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(54) Title: REBAMIPIDE PREPARATION FOR RECTAL ADMINISTRATION TO BE PREPARED BEFORE USING

(57) Abstract: Rebamipide preparation for rectal administration to be prepared before using, which is a solid particle preparation comprising rebamipide and carmellose sodium and having excellent dispersibility in an aqueous vehicle, and can be administered rectally in the form of enema dispersion preparation by dispersing the solid particle preparation in an aqueous vehicle when used. The present rebamipide preparation is in a solid particle form such as a powder or pulverized powder form or a fine granule or granule form, and hence, it has excellent storage stability.



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DESCRIPTION

REBAMIPIDE PREPARATION FOR RECTAL ADMINISTRATION
TO BE PREPARED BEFORE USING

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TECHNICAL FIELD

The present invention relates to a rebamipide preparation for rectal administration to be prepared before using, more particularly, a rebamipide preparation in the form of a solid particle preparation comprising rebamipide and carmellose sodium which is dispersible in an aqueous vehicle to form a rebamipide enema dispersion preparation when used. The present invention relates also to a method for preparing the rebamipide preparation in the form of a solid particle preparation, and a rebamipide enema dispersion preparation which is prepared by dispersing the solid particle preparation in an aqueous vehicle, and a method for preparing said rebamipide enema dispersion preparation.

BACKGROUND ART

Rebamipide (trade name: Mucosta, manufactured by Otsuka Pharmaceutical Co., Ltd.) has been known as an agent for improving subjective symptoms and objective symptoms of diseases such as gastric ulcer, duodenal ulcer, gastritis, etc., and it has been already reported that rebamipide is applicable to the treatment of ulcerative colitis (cf., Kazuya MAKIYAMA, "Study of the treatment of ulcerative colitis by enema therapy of rebamipide ", Grants for Health Science for Research into Treatment for Specific Diseases, Group for survey research on intractable inflammatory bowel diseases, 2001th Research Report of, 2002, pp. 70-71; Takeshi MORI, Mitsuki MIYATA, Megumu KOMIYAMA, Masafumi OHNISHI, Hiroshi OKADA (2003), "Stability Study of Rebamipide Rectal Suspension Enema and a Clinical Case Showing a Good Response", Medical Pharmacy (Jpn. J. Pharma.

Health Care Sci., 29/3, 312-317; Mitsuki MIYATA, Kunio KASUGAI, Sinichi KAGAMI, 2002, "Study of the Treatment of Ulcerative Colitis Localized in the Lower Part by Enema Therapy of Rebamipide", The 88th General Conference of Japanese Society of Gastroenterology, Abstracts, S5-10.

5 When rebamipide is used in the treatment of ulcerative colitis, usually said rebamipide is locally administered to the lower part of the digestive organs in a dispersion form because of the low water solubility thereof. In addition, in order to improve the retention thereof in the lower part of the digestive organs, rebamipide is usually administered in the form
10 of an aqueous dispersion containing carmellose sodium (CMC-Na) (enema preparation).

 The enema preparation of rebamipide has usually been prepared by dispersing powdered rebamipide and carmellose sodium in an aqueous vehicle. However, according to such a method, the procedure for dispersion
15 of rebamipide and carmellose sodium in an aqueous vehicle is not only troublesome but also difficult because of less dispersibility of the compounds in the aqueous vehicle. Moreover, the enema preparation (a rebamipide dispersion preparation) show a poor preservation stability wherein rebamipide particles settle out and accumulate at a comparative high rate.
20 It is not easy to re-disperse the accumulated and solidified rebamipide particles by shaking an enema container containing the same. Under these conditions, such preparation is not easily applicable to the clinical uses.

 Further, the above dispersion has a high viscosity due to the incorporation of CMC-Na, and hence, the dispersion cannot be sterilized by
25 filtration, which method has been widely employed in the sterilization of medicaments as a simple sterilization method. In cases that preparation cannot be sterilized, it may be possible to add an antiseptic agent and/or preservative into such preparation, but the addition of antiseptic agent and/or preservative per se means the undesirable addition of chemical
30 substance other than active ingredient. Further, most of conventional

antiseptic agents are irritable, and when an enema preparation containing such antiseptic agent is administered into the lower part of the digestive organs, the mucosa membrane at the application site of the patient is often injured, and hence, the patient may feel especially severe stimulations. In addition, for example, benzalkonium chloride, one of the representative preservatives, reacts with CMC-Na, and hence, it cannot be used. Further, when other organic acid preservative such as sorbic acid is added, the pH value of the preparation is lowered, by which the preparation becomes more irritative to the patient when administered rectally. Further, preservatives such as parabens may have defects of penetrating out through the wall of a plastic container during the storage of the preparation in the plastic container, and the use thereof is not suitable either.

From the above-mentioned various reasons, rebamipide enema preparations are usually prepared before using in the medical sites such as hospitals when needed. For example, they are prepared by weighing and mixing the described amounts of rebamipide and CMC-Na, and dispersing the obtained mixture in an aqueous vehicle which is previously sterilized.

However, as mentioned above, the conventional procedure of preparation of rebamipide enema preparation, which comprises weighing each component individually and mixing them, and dispersing the resulting mixture in an aqueous vehicle, is very cumbersome and complicated, and further, the control of the viscosity of the obtained enema preparation requires a considerable technical and experimental skill, and hence, the conventional procedure is not a preferable work done at the medical sites.

Therefore, in the medical sites, it has been desired to develop a rebamipide enema preparation having an excellent dispersibility, which can easily be prepared even by a usual medical staff without necessity of specific skill when needed.

DISCLOSURE OF INVENTION

An object of the present invention is to provide a rebamipide preparation for rectal administration to be prepared before using, from which a rebamipide enema dispersion preparation having an excellent dispersibility can be prepared, and further to provide a method for preparing the same.

The present inventors have intensively studied in order to achieve the above-mentioned object, and have found that when rebamipide and carmellose sodium (CMC-Na) are mixed by using an aqueous alcohol solution of carmellose sodium as a binder, the resulting solid particle preparation containing rebamipide and carmellose sodium (CMC-Na), especially in the form of a pulverized powder preparation or a powder preparation, can meet the above object. More particularly, said solid particle preparation shows an excellent water dispersibility, and easily makes a uniform dispersion without unmixed-in lumps or agglomerates by simply dispersing into an aqueous vehicle when used, and further, the present inventors have found that the obtained dispersion is stable and has suitable viscosity and osmotic pressure for an enema preparation. The present invention has been accomplished from further studies and researches based on this finding.

The present invention provides the invention as disclosed in the following embodiments (1) to (8).

(1) A rebamipide preparation for rectal administration to be prepared before using, which is a solid particle preparation comprising rebamipide and carmellose sodium, which has excellent dispersibility in an aqueous vehicle and can be convertible into an enema dispersion by dispersing in an aqueous vehicle when used.

(2) The preparation according to the above (1), wherein carmellose sodium is contained in an amount of 50 to 2500 parts by weight, preferably 100 to 2000 parts by weight, more preferably 150 to 1700 parts by weight, to

100 parts by weight of rebamipide.

(3) The preparation according to the above (1) or (2), which is in the pulverized powder form having an average particle size of 100 to 300 μm , where the ratio of particles having a particle size of less than 75 μm is 20 % or less, and the ratio of particles having a particle size of 500 μm or more is 5 % or less.

(4) A method for preparing the preparation as set forth in any one of the above (1) to (3), which comprises formulating rebamipide and carmellose sodium into a solid particle form by using an aqueous alcohol solution of carmellose sodium as a binder.

(5) The method according to the above (4), wherein the formulation of rebamipide and carmellose sodium into a solid particle form is carried out by wet-kneading a starting material containing rebamipide and carmellose sodium by using an aqueous alcohol solution of carmellose sodium as a binder, drying the resultant by a fluid bed drying method, and regulating the size of the resulting particles.

(6) The method according to the above (5), wherein the binder is an aqueous alcohol (e.g. ethanol) solution containing carmellose sodium in a concentration of 0.1 to 5 % by weight, which is prepared by dissolving carmellose sodium in an aqueous alcohol solution, e.g. in a 25 to 75 % by weight aqueous solution of ethanol.

(7) A rebamipide enema dispersion preparation, which is prepared by dispersing the preparation as set forth in any one of the above (1) to (3) in an aqueous vehicle.

(8) A method for preparing a rebamipide enema dispersion preparation, which comprises dispersing the preparation as set forth in any one of the above (1) to (3) in an aqueous vehicle.

Throughout the specification and claims, the term "preparation to be prepared before using" means a preparation which is in a solid particle form during the storage and transport after the manufacturing thereof, which is

different from an actual form to be administered, and is converted into an actually usable dispersion form before using. However, this term does not intend to indicate only a preparation which is converted into the actually usable dispersion form just before using, but includes also a preparation which is previously converted into a dispersion form and kept at a medical site until it is used. For example, "preparation to be prepared before using" also includes a preparation which is prepared in a dispersion form at a medical site such as hospital, and is stored as it is for a period of several days to about 1 month, and then is finally used for the clinical purpose.

EFFECTS OF INVENTION

The present invention provides a rebamipide preparation for rectal administration to be prepared before using, which shows an excellent water dispersibility, and a method for preparing the same. By utilizing its excellent dispersibility, said preparation for rectal administration can be easily and well dispersed when it is poured into an aqueous vehicle for dispersion such as physiological saline solution when used to give a desired rebamipide enema dispersion preparation having suitable viscosity and osmotic pressure. Further, any specific skill or training is not required for carrying out this procedure. In addition, the preparation for rectal administration to be provided by the present invention is a solid particle preparation, and hence, it shows an excellent stability and does not require any antiseptic agents or preservatives, which is advantageous for medicaments. Further, the present preparation does not require any procedures such as sterilization by filtration, etc., because it is a solid particle preparation. The sterilization procedure is required only for an aqueous vehicle for dispersion when it is used for dispersing the present preparation for rectal administration to be prepared before using, and said sterilization procedure per se is very easy and simple to be carried out, which is also big advantage. In addition to these points, the present

preparation has further advantages from viewpoints of manufacturing cost and transportation cost, and the manufacturing management thereof is advantageously easy.

5 BEST MODE FOR CARRYING OUT THE INVENTION

The present preparation comprising rebamipide and carmellose sodium in the form of a solid particle preparation has an excellent water dispersibility as mentioned above. The excellent water dispersibility of the present preparation is illustrated in Experiment as described hereinafter.

10 The present preparation may be prepared by any method as long as it is prepared in the solid particle form containing both of rebamipide and carmellose sodium by using an aqueous alcohol solution of carmellose sodium as a binder. For example, the present preparation may be prepared by formulating a starting material containing the above-mentioned two
15 components into a solid particle form with a binder an aqueous alcohol solution of carmellose sodium by various conventional methods to be known in the pharmaceutical field.

In a preferable method for preparing the present preparation, the starting material containing rebamipide and carmellose sodium is kneaded
20 and mixed by wet kneading with using an aqueous alcohol solution of carmellose sodium as a binder, dried by fluid bed drying method, and the size of the resulting particles is regulated. According to this method, a solid particle preparation in a pulverized powder form, powder form, etc. is easily obtained where the ratio of particles having a particle size of less than 75 μm
25 is 20 % or less, and the ratio of particles having a particle size of 500 μm or more is 5 % or less.

The above-mentioned preferable method for preparing the present preparation is explained in more detail below.

Starting rebamipide

30 Rebamipide to be used in the present preparation is a compound

having a chemical name of 2-(4-chlorobenzoylamino)-3-[2(1H)-quinolinon-4-yl]propionic acid which has been known as an active medical compound in a trade name of "Mucosta" manufactured by Otsuka Pharmaceutical Co., Ltd. Said rebamipide can be used in a commercially available powder form for manufacturing of the present preparation for rectal administration to be prepared before using. Usually, the starting rebamipide powder may have an average particle size of 1.0 μm and a particle size distribution range of 50%D being 0.9 μm and 90%D being 2.9 μm .

The starting material containing rebamipide and carmellose sodium to be used in the present method may usually contain, in addition to rebamipide and carmellose sodium, a suitable amount of conventional pharmaceutically acceptable carrier (excipient) and additives.

Representative examples of carrier are lactose, sucrose, D-mannitol, sodium chloride, glucose, starch, calcium carbonate, kaolin, crystalline cellulose, sodium silicate, etc.

The additives may be any conventional various additives to be known in the pharmaceutical field, for example, binders, disintegrating agents, lubricants (aggregation inhibitors), fluidizers, pH adjustors, isotonic agents, absorption promoters, etc.

Although the present preparation is prepared by using as a binder an aqueous alcohol solution of carmellose sodium, other conventional binders may further be used. Examples of other binders are water, ethanol, simple syrup, glucose solution, starch solution, gelatin solution, carboxymethyl cellulose, carboxyethylcellulose sodium, shellac, methyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, polyvinylpyrrolidone, polyvinyl alcohol, gelatin, dextrin, pullulan, etc.

The disintegrating agents include carmellose calcium, low substituted hydroxypropyl cellulose (L-HPC), carmellose, croscarmellose sodium, partially pregelatinized starch, dry starch, carboxymethyl starch sodium, crospovidone, polysorbate 80 (polyoxyethylenesorbitan oleate), etc.

The lubricants (aggregation inhibitors) include, for example, talc, magnesium stearate, calcium stearate, colloidal silica, stearic acid, aqueous silicon dioxide, synthetic magnesium silicate, fine granulated silicon oxide, starch, sodium laurylsulfate, boric acid, magnesium oxide, waxes, hydrogenated oil, polyethylene glycol, sodium benzoate, etc. Among them, magnesium stearate is preferable.

The fluidizers include, for example, silicic anhydride such as Adsolider® 101 (manufactured by Freund Corporation), Aerosil® (manufactured by Nippon Aerosil Co., Ltd.), etc. These fluidizers are contained in an amount of 0.5 to about 15 parts by weight, preferably in an amount of 1 to about 10 parts by weight, to 100 parts by weight of rebamipide.

The pH adjustors include, for example, hydrochloric acid, sodium hydroxide, citric acid, citric anhydride, sodium citrate, sodium citrate dihydrate, anhydrous bibasic sodium phosphate, anhydrous monobasic sodium phosphate, etc.

The isotonic agents include, for example, sodium chloride, glucose, D-mannitol, glycerin, etc. The absorption promoters include, for example, quaternary ammonium base, sodium laurylsulfate, etc.

Moreover, the starting material may further contain other carriers and additives, for example, coloring agents, flavors, antioxidants, antibacterial agents, antiseptic agents, etc. The amount of these carriers and additives to be used may preferably be determined according to the kinds thereof.

Carmellose sodium

Carmellose sodium (CMC-Na), which is another essential component to be used in the present preparation, is carboxymethylcellulose sodium, and has conventionally been known as a laxative, a clyster, etc. In the present invention, CMC-Na recorded in the Japanese Pharmacopoeia (Fourteenth Edition) can be utilized without any specific conditions. Among

them, it is preferable to use CMC-Na having a viscosity of 100 to 5000 mPa.s, especially a viscosity of 300 to 400 mPa.s, at 25°C of 2 % aqueous solution thereof. Preferable CMC-Na includes, for example, Celogen® (manufactured by DAI-ICHI KOGYO SEIYAKU CO., LTD.). As for said Celogen, ones of the following grades (produce classes) as shown in Table 1 are known, and the present invention may utilize any of them. Among them, Celogen of grade F-SC is especially preferable.

Table 1

Grade	Viscosity (25°C, Type-B viscometer, mPa.s)		Etherification degree
	2 %	1 %	
PR-S	20-40	-	0.70-0.85
PR	80-140	-	0.60-0.70
F-SC	300-400	-	0.70-0.85
AG gum M	900-1500	-	0.70-0.85
PM-250L	-	150-300	0.60-0.70
P-815C	-	1000-2000	0.70-0.85

The amount of carmellose sodium (CMC-Na) to be added into the present preparation may vary in some extent according to the degree of CMC-Na, but it is usually in the range of 50 to about 2500 parts by weight, preferably in the range of 100 to about 2000 parts by weight, more preferably in the range of 150 to about 1700 parts by weight, to 100 parts by weight of rebamipide. The above-mentioned amount of the carmellose sodium includes both of the amount of carmellose sodium to be incorporated as an essential ingredient and of the amount of carmellose sodium to be used as a binder.

A method for preparing the present preparation

In the wet kneading to be employed in the present method, it is

preferable to use carmellose sodium as a binder. The wet kneading may be carried out by using a suitable apparatus such as a kneader. Namely, an aqueous alcohol solution in which carmellose sodium is dissolved is used as a binder, and the above-mentioned starting rebamipide and carmellose sodium, or a starting material containing an excipient, an additive, etc. in addition to rebamipide and carmellose sodium, are subjected to kneading.

The solution of carmellose sodium to be used as a binder is an aqueous alcohol solution of carmellose sodium, especially an aqueous ethanol solution, while an aqueous solution of carmellose sodium may optionally be used together with or instead of the aqueous alcohol solution. The alcohol concentration of an aqueous alcohol to be used as a solvent for preparing such an aqueous alcohol solution of carmellose sodium is not necessarily specified, but it is preferably in the range of 25 to about 75 %, especially about 50 %. Further, the concentration of carmellose sodium in the aqueous alcohol solution of carmellose sodium to be used as a binder is in the range of 0.1 to about 5 % by weight, and it is especially preferable about 1 % by weight.

The amount of carmellose sodium to be used as a binder in the whole preparation of the present invention is in the range of 0.5 to 15 parts by weight, preferably in the range of 1 to 10 parts by weight, to 100 parts by weight of rebamipide.

The wet kneading to be utilized in the present invention has been well known in the pharmaceutical formulation field, especially for preparing granules and pulverized powders. For example, a medicament is pulverized, and mixed with an excipient, etc., and a suitable wetting agent is added thereto to give a soft mass. Said mass is passed through a rough screen to give particulates, which are further dried. More concretely, first, the starting rebamipide and carmellose sodium and other optional components such as excipients and additives are weighed, and mixed well. Then, the mixture thus obtained is kneaded by using a kneader (e.g., New Speed

Kneader NSK-150, manufactured by Gokyo Seisakusho) with a solution of carmellose sodium as a binder. Further, the resulting kneaded mass is dried by a fluid bed dryer (e.g., Multiplex Model MP-01, manufactured by Powrex Corporation), and the sizes of the resulting granules is regulated.

5 The mass having a particle size larger than the prescribed particle size after size-regulation is pulverized again into particles having a desired particle size. Thus, the present preparation can be obtained in the form of powders, pulverized powders, fine granules or granules.

10 The drying procedure as mentioned above may be carried out, for example, by air-drying, vacuum drying, etc. instead of fluid bed drying.

The pulverization of the product after drying can be carried out by various methods. In the procedure, pin mill (sample mill), speed mill, new speed mill, etc. may be used, and new speed mill is especially preferably used. The pulverization procedure is preferably carried in such a manner
15 that the obtained powder (pulverized powder) has an average particle size in the range of about 100 to 300 μm , and the particle size distribution pattern wherein the ratio of particles having a particle size of less than 75 μm is 20 % or less, and the ratio of particles having a particle size of 500 μm or more is 5 % or less.

20 The present preparation obtained in the above can be commercialized as it stands without sterilization.

In addition, the present preparation may be not only solid particle preparations such as power preparations, pulverized powder preparations, etc. obtained in the above, but also capsule preparations which are prepared
25 by enclosing the obtained solid particle preparations into hard capsules or soft capsules.

The present rebamipide preparation for rectal administration to be prepared before using

30 The possible solid particle form of the present preparation may include powder preparations, pulverized powder preparations, fine granule

preparations, granule preparations, and further capsule preparations which are prepared by enclosing the same into capsules. Among them, the present preparation is preferably in the form of a solid particle preparation having a particle size in the range of 75 μm to about 500 μm . Especially, in order to prevent the occurrence of unmixed-in lumps when dispersing in an aqueous vehicle, it is usual that the present preparation is preferably a solid particle preparation in which the ratio of particles having a particle size of less than 75 μm is 20 % or less, and the ratio of particles having a particle size of 500 μm or more is 5 % or less.

The present solid particle preparation may contain the above-mentioned rebamipide and carmellose sodium within particles constructing said preparation. Moreover, when the mixture containing an excipient, an additive, etc. in addition to rebamipide and carmellose sodium is used as a starting material, then the present solid particle preparation contain the excipient, an additive, etc. as well as rebamipide and carmellose sodium within said particles thereof. The appearance of the present solid particle preparation is usually white pulverized powders, and may contain about 4 to 6 % of water.

The present preparation in said solid particle form may be rapidly disintegrated by adding into an aqueous vehicle such as purified water, physiological saline solution, an aqueous sodium chloride solution, etc., more preferably into an aqueous sodium chloride solution containing 0.1 to 5 % by weight of NaCl, to easily give a uniform dispersion. It is usually preferable to adjust the pH value of the obtained dispersion in the range of pH 4.8 to 6.8.

The dispersion thus obtained is useful as an agent for improving subjective symptoms and objective symptoms of diseases such as gastric ulcer, duodenal ulcer, gastritis, etc.

EXAMPLES

The present invention is illustrated in more detail by the following Examples, but the present invention should not be construed to be limited thereto.

5 Example 1

The present preparation consisting of the following each component was prepared as follows.

Rebamipide	153 mg
Lactose	237 mg
L-HPC	80 mg
CMC-Na	820 mg
CMC-Na (as a binder)	10 mg
Magnesium stearate	5 mg
Silicic anhydride	5 mg

Each component to be used was as follows.

- (1) Rebamipide: manufactured by Otsuka Pharmaceutical Co., Ltd.
- 10 (2) Lactose: defined in the Japanese Pharmacopoeia, Wyndale lactose 200MESH®, manufactured by Lactose Company
- (3) L-HPC (Low-substituted hydroxypropyl cellulose): defined in the Japanese Pharmacopoeia, manufactured by Shin-Etsu Chemical Co., Ltd.
- (4) CMC-Na ("Celogen F-SC®"): manufactured by DAI-ICHI KOGYO
- 15 SEIYAKU CO., LTD.
- (5) Purified water: defined in the Japanese Pharmacopoeia
- (6) Anhydrous ethanol: defined in the Japanese Pharmacopoeia
- (7) Magnesium stearate: defined in the Japanese Pharmacopoeia, manufactured by Taihei Chemical Industrial Co., Ltd.
- 20 (8) Silicic anhydride (light silicic anhydride): defined in the Japanese Pharmacopoeia, "Aerosil®" manufactured by Nippon Aerosil Co., Ltd.

Namely, the above-mentioned amount (amount to be final

concentration) of each rebamipide, lactose, L-HPC and CMC-Na was weighed and mixed (as to CMC-Na, the amount of the upper line). As a binder solution, a 1% CMC-Na (F-SC) solution in 50 % anhydrous ethanol solution was prepared (using the amount of CMC-Na of the lower line). The resulting mixture was kneaded by a kneader (New Speed Kneader NSK-150, manufactured by Gokyo Seisakusho) together with a binder solution. After kneading, the mixture was dried by a fluid bed dryer (Multiplex Model MP-01, manufactured by Powrex Corporation). The conditions for kneading and drying are as follows.

Conditions for kneading

Kneader: New Speed Kneader NSK-150
Blade (rpm): 500 → 1500
Time (sec): 30 → 30

Namely, the kneading was carried out by stirring the mixture by a blade at 500 rpm for 30 seconds while a binder solution was added thereto. Then, the kneading was continued while the mixture was stirred by a blade at 1500 rpm for 30 seconds.

Conditions for fluid bed drying

Fluid bed dryer: Multiplex Model MP-01
Air inlet temperature: 85°C
Air outlet temperature: 45°C
Inlet air (m³/min): 45-50 m³/hr
Drying time: about 15 minutes

Then, the size of the dried particles was regulated by passing through a 500 μm sieve, and the particles completely passing through the sieve was collected as granules. Then, the particles remained on the sieve were pulverized by New Speed Mill Type ND-02 (0.5 mm screen, manufactured by OKADA SEIKO CO., LTD.) to give pulverized particles. The average particle size of the pulverized particles was in the range of 100 to 300 μm.

The average particle size was measured by Robot Sifter (RPS-95C

manufactured by Seishin Enterprise Co., Ltd.). That is, each sample was set on the above sifter, and the sieves to be used were set, and then, when the robot sifter was switched on, it can automatically measure the weight of the sieve without sample. Then, when a sample was put and weighed, the sieve started to shift, and the weight of each sieve was measured. Thus, the average particle size was automatically calculated and output. According to this method, the particle size distribution was simultaneously measured.

Further, the obtained granules and the pulverized particles were mixed to give a pulverized powder preparation.

To this pulverized powder, magnesium stearate and silicic anhydride in a prescribed amount as mentioned above were added and mixed to give 1310 mg of pulverized powder preparation sample for rectal administration having the following particle size distribution and the average particle size (μm).

500 μm or more	0.5 %
From 355 μm upto 500 μm	14.5 %
From 250 μm upto 355 μm	22.2 %
From 150 μm upto 250 μm	29.6 %
From 106 μm upto 150 μm	14.4 %
From 75 μm upto 106 μm	9.2 %
less than 75 μm	9.6 %
Average particle size	206 μm

Examples 2-5

In the same manner as in Example 1 or in a similar manner to Example 1 except that the conditions for kneading and drying were suitably modified, the present preparations consisting of the following each component as described in Table 2 were obtained.

Table 2

(mg)

Example No. Component (mg)	2	3	4	5
Rebamipide	459	306	102	51
Lactose	481	484	178	119
L-HPC	80	80	80	80
CMC-Na	820	820	820	820
CMC-Na	10	10	10	10
Magnesium stearate	5	5	5	5
Silicic anhydride	5	5	5	5
Total	1860	1710	1200	1090

Please note that the amount of CMC-Na of the upper line was an amount to be mixed in the powder, and the amount of the lower line was an amount to be added in a binder solution.

In all of the obtained pulverized powder preparation samples for rectal administration, the ratio of the particles having a particle size of less than 75 μm is 20 % or less, and the ratio of the particles having a particle size of 500 μm or more was about 5 %.

Example 6

The pulverized powder preparation sample obtained in Example 1 (1310 mg) was dispersed in purified water (60 ml) to give a rebamipide enema dispersion preparation.

Experiment 1 (water dispersibility test)

Each pulverized powder preparation sample obtained in Examples 1-5 was subjected to the following experiment just after the preparation thereof, or after they were allowed to be kept at room temperature for one month.

Namely, a 0.73 % aqueous NaCl solution (30 ml) was put into a polypropylene conical tube container (capacity: 50 ml), and a half amount of

the pulverized power preparation sample obtained in each Example, for example, 655 mg of the sample obtained in Example 1 containing 76.5 mg of rebamipide, was put into said container, and the container was vigorously shaken for 30 times in order to disperse well the contents in the container.

5 The condition (appearance) of the obtained liquid mixture was observed visually, and the water dispersibility of each sample was evaluated.

The results were evaluated by three scales, and ones in a good distribution condition were evaluated as Good, and ones having some aggregation were evaluated as No Good, and ones having some unmixed-in
10 lumps or agglomerates were evaluated as Bad.

The results are shown in the following Table 3.

Table 3

Example No.		Water dispersibility
1	Just after preparation	Good
	After one month storage	Good
2	Just after preparation	Good
	After one month storage	Good
3	Just after preparation	Good
	After one month storage	Good
4	Just after preparation	Good
	After one month storage	Good
5	Just after preparation	Good
	After one month storage	Good

As shown in Table 3, it is apparent that the rebamipide preparation
15 for rectal administration of the present invention has an excellent water dispersibility.

INDUSTRIALL APPLICABILITY

The present rebamipide solid particle preparation for rectal administration to be prepared before using shows an excellent water dispersibility, and hence, it can be easily and well dispersed when it is poured into an aqueous vehicle for dispersion such as physiological saline solution without any specific skill or training, and can give a desired rebamipide enema dispersion preparation with proper viscosity and osmotic pressure. Then, the obtained rebamipide enema dispersion preparation can be easily and simply administered rectally to the patient of ulcerative colitis. Further, since the present preparation is in a solid particle form, it shows an excellent stability and does not require any antiseptic agents or preservatives for storage. In addition, the present preparation has further advantages from viewpoints of manufacturing cost and transportation cost, and the manufacturing management thereof is easily done. Thus, the present preparation of rebamipide for rectal administration to be prepared before using is more suitably applied to the treatment of ulcerative colitis than the conventional rebamipide preparations.

CLAIMS

1. A rebamipide preparation for rectal administration to be prepared before using, which is a solid particle preparation comprising rebamipide and carmellose sodium, which is convertible into an enema dispersion preparation by dispersing in an aqueous vehicle when used.

2. The preparation according to Claim 1, wherein carmellose sodium is contained in an amount of 100 to 2000 parts by weight to 100 parts by weight of rebamipide.

3. The preparation according to Claim 1 or 2, which is in the solid particle form having an average particle size of 100 to 300 μm , where the ratio of particles having a particle size of less than 75 μm is 20 % or less, and the ratio of particles having a particle size of 500 μm or more is 5 % or less.

4. A method for preparing the preparation as set forth in any one of Claims 1-3, which comprises formulating rebamipide and carmellose sodium into a solid particle form by using an aqueous alcohol solution of carmellose sodium as a binder.

5. The method according to Claim 4, wherein the formulation of rebamipide and carmellose sodium into a solid particle form is carried out by wet-kneading a starting material containing rebamipide and carmellose sodium by using an aqueous alcohol solution of carmellose sodium as a binder, drying the resultant by fluid bed drying method, and regulating the size of the resulting particles.

6. The method according to Claim 5, wherein the binder is an aqueous alcohol solution of carmellose sodium in a concentration of 0.1 to 5 % by weight.

7. The method according to claim 6, wherein the binder is a 25 to 75 % by weight aqueous ethanol solution of carmellose sodium.

8. A rebamipide enema dispersion preparation, which is

prepared by dispersing the solid particle preparation as set forth in any one of Claims 1-3 in an aqueous vehicle.

9. A method for preparing a rebamipide enema dispersion preparation, which comprises dispersing the solid particle preparation as set forth in any one of Claims 1-3 in an aqueous vehicle.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP2005/016985

A. CLASSIFICATION OF SUBJECT MATTER

Int.Cl.⁷ **A61K31/4704** (2006.01), **A61K9/10** (2006.01), **A61K9/14** (2006.01), **A61K47/38** (2006.01), **A61P1/04** (2006.01), **C07D215/22** (2006.01)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Int.Cl.⁷ **A61K31/4704** (2006.01), **A61K9/10** (2006.01), **A61K9/14** (2006.01), **A61K47/38** (2006.01), **A61P1/04** (2006.01), **C07D215/22** (2006.01)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Published examined utility model applications of Japan 1922-1996
Published unexamined utility model applications of Japan 1971-2005
Registered utility model specifications of Japan 1996-2005
Published registered utility model applications of Japan 1994-2005

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

BIOSIS (STN), CAOLD (STN), CAPLUS (STN), EMBASE (STN), MEDLINE (STN), REGISTRY (STN), JMEDPlus (JOIS), JST7580 (JOIS), JSTPlus (JOIS)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y	HAMAMOTO, T., A Stability Study of a Rebamipide Enema: a Hospital Pharmaceutical Preparation, Journal of Japanese Society of Hospital Pharmacists. (2003), VOL.39, NO.9, pp.1155-1159	8 1-7, 9
X Y	MORI, T., Stability Study of a Rebamipide Rectal Suspension Enema and a Clinical Case Showing a Good Response, Japanese Journal of Pharmaceutical Health Care and Sciences (2003), Vol.29, No.3, pp.312-317	8 1-7, 9
Y	JP 06-157355 A (DAIICHI PHARM CO LTD) 1994.06.03 & WO 94/11033 A1 & AU 9454338 A & JP 06-511927 X & EP 669135 A1 & AU 676515 B & US 5676927 A & SG 46534 A1	1-9

☒ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

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INTERNATIONALSEARCHREPORT

International application No.

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C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	MATSUMOTO, M., The Pharmacy Manual, The First Edition, NANZANDO Inc. (1989), pp.107-113	1-9
A	JP 08-268895 A (CHUGAI PHARM CO LTD) 1996.10.15 & WO 96/23507 A1 & AU 9645483 A & EP 808629 A1 & AU 689366 B & KR 98701891 A & US 5968906 A & CN 1172433 A	1-9