3. Preparation and Evaluation of Ketoprofen Topical Gels

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1. Introduction

Nonsteroidal antiinflammatory drugs (NSAIDs), have been widely used in the treatment of rheumatoid arthritis and its related conditions. However, they carry the risk of certain systemic side effects and gastrointestinal irritation at the ususal dose of oral administration due to the dose dumping effect of the drugs. Since NSAIDs are used for a prolonged period, it is important that the side effects of these drugs should be reduced by any possible means while maintaining their therapeutic concentrations at the receptor site. Considering the fact that most of the inflammatory diseases occur locally and near the surface of the body, topical application of NSAIDs on the inflamed site can offer a potential advantage of delivering the drugs directly to the inflamed site and thus producing locally high concentration of the drugs. This by-passes gastric irritation and also reduces adverse systemic effects.

The objective of this study was to formulate a ketoprofen topical gel preparation using Pluronic F-127. Ketoprofen, one of the most potent NSAIDs against the acute and chronic arthritic inflammations, has been chosen as the candidate for this study, since it has good skin permeability, relatively good solubility and high potency, compared to other NSAIDs. Topical gel formulations of ketoprofen were prepared using Pluronic F-127 as a gel forming agent. Pluronic F-127 is known for its low toxicity and low skin irritation, excellent compatibility with other chemicals, high solubilizing capacity for different drugs and good drug release characteristics. This polymer is particularly useful as a gel base because of its unique property called a reverse thermal behavior. While being a low viscous clear liquid at refrigerated temperature, it becomes a clear semisolid gel at room temperature at more than 20% concentration.

2. Formulation and Preparation of Pluronic Gels

The formulation of the ketoprofen gels used for this study are shown in Table 1. To prepare ketoprofen/Pluronic gels, ketoprofen and the Pluronic were heated at 110℃ for 15 minutes to get homogeneous liquid mixture. After the liquid was cooled down to room temperature, water and other ingredients were added. Then the container was left in a refrigerator until a clear solution was obtained. The gel was formed when the solution was brought back to room temperature.

Table 1. Ketoprofen Gels

Ingredient	Concentration, %
Ketoprofen	0.2, 0.5, 1, 2, 3
Pluronic F-127	20, 25, 30
Ethanol	0, 5, 10, 15, 20
Water (or buffer[a])	q.s. to 100

[a] pH 3-7.8

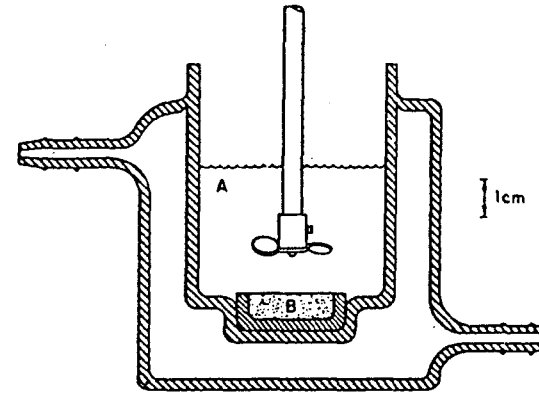

Figure 1—Schematic diagram of diffusion cell used.

3. Evaluation of Ketoprofen Release from Gels

The effect of formulation factors were determined with an *in vitro* diffusion cell which did not involve any membrane. Although the *in vitro* diffusion cell techniques bear little resemblance to drug absorption process, they are considered to be useful especially to identify formulation factors

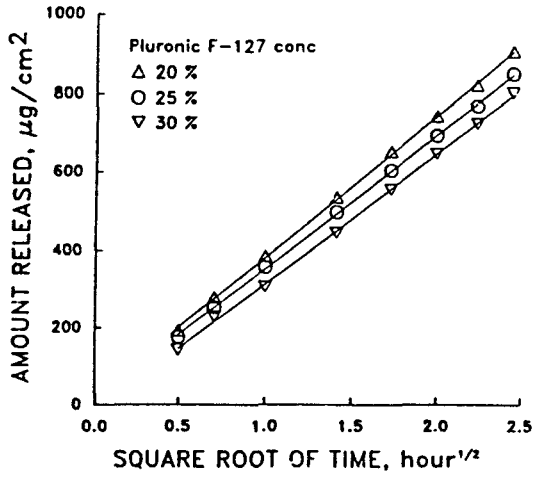

Figure 2—Effect of polymer concentration on ketoprofen release at 37℃ from the gel containing 1% ketoprofen.

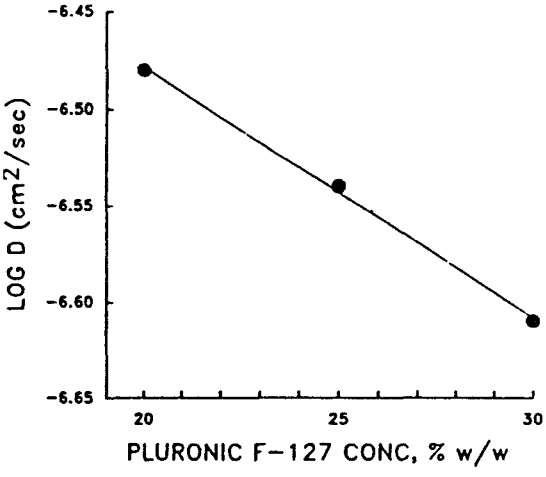

Figure 3—Apparent diffusion coefficients of ketoprofen in the gel containing 1% ketoprofen as a function of polymer concentration.

for topical preparations.

3-1. *In vitro* drug release studies

A drug diffusion cell without membrane has been designed as shown in Fig. 1. The gel was placed in the sample dish and 70 m*l* of isopropyl myristate was used as the receptor phase. The temperature was kept constant by circulating water. Ketoprofen released into isopropyl myristate was quantitated by an HPLC method.

The diffusion coefficients of ketoprofen (D)

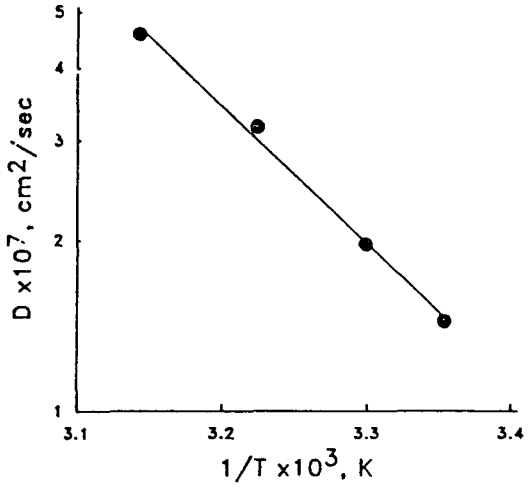

Figure 4—Apparent diffusion coefficients of ketoprofen in 20% Pluronic F-127 gel containing 1% ketoprofen as a function of temperature.

were calculated using the Higuchi equation.

$$q = 2Co(Dt/\pi)^{1/2}$$

where q is the amount of drug released per unit area and square root of time, t, with constants D and Co (the initial concentration of the drug in the gel).

3-2. Effect of Pluronic concentration on drug release

Fig. 2 shows the release profiles of ketoprofen from the 1% ketoprofen gels containing 20, 25 and 30% Pluronic F-127. Shown in Fig. 3, the diffusion coefficients of ketoprofen, calculated from the slope of the release profiles, decreased exponentially as the polymer concentration increased in the gel which may be due to the increase in the number and size of the micelles formed in the gel.

3-3. Effect of temperature on drug release

The effect of temperature on ketoprofen release was studied at different temperatures (25, 30, 37 and 45℃) using the gel containing 1% ketoprofen and 20% Pluronic F-127. The diffusion coefficients of ketoprofen, calculated from the release profiles at these temperatures, are plotted in Fig. 4 based on an Arrhenius equation. The activation energy

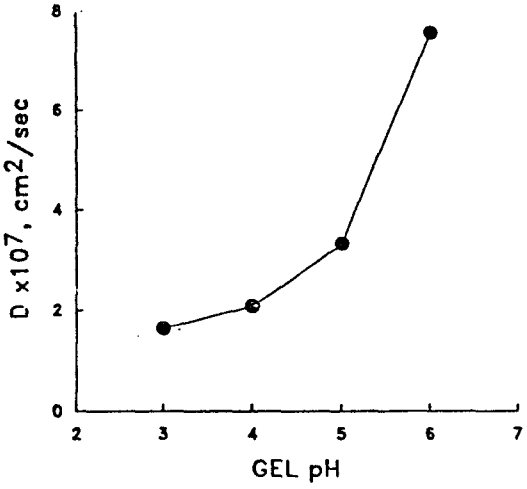

Figure 5—Effect of gel pH on diffusion coefficients of ketoprofen release rate at 37℃ from the gel containing 1% ketoprofen and 25% polymer.

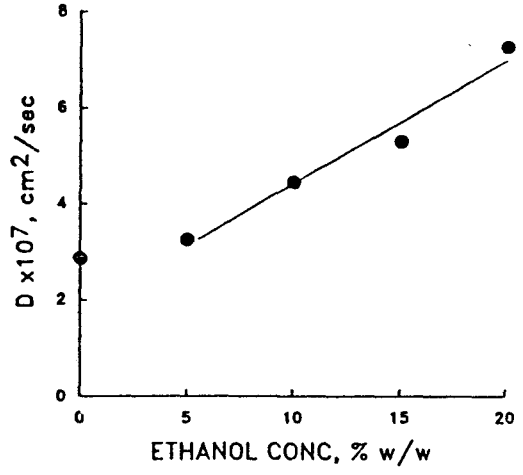

Figure 6—Effect of ethanol on diffusion coefficient of ketoprofen release at 37℃ from 25% Pluronic F-127 gel containing 1% ketoprofen.

Table 2. Effect of Initial Drug Concentration on the Diffusion Coefficient of Ketoprofen, Viscosity and pH of the Gel

	Ketoprofen, %				
	0.2	0.5	1	2	3
Amount released during 6 hrs, μg/cm²	237	492	849	1489	2134
D×10⁷, cm²/sec	5.42	3.81	2.94	2.19	2.00
Viscosity[a] ×10⁻³, cps	113	115	127	140	146
pH of gel[b]	4.6	4.4	4.2	4. 0	3.8

[a] 37℃
[b] ambient temperature

for diffusion of ketoprofen calculated from the plot was 2.8 kcal/mole which is less than those of small nonelectrolytes diffusing in liquid medium ranging 4~5 kcal/mole. Therefore, the primary rate limiting step for release of ketoprofen from the gel is through the liquid phase of the gel.

3-4. Effect of pH on drug release

The pH of the gel containing 1% ketoprofen and 25% polymer was adjusted to between 3 and 6 using buffer solutions to study the effect of the gel pH on the ketoprofen release from the gel. Based on the release profiles, diffusion coefficients of ketoprofen at the different pH were calculated and shown in Fig. 5. It can be seen that the release of ketoprofen was pH dependent and increased greater as the gel pH changed from 3 to 6.

3-5. Effect of initial drug concentration on drug release

The effect of the initial drug loading on ketoprofen release was evaluated using 25% Pluronic gels containing 0.2, 0.5, 1, 2 and 3% ketoprofen. According to Higuchi, the diffusion coefficient should be independent of the initial drug concentration as long as it is below the solubility of the drug in the vehicle. However, diffusion coeficient of ketoprofen, calculated from the release profiles and shown in Table 2, decreased with the increase of initial ketoprofen concentration, which could be due to the decrease of the gel pH and increase of the gel viscosity as the ketoprofen concentration increases in the gel.

3-6. Effec of ethanol concentration on drug release

5, 10 and 20% ethanol were added into the gel containing 25% Pluronic F-127 ketoprofen. In Fig. 6, the diffusion coefficient of ketoprofen, determined from the release profiles, increased linearly

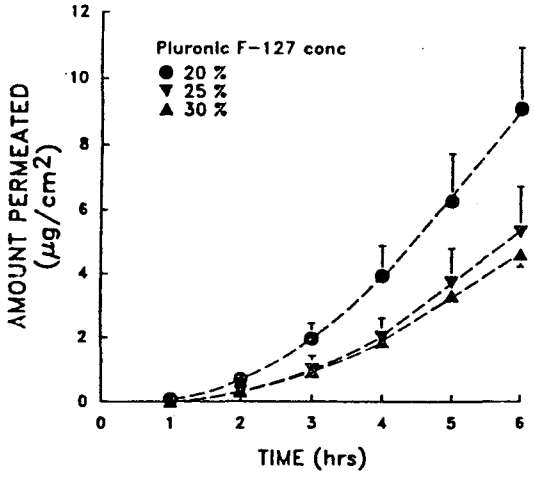

Figure 7—Penetration profiles of ketoprofen through excised rat skin from the 1% ketoprofen gels containing different concentration of Pluronic F-127.

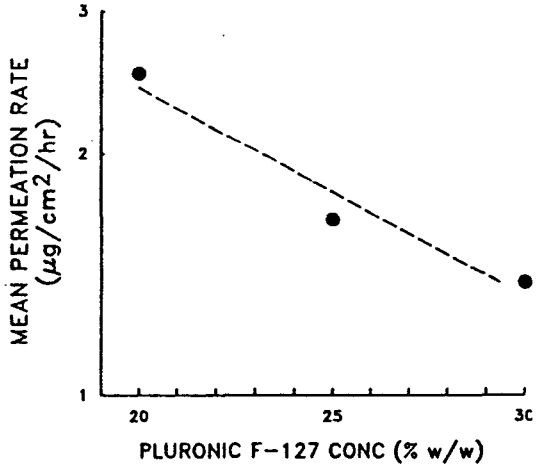

Figure 8—Effect of Pluronic F-127 concentration on mean penetration rate through excised rat skin from the gel containing 1% ketoprofen.

with increasing ethanol concentration, which was due to the increased thermodynamic activity of the drug in the water phase of the gel.

4. *In vitro* Percutaneous Absorption of Ketoprofen from Gels

In this section, the same formulation variables of previous section were evaluated using animal skins to study their effect on the skin permeation

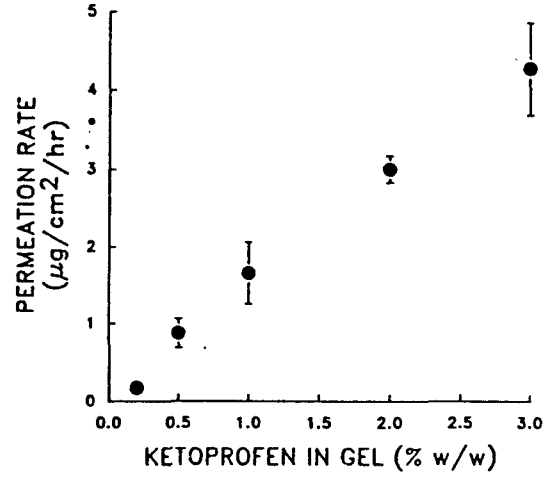

Figure 9—Effect of initial drug concentration on penetration rate through excised rat skin from 25% Pluronic F-127.

of ketoprofen from the gel.

4-1. Formulation of ketoprofen gel

The same gel formulations in Table 1 were used in this section.

4-2. Drug permeation

The extent and rate of ketoprofen permeation through excised rat skins from different gel formulations were determined using the Keshary-Chien diffusion cell. The skin was placed between the donor compartment and the receptor compartment containing pH 7.4 phosphate buffer at 37℃.

4-3. Effect of Pluronic concentration on drug permeation

Fig. 7 shows permeation profiles of ketoprofen from 1% ketoprofen gel containing 20, 25 and 30% Pluronic F-127. The permeation rates, calculated from the linear portion of the curve, decreased exponentially as a function of Pluronic concentrations in the gel which may be due to a reduction in the amount of free drug molecules available for permeation through the skin (Fig. 8).

4-4. Effect of initial drug concentration on drug permeation

The initial drug concentration was varied as 0.2, 0.5, 1, 2 and 3% ketoprofen in 25% Pluronic gels

Table 3. Effect of Ethanol on the Permeation of Ketoprofen through Excised Rat Skin from Pluronic Gel[a]

Ethanol[b] %w/w	J_s[c] μg/cm²/hr	Relative J_s	K[c] 10^{-2}
0	1.66± 0.41	1.00	1.03± 0.16
5	1.33± 0.08	0.80	0.92± 0.03
10	2.94± 0.22[d]	1.77	2.14± 0.21[d]
20	4.72± 0.20[d]	2.84	2.98± 0.08[d]

[a] 25% pluronic F-127 gel containing 1% ketoprofen
[b] % ethanol in the gel
[c] mean ± S.E.
[d] significantly different at an alpha of 0.05 from that of control gel without ethanol

to evaluate the effect of initial drug loading in the gel on ketoprofen permeation through the skin. The calculated permeation rate against the initial drug concentration was not linear as shown in Fig. 9. There was a slight negative deviation from linearity possibly due to a decrease in permeation with decrease in the gel pH with increasing initial drug concentration as previously explained.

4-5. Effect of ethanol on drug permeation

The effect of ethanol concentration on the permeation of ketoprofen through the skin was evaluated with 5, 10 and 20% ethanol in 25% Pluronic gels containing 1% ketoprofen. The permeation constants of ketoprofen calculated from the permeation profiles are listed in Table 3. The presence of 10 and 20% ethanol in the gel increased the permeation rate significantly compared to the control gel which did not contain ethanol.

4-6. Effect of gel pH on drug peremation

The pH of 20% Pluronic gels containing 1% ketoprofen was adjusted between 3 and 7 to study the effect of gel pH on the skin permeation of ketoprofen. Shown in Fig. 10, it is clear that the peremation rate of ketoprofen was pH dependent, reaching a maximum at pH 5, near the pKa of the drug.

Since ketoprofen is a weak acidic compound with the pKa of 5.02, at higher pH than the pKa, the amount of the diffusable unionized form of

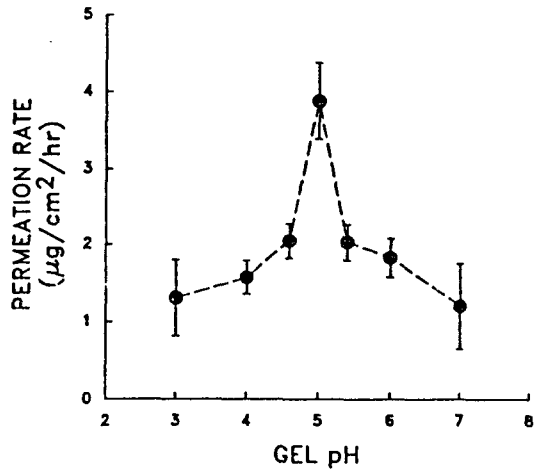

Figure 10—Effect of gel pH on the penetration rate through excised rat skin from the 20% Pluronic F-127 gel containing 1% ketoprofen.

Table 4. Ketoprofen Gels Containing Two Different Gel Forming Bases

Ingredient[a]	Pluronic gel	Carbopol gel
Ketoprofen	3	3
Pluronic F-127	20	
Carbopol 940		1
Ethanol	20	
Isopropanol		25
Triethanolamine		3.5
Water		q.s. to 100
Buffer[b], pH 5.0	q.s. to 100	

[a] %w/w
[b] 0.1 M citric acid/0.2 M disodium phosphate (49 : 51 v/v)

ketoprofen in the aqueous phase decreased due to the ionization and resulted in lower drug permeation. On the other hand, at a lower pH than the pKa, the micellular solubilization was responsible for the low drug permeation.

4-7. Relative peremeation of ketoprofen from Pluronic F-127 gel and Carbopol gel

The skin permeation of ketoprofen from Pluronic gel was compared with that from a Carbopol gel. The two gel formulations are listed in Table 4.

The permeation profiles of ketoprofen from

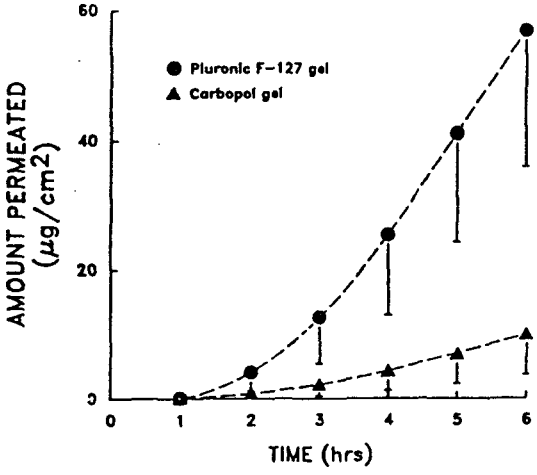

Figure 11—Permeation profiles of ketoprofen through excised rat skin from 3% ketoprofen gel made of Pluronic F-127 and Carbopol.

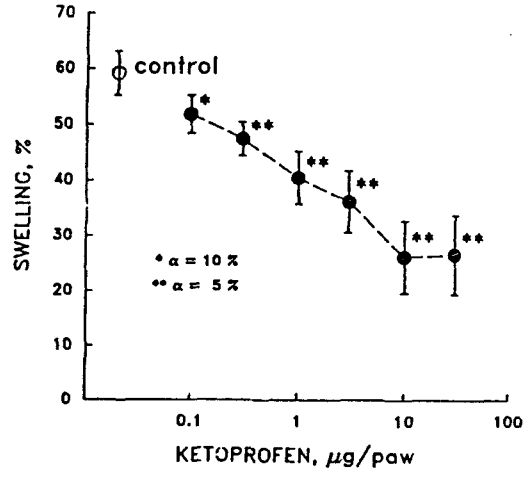

Figure 12—Dose response of ketoprofen after subplantar injections on carrageenan-induced edema model.

Table 5. Pluronic Gel of Ketoprofen

Ingredient	Concentration, %w/w
Ketoprofen	1
Pluronic F-127	20
Buffer, pH 5.0[a]	79

[a] 0.1 M citric acid and 0.2 M disodium phosphate, 49 : 51(v/v)

Pluronic and Carbopol gels are shown in Fig. 11. The permeation rate of ketoprofen from the Pluronic gel was approximately 6 times higher than that from the Carbopol gel. This higher skin permeation may be due to the better drug releasing characteristics of the Pluronic gel as well as the effect of Pluronic as a surface active compound.

4-8. Stability studies on ketoprofen gels

To study the physical and chemical stability of ketoprofen in the gel, 20% Pluronic gels containing 1% ketoprofen and at gel pHs of 3, 4, 5, 6 and 7 were stored at 4, 25 and 40℃. At 2 and 3 months after storage, physical stability of the gel such as color change, recrystallization and precipitation of the drug was evaluated and the amount of the drug remaining was quantitated using and HPLC method.

During the 8 month observation period, no deleterious physical changes were seen. Also, no significant degradation of ketoprofen in the gels ocurred up to 8 months of storage at these temperatures.

5. Evaluation of Antiinflammatory Activity of Ketoprofen Gels

A ketoprofen gel formulation which showed maximum percutaneous absorption was selected based on the *in vitro* experiments and further tested for the *in vivo* antiinflammatory activity of ketoprofen after its topical application using the carrageenan-induced rat paw edema method.

5-1. Ketoprofen gel formulation

The gel formulation in Table 5 was used for this study.

5-2. Determination of the antiinflammatory activity of ketoprofen

Three hrs after the application of 1% ketoprofen gel on the top of the left hind paw, 0.1 ml of 1% carrageenan saline solution was injected subplantarly into the same paw and the paw volume was immediately measured with an instrument based on mercury displacement method. Three hrs after the carrageenan injection, the volume of the same paw was measured again. The percent swelling of the paw and the percent inhibition of the

Table 6. Percent Inhibition of Edema Formation by Ketoprofen in Pluronic F-127 and Carbopol Gel

Group	No. of rat	% swelling (mean± S.E.)	% inhibition
Control	8	32.5± 2.0	
Carbopol gel[a]	6	20.7± 2.8	36.3
PF-127 gel[a]	6	14.2± 2.2	56.3

[a] 50 mg/paw of each 3% ketoprofen gel applied

edema formation were compared to evaluate antiinflammatory activity of ketoprofen in the gels.

5-3. Dose reponse of ketoprofen after subplantar injection

Kotoprofen was injected subplantarly into the rat paw together with carrageenan solution to determine its dose response.

As shown in Fig. 12, a linear correlation was found between % swelling of the paws 3 hrs after the injection of ketoprofen-carrageenan solution and the log dose of ketoprofen injected, in the range between 0.1 and 10 μg. The dose of 10 μg showed approximately 60% inhibition of swelling. Further increase of ketoprofen dose beyond 10 μg showed no additional inhibition of swelling. The linear relationship between log dose and antiinflamatory activity of ketoprofen makes it possible to use this model for the bioassay of ketoprofen in the development of topical preparations.

5-4. Influence of gel base on antiinflammatory activity of ketoprofen and comparison with other topical NSAID preparations

To study the influence of the type of gel base, the antiinflammatory activity of ketoprofen was determined using the two gel formulations of Pluronic F-127 and Carbopol 940 in Table 4 and the results are shown in Table 6.

Also, the antiinflammatory activity of the 1% ketoprofen gel of this study was compared with those of a marketed 1% indomethacin gel and a patented 3% ketoprofen gel. Table 7 shows the % inhibition of edema formation after topical application of these gel preparations. The 1% ketoprofen gel yielded 53.2% inhibition, which is about

Table 7. Percent Inhibition of Edema Formation by Ketoprofen and Indomethacin in Topical Gels

Group	Dose mg/paw	No. of rats	% swelling mean± S.E.	% inhibition
Control	0	8	44.9± 2.8	
1% gel[c]	50	6	21.0± 4.9	53.2
3% gel[a]	50	6	28.1± 4.7	37.5
Inteban[c]	50	6	36.2± 4.5	19.4

[a] 1% ketoprofen gel prepared in this study
[b] 3% ketoprofen gel (9)
[c] 1% indomethacin gel marketed by Sumimoto Chemical Co., Japan

Table 8. Duration of Antiinflammatory Effect of 1% Ketoprofen Gel[a]

Time[b] (hr)	No. of rats	% swelling (mean± S.E.)	% inhibition
Control	8	48.2± 3.3	
0	6	30.2± 3.6	37.3[c]
2	6	23.6± 2.7	51.0[c]
4	6	25.7± 3.5	46.7[c]
6	6	24.1± 4.7	50.0[c]
12	6	21.5± 2.8	55.4[c]
18	6	23.7± 5.0	50.9[c]
24	6	24.5± 2.5	49.3[c]
36	6	37.3± 2.3	22.7
48	6	40.2± 5.7	16.5

[a] dose : 50 mg/rat
[b] gel application time before the injection of 0.1 ml of 1% carrageenan solution
[c] significantly different inhibition of edema formation as compared to the control, at alpha of 0.05

the maximum % inhibition obtainable with this edema method and significant greater inhibition than other gels, indicating higher efficacy compared to other gels. The lower antiinflammatory activity with the marketed and patented NSAID gels may be due to the difference in gel type. Carbopol was used as the gel forming agent in both gel formulations. The lower skin permeation of indomethacin than ketoprofen could attribute to the low inhibition of edema formation by the indomethacin gel.

5-5. Duration of antiinfammatory activity of ke-

toprofen gel

The duration of antiinflammatory activity of ketoprofen after topical application of the 1% ketoprofen gel was measured by changing the length of time between the gel application and the carrageenan injection.

The gel was applied at various time intervals between 0 and 48 hrs before the carrageenan injection and the results are shown in Table 9. When the gel was applied between 0 and 24 hrs before the carrageenan injection, significant % inhibition of edema formation was found in each case compared to the control. the ketoprofen gel applied between 2 and 24 hrs before the carrageenan injection, yielded close to the maximum % inhibition of the swelling. From this experiment it is clear that even when the ketoprofen gel was applied 24 hrs before the carrageenan injection, sufficient high local concentration of ketoprofen was present to yield maximum % inhibition.

5-6. ED_{50} of ketoprofen gel

To determine the ED_{50} of the 1% ketoprofen gel, the gel was applied on the rat hind paws 3 hrs before the carrageenan injection at the dose of 0.6, 1.2, 1.8 and 3.0 mg/kg as ketoprofen. As a reference, oral ED_{50} was also determined. Ketoprofen suspended in physiological saline solution was administered 1 hr before the carrageenan injection at the dose of 1, 2, 5 and 10 mg/kg. Regression equations were determined from the log dose and % inhibition relationship and were used for the calculation of ED_{50}. The topical ED_{50} of the gel was 2.2 mg/kg as ketoprofen and the oral ED_{50} was 6.1 mg/kg, resulting in 280% of relative equiponderal bioavailability for the 1% ketoprofen gel in reference to oral administration.

6. Pharmacokinetic and Ulcerogenic Evaluation of Ketoprofen Gel in Rats

To gain a full insight into the percutaneous absorption of ketoprofen from the gel, pharmacokinetics and percutaneous absorption of ketoprofen into local tissues after topical application of the gel were studied with rats. Also the ulcerogenic activity of ketoprofen after topical dose was determined using rats.

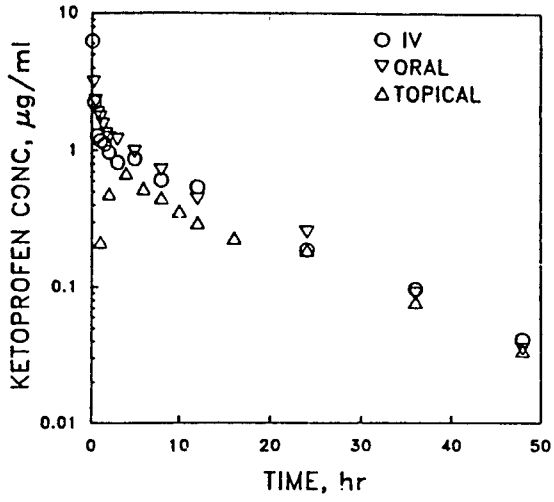

Figure 13—Plasma concentration-time profiles following iv, oral and topical administration of ketoprofen in rats.

6-1. Ketoprofen gel formulation

The gel formulation in Table 5 was used for this sutdy.

6-2. Pharmacokinetic studies

Ketoprofen was injected intravenously at the dose of 2.5 mg/kg for iv bolus dose. For oral administration, rats received the same dose of ketoprofen suspended in physiological saline solution. For topical application, 50 mg of the 1% ketoprofen gel was applied over the shaved ventral skin. Blood samples were collected at the predetermined time intervals and ketoprofen in the rat plasma was quantitated using an HPLC method.

Fig. 13 shows the average plasma levels of ketoprofen as a function of time following IV bolus, oral and topical doses. After topical dose, the absorption of ketoprofen was much slowed compared to oral administration. The C_{max} after the gel application was 20% of that after oral dosing, suggesting that the topical gel has an advantage in reducing the systemic side effects accompanied by oral administration due to high blood concentration of ketoprofen. And the plasma concentration of the drug after topical dose was considerably sustained between 1 and 24 hrs which was in close agree-

Table 9. Pharmacokinetic Parameters of Ketoprofen After IV Bolus, Oral and Topical Route of Administration in Rats[a]

Parameters	Administration route		
	IV	Oral[b]	Topical[c]
Dose(mg/kg)	2.50	2.79	2.34
$\lambda_z(hr^{-1})$	0.071	0.073	0.071
	(0.010)[d]	(0.009)	(0.016)
$t_{1/2}$(hr)	9.97	9.62	10.18
	(1.31)	(1.12)	(2.69)
Cl(L/h/kg)	0.141	–	–
	(0.018)		
Vd_{ss}(L/kg)	1.901	–	–
	(0.421)		
AUC(mg×h/L)	17.88	18.41	10.65
	(2.25)	(1.43)	(2.10)
Absolute BA(%)	–	92.2	63.5
	–	(6.5)	(11.7)
Relative BA[e](%)	–	–	68.8
			(12.7)

[a] n=4
[b] ketoprofen suspended in physiological saline solution
[c] 1% ketoprofen gel
[d] ( ) : S.D.
[e] in reference to oral administration

ment with the duration of antiinflammatory activity of the gel determined previously. This sustained antiinflammatory activity and blood level of ketoprofen over one day is due to the unique characteristics of Pluronic F-127. Pluronic F-127 forms a solid artificial barrier and sustained release film after the application of the gel on the skin.

6-3. Bioavailability

The plasma level vs. time profiles were analyzed individually using the area/moment analysis. The pharmacokinetic parameters determined from each route of administration are listed in Table 9.

Based on the AUCs for three administration routes, the absolute and relative bioavailability of the topical gel were 63.5% and 68.8%, respectively. This indicates that at least 60% of the applied dose of ketoprofen was absorbed from the topical

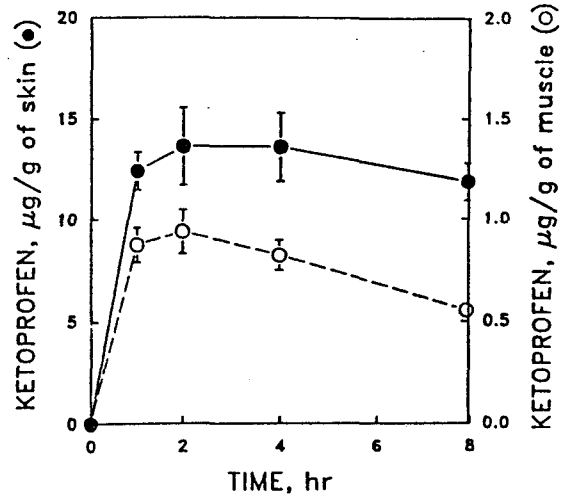

Figure 14—Drug concentration profiles in skin and muscle under the applied site as a function of time after topical application of 1% ketoprofen gel on ventral skin of rats.

gel. The reported bioavailabilities of other NSAID topical preparations ranged between 1 and 20%. The greater bioavailability of the ketoprofen gel may be due to the good skin permeability of ketoprofen, excellent drug release characteristics of Pluronic gels and skin penetration enhancing effect by Pluronic.

6-4. Percutaneous Absorption

The drug concentrations in the skin and muscle tissues after topical application of the gel on them were determined using rats to see the actual amount of ketoprofen absorbed from the gel into these tissues. Fifty mg of the 1% ketoprofen gel was applied on the shaved ventral skin. After 1, 2, 4 and 8 hrs postdose, the skin and muscle tissues under the applied area were removed and the drug concentration in these tissues were quantitated using an HPLC method.

Fig. 14 shows the ketoprofen concentration in the skin and muscle tissues as a function of time after the gel application. The maximum skin concentration appeared at 2 hr postdose and was continuously sustained over the next 6 hrs. The overall profile in the muscle was parallel to that in the skin. The high local drug concentration in the muscle suggested the good percutaneous absorp-

Table 10. Ulcerogenic Activity of Ketoprofen in the Stomach of Fasted Rats after Topical Application of 1% Ketoprofen Gel and Oral Administration of the Drug as a Suspension

Admin. route	Dose[a] (mg/kg)	Ulcerogenic lesions: Ulcer rats[b]	Ulcerogenic lesions: Mean score ± S.E.	UD_{50} (mg/kg)
Oral	0	0/6	0.17± 0.17	
	1	0/6	0.50± 0.22	
	2	1/6	1.00± 0.26	4.6(2.6-8.1)[c]
	5	3/6	1.67± 0.49	
	10	5/6	2.50± 0.62	
Topical	0	0/7	0.14± 0.14	
	5	0/7	0.29± 0.18	
	10	1/6	0.67± 0.49	39(10-157)[c]
	20	2/6	1.33± 0.61	
	50	4/7	1.57± 0.36	

[a] as ketoprofen
[b] number of rats showing ulcers/number of rats tested
[c] ( ) : 95% confidence limit

tion of ketoprofen from the Pluronic gel.

6-5. Ulcerogenic Activity

The ulcerogenic activity of ketoprofen after topical dose of the 1% ketoprofen gel was determined with rats. The gel was applied on the shaved dorsal skin at the dose of 0, 5, 10, 20 and 50 mg/kg as ketoprofen. As a reference, the ulcerogenicity of ketoprofen following oral administration was determined. Ketoprofen suspended in a physiological saline solution was administered at the dose of 0.1, 2, 5 and 10 mg/kg. At 6 hrs postdose, the rats were sacrificed and the stomachs were examined for ulcer formation. Gastric lesions were scored using a grading system reported by Nakamura.

As shown in Table 10, the oral dose of 10 mg/kg induced ulcers in 5 among 6 rats, while the higher topical dose of 50 mg/kg induced ulcers only in 4 among 7 rats. The UD_{50}s calculated according to the Litchfield-Wilcoxon method were 39 mg/kg for the topical route and 4.6 mg/kg for the oral route, respectively, indicating about 8.5 times less gastric toxicity by the topical gel than oral dose.

Conclusions

To reduce the gastrointestinal irritation, while maintaining the therapeutic effect on the receptor site, 1% ketoprofen gel was developed using 20% Pluronic F-127 of pH 5 based on the studies of *in vitro* experiments for the release and percutaneous absorption of ketoprofen from the various gel formulations.

1) The ED_{50} of the topical gel was 2.2 mg/kg as ketoprofen, while the ED_{50} of the oral dose was 6.1 mg/kg, indicating about 3 times greater potency by the topical gel.

2) The antiinflammatory activity of ketoprofen after topical application of the gel was sustained for one day which was in agreement with the duration of sustained plasma drug concentration after topical dose of the gel.

3) Compared to other existing NSAID topical preparations, it showed greater antiinflammatory activity.

4) The relative equidosal bioavailability of the topical gel was 69%, while the relative equiponderal bioavailability was 280% in reference to oral dose.

5) The topical gel showed 8.5 times less gastric toxicity than the oral dose of the drug.

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