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(54) **NOVEL PREPARATION CONTAINING BENZIMIDAZOLE DERIVATIVE**

NEUARTIGES PRÄPARAT MIT BENZIMIDAZOLDERIVAT

NOUVELLE PRÉPARATION CONTENANT UN DÉRIVÉ DE BENZIMIDAZOLE

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(73) Proprietor: **HK inno.N Corporation**
Seoul 04551 (KR)

(72) Inventors:
- **LIM, Hyungsuk**
  Suwon-si
  Gyeonggi-do 16700 (KR)
- **LYU, Chun Seon**
  Yongin-si
  Gyeonggi-do 17072 (KR)
- **PARK, Sun Young**
  Yongin-si
  Gyeonggi-do 16959 (KR)
- **SHIN, Kyungmin**
  Seoul 05509 (KR)
- **OH, Da Won**
  Yongin-si
  Gyeonggi-do 16951 (KR)

(74) Representative: **Lederer & Keller Patentanwälte Partnerschaft mbB**
Unsöldstraße 2
80538 München (DE)

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Description

[Technical Field]

[0001] The present invention relates to a formulation for oral administration comprising a benzimidazole derivative or a pharmaceutically acceptable salt thereof; and at least one disintegrant selected from the group consisting of croscarmellose sodium, sodium starch glycolate and low-substituted hydroxypropylcellulose.

[Background Art]

[0002] It is obviously known in the art that even formulations comprising the same active component may show a difference in pharmaceutically important properties such as the solubility, dissolution characteristics and bioavailability of the active component comprised in the formulations depending on an additional constitutional component comprised therein. Thus, in addition to a development of a novel compound, it is also very important to develop a constituent comprised in a formulation so as to maximize a pharmacological effect of the novel, developed compound.

[0003] Meanwhile, (S)-4((5,7-difluorochroman-4-yl)oxy)-N,N-2-trimethyl-1H-benzo[d]imidazole-6-carboxamide is known to have a use for preventing and treating diseases mediated by an acid pump antagonistic activity, such as gastrointestinal diseases, for example, a gastroesophageal disease, a gastroesophageal reflux disease (GERD), a peptic ulcer, a gastric ucler, a duodenal ulcer, an NSAID-induced ulcer, gastritis, a Helicobacter pylori infection, dyspepsia, functional dyspepsia, Zollinger-Ellison syndrome, a nonerosive reflux disease (NERD), a visceral pain, purosis, nausea, esophagitis, dysphagia, salivation, an airway lesion or asthma (WO 2007/072146).

[0004] However, the above compound has a problem in that its bioavailability and onset of drug action may become instable due to a phenomenon of decline in dissolution rate with an elapsed time of storage, thus still requiring a more research on solving such problem.

[0005] WO2016/200148 discloses tablets of racemates thereof including croscarmellose sodium as disintegrant.

[Prior Art References]

[Patent Document]

[0006]

(Patent Document 1) International Patent No. WO 2007/072 146

(Patent Document 2) International Patent No. WO 2016/200 148

[Disclosure]

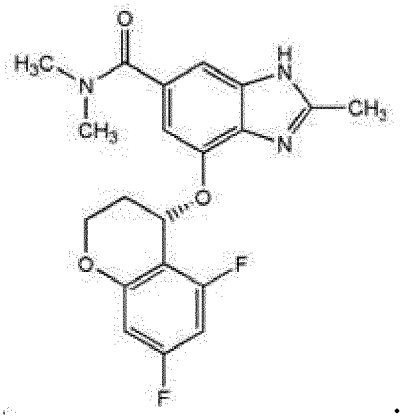
[Technical Problem]

[0007] The objective of the present invention is to provide a novel formulation comprising a benzimidazole derivative, which is protected from having a phenomenon of decline in dissolution rate and also has an excellent storage stability.

[Technical Solution]

[0008] In one aspect for solving the above problem, the present invention provides a formulation for oral administration comprising a compound of (S)-4((5,7-difluorochroman-4-yl)oxy)-N,N-2-trimethyl-1H-benzo[d]imidazole-6-carboxamide of the following Formula 1 or a pharmaceutically acceptable salt thereof; and at least one disintegrant selected from the group consisting of croscarmellose sodium, sodium starch glycolate and low-substituted hydroxypropylcellulose:

[Formula 1]



[0009] The above formulation for oral administration is a tablet.

[0010] In the present invention, a compound of the above Formula 1 is a novel substance for preventing and treating gastrointestinal diseases and bleeding associated therewith by means of a pharmacological mechanism of a potassium competitive acid blocker (P-CAB). The compound of the above Formula 1 has difficulty in effectively exerting its drug action because the compound shows a serious phenomenon of decline in dissolution rate with an elapsed time of storage.

[0011] Accordingly, the present inventors have tried to prepare the compound of the above Formula 1 into various formulations, thus, to our surprise, finding that a formulation, which uses croscarmellose sodium, sodium starch glycolate or low-substituted hydroxypropylcellulose as a disintegrant, is protected from having a phenomenon of decline in dissolution rate and exhibits an excellent storage stability at the same time, such that the compound could be used as a formulation, of which dissolution is stable and storage stability is secured as well. More particularly, the inventive compound of Formula 1 can be combined with specific disintegrants of croscarmellose sodium, sodium starch glycolate or low-substituted hydroxypropylcellulose, such that a storage stability of the inventive compound can be secured just by means of a simple preparation process without an addition of a stabilizer constituent for securing the storage stability of drugs, or without a special preparation process or packing process. By doing so, the inventive compound can be unaffected by packing and storage conditions, and its dissolution can be stable and its storage stability can be secured at pH 4.0, which corresponds to a biological environment in stomach and intestines.

[0012] In the present invention, the above "(S)-4((5,7-difluorochroman-4-yl)oxy)-N,N-2-trimethyl-1H-benzo[d]imidazole-6-carboxamide," which is a type of benzimidazole derivative, exhibits an acid pump inhibitory activity.

[0013] In the present invention, a pharmaceutically acceptable salt of the compound of the above Formula 1 can be a pharmaceutically acceptable acid-addition salt.

[0014] Particularly, the above acid-addition salt can be selected from the group consisting of acetate, adipate, aspartate, benzoate, besylate, bicarbonate/carbonate, bisulfate/ sulfate, borate, camsylate, citrate, cyclamate, edisylate, esylate, formate, fumarate, gluceptate, gluconate, glucuronate, hexafluorophosphate, hybenzate, hydrochloride/chloride, hydrobromide/bromide, hydroiodide/iodide, isethionate, lactate, malate, maleate, malonate, mesylate, methylsulfate, naphthalate, 2-napsylate, nicotinate, nitrate, orotate, palmitate, pamoate, phosphate/hydrogen phosphate/dihydrogen phosphate, pyroglutamate, saccharate, stearate, succinate, tannate, tartrate, tosylate, trifluoroacetate and xinafoate salts, but is not limited thereto, and a salt, which may conventionally exhibit a pharmacological activity of the compound of the above Formula 1, can be used without a limitation.

[0015] A content of the compound of the above Formula 1 comprised in the inventive formulation as an active component or pharmaceutically acceptable salt thereof can be amount to 10 to 140 mg, particularly 20 to 120 mg, or 10 to 40 wt% with regard to the total weight of the formulation, but is not limited thereto, and can be a conventional one, at which the above compound or the pharmaceutically acceptable salt thereof can exhibit its pharmacological activity.

[0016] The formulation of the present invention comprises at least one disintegrant selected from the group consisting of croscarmellose sodium, sodium starch glycolate and low-substituted hydroxypropylcellulose.

[0017] In the present invention, the above low-substituted hydroxypropylcellulose is formed as a low-substituted hydroxypropyl ether of cellulose, a substitution degree of hydropropoxy group can amount to 5 to 16 mass%.

[0018] In one embodiment of the present invention, as a result of identifying a storage stability of a formulation, which was prepared by using croscarmellose sodium, sodium starch glycolate or low-substituted hydroxypropylcellulose as a disintegrant, it could be seen that the formulation was excellent in its storage stability because the formulation produced almost no impurities even after being stored for 7 days under a stress condition (60°C, 80%RH) (Tables 7 and 8).

[0019] Also, in one embodiment of the present invention, as a result of identifying a dissolution rate of a formulation, which was prepared by using croscarmellose sodium, sodium starch glycolate or low-substituted hydroxypropylcellulose as a disintegrant, it could be seen that the formulation was stable in its dissolution because the formulation exhibited

almost no phenomenon of decline in dissolution rate under a condition similar to a biological environment in stomach and intestines, unlike a formulation, which was prepared by using crospovidone or Starch 1500 as a disintegrant (Tables 9 to 11 and FIGS. 1 to 4).

[0020] In the present invention, a content of the above disintegrant can be amount to 1 to 20 wt% with regard to the total weight of the formulation. If the content of the above disintegrant is comprised by less than 1 wt% with regard to the total weight of the formulation, a desired bioavailability rate cannot be obtained due to an excessive delay in disintegration, and if being comprised by more than 20 wt%, a property of the formulation and a quality conformance thereof cannot be secured due to its swelling phenomenon caused by a wetting property of the disintegrant.

[0021] The formulation according to the present invention can further comprise at least one selected from the group comprising a binder, a filler and a lubricant.

[0022] In the present invention, the term "filler" and "excipient" can be used interchangeably.

[0023] The formulation of the present invention comprises a binder, particularly wherein the binder can be at least one selected from the group comprising starch, microcrystalline cellulose, colloidal silicon dioxide, mannitol, lactose, polyethylen glycol, polyvinylpyrrolidone co-polymer, hydroxypropylcellulose, gelatin and a mixture thereof, and more particularly wherein it can be at least one selected from hydroxypropylcellulose, polyvinylpyrrolidone and copovidone.

[0024] A content of the above binder can be within a range of 1 to 40 wt% with regard to the total weight of the formulation. If the content of the above binder amounts to less than 1 wt%, it is difficult to prepare a granule having a desired hardness and size due to a lack of agglutination of the formulation. If the content amounts to more than 40 wt%, a desired bioavailability cannot be obtained due to an excessive delay in disintegration.

[0025] The formulation of the present invention comprises a filler, particularly wherein the filler can be at least one selected from the group comprising lactose, microcrystalline cellulose, mannitol and colloidal silicon dioxide, and more particularly wherein it can be one selected from the group comprising mannitol, microcrystalline cellulose and lactose, but is not limited thereto, and may be one conventionally used in the art.

[0026] A content of the above filler can be one conventionally used in the art, particularly wherein it can be properly chosen within a range of 1 to 99 wt% with regard to the total weight of the formulation.

[0027] The formulation of the present invention comprises a lubricant, particularly wherein the lubricant can be at least one selected from the group comprising stearic acid, magnesium stearate, calcium stearate, sodium benzoate, sodium stearyl fumarate, glyceryl monooleate, glyceryl monostearate, glyceryl behenate, glyceryl palmitostearate, zinc stearate and paraffin group, and more particularly wherein it can be magnesium stearate, but is not limited thereto and maybe one conventionally used in the art.

[0028] A content of the above lubricant can be one conventionally used in the art, particularly wherein it can be properly chosen within a range of 0.5 to 10 wt% with regard to the total weight of the formulation.

[0029] The formulation of the present invention can be coated with a film coating agent, wherein the coating agent can be constituted by 0.5 to 10 wt% with regard to the total weight of the formulation.

[0030] In other aspect for solving the above problem, the present invention provides the use of a formulation comprising a compound of (S)-4((5,7-difluorochroman-4-yl)oxy)-N,N-2-trimethyl-1H-benzo[d]imidazole-6-carboxamide of Formula 1 or a pharmaceutically acceptable salt thereof; and at least one disintegrant selected from the group consisting of croscarmellose sodium, sodium starch glycolate and low-substituted hydroxypropylcellulose for oral administration.

[Advantageous Effects]

[0031] A formulation comprising a compound of Formula 1 according to the present invention or a pharmaceutically acceptable salt thereof; and at least one disintegrant selected from the group consisting of croscarmellose sodium, sodium starch glycolate, and low-substituted hydroxypropylcellulose, exhibits an excellent storage stability and has an effect on preventing a phenomenon of decline in dissolution rate, thus being usefully used as a formulation for oral administration.

[Description of Drawings]

[0032]

FIG. 1 illustrates a graph of comparing dissolution rates of a tablet according to Example 1 with each other, respectively under initial and stress conditions, wherein the Example 1 comprises croscarmellose sodium.

FIG. 2 illustrates a graph of comparing dissolution rates of a tablet according to Example 12 with each other, respectively under initial and stress conditions, wherein the Example 12 comprises low-substituted hydroxypropylcellulose.

FIG. 3 illustrates a graph of comparing dissolution rates of a tablet according to Comparative Example 1 with each other, respectively under initial and stress conditions, wherein the Comparative Example 1 comprises crospovidone.

FIG. 4 illustrates a graph of comparing dissolution rates of a tablet according to Comparative Example 2 with each other, respectively under initial and stress conditions, wherein the Comparative Example 2 comprises Starch 1500.

[Mode for Invention]

[0033] Hereinafter, configuration and effects of the present invention will be described in more detail through preparation examples, examples and experimental examples. However, the following preparation examples, examples and experimental examples are provided only for the purpose of illustrating the present invention, and thus the present invention is not limited thereto.

Preparation Example 1: Preparing of a Tablet Containing Croscarmellose Sodium

[0034] A method for preparing a tablet of Example 1 is as follows.

[0035] A main active ingredient (S)-4((5,7-difluorochroman-4-yl)oxy)-N,N-2-trimethyl-1H-benzo[d]imidazole-6-carboxamide was mixed with mannitol, microcrystalline cellulose and croscarmellose sodium. Then, a binder solution comprising hydroxypropylcellulose and distilled water was added to a mixture resulting from the above mixing process, then a kneading and drying process, and then an sizing was carried out. After that, a substance resulting from the above sizing process was mixed with colloidal silicon dioxide and magnesium stearate, after which a resulting mixture was compressed into and prepared as a tablet. Contents of components comprised in the tablet of the above Example 1 are such as those shown in the following Table 1.

[0036] Tablets of Examples 2 and 3 were prepared by respectively using lactose and starch instead of mannitol, in comparison with the tablet of Example 1, but, except for that, they were prepared by means of the same method for preparing a tablet as described in the above Example 1. Contents of components comprised in the tablets of the above Examples 2 and 3 are such as those shown in the following Table 1.

[0037] Tablets of Examples 4 and 5 were prepared by respectively using polyvinylpyrrolidone and copovidone instead of hydroxypropylcellulose, in comparison with the tablet of Example 1, but, except for that, they were prepared by means of the same method for preparing a tablet as described in the above Example 1. Contents of components comprised in the tablets of the above Examples 4 and 5 are such as those shown in the following Table 1.

[0038] Tablets of Examples 6 to 9 were prepared by varying an amount of croscarmellose sodium, in comparison with the tablet of Example 1, but, except for that, they were prepared by means of the same method for preparing a tablet as described in the above Example 1. Contents of components comprised in the tablets of the above Examples 6 to 9 are such as those shown in the following Table 1.

[0039] A tablet of Example 10 was prepared by doubling an amount of a main active ingredient, in comparison with the tablet of Example 1, but, except for that, they were prepared by means of the same method for preparing a tablet as described in the above Example 1. Contents of components contained in the tablet of the above Example 10 are such as those shown in the following Table 1.

[Table 1]

Classification	Component	Example (Amount Used, mg)									
		1	2	3	4	5	6	7	8	9	10
Main active ingredient	(S)-4((5,7-difluorochroman-4-yl)oxy)-N,N-2-trimethyl-1H-benzo[d] imidazole-6-carboxamide	50	50	50	50	50	50	50	50	50	100
Excipient	Mannitol	50	-	-	50	50	54	44	40	30	100
	Lactose	-	62	-	-	-	-	-	-	-	-
	Starch	-	-	62	-	-	-	-	-	-	-
	Microcrystalline cellulose	80	68	68	80	80	80	80	80	80	160
	Colloidal silicon dioxide	2	2	2	2	2	2	2	2	2	4
Disintegrant	Croscarmellose sodium	10	10	10	10	10	6	16	20	30	20
Binder	Hydroxypropylcellulose	6	6	6	-	-	6	6	6	6	12
	Polyvinylpyrrolidone	-	-	-	6	-	-	-	-	-	-
	Copovidone	-	-	-	-	6	-	-	-	-	-
Lubricant	Magnesium stearate	2	2	2	2	2	2	2	2	2	4
Total Weight		200	200	200	200	200	200	200	200	200	400

Preparation Example 2: Preparing of a Tablet Containing Sodium Starch Glycolate

[0040] Tablets of Examples 11 and 12 were prepared by using sodium starch glycolate instead of croscarmellose sodium as a disintegrant in comparison with the tablet of Example 1, but, except for that, they were prepared by means of the same method for preparing a tablet as described in the above Example 1. Contents of components comprised in the tablets of the above Examples 11 and 12 are such as those shown in the following Table 2.

[Table 2]

Classification	Component	Example (Amount Used, mg)	
		11	12
Main active ingredient	(S)-4((5,7-difluorochroman-4-yl)oxy)-N,N-2-trimethyl-1H-benzo[d] imidazole-6-carboxamide	50	50
Excipient	Mannitol	50	62
	Microcrystalline cellulose	80	58
	Colloidal silicon dioxide	2	2
Disintegrant	Sodium starch glycolate	10	20
Binder	H ydroxypropylcellulose	6	6
Lubricant	Magnesium stearate	2	2
Total Weight		200	200

Preparation Example 3: Preparing of a Tablet Containing Low-Substituted Hydroxypropylcellulose

[0041] A tablet of Example 13 was prepared by using low-substituted hydroxypropylcellulose instead of croscarmellose sodium as a disintegrant in comparison with the tablet of Example 1, but, except for that, they were prepared by means of the same method for preparing a tablet as described in the above Example 1. Contents of components comprised in the tablet of the above Example 13 are such as those shown in the following Table 3.

[Table 3]

Classification	Component	Example 13 (Amount Used, mg)
Main active ingredient	(S)-4((5,7-difluorochroman-4-yl)oxy)-N,N-2-trimethyl-1H-benzo[d] imidazole-6-carboxamide	50
Excipient	Mannitol	50
	Microcrystalline cellulose	80
	Colloidal silicon dioxide	2
Disintegrant	Low-substituted hydroxypropylcellulose	10
Binder	Hydroxypropylcellulose	6
Lubricant	Magnesium stearate	2
Total Weight		200

Preparation Example 4: Preparing of a Simple Mix Tablet Containing Sodium Starch Glycolate

[0042] An excipient and a disintegrant, including a main active ingredient, were simply mixed and sized, after which a lubricant was further mixed therewith and a resulting mixture was pressed into a tablet, such that the tablet for oral administration of Example 14 was prepared. Contents of components comprised in the tablet of the above Example 14 are such as those shown in the following Table 4.

[Table 4]

Classification	Component	Example 14 (Amount Used, mg)
Main active ingredient	(S)-4((5,7-difluorochroman-4-yl)oxy)-N,N-2-trimethyl-1H-benzo[d]imidazole-6-carboxamide	50
Excipient	Lactose	84
	Silicified microcrystalline cellulose	56
	Colloidal silicon dioxide	2
Disintegrant	Sodium starch glycolate	6
Lubricant	Magnesium stearate	2
Total Weight		200

Preparation Example 5: Preparing of a Tablet Containing Crospovidone

[0043] A tablet for oral administration of Comparative Example 1, which used crospovidone as a disintegrant, was prepared by means of the same method for preparing a tablet as described in Example 1, with contents of components shown in the following Table 5.

[Table 5]

Classification	Component	Comparative Example 1 (Amount Used, mg)
Main active ingredient	(S)-4((5,7-difluorochroman-4-yl)oxy)-N,N-2-trimethyl-1H-benzo[d]imidazole-6-carboxamide	50
Excipient	Mannitol	62
	Microcrystalline cellulose	68
	Colloidal silicon dioxide	2
Binder	Hydroxypropylcellulose	6
Disintegrant	Crospovidone	10
Lubricant	Magnesium stearate	2
Total Weight		200

Preparation example 6: Preparing of a Tablet Containing Starch 1500

[0044] A tablet for oral administration of Comparative Example 2, which used Starch 1500 as a disintegrant, was prepared by means of the same method for preparing a tablet as described in Example 1, with contents of components shown in the following Table 6.

[Table 6]

Classification	Component	Comparative Example 1 (Amount Used, mg)
Main active ingredient	(S)-4((5,7-difluorochroman-4-yl)oxy)-N,N-2-trimethyl-1H-benzo[d]imidazole-6-carboxamide	50
Excipient	Mannitol	50
	Microcrystalline cellulose	80
	Colloidal silicon dioxide	2

(continued)

Classification	Component	Comparative Example 1 (Amount Used, mg)
Binder	Hydroxypropylcellulose	6
Disintegrant	Starch 1500	10
Lubricant	Magnesium stearate	2
Total Weight		200

Experimental Example 1: Storage Stability Test

[0045] Tablets of Examples 1 to 14, prepared according to the above Preparation Examples 1 to 4, were inserted into each of high-density polyethylene (HDPE) bottles, after which resulting bottles were stored under a stress condition (60°C, 80%RH) for

[0046] 7 days, such that properties of the tablets were identified and a purity test thereof was carried out as well.

(1) Impurity Test Evaluation on Tablet Comprising Croscarmellose Sodium

[0047] Particularly, as a result of carrying out an evaluation on the occurrence or increase of impurities after the storage of the tablets of Examples 1 to 10, as prepared by using croscarmellose sodium as a disintegrant, no pattern of occurrence or increase of impurities was identified in all the tablets of Examples 1 to 10 (Table 7).

[Table 7]

Component (%)		Example						
		1	2	3	4	5	9	10
Initial Condition	Content (API)	99.94	99.94	99.81	99.94	99.79	99.93	100.00
	Total impurities	0.06	0.06	0.19	0.06	0.21	0.07	0.00
Stress Condition Storage for 7 Days	Content (API)	99.94	99.94	99.80	99.94	99.81	99.93	99.98
	Total impurities	0.06	0.06	0.2	0.06	0.19	0.07	0.02

[0048] Accordingly, the formulation comprising the compound of Formula 1, which used croscarmellose sodium as a disintegrant, produced almost no impurities, thus identifying that the formulation was excellent in storage stability.

(2) Purity Test Evaluation on Tablet Comprising Sodium Starch Glycolate or Low-Substituted Hydroxypropylcellulose

[0049] Particularly, as a result of carrying out an evaluation on a production or increase of impurities after the storage of the tablets of Examples 11 to 12, as prepared by using sodium starch glycolate as a disintegrant, as well as the tablet of Example 13, as prepared by using low-substituted hydroxypropylcellulose as a disintegrant, it was identified that no pattern of occurrence or increase of impurities was identified in all the tablets of the Examples 11 to 13 (Table 8).

[Table 8]

Component (%)		Example	
		11	13
Initial Condition	Content (API)	99.84	99.94
	Total impurities	0.16	0.06
Stress Condition Storage for 7 Days	Content (API)	99.83	99.93
	Total impurities	0.17	0.07

[0050] Accordingly, a formulation comprising the compound of Formula 1, which used sodium starch glycolate or low-substituted hydroxypropylcellulose as a disintegrant, produced almost no impurities, thus identifying that the formulation was excellent in storage stability.

Experimental Example 2: Dissolution Stability Test

[0051] Tablets of Examples 1 to 14, prepared according to the above Preparation Examples 1 to 4, were inserted into each of high-density polyethylene (HDPE) bottles, after which resulting bottles were stored under a stress condition (60°C, 80%RH) for 7 days, such that an in vitro dissolution test and an HPLC analysis were carried out.

(1) Evaluation on Dissolution Rate of Tablet Comprising Croscarmellose Sodium

[0052] Particularly, a dissolution experiment was carried out on tablets of Examples 1 to 10, as prepared by using croscarmellose sodium as a disintegrant, wherein conditions for the dissolution experiment were such as those described below:

1) Basis of dissolution test: Dissolution test method in general test methods in the 11th Revision of the Korean Pharmacopoeia
2) Dissolution test method: Dissolution test method II, paddle method
3) Dissolution test solution: 900 ml of pH 4.0 acetate buffer solution
4) Temperature condition: Maintained at 37.2°C±0.5°C
5) Analysis method: HPLC method

- Detector: Ultraviolet absorptiometer (measurement wavelength: 262 nm)
- Column: C18 5 um / 4.6 x 150 mm column
- Mobile phase: Acetonitrile: Distilled water [gradient]

[0053] As a result of comparing dissolution rates with each other at a time of 15 minutes after onset of dissolution, it was found that the dissolution rates fall within the specified criteria, and it was identified that there occurred no phenomenon of decline in dissolution rate in all the tablets of the Examples 1 to 10 (Table 9 and FIG. 1).

[Table 9]

Time (15 Minutes)	Example									
	1	2	3	4	5	6	7	8	9	10
Dissolution Rate (%) under Initial Condition	85.0	80.6	80.7	86.5	81.5	85.0	88.8	86.0	81.9	77.1
Dissolution Rate (%) under Stress Condition (7 days in storage)	85.7	78.1	75.5	84.0	85.1	81.3	89.4	84.2	82.0	76.6

(2) Evaluation on Dissolution Rate of Tablet Comprising Sodium Starch Glycolate or Low-Substituted Hydroxypropylcellulose

[0054] Particularly, a dissolution experiment was carried out on tablets of Examples 11, 12 and 14, as prepared by using sodium starch glycolate as a disintegrant, as well as a tablet of Example 13, as prepared by using low-substituted hydroxypropylcellulose as a disintegrant, wherein conditions for the dissolution experiment were such as those described below:

1) Basis of dissolution test: Dissolution test method in general test methods in the 11th Revision of the Korean Pharmacopoeia
2) Dissolution test method: Dissolution test method II, paddle method
3) Dissolution test solution: 900 ml of pH 4.0 acetate buffer solution
4) Temperature condition: Maintained at 37.2°C±0.5°C
5) Analysis method: HPLC method

- Detector: Ultraviolet absorptiometer (measurement wavelength: 262 nm)
- Column: C18 5 um / 4.6 x 150 mm column
- Mobile phase: Acetonitrile: Distilled water [gradient]

[0055] As a result of comparing dissolution rates with each other at a time of 15 minutes after onset of dissolution, it was found that the dissolution rates fall within the specified criteria, it was identified that there occurred no phenomenon of decline in dissolution rate in all the tablets of the Examples 11 to 14 (Table 10 and FIG. 2).

[Table 10]

Time (15 Minutes)	Example			
	11	12	13	14
Dissolution Rate (%) under Initial Condition	85.5	84.8	76.8	81.1
Dissolution Rate (%) under Stress Condition (7 days in storage)	82.3	84.7	75.3	79.6

(3) Evaluation on Dissolution Rate of Tablet Comprising Crospovidone or Starch 1500

[0056] Particularly, a dissolution experiment was carried out on tablets of Comparative Examples 1 and 2, as prepared by using crospovidone or Starch 1500 as a disintegrant, wherein conditions for the dissolution experiment were such as those described below:

1) Basis of dissolution test: Dissolution test method out of general test methods in the 11th Revision of the Korean Pharmacopoeia
2) Dissolution test method: Dissolution test method II, paddle method
3) Dissolution test solution: 900 ml of pH 4.0 acetate buffer solution
4) Temperature condition: Maintained at 37.2°C±0.5°C
5) Analysis method: HPLC method

- Detector: Ultraviolet absorptiometer (measurement wavelength: 262 nm)
- Column: C18 5 um / 4.6 x 150 mm column
- Mobile phase: Acetonitrile: Distilled water [gradient]

[0057] As a result of comparing dissolution rates with each other at a time of 15 minutes after onset of dissolution, it was identified that there occurred a phenomenon of decline in dissolution rate after storage in the stress condition in comparison with the initial condition (Table 11 and FIGS. 3 and 4).

[Table 11]

Time (15 Minutes)	Comparative Example	
	1	2
Dissolution Rate (%) under Initial Condition	85.2	61.7
Dissolution Rate (%) under Stress Condition (7 days in storage)	68.6	40.3

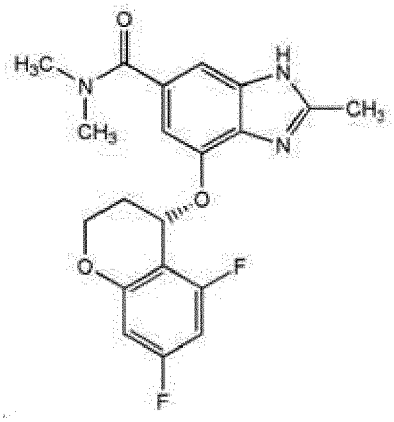
[0058] According to the Experimental Example 2 above, it was identified that the formulation, as prepared by using croscarmellose sodium, sodium starch glycolate or low-substituted hydroxypropylcellulose as a disintegrant, showed almost no phenomenon of decline in dissolution rate at pH 4.0, which is a biological environment in stomach and intestines, when compared to the formulation, as prepared by using crospovidone or Starch 1500 as a disintegrant.

[0059] While certain portions of the present invention have been described in detail above, such specific descriptions are set forth only to illustrate preferred exemplary embodiments, so it is obvious to those skilled in the art that the scope of the present invention is not limited thereto.

Claims

1. A formulation for oral administration comprising a compound of (S)-4((5,7-difluorochroman-4-yl)oxy)-N,N-2-trimethyl-1H-benzo[d]imidazole-6-carboxamide of Formula 1 or a pharmaceutically acceptable salt thereof; and at least one disintegrant selected from the group consisting of croscarmellose sodium, sodium starch glycolate and low-substituted hydroxypropylcellulose,
wherein the formulation is a tablet:

[Formula 1]



2. The formulation for oral administration according to claim 1, wherein the disintegrant is contained by 1 to 20 wt% with regard to the total weight of the formulation.

3. The formulation for oral administration according to claim 1, wherein the low-substituted hydroxypropylcellulose is that a substitution degree of a hydroxypropoxy group amounts to 5 to 16 mass%.

4. The formulation for oral administration according to claim 1, wherein the formulation further comprises at least one selected from the group comprising a binder, a filler and a lubricant.

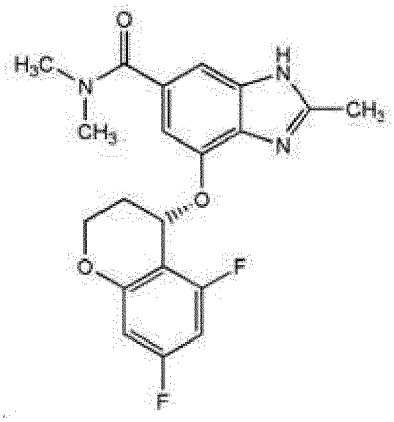
5. The formulation for oral administration according to claim 4, wherein the binder is at least one selected from the group comprising starch, microcrystalline cellulose, colloidal silicon dioxide, mannitol, lactose, polyethylen glycol, polyvinyl pyrrolidone co-polymer, hydroxypropyl cellulose, gelatin and a mixture thereof.

6. The formulation for oral administration according to claim 4, wherein the filler is at least one selected from the group comprising lactose, microcrystalline cellulose, mannitol and colloidal silicon dioxide.

7. The formulation for oral administration according to claim 4, wherein the lubricant is at least one selected from the group comprising stearic acid, magnesium stearate, calcium stearate, sodium benzoate, sodium stearyl fumarate, glyceryl monooleate, glyceryl monostearate, glyceryl behenate, glyceryl palmitostearate, zinc stearate and a paraffin group.

8. The use of a formulation comprising a compound of (S)-4((5,7-difluorochroman-4-yl)oxy)-N,N-2-trimethyl-1H-benzo[d]imidazole-6-carboxamide of Formula 1 or a pharmaceutically acceptable salt thereof; and at least one disintegrant selected from the group consisting of croscarmellose sodium, sodium starch glycolate and low-substituted hydroxypropylcellulose for oral administration,
wherein the formulation is a tablet:

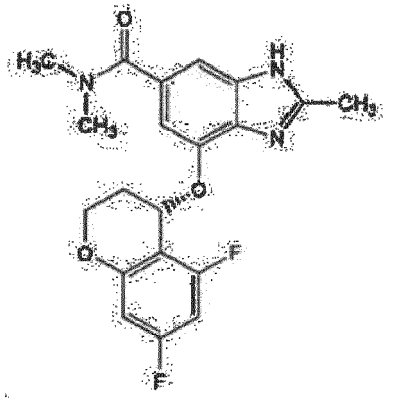
[Formula 1]



Patentansprüche

1. Formulierung zur oralen Verabreichung, umfassend die Verbindung (S)-4((5,7-Difluorchroman-4-yl)oxy)-N,N-2-trimethyl-1H-benzo[d]imidazol-6-carboxamid der Formel 1 oder ein pharmazeutisch akzeptables Salz davon und mindestens eine den Zerfall bewirkende Substanz, ausgewählt aus der Gruppe, bestehend aus Croscarmellose-Natrium, Natriumstärkeglycolat und niedrig substituierter Hydroxypropylcellulose,
wobei die Formulierung eine Tablette ist:

[Formel 1]



2. Formulierung zur oralen Verabreichung nach Anspruch 1, wobei die den Zerfall bewirkende Substanz mit 1 bis 20 Gew.-% bezogen auf das Gesamtgewicht der Formulierung enthalten ist.

3. Formulierung zur oralen Verabreichung nach Anspruch 1, wobei niedrig substituierte Hydroxypropylcellulose bedeutet, dass ein Substitutionsgrad einer Hydroxypropoxygruppe 5 bis 16 Masse-% ausmacht.

4. Formulierung zur oralen Verabreichung nach Anspruch 1, wobei die Formulierung ferner mindestens eines, ausgewählt aus der Gruppe, umfassend ein Bindemittel, einen Füllstoff und ein Schmiermittel, umfasst.

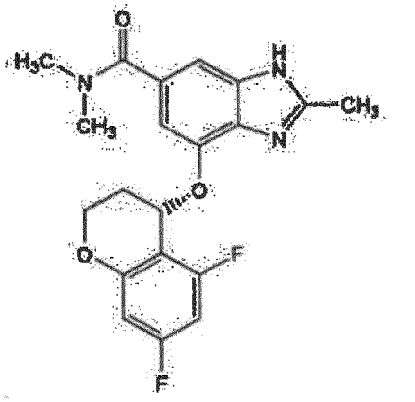
5. Formulierung zur oralen Verabreichung nach Anspruch 4, wobei das Bindemittel mindestens eines, ausgewählt aus der Gruppe, umfassend Stärke, mikrokristalline Cellulose, kolloidales Siliciumdioxid, Mannitol, Lactose, Polyethylenglycol, Polyvinylpyrrolidoncopolymer, Hydroxypropylcellulose, Gelatine und ein Gemisch davon, ist.

6. Formulierung zur oralen Verabreichung nach Anspruch 4, wobei der Füllstoff mindestens einer, ausgewählt aus der Gruppe, umfassend Lactose, mikrokristalline Cellulose, Mannitol und kolloidales Siliciumdioxid, ist.

7. Formulierung zur oralen Verabreichung nach Anspruch 4, wobei das Schmiermittel mindestens eines, ausgewählt aus der Gruppe, umfassend Stearinsäure, Magnesiumstearat, Calciumstearat, Natriumbenzoat, Natriumstearylfumarat, Glycerylmonooleat, Glycerylmonostearat, Glycerylbehenat, Glycerylpalmitostearat, Zinkstearat und eine Paraffingruppe, ist.

8. Verwendung einer Formulierung, umfassend die Verbindung (S)-4((5,7-Difluorchroman-4-yl)oxy)-N,N-2-trimethyl-1H-benzo[d]imidazol-6-carboxamid der Formel 1 oder ein pharmazeutisch akzeptables Salz davon und mindestens eine den Zerfall bewirkende Substanz, ausgewählt aus der Gruppe, bestehend aus Croscarmellose-Natrium, Natriumstärkeglycolat und niedrig substituierter Hydroxypropylcellulose, zur oralen Verabreichung,
wobei die Formulierung eine Tablette ist:

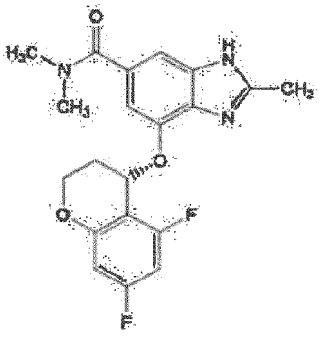
[Formel 1]



Revendications

1. Formulation pour administration orale comprenant un composé de (S)-4((5,7-difluorochroman-4-yl)oxy)-N,N-2-triméthyl-1H-benzo[d]imidazole-6-carboxamide de Formule 1 ou un sel pharmaceutiquement acceptable de celui-ci; et au moins un désintégrant choisi dans le groupe constitué de croscarmellose sodique, glycolate d'amidon sodique et hydroxypropylcellulose faiblement substituée,
dans laquelle la formulation est un comprimé :

[Formule 1]



2. Formulation pour administration orale selon la revendication 1, dans laquelle le désintégrant est contenu à raison de 1 à 20 % en poids par rapport au poids total de la formulation.

3. Formulation pour administration orale selon la revendication 1, dans laquelle l'hydroxypropylcellulose faiblement substituée est telle que le degré de substitution d'un groupe hydroxypropoxy s'élève à 5 à 16 % en masse.

4. Formulation pour administration orale selon la revendication 1, dans laquelle la formulation comprend en outre au moins un élément choisi dans le groupe comprenant un liant, une charge et un lubrifiant.

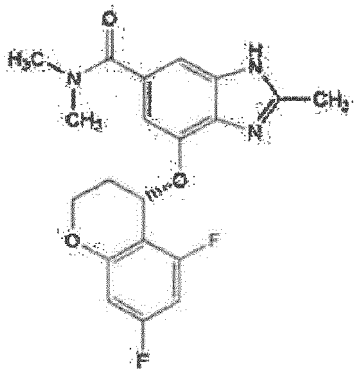
5. Formulation pour administration orale selon la revendication 4, dans laquelle le liant est au moins un élément choisi dans le groupe comprenant l'amidon, la cellulose microcristalline, le dioxyde de silicium colloïdal, le mannitol, le lactose, le polyéthylèneglycol, le copolymère de polyvinylpyrrolidone, l'hydroxypropylcellulose, la gélatine et un mélange de ceux-ci.

6. Formulation pour administration orale selon la revendication 4, dans laquelle la charge est au moins une charge choisie dans le groupe comprenant le lactose, la cellulose microcristalline, le mannitol et le dioxyde de silicium colloïdal.

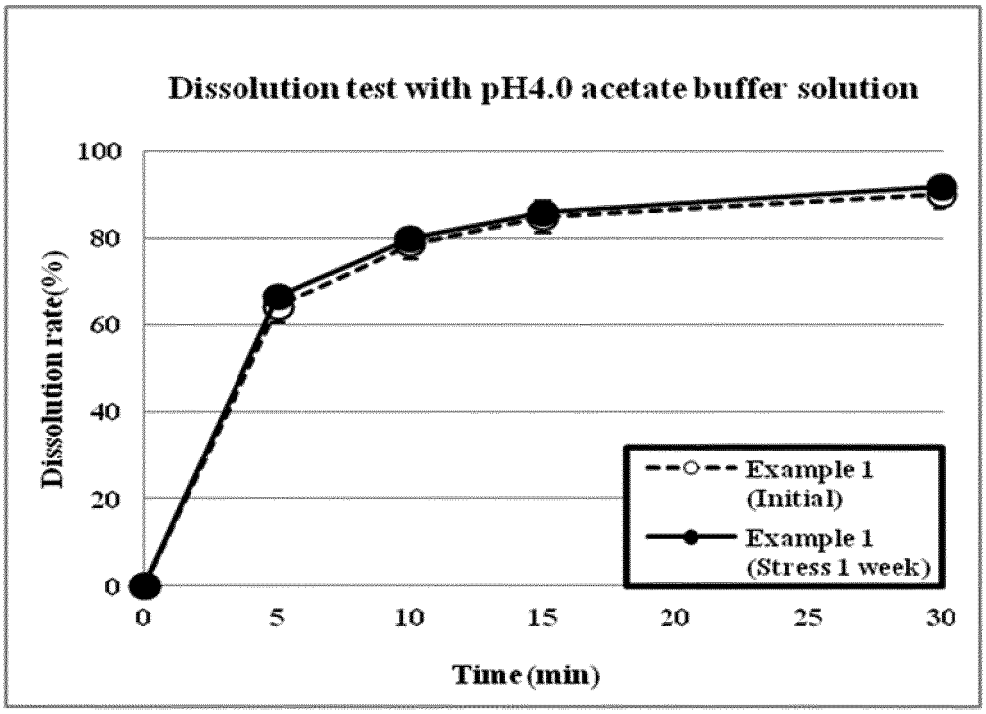
7. Formulation pour administration orale selon la revendication 4, dans laquelle le lubrifiant est au moins un élément choisi dans le groupe comprenant l'acide stéarique, le stéarate de magnésium, le stéarate de calcium, le benzoate de sodium, le fumarate de stéaryle de sodium, le monooléate de glycéryle, le monostéarate de glycéryle, le béhénate de glycéryle, le palmitostéarate de glycéryle, le stéarate de zinc et un groupe paraffine.

8. Utilisation d'une formulation comprenant un composé de (S)-4((5,7-difluorochroman-4-yl)oxy)-N,N-2-triméthyl-1H-benzo[d]imidazole-6-carboxamide de formule 1 ou un sel pharmaceutiquement acceptable de celui-ci ; et au moins un désintégrant choisi dans le groupe constitué de croscarmellose sodique, glycolate d'amidon sodique et hydroxypropylcellulose faiblement substituée pour une administration orale,
dans laquelle la formulation est un comprimé :

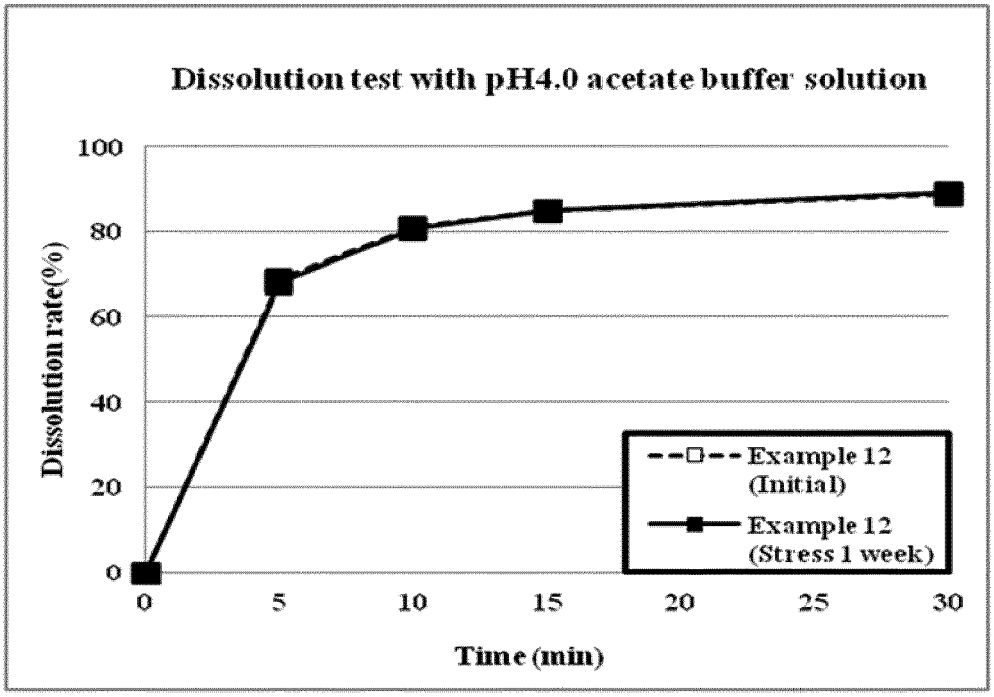
[Formule 1]



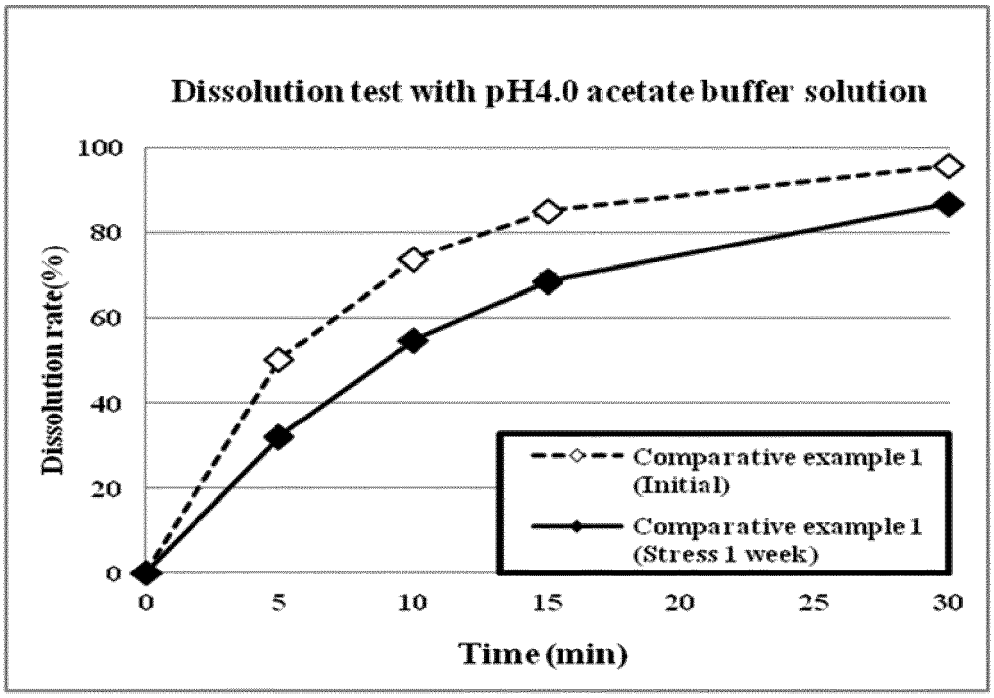
【Figure 1】


Dissolution test with pH4.0 acetate buffer solution
Dissolution rate(%)
100
80
60
40
20
0
0
5
10
15
20
25
30
Time (min)
Example 1 (Initial)
Example 1 (Stress 1 week)

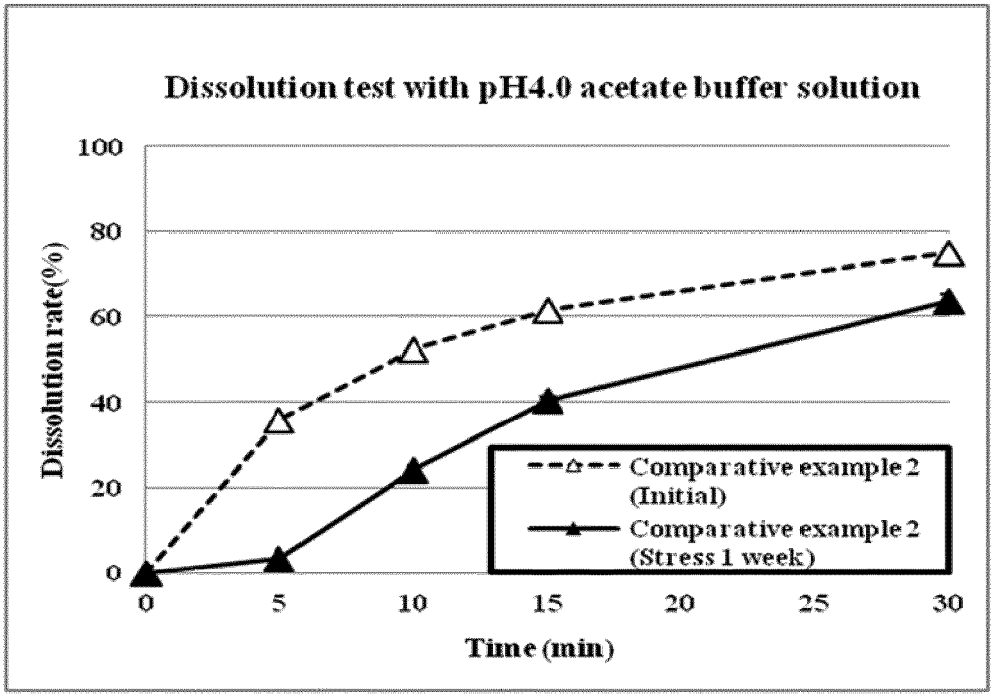
【Figure 2】


Dissolution test with pH4.0 acetate buffer solution
Dissolution rate(%)
100
80
60
40
20
0
0
5
10
15
20
25
30
Time (min)
Example 12 (Initial)
Example 12 (Stress 1 week)

【Figure 3】


Dissolution test with pH4.0 acetate buffer solution
Dissolution rate(%)
100
80
60
40
20
0
0
5
10
15
20
25
30
Time (min)
Comparative example 1 (Initial)
Comparative example 1 (Stress 1 week)

【Figure 4】


Dissolution test with pH4.0 acetate buffer solution
Dissolution rate(%)
100
80
60
40
20
0
0
5
10
15
20
25
30
Time (min)
Comparative example 2 (Initial)
Comparative example 2 (Stress 1 week)

REFERENCES CITED IN THE DESCRIPTION

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Patent documents cited in the description

- WO 2007072146 A **[0003] [0006]**
- WO 2016200148 A **[0005] [0006]**