DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 21(14), 1631-1648 (1995)

A STRATEGY TO OPTIMIZE THE OPERATION CONDITIONS IN IONTOPHORETIC TRANSDERMAL DELIVERY OF PILOCARPINE

Yi-You Huang, Shian-Min Wu†,Cheng-Yi Wang and Tsung-Shann Jiang†

Center for Biomedical Engineering ,College of Medicine

National Taiwan University, Taipei, Taiwan

†Dept. of Chemical Engineering, Tunghai University,Taichung, Taiwan

ABSTRACT

Optimization via experiments in iontophoresis was investigated. A response surface method was applied in optimizing the operating conditions in iontophoretic transdermal delivery of pilocarpine. With an objective for a transitory application of pilocarpine, i.e. in diagnosis of cystic fibrosis or in treatment of hyperhidrosis, the best operating condition was achieved via a response surface method by adjusting the pH of the buffer, ionic strength, current amplitude and frequency of pulsed current or active temporal ratio etc. based on unknown structural models with stationary or slowly varying optima in the region of interest. This strategy was easy to approach and efficient in seeking optimal experimental conditions for multiple variables and an unknown structural system. Satisfactory results in

Address correspondence to: Yi-You Huang Ph.D., Center for Biomedical Engineering, College of Medicine, National Taiwan University, No. 1, Sec. 1, Jen-ai Road, Taipei, Taiwan., Fax: 886-2-3940049

optimizing the operating conditions in iontophoretic transdermal delivery of pilocarpine were thereby achieved.

INTRODUCTION

Iontophoresis is used to enhance the transdermal flux of many compounds (1,2) and at present receives considerable attention (3). In dermatology, diverse medications with an iontophoretic system to delivery drug, ranging from steroids and antibiotics to local anesthetics, and the treatment of hyperhidrosis or diagnosis of cystic fibrosis, are used (4). In more recent work, transdermal iontophoresis is also investigated as a system to deliver peptide and protein drugs in systemic medication (5,6,7). Transdermal iontophoresis can avoid hepatic first-pass effects, can provide a controlled and large rate of delivery, and can be employed for varying periods. Iontophoresis is a process or technique that causes an increased penetration of ionic or charged molecules into tissue using electrical potential or current, in either continuous (8) or pulsed mode (9).

In the application of iontophoresis, there are many factors that influence delivery of drugs, including physicochemical and electric properties of the system. The physicochemical factors are the charges that drugs possess, the conductivity of the system, the pH of the donor solution, the ionic strength of the buffer, concentration of drug etc. For the electric factors, the rate of delivering a drug depends on the electrical potential applied, the type of electrical potential---constant voltage or constant current, the mode we used---continuous mode or pulsed mode, the electrode, the current amplitude, the frequency of pulsed current, or active temporal ratio etc. Each factor has its individual influence. Some effect would be counterbalanced by an other. The significance of the influence of these parameters also varies from one drug being delivered to another.

Pilocarpine, a cholinergic agent that was chosen as a model drug, is a widely used drug for diagnosis of cystic fibrosis. Cystic fibrosis is an inherited systemic disorder of mucus-producing exocrine glands affecting the pancreas in addition to the bronchi, intestine and liver. There is a diagnostically abnormal content of

sodium and chloride in perspiration. A physician invariably analyzes the patient's perspiration to diagnose the syndrome of cystic fibrosis. The major effect of pilocarpine on the body is producing marked sweating. In order to improve control of perspiration and to decrease the total water lost, transdermal iontophoresis of pilocarpine is the best choice (10). As for rapid diagnosis, a quick action is needed. Transitory application and immediate pharmacodynamic response are the main objectives of this application. In this work, optimization based on a response surface method via experiments in iontophoresis with periodic pulsed current was investigated.

OPTIMIZING METHOD

The response surface method is a useful and efficient tool to obtain an appropriate model with minimum experiments. It is used in pharmaceutial processes in optimization of granulation (11,12), capsule and tablet formulation (13), or oral solution (14). The structure of this method is outlined as follows (Figure 1). Before experiments are designed, a definite purpose of experiments and a quantitative objective function of the system should be clearly defined. In iontophoretic transdermal delivery of pilocarpine for marked sweating, for example, it can be defined as the maximum rate of permeation of pilocarpine in the first hour. Then we need to select the most important variables that affect the system response and to predetermine the range of each input variable. Systematic experiments proceed according to a two-level factorial design.

A. Two-level factorial design

In the case of transdermal iontophoresis of pilocarpine under a periodically pulsed current device, the most important factors affecting the rate of permeation of pilocarpine include pH and ionic strength of the donor solution, the frequency of pulsed current, the magnitude of the current, the duty cycle etc. In these tests, the variables of pH (x_1), ionic strength (x_2), frequency (x_3),and duty cycle (x_4) were chosen as key parameters. Based on previous tests on the literature and our preliminary experiments of iontophoretic delivery of pilocarpine, the condition x^0

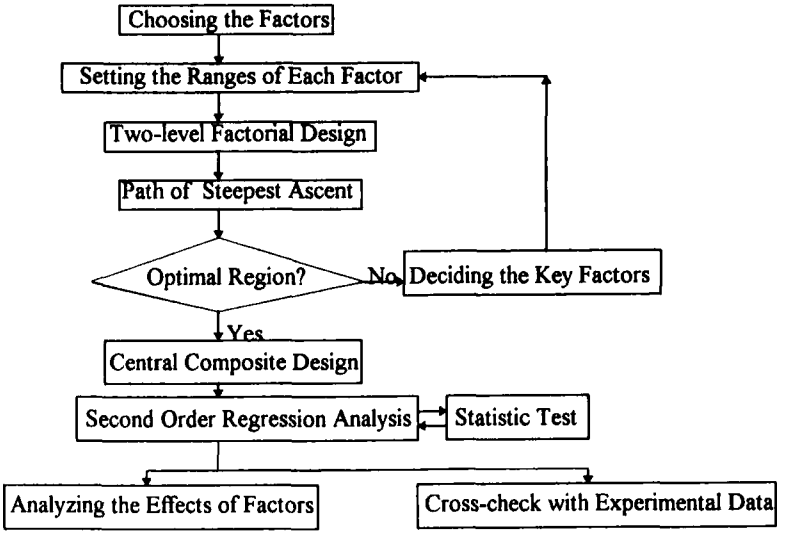

FIGURE 1.
Outline of the response surface method

=(4, 0.012, 2000, 50) was chosen as a starting point and the spacing s=(±1, ±0.008, ±1000, ±10) was used. To simplify the calculation, all variables are normalized in coded level, -1(low)~+1(high). 2^{4-1} experiments were conducted first to find the path of steepest ascent.

B. First-order response surface methods and path of steepest ascent

A first-order response surface can be constructed based on these experimental results by a method of least squares. The gradient direction $\nabla g(x^k)$ for the next step can be estimated subsequently. Experiments are then conducted at points along this direction to a new point x^{k+1} that represents the best solution obtained along the direction $\nabla g(x^k)$. If the optimal objective function is in the region of the corresponding current point x^k, a detailed and complete experimental design (central composite design) should be performed to improve understanding of the response surface by using response surface model of high order. If the optimal objective function is outside the region of the current point x^k, another starting

point near this optimal point and spacing should be chosen. The corresponding two-level coded factorial experiments should be conducted again to obtain a new path of steepest ascent, proceeding repeatedly as above until response surface model of higher order is established and a maximum of the objective function is attained.

C. Central composite design

If an "optimum" region is once decided according to the method of the path of steepest ascent, it is necessary to conduct extra experiments to achieve a more detailed description of the response surface, i.e. a response surface model of greater order. we generally add design points near the center to complete a second-order response surface to test this optimum solution. Such a model with more than three variables is expressed mathematically as

$$Y = a_0 + \sum_{i=1}^{n} a_1 x_i + \sum_{i=1}^{n} \sum_{j=i+1}^{n} a_{ij} x_i x_j + \varepsilon \qquad (1)$$

in which Y is the value of response, the dependent variable; a_0 is equivalent to the response at the central point; a_i shows the degree of effect of x_i on Y; a_{ij} shows the interaction of x_i and x_j, and ε is the vector of errors.

If several successive experiments are performed at scattered points about the known experimental region without achieving an improved solution, the search can be terminated and the best available solution can be adopted.

D. Effect analysis of factors

From the final surface response of high order, the degree of effect of x_i on $\hat{Y}$; and the interaction of x_i and x_j can be determined from the coefficients of a_i and a_{ij}. Student's t test was used to verify the significance of these coefficients and the validity of this model.

MATERIALS AND METHODS

Pilocarpine hydrochloride (reagent grade) was obtained from Nacalai Tesque (Japan). All other chemicals used in experiments and analysis were also reagent

grade (Sigma Chemical Company, St. Louis, MO, USA or Wako Chemicals, Japan).

Iontophoretic flux determination in vitro

Iontophoretic diffusion experiments were carried out in vitro in the Valia-Chien side-by-side diffusion cell (model VSC-1, Crown Glass, Somerville, NJ, USA), with a controlled rate of stirring (600 rpm) in both half cells. An isothermal condition 37±0.2 °C was maintained in both half cells by circulating temperature controlled water through water jacket cells. A orifice (0.69 cm^2) connected the two diffusion cells. The volume of each cell was 3.5 mL. Platinum wires were used as electrodes. The electrodes were connected to a universal power source, (Hewlett Packard, HP 3245A, Palo Alto, CA, USA), that produces a constant current or a periodically pulsed current as output. A periodically pulsed current was used in all experiments. A constant current 0.6mA was maintained in all experiments. The frequency and duty cycle were varied according to experimental conditions.

Skin was mounted between diffusion cells. In the donor side, pilocarpine (1 mg/mL) was loaded in the donor buffer. Pilocarpine permeates from the donor side through the skin to the receiver side. To simulate the body fluid, a Sorensen phosphate buffer (pH=7.4) was used as the receiver solution. Phosphate buffer was used also in the donor solution, but the pH and buffer capacity were adjusted with weak acid and NaOH (0.1N) to meet the requirement of each experiment. In some cases, acetate buffer was also used in an acidic environment for the donor solution.

Rabbit inner pinna skin were used in all experiments. Skin was freshly excised from New Zealand white rabbits, about 3-5 kg, obtained from our animal center in the College of Medicine. The outermost layers of skin (epidermis skin) were taken from the animals immediately after being sacrificed and were used as soon as possible.

A sample (100 μl) from the receptor cell was withdrawn at preset intervals to determine the rate of permeation of pilocarpine. The same volume of fresh buffer

was added each time that a sample was taken. Samples were analyzed immediately by capillary electrophoresis.

Determination of the pilocarpine

Pilocarpine was assayed on a micellar electrokinetic capillary chromatograph in capillary electrophoresis, (P/ACE System 2100, Beckman Instruments, Palo Alto, CA). The capillary cartridge contained a capillary of fused silica of length 57 cm (but 50 cm to detector) and internal diameter 75 μm. On-line UV detection was monitored at 214 nm and the temperature of the capillary was maintained at 30± 0.1 °C. A separation buffer was prepared using borate buffer (pH 9.0) with sodium dodecyl sulfate (SDS, 2.5 %) and an ionic strength 0.002M. Before each injection, the column was preconditioned by flushing with NaOH (0.1M) for two min, with deionized water for two min, and finally with separation buffer for 2 min. The sample was introduced into the column using pressure injection for 5 sec, corresponding to approximately 30 nL. All separations were performed for 15 min using a constant high voltage 20kV. The retention time of pilocarpine was about 10 min. The sample singles were analyzed with software (Beckman System Gold, version 8.1).

RESULTS AND DISCUSSION

The response surface method was applied to seek the maximal rate of iontophoretic permeation of pilocarpine crossing skin. As in diagnosis of cystic fibrosis (10,15), or in the development of noninvasive monitoring of the concentration of glucose in plasma (16), a quick pharmacological response and much perspiration were needed. In the experiments of Gibson & Cooke (10), iontophoresis of pilocarpine proceeded for only five minuets. Other applications or other drugs may required a prolonged application. Here, our quantitative objective function was defined as "the maximum permeation of drug in the first hour". In order to prevent the polarization of the skin, a periodic monophase current was preferably used in iontophoresis. For iontophoresis with a monophase pulsed current, Chien et al. (9) concluded that in iontophoretic experiments with insulin,

greater flux of permeation was obtained with a periodically pulsed wave of current with frequency 2000Hz and duty cycle 50% (i.e. the ratio of current on and off equals 1). In solution, pilocarpine is subject to serious degradation when the pH exceeds 7. To avoid such degradation, the pH of the donor solution was restricted below this condition. The starting point to design the first two-level factorial experiment was as follows:

Donor solution pH was 4, with increment ±1pH.
Donor solution ionic strength 0.012M, with increment ±0.008M.
Pulse frequency 2000 Hz, with increment ±1000Hz.
Current duty cycle 50%, with increment ±10%.

With four variables, 2^{4-1} experiments were conducted. Table I presents the conditions of the first eight experiments and the corresponding transdermal cumulative amount of permeation of pilocarpine in the first hour under pulsed current iontophoresis. The rate of permeation of pilocarpine varies greatly depending on operating conditions, from 218.69μg to 918.27μg---almost a five-fold variation. A donor solution with a greater pH (pH=5, open symbols in Figure 2) yields greater permeation than a smaller pH value(pH=3, closed symbols in Figure 2). A smaller ionic strength yields a greater flux.

The surface response Y (objective function, the maximum permeation of drug in the first hour, μg) of first order was obtained with the method of least squares.

$$Y=379.5+210.3x_1-141.8x_2-1.5x_3+71.9x_4 \qquad (2)$$

Equation (2) indicates that pH is the most important parameter to control the transdermal iontophoretic permeation of pilocarpine. Each variation of pH value caused 210.3 μg/pH variation of pilocarpine permeation. The ionic strength has obviously a negative effect on the drug permeation. A large ionic strength implies that more ionic species compete with the drug ion with the same opportunity so as to diminish the rate of permeation of drug. The influence of frequency on the

Table I. Experimental conditions of the first two-level factorial design in iontophoretic transdermal delivery of pilocarpine

Factor	pH (x1)	μ (x2)	f (x3)	duty (x4)	Cum. amount for 1hr (μg)
center	4	0.012	2000	50	
unit	1	0.008	1000	10	
exp1	3 (-1)	0.004 (-1)	1000 (-1)	40 (-1)	218.69
exp2	3 (-1)	0.004 (-1)	3000 (1)	60 (1)	324.24
exp3	3 (-1)	0.02 (1)	1000 (-1)	60 (1)	66.71
exp4	3 (-1)	0.02 (1)	3000 (1)	40 (-1)	67.31
exp5	5 (1)	0.004 (-1)	1000 (-1)	60 (1)	918.27
exp6	5 (1)	0.004 (-1)	3000 (1)	40 (-1)	623.85
exp7	5 (1)	0.02 (1)	1000 (-1)	40 (-1)	320.52
exp8	5 (1)	0.02 (1)	3000 (1)	60 (1)	496.41

transdermal iontophoretic drug delivery is insignificant, shown in Figure 2 or from the coefficient of x_3 in Equation (2) that at only 1.5 is far smaller than the others. In this batch of experiments, the amplitude of current was maintained constant. A large duty cycle signifies that much work is done by the external electrical field and implies much more ions are carried by the electric field.

Equation (2) also provides the path of steepest ascent toward the optimal objective function. A large rate of permeation is attained on decreasing the donor pH, on decreasing the ionic strength, or on increasing the current duty cycle. Because of the small influence of frequency on pilocarpine permeation, the frequency was maintained constant for the succeeding experiments. From the start point x^0=(4, 0.012, 2000, 50), we designed five other experiments along the direction of steepest ascent, $\nabla g(x^0)$. The experimental conditions and results are

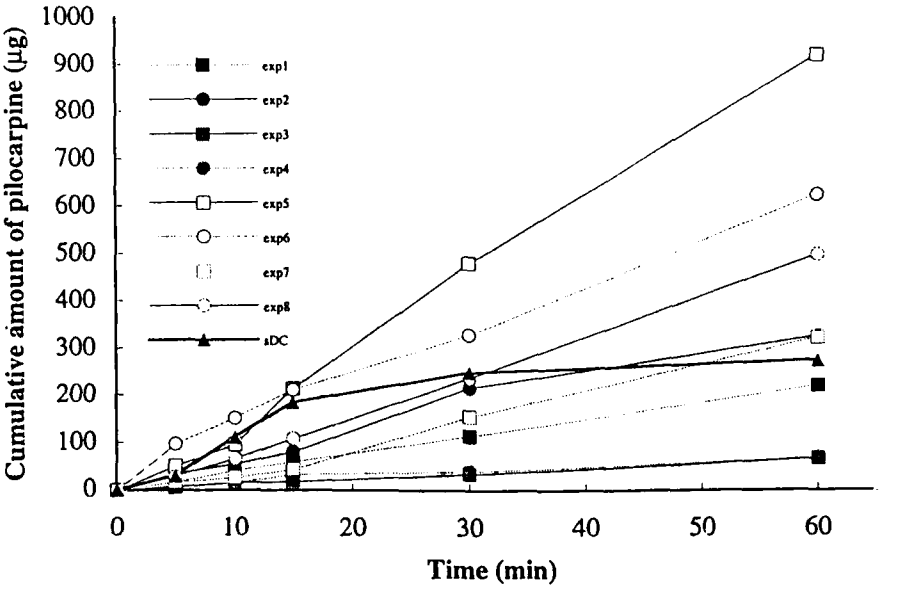

FIGURE 2.
Cumulative amount of pilocarpine within the first hour for the first factorial direction determining block (corresponding to experimental conditions in Table I)

shown in Table II and Figure 3. The greatest amount of cumulative permeation was in Exp. 3 of this batch experiments, pH=5.5, ionic strength =0.0045M, and duty cycle=56%. Because this point (5.5, 0.0045, 2000, 56) was outside the range of the original two-level factorial experimentation design (4±1, 0.012±0.008, 2000±1000, 50±10), another new starting point was chosen and the procedures were repeated as stated above (Figure 1).

Table III presents the new two-level factorial experimental design with Exp 3 in second batch, pH=5.5, ionic strength =0.0045M, and duty cycle=56%, x^1=(5.5, 0.0045, 2000, 56) as starting point. Increments were (±0.3. ±0.0015, ±0, ±10). Because the frequency was maintained constant, only 2^{3-1} experiments were needed in this batch of screening. The results appear in Figure 4. In this region, Exp 1 had a maximal cumulative amount of permeation. The total amount of pilocarpine was 1182.42 µg/h, better than in other experiments. The corresponding

Table II. Experimental design of the first factorial step determining block along the direction of steepest ascent

Factor	pH (x1)	μ (x2)	f (x3)	duty (x4)	Cum. amount for 1hr (μg)
center	4	0.012	2000	50	
unit	1	0.008	1000	10	
slope	135.7	-91.5	1	46.4	
proportion	135.7	-0.732	1000	464	
scale	0.5	-0.002	3.4	1.5776	
exp1	4.5	0.0095	2000	52	660.31
exp2	5.0	0.007	2000	54	828.85
exp3	5.5	0.0045	2000	56	949.59
exp4	6.0	0.002	2000	58	725.88
exp5	6.5	0	2000	60	452.08

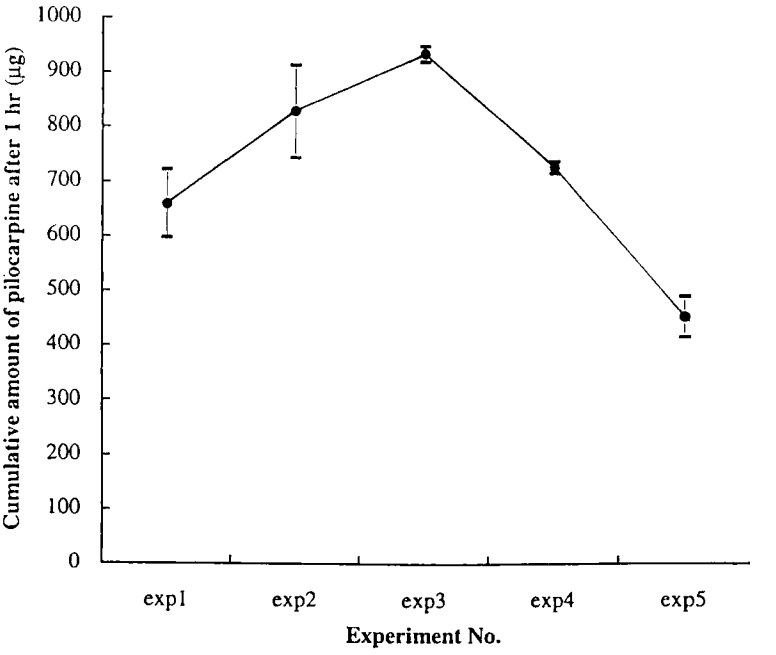

FIGURE 3.
Cumulative amount of pilocarpine for the first factorial step determining block (corresponding to experimental conditions in Table II)

Table III. Experimental conditions of the second two-level factorial design in iontophoretic transdermal delivery of pilocarpine

Factor	pH (x1)	μ (x2)	f (x3)	duty (x4)	Cum. amount for 1 hr (μg)
center	5.5	0.0045	2000	56	
unit	0.3	0.0015	0	10	
exp1	5.2 (-1)	0.003 (-1)	2000	66 (1)	1118.42
exp2	5.2 (-1)	0.006 (1)	2000	46 (-1)	759.38
exp3	5.8 (1)	0.003 (-1)	2000	46 (-1)	967.47
exp4	5.8 (1)	0.006 (1)	2000	66 (1)	1047.41

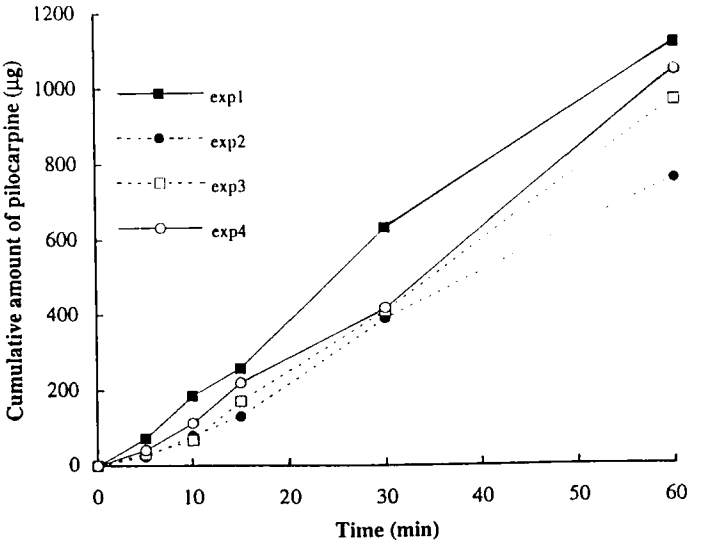

FIGURE 4.
Cumulative amount of pilocarpine within the first hour for the second factorial direction determining block (corresponding to experimental conditions in Table III)

response surface in first order obtained according to the method of least squares was as follows.

$$Y=973.2 +34.3x_1-69.8x_2+109.7x_4 \quad (3)$$

Along this path of steepest ascent, $\nabla g(x^1)$. Four steps of experiments were performed to treat the possibility of a local maximum. In these four experiments, the rate of permeation increased minutely and decreased as shown in Figure 5. There was no significant variation of permeation amount among Exp.1 to Exp.3, because such variation may be caused by experimental error or skin disparity. The optimal objective function is considered to be at the starting point. The optimal operating condition is certainly located in this region. To understand further the response surface of this region, we needed a model of large order. Extra experiments near the center or a star-shaped experimental design should be conducted to construct the detailed response surface. By using a central composite design about the central point, we chose eight other experiments about the center. The experimental design and operating conditions are presented in Table V. From the experimental results and mathematical regression, the response surface of second order is

$$Y=995.79+4.24x_1+20.81x_2+44.87x_3-13.05x_1^2-54.22x_2^2-13.21x_3^2+64.88x_1x_2-90.59x_1x_3+30.03x_2x_3 \quad (4)$$

Optimal operating conditions were obtained by differentiating this equation. In iontophoretic transdermal delivery of pilocarpine with periodically pulsed current, the best operating conditions are pH=5.98, μ=0.0055M, and duty cycle=59% and the corresponding maximal amount of pilocarpine delivered in the first hour is 1011.4μg.

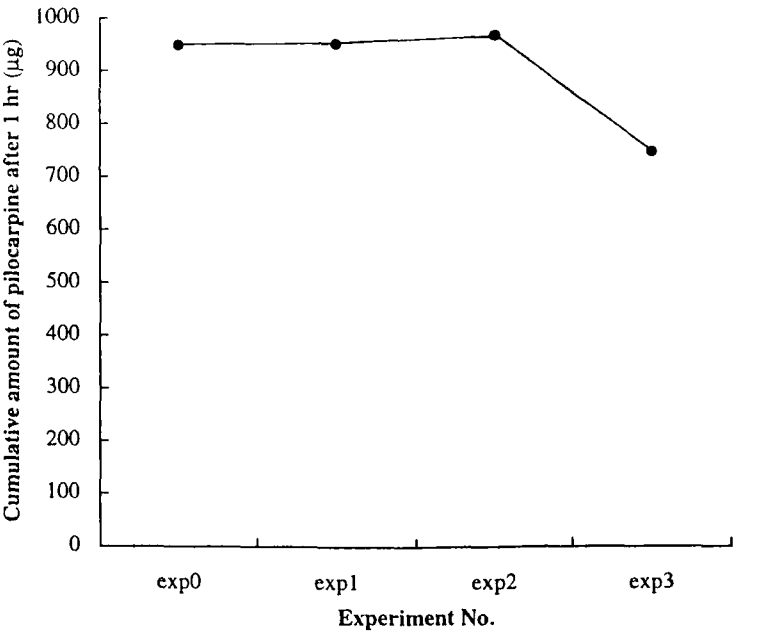

FIGURE 5.
Cumulative amount of pilocarpine for the second factorial step determining block (corresponding to experimental conditions in Table IV)

Table IV. Experimental design of the second factorial step determining block along the direction of steepest ascent

Factor	pH (x1)	μ (x2)	f (x3)	duty (x4)	Cum. amount for 1hr (μg)
center	5.5	0.0045	2000	56	
unit	0.3	0.0015	1000	10	
slope	1	-2	0	3.2	
proportion	0.3	-0.003	0	32	
scale	0.1	-0.001	0	10	
exp0	5.5	0.0045	2000	56	949.59
exp1	5.6	0.0035	2000	66	954.58
exp2	5.7	0.0025	2000	76	969.2
exp3	5.8	0.0015	2000	86	747.71

Table V. Experimental conditions of central composite designs to determine the response surface of second order

Factor	pH (x1)	μ (x2)	f (x3)	duty (x4)	Cum. amount for 1 hr (μg)
center	5.5	0.0045	2000	56	
unit	0.3	0.0015	0	10	
exp5	4.9 (-2)	0.0045 (0)	2000	56 (0)	906.18
exp6	6.1 (2)	0.0045 (0)	2000	56 (0)	923.13
exp7	5.5 (0)	0.0015 (-2)	2000	56 (0)	708.37
exp8	5.5 (0)	0.0075 (2)	2000	56 (0)	791.61
exp9	5.5 (0)	0.0045 (0)	2000	36 (-2)	854.17
exp10	5.5 (0)	0.0045 (0)	2000	76 (2)	1153.25
exp11	5.5 (0)	0.0045 (0)	2000	86 (3)	931.73
exp12	5.5 (0)	0.0045 (0)	2000	56 (0)	921.27
exp13	5.5 (0)	0.0045 (0)	2000	56 (0)	977.91
exp14	5.5 (0)	0.0045 (0)	2000	56 (0)	884.23
exp15	5.5 (0)	0.0045 (0)	2000	56 (0)	1042.21

To gain an understanding of the nature of the response surface, canonical analysis, described by Box and Wilson (17), was used. Equation (4) becomes transformed to the canonical form

$$Y=1011.4-24.1\ Z_1^2.4-24.1\ Z_1^2+34.2\ Z_2^2-90.5\ Z_3^2 \quad (5)$$

Because the coefficients of Z_i^2 are not all negative, only a local maximum was obtained in these experiments. This point is a saddle point, not an absolute

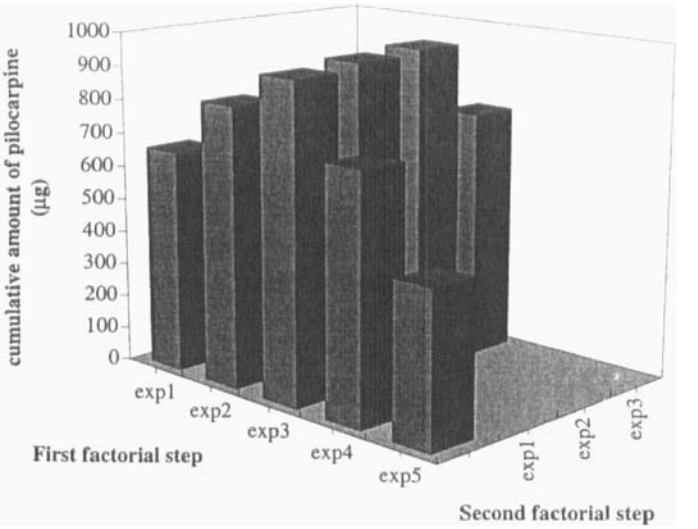

FIGURE 6.
Two steps in approaching the maximal rate of permeation of pilocarpine in transdermal iontophoresis facilitated by periodically pulsed current

maximum. Statistical tests recommend that a response surface of second order is inadequate to describe this complicated system because of the complexity of transdermal iontophoresis, skin disparity, and experimental variation. Although the objective function of the absolute maximum rate of delivery in iontophoretic transdermal delivery of pilocarpine was not achieved, a local large rate of permeation of pilocarpine crossing skin under iontophoresis was obtained. There is a significant increase in the cumulative amount of pilocarpine from 271.37 μg/h (constant current iontophoresis, bold line in Figure 2) to 1011.4 μg/h , nearly a four-fold increase after systematic searching with the response surface method (Figure 6).

CONCLUSIONS

Iontophoresis is a satisfactory method to enhance the permeation of drugs through the skin. It is complicated and not well known. Many physicochemical

and electric variables are involved in operating this system. Four experimental variables-- pH, ionic strength, current frequency, and duty cycle-- were selected as key parameters from results of previous preliminary tests in this complex system. Optimization via experiments based on the response surface method was applied in seeking optimal operating conditions of iontophoretic transdermal delivery of pilocarpine under a periodically pulsed current mode. The maximum rate of permeation of pilocarpine crossing skin was achieved at a small ionic strength, moderate pH and large current duty cycle: pH (x_1) =5.98, ionic strength (x_2)=0.0055, and current duty cycle (x_4)=59%, under the constraint of pulsed current density less than 1 mA/cm^2.

The response surface method is a powerful, efficient and systematic method of optimization via experiments for a complicated unknown system, as in transdermal iontophoresis. Only two steps were executed to approach the maximum objective function for this complicated system and satisfactory results were achieved. The response surface method is much more efficient than the traditional method. Another attractive feature of the response method is that conclusions can be drawn from the first experiments. The experiments can be terminated whenever further experiments appear uneconomic.

REFERENCES

1. A.K. Banga and Yie W. Chien, , J. of Controlled Release, **7,** 1 (1988).
2. P. Tyle, Pharm. Res., **3,** 318 (1986).
3. R. H. Guy, Advanced Drug Delivery Rev. **9,** R7 (1992).
4. J.B. Sloan and K. Soltani, J. Am. Acad. Dermatol., **15,** 671 (1986).
5. J.C. Liu, Y. Sun, O. Siddiqui, Yie W. Chien, W.M. Shi, and J. Li, Int. J. of Pharm., **44**,197 (1988).
6. Philip Green, B. Shroot, F. Bernerd, W.R. Pilgrim and R.H.Guy, J. Controlled Release, **20,** 209 (1992).
7. V. Srinivasan, W.I. Higuchi, S.M. Sim, A.H. Ghanem and C.R. Behl, J. Pharm. Sci., **78,** 370 (1989).

8. T. Bagniefski and R.R. Burnette, J. Controlled Release, **11,** 113 (1990).

9. Y.W. Chien and F.F. Farps, Biomedical Engn. Applica. Basis and Commu., **5,** 212 (1993).

10. L.E. Gibson, and R.E. Cooke, Pediatrics, **23,** 545 (1959).

11. D. Vojnovic, M. Moneghini, and F. Rubessa, Drug Dev. Ind. Pharm., **20,** 1035 (1994).

12. P. Wehrle, Ph. Nobelis, A. Cuine and A. Stamm, Drug Dev. Ind. Pharm., **19,** 1637 (1993).

13. B.Iskandarani, J.H. Clair, P. Patel, P.K. Shiromani and R.E. Dempski, Drug Dev. Ind. Pharm., **19,** 2089 (1993).

14. E. Senderak, H. Bonsignore and D. Mungan, Drug Dev. Ind. Pharm., **19,** 405 (1993).

15. O.H. Nielsen and E. W. Flensberg, Current Therap. Research, **41,** 367 (1987).

16. C. Rao, P. Glikfeld, and R. H. Guy, Pharm. Res., **10,** 1751 (1993).

17. G. E. Box and N. R. Draper, " Emperical model building and response surfaces", Wiley, New York, 1987.