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MEDICAMENT RELEASE FROM OINTMENT BASES: V. NAPROXEN IN-VITRO RELEASE AND IN-VIVO PERCUTANEOUS ABSORPTION IN RABBITS

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ABSTRACT

The in-vitro release of Naproxen from various ointment bases, including a water-washable base with the drug in the water phase (I) and the drug in the oil phase (II), a hydrophilic base with the drug in the water phase (III), and the drug in the oil phase (IV), and an anhydrous ointment (V), a gel (VI) and a modified University of California (U.C.H.) base (VII) were studied. In addition, the effects of various additives (urea, ethanol, dimethyl sulfoxide and polyethylene glycol-400) on the release of Naproxen from formulations (I) and (II) were determined. Low concentrations of urea and ethanol in the formulations increased the release of the drug from both these bases, however, higher concentrations adversely affected the release of the drug. While dimethyl sulfoxide (DMSO) had no significant effect on the drug release, the inclusion of polyethylene glycol-400 in both bases decreased the release of Naproxen.

The percutaneous absorption of Naproxen from the water-washable base (drug in the oil phase) and hydrophilic base (drug in the oil phase) were studied by applying the ointments on

rabbit's skin. It was observed that the bioavailability of Naproxen from the hydrophilic base was slightly greater than that from the water-washable base, and that DMSO had no effect in enhancing the in-vivo release of Naproxen from the ointments evaluated. Using the in-vivo data, the absorption and elimination rate constants, the half-life and AUC were calculated.

INTRODUCTION

Rheumatoid arthritis and related inflammatory diseases present a major challenge to the medical and pharmaceutical practices. The occurrence of rheumatic disorders is very widespread. They are chronic in nature and usually last longer than most persistent diseases. Although rheumatic complaints are the second greatest cause of incapacitance (1-7), arthritis and rheumatism are responsible for the largest share of chronic disability in the United States (8,9). More than 27 million work days are lost annually because of these conditions (10). Naproxen is a member of the nonsteroidal anti-inflammatory drugs and it was introduced into the market in 1976 by Syntex Laboratories Inc., under the trade name, Naprosyn®.

It possesses anti-inflammatory, analgesic, and antipyretic properties. However, the oral administration of such drugs produce gastric irritation and sometimes patients with gastrointestinal ailments develop ulceration and severe gastrointestinal bleeding (11,12). To overcome these complications, pharmaceutical and medical scientists are engaged in the search for a suitable alternate dosage form that will provide optimum delivery of the drug with the least possible side effects (13).

The objectives of this study were: (a) to formulate a series of ointments containing Naproxen, (b) to determine the in-vitro release of the drug from these bases, (c) to investigate the influence of various additives on the drug release, (d) based on

the in-vitro release data, to evaluate suitable formulations for their in-vivo percutaneous absorption in rabbits.

EXPERIMENTAL

Materials

The following materials were used: Naproxen[1], white petrolatum[2], amerchol CAB® (multisterol extract of lanolin)[3], amerlate P® (isopropyl ester of lanolin fatty acids) , modulan (acetylated lanolin), glucam E-20® (20 moles ethoxylate of methyl glucoside), glucamate® SSE-20 (20 moles ethoxylate of methyl glucoside sequistearate)[3], glucamate SS (methyl glucoside sesquistearate)[3], Amerchol L-101® (lanolin alcohols in mineral oil)[3], glyceryl monostearate (self-emulsifying)[4], polyethylene glycol-400, Myrj® 52 (polyoxyethylene monostearate)[4], methylparaben[4], cetyl alcohol[5], dimethyl sulfoxide[5], acetonitrile[5], chloroform[5], potassium chloride[5], methanol[5], ethanol[5], dibutylamine phosphate[6], propylparaben[7], sodium lauryl sulfate[5], propylene glycol[7], stearyl alcohol[7], glycerin[7], indomethacin[8], urea[9], and cellophane membrane (M.W. cut-off point 1000)[10].

Preparations of Ointments

A number of formulations are given in Table I and were prepared as follows. The water and oil phase ingredients were accurately weighed and placed into two separate containers. The water and the oil phases were heated to 75 ± 5°C, and then the water phase was added to the oil phase at this temperature with continuous stirring and mixed for 15 ± 5 minutes, and cooled to room temperature. Ointments containing different concentrations (1%, 5%, and 10%) of various additives (urea, DMSO, ethanol and polyethylene glycol-400) were prepared by incorporating the additives in the water phase.

Content Uniformity

One gram of the ointment sample was accurately weighed and placed in a 100 ml beaker. The ointment was melted by gentle heat

TABLE I

Naproxen Formulations

Ingredient	(I)	(II)	(III)	(IV)	(V)	(VI)	(VII)
Amerchol CAB	5.00	5.00	-	-	15.00	-	-
Amerlate P	2.00	2.00	-	-	5.00	-	-
White Petrolatum	20.00	20.00	25.00	25.00	43.96	-	14.30
Glyceryl Monostearate, SE	5.00	5.00	-	-	-	-	-
Myrj 52	4.00	4.00	-	-	-	-	-
Stearyl Alcohol	3.00	3.00	10.00	10.00	-	-	10.00
Mineral Oil	-	-	-	-	10.00	-	16.30
Brij 56	-	-	-	-	-	20.00	-
Ameroxol DE-20	-	-	-	-	-	5.00	-
Glucamate SSE-20	-	-	-	-	-	5.00	-
Amerchol L-101	-	-	-	-	10.00	10.00	-
Arlacel 83	-	-	-	-	5.00	-	-
Modulan	-	-	-	-	10.00	-	-
Propyl Paraben	0.07	0.07	0.02	0.02	-	-	0.02
Glycerin	5.00	5.00	-	-	-	-	-
Propylene Glycol	-	-	12.00	12.00	-	-	-
Glucam E-20	-	-	-	-	-	5.00	-
Naproxen	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Sodium bicarbonate	0.37	-	0.37	-	-	-	0.37
Methyl Paraben	0.15	0.15	0.03	0.03	0.04	0.05	0.05
Sodium Lauryl Sulfate	-	-	1.00	1.00	-	-	1.50
Cetyl Alcohol	-	-	-	-	-	-	6.40
Water purified q.s. to	100.00	100.00	100.00	100.00	100.00	100.00	100.00

* Additive Ingredients were added at 0. 1, 5, and 10% levels

and 10 ml of methanol were added to it and thoroughly mixed. The methanol solution was then transferred to 100 ml of volumetric flask and brought to volume with methanol. A small volume of this solution was filtered through an acrodisc and o.5 ml of the filtrate was taken into a small test tube and mixed with 2 ml of the internal standard solution (20 mcg/ml of indomethacin in methanol). Twenty-five microliters of this solution were then injected into an HPLC to determine the Naproxen content. Only samples with 100% ± 5% of Naproxen were used for the in-vitro and in-vivo release studies.

IN-VITRO RELEASE STUDIES

One-ounce plastic ointment jars were used for the in-vitro release studies of the drug. The clean, pre-weighed jar was completely filled with the sample, and the excess of ointment was removed from the surface with the edge of a spatula to obtain an even and smooth surface. This was weighed again to determine the exact amount of ointment employed in the experiment.

The surface of the ointment was covered with a semipermeable membrane, and was secured with a silk thread. The jar was then inverted and immersed into 400 ml of phosphate buffer (pH = 6), contained in a 600 ml beaker maintained at 37° ± 1° C in a water bath.

At each sampling interval (5, 15, 30, 45, 60, 90 and 120 minutes), 3 ml of the diffusion medium was withdrawn and was replaced with an equal volume of phosphate buffer solution. The diffusion medium was stirred constantly to prevent the development of any concentration gradient within the medium. The samples were analyzed spectrofluorometrically for their Naproxen contents, using an excitation maxima at 330 nm and an emission maxima of 355 nm (15). The experiment was repeated three times for each ointment sample.

IN-VIVO RELEASE STUDIES

Percutaneous Absorption in Rabbits

White male New Zealand rabbits, weighing 2-4 kg, were used for in-vivo release studies. Three rabbits were utilized for each sample. The hair was removed from the midback portion of the rabbit by shaving an area of 9.5 cm^2 and was evenly covered with a known amount of ointment sample, and the time of application was recorded.

Following application, blood samples, each equal to (3 ml) were collected from the ear vein of the rabbit at the time intervals of 5, 15, 30, 45, 60, 90 and 120 minutes. During the experiment, the animal was kept in a restrainer so that the blood samples could be drawn conveniently. The samples were allowed to clot at room temperature for 15 minutes and then centrifuged for 30 minutes at 2000 rpm. The serum was separated and kept in a freezer until analyzed.

Extraction of Naproxen from Serum

Naproxen was extracted from the serum using the method developed by Broquaire et al (16). One-half ml of the serum was taken into a test tube and 1.0 ml of 1 M potassium chloride buffer (pH = 2) was added to it. The mixture was shaken on a vortex mixer and was extracted with 6 ml of chloroform on a rock and roll shaker for 20 minutes. The two phases were then separated by centrifugation at 2000 rpm for 10 minutes and the aqueous phase was discarded. The chloroform extract was transferred into a test tube and evaporated to dryness at 60° C under a gentle stream of nitrogen.

HPLC Analysis

There are several methods available for the determination of Naproxen from the plasma. However, for the determination of Naproxen from the serum, a new method was developed in this laboratory. A high performance liquid chromatograph equipped with

a universal liquid chromatographic injector, an ultraviolet detector set at 254 nm, a strip chart recorder and a minigrator were used. The samples were chromatographed on a cyanide bonded column using a mobile phase of acetonitrile 0.005 M/dibutylamine phosphate (20:80 v/v).

The flow rate was adjusted to 2 ml per minute with an inlet pressure of 2000 psig. The recorder chart speed was adjusted to 0.2 inches per minute. The column effluent was continuously monitored by the ultraviolet detector set at 254 nm, with the sensitivity set at 0.02. The peak area was directly obtained from the minigrator printout and the ratio of the peak area of Naproxen to that of the internal standard was used to calculate the concentration of Naproxen in the sample, using the calibration curve constructed previously from known concentrations of Naproxen and fixed concentration of internal standard.

Internal Standard

Indomethacin was used as the internal standard. It was used at a concentration of 20 mcg/ml. Under the conditions of chromatography it had a retention time of 4 minutes, while Naproxen had the retention time of 2.6 minutes.

Assay Procedure

The dried extract previously obtained was dissolved in 0.25 ml of methanolic solution of Naproxen (having a concentration of 2 mcg/ml of Naproxen). One ml of the internal standard solution was added to it and mixed thoroughly. A 25 µl portion of this solution was injected into the column through a stop flow injector port for the determination of Naproxen content according to the previously described conditions.

RESULTS AND DISCUSSION

In-Vitro Studies

The percent release of Naproxen from different semi-solid bases over a period of two hours are shown in Figures 1 and 2.

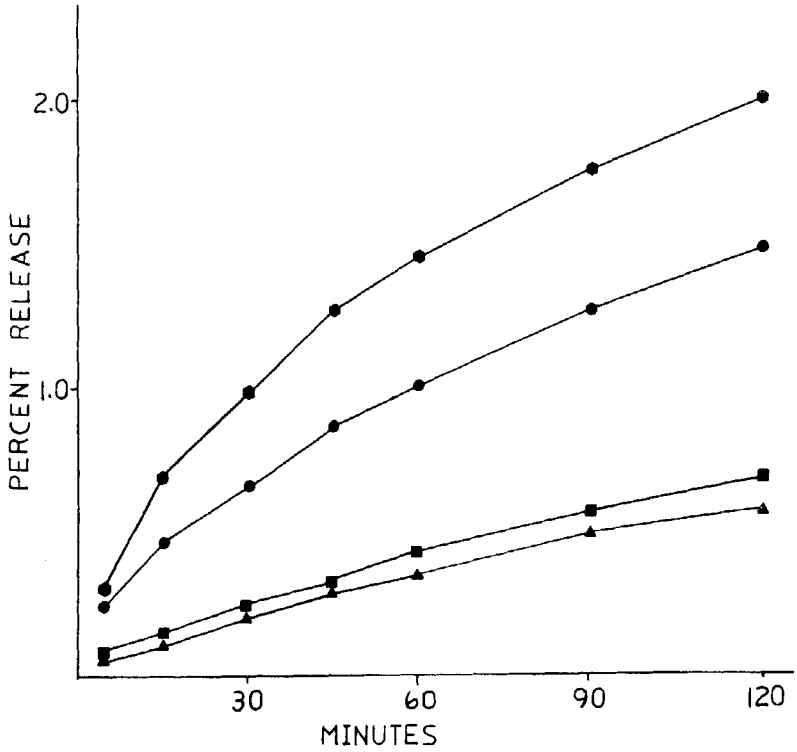

Figure 1 —In vitro release of naproxen from ointment bases. Key: ▲—▲ Water Washable Base (drug in the oil phase); ■—■ Hydrophilic Base (drug in the oil phase); ●—● Water Washable Base (drug in the water phase); and ●—● Hydrophilic Base (drug in the water phase).

The general rank order of the drug release from various bases was: (III) > (I) > (VII) > (IV) > (II) > (VI) > (V). From this data, it is apparent that a higher amount of drug was released when the active ingredient was incorporated into the water phase of the formulations. This was accomplished by the presence of sodium bicarbonate, which converted Naproxen to its sodium salt, which gave higher solubility in the receiving medium (pH = 6) than that of the free acid form.

For meaningful interpretation of diffusion rate data from the different samples, the simplified Higuchi equation (17,18) which

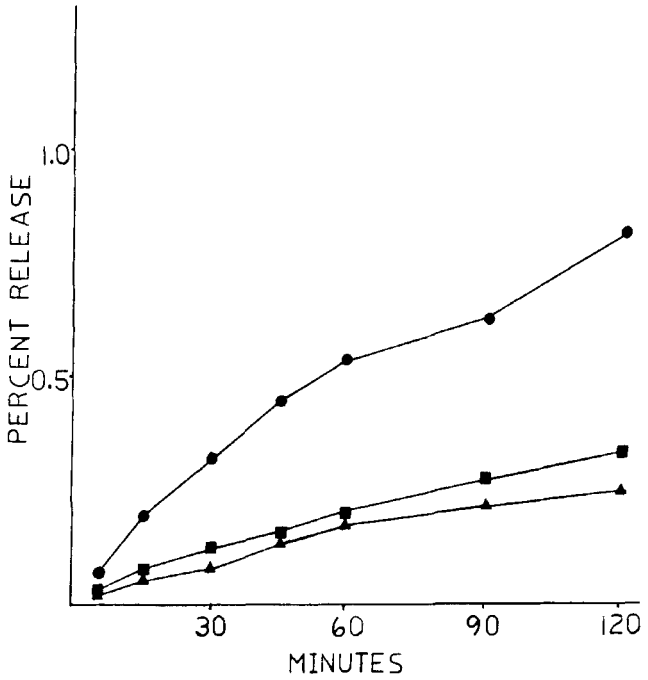

Figure 2—In vitro release of naproxen from other bases. Key: ▲—▲ Anhydrous Ointment Base; ■—■ Gel; and ●—● University of California Hospital Base.

is valid for drugs with release of less than 30% was utilized.

$$M = 2\,C_o\,(D\,t/\pi)^{\frac{1}{2}} \qquad \text{(Eq. 1)}$$

where, M = amount of drug released per unit area of application (mg/cm), C_o = initial concentration of drug in the ointment (mg/ml), D = diffusion coefficient (cm^2/sec), t = time after the application (seconds) and π = a constant.

Equation 1 is based on the following assumptions: (1) only a single drug species is important in the ointment, (2) only the drug diffuses out of the vehicle, (3) the diffusion coefficient is in varient with respect to time or position within the ointment, (4) the percentage release of the drug is less than 30%, (5) the drug reaching the receptor site is removed instantaneously.

The experimental conditions employed in the present study appeared to conform to the above model, namely: (1) only Naproxen was important in the ointments, (2) only Naproxen diffused out of the vehicle, (3) D, was constant with respect to both time and position within the ointment, (4) the maximum release of Naproxen obtained from various bases was less than the upper limit of 30%, and (5) the receiving medium provided the sink condition because of the large volume (400 ml) and continuous stirring.

Furthermore, when the amount of drug released was plotted against the square root of time, a straight line was obtained as shown in Figure 3. This suggests that the release of Naproxen from various ointments followed the Higuchi equation (Eq. 1). The diffusion coefficient of Naproxen from different bases was calculated using Eq. 1 and are shown in Table II. The highest diffusion coefficient value, 7.0×10^{-7} cm^2/sec, was obtained for the base (III) and the lowest value, 0.08×10^{-7} cm /sec, was for the base (V). This can be attributed to the fact that the sodium salt of Naproxen in the hydrophilic base (drug in the water phase) was less soluble in the oil phase components of the base and readily available for diffusion.

On the other hand, in the anhydrous ointment base, the free form of the active ingredient was highly soluble in the oil phase components of the ointment and, as a result, very little drug was available for diffusion. Therefore, the diffusibility of any drug through different bases depends on the nature and composition of the bases and the release rate of a penetrant can be altered by changing the nature and composition of the bases.

Also, it is evident from Figure 3 that a lag time exists in the release of Naproxen from different preparations. This lag time is minimum for the (III) and maximum for the (V). This indicates that the drug was more readily available from (III) than any other base studied.

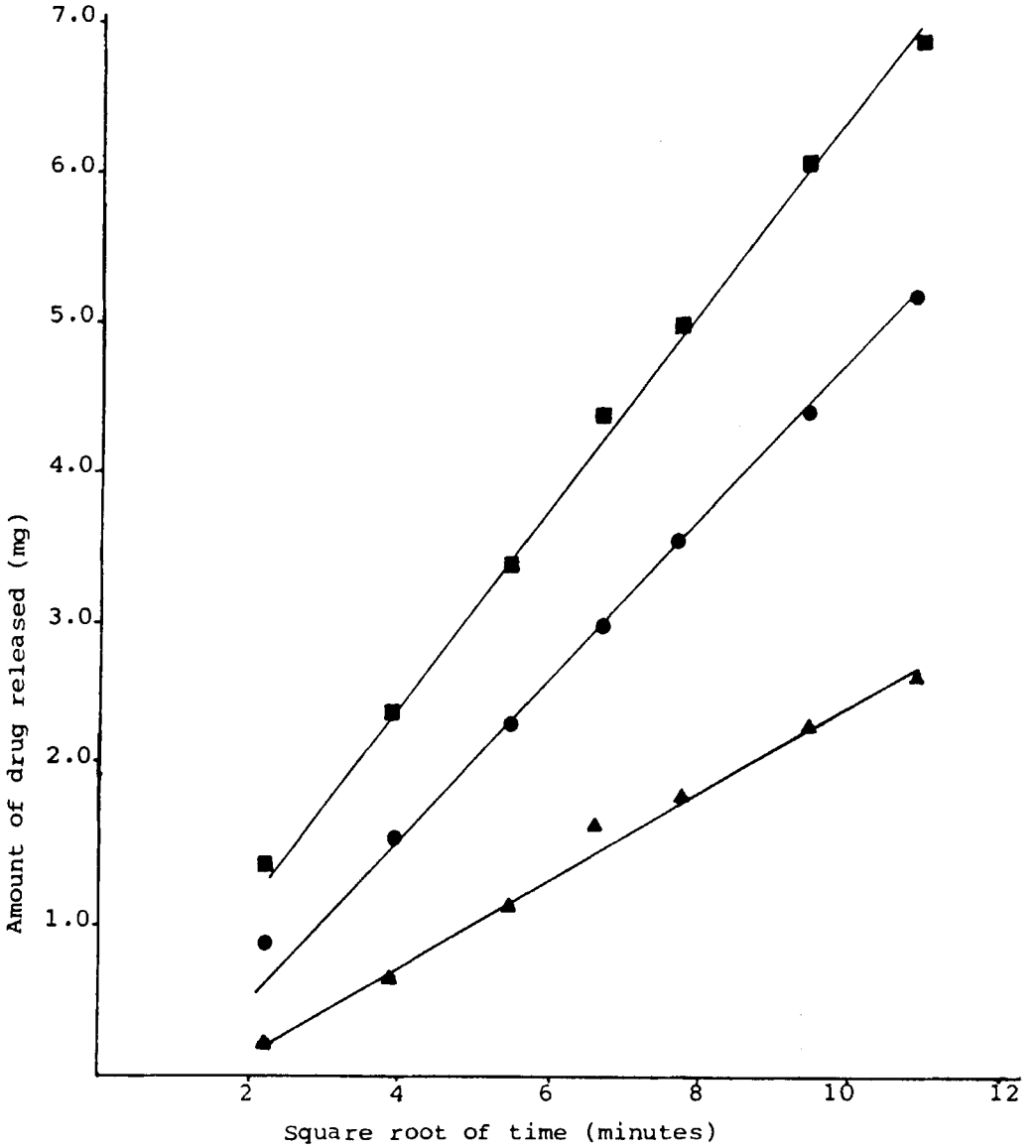

Figure 3—A plot of amount of drug released versus square root of time for different ointments. Key: ●—● Water Washable Base (drug in the water phase); ■—■ Hydrophilic Base (drug in the water phase); and ▲—▲ U.C.H. Base.

TABLE II

Values of Diffusion, Permeability, and Partition Coefficient as Calculated from the In Vitro Data of Different Ointment Formulations

Formulation	Diffusion Coefficient (D) ($D \times 10^7$) cm^2/sec	Permeability Coefficient (p) ($P \times 10^6$) cm/sec	Partition Coefficient (Kp)	Apparent First Order Kinetic $K_1 \times 10^5 min^{-1}$
I	3.54	11.19	1.04	14.62
II	0.49	3.89	2.89	5.18
III	7.00	15.74	0.74	16.75
IV	0.55	4.42	2.65	5.72
V	0.08	1.71	6.67	2.56
VI	0.13	2.05	5.24	2.88
VII	0.89	5.69	2.11	7.48

The in-vitro permeability coefficient values of Naproxen were calculated using Equation 2:

$$q = P\ A\ C_o\ t \qquad \text{(Eq. 2)}$$

where, q = amount of the drug released (mg), P = permeability coefficient (cm/sec), C_o = initial concentration of drug in the ointment (mg/ml), and t = time (seconds). The calculated values are exhibited in Table II. From this data, the permeability coefficient values were found to be directly proportional to the diffusion coefficient values and the highest and lowest values were obtained for the bases III and V, respectively.

The partition coefficient values of Naproxen between the various ointment formulations, and the receiving medium were calculated using Equation 3:

$$P = K_p\ D/h \qquad \text{(Eq. 3)}$$

where, P = permeability coefficient (cm/sec), K = partition coefficient, D = diffusion coefficient (cm /sec), and h = thickness of the barrier membrane (cm). The values of partition coefficient for different bases are also shown in Table II.

It can be seen that in formulation (III), where the sodium salt of Naproxen had little affinity for the base, the K value is low (0.740), compared to the formulation (V), where most of the drug remained in the base (K = 6.67).

When the release of drug from the ointment is below 5%, the release rate constant is essentially the same whether it is calculated by the zero order or by the first order kinetics equation. Since the release of Naproxen from different bases was less than 3%, the in-vitro data were treated by the first order kinetics. The obtained apparent first order release rate constants are shown in Table II. The effects of different additives (urea, DMSO, ethanol, PEG 400) on Naproxen release from formulation (I) and (III) were studied and the results are shown in Table III.

TABLE III

Effects of Different Additives on the Release of Naproxen from Water Washable Base (I) and from Hydrophilic Base (III)

Additives	Per Cent Release after Two Hours (± SD) FORMULATIONS	
	(I)	(III)
No additive	1.47 (± 0.010)	1.98 (± 0.049)
1% DMSO	1.47 (± 0.010)	1.96 (± 0.017)
5% DMSO	1.40 (± 0.006)	1.95 (± 0.025)
10% DMSO	1.38 (± 0.010)	1.97 (± 0.006)
1% PEG 400	1.45 (± 0.005)	1.92 (± 0.023)
5% PEG 400	1.31 (± 0.010)	1.14 (± 0.012)
10% PEG 400	1.05 (± 0.010)	0.98 (± 0.010)
1% Urea	1.56 (± 0.015)	2.18 (± 0.015)
5% Urea	1.48 (± 0.007)	2.13 (± 0.006)
10% Urea	1.44 (± 0.025)	1.99 (± 0.010)
1% Ethanol	1.59 (± 0.010)	2.08 (± 0.026)
5% Ethanol	1.69 (± 0.012)	2.09 (± 0.021)
10% Ethanol	1.62 (± 0.006)	2.05 (± 0.010)

a = Average of three determinations

Low concentrations of DMSO (1%) had no effect on the release of Naproxen from the water-washable base, however, higher concentrations (5% and 10%) had reversably proportional effects on the release rate. This may be due to an increase in the apparent viscosity of the ointments. In addition, DMSO did not have any effect on the release of Naproxen from the hydrophilic base (III). Polyethylene glycol-400 (PEG 400) decreased the release of

Naproxen from both bases and the releases were observed to be inversely proportional to the concentration of PEG 400, which decreased the thermodynamic activity of the drug and possibly the penetration rate (19,20), and also, this could be due to the increase in the apparent viscosity of the preparation. Urea, at the 1% and 5% levels, increased the availability of Naproxen from both the bases studied, while at the 10% level the release was decreased.

Ethanol at all concentrations increased the release of the Naproxen from both the water-washable and hydrophilic bases. The relative increase in the release was probably due to the fact that at these concentrations, ethanol increased the solubility of the drug in the base, causing an increase in the thermodynamic activity and an enhanced permeation.

In-Vivo Studies

The in-vivo release of Naproxen from four selected formulations was studied in rabbits. The serum Naproxen concentrations versus time relationships obtained after application of the ointments in rabbits are shown in Table IV.

After the application of ointment, the absorption of the drug through the skin followed the first order kinetics. As soon as the active ingredient enters the body system, it undergoes metabolism and excretion and the rate of change of the amount of drug (dx/dt) at any time t can be expressed as follows (21):

$$dx/dt = k_a X_a - KX \qquad \text{(Eq. 4)}$$

where, K_a = absorption rate constant, X_a = amount of drug remaining at the site of application, K = overall elimination rate constant, and X = amount of drug in the body. Upon integration, and rearrangement, Equation 4 yields Equation 5, which can be used to calculate the amount of drug in the body at any time t.

$$\log C = \frac{K_a F X_o}{V (k_a - k)} (e^{-Kt} - e^{-K_a t}) \qquad \text{(Eq. 5)}$$

TABLE IV

Average Serum Concentration of Naproxen (mcg/ml)

In Rabbits

	FORMULATIONS			
Time (min)	(II)	(III)+10% DMSO	(IV)	(V)+10% DMSO
5	0.58(±0.07)	0.73(±0.25)	0.78(±0.10)	0.74(±0.03)
15	0.95(±0.13)	1.27(±0.68)	1.27(±0.66)	1.18(±0.11)
30	0.26(±0.23)	1.57(±0.50)	1.03(±0.58)	1.53(±0.15)
45	1.45(±0.28)	1.90(±0.64)	1.24(±0.66)	1.93(±0.31)
60	1.26(±0.08)	1.65(±0.39)	1.41(±0.51)	1.70(±0.30)
90	0.99(±0.21)	1.45(±0.39)	1.19(±0.46)	1.67(±0.65)
100	0.79(±0.10)	1.28(±1.10)	1.01(±0.63)	1.25(±0.22)

* Each is the average of three determinations

As the amount of drug remaining at the site of application decreases, the rate of absorption decreases until $e^{-K_a t} \cong 0$, and under this condition, the plasma concentration is described only by the elimination rate constant of the drug; as a result, Equation 5 changes to Equation 6:

$$\log C' = \log A - Kt/2.303 \qquad \text{(Eq. 6)}$$

where, $A = K_a FX_o/V (k_a - k)$ and C' = plasma concentration during the post-absorption phase. If log C is plotted against time, a straight line was obtained with a slope of - K/2.303, as shown in Figure 4. From the value of the slope, the elimination rate constant as well as the elimination half-life of Naproxen in rabbits, after application of different ointments, were calculated and are shown in Table V. The half-life of Naproxen from different ointments in rabbits was found to be in the range of 82 to 150 minutes.

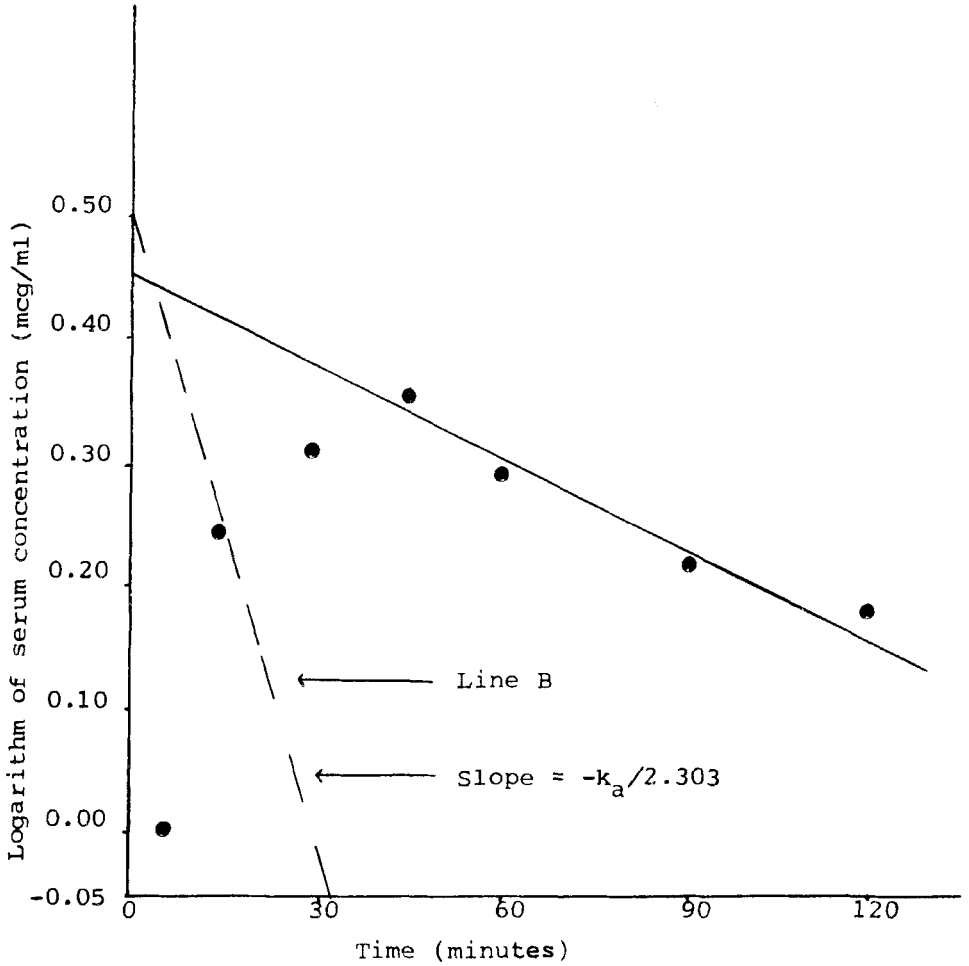

Figure 4 —A plot of logarithm of serum concentration versus time for the calculation of absorption rate constant.

In humans, the plasma half-life of Naproxen has been reported to be 12 hours (22). This decrease in half-life in rabbits may be attributed to species variation, skin metabolism and circulatory changes, and strains endured during blood sampling. Furthermore, by using the feathering technique the absorption rate constants were calculated and are also shown in Table V. It is evident from these data that the incorporation of 10% DMSO slightly increased the absorption rate constant of Naproxen from both the hydrophilic and water-washable bases.

TABLE V

Bioavailability Parameters Obtained after Application of Various Ointment on Rabbits Skin

Ointment Bases[a]	Rabbits	Absorption Rate Constant [k_a] $^{-1}$ (ka X 10) min		Elimination Rate constant (k) (k x 10) min^{-1}		Half-life + 0.5 (minutes)	
		(ka)	Average	K	Average	+ 0.5	Average
Water Washable	Rabbit I						
	Rabbit II	4.15	4.24	8.34	7.68	82.07	90.88
	Rabbit III	3.99		7.68		90.27	
Water Washable with 10% DMSO	Rabbit I	4.73		5.76		120.36	
	Rabbit II	4.64	4.61	4.61	6.02	150.45	120.36
	Rabbit III	4.47		7.68		90.27	
Hydrophilic	Rabbit I	3.95		6.29		101.51	
	Rabbit II	4.79	4.26	7.20	7.05	96.29	96.06
	Rabbit III	4.05		7.67		90.39	
Hydrophilic with 10% DMSO	Rabbit I	4.11		5.67		120.36	
	Rabbit II	4.32	4.35	6.14	5.84	112.84	118.77
	Rabbit III	4.61		5.63		123.10	

a = Drug in the Oil Phase.

TABLE VI

Bioavailability Parameters of Naproxen in Rabbits After Oinment Application

Ointment Base[a]	Time of Peak Serum Concentration (minutes)	Average Peak Serum Concentration (mcg/ml)	Average AUC min. (mcg/ml) (min.)
Water Washable	45	1.26	123.68
Water Washable with 10% DMSO	45	1.90	168.87
Hydrophilic	45	1.53	151.48
Hydrophilic with 10% DMSO	45	1.93	178.00

a = Drug in the oil phase

The areas under the serum concentration versus time profile obtained after application of different ointments in rabbits were calculated by utilizing the trapezoidal method and are shown in Table VI. A good correlation has been observed between the in-vitro and in-vivo release data of formulation (II) and (IV). The in-vitro release data indicates that the percent release of Naproxen from formulation (IV) was approximately 25% greater than that from (II).

And the in-vivo data shows that the AUC for (IV) was 25% greater than that from (II). Also, a correlation was found between the effects of DMSO on the in-vitro and in-vivo release of Naproxen from the water-washable and hydrophilic bases. This additive, at a concentration of 10%, had little or no effect on the in-vitro and in-vivo availability of the drug from both the bases studied. These findings are in agreement with the previously

reported studies (23,24) that at least 60% dimethyl sulfoxide is necessary for a significant increase in permeation rate.

Statistical analysis of the in-vivo data shows that there is a significant correlation between Naproxen in a water-washable base (drug in the oil phase) and Naproxen in the water-washable base with 10% DMSO (R^2 = 0.918, No. of observations 7, degrees of freedom 5). However, the correlation was not as significant between Naproxen in the hydrophilic base (drug in the oil phase) and Naproxen in the hydrophilic base with 10% DMSO (R^2 = 0.83, No. of observations 7, degrees of freedom 5).

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FOOTNOTES

1. Syntex Corporation, CA.
2. Pharmaderm Inc., NY.
3. Amerchol Corporation, NJ.
4. Ruger Chemical Co., NJ.
5. Fisher Scientific Co., NJ.
6. Water Associates, MA.
7. Amend Drug and Chemical Co. Inc., NJ.
8. Merck Sharp and Dohme, PA.
9. J.T. Baker Chemical Co., NJ.
10. Spectrum Medical Industries Inc., CA.

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