TOPICAL ANTI-INFLAMMATORY PHARMACEUTICAL COMPOSITION WITH ZILEUTON CREAM FORMULATION

Field

[0001] The present invention relate to a topical pharmaceutical composition with zileuton cream formulation for treatment of skin diseases caused by leukotriene.

Background

[0002] Leukotriene is a metabolite of arachidonic acid, and is well known as an inflammatory factor that is deeply involved in causing inflammation, edema, and secretion of mucus and the like. A well-known leukotriene inhibitor developed so far is zileuton ((±)-1-(1-(benzo[b]thiophen-2-yl)ethyl)-1-hydroxyurea).

[0003] Zileuton is a mixture of stereoisomers: (R)-1-(1-(benzo[b]thiopen-2-yl)ethyl)-1-hydroxyure and (S)-1-(1-(benzo[b]thiophen-2-yl)ethyl)-1-hydroxyurea. It has been approved as an oral drug for treatment of asthma, and is known to be administrable twice a day. Clinical trials have shown that zileuton exhibits an effective anti-inflammatory pharmaceutical effect against inflammation reaction of asthma.

[0004] Clinical trials have revealed that oral administration of

zileuton alleviates atopic dermatitis symptoms. However, zileuton is not being widely used despite its excellent anti-inflammatory effects due to toxicity of the compound.

[0005] Zileuton has significant hepatotoxicity, and thus an oral administration of zileuton should be accompanied by monitoring of liver functions of the patient.

SUMMARY

[0006] Therefore, a purpose of the present invention is to provide a topical pharmaceutical composition with a cream formulation, capable of applying zileuton topically to skin lesions of diseases caused by topical skin inflammation reactions such as atopic dermatitis, acne, various types of urticaria, psoriasis, eczema, bullous skin diseases such as bullous pemphigoid, collagenoses, Sjogren-Larsson syndrome, mastocytosis and the like, and maximizing pharmaceutical effects of zileuton while minimizing absorption to an entirety of a patient's body so as to minimize toxicity of the compound.

[0007] Further, another purpose of the present invention is to provide a method for preparing a topical pharmaceutical composition with zileuton cream formulation.

[0008] In order to achieve the purposes, the present invention provides a cream type topical pharmaceutical composition comprising zileuton of 0.05 to 2 weight% as an active pharmaceutical ingredient; water of 30 to 34 weight%; white petrolatum of 36 to 40 weight%; white

wax of 4 to 8 weight%; propylene glycol of 16 to 22 weight%; phospholipon 90H of 2 to 6 weight%; and preservative of 0.005 to 0.04 weight%.

[0009] The composition may comprise zileuton of 0.1 to 1 weight%; water of 31 to 33 weight%; white petrolatum of 37 to 39 weight%; white wax of 5 to 7 weight%; propylene glycol of 18 to 20 weight%; phospholipon 90H of 3 to 5 weight%; and preservative of 0.01 to 0.03 weight%.

[0010] The composition may be used for relieving or treating atopic dermatitis, acne, various types of urticaria, psoriasis, eczema, bullous skin diseases such as bullous pemphigoid, collagenoses, Sjogren-Larsson syndrome, acne in skin lesions of mastocytosis and the like.

[0011] The composition may be for topical application to human skin, and the zileuton may be racemic zileuton.

[0012] Another embodiment of the present invention provides a method for preparing a cream type topical anti-inflammatory pharmaceutical composition, including mixing zileuton of 0.05 to 2 weight% as an active pharmaceutical ingredient, water of 30 to 34 weight%; white petrolatum of 36 to 40 weight%; white wax of 4 to 8 weight%; propylene glycol of 16 to 22 weight%; phospholipon 90H of 2 to 6 weight%; and preservative of 0.005 to 0.04 weight% under a mixing condition of a temperature of 30 to 80 ℃ and 600 to 1200 rpm, for 10 to 60 minutes.

[0013] The method may further include cooling the mixed active ingredients at a temperature of 20 and 30 ℃ while stirring at 600 rpm or less.

[0014] In the method, the zileuton may be racemic zileuton.

[0015] As aforementioned, the present invention provide a cream type topical pharmaceutical composition that comprises zileuton as an active pharmaceutical ingredient and exhibits treatment effects to diseases caused by topical skin inflammation reactions such as atopic dermatitis, acne, various types of urticaria, psoriasis, eczema, bullous skin diseases such as bullous pemphigoid, collagenoses, Sjogren-Larsson syndrome, skin lesions of mastocytosis, and the like.

[0016] Furthermore, the cream type pharmaceutical composition according to the present invention has a pharmacokinetic profile that enables zileuton that is a leukotriene inhibitor to be absorbed to skin effectively but minimizing the amount of absorption to an entirety of a patient's body, and a physiochemical stability.

BRIEF DESCRIPTION OF THE DRAWINGS

[0017] FIG. 1 is a schematic diagram illustrating results of a test conducted to verify medical effects of the pharmaceutical composition according to the present invention by applying the same to an atopic mouse model;

[0018] FIG. 2 is a graph showing thicknesses of a mouse's ear measured after topically applying the pharmaceutical composition

according to the present invention to an atopic mouse model; and

[0019] FIGs. 3 and 4 show research results of the pharmacokinetic profile of the pharmaceutical composition according to the present invention in a minipig.

DETAILED DESCRIPTION

[0020] In order to provide a cream type topical formulation comprising zileuton as an active pharmaceutical ingredient, which exhibits effective treatment effects to atopic dermatitis and acne and the like, the inventors of the present invention sought for ingredients that can be applied with zileuton among the ingredients being used in cream type formulations, and sought for amount ratio of the ingredients for preparing a cream formulation comprising them, and then defined optimal concentration of the zileuton and stabilization conditions for realizing physiochemical stability, and thereby completed the present invention.

[0021] Therefore, there is provided a cream type topical pharmaceutical composition comprising zileuton of 0.05 to 2 weight% as an active pharmaceutical ingredient,; water of 30 to 34 weight%; white petrolatum of 36 to 40 weight%; white wax of 4 to 8 weight%; propylene glycol of 16 to 22 weight%; phospholipon 90H of 2 to 6 weight%; and preservative of 0.005 to 0.04 weight%.

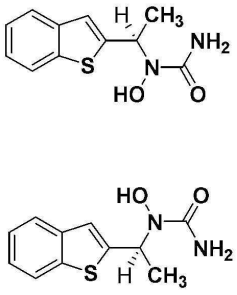
[0022] More specifically, the cream type pharmaceutical composition according to the present invention may comprise zileuton of 0.1 to 1 weight%; water of 31 to 33 weight%; white petrolatum of 37 to

39 weight%; white wax of 5 to 7 weight%; propylene glycol of 18 to 20 weight%; phospholipon 90H of 3 to 5 weight%; and preservative of 0.01 to 0.03 weight%.

[0023] Most specifically, the cream type topical pharmaceutical composition may consist of zileuton of 0.1 to 1 weight%; water of 32 weight%; white petrolatum of 38 weight%; white wax of 6 weight%; propylene glycol of 18 to 20 weight%; phospholipon 90H of 4 weight%; and preservative of 0.02 weight%.

[0024] Herein, zileuton is a mixture of stereoisomer: (R)-1-(1-(benzo[b]thiopen-2-yl)ethyl)-1-hydroxyure and (S)-1-(1-(benzo[b]thiophen-2-yl)ethyl)-1-hydroxyurea, in a white powder form, and may be racemic zileuton. That is, the present invention provides a cream type composition optimized to racemic zileuton as an active pharmaceutical ingredient.

[0025] [Chemical formula 1]



[0026] The zileuton may be synthesized chemically, or is available commercially (Cornerstone Therapeutics Inc., product name: ZYFLO, ZYFLO CR etc.)

[0027] White petrolatum, white wax, propylene glycol, and phospholipon 90H to be used in the pharmaceutical composition of the present invention is available commercially.

[0028] As the preservative, methylparaben, ethylparaben, propylparaben, isobutylparaben, butyl paraben, 2-phenoxy ethanol, 4-hydroxybenzoic acid or the like may be used, but without limitation. The preservative is available commercially as well.

[0029] The pharmaceutical composition according to the present invention is characterized to retain its physical and chemical stability for 4 weeks under the temperature condition of 25 to 40 ℃.

[0030] According to an embodiment of the present invention, the medical effect of the cream type topical pharmaceutical composition has been verified in a Delayed Type Hypersensitivity Reaction in mouse induced by DNFB. The test article was applied to a mouse's skin 3 times a day, and then the medical effect was measured. Furthermore, an excess amount of the zileuton was injected using a non-optimized test vehicle, acetone. Test results showed that an increase of thickness of the mouse's ear caused by inflammation and edema in the mouse model administered with the cream type pharmaceutical composition of the present invention was effectively inhibited, proving that the composition has an effective anti-inflammation function.

[0031] In order to determine whether or not a medical effect caused by absorption to an entirety of body is included, absorption to skin and body absorption pattern were evaluated. For this purpose, a skin PK was

examined from a minipig having a skin structure most similar to human. Test results showed effective skin absorption patterns, but showed no systemic exposure pattern. That is, it was identified that a cream type topical pharmaceutical composition according to the present invention effectively induces skin absorption, and minimizes body absorption, proving that the composition according to the present invention is suitable formulation for administration to human skin.

[0032] Therefore, a cream type topical pharmaceutical composition according to the present invention exhibits an anti-inflammatory effect by inhibiting formation of leukotriene, and thus is effective in relieving or treating diseases caused by topical skin inflammation reaction such as atopic dermatitis, acne, various types of urticaria, psoriasis, eczema, bullous skin diseases such as bullous pemphigoid, collagenoses, Sjogren-Larsson syndrome, skin lesions of mastocytosis, and the like.

[0033] The acne may be an inflammatory acne selected from a group consisting of acne papulosa, acne pustulosa, acne papulopustolosa, and severe inflammatory acne.

[0034] The cream type pharmaceutical composition may be for topical application to human skin. More specifically, it may be applied topically once to four times a day.

[0035] The present invention also relates to a preparation method for a cream type topical pharmaceutical composition, the method including mixing zileuton of 0.05 to 2 weight% as an active pharmaceutical ingredient; water of 30 to 34 weight%; white petrolatum

of 36 to 40 weight%; white wax of 4 to 8 weight%; propylene glycol of 16 to 22 weight%; phospholipon 90H of 2 to 6 weight%; and preservative of 0.005 to 0.04 weight% under a mixing condition of a temperature of 30 and 80 ℃ and 600 to 1200 rpm, for 10 to 60 minutes.

[0036] More specifically, the preparation method for a cream type topical pharmaceutical composition may include mixing zileuton of 0.1 to 1 weight%; water of 31 to 33 weight%; white petrolatum of 37 to 39 weight%; white wax of 5 to 7 weight%; propylene glycol of 18 to 20 weight%; phospholipon 90H of 3 to 5 weight%; and preservative of 0.01 to 0.03 weight%.

[0037] Most specifically, the preparation method for a cream type topical pharmaceutical composition may include mixing zileuton of 0.1 to 1 weight%; water of 32 weight%; white petrolatum of 38 weight%; white wax of 6 weight%; propylene glycol of 18 to 20 weight%; phospholipon 90H of 4 weight%; and preservative of 0.02 weight%.

[0038] The preparation method for a cream type topical pharmaceutical composition may further include cooling the mixed active ingredients under the condition of a temperature of 20 and 30 ℃ while stirring at 600 rpm or less.

[0039] The cream type topical pharmaceutical composition prepared through the aforementioned method may retain its stability for 4 weeks at a temperature of 25 to 40 ℃, and may thus be suitable to topical application.

[0040] Hereinafter, examples of a cream type topical

pharmaceutical composition of the present invention will be explained. However, the examples are intended for just illustrating, but not limiting the scope of the present invention thereto.

[0041] <Example> Preparing zileuton cream type composition

[0042] 1. Screening test for suitability of the cream type composition

[0043] Suitability of components generally used in cream formulation with respect to zieluton was screened, prior to preparing a zieluton cream formulation. For this purpose, 5 mg of zileuton (product name: Q301) was dissolved in 5 mg of excipient, and then changes of TRS%(Total Related Substances) were observed for up to 4 weeks under a 50 ℃ condition. That is, the stability of excipient at 50 ℃ was tested.

[0044] As a result, as illustrated in Table 1 shown below, stearyl alcohol, phospholipon 90H, white wax, titanium dioxide, HPMC F4M, carbomer(carbopol 940), propylene glycol stearate, and aluminum starch octenylsuccinate were found to be suitable, whereas Ceteareth-20 was found to be unsuitable.

[0045] 【Table 1】

No.	Excipient	API: Excipient ratio	Day 0			2 weeks, 50 ℃			4 weeks, 50 ℃		
			Appearance	Recovery %	TRS. %	Appearance	Recovery %	TRS. %	Appearance	Recovery %	TRS. %
1	Zileuton (Q301)	API	-	-	2.378	White powder	101.47 101.30	3.311 3.006	White powder	99.12 98.23	2.711 2.493
2	Stearyl alcohol	1:1	White powder	98.71	3.311	White powder	101.69 101.28	2.935 2.796	White powder	102.91 98.77	2.512 2.567
3	Ceteareth-20	1:1	White powder	100.34	2.394	White power	99.99 100.36	3.445 3.365	White semisolid	97.59 96.39	3.632 3.549
4	Phospholipon	1:1	White	100.61	2.400	White	101.50	2.820	White	97.26	2.557

	90H		powder			powder	102.21	2.846	powder	103.30	2.429
5	White wax	1:1	White powder	99.46	2.372	White powder	100.70 102.20	2.863 2.843	White powder	98.77 97.31	2.459 2.381
6	Titanium dioxide	1:1	White powder	100.59	2.344	White powder	102.55 102.86	2.803 2.839	White powder	99.14 99.17	2.507 2.504
7	Hypromellose (HPMC)	1:1	White powder	103.72	2.610	White powder	102.67 102.97	2.864 2.949	White powder	98.86 100.86	2.555 2.580
8	Carbomer	1:1	White powder	99.34	3.326	White powder	102.45 103.39	2.385 3.067	White powder	99.63 97.65	2.330 2.403

[0046] In the solution stability test, suitability with solvents for solubilizing zileuton (ethanol, PEG400, propylene glycol, hexylene glycol, capryol 90, benzyl alcohol, water) was screened. For this purpose, 10 mg of zileuton was dissolved in a 2mL vehicle, and then changes of TRS% were observed in conditions of 25 ℃, 40 ℃, and 70 ℃, respectively.

[0047] As a result, as illustrated in Tables 2 and 3 below, most of the solvents were suitable to zileuton under the 25 ℃ condition, but were unstable under the condition of 40 ℃ or 70 ℃. Table 2 shows the result of stability test of the solution at 25 ℃, and Table 3 shows the result of stability test of the solution at 40 ℃ or 70 ℃.

[0048] [Table 2]

Solvents	Temperature	TRS (%)				TRS increase rate %
		Day 0	Day 1	Day 3	Day 8	
Ethanol	25 ℃	1.255	1.014	1.951	2.137	0.882
Polyethylene glycol (PEG-400)	25 ℃	1.427	1.491	2.897	4.065	2.638
Propylene glycol	25 ℃	1.457	1.624	1.478	2.132	0.675
Hexylene glycol	25 ℃	1.505	1.448	1.583	1.980	0.475
Capryol 90	25 ℃	1.623	1.444	1.478	2.201	0.578
Benzyl alcohol	25 ℃	1.642	0.869	1.806	2.023	0.381

Water	25 ℃	1.424	1.879	1.816	1.965	0.541

[0049] 【Table 3】

Solvents	Temperature	TRS (%)				TRS increase rate %
		Day 0	Day 1	Day 3	Day 8	
Ethanol	40 ℃	1.255	1.778	2.375	4.704	3.449
Polyethylene glycol (PEG-400)	70 ℃	1.427	43.725	94.366	97.142	95.715
Propylene glycol	70 ℃	1.457	26.382	82.228	96.325	94.868
Hexylene glycol	70 ℃	1.505	8.061	29.999	60.352	58.847
Capryol 90	70 ℃	1.623	10.312	39.603	76.445	74.822
Benzyl alcohol	70 ℃	1.642	11.350	20.397	24.250	22.608
Water	70 ℃	1.424	35.171	80.268	91.994	90.570

[0050] 2. Composition optimization test

[0051] The components determined as being suitable in the aforementioned suitability screen test were combined, and amount ratios of solvents and ingredients stable under an acceleration condition (30 ℃, 40 ℃) were screened.

[0052] For this purpose, by mixing the ingredients other than solvents such as propylene glycol and water and the like under 70 ℃ according to the amount ratios disclosed in Table 4, and then adding and mixing the remaining solvents while stirring for 30 minutes under a condition of 70 ℃ and 800 rpm or less. The mixed composition was stirred at 100 rpm or less, and cooled to room temperature. That is, Table 4 below shows results of the test regarding optimized ingredient ratios.

[0053] 【Table 4】

Ingredients (%)	022-1	022-4	023-5	023-7	029-10	028-1	028-2	028-5	028-6	028-7	029-12	029-14
Zileuton (Q301)	-	-	-	-	-	-	-	-	-	-	-	-
Water	-	-	-	57	16	-	-	10~31				
White petrolatum	43	38~48		24	20	43	38	18~31				
White wax	6	6	6	6	5	7	7	5~9				
Propylene glycol(PG)	24	32~42		10	55	47	52	25~55				
Stearyl Alcohol	16	-	-	-	-	-	-	-	-	-	-	-
Propylene glycol stearate	-	-	-	-	-	-	-	-	-	-	-	-
Phospholipon 90H	-	3	3	3	4	3	3	4	4	4	4	4
Ethanol	-	-	-	-	-	-	-	-	-	-	10.5	10.5
Aluminum starch octenyl-succinate	11	11	11	-	-	-	-	-	-	-	-	-
Appearance	Little dry cream	Cream	Cream	Liquid	Ointment	Oily cream	Very oily cream	Cream	Cream	Cream	Cream	Cream
Approximate solubility (%)	-	-	-	-	<1.3%	<3%	-	<0.1%	<0.3%	<0.7%	<2.3%	<2.5%

[0054] As shown in Table 4, it was found the composition ratios of 022-4, 023-5, 028-5, 028-6, 028-7, 029-12, and 029-14 provide suitable cream type formulation. From the aforementioned result, it was confirmed that the amount ratios of water, white petrolatum, white wax, and propylene glycol have critical significance in the aforementioned ranges.

[0055] 3. Optimization test of cream processing method

[0056] A condition that satisfies the physical and chemical stability with a target drug concentration (1%) was screened based on the amount ratios discovered in the composition optimization test. For this purpose, the ingredients other than the solvents such as propylene glycol and water were mixed according to the amount ratios disclosed in Table 5 under 70 ☐, and then the remaining solvents were mixed at 70 ☐ and 800 rpm or less. The mixed cream composition was stirred at or less

than 100 rpm and cooled to room temperature.

[0057] Physical stabilities were measured by checking with the naked eye whether or not phase separation occurred after leaving a sample for a certain period of time at a condition of 25 □, 30 □ or 40 □. This is a test to discover an optimized processing method for obtaining a cream formulation.

[0058] 【Table 5】

Ingredients (%)	030-1	030-2	030-3	030-4	032-4	033-1	033-2	033-3	033-4	033-5	033-6	033-7
Zileuton (Q301)	-	-	-	-	-	-	-	-	-	-	-	-
Water	10~12								17~21			
White petrolatum	18~20								17~21			
White wax	6	6	6	6	6	6	6	6	6	6	6	6
Propylene glycol(PG)	51	51	53	55	55	51	54	51	48	52	54	56
Phospholipon 90H	4	4	4	4	4	5	5	4	4	4	4	4
Ethanol	4.5~9								-	-	-	-
Stirring time(min)	20	20	20	20	20	20	20	20	20	20	20	20
Shape	Cream	Cream	Cream	Cream	Cream	Cream	Cream	Cream	Cream	Cream	Cream	Cream
Approximate solubility (%)	<2.1%	<1.8%	<2.7%	<2.7%	<2.3%	<2.1%	<2.1%	<2.1%	<1.3%	<1.5%	<1.7%	<2.1%
Physical stability at 25℃	Bad	Bad	Bad	Bad	Bad	Bad	Bad	Bad	Good	Good	Good	Good

[0059] As disclosed in Table 5, it was found that the formulation conditions of 033-4, 033-5, 033-6, and 033-7 provide excellent physical stability at 25 ℃ so as to dissolve active pharmaceutical ingredient 1% or more. Furthermore, the aforementioned cream formulations do not comprise ethanol, and this is because ethanol deteriorates physical stability.

[0060] Next, as a test for optimizing the processing method for cream type formulation, in order to find out whether the stirring time affects the shape of the cream, stirring times of 5 minutes, 30 minutes

and 60 minutes were applied and then observed. As a result, as illustrated in Table 6 below, the stirring time of 30 minutes was confirmed as the optimized condition.

[0061] 【Table 6】

Ingredients(%)	031-1	062-1	037-1
Zileuton(Q301)	-	-	-
Water	10~26		
White petrolatum	17~29		
White wax	6	6	6
Propylene glycol(PG)	35~56		
Phospholipon 90H	4	4	4
Ethanol	6.5	-	-
Total sum of ingredients	100	100	100
Stirring time(min)	5	30	60
Appearance	Liquid like Cream	Cream	Cream
Approximate solubility (%)	-	0.3%	<1.3%
Physical stability at 30 ℃		Good	

[0062] 4. Optimization test of solvent

[0063] It was determined that using an excessive amount of propylene glycol to adjust to 1% of drug concentration has a negative effect on the physical stability of the composition, and thus a composition ratio of high stability with a lower drug concentration was sought for.

[0064] In a case of increasing a scale of a sample, cream formulations 036-1 and 040-1 showed low physical stability but high chemical stability. Therefore, in order to improve the physical stability of the composition after increasing the scale of sample, a cream type formulation with a reduced loading amount of drugs was prepared. For this purpose, formulation 062-1 was selected, and based on this cream type composition, the amount of drug loading was raised up to 1%, and

then a solvent capable of obtaining chemical stability while retaining physical stability was screened.

[0065] The aforementioned screening test was conducted by mixing ingredients other than the solvents such as propylene glycol, water and the like at 70 ℃ in accordance with the composition ratio disclosed in Table 7 below, and then mixing the remaining solvents according to the composition ratio of Table 7 under a stirring condition of 800 rpm or less for 30 minutes at 70 ℃. The mixed composition was stirred at or less than 100 rpm and cooled to room temperature.

[0066] The chemical stability was evaluated by measuring changes in TRS% through LC analysis after leaving a sample for a certain period of time under a temperature of 25 ℃ or 40 ℃.

[0067] 【Table 7】

Ingredients (%)	N-methyl pyrrolidone (NMP)			Capyrol 90			Benzyl alcohol			
	064-1	066-1	067-1	078-2	080-1	080-2	073-4	073-5	073-6	073-7
Zileuton (Q301)	-	-	-	-	-	-	-	-	-	-
Water	24~26			20~24			37~41			
White petrolatum	29~33			29~33			38~42			
White wax	6	6	6	12~24			6			
Propylene glycol(PG)	24	24	24	-	-	-	-	-	-	-
Stearyl Alcohol	-	-	-	-	-	-	4	-	-	-
Propylene glycol stearate	-	-	-	-	-	-	-	4	-	-
Phospholipon 90H	4	4	4	4	4	4	-	-	4	4
Ethanol	-	-	-	-	-	-	-	-	-	-
Aluminum starch octenyl-	-	-	-	-	-	-	-	-	-	-

succinate										
N-methyl pyrrolidone (NMP)	10	10	8	-	-	-	-	-	-	-
Benzyl alcohol	-	-	-	-	-	-	14	14	10	10
Capyrol 90	-	-	-	28	28	28	-	-	-	-
Dimethyl sulfoxide	-	-	-	-	-	-	-	-	-	-
Stirring time (min)	30	30	30	30	30	30	30	30	30	30
Appearance	Liquid	Liquid	Cream	Cream	Cream	Cream	Cream	Cream	Cream	Cream
Approximate solubility (%)	1%	1%	0.8%	0.8%	0.8%	0.8%				
Physical stability at 30 ℃			Bad							
Physical stability at 40 ℃				Bad	Bad	Bad	Bad	Bad	Bad	Bad

[0068] As illustrated in Table 7, NMP and benzyl alcohol were screened as solvents, but both showed bad physical stability with phase separation. Furthermore, capryol 90 was screened as a solvent, but all showed bad physical stability due to phase separation.

[0069] Consequently, the processing method was changed from 062-1 condition, and an amount of drug loading was increased to 1%, and thereby a cream type composition that satisfies both the target drug concentration and physical stability was discovered. However, regarding the chemical stability, a significant TRS% change was observed after 3 weeks under a temperature condition of 40 ℃.

[0070] Furthermore, as illustrated in Table 8 below, a test for determining a critical amount range was conducted after selecting an excipient and an approximate composition ratio that could satisfy criteria as a topical cream.

[0071] 【Table 8】

Ingredients (%)	Criteria	079-1	083-1
Zileuton (Q301)	-	-	-
Water	30~40	32	32
White petrolatum	36~40	33	38
White wax	4~8	6	6
Propylene glycol(PG)	16~22	25	19
Phospholipon 90H	2~6	4	4
Appearance	Cream	Cream	Cream
Physical stability for 4 weeks under 40℃	Stable	Phase separation observed at the 4th week	Stable

[0072] As shown in Table 8, it was observed that in the case of a formulation wherein an excipient was used in an amount out of the critical amount range, the physical stability was deteriorated. That is, as in the formulation 079-1 in Table 8, when the amount ratio of white petrolatum and propylene glycol are 33 and 25, respectively, that is out of the critical amount range, it was observed by naked eyes that the physical stability was deteriorated due to separation of oil phase and water phase starting from the 4th week.

[0073] Table 9 below shows candidate formulations according to the test result.

[0074] 【Table 9】

	Candidate formulations	
Ingredients (%)	081-1	081-2
Zileuton (Q301)	1	1
Water	32	26
White petrolatum	32	29
White wax	6	6
Propylene glycol (PG)	25	34
Phospholipon 90H	4	4
Total sum of ingredients	100	100

Stirring time (min)	30	30
Appearance	Cream	Cream
Approximate solubility (%)	1%	1%
Physical stability at 40 ℃	Good	Good
Chemical stability at 40 ℃ (TRS %)	6.65% of changes for 3 weeks	9.79% of changes for 3 weeks

[0075] As shown in Table 9, the formulations 081-1 and 081-2 satisfied conditions required for development up to clinical phase 2. Further, in order to develop the final formulation, an experiment for developing a new composition ratio and processing method was additionally conducted while measuring the chemical stability under 30 ℃ acceleration condition of 062-1.

[0076] Accordingly, as shown in Table 10 below, the amount of propylene glycol was optimized, and propylene paraben was added as a preservative. As a result, the cream formulations 089-1 and 089-2 of the composition ratios of Table 10 satisfied chemical/physical stabilities under 30 ℃ acceleration condition.

[0077] 【Table 10】

Ingredients	089-1 (weight%)	089-2 (weight%)
Q301 (zileuton)	0.1	1
Water	32	32
White Petrolatum	38	38
White wax	6	6
Propylene glycol	19.88	18.98
Phospholipon 90H	4	4
Preservative (Propylparaben)	0.02	0.02
Total sum of ingredients	100	100
Stirring time (min)	30	30

Appearance	Cream	Cream
Physical stability	Good for 4 weeks	Good for 4 weeks
Chemical stability (TRS %)	1.4% of changes for 4 weeks at 30 ℃	1.4% of changes for 4 weeks at 30 ℃

[0078] On the other hand, it was confirmed that the cream formulations of the comparative examples having composition ratios of Table 11 below do not exhibit good chemical/physical stabilities under 30 ℃ acceleration condition in the target drug concentration range which can provide efficacious pharmaceutical activity.

[0079] 【Table 11】

Ingredients	058-1 (weight%)	059-1 (weight%)
Q301 (zileuton)	0.7	0.7
Water	24	22
White Petrolatum	25	27
White wax	3	3
Propylene glycol	46	46
Phospholipon 90H	1	1
Preservative (Propylparaben)	0.02	0.02
Stirring time (min)	30	30
Appearance	Cream	Cream
Physical stability	Phase separation observed at 30 ℃	Phase separation observed at 30 ℃

[0080] <Experiment 1> Evidence of concept research using formulation 089

[0081] An in vivo test was conducted to identify whether or not formulation 089 of the above example shows medical effects when administered to skin in a generally used mouse atopic dermatitis animal model. For this purpose, BALB/c mice were divided into 4 groups, each consisting of 10 mice. The groups were divided into a vehicle (acetone),

positive control group (dexamethasone 0.05 mg/ear), and zileuton groups. And the zileuton groups were divided into cases where acetone (1 mg/ear) and cream formulation of 089 (0.2 mg/ear and 0.02 mg/ear) as a vehicle were used, respectively.

[0082] As illustrated in FIG. 1, on day 0 and day 1, 25 ㎕ of 0.5% DNFB (dinitrofluorobenzene) solution was applied once on ears of all groups to cause inflammation. Then, on day 5, 20 ㎕ of 0.3% DNFB was applied once again to cause inflammation in the ears. Then, dexamethasone and zileuton dissolved in acetone vehicle were applied to the ears at 1 hour, 6 hours, and 23 hours after the stimulation on day 5. Thicknesses of the ears were measured at 24 hours after the stimulation on day 5, and then ear tissues were taken for histopathological observation.

[0083] As illustrated in FIG. 2, in the group where formulation 089 was used as vehicle, Q301 (API: Active Pharmaceutical Ingredient) was effectively delivered to the skin, thereby effectively inhibiting increase of ear thickness caused by inflammation and edema compared to groups where acetone was used.

[0084] Through histopathological observation, excellent anti-inflammation function of zileuton was observed.

[0085] 【Table 12】

Test model	BALB/c mouse, female 6~8 weeks of age (17~20g)						
Dosing							
Group	Drug (formulation)	No.	Route	Concentration (mg/mL or %)	mL or mg/ear	API mg/ear	Regimen (Time)
1	Vehicle	10	Topical	N/A	0.02 mL	N/A	1,6,23

	(Acetone)						
2	Dex (Acetone)	10	Topical	2.5 mg/mL	0.02 mL	0.05	1,6,23
3	Q301 (Acetone)	10	Topical	50 mg/mL	0.02 mL	1	1,6,23
4	Q301 (formulation089-2)	10	Topical	1%	20 mg	0.2	1,6,23
5	Q301 (formulation 089-1)	10	Topical	0.1%	20 mg	0.02	1,6,23
Measure	* Weight * Ear thickness * Histopathological observation (edema, inflammation, crust formation)						

[0086] <Experiment 2> PK research test using minipigs

[0087] It is necessary to find out from the Experiment 1 whether or not medical effects by absorption to an entirety of body are included. In order to identify the skin absorption and systemic exposure level of the final formulation, minipigs having skin structures most similar to those of humans may be used. Therefore, skin PK was observed in minipigs having the most similar skin structures as humans using the 089 formulation which is for the clinical formulation derived in the process of developing the cream formulation.

[0088] For this purpose, 20 mg of Q301 (API: Active Pharmaceutical Ingredient) was applied to 100 cm^2 of skin using the 089 formulation. After applying the 089 formulation, concentration of zileuton in plasma was measured 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, and 8 hours afterwards. After applying the 089 formulation, zileuton concentration in the skin was measured 1 and 8 hours afterwards. For the measurement of zileuton

concentration in the skin, the skin was separated into surface, subcutaneous, dermas, and epidermis layers. The subcutaneous layer was separated using the tape stripping method, and the measurements of zileuton concentrations were conducted for different depths of strip 1, strip 2-5, strip 6-12, and strip 13-24. Test conditions are as illustrated in Tables 13 and 14.

[0089] 【Table 13】

Group	Number of Bamma pigs (#/ Gender)	Treatment					
		Test drug	Dose (mg/㎠)	Concentration (mg API/g cream)	Vehicle	Route	Type of specimen obtained
1	6 females	Zileuton (Q301)	0.2(API)	10	089-1 Formulation	Topical administration	Plasma, skin
Test article storage: Desiccated at 4 ℃		Comments: Animals of body weights of 15~20kg were used, and administration area was 10cm X 10cm					
Overnight Fast of Animals : None							

[0090] 【Table 14】

Group	Administration route	Animal ID	Sampling and administration schedule (time)										
			-0.5	0	0.25	0.5	1	1.5	2	3	4	6	8
1	Topical	1~3	P	D	P	0	P+S	-	-	-	-	-	-
		4~6	P	D	-	P	-	P	P	P	P	P	P+S
P: Collect blood and separate plasma D: Administer drug to animals at determined time P+S: Collect blood and skin, and separate plasma from blood. Extract corneum layer before obtaining skin sample. Separate dermas and epidermis layers from skin.													
Anticoagulant: K2-EDTA													

[0091] As illustrated in FIGs. 3 and 4, the 089 formulation showed effective skin absorption pattern, whereas it did not show any systemic exposure pattern in the minipigs. It can be seen that the cream

formulation using propylene glycol effectively induces skin absorption, and minimizes body absorption, and is thus suitable as a future candidate formulation of zileuton for skin administration.

[0092] While this invention has been described in connection with what is presently considered to be preferable embodiments, it is to be understood that the present invention is intended to cover various changes, modifications and equivalent arrangements. It is obvious that the present invention may be practiced by appropriate modifications of the aforementioned embodiments. Therefore, the aforementioned embodiments do not limit the scope of the present invention which is determined by the claims.

[0093] 【Industrial applicability】

[0094] The present invention is for providing a zileuton cream formulation for topical treatment of skin disease caused by leukotriene, and is an industrially applicable invention.

WHAT IS CLAIMED IS:

1. A cream type topical anti-inflammatory pharmaceutical composition, comprising:

zileuton of 0.05 to 2 weight% as an active ingredient; water of 30 to 34 weight%; white petrolatum of 36 to 40 weight%; white wax of 4 to 8 weight%; propylene glycol of 16 to 22 weight%; phospholipon 90H of 2 to 6 weight%; and preservative of 0.005 to 0.04 weight.

2. The composition according to claim 1,

wherein the composition comprises zileuton of 0.1 to 1 weight% as an active ingredient; water of 31 to 33 weight%; white petrolatum of 37 to 39 weight%; white wax of 5 to 7 weight%; propylene glycol of 18 to 20 weight%; phospholipon 90H of 3 to 5 weight%; and preservative of 0.01 to 0.03 weight%.

3. The composition according to claim 1,

wherein the preservative is one or more selected from a group consisting of methylparaben, ethylparaben, propylparaben, isobutylparaben, butyl paraben, 2-phenoxy ethanol, and 4-hydroxybenzoic acid.

4. The composition according to claim 1,

wherein the composition is used for relieving or treating atopic

dermatitis, acne, urticaria, psoriasis, eczema, bullous skin diseases such as bullous pemphigoid, collagenoses, Sjogren-Larsson syndrome, or acne in skin lesions of mastocytosis.

5. The composition according to claim 1,

wherein the composition is for topical application to human skin.

6. The composition according to claim 1,

wherein zileuton is racemic zileuton.

7. A method for preparing a cream type topical anti-inflammatory pharmaceutical composition, comprising:

mixing zileuton of 0.05 to 2 weight% as an active ingredient; water of 30 to 34 weight%; white petrolatum of 36 to 40 weight%; white wax of 4 to 8 weight%; propylene glycol of 16 to 22 weight%; phospholipon 90H of 2 to 6 weight%; and preservative of 0.005 to 0.04 weight% under a mixing condition of a temperature of 30 to 80 ℃ and 600 to 1200 rpm, for 10 to 60 minutes.

8. The method according to claim 7,

wherein the method comprises mixing zileuton of 0.1 to 1 weight%; water of 31 to 33 weight%; white petrolatum of 37 to 39 weight%; white wax of 5 to 7 weight%; propylene glycol of 18 to 20 weight%; phospholipon 90H of 3 to 5 weight%; and preservative of 0.01 to 0.03

weight%.

9. The method according to claim 7,

wherein the preservative is one or more selected from a group consisting of methylparaben, ethylparaben, propylparaben, isobutylparaben, butyl paraben, 2-phenoxy ethanol, and 4-hydroxybenzoic acid.

10. The method according to claim 7,

further comprising cooling the mixed active ingredients at a temperature of 20 to 30 ℃ while stirring at 600 rpm or less.

11. The method according to claim 7,

wherein zileuton is racemic zileuton.