(12) STANDARD PATENT (11) Application No. **AU 2019283247 B2**
(19) AUSTRALIAN PATENT OFFICE

(54) Title
Fluticasone furoate nasal preparation composition

(51) International Patent Classification(s)
A61K 31/58 (2006.01)
A61K 9/08 (2006.01)
A61K 9/12 (2006.01)
A61K 47/02 (2006.01)
A61K 47/10 (2017.01)
A61K 47/18 (2017.01)
A61K 47/32 (2006.01)
A61K 47/34 (2017.01)
A61P 11/02 (2006.01)
A61P 29/00 (2006.01)
A61P 37/08 (2006.01)

(21) Application No: **2019283247** (22) Date of Filing: **2019.06.07**

(87) WIPO No: **WO19/235616**

(30) Priority Data

(31) Number	(32) Date	(33) Country
2018-110634	**2018.06.08**	**JP**

(43) Publication Date: **2019.12.12**
(44) Accepted Journal Date: **2025.03.27**

(71) Applicant(s)
Toko Yakuhin Kogyo Co., Ltd.

(72) Inventor(s)
KAMISHITA, Taizou;MIYAZAKI, Takashi

(74) Agent / Attorney
Davies Collison Cave Pty Ltd, Level 15 1 Nicholson Street, MELBOURNE, VIC, 3000, AU

(56) Related Art
EP 2014305 B1
Nambiar V et al. Int J Otorhinolaryngol Head Neck Surg. 2016 Jan;2(1):35-39
Eli O. Meltzer, et al Annals of Allergy, Asthma & Immunology, 104(4),2010, 331-338.
CN 101474192 A

(12) 特許協力条約に基づいて公開された国際出願

(19) 世界知的所有権機関
国際事務局

(43) 国際公開日
2019年12月12日(12.12.2019)

WIPO | PCT

(10) 国際公開番号
WO 2019/235616 A1

(51) 国際特許分類:
A61K 31/58 (2006.01)
A61K 9/08 (2006.01)
A61K 9/12 (2006.01)
A61K 47/02 (2006.01)
A61K 47/10 (2017.01)
A61K 47/18 (2017.01)
A61K 47/32 (2006.01)
A61K 47/34 (2017.01)
A61P 11/02 (2006.01)
A61P 29/00 (2006.01)
A61P 37/08 (2006.01)

(21) 国際出願番号： PCT/JP2019/022743

(22) 国際出願日： 2019年6月7日(07.06.2019)

(25) 国際出願の言語： 日本語

(26) 国際公開の言語： 日本語

(30) 優先権データ：
特願 2018-110634 2018年6月8日(08.06.2018) JP

(71) 出願人: 東興薬品工業株式会社 **(TOKO YAKUHIN KOGYO CO., LTD.)** [JP/JP]; 〒5300022 大阪府大阪市北区浪花町１４番２５号 Osaka (JP).

(72) 発明者: 上下 泰造 **(KAMISHITA, Taizou)**; 〒5300022 大阪府大阪市北区浪花町１４番２５号 東興薬品工業株式会社内 Osaka (JP). 宮崎 隆**(MIYAZAKI, Takashi)**; 〒5300022 大阪府大阪市北区浪花町１４番２５号 東興薬品工業株式会社内 Osaka (JP).

(74) 代理人: 山尾 憲人, 外 **(YAMAO, Norihito** et al.); 〒5300017 大阪府大阪市北区角田町８番１号梅田阪急ビルオフィスタワー青山特許事務所 Osaka (JP).

(81) 指定国(表示のない限り、全ての種類の国内保護が可能): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) 指定国(表示のない限り、全ての種類の広域保護が可能): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), ユーラシア (AM, AZ, BY, KG, KZ, RU, TJ, TM), ヨーロッパ (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

添付公開書類：
一 国際調査報告（条約第21条(3)）

WO 2019/235616 A1

(54) **Title:** FLUTICASONE FUROATE NASAL PREPARATION COMPOSITION

(54) 発明の名称： フルチカゾンフランカルボン酸エステル点鼻組成物

(57) **Abstract:** The present invention relates to a pharmaceutical composition containing fluticasone furoate and a carboxyvinyl polymer.

(57) 要約: 本発明は、フルチカゾンフランカルボン酸エステルおよびカルボキシビニルポリマーを含む医薬組成物に関する。

FLUTICASONE FUROATE NASAL PREPARATION COMPOSITION

TECHNICAL FIELD

[0001]

The present invention relates to a homogeneous composition comprising fluticasone furoate, and a process for preparing the composition. The present invention may be also used for treating allergic rhinitis.

BACKGROUND ART

[0002]

Corticoid steroids having anti-inflammatory activity are broadly used for treating inflammatory diseases such as dermatitis, asthma, and rhinitis. Fluticasone furoate which is one of corticoid steroids is a glucocorticoid that is topically used for lowering inflammation of skin or airway, which has been already sold on the open market as a nasal drops for treating allergic rhinitis (Patent Reference 1).

[0003]

Fluticasone furoate is very slightly soluble in water. In order to increase the water-solubility of fluticasone furoate to prepare nasal drops thereof for treating allergic rhinitis, it may be effective to add an organic solvent such as ethanol or an additive for increasing the

solubility. Considering the administration to delicate nasal mucosa, however, it is difficult to use a stimulant organic solvent such as ethanol in nasal drops, or it is limited to choose a safe solubilizing agent having little irritating property for nasal mucosa. After all, nasal drops of fluticasone furoate were developed as an aqueous suspension and the aqueous suspension has been already sold on the open market (Allermist™ nasal spray).

[0004]

When nasal drops are developed as an aqueous suspension, the selection of suspending agents used therein is important. The selection should be done considering the character of formulations. That is, the selection of suspending agents may greatly influence the suspension character such as suspension stability, redispersibility, spray-performance, retention on mucosa (viscosity), and nasal-mucosal irritation, and may also have no small influence on the efficacy or stability of nasal drops (Patent Reference 2).

[0005]

In the above-mentioned commercial product Allermist nasal spray, after all, microcrystalline cellulose and carboxymethylcellulose sodium (carmellose sodium) have been used as suspending agents. However, the suspension dispersibility of the preparation is not necessarily stable,

2019283247 18 Nov 2024

and thus the preparation contains a reminder of shaking the bottle before using. The fact that the suspension dispersibility is not stable means to influence the stability of drug-formulation or the spray-performance. And, by shaking the preparation before using, the viscosity of the preparation decreases, and such low viscosity makes it difficult to long keep the preparation in the nasal cavity. Consequently, the adverse effect on the drug efficacy has been of increasing concern.

PRIOR ART

[Patent Reference]

[0006]

[Patent Reference 1] WO 2002/012265

[Patent Reference 2] JP 4838493 B

SUMMARY OF INVENTION

[0007]

The present invention provides a pharmaceutical composition that is a nasal-spray preparation comprising poorly-water-soluble fluticasone furoate as an aqueous suspension, which does not need to be shaken before using because the suspension-dispersing state is stable, and has a good retention in the nasal cavity

2019283247 18 Nov 2024

after spray-administration.

[0008]

The present inventors have found that fluticasone furoate can become a very stable unprecedented suspension-dispersing state by adding carboxy vinyl polymer which is usually used as a viscous agent or a thickener and does not belong to a general suspending agent.

[0009]

The present invention may provide the following embodiments.

(Term 1) A pharmaceutical composition comprising fluticasone furoate and carboxy vinyl polymer.

[0010]

(Term 2) The pharmaceutical composition of Term 1 which is an aqueous suspension.

[0011]

(Term 3) The pharmaceutical composition of Term 1 or 2, which contains 0.1 to 2 % (w/w) carboxy vinyl polymer.

[0012]

(Term 4) The pharmaceutical composition of any one of Terms 1 to 3, which contains 0.005 to 1 % (w/w) fluticasone furoate.

[0013]

(Term 5) The pharmaceutical composition of any one of Terms 1 to 4, further comprising at least one suspending agent.

[0014]

(Term 6) The pharmaceutical composition of Term 5, wherein the suspending agent comprises polysorbate 80.

[0015]

(Term 7) The pharmaceutical composition of any one of Terms 1 to 6, further comprising at least one antiseptic agent.

[0016]

(Term 8) The pharmaceutical composition of Term 7, wherein the antiseptic agent comprises benzalkonium chloride.

[0017]

(Term 9) The pharmaceutical composition of Term 7 or 8, wherein the antiseptic agent comprises disodium edetate.

[0018]

(Term 10) The pharmaceutical composition of any one of Terms 1 to 9, further comprising at least one tonicity agent.

[0019]

(Term 11) The pharmaceutical composition of Term 10, wherein the tonicity agent comprises sodium chloride and/or glycerin.

[0020]

(Term 12) The pharmaceutical composition of Term 10 or 11,

which contains 0.1 to 10 % (w/w) tonicity agent.

[0021]

(Term 13) The pharmaceutical composition of any one of Terms 1 to 12, which is isotonic.

[0022]

(Term 14) The pharmaceutical composition of any one of Terms 1 to 13, wherein the pH is 5 to 7.

[0023]

(Term 15) The pharmaceutical composition of Term 14, wherein the pH is adjusted with sodium hydroxide and/or L-arginine.

[0024]

(Term 16) The pharmaceutical composition of any one of Terms 2 to 15, wherein the liquid particle size of the aqueous suspension has a mean particle size of 30 to 100 μm.

[0025]

(Term 17) The pharmaceutical composition of Term 15 or 16, wherein the suspending agent comprises polysorbate 80, the antiseptic agent comprises disodium edetate and benzalkonium chloride, the tonicity agent comprises glycerin and sodium chloride, and the pH adjusting agent comprises L-arginine and sodium hydroxide.

[0026]

(Term 18) A nasal-spray preparation for intranasal administration, comprising the pharmaceutical composition

2019283247 18 Nov 2024

of any one of Terms 1 to 17.

[0026a]

(Term 18a) Use of the pharmaceutical composition of any one of Terms 1 to 17 as a nasal-spray preparation for intranasal administration.

[0027]

(Term 19) A method for stabilizing the suspensibility of an aqueous suspension comprising fluticasone furoate by adding carboxy vinyl polymer.

[0028]

(Effect of the Invention)

Thanks to the discovery of the present invention, the suspensibility of a nasal-spray preparation comprising fluticasone furoate as an aqueous suspension has got stabilized a lot and it has become unnecessary to be shook before using. In addition, as the shaking before using becomes unnecessary, the problem of viscosity-decrease due to shaking has been removed. Thereby, it is expected that the drug is long kept in the nasal cavity after it is administered into the nasal cavity, and the drug efficacy is improved to be sustainable and effective.

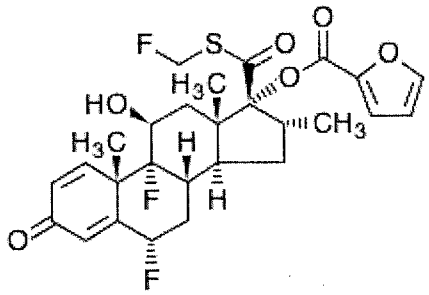
2019283247 18 Nov 2024

DESCRIPTION OF EMBODIMENTS

[0029]

Fluticasone furoate is the general name of 6α,9-difluoro-17β-[(fluoromethylsulfanyl)carbonyl]-11β-hydroxy-16α-methyl-3-oxoandrosta-1,4-dien-17α-yl furan-2-carboxylate whose chemical structure is shown below, which has been broadly used in the treatment of allergic rhinitis.

The content of fluticasone furoate in the present preparation is 0.005 to 1 % (w/w), preferably 0.025 to 0.1 %.



[0030]

Carboxy vinyl polymer used herein should not be limited as long as it is what is usually used in a medical formulation. Preferably, it is carboxy vinyl polymer whose viscosity is adjusted by adding an outside shearing force. The method of the adjustment and the effect of the modified carboxy vinyl polymer are disclosed in WO 2007/123193. For example, the outside shearing force may be added with a known device giving a shearing force such as a high-speed spinning-type emulsifying device, a colloidal mill-type emulsifying device, a high-pressure emulsifying device, a roll mill-type emulsifying device, an ultrasonic-type emulsifying device and a membrane-type emulsifying device. Especially, a homo mixer-type, a comb-type, and an intermittently-jet-stream-generating-type, high-speed spinning-type emulsifying devices are preferable. The content of carboxy vinyl polymer is 0.1 to 2 % (w/w),

preferably 0.25 to 1.0 %.

[0031]

The suspending agent used herein includes, for example, polysorbate 80, polyoxyl 40 stearate, and/or polyoxyethylene hydrogenated castor oil 60, preferably polysorbate 80. The content of the suspending agent is 0.01 to 1 % (w/w), preferably 0.025 to 0.5 %.

[0032]

The antiseptic agent used herein includes, for example, benzalkonium chloride, benzethonium chloride, chlorobutanol, and/or disodium edetate, preferably benzalkonium chloride and/or disodium edetate. The content of each antiseptic agent is 0.005 to 1 % (w/w), preferably 0.01 to 0.02 %.

[0033]

Preferably, the aqueous suspension of the present invention is isotonic or around isotonic. The isotonicity may be adjusted with a tonicity agent such as sodium chloride, boric acid, glycerin and/or glucose. The content of each tonicity agent is 0.1 to 10 % (w/w), preferably 0.1 to 1.0 %.

[0034]

The aqueous suspension of the present invention preferably has a pH of mild-acidity to around neutrality, in more detail, pH of 5 to 7. The pH may be adjusted with sodium hydroxide, potassium hydroxide, L-arginine, and the

like, preferably sodium hydroxide and/or L-arginine.

[0035]

The liquid particle size of sprayed aqueous suspension of the present invention is preferably a mean particle size of 30 to 100 μm, more preferably 40 to 80 μm.

[0036]

The nasal-spray preparation for intranasal administration of the present invention is directed to the nasal-spray preparation in a normal nasal spray container, or in an upper-pressure-relief airless-type spray container disclosed in WO 2007/123193 and WO 2007/123207.

EXAMPLES

[0037]

Hereinafter, the present invention is illustrated based on Examples, Reference examples, and Stability tests, but are not limited thereto. The evaluations of the Examples and Reference examples prepared below, and the stability tests were carried out according to Japanese Pharmacopoeia, unless otherwise indicated.

[0038]

The viscosity measurement was carried out according to Japanese Pharmacopoeia/General Tests/Viscosity Determination Method II Viscosity measurement by rotational viscometer 2.1.3. Cone-flat plate-type rotational

viscometer (20°C, 2.5 rotations per minute), and the details are as follows.

(Measuring method)

1.1 mL of the test sample (test preparation) was charged into a sample cup of a cone-flat plate-type rotational viscometer (cone plate type) which was beforehand set for 20°C, while being careful not to put air bubble. The sample was let stand for 5 minutes, and then subjected to a shearing force for 3 minutes. Subsequently, the viscosity of the sample was measured according to the following condition.

(Measuring condition)

Apparatus: TOKI SANGYO CO.,LTD. TVE-25 type viscosity meter

Measuring range: R (full-scale torque 1437.4 μN·m)

Shearing rate: 9.575 s^{-1} (2.5 rotations per minute)

Rotor: 1°34′×R24

[0039]

The liquid particle size (mean liquid particle size, 10 to 100 μm(%)) was measured by filling a nasal-spray device having a 55 mg (= 50 μL)-sprayable pump with the produced preparation, spraying the preparation, and analyzing the sprayed liquid particle with a laser diffraction/scattering particle-size-distribution analyzer according to the following condition.

(Measuring condition)

Apparatus: Malvern SprayTec

Reading distance: 30 mm

Spray angle: 40°

Extrusion speed: 100 mm/s

[0040]

Example 1

(Production method)

Ingredients	Amount (% by weight)
fluticasone furoate	0.05
carboxy vinyl polymer	0.56
L-arginine	0.98
polysorbate 80	0.1
disodium edatate hydrate	0.05
benzalkonium chloride	0.01
concentrated glycerin	1.0
sodium chloride	0.5
purified water	q.s. (96.75)
Total	100.0

Carboxy vinyl polymer was dispersed, mixed, and dissolved in purified water. To the solution was added a solution of L-arginine, disodium edatate hydrate, and sodium chloride in purified water, and the mixture was stirred. A solution of benzalkonium chloride in purified water was added to the mixture, and the mixture was stirred. Separately, fluticasone furoate was wetted with concentrated glycerin, and then polysorbate 80 and purified water were added thereto. The mixture was homogeneously dispersed to prepare a homogeneous wet solution of fluticasone furoate. The wet solution of fluticasone

furoate was added to the above-prepared solution comprising carboxy vinyl polymer, and the mixture was stirred to give a homogeneous nasal preparation.

[0041]

(Evaluation result)

The evaluation results of the obtained nasal preparation are shown below.

Aspect	A white suspensible viscous liquid, which is practically odorless
pH	6.2
Viscosity (mPa·s)	1250
Osmolality (mOs/L)	280
Mean liquid particle size (μm)	75
Liquid particle size of 10 to 100 μm (%)	81.4

[0042]

Example 2

(Production method)

Ingredients	Amount (% by weight)
fluticasone furoate	0.0275
carboxy vinyl polymer	0.52
L-arginine	0.91
polysorbate 80	0.1
disodium edatate hydrate	0.05
benzalkonium chloride	0.01
sodium chloride	0.25
ethanol	1.0
purified water	q.s.(97.1325)
Total	100.0

A solution of L-arginine, disodium edatate hydrate, and sodium chloride in purified water was charged into a vacuum mixer, then a solution of benzalkonium chloride and

polysorbate 80 in purified water was added thereto, and the mixture was stirred. Separately, carboxy vinyl polymer was dissolved in purified water with stirring and the solution was added to the mixture in the vacuum mixer. The mixture was stirred in the vacuum mixer. Separately, fluticasone furoate was wetted with concentrated glycerin, and then polysorbate 80 and purified water were added thereto. After wetting the mixture, the wet solution of fluticasone furoate was added to the stirred mixture prepared above. The mixture was stirred in the vacuum mixer. Further, the mixture was subjected to a high-speed shearing force to adjust the viscosity to 1250 mPa·s with stirring.

[0043]

(Evaluation result)

The evaluation results of the obtained nasal preparation are shown below.

Aspect	A white suspensible viscous liquid, which is practically odorless
pH	6.3
Viscosity (mPa·s)	1250
Osmolality (mOs/L)	265
Mean liquid particle size (μm)	67
Liquid particle size of 10 to 100 μm (%)	86.8

[0044]

Example 3

(Production method)

Ingredients	Amount (% by weight)

fluticasone furoate	0.0275
carboxy vinyl polymer	0.53
L-arginine	0.95
polysorbate 80	0.1
disodium edatate hydrate	0.05
benzalkonium chloride	0.01
concentrated glycerin	1.0
sodium chloride	0.5
purified water	q.s.(96.8325)
Total	100.0

Carboxy vinyl polymer was dispersed, mixed, and dissolved in purified water. To the solution was added a solution of L-arginine, disodium edatate hydrate, and sodium chloride in purified water, and the mixture was stirred. A solution of benzalkonium chloride in purified water was added to the mixture, and the mixture was stirred. Separately, fluticasone furoate was wetted with concentrated glycerin, and then polysorbate 80 and purified water were added thereto. The mixture was sufficiently wetted. The wet mixture of fluticasone furoate was added to the above-prepared mixture comprising carboxy vinyl polymer, and the obtained mixture was stirred in a vacuum mixer.

[0045]

(Evaluation result)

The evaluation results of the obtained nasal preparation are shown below.

Aspect	A white suspensible viscous liquid, which is practically odorless
pH	6.2

Viscosity (mPa·s)	1150
Osmolality (mOs/L)	281
Mean liquid particle size (μm)	72
Liquid particle size of 10 to 100 μm (%)	81.5

[0046]

Example 4

(Production method)

Ingredients	Amount (% by weight)
fluticasone furoate	0.05
carboxy vinyl polymer	0.53
L-arginine	0.2
polysorbate 80	0.1
disodium edatate hydrate	0.05
benzalkonium chloride	0.01
sodium chloride	0.035
concentrated glycerin	0.875
ethanol	0.8
purified water	q.s.(97.1325)
Total	100.0

A solution of L-arginine, disodium edatate hydrate, and sodium chloride in purified water was charged into a vacuum mixer, then a solution of benzalkonium chloride and polysorbate 80 in purified water was added thereto, and the mixture was stirred. Separately, carboxy vinyl polymer was dissolved in purified water with stirring and the solution was added to the mixture in the vacuum mixer. The mixture was stirred in the vacuum mixer. Separately, fluticasone furoate was wetted with concentrated glycerin, and then polysorbate 80 and purified water were added thereto. After wetting the mixture, the wet solution of fluticasone furoate was added to the stirred mixture prepared above.

The mixture was stirred in the vacuum mixer. Further, the mixture was subjected to a high-speed shearing force to adjust the viscosity to 1000 mPa·s with stirring.

[0047]

(Evaluation result)

The evaluation results of the obtained nasal preparation are shown below.

Aspect	A white suspensible viscous liquid, which is practically odorless
pH	4.5
Viscosity (mPa·s)	1000
Osmolality (mOs/L)	273
Mean liquid particle size (μm)	88
Liquid particle size of 10 to 100 μm (%)	68.4

[0048]

Example 5

(Production method)

Ingredients	Amount (% by weight)
fluticasone furoate	0.05
carboxy vinyl polymer	0.35
L-arginine	0.50
polysorbate 80	0.025
disodium edatate hydrate	0.015
benzalkonium chloride	0.01
sodium chloride	0.035
concentrated glycerin	0.875
ethanol	0.5
purified water	q.s.(97.64)
Total	100.0

A solution of L-arginine, disodium edatate hydrate, and sodium chloride in purified water was charged into a vacuum mixer, then a solution of benzalkonium chloride and

polysorbate 80 in purified water was added thereto, and the mixture was stirred. Separately, carboxy vinyl polymer was dissolved in purified water with stirring and the solution was added to the mixture in the vacuum mixer. The mixture was stirred in the vacuum mixer. Separately, fluticasone furoate was wetted with concentrated glycerin, and then polysorbate 80 and purified water were added thereto. After wetting the mixture, the wet solution of fluticasone furoate was added to the stirred mixture prepared above. The mixture was stirred in the vacuum mixer. Further, the mixture was subjected to a high-speed shearing force to adjust the viscosity to 1000 mPa·s with stirring.

[0049]

(Evaluation result)

The evaluation results of the obtained nasal preparation are shown below.

Aspect	A white suspensible viscous liquid, which is practically odorless
pH	6.0
Viscosity (mPa·s)	1000
Osmolality (mOs/L)	275
Mean liquid particle size (μm)	75
Liquid particle size of 10 to 100 μm (%)	81.2

[0050]

Reference example 1 (According to Example 1 in JP 4838493 B)

(Production method)

Ingredients	Amount (% by weight)
fluticasone furoate	0.05
polysorbate 80	0.025
Avicel RC591*	1.5
glucose	5.0
disodium edatate hydrate	0.015
benzalkonium chloride	0.015
1 N hydrochloric acid	q.s.
purified water	q.s.
Total	100.0
*: a mixture of microcrystalline cellulose and carboxymethylcellulose sodium	

Glucose was dissolved in purified water to prepare a solution of glucose, and disodium edatate hydrate was added thereto and dissolved. Avicel RC591 was added to the solution with stirring to prepare a hydrated Suspension A. Separately, polysorbate 80 was dissolved in purified water at 50 to 60°C, and fluticasone furoate was added thereto to prepare Suspension B. Suspension A and Suspension B were mixed and stirred. To the suspension mixture was added a solution of benzalkonium chloride in purified water, and the obtained mixture was stirred. To the mixture was added 1 N hydrochloric acid to adjust the pH to 6.0. Purified water was added thereto to adjust the total weight as shown in the above table.

[0051]

(Evaluation result)

The evaluation results of the obtained nasal preparation are shown below.

Aspect	A white opaque suspension
pH	6.0

Viscosity (mPa·s)	38
Osmolality (mOs/L)	278
Mean liquid particle size (μm)	67
Liquid particle size of 10 to 100 μm (%)	84.4

[0052]

Reference examples 2 to 6

In the same manner, each reference example was prepared using each suspending agent shown in the table below.

Example / Ingredients	Amount (% by weight)				
	Reference example 2	Reference example 3	Reference example 4	Reference example 5	Reference example 6
fluticasone furoate	0.05	0.05	0.05	0.05	0.05
polysorbate 80	0.025	0.025	0.025	0.025	0.025
glucose	5.00	5.00	5.00	5.00	5.00
disodium edatate hydrate	0.015	0.015	0.015	0.015	0.015
benzalkonium chloride	0.015	0.015	0.015	0.015	0.015
hydroxypropyl methylcellulose 2910*1	0.55	-	-	-	-
polyvinyl alcohol *2	-	2.00	-	-	-
sodium alginate *3	-	-	1.00	-	-
macrogol 4000 *4	-	-	-	45.0	-
chondroitin sulfate sodium *5	-	-	-	-	2.00
1N hydrochloric acid	q.s.	q.s.	q.s.	q.s.	q.s.
1N sodium hydroxide	q.s.	q.s.	q.s.	q.s.	q.s.
purified water	q.s. (up to 100 %)				

*1 to *5: Each indicated amount is the amount of each suspending agent which was added to obtain sufficient viscosity.

[0053]

(Evaluation result)

The evaluation results of the obtained nasal preparation are shown below.

	Reference example 2	Reference example 3	Reference example 4	Reference example 5	Reference example 6

2019283247 18 Nov 2024

pH	6.0	6.0	6.0	6.0	6.0
Viscosity (mPa·s)	47	7	320	60	10
Spray geometry	bad (jet-like)	good (fine mist)	bad (jet-like)	bad (jet-like)	good (fine mist)
Mean liquid particle size (μm)	249	72	163	110	81
Liquid particle size of 10 to 100 μm (%)	21.4	76.9	36.8	40.9	72.1

[0054]

Stability test 1

Using Example 5, Reference example 1, and a commercial product Allermist 27.5 μg 56 metered Nasal Spray (hereinafter, referred to as "Allermist nasal spray"), the following test was carried out.

(Test method)

The test sample (test preparation) is sufficiently stirred and then the assay sample is taken from the test sample in homogeneous state. The content of fluticasone furoate in the assay sample is determined by high-performance liquid chromatography to give each initial content in homogeneous state (Content A).

Then, 12 g of each test sample in homogeneous state is put into a 13.5 mL glass screw-capped-bottle, and the bottle is well shaken again to be in homogeneous state. The bottled test sample is left to stand at ambient temperature for 24 hours or for a week. Separately, the freshly-prepared test sample is centrifuged (5000 rpm, 10 minutes).

Before and after putting the sample into the screw-capped-bottle and shaking it, after 24-hour and one-week leaving to stand, and after centrifuging the sample, the sample in each state is evaluated about the aspect and the content of fluticasone furoate. In determining the content, each test sample is divided into an upper layer (3 g), a middle layer (4 g), and the left lower layer (3 g). Each 2 g of the upper and lower layers is weighed as assay samples, and each content of fluticasone furoate is determined by high-performance liquid chromatography (Content B). The suspension stability is evaluated based on the rate of suspension stability which can be given through the following formula.

Rate of suspension stability (%) =

(Content B)/(Content A) x 100

[0055]

(Test Result)

Change in Aspect

		Example 5	Reference example 1	Allermist nasal spray
before shake	upper layer	No phase separation between upper layer and lower layer. A white semi-transparent viscous suspension.	No phase separation between upper layer and lower layer. A white semi-transparent viscous suspension.	No phase separation between upper layer and lower layer. A white semi-transparent viscous suspension.
	lower layer			
immediately after shake	upper layer	No phase separation between upper layer and lower layer. A white semi-transparent viscous suspension.	No phase separation between upper layer and lower layer. A white semi-transparent viscous suspension.	No phase separation between upper layer and lower layer. A white semi-transparent viscous suspension.
	lower layer			
24 hours after shake	upper layer	No phase separation between upper layer and lower layer. A white semi-transparent viscous suspension.	A white opaque suspension.	A white opaque suspension.
	lower layer		A white opaque suspension. There was a small amount of precipitate at the vessel bottom.	A white opaque suspension. There was a small amount of precipitate at the vessel bottom.
one week after shake	upper layer	No phase separation between upper layer and lower layer. A white semi-transparent viscous suspension.	A white opaque suspension.	A white opaque suspension.
	lower layer		A white opaque suspension. There was a precipitate at the vessel bottom.	A white opaque suspension. There was a precipitate at the vessel bottom.
centrifugation (5000 rpm, 10 min) after shake	upper layer	No phase separation between upper layer and lower layer. A white semi-transparent viscous suspension.	A white opaque suspension.	A white opaque suspension.
	lower layer		A white opaque suspension. There was a volume of precipitate at the vessel bottom.	A white opaque suspension. There was a volume of precipitate at the vessel bottom.

Suspension Stability

		Example 5	Reference example 1	Allermist nasal spray
immediately after well stirring	upper layer	100.5 %	100.9 %	101.2 %
	lower layer	100.3 %	100.7 %	101.8 %
24 hours after shake	upper layer	100.1 %	101.4 %	101.4 %
	lower layer	100.8 %	100.2 %	101.0 %
one week after shake	upper layer	100.3 %	97.7 %	98.4 %
	lower layer	100.6 %	104.0 %	102.2 %
centrifugation (5000 rpm, 10 min) after shake	upper layer	100.2 %	77.3 %	88.4 %
	lower layer	100.5 %	105.3 %	107.6 %

[0056]

Stability test 2

Using Example 4 and Reference examples 2 to 6, the same test as Stability test 1 was carried out, in which the assay frequency was more than that of Stability test 1. The results are shown below.

Change in Aspect

		Example 4	Reference example 2	Reference example 3	Reference example 4	Reference example 5	Reference example 6
before shake	upper layer	No phase separation between upper layer and lower layer. A white semi-transparent viscous suspension.	A semi-transparent suspensible liquid	A transparent liquid	A white semi-transparent viscous suspension	A semi-transparent suspensible liquid	A transparent liquid
	lower layer		There was a small amount of precipitated crystal at the vessel bottom.	There was a precipitated crystal at the vessel bottom.	There was a slight amount of precipitated crystal at the vessel bottom.	There was a small amount of precipitated crystal at the vessel bottom.	There was a precipitated crystal at the vessel bottom.
immediately after shake	upper layer	No phase separation between upper layer and lower layer. A white semi-transparent viscous suspension.	No phase separation between upper layer and lower layer. A white semi-transparent viscous suspension.	No phase separation between upper layer and lower layer. A white semi-transparent viscous suspension.	No phase separation between upper layer and lower layer. A white semi-transparent viscous suspension.	No phase separation between upper layer and lower layer. A white semi-transparent viscous suspension.	No phase separation between upper layer and lower layer. A white semi-transparent viscous suspension.
	lower layer						
3 hours after shake	upper layer	No phase separation between upper layer and lower layer. A white semi-transparent viscous suspension.	A semi-transparent suspensible liquid	A semi-transparent suspensible liquid	No phase separation between upper layer and lower layer. A white semi-transparent viscous suspension.	A semi-transparent suspensible liquid	A transparent liquid
	lower layer		There was a small amount of precipitated crystal at the vessel bottom.	There was a precipitated crystal at the vessel bottom.		There was a small amount of precipitated crystal at the vessel bottom.	There was a precipitated crystal at the vessel bottom.

6 hours after shake	upper layer	No phase separation between upper layer and lower layer. A white semi-transparent viscous suspension.	A semi-transparent suspensible liquid	A transparent liquid	No phase separation between upper layer and lower layer. A white semi-transparent viscous suspension.	A semi-transparent suspensible liquid	A transparent liquid
	lower layer		There was a small amount of precipitated crystal at the vessel bottom.	There was a precipitated crystal at the vessel bottom.		There was a small amount of precipitated crystal at the vessel bottom.	There was a precipitated crystal at the vessel bottom.
24 hours after shake	upper layer	No phase separation between upper layer and lower layer. A white semi-transparent viscous suspension.	A semi-transparent suspensible liquid	A transparent liquid	A white semi-transparent viscous suspension	A semi-transparent suspensible liquid	A transparent liquid
	lower layer		There was a small amount of precipitated crystal at the vessel bottom.	There was a precipitated crystal at the vessel bottom.	There was a slight amount of precipitated crystal at the vessel bottom.	There was a small amount of precipitated crystal at the vessel bottom.	There was a precipitated crystal at the vessel bottom.
one week after shake	upper layer	No phase separation between upper layer and lower layer. A white semi-transparent viscous suspension.	A semi-transparent suspensible liquid	A transparent liquid	A white semi-transparent viscous suspension	A semi-transparent suspensible liquid	A transparent liquid
	lower layer		There was a precipitated crystal at the vessel bottom.	There was a precipitated crystal at the vessel bottom.	There was a slight amount of precipitated crystal at the vessel bottom.	There was a precipitated crystal at the vessel bottom.	There was a precipitated crystal at the vessel bottom.

centrifugation (5000 rpm, 10 min) after shake	upper layer	No phase separation between upper layer and lower layer. A white semi-transparent viscous suspension.	A semi-transparent suspensible liquid	A transparent liquid	A white semi-transparent viscous suspension	A transparent liquid	A transparent liquid
	lower layer		There was a precipitated crystal at the vessel bottom.	There was a precipitated crystal at the vessel bottom.	There was a small amount of precipitated crystal at the vessel bottom.	There was a precipitated crystal at the vessel bottom.	There was a precipitated crystal at the vessel bottom.

Suspension Stability

		Example 4	Reference example 2	Reference example 3	Reference example 4	Reference example 5	Reference example 6
immediately after well stirring	upper layer	100.3 %	99.3 %	96.2 %	98.7 %	100.5 %	101.6 %
	lower layer	100.8 %	100.1 %	101.9 %	100.1 %	99.2 %	100.1 %
24 hours after shake	upper layer	100.5 %	20.5 %	1.4 %	98.4 %	33.8 %	2.3 %
	lower layer	99.8 %	178.3 %	209.7 %	99.8 %	170.6 %	194.8 %
one week after shake	upper layer	100.5 %	18.4 %	0.6 %	97.1 %	6.8 %	1.2 %
	lower layer	100.1 %	188.6 %	199.2 %	104.3 %	192.7 %	199.0 %
centrifugation (5000 rpm, 10 min) after shake	upper layer	99.7 %	1.4 %	0.3 %	91.4 %	5.4 %	0.9 %
	lower layer	99.3 %	204.6 %	221.0 %	108.2 %	200.4 %	201.7 %

2019283247 18 Nov 2024

[0057] Throughout this specification and the claims which follow, unless the context requires otherwise, the word "comprise", and variations such as "comprises" and "comprising", will be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integers or steps.

[0058] The reference in this specification to any prior publication (or information derived from it), or to any matter which is known, is not, and should not be taken as an acknowledgment or admission or any form of suggestion that that prior publication (or information derived from it) or known matter forms part of the common general knowledge in the field of endeavour to which this specification relates.

2019283247 27 Feb 2025

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. An aqueous suspension for intranasal administration comprising fluticasone furoate and a carboxy vinyl polymer.

2. The aqueous suspension of claim 1, which contains 0.1 to 2 % (w/w) carboxy vinyl polymer.

3. The aqueous suspension of claim 1 or 2, which contains 0.005 to 1 % (w/w) fluticasone furoate.

4. The aqueous suspension of any one of claims 1 to 3, further comprising at least one suspending agent.

5. The aqueous suspension of claim 4, wherein the suspending agent comprises polysorbate 80.

6. The aqueous suspension of any one of claims 1 to 5, further comprising at least one antiseptic agent.

7. The aqueous suspension of claim 6, wherein the antiseptic agent comprises benzalkonium chloride.

8. The aqueous suspension of claim 6 or 7, wherein the antiseptic agent comprises disodium edetate.

2019283247 27 Feb 2025

9. The aqueous suspension of any one of claims 1 to 8, further comprising at least one tonicity agent.

10. The aqueous suspension of claim 9, wherein the tonicity agent comprises sodium chloride and/or glycerin.

11. The aqueous suspension of claim 9 or 10, which contains 0.1 to 10 % (w/w) tonicity agent.

12. The aqueous suspension of any one of claims 1 to 11, which is isotonic.

13. The aqueous suspension of any one of claims 1 to 12, wherein the pH of the aqueous suspension is 5 to 7.

14. The aqueous suspension of claim 13, further comprising a pH adjusting agent comprising sodium hydroxide and/or L-arginine.

15. The aqueous suspension of any one of claims 1 to 14, wherein the liquid particle size of the aqueous suspension has a mean particle size of 30 to 100 μm.

16. The aqueous suspension of claim 14 or 15, comprising: a suspending agent comprising polysorbate 80; an antiseptic

2019283247 27 Feb 2025

agent comprising disodium edetate and benzalkonium chloride; a tonicity agent comprising glycerin and sodium chloride; and a pH adjusting agent comprising L-arginine and sodium hydroxide.

17. A nasal-spray preparation comprising the aqueous suspension of any one of claims 1 to 16.

18. A method for stabilizing the suspensibility of an aqueous suspension comprising fluticasone furoate by adding to the aqueous suspension a carboxy vinyl polymer.

19. The method of claim 18, wherein the aqueous suspension is prepared as a nasal-spray preparation for intranasal administration.

20. Use of the aqueous suspension of any one of claims 1 to 16 for intranasal administration.