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(54) **COATED SOLID PREPARATION**

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Description

TECHNICAL FIELD

5 **[0001]** The present invention relates to a coated solid preparation.

BACKGROUND ART

10 **[0002]** Leukotriene is a lipid mediator produced from arachidonic acid by 5-lipoxygenase and involved in inflammation and contraction of airway muscle and decrease/accumulation of the fluid amount in lung. Leukotriene C4, D4, and E4, which contain cysteine in their molecules, are called cysteinyl leukotriene, and cysteinyl leukotriene 1 (hereinafter referred to as "CysLT1") receptor and cysteinyl leukotriene 2 (hereinafter referred to as "CysLT2") receptor are known as a receptor thereof. CysLT1 receptors and CysLT2 receptors, both of which are expressed in mastocytes, eosinophils, and endothelial cells, induce inflammation in endothelial cells under the stimulus of cysteinyl leukotriene, provide stimulation of chemokine production by mast cells, and are responsible for causing bronchial asthma and inflammatory disease.

15 **[0003]** Montelukast is an orally-active leukotriene receptor antagonist that selectively inhibits CysLT1 receptors. Sodium salts of montelukast (hereinafter referred to as "montelukast sodium") have been used as a useful therapeutic agent for respiratory disease, asthma, and allergic rhinitis. However, montelukast sodium has very high hygroscopicity, and it has been reported that Singulair (registered trademark) tablets and Kipres (registered trademark) tablets, which are commercially available as a pharmaceutical, have a problem in that they cause delayed disintegration and delayed dissolution due to moisture absorption upon storage for 4 weeks under conditions of 25°C and a relative humidity of 85% (hereinafter referred to as "85% RH") (Non-patent Document 1).

20 **[0004]** As a method of improving the hygroscopicity of montelukast sodium, using montelukast sodium after converting it into free acid has been reported (Patent Document 1). However, a method of improving the hygroscopicity of montelukast sodium using a formulation approach has not been reported yet.

25 **[0005]** In general, as a method of improving hygroscopic stability of a solid preparation, sugar-coating of a solid preparation and film-coating of a solid preparation with a macromolecular substance have been put to practical use. For the latter film-coating, an aminoalkyl methacrylate copolymer E (Eudragit EPO (registered trademark); Degussa) is known as a macromolecular substance that exhibits moisture barrier properties, and a film coating agent having an improved moisture barrier performance by adding stearic acid to an aminoalkyl methacrylate copolymer E (Patent Document 2) have been developed.

30 **[0006]** Even in the case where a solid preparation is not coated directly with a film, there is the case where hygroscopic stability is secured by packaging with packaging materials having high water vapor barrier properties. Examples of such a case include the case where a solid preparation is indirectly protected from moisture by placing the solid preparation in a PTP (press through pack) sheet laminated with polyvinylidene chloride and sealing the sheet.

35 **[0007]** On the other hand, from the standpoint of preventing forgetting to take prescribed drugs or taking a wrong dose, one-dose packages have been widely used at clinical sites and dispensing pharmacies recently. One-dose packages are provided to patients in such a manner that a pharmacist takes out a plurality of solid preparations to be taken in one dose from a packaging material such as a PTP sheet and puts them in one package for each patient. In addition, in western countries, patients often subdivide a pharmaceutical taken out from a package such as a PTP sheet for storage in a pill case or the like, and therefore methods for improving the water vapor barrier properties of a solid preparation itself have been demanded.

PRIOR ART DOCUMENTS

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PATENT DOCUMENTS

[0008]

50 Patent Document 1: JP 2007-508271 W
 Patent Document 2: JP 2004-518750 W

NON-PATENT DOCUMENTS

55 **[0009]** Non-patent Document 1: "Information on the stability of tablets and capsules in unpacked condition" (6th revised edition), Nishioka et al., Iyaku (Medicine and Drug) Journal Co., Ltd., 2009, p.237

[0010] The research disclosure "Coated tablet formulation of montelukast" (Mason Publications, vol. 525, no. 14, 2008, ISSN 0374-4353) describes a coated tablet for the oral administration of montelukast sodium, the coating presents

preferably polyvinyl alcohol as filmogenic agent and it may comprise thickening agents, such as bentonite, among other ingredients.

SUMMARY OF THE INVENTION

PROBLEMS TO BE SOLVED BY THE INVENTION

[0011] However, in one-dose packaging, since each solid preparation will be stored for a long period of time in an automatic packing machine in a naked state as taken out in advance from a packaging material such as a PTP sheet, the protective effect of the packaging material against humidity wears off, and particularly for a solid preparation containing montelukast sodium which has high hygroscopicity as an active ingredient, it is extremely difficult at present to formulate in a one-dose package because of being susceptible to humidity during storage. In other words, patients who receive a preparation containing montelukast sodium as an active ingredient have not gained the advantage of one-dose package that it improves drug compliance to enhance a therapeutic effect, and therefore there is a need to develop, using a formulation approach, a preparation adaptable to one-dose package containing montelukast sodium as an active ingredient.

[0012] Thus, an object of the present invention is to provide a montelukast-containing coated solid preparation that can be applied to one-dose package, wherein the humidity stability of montelukast or a pharmacologically acceptable salt thereof contained therein is maintained even when the preparation is unpacked.

MEANS FOR SOLVING THE PROBLEMS

[0013] To achieve the above object, the present inventors intensively studied to discover that a coated solid preparation with significantly improved stability to humidity can be obtained by coating a solid preparation containing as an active ingredient montelukast or a pharmacologically acceptable salt thereof with a coating agent containing a particular component in a particular state without increasing the size of the coated solid preparation (without posing any problem in patients' taking the coated solid preparation).

[0014] Thus, the present invention provides a coated solid preparation containing as an active ingredient montelukast or a pharmacologically acceptable salt thereof and being coated with a coating layer comprising polyvinyl alcohol and bentonite according to claim 1.

[0015] In the coating layer of the coated solid preparation described above, the bentonite has a labyrinth-like structure to exert the effect of preventing the contact of the solid preparation with water vapor (hereinafter referred to as "labyrinth effect") under the influence of the mass ratio of polyvinyl alcohol to bentonite and the swollen state of bentonite. Therefore, the humidity stability of the coated solid preparation and of the medicinal ingredient montelukast can be improved, and the delayed disintegration and delayed dissolution of the coated solid preparation caused by moisture absorption can also be prevented. Further, the above-described coated solid preparation exerts a sufficient labyrinth effect even when the coating layer is in the state of a thin film, and therefore there is no problem in patients' taking the coated solid preparation.

[0016] In the above-described coated solid preparation, the above-described bentonite is dispersed as a laminated structure, and the increase in moisture absorption of the coated solid preparation at 40°C and a relative humidity of 75% is preferably not more than 3% by mass.

[0017] In the coating layer of the coated solid preparation described above, the bentonite is dispersed as a laminated structure, the labyrinth effect is strongly exerted, and the humidity stability of the coated solid preparation and of the medicinal ingredient montelukast can be further improved. Further, when the increase in moisture absorption of the above-described coated solid preparation under the environment of room temperature 40°C and a relative humidity of 75% is not more than 3% by mass, such a quality stability that there is no problem in handling under a normal room-temperature environment can be maintained for a long period of time, and the delayed disintegration and delayed dissolution can also be stably prevented.

[0018] In the above-described coated solid preparation, the above-described swelling clay is bentonite.

[0019] Bentonite is able to further improve the humidity stability of the coated solid preparation because it produces a larger labyrinth effect in the coating layer formed on the surface of the solid preparation.

EFFECTS OF THE INVENTION

[0020] According to the present invention, the humidity stability of the coated solid preparation and of montelukast or a pharmacologically acceptable salt thereof contained in the coated solid preparation can be maintained even when the preparation is unpacked. In addition, the present invention provides a montelukast-containing coated solid preparation that can be applied to one-dose package even when the preparation is unpacked, and the present invention contributes

to improving the drug compliance of patients who receive the coated solid preparation to enhance a therapeutic effect. Further, the coated solid preparation of the present invention is applicable not only to tablets but also granule preparations.

BRIEF DESCRIPTION OF THE DRAWINGS

[0021]

Figure 1 is a release profile of Reference Example;
 Figure 2 is a focused ion beam transmission electron micrograph of the film of Example 1;
 Figure 3 is a focused ion beam transmission electron micrograph of the film of Example 2;
 Figure 4 is a focused ion beam transmission electron micrograph of the film of Example 3;
 Figure 5 is a focused ion beam transmission electron micrograph of the film of Comparative Example 3; and
 Figure 6 is a focused ion beam transmission electron micrograph of the film of Comparative Example 4.

BEST MODE FOR CARRYING OUT THE INVENTION

[0022] Preferred embodiments for carrying out the present invention will now be described. It should be understood, however, that the present invention is not limited to the following embodiments, and unless otherwise specified, "%" means "% by mass (w/w%)".

[0023] The coated solid preparation of the present invention is characterized by containing as an active ingredient montelukast or a pharmacologically acceptable salt thereof and being coated with a coating layer comprising polyvinyl alcohol and bentonite according to claim 1.

[0024] "Solid preparation" refers to a pharmaceutical formulated to be a solid, examples of which include tablets (including sublingual tablets and orally disintegrating tablets), capsules (including soft capsules and microcapsules), granules, fine granules, powders, balls, troches, or filming agents.

[0025] "Coated solid preparation" refers to a preparation in which a coating layer is formed to prevent the pharmacologically active components from, for example, being decomposed by oxygen, water vapor, light, and the like by coating the surface of the above-described solid preparation with a coating agent.

[0026] Examples of "montelukast or a pharmacologically acceptable salt thereof" include, for example, montelukast or montelukast sodium. Examples of commercially available preparations of montelukast sodium include, for example, Singulair tablets 10 mg (Banyu Pharmaceutical Co., Ltd.), Singulair chewable tablets (Banyu Pharmaceutical Co., Ltd.), Singulair fine granules 4 mg (Banyu Pharmaceutical Co., Ltd.), Kipres tablets (KYORIN Pharmaceutical Co., Ltd.), Kipres chewable tablets (KYORIN Pharmaceutical Co., Ltd.), or Kipres fine granules 4 mg (KYORIN Pharmaceutical Co., Ltd.).

[0027] "Polyvinyl alcohol" (hereinafter referred to as "PVA") refers to an alcohol obtained by saponifying polyvinyl acetate, including from partially saponified PVA having several ten percent of residual acetic acid groups to completely saponified PVA having only a few percent of residual acetic acid groups.

[0028] The saponification degree of PVA is preferably 70 to 97 mol%. The average degree of polymerization of PVA is preferably 200 to 3000 and more preferably 600 to 2400.

[0029] The above-described PVA may be used by mixing two or more PVAs having different saponification degree and different average degree of polymerization. When mixing two or more PVAs, for example, it is preferable to add a PVA of high polymerization grade to a PVA of low polymerization grade and mix them.

[0030] Examples of PVAs include, for example, various types of Poval (Kuraray Co., Ltd.) or Gohsenol (Nippon Synthetic Chemical Industry Co., Ltd.).

[0031] "Swelling clay" refers to clay having swelling properties, and particularly to bentonite, a substance having swelling properties among finely-powdered substances that exhibit viscosity and plasticity when containing an appropriate amount of water.

[0032] The above-described bentonite is dispersed as a laminated structure. "Laminated structure" refers to a laminated structure formed by stacking of a plurality of layer-shaped structures, particularly to a structure in which 10 to 100 layers of the strips of bentonite are stacked. For dispersing the bentonite as a laminated structure, it is to coat the surface of the solid preparation with a coating agent containing bentonite in a swollen state.

[0033] In the cross section in the thickness direction of the film formed from a coating agent containing bentonite, strips of the bentonite are dispersed in a mesh pattern and planarly oriented. The state of the strips of the bentonite in the cross section in the thickness direction of the film can be observed by using, for example, a transmission electron microscope (TEM).

[0034] "In a mesh pattern" refers to the situation where strips of the bentonite are forming literally a mesh when the dispersion state of the strips of the bentonite in the cross section in the thickness direction of the film is expressed two-dimensionally.

[0035] "Planarly oriented" refers to the situation where the strips of the bentonite are laminated in the thickness direction

of the film.

[0036] "Swollen state of bentonite refers to the state in which the bentonite is swollen by containing a dispersion medium. Examples of the bentonite in a swollen state include, for example, a dispersion obtained by suspending bentonite in a dispersion medium and stirring the suspension, for example, with a homogenizer, and it is preferable to be dispersed to the extent that all the bentonite is able to pass through a filter paper when the dispersion is filtered. Examples of the filter paper used in the above-described filtering operation include, for example, No.5B quantitative filter paper (ADVANTEC) and a glass fiber filter paper GF/D (particle holding capacity; 2.7 μm , Whatman).

[0037] Examples of dispersion media for a coating agent containing bentonite, i.e., solvents used in preparation of a coating agent include, for example, water, organic solvents such as lower alcohols having 5 or less carbon atoms, or mixed solvents thereof, among which water is preferred.

[0038] To the above-described coating agent, pharmaceutically acceptable additives may be added; for improving the dispersibility of the bentonite, surfactants can be added, and for improving the disintegration properties of the coated solid preparation, for example, saccharides and sugar alcohols, such as maltose, maltitol, sorbitol, xylitol, fructose, glucose, lactitol, isomaltose, lactose, erythritol, mannitol, trehalose, or sucrose; croscarmellose sodium; or low-substituted hydroxypropylcellulose can be added.

[0039] To the above-described coating agent, additives generally used for coating in the pharmaceutical field may be further added, and examples of such additives include, for example, coloring agents such as dyes extracted from plants, titanium oxide, calcium carbonate, or silicon dioxide, which serve as a masking agent.

[0040] "Coating layer" refers to a layer of a film formed by coating a solid preparation with a coating agent. The coating layer of the present invention contains PVA and bentonite, and the mass ratio of the PVA to the bentonite is 8:2 to 3:7 and preferably 6: 4 to 3:7.

[0041] The reason is that, when the mass of bentonite is less than one fourth of the mass of PVA, the labyrinth effect of swelling clay is reduced, so that the humidity stability of montelukast or a pharmacologically acceptable salt thereof cannot be sufficiently obtained, and when the mass of swelling clay is above 2.3 times the mass of PVA, the laminated structure of the coating layer becomes nonuniform because of the too high ratio of swelling clay, so that the humidity stability of montelukast or a pharmacologically acceptable salt thereof cannot be sufficiently obtained again. The percentage of bentonite in the above-described coating layer is preferably 5% or more based on the total coating layer.

[0042] The increase in moisture absorption of tablets after the above-described coated solid preparation has been stored under the environment of 40°C and a relative humidity of 75% for 1 week is preferably 3% or less and more preferably 2% or less.

[0043] The water vapor transmission of the above-described coating layer is preferably 1.0×10^{-5} to 1.0×10^{-4} g·mm/cm²·24 hr·atm, more preferably 1.0×10^{-5} to 6.0×10^{-5} g·mm/cm²·24 hr·atm, and still more preferably 1.0×10^{-5} to 3.5×10^{-5} g·mm/cm²·24 hr·atm.

[0044] The above-described coating layer preferably covers the solid preparation at a mass percentage of 2 to 200% based on the solid preparation, and when the solid preparation is tablets, the mass percentage is preferably 3 to 30%, more preferably 3 to 20%, and still more preferably 3 to 15%.

[0045] Examples of the method for coating the surface of the solid preparation with a coating agent include, for example, the use of a coating pan or a coating machine for tablets in the case where the solid preparation is in the form of tablets, and, for example, the use of a fluidized-bed coating machine or a rolling fluidized-bed coating machine in the case where the solid preparation is in the form of granules or powders.

[0046] The above-described coated solid preparation may be further coated with a functional film, for example, of gastric-soluble or enteric-soluble macromolecular substances. Further, the inner side of the coating layer containing PVA and swelling clay according to the present invention may be coated in advance with a functional film, for example, of gastric-soluble or enteric-soluble macromolecular substances.

EXAMPLES

[0047] The present invention will now be specifically described by way of examples, but the present invention is not limited thereto.

(Reference Example)

[0048] For the tablets obtained by storing montelukast sodium tablets (Singulair tablets 10 mg; Banyu Pharmaceutical Co., Ltd.) for 1 week under conditions of 40°C and a relative humidity of 75% (hereinafter referred to as "1-week stored tablets at 40°C and 75% RH"), dissolution tests and measurements of disintegration time were performed. The dissolution tests were carried out in accordance with the Japanese Pharmacopoeia, 15th Edition, Dissolution Test, Second Method; the tablets were placed into a 900 mL of a test solution obtained by adding polysorbate 80 of 0.5% concentration to

distilled water, and dissolved solutions were collected over time for a quantitative determination under the HPLC conditions below. The release profile is shown in Figure 1.

(HPLC conditions)

[0049]

Mobile phase: acetate buffer (pH 3.5)/methanol = 15/85 (v/v)

Column: Hypersil ODS (4.6 × 250 mm)

Detection wavelength: 254 nm

[0050] From the release profile shown in Figure 1, it is clear that the 1-week stored tablets at 40°C and 75% RH exhibit significantly delayed dissolution compared to montelukast sodium tablets before storage (hereinafter referred to as "pre-storage tablets"). Also for disintegration time, the disintegration time of the pre-storage tablets is within 10 minutes, whereas the disintegration time of the 1-week stored tablets at 40°C and 75% RH reached as long as 40 minutes. The conditions of storage at 40°C and a relative humidity of 75% for 1 week can be considered as further accelerated conditions of the conditions of storage at 85% RH for 4 weeks reported in the prior art reference (Non-patent Document 1). Thus, as described below, the tablets after storage at 40°C and a relative humidity of 75% for 1 week were evaluated for increase in moisture absorption and disintegration delay time to thereby confirm the excellent effect of the present invention.

(Method for calculating increase in moisture absorption)

[0051] The mass of the pre-storage tablets and the post-storage tablets were measured, and the increase in moisture absorption was calculated by Equation 1 below.

$$\text{Increase in moisture absorption (\% by mass)} = ((W - W_s) / W_s) \times 100$$

Equation 1

W: Mass of post-storage tablets (g)

Ws: Mass of pre-storage tablets (g)

(Method of measuring disintegration time)

[0052] Disintegration tests were performed in accordance with Japanese Pharmacopoeia, 15th Edition, Disintegration Test, to measure disintegration time. Specifically, using distilled water as a test solution, the time until tablets lose their shape under conditions of a stroke of 30 times/min was taken as the disintegration time.

(Method for calculating disintegration delay time)

[0053] The disintegration time of the pre-storage tablets and post-storage tablets were measured, and the disintegration delay time was calculated by Equation 2 below.

$$\text{Disintegration delay time (min)} = T - T_s \quad \text{Equation 2}$$

T: Disintegration time of post-storage tablets (min)

Ts: Disintegration time of pre-storage tablets (min)

(Method of measuring water vapor transmission)

[0054] The measurement of the water vapor transmission of the coating layer constituting the coated solid preparation of the present invention was performed in accordance with JIS K 8123 (1994) with minor modifications.

[0055] Specifically, a film of a coating layer formed with a coating agent prepared as appropriate was cut, with light passing therethrough, selectively at a portion of uniform thickness without a pinhole into a circle with a diameter of 3.5

cm, and the thickness of the film was measured at arbitrary five points.

[0056] Next, 3 g of calcium chloride (particle size: 850 to 2000 μm) was placed in an aluminum cup (diameter: 30 mm), and the film of a coating layer cut into a circle and a ring for fixing the film were sequentially placed on the aluminum cup. The ring was fixed by placing a weight on the ring, and in this state, molten paraffin wax was poured into the edge of the aluminum cup. After the paraffin wax was solidified, the weight was removed, and the mass of the whole aluminum cup was measured to determine the initial mass. Then, the aluminum cup was placed in a thermostat bath at 40°C and 75% RH. The aluminum cup was taken out every 24 hours for measuring the mass to calculate the water vapor transmission coefficient by using Equation 3 below. In all of the tests for measuring the water vapor transmission described below, $r = 1.5 \text{ cm}$; $t = 24 \text{ hours}$; and $C = 1 \text{ atm}$.

$$\text{Water vapor transmission } P \text{ (g}\cdot\text{mm/cm}^2\cdot\text{24 hr}\cdot\text{atm)} = W \times A / B \times t \times C$$

Equation 3

W: Mass increased in 24 hours (g)

A: Average value of film thickness at five points (mm)

B: Transmission area πr^2 (cm^2)

t: Elapsed time (hr)

C: Atmospheric pressure (atm)

(Example 1)

[0057] To 234.6 parts by mass of water, added were 6.9 parts by mass of PVA (EG-05; Nippon Synthetic Chemical Industry Co., Ltd.), 505.3 parts by mass of a 3.2 bentonite (hereinafter referred to as BT) solution, and 3.2 parts by mass of sorbitan monolaurate (hereinafter referred to as "Span 20"), and the resulting mixture was stirred with a homogenizer (Polytron Model KR) to obtain a coating agent (hereinafter referred to as "Example 1 coating agent"). As a 3.2% BT solution, used was a filtrate obtained by adding 32 parts by mass of BT (Kunipia-F; KUNIMINE INDUSTRIES CO., LTD., cation exchange capability: 115 meq/100 g) to 968 parts by mass of stirred water, stirring the resulting mixture with the homogenizer for uniform dispersion, and then suction-filtering the resultant through a filter paper.

[0058] Twenty grams of montelukast sodium tablets (Singulair tablets 10 mg; Banyu Pharmaceutical Co., Ltd.) and 280 g of placebo tablets were placed in a coating pan (HI-COATER MINI; Freund Industrial Co., Ltd.), and Example 1 coating agent was applied to the tablets until the thickness of the coating layer reached 50 to 60 μm . For the coated montelukast sodium tablets obtained, the increase in moisture absorption and the disintegration delay time after storage for 1 week under conditions of 40°C and a relative humidity of 75% were calculated.

[0059] Example 1 coating agent was sprayed onto the back of a polypropylene balance tray, and immediately dried with hot air from a dryer. After repeating these operations several times, the balance tray was allowed to stand in an oven at 50°C and dried overnight, and a film was separated from the balance tray to measure the water vapor transmission.

(Example 2)

[0060] From a coating agent obtained by adding 14.0 parts by mass of PVA and 656.2 parts by mass of a 3.2% BT solution to 329.8 parts by mass of water and stirring the resulting mixture with a homogenizer, a film was produced in the same manner as in Example 1, and the water vapor transmission was measured.

(Example 3)

[0061] Using a coating agent obtained by adding 20.0 parts by mass of PVA and 625.0 parts by mass of a 3.2% BT solution to 355.0 parts by mass of water and stirring the resulting mixture with a homogenizer, coated montelukast sodium tablets was obtained in the same manner as in Example 1, and the increase in moisture absorption after storage for 1 week under conditions of 40°C and a relative humidity of 75% RH was calculated. Further, a film was produced from the coating agent in the same manner as in Example 1, and the water vapor transmission was measured.

(Example 4)

[0062] Using a coating agent obtained by adding 21.0 parts by mass of PVA and 437.5 parts by mass of a 3.2% BT solution to 541.5 parts by mass of water and stirring the resulting mixture with a homogenizer, coated montelukast sodium tablets was obtained in the same manner as in Example 1, and the increase in moisture absorption after storage

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for 1 week under conditions of 40°C and a relative humidity of 75% RH was calculated. Further, a film was produced from the coating agent in the same manner as in Example 1, and the water vapor transmission was measured.

(Example 5)

[0063] Using a coating agent obtained by adding 32.0 parts by mass of PVA and 250.0 parts by mass of a 3.2% BT solution to 718.0 parts by mass of water and stirring the resulting mixture with a homogenizer, coated montelukast sodium tablets was obtained in the same manner as in Example 1, and the increase in moisture absorption after storage for 1 week under conditions of 40°C and a relative humidity of 75% RH was calculated. Further, a film was produced in the same manner as in Example 1, and the water vapor transmission was measured.

(Reference Example 6)

[0064] To 234.6 parts by mass of water, added were 6.9 parts by mass of PVA, 505.3 parts by mass of a 3.2% magnesium aluminum silicate solution, and 3.2 parts by mass of Span 20, and the resulting mixture was stirred with a homogenizer to prepare a coating agent. A film was produced in the same manner as in Example 1, and the water vapor transmission was measured. As a 3.2% magnesium aluminum silicate solution, used was a filtrate obtained by adding 32 parts by mass of magnesium aluminum silicate (Veegum-HV; R.T. Vanderbilt Company, Inc.) to 968 parts by mass of stirred water, stirring the resulting mixture with the homogenizer for uniform dispersion, and then suction-filtering the resultant through a filter paper.

(Comparative Example 1)

[0065] The increase in moisture absorption and the disintegration delay time after montelukast sodium tablets (Singulair tablets 10 mg; Banyu Pharmaceutical Co., Ltd.) have been stored for 1 week under conditions of 40°C and a relative humidity of 75% were calculated.

(Comparative Example 2)

[0066] Using a coating agent obtained by adding 7.0 parts by mass of PVA and 875.0 parts by mass of a 3.2% BT solution to 118.0 parts by mass of water and stirring the resulting mixture with a homogenizer, coated montelukast sodium tablets was obtained in the same manner as in Example 1, and the increase in moisture absorption after storage for 1 week under conditions of 40°C and a relative humidity of 75% was calculated. Further, a film was produced from the coating agent obtained in the same manner as in Example 1, and the water vapor transmission was measured.

(Comparative Example 3)

[0067] Using a coating agent obtained by adding 36.0 parts by mass of PVA and 125.0 parts by mass of a 3.2% BT solution to 839.0 parts by mass of water and stirring the resulting mixture with a homogenizer, coated montelukast sodium tablets was obtained in the same manner as in Example 1, and the increase in moisture absorption after storage for 1 week under conditions of 40°C and a relative humidity of 75% was calculated. Further, a film was produced from the coating agent obtained in the same manner as in Example 1, and the water vapor transmission was measured.

(Comparative Example 4)

[0068] From a coating agent obtained by adding 3.0 parts by mass of PVA and 843.8 parts by mass of a 3.2% BT solution to 153.2 parts by mass of water and stirring the resulting mixture with a homogenizer, a film was produced in the same manner as in Example 1, and the water vapor transmission was measured.

[0069] The mass ratio of PVA to BT to the third component contained in each coating agent of Examples 1 to 6 and Comparative Examples 1 to 4, the increase in moisture absorption calculated in Examples 1, 3 to 5 and Comparative Examples 1 to 3, and the water vapor transmission measured in Examples 1 to 6 and Comparative Examples 2 to 4 are shown in Table 1.

[Table 1]

	PVA	Swelling clay	Third component	1-week storage	Water vapor transmission of film (g·mm/cm ² ·24 hr·atm)
				Increase in moisture absorption (% by mass)	
Comparative Example 1	-	-	-	3.9	-
Comparative Example 2	20	80	-	3.8.	1.4×10^{-4}
Comparative Example 3	90	10	-	3.3	2.3×10^{-4}
Comparative Example 4	10	90	-	-	6.2×10^{-4}
Example 1	26.4	61.6	12	1.1	1.9×10^{-5}
Example 2	40	60	-	-	3.4×10^{-5}
Example 3	50	50	-	1.4	2.5×10^{-5}
Example 4	60	40	-	2.4	3.2×10^{-5}
Example 5	80	20	-	2.9	5.8×10^{-5}
Reference Example 6	30	70	-	-	9.1×10^{-5}

[0070] From the results in Table 1, it is clear that when the mass ratio of PVA to swelling clay is in the range of 8:2 to 3:7, the increase in moisture absorption of the montelukast sodium tablets is not more than 3.0% by mass, and the water vapor transmission of the film is not more than 1.0×10^{-4} ; therefore, the coated solid preparation of the present invention is very stable to humidity.

[0071] Further, the disintegration delay time in Comparative Example 1 is 30 minutes, whereas the disintegration delay time in Example 1 is 4 minutes. Also from these results, it is clear that the disintegration delay time of the coated solid preparation of the present invention is significantly short, and the disintegration performance can be maintained even if the preparation has been stored under a high humidity environment.

(Measurement of films under transmission electron microscope)

[0072] Using the focused ion beam technique, the longitudinal section of each film obtained in Examples 1 to 3 and Comparative Examples 3 and 4 was observed under a transmission electron microscope. The micrograph of Example 1, the micrograph of Example 2, the micrograph of Example 3, the micrograph of Comparative Example 3, and the micrograph of Comparative Example 4 are shown in Figure 1, Figure 2, Figure 3, Figure 4, and Figure 5, respectively.

[0073] In the micrographs of Figures 2 to 4, BT was uniformly dispersed as a laminated structure in the film, but in Figure 5, BT formed little or no laminated structure. Also in Figure 6, areas where BT is not planarly oriented are found here and there. From the observations above, it is presumed that the uniform dispersion of the laminated structure of BT significantly contributes to the water vapor transmission of the film and the humidity stability of solid preparations such as montelukast sodium tablets.

(Comparative Example 5)

[0074] From a coating agent obtained by adding 16.0 parts by mass of PVA and 4.0 parts by mass of BT to 480.0 parts by mass of water and stirring the resulting mixture with a magnetic stirrer for 15 minutes, a film was produced in the same manner as in Example 1, and the water vapor transmission was measured.

(Example 7)

[0075] Using a coating agent obtained by adding 6.9 parts by mass of PVA, 505.3 parts by mass of a 3.2% BT solution, 3.2 parts by mass of Span 20, and 3.94 parts by mass of maltitol to 343.5 parts by mass of water and stirring the resulting mixture with a homogenizer, coated montelukast sodium tablets was obtained in the same manner as in Example 1,

and the increase in moisture absorption after storage for 1 week under conditions of 40°C and a relative humidity of 75% was calculated. Further, a film was produced in the same manner as in Example 1, and the water vapor transmission was measured.

[0076] The increase in moisture absorption and the water vapor transmission measured and calculated in Examples 1 and 7 and Comparative Example 5 are shown in Table 2.

[Table 2]

	Composition	Increase in moisture absorption (% by mass)	Water vapor transmission of film (g·mm/cm ² ·24 hr·atm)
		1-week storage	
Example 1	PVA/BT/Span 20 = 26.4/61.6/12	1.1	1.9×10^{-5}
Example 7	PVA/BT/Span 20/Maltitol = 23/53.6/10.4/13	2.8	3.7×10^{-5}
Comparative Example 5	PVA/BT = 8/2	-	2.7×10^{-4}

[0077] The results in Table 2 show that, in both the case where a nonionic surfactant was added to PVA and BT (Example 1) and the case where sugar alcohol was further added (Example 7), the increase in moisture absorption was not more than 3% by mass, and the water vapor transmission of the film was not more than 1.0×10^{-4} .

[0078] The comparison of Example 5 and Comparative Example 5 showed that BT is preferably added not as a powder but in a swollen state.

INDUSTRIAL APPLICABILITY

[0079] The coated solid preparation of the present invention can be suitably used as a pharmaceutical applicable to one-dose package.

Claims

1. A coated solid preparation containing as an active ingredient montelukast or a pharmacologically acceptable salt thereof and being coated with a coating layer comprising polyvinyl alcohol and bentonite, wherein the mass ratio of said polyvinyl alcohol to said bentonite in said coating layer is 8:2 to 3:7, said bentonite is uniformly dispersed as a laminated structure, strips of the bentonite are dispersed in a mesh pattern and planarly oriented, and said coating layer is formed with a coating agent containing bentonite in a swollen state.
2. The coated solid preparation according to claim 1, wherein the increase in moisture absorption of the coated solid preparation at 40°C and a relative humidity of 75% is not more than 3% by mass.

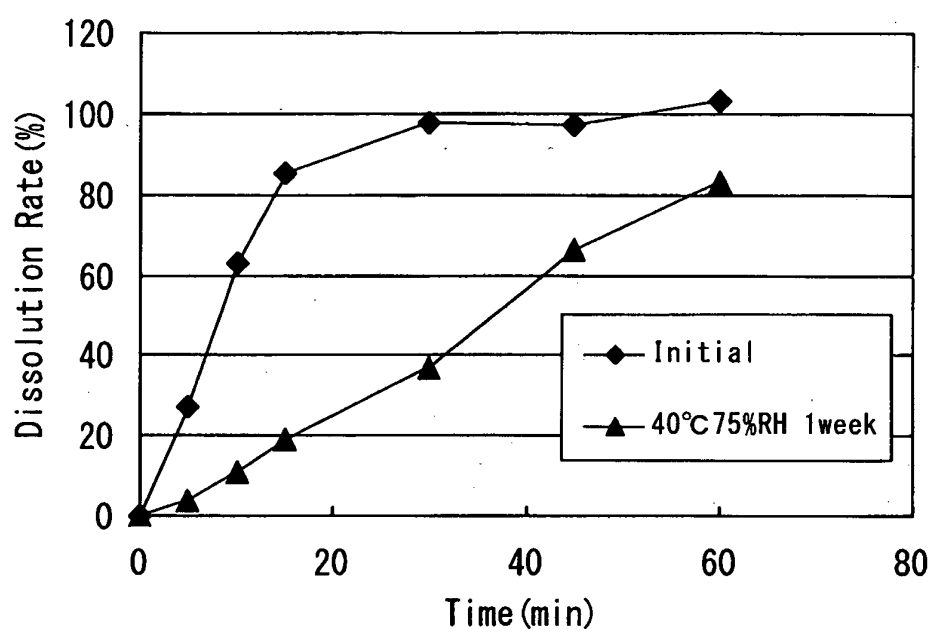
Patentansprüche

1. Beschichtetes Festpräparat, das als einen wirksamen Bestandteil Montelukast oder ein pharmakologisch akzeptables Salz davon enthält und das mit einer Beschichtungsschicht beschichtet ist, die Polyvinylalkohol und Bentonit umfasst, wobei das Massenverhältnis des Polyvinylalkohols zu dem Bentonit in der Beschichtungsschicht 8 : 2 bis 3 : 7 ist; wobei das Bentonit gleichmäßig als eine laminierte Struktur verteilt ist, wobei Streifen des Bentonits in einem Maschenmuster verteilt und planar ausgerichtet sind, und wobei die Beschichtungsschicht mit einem Beschichtungsmittel gebildet wird, das Bentonit in einem gequollenen Zustand enthält.
2. Beschichtetes Festpräparat nach Anspruch 1, wobei die Zunahme in der Feuchtigkeitsaufnahme von den dem beschichteten Festpräparat bei 40 °C und einer relativen Luftfeuchtigkeit von 75 % nicht mehr als 3 Massen-% beträgt.

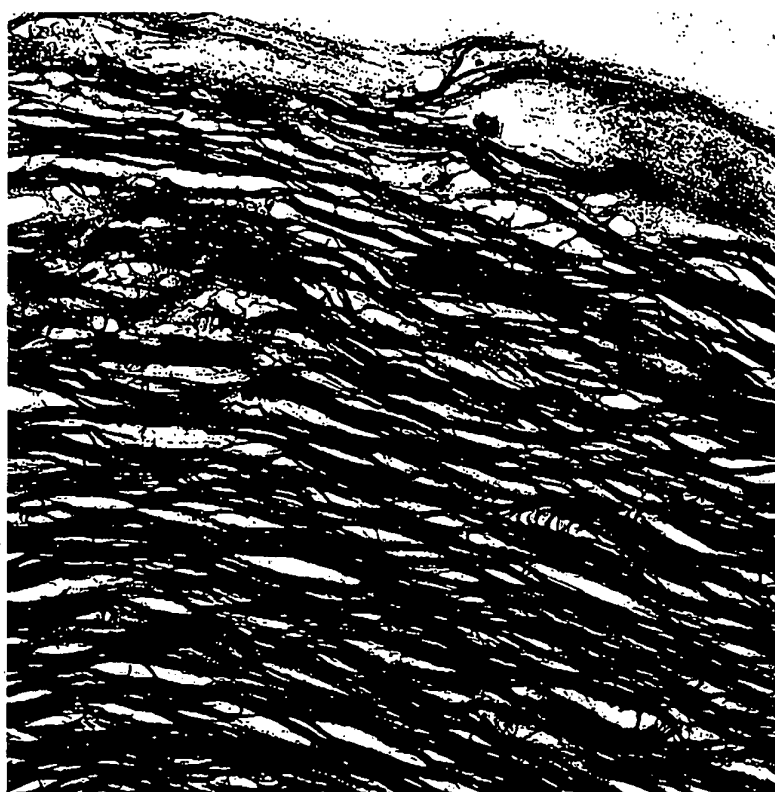
Revendications

- 5
1. Préparation solide enrobée contenant, à titre d'agent actif, du montélukast ou un sel pharmaceutiquement acceptable de celui-ci, et qui est enrobée avec une couche d'enrobage comprenant du poly(alcool vinylique) et de la bentonite, dans laquelle
- 10 le rapport en masse dudit poly(alcool vinylique) à ladite bentonite dans ladite couche d'enrobage est de 8/2 à 3/7, ladite bentonite est uniformément dispersée sous la forme d'une structure stratifiée, des bandes de la bentonite sont dispersées selon un motif en treillis et sont orientées dans le plan, et ladite couche d'enrobage est formée avec un agent d'enrobage contenant de la bentonite à l'état gonflé.
- 15
2. Préparation solide enrobée selon la revendication 1, dans laquelle l'augmentation de l'absorption d'humidité de la préparation solide enrobée à 40 °C sous une humidité relative de 75 % ne dépasse pas 3 % en masse.
- 20
- 25
- 30
- 35
- 40
- 45
- 50
- 55

[Fig. 1]



[Fig. 2]



500 nm

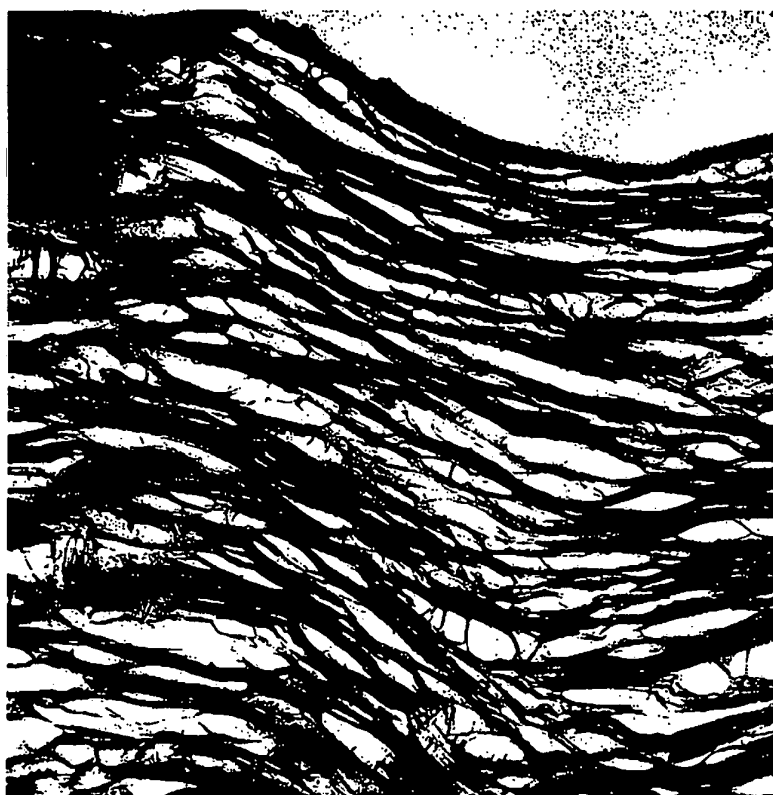
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Direct Mag: 8000x

[Fig. 3]



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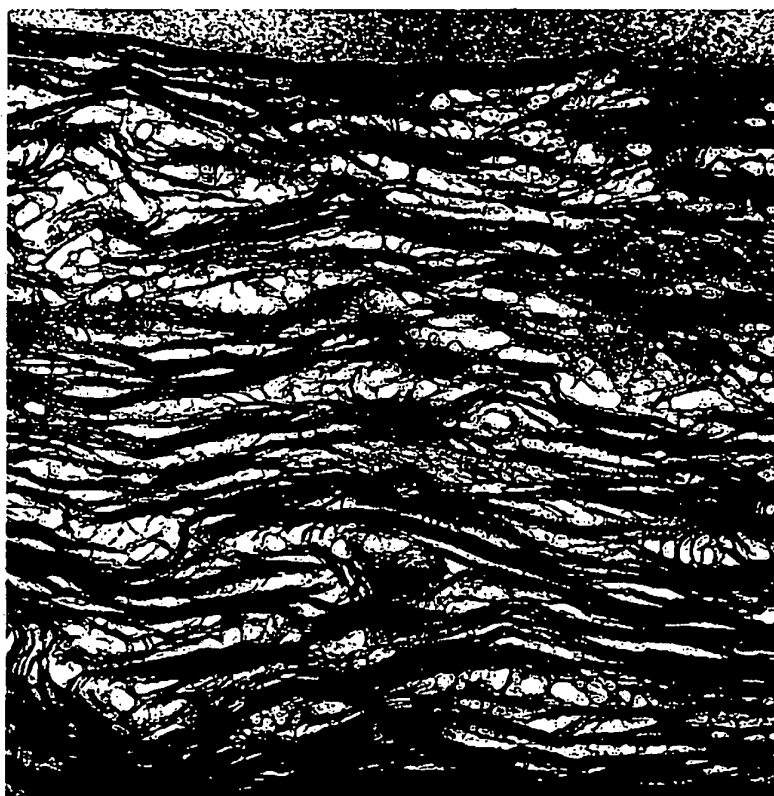
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500 nm

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[Fig. 4]



500 nm

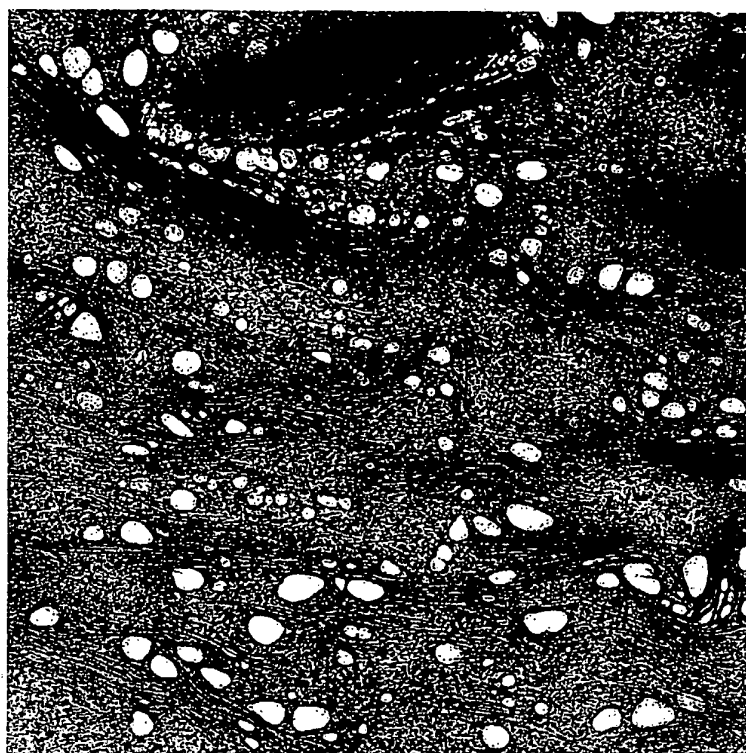
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HV=300kV

Print Mag: 68000x @ 7.0 in

Direct Mag: 8000x

[Fig. 5]



500 nm

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HV=300kV

Print Mag: 68000x @ 7.0 in

Direct Mag: 8000x

[Fig. 6]



S3.01.008k.tif

Print Mag: 68000x @ 7.0 in

500 nm

HV=300kV

Direct Mag: 8000x

REFERENCES CITED IN THE DESCRIPTION

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