Arch Pharm Res Vol 24, No 6, 578-583, 2001

Archives of Pharmacal Research
http://apr.psk.or.kr

In Vitro Percutaneous Absorption of Tenoxicam from Pressure-sensitive Adhesive Matrices across the Hairless Mouse Skin

Hye Sun Gwak and In Koo Chun

Laboratory of Pharmaceutics, College of Pharmacy, Dongduk Women's University, Seoul 136-714, Korea

(Received September 25, 2001)

To investigate the feasibility of developing a new tenoxicam plaster, the effects of vehicles and penetration enhancers on the *in vitro* permeation of tenoxicam from a pressure-sensitive adhesive (PSA) matrices across the dorsal hairless mouse skin were studied. Vehicles employed in this study were propylene glycol (PG)-oleyl alcohol (OAl), PG-oleic acid (OA), and diethylene glycol monoethyl ether (DGME)-propylene glycol monolaurate (PGML) cosolvents with/without fatty acids. In this study, amines such as triethanolamine (TEA) and tromethamine (TM) were additionally used as a solubilizer. Among PSAs used, Duro-Tak® 87-2510 showed much higher release rate than either Duro-Tak® 87-2100 or Duro-Tak® 87-2196. The relatively high flux rate was obtained with the formulation of DGME-PGML (40:60, v/v) with 3% OA and 5% TM, and the flux increased as a function of the dose; the initial flux up to 12 h was 4.98 ± 1.38 μg/cm^2/h at the tenoxicam dose of 50 mg/70 cm^2. This flux was much higher than that of a commercial piroxicam patch (Trast®) (1.24 ± 0.73 μg/cm^2/hr) with almost only one-third that of the commercial patch. Therefore, these observations indicated that these composition of tenoxicam plaster may be practically applicable.

Key words: Tenoxicam plasters, Vehicles, Penetration enhancers, Percutaneous absorption, Pressure-sensitive adhesive matrices

INTRODUCTION

Tenoxicam is a thienothiazine derivative of the oxicam class of nonsteroidal anti-inflammatory drugs (NSAIDs), with a structure closely related to piroxicam. Oxicam drugs are generally characterized by strong binding to plasma proteins with a long elimination half-lives (Todd and Clissold, 1991). The average plasma half-life of tenoxicam is 66 hrs (range 42 to 98), which allows the administration of a single daily dose for the treatment of rheumatic and inflammatory disorders (Valdes et al., 1985). Tenoxicam is completely absorbed by the oral route, however, its use has been associated with a number of gastrointestinal disorders (Barclay and Traballi, 1987; Caughey and Waterworth, 1989).

The transdermal delivery has been recognized as an alternative route for an oral administration due to its several advantages, which include avoidance first pass metabolism by the liver and enzymatic degradation by the gastrointestinal tract, and maintenance of relatively constant plasma concentration in the body. Many studies have been conducted for the transdermal delivery of piroxicam using various formulations (Hsu *et al.*, 1994; Pellett *et al.*, 1994; Santoyo *et al.*, 1995). However, it appears that little or no attention has been paid to the tenoxicam transdermal delivery system.

We have previously reported the effects of vehicles and enhancers on the skin permeation of tenoxicam from saturated solutions across excised hairless mouse skins (Gwak and Chun, 2001). Based on the results from the previous study, in the present study, the effects of vehicles and penetration enhancers on the permeation of tenoxicam from pressure-sensitive adhesive (PSA) matrices across excised hairless mouse skins were evaluated to examine the feasibility for commercial development of tenoxicam PSA plasters.

MATERIALS AND METHODS

Materials

Tenoxicam and piroxicam were kindly provided by Dong-A Pharm. Ind. Co., Ltd. (Yongin, Korea). Propylene

Correspondence to: In Koo Chun, College of Pharmacy, Dongduk Women's University, Seoul 136-714, Korea
E-mail: ikchun@dongduk.ac.kr

glycol monolaurate (PGML, Lauroglycol® 90), propylene glycol monocaprylate (PGMC, Capryol® 90) and diethylene glycol monoethyl ether (DGME, Transcutol® P) were obtained from Gattefossé (Gennevilliers Cedex, France). Oleyl alcohol (OAl) and triethanolamine (TEA) were of analytical grade. Acetonitrile and methanol used were of HPLC grade. Isopropyl myristate (IPM), oleic acid (OA), linoleic acid (LOA), tromethamine (TM) and prazosin hydrochloride were purchased from Sigma Chemical Co. (St. Louis, MO, USA). Acrylic pressure-sensitive adhesive solutions in organic solvents which were Duro-Tak® 87-2196 (copolymer: acrylate-vinylacetate, functional group: -COOH, 45% solution of self-crosslinking acrylic copolymer, 3000 cps, solubility parameter 16), Duro-Tak® 87-2100 (copolymer: acrylate, functional group: -COOH, 51.5% solution of self-crosslinking acrylic copolymer, 8500 cps, solubility parameter 16) and Duro-Tak® 87-2510 (copolymer: acrylate, functional group: -OH, 40.5% solution of non-crosslinking acrylic copolymer, 4500 cps, solubility parameter 16) were obtained from National Starch and Chemical Company (Bridgewater, NJ, USA). Other reagents were of analytical grade.

Animals

Male hairless mice aged 6~8 weeks were purchased from Samtako Bio Korea Co., Ltd. (Osan, Korea).

Analysis

Samples from release and permeation studies were analyzed by high-performance liquid chromatography (HPLC). The HPLC system consisted of a pump (Model SCL-100, Samsung, Korea) with a detector (Model LC 90, Perkin-Elmer, USA) set at 355 nm and an integrator (Model 4290, Varian, USA). An ODS column (μ Bondapak C18, Waters, USA) equipped with a C18 Radial Pak insert was used. The mobile phase was composed of pH 2.8 phosphate buffer and acetonitrile (65:35 for tenoxicam and 55:45 for piroxicam), and delivered at a flow rate of 1.0 ml/min. The injection volume was 20 μl. Internal standards (IS) used for HPLC assays of tenoxicam and piroxicam were prazosin hydrochloride and tenoxicam, respectively. Calibration curves were constructed by plotting the peak area ratios of tenoxicam to IS versus the concentrations of tenoxicam in solution.

Preparation of tenoxicam plasters

An appropriate amount of tenoxicam was dissolved in various pure solvents or cosolvents with/without permeation enhancers, and then mixed with three types of acrylic adhesive solutions: Duro-Tak® 87-2196, Duro-Tak® 87-2510, and Duro-Tak® 87-2100. Tenoxicam PSA plasters were prepared by casting the above solutions on a polyester release liner coated with silicone (Gelroflex ALU-PET 100 m-2S DR, 3M, USA) using a casting knife. The area of the cast solutions was 10 cm × 7 cm per 2.5 g solution, which consisted of 0.5 ml of drug solution in the vehicle and 2 g of acrylic adhesive solution. They were set at room temperature for 4 h to evaporate the solvents, and then dried overnight in an oven (37°C). The dried film was transferred onto a backing film (Scotchpak 1109, 3M, USA). Table I shows compositions of the formulation for the preparation of tenoxicam plasters.

Procedure for tenoxicam release from tenoxicam plasters

Plasters prepared were mounted on a side-by-side permeation system (Valia-Chien Permeation System, Crown Bioscientific Inc., NJ, USA); the drug loaded-layer was in contact with the receptor compartment. The area of cell openings was 0.64 cm^2. Receptor compartment cells were filled with 40% PEG 400 in saline and the media were stirred by a Teflon-coated magnetic bar to keep them well mixed. The released media were maintained at 32°C. At predetermined time intervals, 100 μl of receptor solutions were withdrawn, and the amount of tenoxicam released from various PSA plasters was determined by HPLC.

Procedure for skin permeation *in vitro*

After sacrificing with ether, the dorsal skin of each hairless mouse was excised. Tenoxicam plasters of an appropriate size were applied to the epidermal side of the skin, and mounted on the permeation system; the dermal side was in contact with the receptor compartment. Receptor compartment cells were filled with 40% PEG 400 in saline and the media were stirred by a Teflon-coated magnetic bar to keep them well mixed. The permeation media were maintained at 32°C. At predetermined time intervals, 100 μl of receptor solutions were withdrawn, and the amount of tenoxicam permeated was determined by HPLC.

Data analysis

As described by Barry (1983), the steady-state flux (J_s), lag time (T_L), diffusion coefficient (D), skin / PSA partition coefficient (K), and apparent permeation coefficient (P_{app}) are defined by equations 1-3.

$$J_s = (dQ/dt)_{ss} \cdot 1/A = DKC/h \quad (1)$$

$$D = h^2/6T_L \quad (2)$$

$$P_{app} = dQ/dt \cdot 1/A \cdot 1/C_s \quad (3)$$

where
A: the effective diffusion area
h: the thickness of skin
C: the constant concentration in a plaster
C_s: the solubility of a drug in PSA

Table I. Formulation compositions for the preparation of tenoxicam plasters

FN	Amount loaded (mg/70 cm^2)	Vehicles	PSA (Duro-Tak)	Enhancers
1	15	PG	2196	TEA (1%)
2	15	PG	2510	TEA (1%)
3	10	PG	2196	OA (3%) + TEA (1%)
4	10	PG	2510	OA (3%) + TEA (1%)
5	10	PG	2100	OA (3%) + TEA (1%)
6	15	PG	2510	OA (3%) + TEA (1%)
7	10	PG	2510	OA (3%) + TM (1%)
8	15	PG : OAl (50:50)	2510	-[a]
9	15	PG : OAl (50:50)	2510	OA (3%)
10	15	DGME : PGML(40:60)	2510	-
11	15	DGME : PGMC(40:60)	2510	-
12	15	PG	2510	OA (5%) + TEA (1%)
13	15	PG	2510	LOA (5%) + TEA (1%)
14	15	PG	2510	OA (10%) + TEA (1%)
15	50	DGME : PGML(40:60)	2510	TM (5%)
16	50	DGME : PGML(40:60)	2510	OA (3%) + TM (5%)
17	50	DGME : PGML(40:60)	2510	Cineole (3%) + TM (5%)
18	12.5	DGME : PGML(40:60)	2510	OA (3%) + TM (5%)
19	25	DGME : PGML(40:60)	2510	OA (3%) + TM (5%)

[a]Not added. Data were expressed as the mean ± S.D. (n = 3). For all preparations, the thickness of drug loaded layer was 510 m, and the ratio of PSA solution to drug solution was 4:1 (w/v). FN: formulation number. 70 cm^2: the area (10 cm × 7 cm) of dose loading.

$(dQ/dt)_{ss}$: the steady state slope

RESULTS AND DISCUSSION

Effect of various PSAs on the release from a plaster

In designing a transdermal drug-in-adhesive plasters, it is essential to determine an appropriate vehicle which solubilizes the target drug, that mixes adequately with PSA, and/or enhances the permeation rate. From our previous study using solution formulations of tenoxicam (Gwak and Chun, 2001), the combination of DGME and PGML or PGMC at the 40:60 (v/v) ratio showed a significant permeation enhancing effect. PG-OAl cosolvents also showed an excellent enhancing effect for the drug. The highest flux was obtained by the addition of unsaturated fatty acids like OA or LOA at the concentration of 3% to a hydrophilic vehicle such as PG; their enhancement factors were 348 and 238, respectively. Amines were examined to determine whether the flux is enhanced as a function of solubility. However, even when TM showed a relative enhancing effect, possibly due to the increased solubility, addition of TEA did not lead to a further increase in the flux.

In this study, these vehicles and penetration enhancers were used for the fabrication of tenoxicam plasters, and they appeared consistent with the conditions for plaster preparations. To evaluate the effect of PSA on the tenoxicam release from the matrix formulation, these vehicles were mixed with three types of PSAs: Duro-Tak® 87-2196, Duro-Tak® 87-2510, and Duro-Tak® 87-2100. Recently, various PSAs have been evaluated for fabrication of transdermal delivery systems. To fabricate such a transdermal device, a drug was either dissolved or dispersed in a polymeric solution, and a thin film of desired thickness was then prepared by the solvent-cast method (Borodkin and Tucker, 1974; Kim *et al.*, 2000). The release rate of a drug in an adhesive matrix is thought to be governed by drug solubility and diffusion coefficients in polymer (Roy *et al.*, 1996). The release rates of tenoxicam from the three PSAs are illustrated in Fig. 1. It was found that the releases from all PSAs tested were proportional to the square root of time, consistent with the matrix-controlled diffusion model ($Q' = k't^{1/2}$, Q': amount released, k': release rate constant) (Chien and Lambert, 1974). The release rate of tenoxicam from Duro-Tak® 87-2510 was much higher than that from Duro-Tak® 87-2100 or Duro-Tak® 87-2196. Although the underlying mechanism was not directly investingated in this study, the difference in functional group, (e.g., Duro-Tak® 87-2510 has carboxyl groups, and the others have hydroxyl groups) may be involved in the solubility difference.

Effect of vehicles and enhancers on the permeation of tenoxicam from a pressure-sensitive adhesive matrix

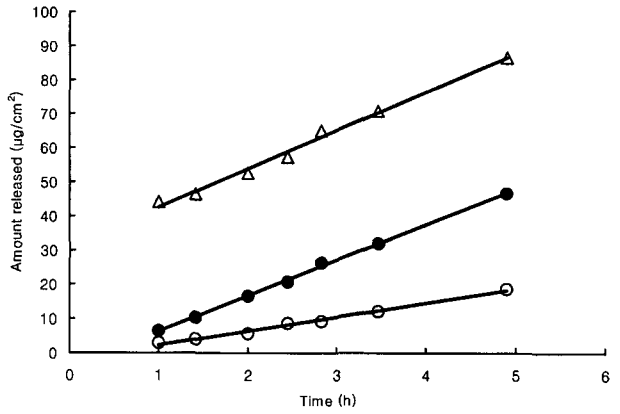

Fig. 1. Effect of various PSAs on the release from tenoxicam plasters (n=3). The vehicle consisted of PC containing 3% OA and 1% TEA, and the loading dose was 10 mg/70 cm^2. Key: blank circle, 2196 (y=4.1036x 1.8185, r^2=0.991); filled circle, 2100 (y=10.413x 4.1434, r^2=0.9987); blank triangle, 2510 (y=11.329x + 31.247, r^2=0.9918).

The stratum corneum has been found to possess a significant barrier property in percutaneous absorption of drugs. To overcome this problem, a number of mechanisms have been suggested, e.g., the reduction of skin resistance as a permeability barrier by disruption of tightly packed lipid regions of stratum corneum (Barry, 1987), increased skin/vehicle partitioning of the drug (Green *et al.*, 1988), increased solvent transport into or across the skin (Yamada, *et al.*, 1987), and increased drug solubility in the vehicle (Aungst *et al.*, 1990).

Two component systems consisting of hydrophilic molecules such as PG and lipophilic molecules such as fatty acids or fatty alcohols proved to be very effective promoters for tenoxicam permeation in the previous study using solution formulations (Gwak and Chun, 2001). Thus, the permeation rates of tenoxicam across excised hairless mouse skin from the matrix formulation containing those binary cosolvent systems were investigated. Duro-Tak® 87-2510 was used for PSA because of its relatively high release rate compared to the others. In this study, the concentration of tenoxicam in each vehicle was saturated. The permeation parameters are summarized in Table II. The permeation fluxes were less than 0.50 μg/cm^2/h regardless of the addition of OA or its concentration, and they were significantly lower when compared with those obtained from solution formulations, probably due to the decrease of solubility and diffusivity of tenoxicam in the PSA layer.

Table III. Permeation flux and lag time of tenoxicam through excised hairless mouse skin from PSA matrix plasters contain-ing DGME-PGML (40:60) cosolvents

FN	Theoretical amount of drug per unit area (μg/cm^2)	J_s (μg/cm^2/h)	T_L (h)
10	214.3	0.24 ± 0.10	1.86 ± 1.56
15	714.3	0.87 ± 0.03	0.95 ± 1.16
16	714.3	2.78 ± 0.70	NA
17	714.3	1.08 ± 0.70	NA
18	178.5	0.91 ± 0.30	1.68 ± 1.39
19	357.1	1.59 ± 0.40	NA

Data were expressed as the mean ± S.D. (n = 3). FN: formulation number based on Table I. NA: not available.

In this study, another co-solvent system, DGME-PGML (40:60, v/v), which showed an adequate enhancing effect, was also evaluated (Gwak and Chun, 2001). The flux of FN 10 in Table I (0.24 ± 0.10 μg/cm^2/h) was much lower than that of solution formulation (20.3 ± 7.0 μg/cm^2/h). As represented in Table III, the flux was increased to 0.87 ± 0.03 μg/cm^2/h as the dose increased from 15 mg to 50 mg per 70 cm^2 by addition of TM (5%). The further increase of flux was achieved by adding OA to the concentration of 3%. However, cineole, a terpenide, did not show a significant enhancing effect. As shown in Fig. 2, in the formulation of DGME-PGML (40:60, v/v) with 3% OA and 5% TM, the flux increased as function of the dose; the highest flux was 2.78 ± 0.70 μg/cm^2/h at the tenoxicam dose of 50 mg/70 cm^2 (FN 16). The piroxicam patch, Trast®, which is now being marketed in Korea, was

Table II. Permeation parameters of tenoxicam through excised hairless mouse skin from PSA matrix plasters containing PG as a vehicle

FN	Permeation parameters				
	J_s (μg/cm^2/h)	T_L (h)	D (× 10^5, cm^2/h)	K	P_{app} (× 10^7, cm/sec)
2	0.30 ± 0.16	NA	NA	NA	0.035 ± 0.018
6	0.44 ± 0.22	NA	NA	NA	0.08 ± 0.04
8	0.23 ± 0.06	0.89 ± 0.18	10.1 ± 5.02	0.07 ± 0.04	0.70 ± 0.18
9	0.13 ± 0.02	3.96 ± 1.28	2.99 ± 1.32	0.13 ± 0.03	0.40 ± 0.05
12	0.09 ± 0.001	NA	NA	NA	0.02 ± 0.0002
13	0.28 ± 0.17	3.11 ± 1.93	5.58 ± 3.47	0.02 ± 0.02	0.05 ± 0.03
14	0.46 ± 0.22	1.12 ± 0.62	15.5 ± 8.2	0.006 ± 0.003	0.09 ± 0.04

Data were expressed as the mean ± S.D. (n = 3). FN: formulation number based on Table I. NA: not available.

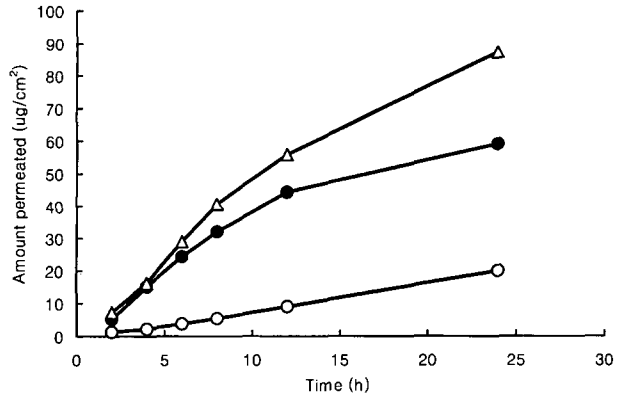

Fig. 2. Effect of drug loading on the cumulative amount of tenoxicam permeated through excised hairless mouse skin from PSA matrix plasters as a function of time (n = 3). The vehicle consisted of DGME:PGML (40:60) containing 3% OA and 5% TM. Key: blank circle, 12.5 mg/70 cm^2; filled circle, 25 mg/70 cm^2; blank triangle, 50 mg/70 cm^2.

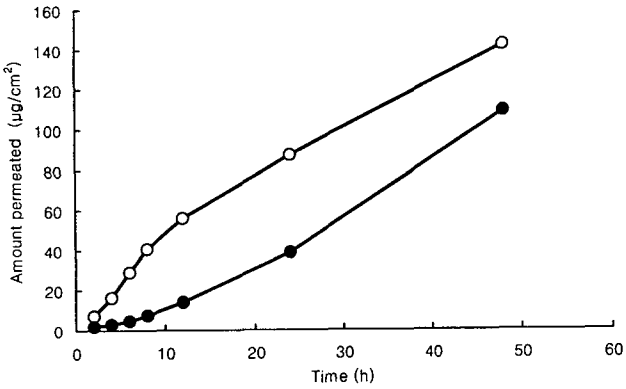

Fig. 3. Comparison of permeation rates of tenoxicam plaster (FN 16) and piroxicam patch (Trast®) (n = 3). FN 16 is composed of DGME:PGMC (40:60) with 3% OA and 5% TM. Key: blank circle, tenoxicam plaster FN 16; filled circle, piroxicam patch (Trast®)

compared with the tenoxicam plaster (FN 16) in terms of delivery rate of the drug. Piroxicam and tenoxicam have proved to have the similar pharmacokinetic parameters, which are characterized by a significant protein binding (98.2 and 98.4%), volume of distribution (0.14 and 0.15 L/kg), total clearance (0.12-0.18 and 0.10-0.25 L/h), and half-life (57 ± 16 and 66 ± 16 h). Typical dose of these drugs is the same for 20 mg once a day (Albengres *et al.*, 1993). As depicted in Fig. 3, FN 16 showed an adequate permeation rate up to 12 h, and the flux decreased as a function of time. On the contrary, for Trast®, the flux was increased with time. From the figure, initial fluxes up to 12 h of application were calculated as 4.98 ± 1.38 and 1.24 ± 0.73 μg/cm^2/h for FN 16 and Trast®, respectively. Considering that the content of the drug per unit area of Trast® (48 mg/20.7 cm^2) was three times that of the tenoxicam plaster (50 mg/70 cm^2), the permeation flux of the tenoxicam plaster was estimated to be much higher than that of Trast®.

In conclusion, the combination of a solution formulation matrix formulation consisting of DGME-PGML (40:60, v/v) cosolvent, 3% OA and 5% TM and a Duro-Tak® 87-2510 PSA could be a candidate for developing a new tenoxicam transdermal plaster. Therefore, these observations indicated that these composition of tenoxicam plaster may be practically applicable.

REFERENCES

Albengres, E., Urien, S., Barre, J., Nguyen, P., Bree, F., Jolliet, P., Tillement J. P., Tsai, R.S., Carrupt, P. A., and Testa, B., Clinical pharmacology of oxicams: new insights into the mechanisms of their dose-dependent toxicity, *Int. J. Tiss. Reac.*, 16, 125-134 (1993).

Aungst, B. J., Blake, J. A., and Hussain, M. A., Contributions of drug solubilization, partitioning, barrier disruption, and solvent permeation to the enhancement of skin permeation of various compounds with fatty acids and amines. *Pharm. Res.*, 7, 712-718 (1990).

Barclay, C. A. and Traballi, C. A., Evaluation of tenoxicam in rheumatology-clinical trial results in Argentina and Brazil. *Eur. J. Rheumatol. Infla.*, 9, 712-718 (1990).

Barry, B. W., 1983. Dermatological Formulations. Marcel Dekker, New York, , pp. 1-48.

Barry, B. W., Mode of action of penetration enhancers in human skin. *J. Controlled Rel.*, 6, 85-97 (1987).

Borodkin, S. and Tucker, F.E., Drug release from hydroxypropyl cellulose-polyvinyl acetate films. *J. Pharm. Sci.*, 63, 1359-1363 (1974).

Caughey, D. and Waterworth, R. F., A study of the safety of tenoxicam in general practice. *New Zealand Med. J.*, 102, 582-583 (1989).

Chien, Y. W. and Lambert, H. J., Controlled drug release from polymeric delivery devices II: differentiation between partition-controlled and matrix-controlled drug release mechanism. *J. Pharm. Sci.*, 63, 515-519 (1974).

Green, P. G., Guy, R. H., and Hadgraft, J., In vitro and in vivo enhancement of skin permeation with oleic and lauric acids. *Int. J. Pharm.*, 48, 103-111 (1988).

Gwak, H. S. and Chun, I. K., Effect of vehicles and penetration enhancers on the *in vitro* percutaneous absorption of tenoxicam through hairless mouse skin. *Int. J. Pharm.*, submitted (2001).

Hsu, L. R., Huang, Y. B., Wu, P. C., and Tsai, Y.H., Percutaneous absorption of piroxicam from FAPG base through rat skin: effects of oleic acid and saturated fatty acid added to FAPG base. *Drug Dev. Ind. Pharm.*, 20, 1425-1437 (1994).

Kim, J. H., Cho, Y. J., and Choi, H. K., Effect of vehicles and pressure sensitive adhesives on the permeation of tacrine across hairless mouse skin. *Int. J. Pharm.*, 196,

105-113 (2000).
Pellet, M. A., Davis, A. F., and Hadgraft, J., Effect of supersaturation on membrane transport: 2. piroxicam. *Int. J. Pharm.*, 111, 1-6 (1994).
Roy, S. D., Gutierrez, M, Flynn, G. L., and Cleary, G. W., Controlled transdermal delivery of fentanyl: characterizations of pressure-sensitive adhesives for matrix patch design. *J. Pharm. Sci.*, 85, 491-495 (1996).
Santoyo, S., Arellano, A., Ygartua, P., and Martin, C., Penetration enhancer effects on the in vitro percutaneous absorption of piroxicam through rat skin. *Int. J. Pharm.*, 117, 219-224 (1995).
Todd, P. A. and Clissold, S. P., An update of its pharmacology and therapeutic efficacy in rheumatic diseases. *Drugs*, 41, 625-646 (1991).
Valdes, E. F., Barclay, C. A., and Traballi, C. A., Tenoxcam, a novel long-acting anti-inflammatory and analgesic drug of the oxicam class: double-blind comparative study with piroxicam in patients with gona or coxarthrosis. *Curr. Ther. Res.*, 37, 937-944 (1985).
Yamada, M., Uda, Y., and Tanigawara, Y., Mechanism of enhancement of percutaneous absorption of molsidomine by oleic acid. *Chem. Pharm. Bull.*, 35, 3399-3406 (1987).