Arch. Pharm. Res. Vol.19, No.3, pp. 183-190, 1996

A Study on Flow Properties of Semisolid Dosage Forms

Sung-Gil Shon and Chi-Ho Lee

College of Pharmacy, Pusan National University, Pusan 609-735, Korea

(Recieved February 13, 1996)

There are a wide variety of semi-solid ointments used for healing the skin diseases, whose therapeutic and skin penetration abililties may greatly differ from one another depending on the compositions of ointment vehicles. A computer optimization technique was applied to obtain the optimum formula of o/w type ointment giving the in vitro maximum absorption rate through hairless rat skin membrane. Some of the formulations were selected to find out a relationship between skin penetration of ointment and its rheological characteristics. The experimental value of absorption rate obtained from the ointment by optimum formula agreed well with the theoretical value obtained from a polynomial regression analysis. Three kinds of ointments selected among 15 formulations were obtained with a concentric cylinder type rheometer (Model; Rheolab SM-HM Physica, Germany) at 20, 30, 40 and 50°C for rheograms of rhelolgical properties of o/w type ointments. As the temperature was raised, all products showed a decrease in both shear stress and yield values. The higher skin penetration, the lower shear stress showed.

Key Words : Indomethacin, Hairless rat skin membrane, Absorption rate, Optimization, Optimum formula, Shear stress, Rheogram

INTRODUCTION

In recent years, investigators have intensified their interests in the controlled delivery of drugs through human skin, and transdermal drug delivery to achieve systemic effects has been developed as a viable means to administer therapeutic agents (Kydonieus and Berner, 1987; Shaw *et at*, 1976; 1978; Chien, 1987). It has some advantages of escaping hepatic first-pass effect as well as drug decomposition by the gastrointestinal tract. Drug delivery via the skin depends primarily on the physiological state of the skin itself, the physicochemical properties of the drug, and the vehicle in which the drug is incorporated (Barry, 1983: Hadgraft, 1989).

In this experiment, various o/w type ointments were prepared according to the composite exprimental design (Montgomery, 1976) and in vitro drug absorption experiments through the intact skin of hairless rats were carried out using the diffusion cell (Lee and Shin, 1988). The steady shear flow properties were measured on some of o/w type ointments using a concentric cylinder type rheometer. The objective of this study is to get a useful information on the preparations of ointments having an optimum formula via the analysis of a correlationship between the penetration ability of drug through skin membrane from ointments and the flow properties of ointments measured by rheometer.

Correspondence to: Chi-Ho Lee, College of Pharmacy, Pusan National University, Pusan 609-735, Korea

MATERIALS AND METHODS

Materials

Indomethacin, propylene glycol, sodium lauryl sulfate, white petrolatum, stearyl alcohol, tetramethyl urea (TMU) and cellulose membrane (Avg. flat width 33 mm) were purchased from Sigma Chemical Co. (St. Louis, MO). Acetonitrile and methanol were from Merck Sharp Dom Res. Lab. (Westpoint, PA). All other reagents used were analytical grade. Phosphate buffer solution (pH 7.4) was made of monobasic potassium phosphate and dibasic sodium phosphate.

Ointment preparation

In the formulations of ointments, the optimization technique reported by Schwartz *et al* (1973; 1985) was applied with some modifications. The statistical codes and physical amounts of four independent variables are shown in Table I. The experimental design is dependent on the number of variables in the study, i. e., for four independent variables, the modified half factorial design requires a total of 17 experiments as shown in Table II.

All of the o/w type ointments used in this study

Table I. Physical amounts and statistical codes of four independent variables

Factor (W/W%)	Factor level in coded form				
	- 3	-1	0	1	3
X_1 (White petrolatum)	16	20	25	30	34
X_2 (Propylene glycol)	5	8	12	16	19
X_3 (Stearyl alcohol)	11	15	20	25	29
X_4 (Sodium lauryl sulfate)	0.6	1.0	1.5	2.0	2.4

Table II. Experimental design for four independent variables

	Factor level in coded form			
	X_1	X_2	X_3	X_4
1	0	0	0	0
2	1	-1	1	1
3	-1	1	-1	-1
4	1	1	-1	-1
5	1	-1	1	-1
6	-1	1	1	-1
7	1	-1	-1	1
8	-1	1	-1	1
9	-1	-1	1	1
10	$\sqrt{3}$	0	0	0
11	$-\sqrt{3}$	0	0	0
12	0	$\sqrt{3}$	0	0
13	0	$-\sqrt{3}$	0	0
14	0	0	$\sqrt{3}$	0
15	0	0	$-\sqrt{3}$	0
16	0	0	0	$\sqrt{3}$
17	0	0	0	$-\sqrt{3}$

were prepared by a fusion method (Lund, 1994) according to the formulations listed in Table II. That is, hydrophilic and lipophilic phases were heated seperately to 70°C. Hydrophilic phase was added to lipophilic phase with high speed agitation. When uniform, indomethacin methanolic solution was added to a well-mixed mixture heated to 70°C while stirring rapidly. Amount of oimtment prepared was 100 g containing four ingredients and water. The final indomethacin concentration was 1 w/v % and ointments were used after storage for 2 days in an incubator of 30°C.

Skin specimens

Male Sprague-Dawley rats weighing 230 to 270 g were sacrificed by overdosing ether. Full thickness skin membrane was taken from the abdominal skin of the hairless rat which was cut with an electric clipper, and shaved with an electric shaver. A regular square section (55×55 mm) of abdominal skin was excised with surgical scissors and lifted easily from the basement membrane because the skin was not firmly attached to the viscera. Adhering fat and other visceral debris were removed carefully from the undersurface with tweezers.

In vitro absorption test

The donor part of diffusion cell was filled with an ointment and the excess was removed with the edge of a spatula to produce an even, uniform surface of constant dimension (Lee and Shin, 1988). The skin membrane or cellulose membrane was placed on the ointment with the stratum corneum facing the donor compartment and carefully pressed on the ointment. The acryl cell was assembled and tightly secured with bolts and nuts. The donor compartment was placed in the bottom of a 500 ml beaker and the beaker was placed in water bath at 37°C. 300 ml of phosphate buffer solution (pH 7.4), receptor part, previously equilibrated to 37°C, was carefully placed over the vehicle, and it was stirred immediately using a two-blade propeller connected to a 100 rpm motor. At appropriate intervals, 0.5 ml of the receptor phase was withdrawn and replaced with the same volume of prewarmed phosphate buffer. The sampling solution was filtered with 0.5 μm microfilter (Millipore, USA) and assayed by HPLC system.

Analytical method

Indomethacin concentration in the receptor phase was measured using high pressure liquid chromatography (HPLC). The HPLC analysis was performed on a Waters 840 system consisting of two Model 510 pumps, a Model 481 UV detector, and Model 730 data module. The column used was a 3.9 mm×300 mm, 10 μm, μ-Bondapak C_{18} (Waters Ass.) A mobile phase of acetonitrile/ 0.6% acetic acid solution (55 : 45 v/v %) was used at a flow rate of 1.0 ml/min with absorbance monitoring at 260 nm and sensitivity of 0.02 AUFS. The retention time of indomethacin under these conditions was 10.3 min. The drug concentrations of sample solutions were computed from the peak height corresponding to the calibration curve obtained from the standard solution.

Reological behavior

This experiment was performed to find out a relationship between absorption rate of drug through skin membrane from ointment and rheological characteristics of o/w type ointments. Three kinds of o/w type ointments by Formulation No. 1, No. 8 and No. 15 were selected for measurements of rheological characteristics. Among them, Formulation No. 1 was a basic formula of o/w ointment used in this experiment and No. 15 with or without TMU was a formula having an in vitro maximum absorption rate of drug. Formulation No. 8 was a formula having second maximum absorption rate. Rheological beha-

viours were determined using a concentric cylinder type rheometer, Model Rheolab SM-HM (Physica, Germany) whose radiuses of internal (Ri) and external (Ra) cylinder were 7 mm and 7.59 mm, respectively. Fifty shear rates varying from 0 to 1000 sec^{-1} were applied sequentially on the same sample for 600 sec. The shearing stress was measured by an input motion transducer which was connected to a transducer meter. The temperature influence was studied on the same sample at 20, 30, 40 and 50°C.

RESULTS AND DISCUSSION

In vitro absorption

The *in vitro* absorption of indomethacin from each of ointments prepared according to the experimental formulations listed in Table II was measured using HPLC system. When the amounts of indomethacin absorbed or released from ointments were plotted versus time, straight lines were obtained as shown in Fig. 1 and Fig. 2. The absorption rates were calculated from the slopes of straight lines in Fig. 3 by a linear regression method using a personal computer. TMU was used as an enhancer of skin penetration. As shown in Fig. 3, TMU increased its rate about 2-3 times than drug penetration rate through hairless rat skin from ointment without TMU.

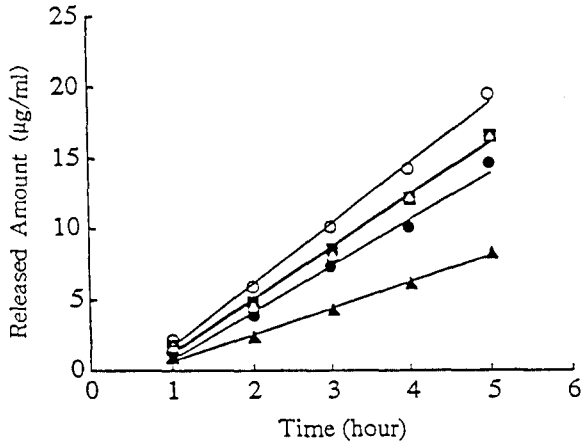

Fig. 1. Release rate profile of indomethacin through cellulose membranes obtained from some of 17 Fomulations. Key. Formulation No. 1, ●; No. 8, ■; No. 11, △; No. 14, ▲; No. 15, ○

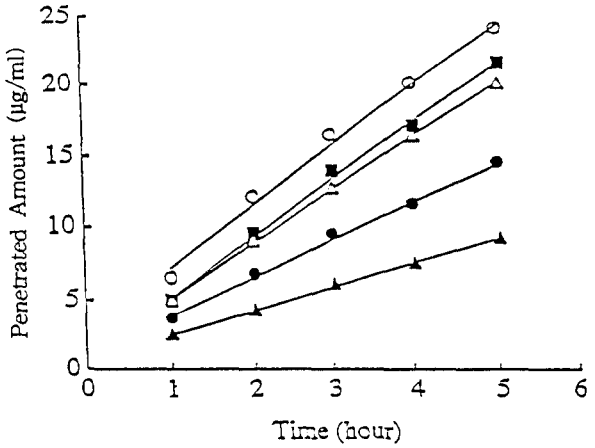

Fig. 2. *In vitro* absorption rate of indomethacin through hairless rat skin obtained from some of 17 Formulations Key. Formulation No. 1, ●; No. 8, ■; No. 11, △; No. 14, ▲; No. 15, ○

Regression equation for absorption rates of drug from ointments

In order to predict characteristics of the model ointment formulations, the amount of white petrolatum (X_1), propylene glycol (X_2), stearyl alcohol (X_3) and sodium lauryl sulfate (X_4) were selected as the independent variables and the *in vitro* absorption rate of drug from ointment through hairless skin membrane was taken as the dependent variable (Y). The overall combinations of four independent variables were investigated via computer analysis at the point of statistical significance in order to determine an optimum regression model, i.e., first, second or more higher-order polynomial regression equation. And the polynomial regression analysis was performed with the aid of the computer using SPSS, a statistical package for social science. The optimum regression equation for the dependent variable was selected on the basis of statistical significance. Coefficient of multiple determination (R^2) was used as an index for the selection of the optimum combination of independent variables and the result of regression analysis was summarized in Table III. The coefficient of multiple determination of second-order polynomial regression mode obtained from this experiment was 0.925. It

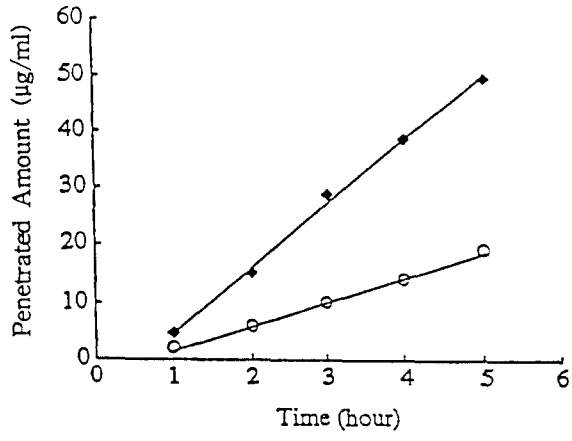

Fig. 3. *In vtro* absorption rate of indomethacin through hairless rat skin obtained from Formulation No. 15 ointment with (■) and without (○) TMU

Table III. The values of each factor (C_1-C_{14}) and a regression equation

Formulation Number	C_1 X_1	C_2 X_2	C_3 X_3	C_4 X_4	C_5 X_1^2	C_6 X_2^2	C_7 X_3^2	C_8 X_4^2	C_9 X_1X_2	C_{10} X_1X_3	C_{11} X_1X_4	C_{12} X_2X_3	C_{13} X_2X_4	C_{14} X_3X_4
1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
2	1	1	1	1	1	1	1	1	1	1	1	1	1	1
3	-1	-1	-1	-1	1	1	1	1	1	1	1	1	1	1
4	1	1	-1	-1	1	1	1	1	1	1	-1	-1	-1	1
5	1	-1	1	-1	1	1	1	1	-1	-1	-1	-1	1	-1
6	-1	1	1	-1	1	1	1	1	-1	1	1	1	-1	-1
7	1	-1	-1	1	1	1	1	1	-1	-1	1	1	-1	-1
8	-1	1	-1	1	1	1	1	1	-1	1	-1	-1	1	-1
9	-1	-1	1	1	1	1	1	1	1	-1	-1	-1	-1	1
10	$\sqrt{3}$	0	0	0	3	0	0	0	0	0	0	0	0	0
11	$-\sqrt{3}$	0	0	0	3	0	0	0	0	0	0	0	0	0
12	0	$\sqrt{3}$	0	0	0	3	0	0	0	0	0	0	0	0
13	0	$-\sqrt{3}$	0	0	0	3	0	0	0	0	0	0	0	0
14	0	0	$\sqrt{3}$	0	0	0	3	0	0	0	0	0	0	0
15	0	0	$-\sqrt{3}$	0	0	0	3	0	0	0	0	0	0	0
16	0	0	0	$\sqrt{3}$	0	0	0	3	0	0	0	0	0	0
17	0	0	0	$-\sqrt{3}$	0	0	0	3	0	0	0	0	0	0

*C_{12} C_{13} C_{14} are highly correlated with other X variables, and have been removed from the equation. The regression equation is Y (Absorption rate)=2.90-0.396 C_1+0.101 C_2-0.530 C_3-0.109 C_4+0.011 C_5+0.008 C_6+0.001 C_7-0.039 C_8-0.347 C_9-0.007 C_{10}-0.091 C_{11} (Lee and Shin, 1988).

Table IV. Comparison with experimental values of absorption rate of indomethacin through hairless rat skin from ointment and calculation values by computer

Formulation Number	Release Rate (μg/ml/hour)	
	Experimental Values	Calculation Values
No. 1	2.665	2.887
No. 2	1.825	1.606
No. 3	2.875	3.475
No. 4	2.575	2.885
No. 5	2.330	2.315
No. 6	3.090	3.311
No. 7	3.025	3.157
No. 8	4.120	4.152
No. 9	2.515	2.195
No. 10	2.275	2.201
No. 11	3.835	3.573
No. 12	3.205	3.063
No. 13	2.885	2.711
No. 14	1.700	1.968
No. 15	4.350	3.806
No. 16	2.285	2.697
No. 17	3.525	3.077

was considered that this regression model was suitable for optimum regression equation. Calculation values for absorption rate of drug from each ointment of 17 formulations in Table II were obtained from the second-order polynomial regression equation and listed in Table IV.

Graphical approach.

Two graphical techniques, that is, the contour graph and the partial derivative graph, have been proven useful in the optimization procedure (Schwartz *et al.*, 1973; Takayama *et al.*, 1985). In the contour graph used in this study, a three-dimensional situation might be plotted two dimensionally by computer. Therefore, while only two interacting factors could be accommodated on a single contour graph, the preparation of a number of such graphs was allowed for the analysis of the effect of many factors on a response. Four types of contour graphs were drawn by computer for two interacting factors keeping two factors at various fixed levels. As shown in Fig. 4, absorption rate of drug was increased with an increase of X_2 and X_4 and a decrease of X_1 and X_3. From these results, it could be found that there were an optimum values of X_1, X_2, X_3, and X_4 producing a maximum absorption rate.

Optimization

The polynomial regression equation in Table III was structured as an optimum regression model for determining the optimum values of independent variables for the in vitro maximum absorption rate of indomethacin. From Fig. 4, $X_1<0$, $1<X_2<\sqrt{3}$, $X_3<0$, and $0<X_4<1$ were selected as the constant limits of X_i values and the absorption rates were calculated by the increment of 0.1 from minimum to maximum value for each of constant limits of X_i. Within the constant limit of X_i values, the optimum formulation was obtained from the computer and listed in Table V. According to the condition of optimum formulation listed in Table V, o/w type ointment was prepared again and absorption rate was determined in the same manner as the *in vitro* absorption test. The ex-

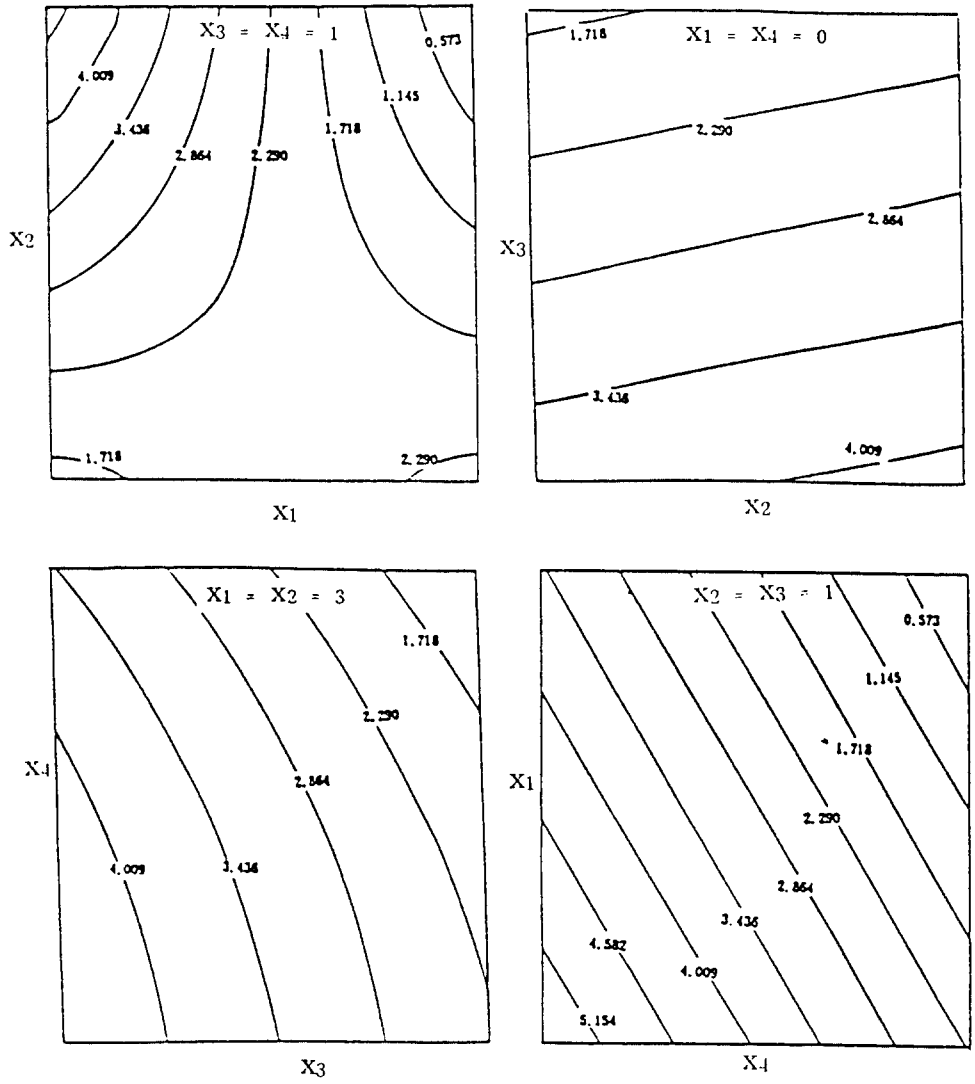

Fig. 4. Contour plots of absorption rate as a function of each of independent variables keeping two factors on the top of figures at various fixed levels

Table V. Compositions of optimum formula of O/W type emulsion ointment obtained from computer optimization

Variable	Code level	Physical Amount(%)
X_1 (White petrolatum)	-1.732	16
X_2 (Propylene glycol)	1.668	18.74
X_3 (Stearyl alcohol)	-1.732	11
X_4 (Sod. lauryl sulfate)	0.668	1.847

perimental value by *in vitro* absorption experiment and the prediction value obtained from computer for absorption rates were summarized in Table VI and they agreed well each other.

Rheological behaviour

The rheological data obtained were plotted as rheograms of shearing stress versus shear rate. Fig. 5 showed that ointments considered always exhibited a yield value greater than zero and they were shear thinning semi-solid products, because slopes of flow curves were decreased with increasing of both shear rate and shearing stress. And, as the temperature was raised from 20 to 50°C, all products studied demonstrated a decrease in yield values. Each individual applies ointment-like materials to the skin with a slightly different motion, stroke, and rate. And the skin temperature may vary during spreading of a topical preparation due to increased blood flow induced by rubbing. Any rheological estimate of this process would be limited accordingly. Henderson *et al.* (1961) have approximated the rate of shear encountered when spreading an ointment on a surface by assuming a stroke averaging 6 cm, a rate of 4 strokes/sec, and an ointment layer thickness of 1 to 3mm. Under these conditions they calculated a shear rate of 120 sec^{-1}. If this value is used as a guide, recognizing its shortcomings, an estimate of the spread-

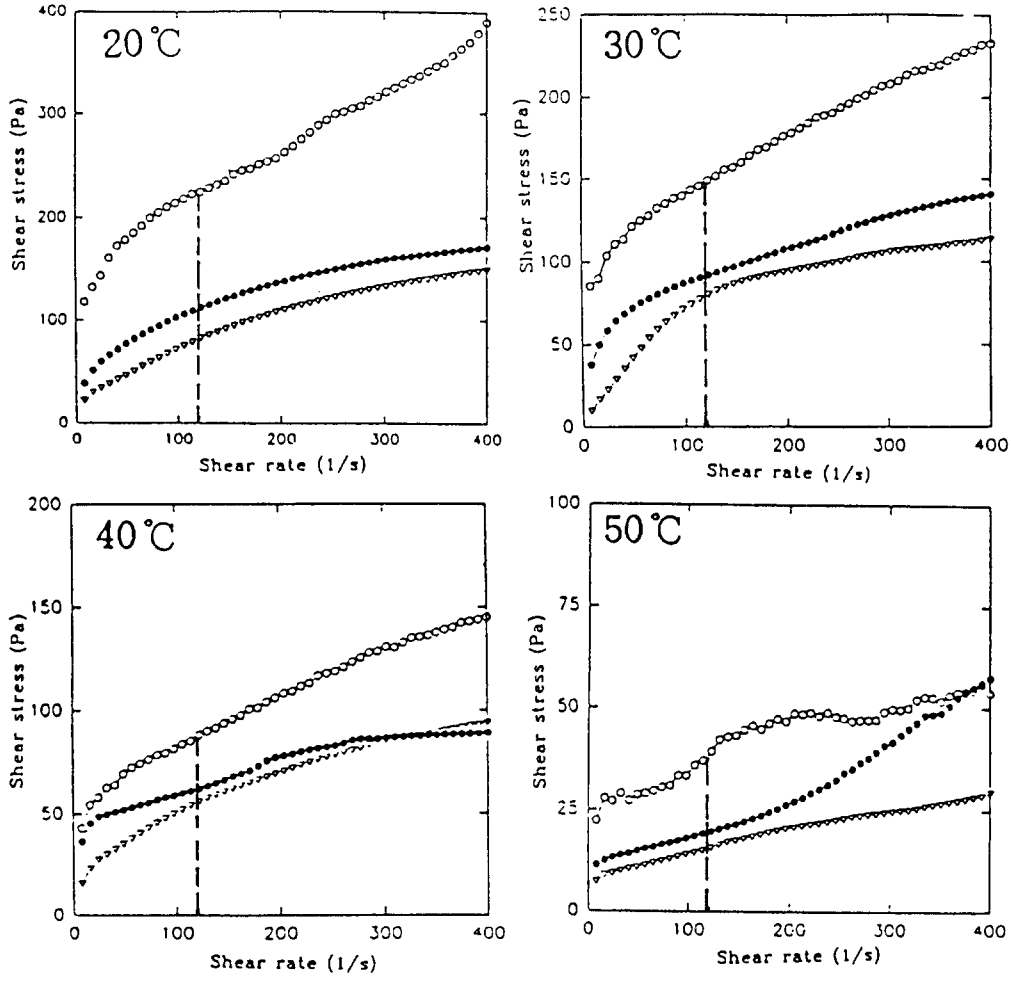

Fig. 5. Rheograms of some ointments of 17 Formulations at various temperatures. Key. Formulation N0. 1, ○; No.8, ●; No. 15, ▽

Table VI. Comparison of experimental and theoretical values by optimum formula

Response	Experimental value	Theoretical value
Absorption rate (μg/5.582 ml/h)		5.727

ing resistance can be graphically shown by extending a dashed line through the rheograms at 120 sec^{-1}. On the upcurve of nearly every rheogram, 120 sec^{-1} occurred in a region of great resistance to flow in the order of Form. No. 15<No. 8<No. 1. For example, in the instances of Form. No. 1 and No. 15, 120 sec^{-1} represents the points of 240 and 90 pa in shearing stress, respectively. The shear stress/shear rates for Form. No. 15 with and without TMU as a penetration enhancer were also determined in the temperature range of 25 and 50°C. As shown in Fig. 6, yield values of ointments were not affected by TMU, but a spreading resistance of ointment containing TMU was decreased in comparison with ointment without TMU. That is, shearing stresses at shear rates of 120 sec^{-1} were 35 and 80 pa at 30°C, respectively.

CONCLUSION

A computer optimization technique was applied to obtain the optimum formula of o/w type ointment giving the in vitro maximum absorption rate through skin membrane. Some of ointments was selected to find out a relationship between skin penetration of ointment and its rheological characteristics. The following results were obtained :

1) The optimum formula of o/w ointment could be obtained from an application of computer optimization technique and the maximum absorption rate of optimum ointment through hairless rat skin membrane was 5.727 μg/ml/hr.

2) The experimental value of absorption rate obtained from ointment prepared according to optimum formula by optimization technique was well agreed with the theoretical value obtained from a polynomial regression analysis by comupter and their values were 5.582 and 5.727 μg/ml/hr, respectively.

3) It was found that the absorption of drug through

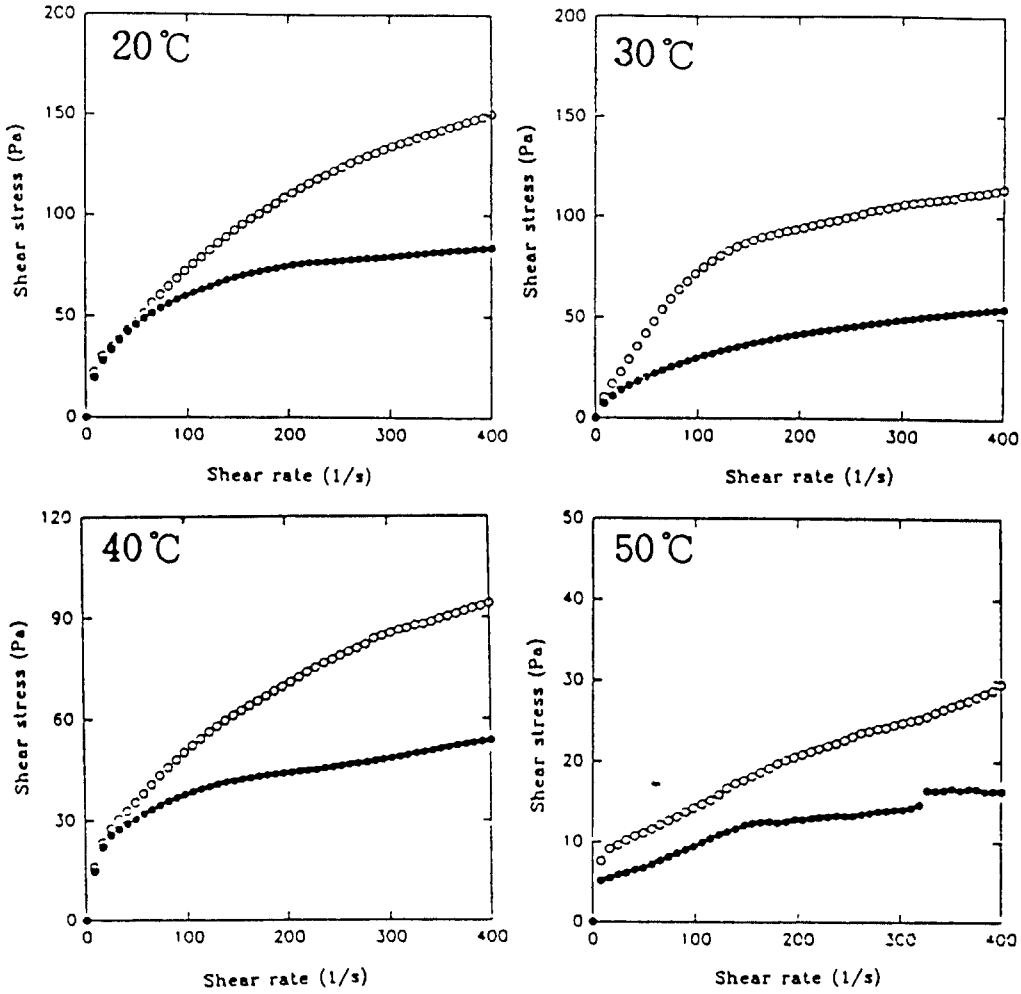

Fig. 6. Rheograms of Formulation No. 15 ointment with (●) and without (○) TMU at various temperatures

skin membrane from ointment had a close relationship with its spreadability and tetramethyl urea reduced the spreading resistance of ointment.

ACKNOWLEDGEMENTS

This work was supported by a grant from Korea Science and Engineering Foundation (KOSEF 951-0710-038-1).

REFERENCES CITED

Barry, B. W., Dermatological formulations; Percutaneous absorption. Marcel Dekker, INC. New York, NY 10016, pp. 127-340 (1983).

Chien, Y. W., Transdermal controlled systemic medications. Marcel Dekker, INC, New York, NY 10016, pp 1-21 (1987).

Hadgraft, J., Transdermal drug delivery. Marcel Dekker, INC., New York, N.Y.10016, pp. 59-77 (1989).

Henderson, N. L., Meer, P. M. and Kostenbauder, H. B., Approximate rates of shear encountered in some pharmaceutical processes. *J. Pharm. Sci.*, 50, 788 (1961).

Kydonieus, A. F. and Berner, B., *Transdermal delivery of drugs. Vol. 1,* CRC press, INC. Boca Raton, Florida 33431, pp. 3-16 (1987).

Lee, C. H. and Shin, Y. H., Studies on computer optimization techniques for hydrophilic vehicle compositions. *Arch. Pharm. Res.*, 11(3), 185-196 (1988).

Lund, W., *The pharmaceutical codex. 12 ed.*, London, The Pharm. Press, pp. 153 (1994).

Montgomery, D. C., *Design and analysis of experiments.* John Wiley & Sons, INC., New York, pp. 355 (1976).

Schwartz, J. B., Flamholz, J. R., and Press, R. H; Computer optimization of pharmaceutical formulations I: General procedure. *J. Pharm. Sci.*, 62, 1165 (1973).

Schwartz, J. B., Optimization techniques in product formulation. *J. Soc. Cosmet. Chem.*, 32, 1536 (1985).

Shaw, J. E., Chandrasekaran, S. K. and Compbell, P., Percutaneous absorption: controlled drug delivery for topical or systemic therapy. *J. Invest. Dermatol.*,

67, 677 (1976).
Shaw, J. E. and Chandrasekaran, S. K., Controlled topical delivery of drug for systemic action. *Drug Metab. Rev.*, 8 , 223 (1978).
Takayama, K., Imaizumi, H., Nambu, N. and Nagai, T., Mathematical optimization of formulation of indomethacin / polyvinyl polypyrrolidone / methy cellulose solid dispersions by the sequential unconstrained minimization technique. *Chem. Pharm. Bull.*, 33, 292 (1985).