetic stirrer, WS-MEGA, Spectra Lab, Mumbai, India) at 600 rpm. Passive permeation was tested without application of any current.

Preparation of Thermosensitive Gel

Gels were prepared by the cold method.[14,15] Gels containing 18%, 20%, and 22% wt/vol of Lutrol F-127 were prepared in phosphate buffer of pH 4.2 to optimize the gelling temperature. For the conductivity study, Gel A having 20% wt/vol Lutrol F-127 in distilled water, and Gel B having 20% wt/vol Lutrol F-127 in pH 4.2 phosphate buffer, were formulated without incorporation of drug.

After optimization, Gel C containing DPH and Lutrol F-127 was prepared as follows. Exactly 25 mg/mL of DPH was dissolved in a phosphate buffer pH 4.2, and the solution was maintained at 5°C using a freezing mixture. It was constantly stirred using a Teflon-coated magnetic bead (Spectra Lab, Mumbai, India). Exactly 20% wt/vol of Lutrol F-127 was dispersed slowly into this drug solution, and the resulting mixture was then refrigerated at 5°C for 48 hours to obtain a completely hydrated, homogeneous, and clear gel.

Conductivity Study

Calibration of the conductometer (Equip-Tronics, Mumbai, India) was done using 0.05% wt/vol NaCl solution, which has a conductivity of 1 mS/cm. The conductance of gels A, B, and C was measured using the calibrated conductometer at 15°C, 20°C, 25°C, 30°C, 32°C, and 37°C.

Viscosity Measurement

The viscosity of gels was determined using a cone and plate viscometer (CAP viscometer, model CAP 2000+L, Brookfield Engineering Laboratories, Middleboro, MA). A sufficient amount of each gel was placed on the sample plate of the viscometer and was allowed to stand for 5 minutes to reach equilibrium temperature. Viscosity was then determined at 20°C, 25°C, 30°C, and 32°C. For each measurement, readings were recorded at 10 rpm for 30 seconds.

Ex Vivo Permeation Studies Using Thermoreversible Gel

The hairless pig skin with the stratum corneum side facing the donor compartment was mounted on a vertical diffusion cell that was maintained at 37°C ± 1°C using a hot water circulator. Exactly 2 mL of 20% wt/vol Lutrol F-127 gel containing 25 mg/mL of DPH was put into the donor compartment. A constant direct current of 0.5 mA was applied for iontophoresis using a silver–silver chloride electrode. Silver wire of 1.5 cm was used as the anode, and silver–silver chloride wire of 4 cm was used as the cathode. Passive permeation was tested without application of any current. The same experiment was repeated by using disc electrodes of 1 cm and 2 cm as anodes, using 0.5 mA constant direct current and a pulsed current having an ON:OFF ratio of 1:1, 2:1, and 3:1.

Sample Collection and Data Analysis

Conductance of gels A, B, and C was determined. Conductance of DPH only was calculated by using Equation 1:

$$\text{DPH conductance} = (\text{Conductance of gel C}) - (\text{Conductance of gel B}) \quad (1)$$

The percentage of drug ionized was calculated using Equation 2[16]:

$$\%\ \text{DPH ionized} = \frac{100}{1 + 10^{(\text{pH}-\text{pKa})}} \quad (2)$$

Exactly 1 mL of the sample was collected after every hour from the side arm of the diffusion cell using a syringe and was replaced with the same volume of prewarmed (37°C) fresh receptor medium. The samples collected were sufficiently diluted and tested for the drug content at 258 nm using a UV spectrophotometer (model V-530, Jasco, Tokyo, Japan).

The real steady-state situation was not observed clearly during permeation studies. For this reason the flux_{ss} was calculated from the slope of the linear portion of the curve.

The enhancement ratio (ER) for the flux_{ss} was calculated by using Equation 3:

$$ER = \frac{\textit{Iontophoretic Flux}}{\textit{Passive Flux}} \quad (3)$$

Statistical analysis of the data was performed by employing Student *t* test, with the significance level set at 0.05. The data were expressed as mean ± SD.

Results and Discussion

Iontophoresis markedly improved the transdermal permeation of DPH. On ionization, diphenhydramine acquires a positive charge. On iontophoresis, the positive charge of the anode pushes positively charged diphenhydramine ions into the skin; this is why its transport across the skin is increased as compared with passive diffusion. As seen in Figure 1, as the pH of the solution is decreased, the permeation of DPH is increased. With the pH of the donor solution at 4.2, the flux_{ss} was 16.30 mg/cm^2 hr, while it was only 10.04 mg/cm^2 hr (ER = 1.62) when the donor pH was 7.4 (*t* test, $P < .05$).

As seen in Equation 2, ionization is a function of the pH of the surrounding medium. Since DPH is a very weak acid (pK_a 9.1), 100% ionization at pH 4.2 was observed. Therefore, increased ionization and greater repulsion resulted in increased permeation. In addition, it is generally accepted that the stratum corneum possesses a net negative background charge.[17,18] A pH of 4.2 neutralizes skin's negative charge and avoids the interruption of skin charge during iontophoretic permeation. Therefore, the remaining studies were performed using pH 4.2 phosphate buffer medium.

Gels are clinically acceptable delivery systems for iontophoresis in terms of stability and ease of handling and refilling of iontophoretic patches. Lutrol F-127 (poloxamer 407) is a non-ionic block copolymer that is an intermediate between hydrophilic and hydrophobic polymers.[19] It forms a thermoreversible hydrogel[20] of polyoxy(ethylene oxide)-b-poly(propylene oxide)-poly(ethylene oxide). Its 3-dimensional network provides sufficient rigidity, while the highly hydrated microscale environment facilitates mass transfer.[21] Thermoreversible gel has additional advantages over conventional gel. Lutrol F-127 was selected because it forms a thermoreversible gel at the optimized iontophoretic conditions with acceptable viscosity and release characteristics.[22,23]

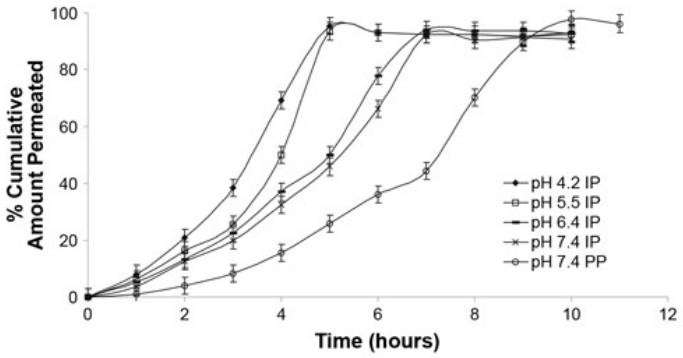

Figure 1. Effect of pH on the iontophoretic permeability of diphenhydramine hydrochloride. Data represent n = 4, mean ± SD. IP indicates iontophoretic permeation; PP, passive permeation.

The concentration of Lutrol F-127 in the gel was optimized to maintain it in a liquid state so that it could be poured into the electrode cavity. On application of this electrode to the skin, the polymeric solution must immediately gel in order to avoid spillage. The viscosity of the polymeric solutions containing 18%, 20%, and 22% wt/vol of Lutrol F-127 in phosphate buffer pH 4.2 was determined at different temperatures to assess their gelling characteristics. Figure 2 demonstrates that an increase in the concentration of Lutrol increases the gelling property of the gel at lower temperatures. The polymeric solution containing 22% wt/vol of Lutrol gelled at 25°C with a high viscosity. The solution containing 18% wt/vol of Lutrol remained in a liquid state at 25°C and gelled at 30°C to 32°C with a very low viscosity that indicates poor gelling. At 20% wt/vol of Lutrol, the gelling property of the gel gradually increased as the temperature increased, with a good viscosity of 17.437 Pa at 32°C. Thus, the concentration of Lutrol was optimized to produce a gel with enough viscosity to hold the formulation in the electrode cavity when the electrode is applied to the skin.

The viscosity of gels A, B, and C was determined to investigate the influence of pH and the drug DPH on the gelling property and the viscosity of the gel. Figure 3 indicates that gel B exhibited no significant effect of pH on the viscosity (*t* test, $P > .05$), but after addition of DPH in the gel, there was a fall in viscosity (3.937 Pa) at 25°C as the polymeric solution did not form a gel. As the temperature increased to 30°C, there was spontaneous gelling indicated by a sudden increase in the viscosity (17.250 Pa). At 32°C the polymeric solution showed good gelling, with a viscosity of 18.0 Pa. The gel formation is a result of micellar entanglement and packing, with an outer aqueous environment (hydrated polyethylene oxide [PEO] chains) and inner hydrophobic core (polypropylene exide [PPO] chains), making the gel suitable for the delivery of both hydrophilic and hydrophobic drugs.[24] In gel C at 25°C, possibly because of the presence of hydrophilic DPH, Lutrol might be unable to form micellar entanglement (formation of PEO chains), resulting in nongelling and low viscosity. Therefore, the presence of DPH in the gel further enhances the flow property of the polymeric solution as it remains in the liquid state at room temperature.

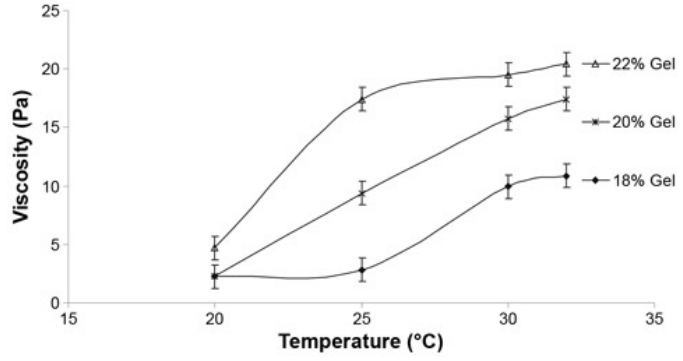

Figure 2. Effect of polymer concentration on the viscosity of the gel. Data represent n = 6, mean ± SD.

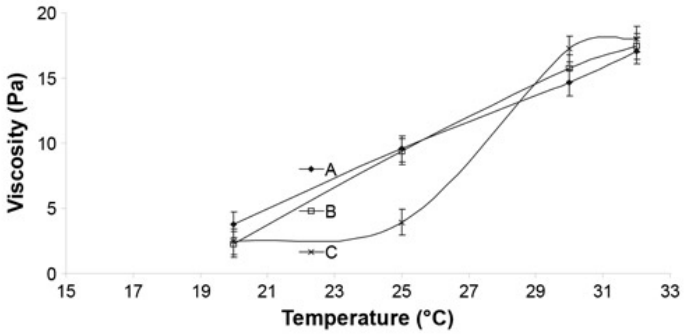

Figure 3. Effect of pH and DPH on viscosity of 20% wt/vol Lutrol gel. A is gel prepared in distilled water, B is gel prepared in pH 4.2 phosphate buffer solution, and C is gel B with 25 mg/mL DPH added. Data represent n = 6, mean ± SD. DPH indicates diphenhydramine hydrochloride.

As reported in many studies,[4,5,7] among the different factors influencing the iontophoretic drug delivery system, one of the prime factors is the charge carried by the co-ions. The extraneous species present in the medium compete with the drug to carry the current. As a result, less charge is available for the drug, resulting in decreased iontophoretic transport. Also, several studies[25,26] have reported that an increase in the viscosity results in a decrease in the formulation conductivity. Therefore, to investigate the influence of Lutrol and the viscosity of the gel on the charge-carrying capacity of DPH, a conductance study was performed. DPH in gel showed 10-fold greater conductance as compared with plain Lutrol gel (*t* test, $P < .05$). This difference indicates that the charge carried by extraneous ions is very minor and will not significantly influence the iontophoretic transport of DPH. Also, the conductance gradually increased with the increase in the temperature/viscosity of the gel. This is possibly because, as temperature increases, the free energy of the DPH ions increases, leading to increased mobility and ultimately conductance. This indicates that the viscosity of the 20% Lutrol gel does not interfere with the mobility of ionized DPH that carries the charge.

Since the gel containing 20% wt/vol Lutrol F-127 showed good gelling property, viscosity, and conductance, it was considered optimum for iontophoretic drug delivery, and further ex vivo permeation studies were performed on it. The passive permeation profile of DPH gel in Figure 4 shows a significant decrease (*t* test, $P < .01$) in the permeation rate of DPH as compared with passive permeation of DPH from the solution of pH 4.2. This indicates that although the viscosity of the gel does not influence the conductance of DPH, it significantly decreases the permeation rate of DPH. Therefore, DPH diffusion through the thermoreversible matrix may

be a rate-determining step. On iontophoresis, the permeation rate of DPH from the gel was significantly increased with a flux of 8.90 mg/cm^2 hour. To further increase the permeation rate, a permeability study was performed using 1 cm and 2 cm disk electrodes, since surface area and permeation rate are directly proportional. As seen in Figure 4, permeation rate was markedly enhanced by disk electrodes as compared with wire electrodes (*t* test, $P < .01$). Approximately 100% of DPH was permeated within 10, 7, and 6 hours using the wire electrode, the 1 cm disk electrode, and the 2 cm disk electrode, respectively. Maximum flux$_{ss}$ of 12.44 mg/cm^2 hour was seen when the 2 cm disk electrode was used. An ER of 1.46 was observed between flux$_{ss}$ of the 2 cm disk electrode and passive permeation, while an ER of 1.40 was observed between the 2 cm disk electrode and the wire electrode.

Instant electronic repulsion and enhanced iontophoretic transport are observed at the disk electrode because of increased surface area. The permeation profile of passive permeation at pH 7.4 in Figure 1 reflects a lag time of 1 hour, which has been gradually decreased with the decrease in pH. The initial slope of the permeation curve was markedly enhanced using disk electrodes as well. Therefore, to have a more immediate pharmacological effect, the disk electrode needs to provide greater initial flux$_{ss}$ than the wire electrode does.

Use of continuous direct current may result in skin polarization, which can reduce the efficiency of iontophoretic delivery proportional to the length of direct current application.[27] The buildup of this polarizable current can be overcome by using pulsed direct current that is delivered periodically.[28] Therefore, to further increase the permeation rate and the flux of DPH across the skin, pulsed iontophoresis using disk electrodes was performed. As seen in Figure 5, the permeation profile of DPH at pulsed iontophoresis of ON:OFF pulse ratios 2:1 and 3:1 was similar to that of the continuous current (*t* test, $P > .05$). However, the permeation rate was significantly increased at the pulse rate 1:1, with a flux

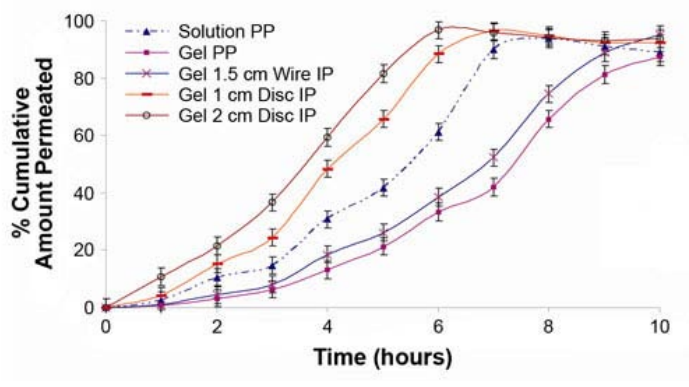

Figure 4. Effect of electrode design on the iontophoretic permeability of diphenhydramine hydrochloride. Data represent n = 4, mean ± SD. PP indicates passive permeation; IP, iontophoretic permeation.

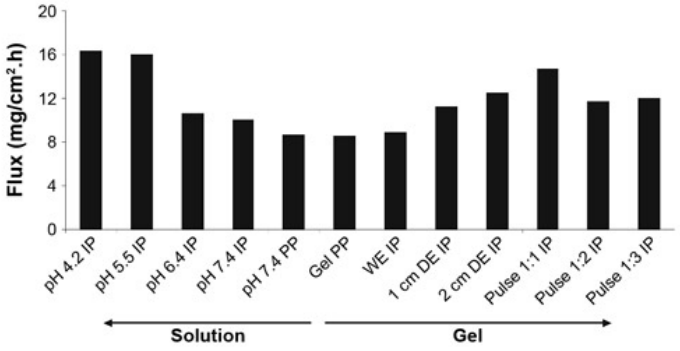

Figure 5. Effect of pH, electrode design, and pulsed current on iontophoretic flux$_{ss}$ of diphenhydramine hydrochloride. IP indicates iontophoretic permeation; PP, passive permeation; WE, wire electrode; DE, disk electrode.

of 14.66 mg/cm^2 hour and an ER of 1.18, as compared with continuous current (*t* test, $P < .05$). The use of pulse current allows the skin to depolarize and return to its initial electric condition when the current phase is put off for a fraction of time.

Figure 5 depicts a maximum flux$_{ss}$ of 14.66 mg/cm^2 hour with a 2 cm disk electrode on 20% wt/vol Lutrol F-127 gel containing DPH. It follows that, to achieve a daily systemic dose of 25 to 50 mg DPH at a 0.5 mA/cm^2 current density of 1:1 pulse, a minimum transport area of 1.7 to 3.4 cm^2 for 1 hour or 4.3 to 8.5 cm^2 for 15 minutes of application will be required. This indicates the feasibility of transdermal iontophoretic delivery of DPH. Further in vivo studies will be required to support in vitro conclusions and develop in vitro–in vivo correlations.

Conclusion

Lutrol F-127 could be used to formulate a thermosensitive gel for iontophoresis that will gel upon application to skin. Because of neutralization of skin charges and complete ionization of DPH, permeation was significantly enhanced at pH 4.2. Because of an increase in surface repulsion and periodic depolarization of skin, pulsed iontophoresis using a disk electrode showed better flux enhancement, and iontophoretic transport of DPH was almost twice as much as for passive transport. The present study demonstrated the feasibility of DPH transdermal transport through Lutrol gel by iontophoresis.

References

1. Holcomb IJ, Fusari SA. Diphenhydramine hydrochloride. In: Florey K, ed. *Analytical Profiles of Drug Substances.* vol. 3. New York, NY: Academic Press; 2005:173–176.

2. Bianchine J. Drugs for Parkinson's disease: centrally acting muscle relaxants. In: Goodman L, Gilman A, eds. *The Pharmacological Basis of Therapeutics.* 6th ed. New York, NY: Macmillan; 1980:485.

3. Truong DD, Sandroni P, van den Noon S, Matsumoto RR. Diphenhydramine is effective in the treatment of idiopathic dystonia. *Arch Neurol.* 1995;52:405–407.

4. Singh P, Maibach HI. Iontophoresis in drug delivery: basic principles and applications. *Crit Rev Ther Drug Carrier Syst.* 1994;11:161–213.

5. Banga AK, Chien YW. Iontophoretic delivery of drugs: fundamentals, developments and biomedical applications. *J Control Release.* 1988;7:1–24.

6. Srinivasan V, Higuchi WI, Sims SM, Ghanem AH, Behl CR. Transdermal iontophoretic drug delivery: mechanistic analysis and applications to polypeptide delivery. *J Pharm Sci.* 1989;78:370–375.

7. Singh P, Maibach HI. Iontophoresis: an alternative to the use of carriers in cutaneous drug delivery. *Adv Drug Deliv Rev.* 1996;18: 379–394.

8. Tomohira Y, Machida Y, Onishi H, Nagai T. Iontophoretic transdermal absorption of insulin and calcitonin in rats with newly-devised switching technique and addition of urea. *Int J Pharm.* 1997;155:231–239.

9. Zhang I, Schung KK, Edwards DA. Hydrogels with enhanced mass transfer for transdermal drug delivery. *J Pharm Sci.* 1996;85:1312–1316.

10. Rowe RC, Sheskey PJ, Weller PJ. Poloxamer. In: Rowe RC, Sheskey PJ, Owen SC, eds. *Handbook of Pharmaceutical Excipients.* London, UK: Pharmaceutical Press; 2003:447–448.

11. Bentley MVL, Marchetti JM, Ricardo N, Ali-Abi Z, Collett JH. Influence of lecithin on some physical chemical properties of poloxamer gels: rheological, microscopic and in vitro permeation studies. *Int J Pharm.* 1999;193:49–55.

12. Phipps JB, Scott ER, Gyory JR, Padmanabhan RV. Iontophoresis. In: Swarbrik J, Boylan P, eds. *Encyclopedia of Pharmaceutical Technology.* New York, NY: Marcel Dekker; 2002:1578–1588.

13. Banga AK. *Electrically Assisted Transdermal and Topical Drug Delivery.* London, UK: Taylor and Francis; 1998.

14. Schmolka IR. Artificial skin, I: preparation and properties of pluronic F-127 gels for treatment of burns. *J Biomed Mater Res.* 1972;6:571–582.

15. Lutrol F. *127, Technical Information.* Ludwigshafen, Germany: BASF; 1999.

16. Block JH. Physicochemical properties in relation to biological action. In: Block JH, Beale JM, eds. *Wilson and Giswold's Textbook of Organic Medicinal and Pharmaceutical Chemistry.* Philadelphia, PA: Lippincott Williams & Wilkins; 2004:15.

17. Aguilella V, Belaya M, Levadny V. Passive transport of small ions through human stratum corneum. *J Control Release.* 1997;44:11–18.

18. DeNuzzio J, Dberner B. Electrochemical and iontophoretic studies of human skin. *J Control Release.* 1990;11:105–112.

19. Su HL, Miller SC. In vitro release of nicotinic acid alkyl esters from poloxamer vehicles. *Int J Pharm.* 1990;66:213–221.

20. Anderson BC, Pandit NK, Mallapragada SK. Understanding drug release from poly(ethylene oxide)-b-poly-(propylene oxide)-b-poly (ethylene oxide) gels. *J Control Release.* 2001;70:157–167.

21. Zhang I, Schung KK, Edwards DA. Hydrogels with enhanced mass transfer for transdermal drug delivery. *J Pharm Sci.* 1996;85:1312–1316.

22. Chen-Chow P, Frank SG. In vitro release of lidocaine from pluronic F-127 gels. *Int J Pharm.* 1981;8:89–100.

23. Miyazaki S, Takeuchi S, Yokouchi C, Takada M. Pluronic F-127 gels as a vehicle for topical administration of anticancer agents. *Chem Pharm Bull (Tokyo).* 1984;32:4205–4208.

24. Moore T, Croy S, Mallapragada SK, Pandit NK. Experimental investigation and mathematical modeling of Pluronic F127 gel dissolution: drug release in stirred systems. *J Control Release.* 2000; 67:191–202.

25. Fang JY, Huang YB, Wu PC, Tsai YH. Transdermal iontophoresis of sodium nonivamide acetate, II: optimization and evaluation on solutions and gels. *Int J Pharm.* 1996;145:175–186.

26. Ho HO, Huang FC, Sokoloski TD, Sheu MT. The influence of cosolvents on the in-vitro percutaneous penetration of diclofenac sodium from a gel system. *J Pharm Pharmacol.* 1994;46:636–642.

27. Lawler JC, Davis MJ, Griffith E. Electrical characteristics of the skin: the impedance of the surface sheath and deep tissues. *J Invest Dermatol.* 1960;34:301–308.

28. Banga A, Chein YW. Iontophoretic delivery of drugs: fundamentals, developments and biomedical applications. *J Control Release.* 1988; 7:1–24.