(19) DANMARK

(10) DK/EP 3218060 T3

(12) Oversættelse af europæisk patentskrift

Patent- og Varemærkestyrelsen

(51) Int.Cl.: *A 61 K 9/12 (2006.01)* *A 61 K 9/08 (2006.01)* *A 61 K 31/19 (2006.01)* *A 61 K 47/12 (2006.01)* *A 61 P 29/00 (2006.01)*

(45) Oversættelsen bekendtgjort den: **2019-12-02**

(80) Dato for Den Europæiske Patentmyndigheds bekendtgørelse om meddelelse af patentet: **2019-10-30**

(86) Europæisk ansøgning nr.: **15859189.1**

(86) Europæisk indleveringsdag: **2015-11-04**

(87) Den europæiske ansøgnings publiceringsdag: **2017-09-20**

(86) International ansøgning nr.: **US2015058927**

(87) Internationalt publikationsnr.: **WO2016077111**

(30) Prioritet: **2014-11-10 US 201462077581 P**

(84) Designerede stater: **AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HR HU IE IS IT LI LT LU LV MC MK MT NL NO PL PT RO RS SE SI SK SM TR**

(73) Patenthaver: **Achelios Therapeutics, Inc., 4363 S. Alston Avenue, Suite 300, Durham, North Carolina 27713, USA**

(72) Opfinder: **BUYUKTIMKIN, Servet, 11772 Carmel Creek Rd. Apt. 105, San Diego, California 92130, USA**
BUYUKTIMKIN, Nadir, 11772 Carmel Creek Rd. Apt. 105, San Diego, California 92130, USA
YEAGER, James L., 476 Oakwood Ave., Lake Forest, Illinois 60045, USA

(74) Fuldmægtig i Danmark: **NORDIC PATENT SERVICE A/S, Bredgade 30, 1260 København K, Danmark**

(54) Benævnelse: **SPRAYBARE ANALGETISKE SAMMENSÆTNINGER**

(56) Fremdragne publikationer:
WO-A2-2007/070694
US-A1- 2003 161 867
US-A1- 2004 126 415
US-A1- 2007 189 978
US-A1- 2007 196 323
US-A1- 2013 243 701
SEBASTIANI P ET AL: "Effect of lactic acid and iontophoresis on drug permeation across rabbit ear skin", INTERNATIONAL JOURNAL OF PHARMACEUTICS, ELSEVIER, NL, vol. 292, no. 1-2, 23 March 2005 (2005-03-23), pages 119-126, XP027623889, ISSN: 0378-5173 [retrieved on 2005-03-23]

Description

FIELD OF INVENTION

[0001] This invention relates to analgesic compositions. More particularly, this invention relates to sprayable compositions containing nonsteroidal anti-inflammatory drugs.

BACKGROUND OF THE INVENTION

[0002] Nonsteroidal anti-inflammatory drugs (NSAIDs) are known medications with analgesic and antipyretic effects. NSAIDs are used to treat pain and discomfort such as muscle strain/sprain, fever, inflammation such as rheumatoid arthritis, joint pain, and the like.

[0003] The document WO 2007/070694 discloses a sprayable composition comprising a drug, for example ketoprofen, and the excipients: polyvinyl alcohol, polyvinylmethylether/maleic anhydride copolymer, glycerol, propylene glycol, ethanol and water.

[0004] The present invention provides topical dosage forms of NSAIDs that can be applied as a spray or as an aerosol.

SUMMARY OF INVENTION

[0005] A sprayable analgesic preparation contains a nonsteroidal anti-inflammatory drug (NSAID) as defined in the claims
together with lauryl lactate, lactic acid, and glyceryl monolaurate dissolved
in a mixture of water and ethanol. The obtained aqueous ethanolic solution is useful for extended pain relief.

[0006] Optionally, the aqueous ethanolic solution can contain propylene glycol, a non-ionic surfactant having a HLB value of at least 12, and a thickener such as cellulose ethers, cross-linked alkyl acrylates, and the like.
The NSAIDs are the propionic acid derivatives selected from ketoprofen, ibuprofen, naproxen, and pharmaceutically acceptable salts thereof, as well as the acetic acid derivatives selected from diclofenac, indomethacin, etodolac, and pharmaceutically acceptable salts thereof.

BRIEF DESCRIPTION OF DRAWINGS

[0007] In the drawings,

FIGURE 1 is a bar graph showing skin permeation by ketoprofen, applied as spray compositions, at selected time intervals after application, and comparison with a commercially available, ketoprofen-containing topical gel (Profenid® Sanofi-Aventis; 2.5% ketoprofen);

FIGURE 2 is a bar graph showing skin permeation by naproxen, applied as spray compositions, at selected time intervals after application, and comparison with a commercially available naproxen-containing topical gel (Naprosyn®, Syntex, 10% naproxen free acid);

FIGURE 3 is a bar graph showing skin permeation by ibuprofen, applied as a spray composition, at selected time intervals after application, and comparison with a commercially available ibuprofen-containing topical gel (Ibuleve®, DDD ltd., 5% ibuprofen);

FIGURE 4 is a bar graph showing skin permeation by diclofenac, and pharmaceutically acceptable salts thereof, applied as spray compositions, and comparison with a commercially available diclofenac sodium gel (Swiss Relief™, Mika Pharma GmbH, Fug, Switzerland, 4% diclofenac sodium);

FIGURE 5 is a bar graph showing the effect of propylene glycol on skin permeation in ibuprofen-containing spray compositions, and comparison with a commercially available ibuprofen-containing topical gel (Ibuleve®, DDD ltd., 5% ibuprofen);

FIGURE 6 is a bar graph showing skin permeation by ketoprofen with Brij 58 as a permeation enhancer, applied as spray compositions, at selected time intervals after application, and comparison with a commercially available, ketoprofen-containing topical gel (Profenid®, Sanofi-Aventis; 2.5% ketoprofen);

FIGURE 7 is a bar graph showing skin permeation by ketoprofen with propylene glycol laurate as a permeation enhancer, applied as spray compositions, at selected time intervals after application, and comparison with a commercially available, ketoprofen-containing topical gel (Profenid®, Sanofi-Aventis; 2.5% ketoprofen);

FIGURE 8 is a bar graph showing skin permeation by ketoprofen with propylene glycol caprylate as a permeation enhancer, applied as spray compositions, at selected time intervals after application, and comparison with a commercially available, ketoprofen-containing topical gel (Profenid®, Sanofi-Aventis; 2.5% ketoprofen);

FIGURE 9 is a bar graph showing skin permeation by ketoprofen with Sorbitan monolaurate as a permeation

enhancer, applied as spray compositions, at selected time intervals after application, and comparison with a commercially available, ketoprofen-containing topical gel (Profenid®, Sanofi-Aventis; 2.5% ketoprofen);

FIGURE 10 is a bar graph showing skin permeation by ketoprofen with various Brij derivatives as a permeation enhancer, applied as spray compositions, at selected time intervals after application, and comparison with a commercially available, ketoprofen-containing topical gel (Profenid®, Sanofi-Aventis; 2.5% ketoprofen);

FIGURE 11 is a bar graph showing skin permeation by ketoprofen, applied as a spray composition after 3 months stored at 25°C and 40°C, at selected time intervals after application, and comparison with a commercially available, ketoprofen-containing topical gel (Profenid®, Sanofi-Aventis; 2.5% ketoprofen);

FIGURE 12 is a bar graph showing skin permeation by naproxen using 5% Naproxen sodium salt and Brij 58, applied as spray compositions, at selected time intervals after application, and comparison with a commercially available naproxen-containing topical gel (Naprosyn®, Syntex, 10% naproxen free acid);

FIGURE 13 is a bar graph showing skin permeation by naproxen using 2.5% Naproxen sodium salt and Brij 58, applied as spray compositions, at selected time intervals after application, and comparison with a commercially available naproxen-containing topical gel (Naprosyn®, Syntex, 10% naproxen free acid);

FIGURE 14 is a bar graph showing skin permeation by ibuprofen with and without isopropyl myristate (IPM), applied as spray compositions, at selected time intervals after application, and comparison with a commercially available ibuprofen-containing topical gel (Ibuleve®, DDD ltd., 5% ibuprofen);

FIGURE 15 is a bar graph showing skin permeation by ibuprofen with isopropyl myristate (IPM) and Brij 58, applied as spray compositions, at selected time intervals after application, and comparison with a commercially available ibuprofen-containing topical gel (Ibuleve®, DDD ltd., 5% ibuprofen);

FIGURE 16 is a bar graph showing skin permeation by diclofenac, and pharmaceutically acceptable salts thereof, applied as cream compositions, and comparison with a commercially available diclofenac sodium gel (Voltaren®, Novartis Pharma Productions GmbH, Wehr, Germany, 1% diclofenac sodium);

FIGURE 17 is a bar graph showing skin permeation by diclofenac, and pharmaceutically acceptable salts thereof, applied as spray compositions, and comparison with a commercially available diclofenac sodium gel (Swiss Relief™, Mika Pharma GmbH, Fug, Switzerland, 4% diclofenac sodium);

FIGURE 18 is a bar graph showing skin permeation by diclofenac sodium with Brij 58, and different levels of propylene glycol and lactic acid, applied as spray compositions, and comparison with a commercially available diclofenac sodium gel (Voltaren®, Novartis Pharma Productions GmbH, Wehr, Germany, 1% diclofenac sodium);

FIGURE 19 is a bar graph showing skin permeation by diclofenac diethylamine with Brij 58, and different levels of propylene glycol and lactic acid, applied as spray compositions, and comparison with a commercially available diclofenac sodium gel (Voltaren®, Novartis Pharma Productions GmbH, Wehr, Germany, 1% diclofenac sodium); and

FIGURE 20 is a bar graph showing skin permeation by ketoprofen compositions containing different levels of propylene glycol and hydroxypropyl cellulose thickeners.

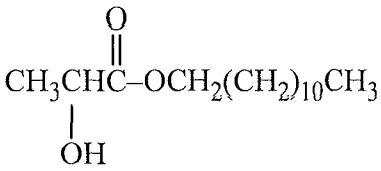
DESCRIPTION OF PREFERRED EMBODIMENTS

[0008] The present topical compositions are clear, sprayable, aqueous ethanolic solutions that contain dissolved therein a nonsteroidal anti-inflammatory drug (NSAID) wherein the drug is either a propionic acid derivative selected from the group consisting of ketoprofen, ibuprofen, naproxen, and pharmaceutically acceptable salts thereof, or an acetic acid derivative selected from the group consisting of diclofenac, indomethacin, etodolac, and pharmaceutically acceptable salts thereof.

[0009] Illustrative NSAID salts suitable for use as active ingredients in the spray compositions are pharmaceutically acceptable salts of the aforementioned acetic acid derivatives, e.g., indomethacin salts such as indomethacin sodium, indomethacin meglumine, and the like, diclofenac salts such as diclofenac sodium, diclofenac diethylamine, diclofenac epolamine, and the like, as well as pharmaceutically acceptable salts of the aforementioned propionic acid derivatives, e.g., ibuprofen salts such as ibuprofen lysine, ibuprofen methylglucamine, and the like, naproxen salts such as naproxen piperazine, naproxen sodium, and the like.

[0010] The aqueous ethanolic solutions preferably contain the NSAID in an amount in the range of about 1 to about 10 percent by weight preferably about 5 percent by weight, based on the total weight of the solution.

[0011] Also present in the solutions is lauryl lactate ($C_{15}H_{30}O_3$), the ester of lauryl alcohol and lactic acid having the formula



[0012] Preferably, lauryl lactate is present in the solution in an amount in the range of about 1 to about 5 weight percent, more preferably about 3 weight percent, based on the total weight of the solution.

[0013] The aqueous ethanolic solution also contains lactic acid ($C_3H_6O_3$; 2-hydroxypropanoic acid), preferably in an amount in the range of about 0.5 to about 5 weight percent, more preferably about 1.5 weight percent, based on the total weight of the solution; glyceryl monolaurate ($C_{15}H_{30}O_4$; dodecanoic acid 2,3-dihydroxypropyl ester), preferably in an amount in the range of about 2 to about 5 weight percent, more preferably about 3 weight percent, based on the total weight of the solution. Optionally, propylene glycol ($C_3H_8O_2$; propane- 1,2-diol) can be present, preferably in an amount in the range of about 5 to about 30 weight percent, more preferably about 10 weight percent, based on the total weight of the solution.

[0014] The remainder of the solution is constituted by water and ethanol, preferably present in a respective weight ratio of about 0.3:1 to about 2.6:1, more preferably in a respective weight ratio of about 1:1.

[0015] The aqueous ethanolic solution can also contain, as an optional ingredient, a non-ionic surfactant having a Hydrophile-Lipophile balance (HLB) value of at least 12. Preferred non-ionic surfactants are the alkoxylated alcohols. Particularly preferred is polyethylene glycol ether of cetyl alcohol represented by the formula $CH_3(CH_2)_{14}CH_2(OCH_2CH_2)_nOH$, where n has an average of 10, and having a HLB value of about 15.7.

[0016] The foregoing clear aqueous ethanolic solutions are prepared by first combining the NSAID with lauryl lactate, lactic acid, and glyceryl monolaurate and thereafter dissolving the obtained admixture by gradual addition, at ambient temperature, of propylene glycol followed by the addition of alternating aliquots of water and ethanol. The non-ionic surfactant, if desired, is added to the admixture prior to the addition of water and ethanol.

[0017] Skin permeation studies of illustrative compositions embodying the invention were performed using dermatoned human female (46 years old) cadaver skin pieces from the back (Science Care, Aurora, CO; 250 Micrometers thick) Franz cells (3.65 ml volume, 0.55 cm^2 surface area) at 35° C. using heating/stirring blocks. Receptor compartment contained saline with sodium azide (pH 7.4). Two or three replicates (25 μl and control 25 mg) were made for each solution. Sampling volume was 300 μl. Fresh buffer was replaced after each sample removal. Sampling was carried out at 2, 4, 6 and 24 hours. The samples were assayed using high performance liquid chromatography (HPLC).

[0018] Respective controls were NSAID containing gels: Profenid® gel (2.5% ketoprofen; Sanofi Aventis, France), Ibuleve® gel (5% ibuprofen; DDD Ltd., UK), Naprosyn® gel (10% naproxen free acid; Syntex, Turkey), Swiss Relief™ Spray Gel (4% diclofenac sodium) Mika Pharma GmbH, Switzerland), and Voltaren® gel (1% diclofenac sodium) Novartis Pharma Productions GmbH, Wehr, Germany.

[0019] The experimental results obtained with a ketoprofen spray composition are presented in Tables 1 and 2 below, and in FIGURE 1.

TABLE 1

Ketoprofen Spray Composition				
Ingredients	Composition, wt.%			
	KeS47	KeS73	KeS74	KeS75
Ketoprofen	5	5	5	5
Propylene glycol	10	10	10	10
Lauryl lactate	3	3	3	3
Lactic acid	1.5	1.5	1.5	1.5
Ceteth-20[1]		3		
Imwitor 412[2]			3	
Capmul PG-8[3]				3
Glyceryl monolaurate	3	3	3	3
Ethanol	37.5	27.25	39.5	34.5
Water	40	47.25	35	40

(continued)

Ketoprofen Spray Composition				
Ingredients	Composition, wt.%			
	KeS47	KeS73	KeS74	KeS75
TOTAL	100	100	100	100

[1] $CH_3(CH_2)_{14}CH_2(OCH_2CH_2)_nOH$, n average value 20; HLB 15.7; also Brij 58
[2] Propylene glycol laurate, HLB 4-5
[3] Propylene glycol monocaprylate, HLB 5-6

TABLE 2

Permeation Data										
Time, hours	Cumulative Amount in Receptor, μg/cm^2									
	KeS47	±SD	KeS73	±SD	KeS74	±SD	KeS75	±SD	Profenid 2.5%	±SD
2	92.35	14.49	112.54	49.36	88.47	16.40	88.95	49.36	2.93	5.93
4	189.43	40.72	252.20	54.87	166.05	52.11	188.46	65.71	15.74	21.11
6	253.32	53.34	363.38	54.64	222.65	77.00	267.87	66.92	32.57	33.53

[0020] The above data show that spray compositions provided better skin permeation for ketoprofen than a ketoprofen containing gel composition, and that skin permeation could be further enhanced by an alkoxylated alcohol having an HLB value of 15.7.

[0021] The experimental results obtained with a naproxen spray composition are presented in Table 3 and 4 below, and in FIGURE 2.

TABLE 3

Naproxen Spray Composition				
Ingredients	Composition, wt.%			
	NapS05	NapS05a	NapS20	Naprosyn®
Naproxen				10
Naproxen Na	5	4.7	5	
Propylene glycol	10	9.5	10	
Lauryl lactate	3	2.8	3	
Isopropyl myristate			3	
Lactic acid	1.5	1.4	1.5	
Ceteth-20[1]		2.8	3	
Glyceryl monolaurate	3	2.8	3	
Ethanol	55.5	42.7	41.5	
Water	22	33.2	30	
TOTAL	100	100	100	

TABLE 4

Naproxen Permeation Data								
Time, hours	Cumulative Amount in Receptor, μg/cm^2							
	NapS05	±SD	NapS05a	±SD	NapS20	±SD	Naprosyn®	±SD
2	78.92	37.94	68.91	0.54	64.42	11.20	1.65	0.28

(continued)

Naproxen Permeation Data								
Time, hours	Cumulative Amount in Receptor, μg/cm^2							
	NapS05	±SD	NapS05a	±SD	NapS20	±SD	Naprosyn®	±SD
4	206.15	65.01	187.63	11.82	187.47	15.16	9.67	1.17
6	293.37	81.72	277.23	23.83	292.88	38.90	20.38	2.42

[0022] The above data show that naproxen containing spray compositions provided better skin permeation for naproxen than the Naprosyn® 10% naproxen gel. The incorporation of higher levels of water did not reduce the permeation of naproxen.

[0023] The experimental results obtained with an ibuprofen spray composition are presented in Tables 5 and 6 below, and in FIGURE 3. The experimental procedure was the same as that for the ketoprofen and naproxen spray compositions, except that the dermatomed cadaver skin was that of a human male, 72 years old.

TABLE 5

Ibuprofen Spray Composition		
	Composition, wt.%	
Ingredients	Ibu17	Ibuleve®
Ibuprofen	5	5
Lauryl lactate	3	
Lactic acid	1.5	
Glyceryl monolaurate	3	
Ethanol	47.5	
Water	40	
TOTAL	100	

TABLE 6

Ibuprofen Permeation Data				
Time, hours	Cumulative Amount in Receptor, μg/cm^2			
	Ibu17	±SD	Ibuleve®	±SD
2	17.59	0.96	4.12	1.22
4	45.81	0.75	16.31	0.45
6	68.39	0.16	31.47	0.32

[0024] The above data show that an ibuprofen containing spray composition provided better skin permeation for ibuprofen than the Ibuleve® ibuprofen gel.

[0025] The experimental results obtained with a diclofenac spray composition are presented in Tables 7 and 8 below, and in FIGURE 4. The experimental procedure was the same as that for the ketoprofen and naproxen spray compositions except that the dermatomed cadaver skin was that of a 79-year old human male.

TABLE 7

Diclofenac Spray Composition			
	Composition, wt.%		
Ingredients	DcS02	DcS03	Swiss Relief™
Diclofenac Na			4[4]
Diclofenac diethylamine		1	

(continued)

Diclofenac Spray Composition			
Ingredients	Composition, wt.%		
	DcS02	DcS03	Swiss Relief™
Propylene glycol	10	10	
Lauryl lactate	3	3	
Lactic acid	1.5	1.5	
Glyceryl monolaurate	3	3	
Ethanol	48.5	48.5	
Water	33	33	
TOTAL	100	100	
[4] Swiss Relief™ spray gel contains 4 wt. % diclofenac sodium together with inactive ingredients isopropyl alcohol, soy bean lecithin, ethanol, disodium phosphate dodecahydrate, sodium dihodrogen phosphate dehydrate, sodium edetate, propylene glycol, peppermint oil, ascorbyl palmitate, hydrochloric acid (10% w/w), sodium hydroxide (10% w/w), purified water.			

TABLE 8

Diclofenac Permeation Data						
Time, hours	Cumulative Amount in Receptor, μg/cm^2					
	DcS-02	±SD	DcS-03	±SD	Swiss Relief™ spray gel	±SD
2	14.16	3.67	9.71	1.25	4.64	3.11
4	21.51	6.42	17.30	0.93	11.08	1.33
6	27.31	8.43	23.39	1.76	16.62	1.70

[0026] The above data show that a diclofenac containing spray composition provided better skin permeation for diclofenac than a spray gel composition that has a relatively larger concentration of diclofenac.

[0027] The effect of propylene glycol in an ibuprofen spray composition was investigated using cadaver skin from a 72 year-old human male. The experimental results are presented in Tables 9 and 10 below, and in FIGURE 5.

TABLE 9

Ibuprofen Spray Compositions			
Ingredients	Composition, wt.%		
	Ibu17	Ibu24	Ibuleve®
Ibuprofen	5	5	5
Propylene glycol		10	
Lauryl lactate	3	3	
Lactic acid	1.5	1.5	
Glyceryl monolaurate	3	3	
Ethanol	47.5	37.5	
Water	40	40	
TOTAL	100	100	

TABLE 10

Ibuprofen Permeation Data						
Time, hours	Cumulative Amount in Receptor, μg/cm^2					
	Ibu17	±SD	Ibu24	±SD	Ibuleve®	±SD
2	20.22	5.59	19.36	12.52	7.17	12.42
4	69.45	5.95	71.08	27.82	8.65	1.80
6	127.06	2.01	138.70	35.68	20.97	8.20

[0028] The above data show that propylene glycol in the spray composition enhanced the skin penetration of ibuprofen.

[0029] The experimental results obtained with a ketoprofen spray composition and a nonionic surfactant, polyoxyethylene (20) cetyl ether (Brij 58), as a permeation enhancer are presented in Tables 11 and 12 below, and in FIGURE 6.

TABLE 11

Ketoprofen and a Nonionic Surfactant Spray Composition The compositions KeS61 and KeS67 are not in the scope of the claims.					
Ingredients	Composition, wt.%				
	KeS47	KeS61	KeS67	KeS73	KeS73a
Ketoprofen	5	5	5	5	5
Propylene glycol	10	10	10	10	10
Lauryl lactate	3	3	0	3	3
Lactic acid	1.5	1.5	1.5	1.5	1.5
Brij 58[1]		3	3	3	3
Glyceryl monolaurate	3	0	3	3	3
Ethanol	37.5	37.5	37.5	27.25	25.25
Water	40	40	40	47.25	49.25
TOTAL	100	100	100	100	100

TABLE 12

Permeation Data										
Time, hours	Cumulative Amount in Receptor, μg/cm^2									
	KeS47	±SD	KeS61	±SD	KeS67	±SD	KeS73	±SD	Profenid 2.5%	±SD
2	92.35	14.49	84.55	25.06	71.71	49.49	112.54	49.36	15.60	5.93
4	189.43	40.72	186.97	15.02	182.54	64.55	252.20	54.87	70.75	21.11
6	253.32	53.34	267.88	3.95	275.99	47.09	363.38	54.64	134.62	33.53

[0030] The above data show that the addition of Brij 58 helped to increase water levels. All formulations exhibited similar permeation behavior; however, KeS73 showed slightly higher permeation. KeS73a was slightly cloudy.

[0031] The experimental results obtained with a ketoprofen spray composition and propylene glycol laurate as a permeation enhancer are presented in Tables 13 and 14 below, and in FIGURE 7.

TABLE 13

Ketoprofen and Propylene Glycol Laurate Spray Composition The compositions KeS62 and KeS68 are not in the scope of the claims.				
Ingredients	Composition, wt.%			
	KeS47	KeS62	KeS68	KeS74
Ketoprofen	5	5	5	5
Propylene glycol	10	10	10	10
Lauryl lactate	3	3	0	3
Lactic acid	1.5	1.5	1.5	1.5
Propylene glycol laurate		3	3	3
Glyceryl monolaurate	3	0	3	3
Ethanol	37.5	42.5	42.5	39.5
Water	40	35	35	35
TOTAL	100	100	100	100

TABLE 14

Permeation Data						
Time, hours	Cumulative Amount in Receptor, μg/cm^2					
	KeS47	±SD	KeS74	±SD	Profenid 2.5%	±SD
2	92.35	14.49	88.47	16.40	15.60	5.93
4	189.43	40.72	166.05	52.11	70.75	21.11
6	253.32	53.34	222.65	77.00	134.62	33.53

[0032] Only formulations KeS47 and KeS74 gave clear solutions. The above data show that the KeS47 and KeS74 formulations exhibited nearly the same permeation behavior.

[0033] The experimental results obtained with a ketoprofen spray composition and propylene glycol caprylate as a permeation enhancer are presented in Tables 15 and 16 below, and in FIGURE 8. The experimental procedure was the same as that for the previous ketoprofen spray compositions, except that the dermatomed cadaver skin was that of a human male, 79 years old.

TABLE 15

Ketoprofen and Propylene Glycol Caprylate Spray Composition The compositions KeS63 and KeS69 are not in the scope of the claims.				
Ingredients	Composition, wt.%			
	KeS47	KeS63	KeS69	KeS75
Ketoprofen	5	5	5	5
Propylene glycol	10	10	10	10
Lauryl lactate	3	3	0	3
Lactic acid	1.5	1.5	1.5	1.5
Propylene glycol caprylate		3	3	3
Glyceryl monolaurate	3	0	3	3
Ethanol	37.5	37.5	37.5	34.5
Water	40	40	40	40
TOTAL	100	100	100	100

TABLE 16

Permeation Data										
Time, hours	Cumulative Amount in Receptor, μg/cm^2									
	KeS47	±SD	KeS63	±SD	KeS69	±SD	KeS75	±SD	Profenid 2.5%	±SD
2	77.12	12.81	64.90	9.02	57.22	10.33	58.98	10.81	2.27	0.44
4	140.68	16.03	144.77	13.15	131.23	21.40	128.25	34.31	13.60	2.05
6	183.17	22.46	198.59	10.20	184.99	21.11	172.43	52.30	21.69	4.50

[0034] The above data show that all of the formulations exhibited comparable permeation behavior.

[0035] The experimental results obtained with a ketoprofen spray composition and Sorbitan monolaurate as a permeation enhancer are presented in Tables 17 and 18 below, and in FIGURE 9. The experimental procedure was the same as that for the previous ketoprofen spray compositions, except that the dermatomed cadaver skin was that of a human male, 79 years old.

TABLE 17

Ketoprofen and Sorbitan Monolaurate Spray Composition The compositions KeS66 and KeS72 are not in the scope of the claims.				
Ingredients	Composition, wt.%			
	KeS47	KeS66	KeS72	KeS78
Ketoprofen	5	5	5	5
Propylene glycol	10	10	10	10
Lauryl lactate	3	3	0	3
Lactic acid	1.5	1.5	1.5	1.5
Sorbitan monolaurate		3	3	3
Glyceryl monolaurate	3	0	3	3
Ethanol	37.5	57.5	57.5	34.5
Water	40	20	20	40
TOTAL	100	100	100	100

TABLE 18

Permeation Data						
Time, hours	Cumulative Amount in Receptor, μg/cm^2					
	KeS47	±SD	KeS78	±SD	Profenid 2.5%	±SD
2	77.12	12.81	45.37	4.10	2.27	0.44
4	140.68	16.03	101.16	16.60	13.60	2.05
6	183.17	22.46	137.44	27.22	21.69	4.50

[0036] Only formulations KeS47 and KeS78 gave clear solutions. The above data show that permeation from KeS78 was slightly lower than KeS47.

[0037] The experimental results obtained with a ketoprofen spray composition and various Brij derivatives as a permeation enhancer are presented in Tables 19 and 20 below, and in FIGURE 10. The experimental procedure was the same as that for the previous ketoprofen spray compositions, except that the dermatomed cadaver skin was that of a human male, 79 years old.

TABLE 19

Ketoprofen and Non-ionic Surfactant Spray Composition						
Ingredients	Composition, wt.%					
	KeS73	KeS79	KeS80	KeS81	KeS82	KeS83
Ketoprofen	5	5	5	5	5	5
Propylene glycol	10	10	10	10	10	10
Lauryl lactate	3	3	3	3	3	3
Lactic acid	1.5	1.5	1.5	1.5	1.5	1.5
Brij 58[1]	3					
Brij 30[5]		3				
Brij 35[6]			3			
Brij 72[7]				3		
Brij 98[8]					3	
Brij 721[9]						3
Glyceryl monolaurate	3	3	3	3	3	3
Ethanol	27.25	27.25	27.25	27.25	27.25	27.25
Water	47.25	47.25	47.25	47.25	47.25	47.25
TOTAL	100	100	100	100	100	100

[5] poly(oxyethylene)(4) lauryl ether
[6] poly(oxyethylene)(23) lauryl ether
[7] poly(oxyethylene)(2) stearyl ether
[8] poly(oxyethylene)(20) oleyl ether
[9] poly(oxyethylene)(21) stearyl ether

TABLE 20

Permeation Data

Time, hours	Cumulative Amount in Receptor, µg/cm²													
	KeS73	±SD	KeS79	±SD	KeS80	±SD	KeS81	±SD	KeS82	±SD	KeS83	±SD	Profenid 2.5%	±SD
2	58.92	11.11	53.39	10.39	54.79	13.75	61.91	16.23	67.06	20.54	59.12	6.21	7.15	0.42
4	138.70	11.05	125.49	22.77	125.93	21.40	141.07	30.91	139.71	32.62	134.15	17.36	21.66	1.94
6	185.84	18.67	176.90	31.52	171.52	24.45	191.21	38.25	189.49	39.15	178.84	23.19	37.41	3.53

[0038] The above data show that all formulations containing the non-ionic surfactants permitted higher water content while showing similar behavior with respect to permeation.

[0039] The experimental results showing permeation of a ketoprofen spray composition after storage for three (3) months at 25°C and 40°C is presented in Tables 21 and 22 below, and in FIGURE 11. The experimental procedure was the same as that for the previous ketoprofen spray compositions, except that the dermatomed cadaver skin was from the thigh of a human male, 79 years old.

TABLE 21

Ketoprofen Spray Composition		
	Composition, wt.%	
Ingredients	KeS38/25°C	KeS38/40°C
Ketoprofen	5	5
Lauryl lactate	3	3
Lactic acid	1.5	1.5
Glyceryl monolaurate	3	3
Ethanol	47.5	47.25
Water	40	40
TOTAL	100	100

TABLE 22

Permeation Data						
	Cumulative Amount in Receptor, μg/cm^2					
Time, hours	KeS38/25°C	±SD	KeS38/40°C	±SD	Profenid 2.5%	±SD
2	85.61	35.14	72.35	7.44	6.97	1.23
4	178.97	66.42	154.72	19.61	25.34	3.96
6	251.24	89.44	220.46	29.64	45.35	6.86

[0040] The above data show that both formulations exhibited similar permeation behavior after three months of storage.

[0041] The experimental results obtained with a naproxen spray composition using 5% Naproxen sodium and Brij 58 are presented in Table 23 and 24 below, and in FIGURE 12. The experimental procedure was the same as that for the previous spray compositions, except that the dermatomed cadaver skin was from the thigh of a human male, 79 years old.

TABLE 23

Naproxen Spray Composition Using 5% Naproxen Sodium and a Non-ionic Surfactant					
	Composition, wt.%				
Ingredients	NapS05	NapS21a	NapS22a	NapS23a	NapS24
Naproxen	0	0	0	0	0
Naproxen Na	5	5	5	5	5
Propylene glycol	10	10	10	10	10
Lauryl lactate	3	3	3	3	3
Lactic acid	1.5	0.5	3	0.5	3
Brij 58[1]		0	0	3	3
Glyceryl monolaurate	3	3	3	3	3
Ethanol	55.5	34.5	46	30	47
Water	22	44	30	45.5	26
TOTAL	100	100	100	100	100

TABLE 24

Naproxen Permeation Data								
	Cumulative Amount in Receptor, μg/cm^2							
Time, hours	NapS05	±SD	NapS21a	±SD	NapS23a	±SD	Naprosyn®	±SD
2	60.77	16.57	44.92	14.84	22.70	18.23	1.67	2.90
4	139.90	28.22	101.66	22.94	52.91	36.06	2.37	4.10
6	186.06	27.93	147.81	27.39	77.01	48.09	3.61	6.25

[0042] The above data show that by decreasing the level of water and lactic acid, formulations with higher levels of ethanol were prepared. Reduction in lactic acid and addition of Brij 58 resulted in lower skin permeation. A precipitate was noted in NapS22a and NapS24.

[0043] The experimental results obtained with a naproxen spray composition using 2.5% Naproxen sodium and Brij 58 are presented in Table 25 and 26 below, and in FIGURE 13. The experimental procedure was the same as that for the previous spray compositions, except that the dermatomed cadaver skin was from the thigh of a human male, 79 years old.

TABLE 25

Naproxen Spray Composition Using 2.5% Naproxen Sodium and a Non-ionic Surfactant							
	Composition, wt.%						
Ingredients	NapS05	NapS25	NapS25a	NapS26	NapS26a	NapS27	NapS28
Naproxen	0	0	0	0	0	0	0
Naproxen Na	5	2.5	2.5	2.5	2.5	2.5	2.5
Propylene glycol	10	10	10	10	10	10	10
Lauryl lactate	3	3	3	3	3	3	3
Lactic acid	1.5	0.5	0.5	1.5	1.5	0.5	1.5
Brij 58[1]		3	3	3	3	0	0
Glyceryl monolaurate	3	3	3	3	3	3	3
Ethanol	55.5	22	32	37	40	36	45
Water	22	56	46	40	37	45	35
TOTAL	100	100	100	100	100	100	100

[0044] A precipitate was noted in NapS05, NapS25, NapS26 and NapS28.

TABLE 26

Naproxen Permeation Data										
	Cumulative Amount in Receptor, μg/cm^2									
Time, hours	NapS05	±SD	NapS25a	±SD	NapS26a	±SD	NapS27	±SD	Naprosyn®	±SD
2	60.77	16.57	26.05	7.07	43.55	1.01	34.57	11.52	1.67	2.90
4	139.90	28.22	57.48	16.40	79.99	7.85	83.28	17.65	2.37	4.10
6	186.06	27.93	82.19	21.96	104.69	8.99	119.11	23.73	3.61	6.25

[0045] The above data show that reduction of Naproxen levels to 2.5% caused a significant reduction in skin permeation.

[0046] The effect of isopropyl myristate in an ibuprofen spray composition was investigated. The experimental results are presented in Tables 27 and 28 below, and in FIGURE 14. The experimental procedure was the same as that for the previous spray compositions, except that the dermatomed cadaver skin was from the thigh of a human male, 79 years old.

TABLE 27

Ibuprofen with and without Isopropyl Myristate Spray Compositions		
	Composition, wt.%	
Ingredients	Ibu24	Ibu30
Ibuprofen	5	5
Propylene glycol	10	10
Isopropyl myristate	0	3
Lauryl lactate	3	3
Lactic acid	1.5	1.5
Glyceryl monolaurate	3	3
Ethanol	37.5	39.5
Water	40	35
TOTAL	100	100

TABLE 28

Ibuprofen with and without Isopropyl Myristate Permeation Data						
Time, hours	Cumulative Amount in Receptor, μg/cm^2					
	Ibu24	±SD	Ibu30	±SD	Ibuleve®	±SD
2	177.88	34.92	149.67	43.10	53.86	36.32
4	324.99	58.07	271.38	62.99	129.82	74.30
6	415.42	62.34	344.02	61.75	177.62	89.78

[0047] The above data show that addition of isopropyl myristate in the spray composition did not further enhance the skin permeation of ibuprofen.

[0048] The effect of isopropyl myristate and Brij 58 in an ibuprofen spray composition was investigated. The experimental results are presented in Tables 29 and 30 below, and in FIGURE 15. The experimental procedure was the same as that for the previous spray compositions, except that the dermatomed cadaver skin was from the back of a human male, 46 years old.

TABLE 29

Ibuprofen with Isopropyl Myristate and Brij 58 Spray Compositions			
	Composition, wt.%		
Ingredients	Ibu30	Ibu32	Ibu33
Ibuprofen	5	5	5
Propylene glycol	10	10	10
Isopropyl myristate	3	0	3
Lauryl lactate	3	3	3
Lactic acid	1.5	1.5	1.5
Brij 58[1]		3	3
Glyceryl monolaurate	3	3	3
Ethanol	39.5	28	31.5
Water	35	46.5	40
TOTAL	100	100	100

TABLE 30

Ibuprofen Permeation Data								
Time, hours	Cumulative Amount in Receptor, μg/cm^2							
	Ibu30	±SD	Ibu32	±SD	Ibu33	±SD	Ibuleve®	±SD
2	58.28	27.72	47.79	10.56	33.70	17.05	7.06	3.27
4	127.23	21.44	117.41	18.49	93.08	25.68	50.52	17.68
6	193.89	9.97	187.01	36.12	159.15	43.60	106.53	28.78

[0049] The above data show that addition of Brij 58 helped to increase the level of water in the formulation; however, the addition of isopropyl myristate and Brij 58 in the spray composition did not further enhance the skin permeation of ibuprofen.

[0050] The effects of two types of diclofenac were investigated. The experimental results obtained with a diclofenac cream composition (which is not in the scope of the claims) using diclofenac sodium and diclofenac diethylamine are presented in Tables 31 and 32, below, and in FIGURE 16. The dermatomed cadaver skin was from the back of a human male, 79 years old.

TABLE 31

Diclofenac Cream Composition		
Ingredients	Composition, wt.%	
	Dc-05	Dc-07
Diclofenac Na		
Diclofenac diethylamine		1
Carbopol 980 NF[10]	0.5	0.5
Ultrez 10[11]	1	1
Deionized water	63.95	63.95
Disodium EDTA	0.05	0.05
Isopropyl myristate	3	3
Ethanol	10	10
Propylene glycol	10	10
Isopropanol	9	9
Triethanolamine, NF	1.5	1.5
TOTAL	100	100

[10] acrylic acid homopolymer
[11] cross-linked polyacrylic acid polymer

TABLE 32

Diclofenac Permeation Data						
Time, hours	Cumulative Amount in Receptor, μg/cm^2					
	Dc-05	±SD	Dc-07	±SD	Voltaren 1%	±SD
2	1.94	1.95	1.70	2.95	0.00	0.00
4	6.28	2.27	6.62	4.46	3.70	0.70
6	10.10	2.85	10.60	5.96	6.13	1.14

[0051] The above data show that skin permeation for diclofenac sodium and diclofenac diethylamine cream formulations was similar.

[0052] The experimental results obtained with a diclofenac spray composition using diclofenac sodium and diclofenac diethylamine are presented in Tables 33 and 34, below, and in FIGURE 17. The experimental procedure was the same

as that for the previous spray compositions, except that the dermatomed cadaver skin was from the back of a human male, 79 years old.

TABLE 33

Diclofenac Spray Composition		
	Composition, wt.%	
Ingredients	DcS02	DcS03
Diclofenac Na	1	
Diclofenac diethylamine		
Propylene glycol	10	10
Lauryl lactate	3	3
Lactic acid	1.5	1.5
Glyceryl monolaurate	3	3
Ethanol	48.5	48.5
Water	33	33
TOTAL	100	100

TABLE 34

Diclofenac Permeation Data						
	Cumulative Amount in Receptor, μg/cm^2					
Time, hours	DcS-02	±SD	DcS-03	±SD	Swiss Relief™ spray gel	±SD
2	9.29	1.06	9.98	4.16	0	0
4	17.69	1.30	18.91	6.47	2.57	0.93
6	23.43	1.38	25.33	7.99	4.31	1.44

[0053] The above data show that a diclofenac containing spray composition provided better skin permeation for diclofenac than a spray gel composition that has a relatively larger concentration of diclofenac.

[0054] The effects of propylene glycol, Brij 58 and lactic acid on diclofenac skin permeation were investigated. The experimental results obtained with a diclofenac spray composition using diclofenac sodium, Brij 58, and different levels of propylene glycol and lactic acid are presented in Tables 35 and 36, below, and in FIGURE 18. The experimental procedure was the same as that for the previous spray compositions, except that the dermatomed cadaver skin was from the thigh of a human male, 79 years old.

TABLE 35

Diclofenac Spray Composition				
	Composition, wt.%			
Ingredients	DcS02	DcS12	DcS12a	DcS14
Diclofenac Na			1	
Propylene glycol	10	15	10	10
Lauryl lactate	3	3	3	3
Lactic acid	1.5	1.5	1.5	0.5
Brij 58[1]		3	3	3
Glyceryl monolaurate	3	3	3	3
Ethanol	48.5	25	43.5	34.5
Water	33	53.5	35	45
TOTAL	100	100	100	100

[0055] Composition DcS12 was cloudy.

TABLE 36

Diclofenac Permeation Data								
Time, hours	Cumulative Amount in Receptor, μg/cm^2							
	DcS02	±SD	DcS12a	±SD	DcS14	±SD	Voltaren 1%	±SD
2	5.98	2.94	5.97	3.42	2.47	2.17	0.00	0.00
4	16.33	6.10	14.68	5.39	7.24	6.34	3.36	1.11
6	25.37	8.82	22.33	6.67	11.52	10.23	7.10	1.33

[0056] Addition of a higher level of propylene glycol enhanced the water content but caused formulation DcS12 to precipitate. The above data show that a diclofenac spray composition with a lower level of lactic acid showed a lower level of skin permeation of diclofenac.

[0057] The effects of propylene glycol, Brij 58 and lactic acid on diclofenac skin permeation were investigated. The experimental results obtained with a diclofenac spray composition using diclofenac diethylamine, Brij 58, and different levels of propylene glycol and lactic acid are presented in Tables 37 and 38, below, and in FIGURE 19. The experimental procedure was the same as that for the previous spray compositions, except that the dermatomed cadaver skin was from the thigh of a human male, 79 years old.

TABLE 37

Diclofenac Spray Composition						
Ingredients	Composition, wt.%					
	DcS03	DcS13	DcS13a	DcS13a-2	DcS15	DcS15a
Diclofenac diethylamine	1	1	1	1	1	1
Propylene glycol	10	15	10	15	10	10
Lauryl lactate	3	3	3	3	3	3
Lactic acid	1.5	1.5	1.5	1.5	0.5	0.5
Brij 58[1]	0	3	3	3	3	3
Glyceryl monolaurate	3	3	3	3	3	3
Ethanol	48.5	23	38	45	26	39.5
Water	33	55.5	40.5	28.5	53.5	40
TOTAL	100	105	100	100	100	100
Compositions DcS13, DcS13a and DCS15 were cloudy.						

TABLE 38

Diclofenac Permeation Data								
Time, hours	Cumulative Amount in Receptor, μg/cm^2							
	DcS03	±SD	DcS13a-2	±SD	DcS15a	±SD	Voltaren 1%	±SD
2	5.99	2.58	4.84	3.56	3.42	0.79	0.00	0.00
4	14.39	6.54	11.65	5.16	10.00	1.87	3.36	1.11
6	21.60	9.52	17.61	6.29	16.14	3.04	7.10	1.33

[0058] Formulations DcS13, DcS13a, and DcS15 were cloudy. The above data show that incorporation of Brij 58 reduced skin permeation of diclofenac.

[0059] The effects of propylene glycol and thickeners on ketoprofen skin permeation were investigated. The experimental results obtained with a ketoprofen spray formulation using ketoprofen, different levels of propylene glycol, and thickeners hydroxypropyl cellulose (100 cps) and hydroxypropyl cellulose (150-400 cps) are presented in Tables 39 and

40, below and in FIGURE 20. The experimental procedure was the same as that for the previous spray compositions, except that the dermatomed cadaver skin was from the thigh of a human male, 79 years old.

TABLE 39

Ketoprofen and Thickeners Spray Composition					
	Composition, wt.%				
Ingredients	KeS47	KeS84	KeS85	KeS86	KeS89
Ketoprofen	5	5	5	5	5
Propylene glycol	10	20	20	10	10
Lauryl lactate	3	3	3	3	3
Lactic acid	1.5	1.5	1.5	1.5	1.5
HPC HY117[12]	0	0	0.5	0.5	0
HPC HY119[13]	0	0	0	0	0.25
Glyceryl monolaurate	3	3	3	3	3
Ethanol	37.5	27.5	27.5	32.5	32.25
Water	40	40	39.5	44.5	45
TOTAL	100	100	100	100	100

[12] hydroxypropyl cellulose (100 cps)
[13] hydroxypropyl cellulose (150-400 cps)

TABLE 40

Permeation Data

	Cumulative Amount in Receptor, µg/cm^2											
Time, hours	KeS47	±SD	KeS84	±SD	KeS85	±SD	KeS86	±SD	KeS89	±SD	Profenid 2.5%	±SD
2	82.63	27.60	94.36	51.62	104.05	13.26	80.82	22.75	117.71	21.55	12.75	3.00
4	167.45	34.34	221.64	118.40	213.69	37.65	157.90	42.69	221.11	6.86	42.43	5.90
6	232.80	42.90	309.28	144.22	311.38	48.99	214.48	57.66	290.61	25.07	71.36	8.79

[0060] All formulations above gave clear solutions. The above data show that KeS84, KeS85, and KeS89 all exhibited significant permeation enhancement compared to KeS47. KeS86, with lower propylene glycol, showed similar permeation to KeS47.

REFERENCES CITED IN THE DESCRIPTION

This list of references cited by the applicant is for the reader's convenience only. It does not form part of the European patent document. Even though great care has been taken in compiling the references, errors or omissions cannot be excluded and the EPO disclaims all liability in this regard.

Patent documents cited in the description

- WO 2007070694 A **[0003]**

PATENTKRAV

1. Spraybar opløsning, der omfatter et ikke-steroidt anti-inflammatorisk lægemiddel (NSAID); lauryllactat; mælkesyre; glycerylmonolaurat; ethanol og vand, hvor NSAID'et er

a) et propionsyrederivat udvalgt fragruppen bestående af ketoprofen, ibuprofen, naproxen, og farmaceutisk acceptable salte deraf; eller

b) et eddikesyrederivat udvalgt fragruppen bestående af diclofenac, indomethacin, etodolac og farmaceutisk acceptable salte deraf.

2. Spraybar opløsning ifølge krav 1, der endvidere omfatter et ikke-ionisk overfladeaktivt middel med en HLB-værdi på mindst 12.

3. Spraybar opløsning ifølge krav 2, hvor det ikke-ioniske overfladeaktive middel er en alkoxyleret alkohol.

4. Spraybar opløsning ifølge krav 1, hvori NSAID'et er ketoprofen.

5. Spraybar opløsning ifølge krav 1, hvori vægtforholdet mellem vand og ethanol ligger i intervallet fra ca. 0,3:1 til ca. 2,6:1.

6. Spraybar opløsning ifølge krav 1, hvori lauryllactatet er til stede i en mængde i intervallet fra ca. 1 til ca. 5 vægtprocent, baseret på opløsningens totalvægt.

7. Spraybar opløsning ifølge krav 1, der er en spraybar klar opløsning, som omfatter, baseret på opløsningens totalvægt, det ikke-steroide antiinflammatoriske lægemiddel (NSAID) i en mængde i intervallet fra ca. 1 til ca. 10 vægtprocent,

lauryllactat i en mængde i intervallet fra ca. 1 til ca. 5 vægtprocent,

mælkesyre i en mængde i intervallet fra ca. 0,5 til ca. 5 vægtprocent;

glycerylmonolaurat i en mængde i intervallet fra ca. 2 til ca. 5 vægtprocent;

propylenglycol i en mængde i intervallet fra ca. 5 til ca. 30 vægtprocent;

alkoxyleret alkohol med en HLB-værdi på mindst 12 i en mængde i intervallet fra 0 til ca. 7 procent; og

det resterende en blanding af vand og ethanol i et tilsvarende vægtforhold i intervallet fra ca. 0,3:1 til ca. 2,6:1.

8. Spraybar klar opløsning ifølge krav 7, der omfatter ca. 5 vægtprocent ketoprofen;

ca. 3 vægtprocent lauryllactat; ca. 1,5 vægtprocent mælkesyre; ca. 3 vægtprocent glycerylmonolaurat;

ca. 3 vægtprocent polyethylenglycolether af cetylalkohol med en HLB-værdi på ca. 15,7 og repræsenteret ved formlen $CH_3(CH_2)_{14}CH_2(OCH_2CH_2)_nOH$, hvor n har en middelværdi 20;

ca. 10 vægtprocent propylenglycol; og det resterende en vand-ethanolblanding i et tilsvarende vægtforhold på ca. 1,7.

DRAWINGS

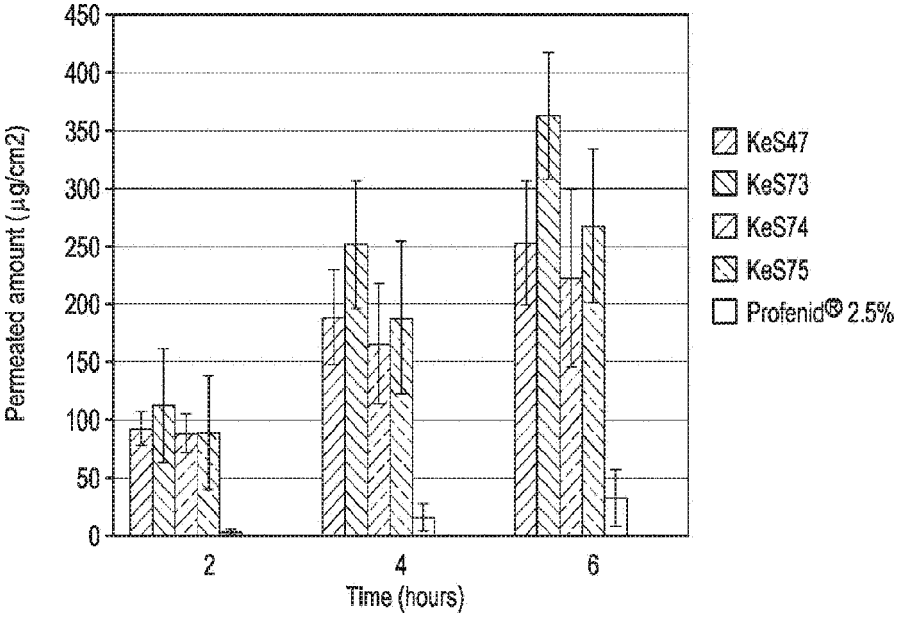


FIG. 1

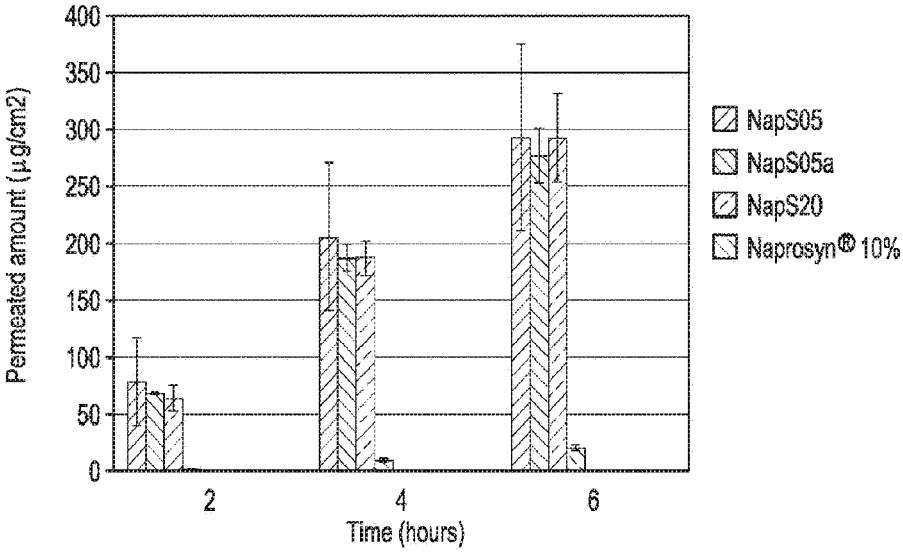


FIG. 2

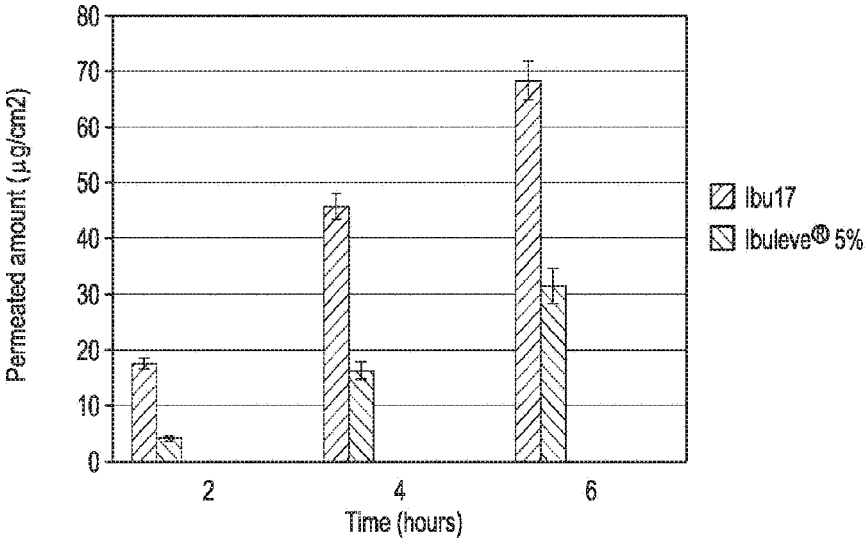

Permeated amount (µg/cm2)
80
70
60
50
40
30
20
10
0
2
4
6
Time (hours)
Ibu17
Ibuleve® 5%

FIG. 3

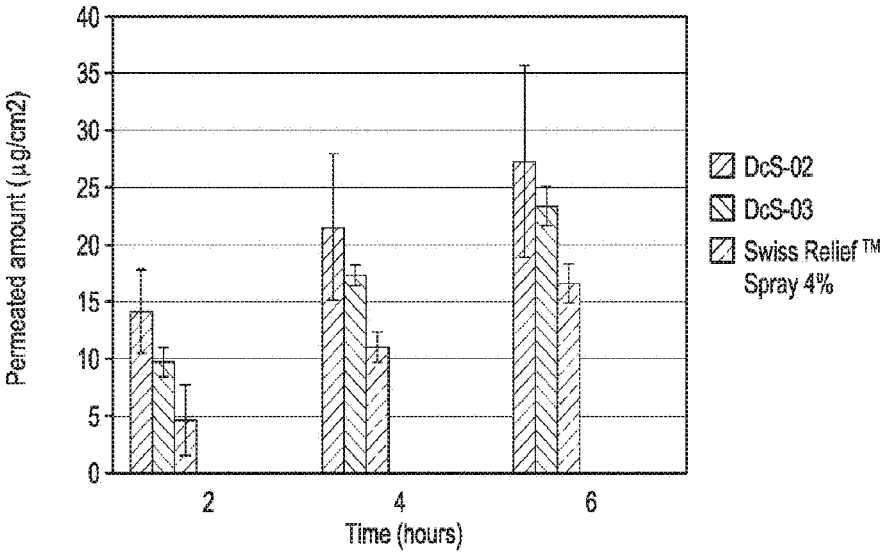

Permeated amount (µg/cm2)
40
35
30
25
20
15
10
5
0
2
4
6
Time (hours)
DcS-02
DcS-03
Swiss Relief ™ Spray 4%

FIG. 4

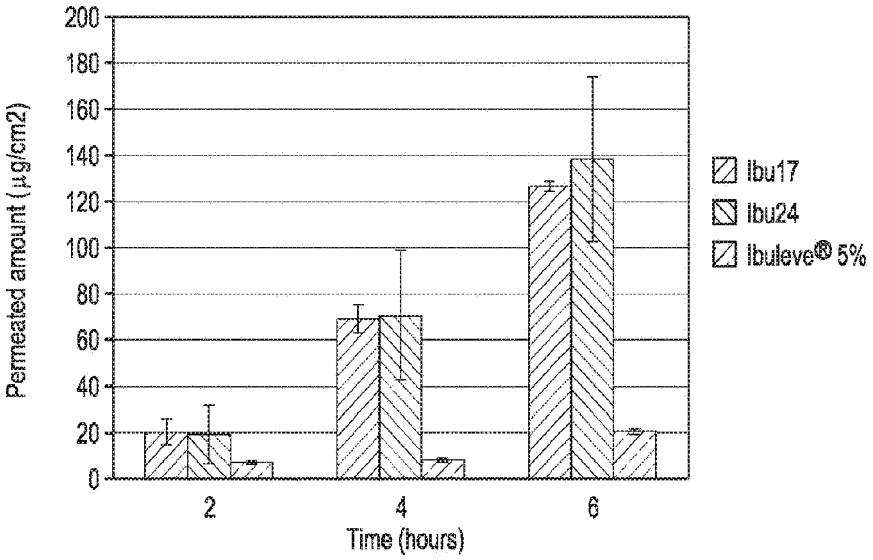

Permeated amount (µg/cm2)
200
180
160
140
120
100
80
60
40
20
0
2
4
6
Time (hours)
Ibu17
Ibu24
Ibuleve® 5%

FIG. 5

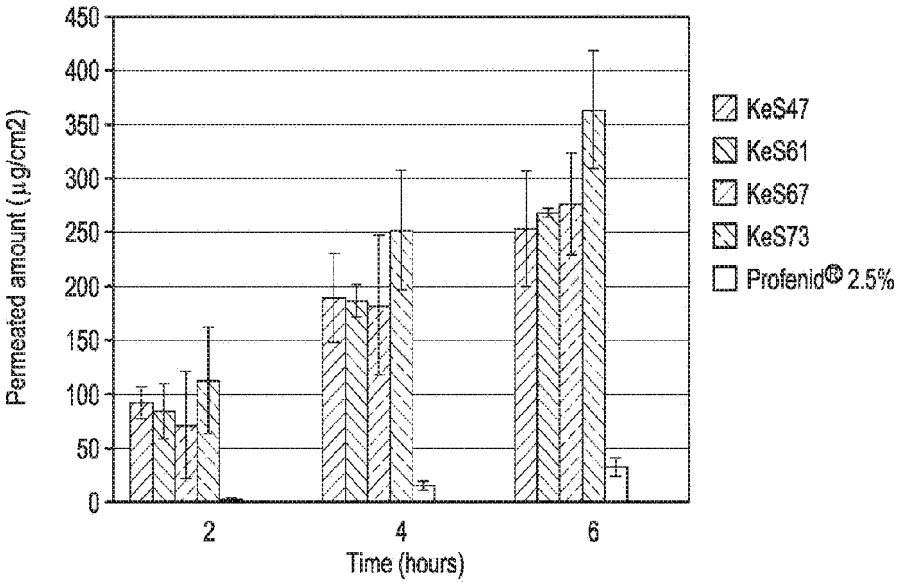

Permeated amount (µg/cm2)
450
400
350
300
250
200
150
100
50
0
2
4
6
Time (hours)
KeS47
KeS61
KeS67
KeS73
Profenid® 2.5%

FIG. 6

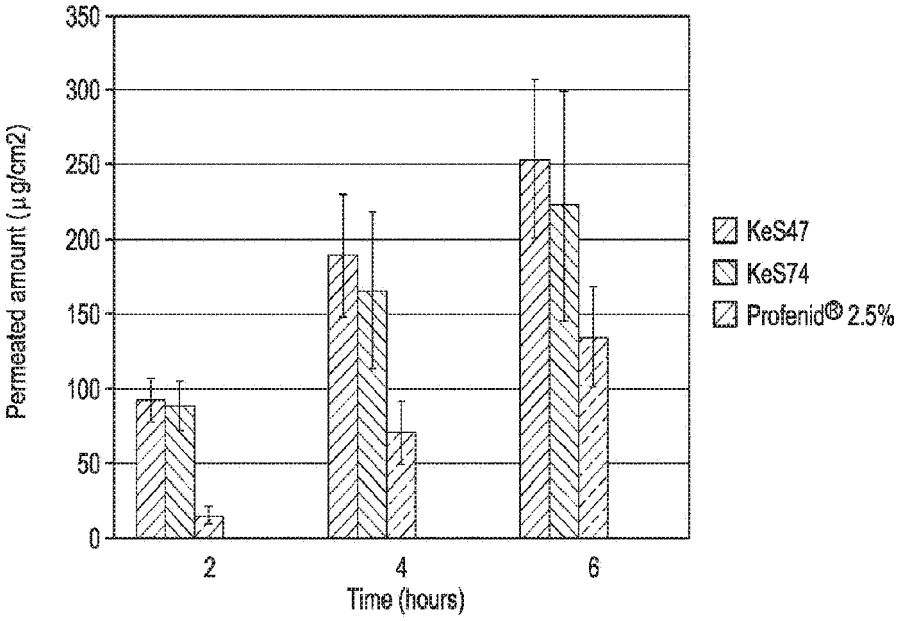

350
300
250
200
150
100
50
0
Permeated amount (µg/cm2)
2
4
6
Time (hours)
KeS47
KeS74
Profenid® 2.5%

FIG. 7

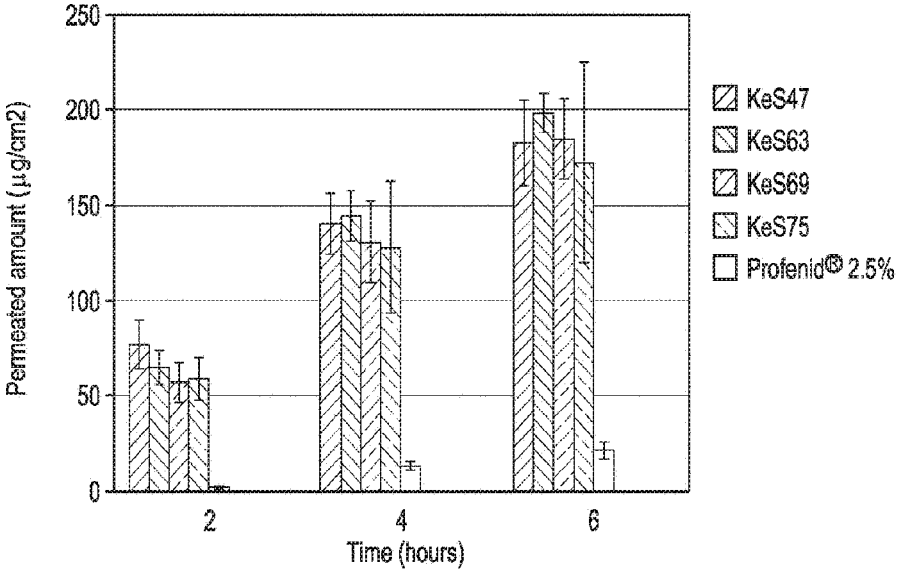

250
200
150
100
50
0
Permeated amount (µg/cm2)
2
4
6
Time (hours)
KeS47
KeS63
KeS69
KeS75
Profenid® 2.5%

FIG. 8

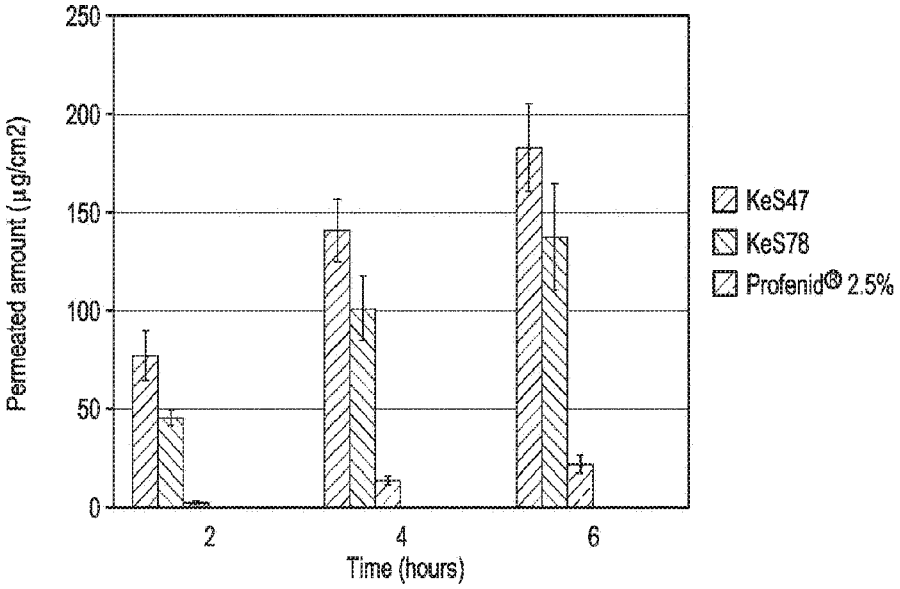

250
200
150
100
50
0
Permeated amount (µg/cm2)
2
4
6
Time (hours)
KeS47
KeS78
Profenid® 2.5%

FIG. 9

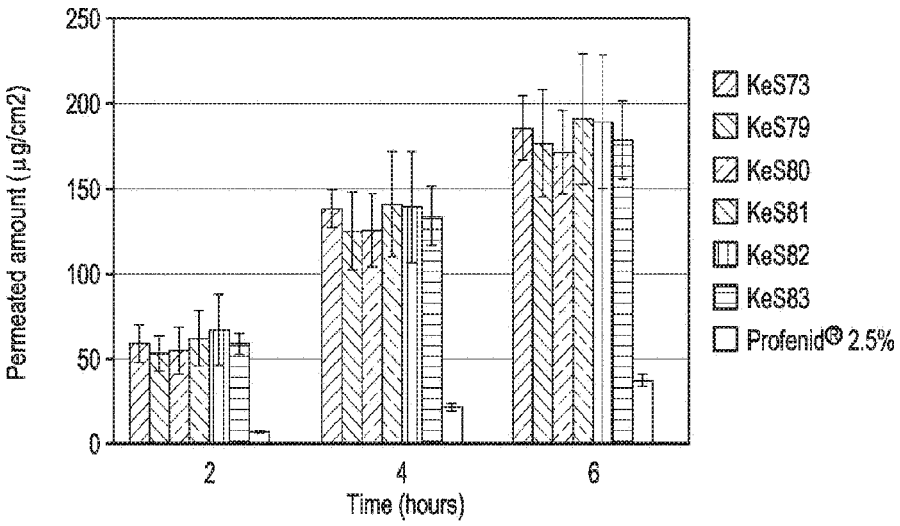

250
200
150
100
50
0
Permeated amount (µg/cm2)
2
4
6
Time (hours)
KeS73
KeS79
KeS80
KeS81
KeS82
KeS83
Profenid® 2.5%

FIG. 10

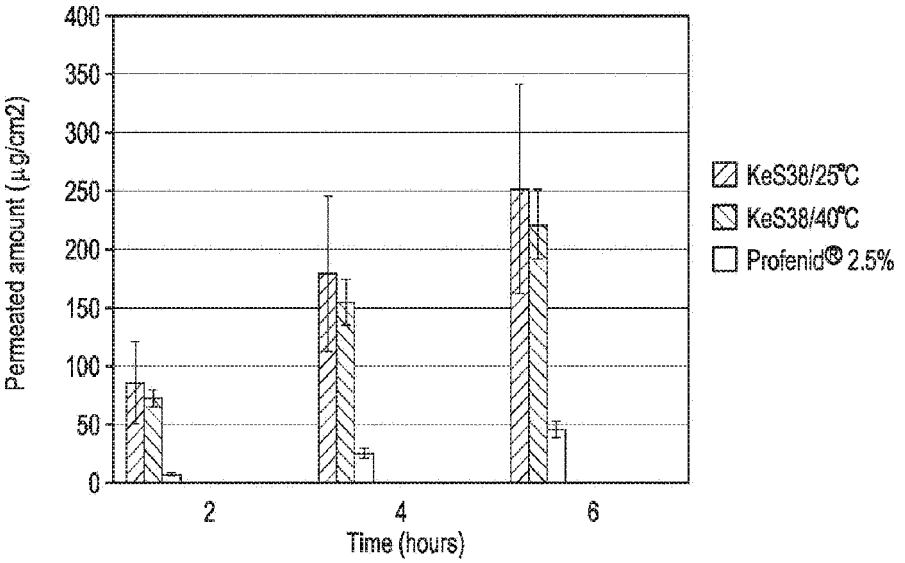

400
350
300
250
200
150
100
50
0
Permeated amount (µg/cm2)
2
4
6
Time (hours)
KeS38/25°C
KeS38/40°C
Profenid® 2.5%

FIG. 11

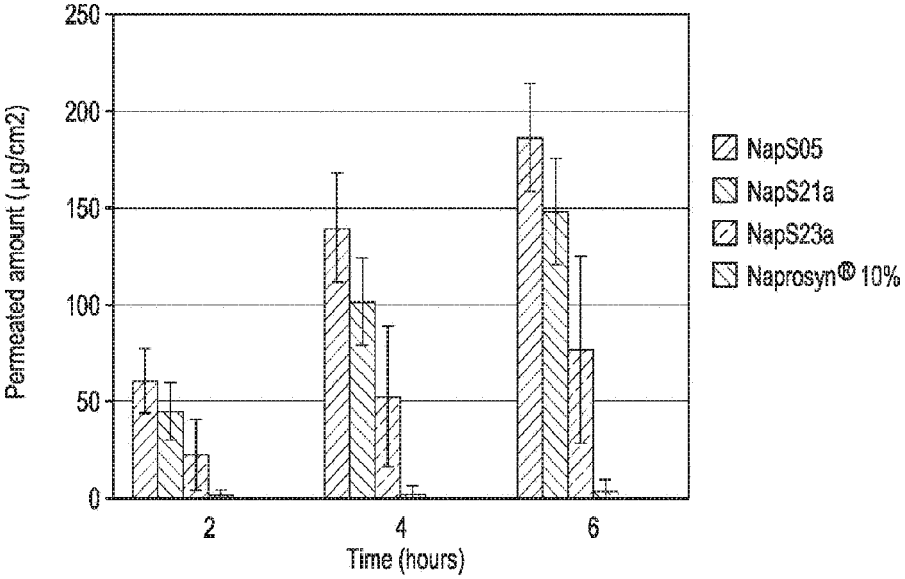

250
200
150
100
50
0
Permeated amount (µg/cm2)
2
4
6
Time (hours)
NapS05
NapS21a
NapS23a
Naprosyn® 10%

FIG. 12

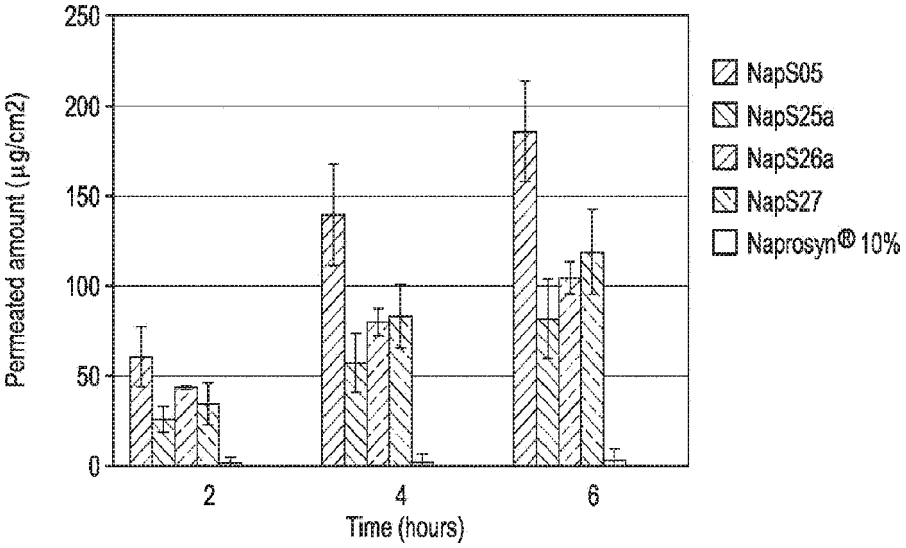

250
200
150
100
50
0
Permeated amount (µg/cm2)
2
4
6
Time (hours)
NapS05
NapS25a
NapS26a
NapS27
Naprosyn® 10%

FIG. 13

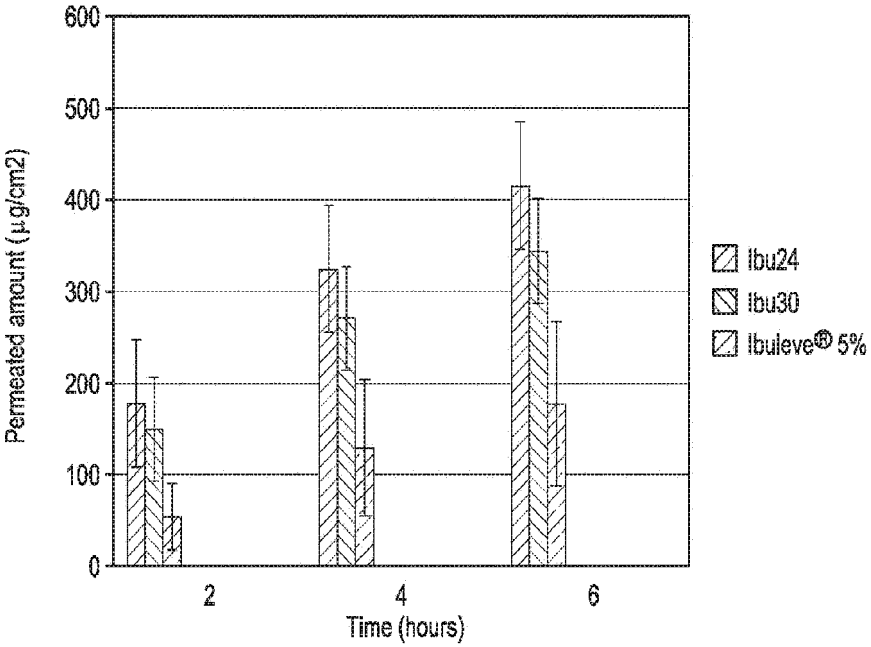

600
500
400
300
200
100
0
Permeated amount (µg/cm2)
2
4
6
Time (hours)
Ibu24
Ibu30
Ibuleve® 5%

FIG. 14

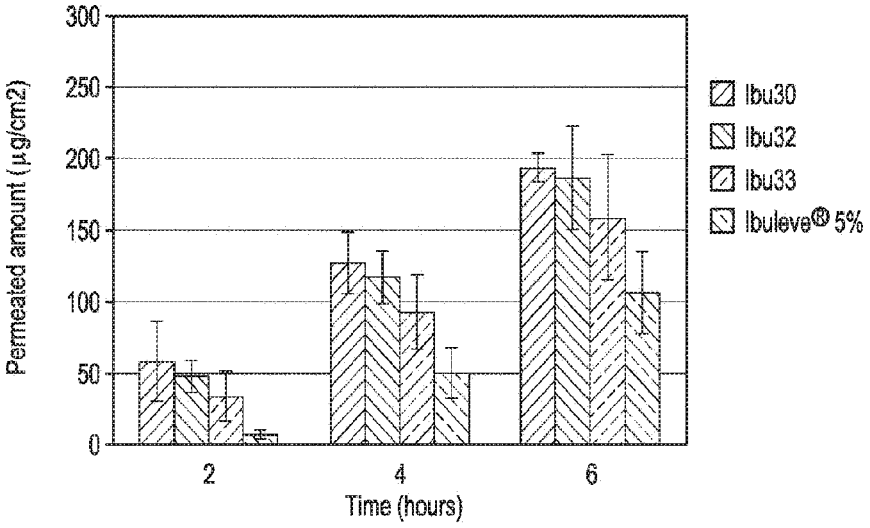

300
250
200
150
100
50
0
Permeated amount (µg/cm2)
2
4
6
Time (hours)
Ibu30
Ibu32
Ibu33
Ibuleve® 5%

FIG. 15

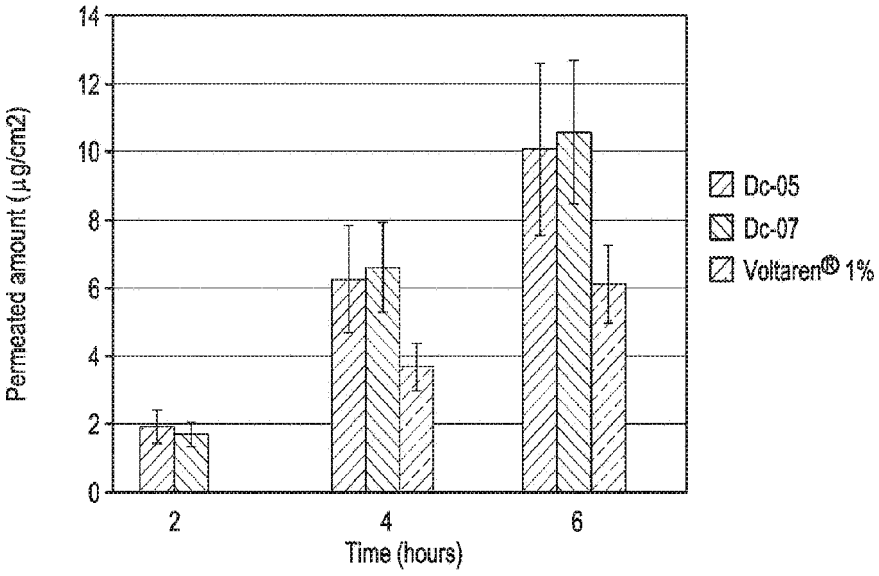

14
12
10
8
6
4
2
0
Permeated amount (µg/cm2)
2
4
6
Time (hours)
Dc-05
Dc-07
Voltaren® 1%

FIG. 16

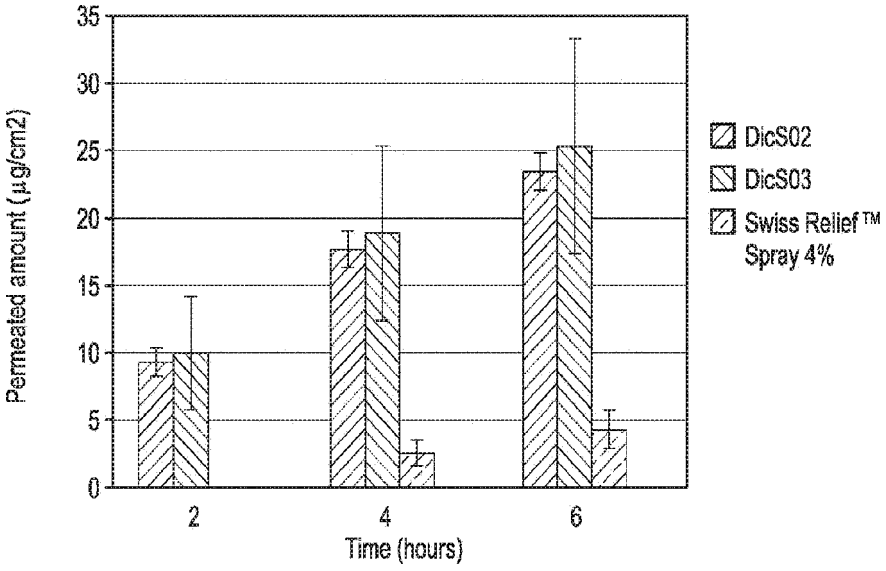

Permeated amount (µg/cm2)
35
30
25
20
15
10
5
0
2
4
6
Time (hours)
DicS02
DicS03
Swiss Relief™ Spray 4%

FIG. 17

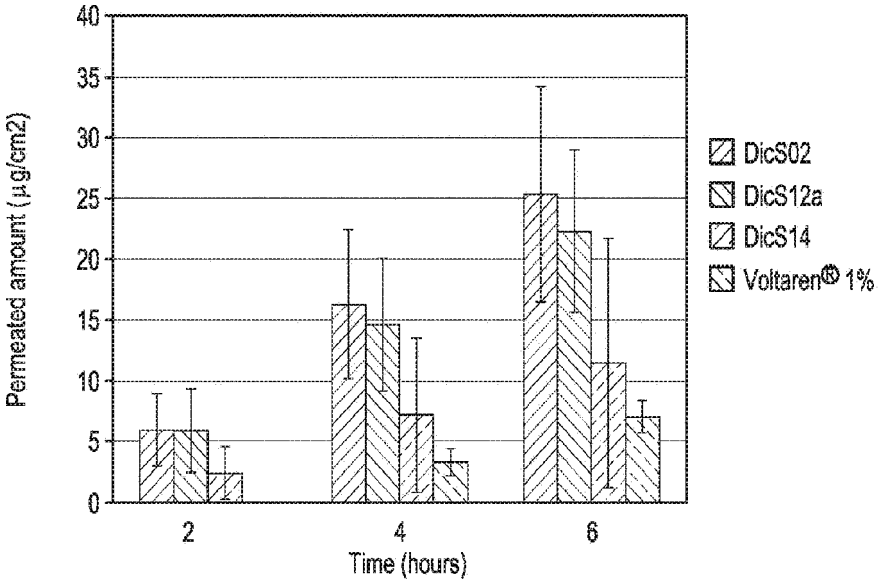

Permeated amount (µg/cm2)
40
35
30
25
20
15
10
5
0
2
4
6
Time (hours)
DicS02
DicS12a
DicS14
Voltaren® 1%

FIG. 18

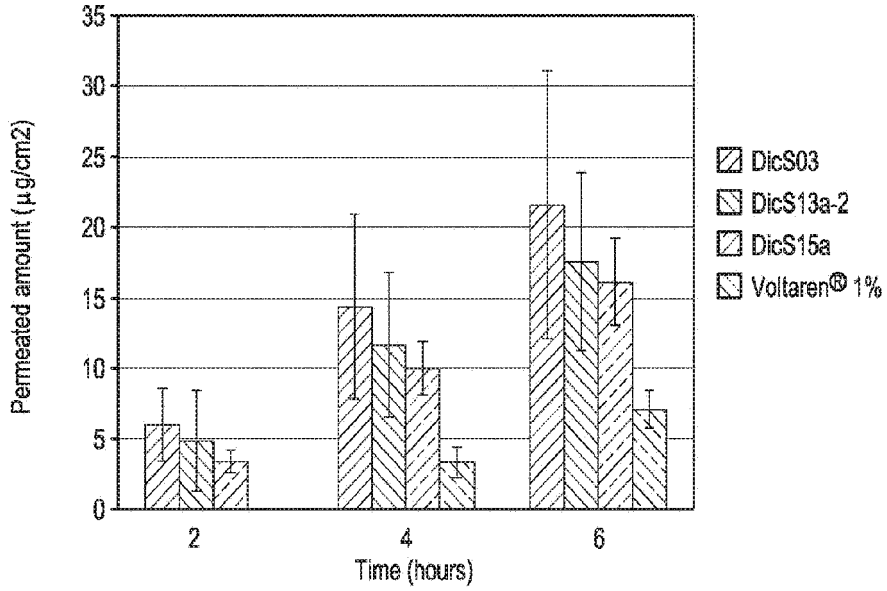

Permeated amount (µg/cm2)
35
30
25
20
15
10
5
0
2
4
6
Time (hours)
DicS03
DicS13a-2
DicS15a
Voltaren® 1%

FIG. 19

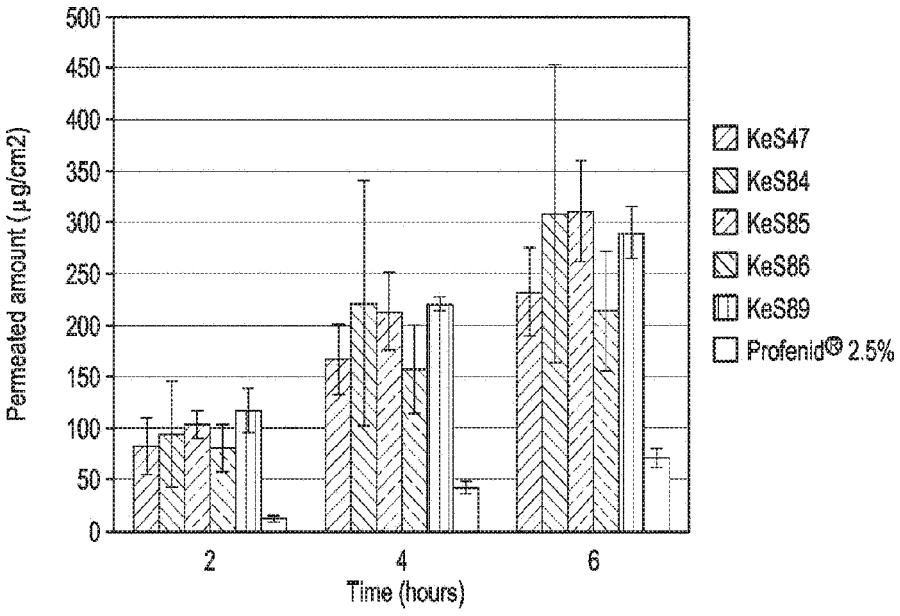

Permeated amount (µg/cm2)
500
450
400
350
300
250
200
150
100
50
0
2
4
6
Time (hours)
KeS47
KeS84
KeS85
KeS86
KeS89
Profenid® 2.5%

FIG. 20