

DESCRIPTION

ORAL TIPEPIDINE PREPARATION

TECHNICAL FIELD

[0001] The present invention relates to extended-release oral preparations that comprise tipepidine or pharmaceutically acceptable salts thereof and which are applicable in the field of medicaments.

BACKGROUND ART

[0002] Tipepidine is a substance that has an antitussive action equal to or greater than that of codeine phosphate and it also features an expectorant action. What is more, being non-opioid, tipepidine has long been used, both in prescription settings and by general consumers, as a medicament antitussive/expectorant or cough medicine.

[0003] It has recently been found that tipepidine suppresses G protein-coupled inwardly-rectifying potassium channels (GIRKs) and in addition to its use as the above-mentioned antitussive/expectorant or cough medicine, there are also reports about its use in various applications such as central dysfunctions including, for example, attention-deficit hyperactivity disorder, mood or emotion disorders such as depression, brain dysfunctions caused by environmental chemical substances, etc., obsessive-compulsive disorder, Parkinson's disease, schizophrenia, neuropathic pain, dysuria, dementia induced by β amyloid protein, Alzheimer's disease, and so forth (Patent Documents 1-9).

[0004] Tipepidine has heretofore been used as an antitussive/expectorant or cough medicine in the form of oral preparations such as tablets, powders, syrups, etc. that contain tipepidine hibenazate as the active ingredient. Upon oral administration, tipepidine hibenazate takes about 1.3 hours to reach a maximum plasma concentration, and having a plasma half-life of about 1.8 hours, it is effective for only a short duration and has conventionally been prescribed to patients as an oral drug of three-times-a-day dosage type.

[0005] In recently discovered uses of tipepidine in prophylactics or therapeutics that are specifically indicated for such diseases as attention-deficit hyperactivity disorder and

depression, the effect desirably acts in a consistent and sustained manner, and oral preparations of once- or twice-a-day dosage type that can be administered with the least possible frequency when the patient goes out to school, workplace, etc. are expected to fully exert their preventive or therapeutic effects against those indications by reducing the chance of the patient forgetting to take those medicines. What is more, the above-mentioned applications of tipepidine are predicated on its administration for several months, sometimes longer for a period of several years, so the required oral preparations of once- or twice-a-day dosage type are those which also take into account better compliance in medication. Típepidine hibenrate, however, has problems in that although it shows good solubility under acidic conditions in the stomach, it is so sparingly soluble in water that its solubility greatly drops in the lower part of the digestive tract where a neutral and low-moisture environment is dominant; it is therefore difficult to ensure a consistent and sustained release of tipepidine hibenrate in the stomach and intestines.

CITATION LIST

PATENT LITERATURE

- [0006] Patent Document 1: JP 2007-37258 A
- Patent Document 2: JP 2009-227631 A
- Patent Document 3: JP 2007-139153 A
- Patent Document 4: JP 2012-62272 A
- Patent Document 5: JP 2011-246446 A
- Patent Document 6: JP 2013-63958 A
- Patent Document 7: JP 2012-118172 A
- Patent Document 8: JP 2007-204366 A
- Patent Document 9: JP 2017-36242 A

SUMMARY OF INVENTION

TECHNICAL PROBLEM

- [0007] An object of the present invention is to provide a new extended-release oral preparation comprising tipepidine, in particular, an extended-release oral preparation of once-

or twice-a-day dosage type.

SOLUTION TO PROBLEM

[0008] The present inventors conducted an intensive study with a view to attaining the stated object and have found that in spite of the above-described pharmacokinetics of tipepidine, it is possible to control the rate of dissolution of tipepidine in the stomach so as to formulate an extended-release oral preparation that is capable of consistent and sustained release of tipepidine in the stomach and intestines.

[0009] Briefly, the present invention provides:

- (1) An extended-release oral solid composition comprising tipepidine or a pharmaceutically acceptable salt thereof as an active ingredient;
- (2) An extended-release oral solid composition of once- or twice-a-day dosage type comprising tipepidine or a pharmaceutically acceptable salt thereof as an active ingredient;
- (3) The composition recited in (1) or (2) comprising tipepidine or a pharmaceutically acceptable salt thereof as an active ingredient, further comprising a water-soluble polymeric base;
- (4) The composition recited in (3), wherein the water-soluble polymeric base is hypromellose or a carboxyvinyl polymer;
- (5) The composition recited in (3), wherein the water-soluble polymeric base is hypromellose;
- (6) The composition recited in (5), wherein the content of hypromellose ranges from 5 to 90 mass% of the composition;
- (7) The composition recited in any one of (4) to (6), wherein hypromellose is a mixture of different viscosities of hypromellose;
- (8) The composition recited in (7), wherein the mixture of different viscosities of hypromellose is a combination of at least one kind of hypromellose having a viscosity of 50 to 100 mPa•s and at least one kind of hypromellose having a viscosity of 4000 to 100000 mPa•s;
- (9) The composition recited in (7), wherein the mixture of different viscosities of

hypromellose is a combination of hypromellose having a viscosity of 100 mPa•s and at least one kind of hypromellose having a viscosity of 4000 to 15000 mPa•s;

(10) The composition recited in any one of (7) to (9), wherein the content of the mixture of different viscosities of hypromellose ranges from 5 to 45 mass% of the composition;

(11) The composition recited in any one of (7) to (9), wherein the content of the mixture of different viscosities of hypromellose ranges from 10 to 30 mass% of the composition;

(12) The composition recited in any one of (7) to (11), wherein the different viscosities of hypromellose consist of the lower and higher viscosities that are mixed at a mass ratio ranging between 25:75 and 90:10;

(13) The composition recited in any one of (7) to (11), wherein the different viscosities of hypromellose consist of the lower and higher viscosities that are mixed at a mass ratio ranging between 25:75 and 80:20;

(14) The composition recited in any one of (7) to (11), wherein the different viscosities of hypromellose consist of the lower and higher viscosities that are mixed at a mass ratio ranging between 40:60 and 60:40;

(15) The composition recited in any one of (1) to (14), comprising granules further comprising an excipient;

(16) The composition recited in (15), wherein the granules are produced by wet or dry granulation;

(17) The composition recited in (16), wherein a solvent used in the wet granulation is one that consists of water and ethanol mixed at a mass ratio ranging between 100:0 and 20:80;

(18) The composition recited in (16), wherein a solvent used in the wet granulation is one that consists of water and ethanol mixed at a mass ratio ranging between 100:0 and 40:60;

(19) The composition recited in any one of (1) to (18), wherein the tipepidine or pharmaceutically acceptable salt thereof is tipepidine hibenazate;

(20) The composition recited in any one of (1) to (19), wherein the oral solid composition is selected from a tablet, a capsule or a granule;

(21) The composition recited in any one of (1) to (20) for preventing or treating cough,

difficulty in phlegm expectoration, attention-deficit hyperactivity disorder, depression (e.g. treatment-resistant depression), bipolar disorder, schizophrenia, anxiety disorder, dementia, obsessive-compulsive disorder (e.g. treatment-resistant obsessive-compulsive disorder), Parkinson's disease, dysuria, pain, dementia induced by β amyloid protein, Alzheimer's disease, or the like.

ADVANTAGEOUS EFFECTS OF INVENTION

[0010] The oral solid composition of the present invention controls the rate of dissolution of tipepidine in the stomach so as to enable its consistent and sustained release in the stomach and intestines. In the oral solid composition of the present invention, tipepidine or a pharmaceutically acceptable salt thereof was observed to be capable of extended release at a controlled rate of dissolution and this helps provide a preparation of once- or twice-a-day dosage type which takes into account better compliance in medication.

BRIEF DESCRIPTION OF DRAWINGS

[0011] FIG. 1 shows the results of dissolution tests conducted in Examples 1 and 2.

FIG. 2 shows the results of dissolution tests conducted in Examples 3 and 4.

FIG. 3 shows the results of dissolution tests conducted in Examples 1 and 5.

FIG. 4 shows the results of dissolution tests conducted in Examples 6 and 7.

FIG. 5 shows the results of dissolution tests conducted in Examples 8 and 9.

FIG. 6 shows the results of dissolution tests conducted in Examples 9 and 10.

FIG. 7 shows the results of dissolution tests conducted in Examples 11 and 12.

FIG. 8 shows the result of a dissolution test conducted in Comparative Example 1.

FIG. 9 shows the results of dissolution tests conducted in Example 6 using test fluids with different pHs.

FIG. 10 shows the results of dissolution tests conducted in Example 7 using test fluids with different pHs.

FIG. 11 shows the results of dissolution tests conducted in Example 13 using test fluids with different pHs.

FIG. 12 shows the results of dissolution tests conducted in Example 14 using test

fluids with different pHs.

DESCRIPTION OF EMBODIMENTS

[0012] One embodiment of the present invention is an extended-release oral composition comprising tipepidine or a pharmaceutically acceptable salt thereof as an active ingredient.

[0013] Tipepidine can be used in its free form or as a pharmaceutically acceptable salt of tipepidine. Pharmaceutically acceptable salts of tipepidine include tipepidine hibenzate, tipepidine succinate, tipepidine stearyl sulfate salts, etc.

[0014] The content of tipepidine or a pharmaceutically acceptable salt thereof is typically from 10 to 50 mass% of the whole composition.

[0015] The “extended-release” property as used in the present invention may be evaluated by the second method for dissolution test (paddle method) specified in the Japanese Pharmacopoeia; in this method, 900 mL of the second fluid for dissolution test (one volume of a phosphate buffer with a pH of 6.8 to which is added one volume of water) is used as a test fluid and the active ingredient is dissolved at a paddle rotation speed of 50 rpm; the “extended-release” property means such that the relative dissolution of the active ingredient at the point in time of 2 hours after the start of the test is controlled at between 5 and 70%, preferably, the relative dissolution of the active ingredient at the point in time of 2 hours after the start of the test is controlled at between 5 and 60%, and more preferably, the relative dissolution of the active ingredient at the point in time of 6 hours after the start of the test is controlled between 30 and 80%.

[0016] The extended-release preparation of the subject invention may optionally be mixed with an inert carrier and processed in the usual manner so that it can be provided as granules, powders, capsules, tablets, etc. The inert carrier that may be used in the present invention refers to ingredients other than the water-soluble polymeric base that may be contained in the preparation together with the active ingredient but which show no efficacy. Examples included in the category of the inert carrier are an excipient, a lubricant, a disintegrant, a binder, a fluidizer, an antioxidant, a coating agent, a coloring agent, a flavoring agent, a surfactant, a plasticizer, etc.

[0017] The water-soluble polymeric base to be used in the present invention is a water-soluble polymer that serves as an extended-release base, and polymers selected from the following group may be used as the water-soluble polymer either individually or in admixture of two or more species: hypromellose, hydroxypropylcellulose, hydroxypropylmethylcellulose phthalate, hydroxypropylmethylcellulose acetate succinate, carboxymethylethylcellulose, carboxymethylcellulose sodium, hydroxyethylcellulose, methylcellulose, cellulose acetate phthalate, polyethylene glycol, polyvinylalcohol, polyvinylpyrrolidone, polyvinyl acetal diethylaminoacetate, aminoalkyl methacrylate copolymer E, aminoalkyl methacrylate copolymer RS, methacrylate copolymer L, methacrylate copolymer LD, methacrylate copolymer S, carboxyvinyl polymer, gum arabic, sodium alginate, propylene glycol alginate, agar, gelatin, tragacanth, and xanthan gum.

[0018] Examples of the excipient for use in the preparation of the present invention are selected from the following, which may be used either individually or in admixture of two or more species: lactose, microcrystalline cellulose, sucrose, powdered sugar, granulated sugar, glucose, mannitol, sorbitol, corn starch, starches, gum arabic, dextrin, pullulan, light silicic anhydride, low-substitution hydroxypropylcellulose, carboxymethylcellulose sodium, synthetic aluminum silicate, magnesium aluminometasilicate, dibasic calcium phosphate, and anhydrous dibasic calcium phosphate.

[0019] Examples of the lubricant for use in the preparation of the present invention are selected from the following, which may be used either individually or in admixture of two or more species: magnesium stearate, calcium stearate, stearic acid, talc, light silicic anhydride, colloidal silica, synthetic aluminum silicate, and magnesium aluminometasilicate.

[0020] Examples of the disintegrant for use in the preparation of the present invention are selected from the following, which may be used either individually or in admixture of two or more species: crospovidone, croscarmellose sodium, carmellose, carboxymethyl starch sodium, low-substitution hydroxypropylcellulose, carboxymethylcellulose calcium, microcrystalline cellulose, hydroxypropyl starch, corn starch, potato starch, and partially gelatinized starch.

[0021] Examples of the binder for use in the preparation of the present invention are selected from the following, which may be used either individually or in admixture of two or more species: hydroxypropylcellulose, polyvinylpyrrolidone, pullulan, and starch paste, etc.

[0022] The water-soluble polymer is not the sole example of the extended-release base of the present invention and a fat-soluble polymer may be used either alone or in combination with the water-soluble polymer. Water-soluble polymers are more preferred.

[0023] The water-soluble polymer in the present invention is preferably hypromellose or carboxyvinyl polymers, and hypromellose is more preferred.

[0024] Hypromellose as used in the present invention is synonymous with hydroxypropylmethylcellulose, which is a methyl and hydroxypropyl mixed cellulose ether. Hypromellose that can be used in the present invention may have different degrees of substitution by methoxy group and hydroxypropoxy group. Typical examples of hypromellose include those of substitution types 1828, 2208, 2906 and 2910 (see, for example, page 1305 of the 17th edition of the Japanese Pharmacopoeia) and each of these types can be used in the extended-release preparation of the present invention. In addition, various viscosities of hypromellose can be used. The viscosity of hypromellose here referred to is the value as measured in accordance with the 17th edition of the Japanese Pharmacopoeia (labeled viscosity: defined as the viscosity of a 2% aqueous solution at 20°C in the 17th edition of the Japanese Pharmacopoeia). A preferred viscosity is between 50 and 100000 mPa•s, more preferably between 100 and 15000 mPa•s.

[0025] In the present invention, hypromellose is preferably incorporated in an amount of 3 to 90 mass%, more preferably 5 to 60 mass%, and most preferably 5 to 45 mass%, of the oral composition. The amount of incorporation of hypromellose sometimes varies with the viscosity of hypromellose. For example, if hypromellose has a viscosity of 50 to 100 mPa•s, it is preferably incorporated in an amount of 15 to 90 mass%, more preferably 35 to 90 mass%, even more preferably 35 to 60 mass%. With viscosities of 4000 to 100000 mPa•s, say, 4000, 15000 or 100000 mPa•s, hypromellose is preferably incorporated in an amount of 5 to 40 mass%, more preferably 10 to 30 mass%.

[0026] Further in addition, in order to provide a more consistent extended-release property for the active ingredient, different viscosities of hypromellose are preferably used. Different viscosities of hypromellose may preferably be provided by using hypromellose of low viscosity, say, 50 to 100 mPa•s in combination with hypromellose of high viscosity, say, 4000 to 100000 mPa•s; the mass ratio at which the low-viscosity hypromellose is mixed with the high-viscosity hypromellose is preferably in the range between 25:75 and 90:10, more preferably between 25:75 and 80:20, even more preferably between 40:60 and 60:40, and most preferably 50:50. By using the low-viscosity hypromellose and the high-viscosity hypromellose at the above-specified mixing ratios, it is possible to achieve a significantly consistent extended-release property for the active ingredient,

[0027] The viscosity of the carboxyvinyl polymer refers to the viscosity of a 0.5 mass% aqueous solution (pH 7.5) and it is preferably from 4000 to 39400 mPa•s. In the present invention, the carboxyvinyl polymer is preferably incorporated in an amount of 15 to 90 mass% of the oral composition.

[0028] Tipepidine or a pharmaceutically acceptable salt thereof can be used in a granulated or yet-to-be granulated state together with an excipient. What is more, hypromellose can be used in a granulated or yet-to-be granulated state after it is mixed with tipepidine or a pharmaceutically acceptable salt thereof. For instance, an adequate extended-release property will be realized irrespective of the difference in production method. More preferably, hypromellose is mixed with tipepidine or a pharmaceutically acceptable salt thereof and the mixture is granulated and tableted to produce an oral preparation.

[0029] Water and ethanol which are solvents for use in wet granulation may be mixed in a mass ratio in the range between 100:0 and 0:100. More preferably, the water-to-ethanol mass ratio is in the range between 100:0 and 20:80, even more preferably in the range between 100:0 and 40:60.

[0030] The extended-release pharmaceutical composition of the present invention is used as an antitussive/expectorant or a cough medicine for preventing or treating cough, difficulty in phlegm expectoration, etc. In addition to these uses, tipepidine which has the ability to

suppress G protein-coupled inwardly-rectifying potassium channels (GIRKs) allows the extended-release pharmaceutical composition of the present invention to be used in the following applications.

[0031] Use as prophylactis or therapeutics for attention-deficit hyperactivity disorder, depression (e.g. treatment-resistant depression), bipolar disorder, schizophrenia (with positive symptoms, negative symptoms, cognitive disorder), anxiety disorder, dementia (Alzheimer-type, Lewy body-type), obsessive-compulsive disorder (e.g. treatment-resistant obsessive-compulsive disorder), Parkinson's disease, dysuria, pain, and so forth.

EXAMPLES

[0032] Hereinafter, the present invention will be described in greater detail by reference to Examples which, however, are by no means intended to limit the present invention and may be modified over a scope that will not depart from the spirit of the present invention.

[0033] Examples 1 and 2

Ingredients 1 to 4 listed in Table 1 were mixed, granulated using water, and dried to prepare granules. The thus prepared granules were mixed with ingredients 5 to 7 also listed in Table 1, and pressed to prepare tablets.

[0034] [Table 1]

	Ingredient	Mass (%)	
		Example 1	Example 2
1	Tipepidine hibenazate	27.7	27.7
2	Lactose hydrate	41.4	25.2
3	Microcrystalline cellulose	10.4	6.3
4	Hydroxypropylcellulose	5	5.3
5	Hypromellose (substitution type: 2208; viscosity: 15000 mPa•s)	15	0
6	Carboxyvinyl polymer (viscosity: 29400-39400 mPa•s)	0	35
7	Magnesium stearate	0.5	0.5
	Total	100	100

[0035] Examples 3 and 4

Ingredients 1 to 5 listed in Table 2 were mixed and pressed to prepare tablets.

[0036]

[Table 2]

	Ingredient	Mass (%)	
		Example 3	Example 4
1	Tipepidine hibenazate	22.1	22.1
2	Lactose hydrate	61.2	31.2
3	Light silicic anhydride	1	1
4	Hypromellose (substitution type: 2208; viscosity: 100 mPa•s)	15	45
5	Magnesium stearate	0.7	0.7
	Total	100	100

[0037] Example 5

Ingredients 1 to 4 listed in Table 3 were mixed, granulated using water, and dried to prepare granules. The thus prepared granules were mixed with ingredients 5 and 6 also listed in Table 3, and pressed to prepare tablets.

[0038] [Table 3]

	Ingredient	Mass (%)
		Example 5
1	Tipepidine hibenazate	27.7
2	Lactose hydrate	41.4
3	Microcrystalline cellulose	10.4
4	Hydroxypropylcellulose	5
5	Hypromellose (substitution type: 2208; viscosity: 4000 mPa•s)	15
6	Magnesium stearate	0.5
	Total	100

[0039] Examples 6 and 7

Ingredients 1 to 4 listed in Table 4 were mixed, granulated using a water/ethanol (mass ratio: 50/50) liquid mixture, and dried to prepare granules. The thus prepared granules were mixed with ingredients 5 to 7 also listed in Table 4, and pressed to prepare tablets.

[0040]

[Table 4]

	Ingredient	Mass (%)	
		Example 6	Example 7
1	Tipepidine hibenazate	23.7	23.7
2	Lactose hydrate	28.9	28.9
3	Microcrystalline cellulose	19.6	19.6
4	Hydroxypropylcellulose	6.3	6.3
5	Hypromellose (substitution type: 2208)	20 ¹⁾	20 ²⁾
6	Light silicic anhydride	1	1
7	Magnesium stearate	0.5	0.5
	Total	100	100

¹⁾ Hypromellose with a viscosity of 100 mPa•s and hypromellose with a viscosity of 4000 mPa•s were used in combination at a ratio of 90:10 (ratio is by mass, hereinafter the same).

²⁾ Hypromellose with a viscosity of 100 mPa•s and hypromellose with a viscosity of 4000 mPa•s were used in combination at a ratio of 50:50.

[0041] Examples 8 and 9

For Example 8, ingredients 1 to 7 listed in Table 5 were mixed and pressed to prepare tablets. For Example 9, ingredients 1 to 4 also listed in Table 5 were mixed, granulated using water, and dried to prepare granules. The thus prepared granules were mixed with ingredients 5 to 7 also listed in Table 5, and pressed to prepare tablets.

[0042] [Table 5]

	Ingredient	Mass (%)	
		Example 8	Example 9
1	Tipepidine hibenazate	22.1	22.1
2	Lactose hydrate	41.2	30.2
3	Microcrystalline cellulose	0	8
4	Hydroxypropylcellulose	0	4
5	Light silicic anhydride	1	0
6	Hypromellose (substitution type: 2208; viscosity: 100 mPa•s)	35	35
7	Magnesium stearate	0.7	0.7
	Total	100	100

[0043] Example 10

Ingredients 1 to 4 listed in Table 6 were mixed, granulated using a water/ethanol (mass ratio: 20/80) liquid mixture, and dried to prepare granules. The thus prepared granules

were mixed with ingredient 5 also listed in Table 6, and pressed to prepare tablets.

[0044] [Table 6]

	Ingredient	Mass (%)
		Example 10
1	Tipepidine hibenazate	22.1
2	Lactose hydrate	32.2
3	Microcrystalline cellulose	10
4	Hypromellose (substitution type: 2208; viscosity: 100 mPa•s)	35
5	Magnesium stearate	0.7
	Total	100

[0045] Examples 11 and 12

In Example 11, ingredients 1 to 4 listed in Table 7 were mixed, granulated using a water/ethanol (mass ratio: 50/50) liquid mixture, and dried to prepare granules. The thus prepared granules were mixed with ingredients 5 to 7 also listed in Table 7, and pressed to prepare tablets. In Example 12, ingredient 8 dispersed in a solvent was coated onto the tablets of Example 11 to prepare coated tablets.

[0046] [Table 7]

	Ingredient	Mass (%)	
		Example 11	Example 12
1	Tipepidine hibenazate	23.7	22.9
2	Lactose hydrate	28.9	27.8
3	Microcrystalline cellulose	19.6	19
4	Hydroxypropylcellulose	6.3	6.1
5	Hypromellose (substitution type: 2208; hypromellose with a viscosity of 100 mPa•s and hypromellose with a viscosity of 4000 mPa•s were used in combination at a ratio of 50:50)	20	19.3
6	Light silicic anhydride	1	1
7	Magnesium stearate	0.5	0.5
8	Hypromellose 2910/titanium oxide/macrogol 400 mixture	0	3.4
	Total	100	100

[0047] Examples 13 and 14

Ingredients 1 to 4 listed in Table 8 were mixed, granulated using a water/ethanol (mass ratio: 50/50) liquid mixture, and dried to prepare granules. The thus prepared granules were mixed with ingredients 5 to 7 also listed in Table 8, and pressed to prepare tablets.

[0048] [Table 8]

	Ingredient	Mass (%)	
		Example 13	Example 14
1	Tipecidine hibenazate	11.9	11.9
2	Lactose hydrate	40.7	40.7
3	Microcrystalline cellulose	19.6	19.6
4	Hydroxypropylcellulose	6.3	6.3
5	Hypromellose (substitution type: 2208)	20 ³⁾	20 ⁴⁾
6	Light silicic anhydride	1	1
7	Magnesium stearate	0.5	0.5
	Total	100	100

³⁾ Hypromellose with a viscosity of 100 mPa•s and hypromellose with a viscosity of 4000 mPa•s were used in combination at a ratio of 80:20.

⁴⁾ Hypromellose with a viscosity of 100 mPa•s and hypromellose with a viscosity of 4000 mPa•s were used in combination at a ratio of 40:60.

[0049] Test 1: Dissolution Test

The tablets prepared in Examples 1 to 12 and Comparative Example 1 were checked for their dissolvability. In accordance with the dissolution test method (paddle method) specified in the Japanese Pharmacopoeia under the General Tests, Processes and Apparatus, 900 mL of the second fluid for dissolution test was used as the test fluid and dissolution tests were conducted at a rotational speed of 50 rpm by means of automatic sampling and automated absorbance measurement. From the obtained values of measurement, the percent dissolution at each sampling time was determined.

[0050] The results with the samples of Examples 1 and 2 are shown in FIG. 1, from which one can see that the sample of Example 1 containing hypromellose and that of Example 2 containing the carboxyvinyl polymer showed a superior extended-release property.

[0051] The results with the samples of Examples 3 and 4 are shown in FIG. 2, from which one can see that the dissolution rate of tipecidine was controlled by changing the content of hypromellose.

[0052] The results with the samples of Examples 1 and 5 are shown in FIG. 3, from which one can see that the dissolution rate of tipecidine was controlled by changing the viscosity of hypromellose.

[0053] The results with the samples of Examples 6 and 7 are shown in FIG. 4, from which one can see that the dissolution rate of tipecidine was controlled by using different viscosities of hypromellose in combination.

[0054] The results with the samples of Examples 8 and 9 are shown in FIG. 5, from which one can see that the sample of Example 8 prepared by direct tableting and that of Example 9 prepared by wet granulation showed a superior extended-release property.

[0055] The results with the samples of Examples 9 and 10 are shown in FIG. 6, from which one can see that the sample of Example 9 using water as the solvent for granulation and that of Example 10 using a water/ethanol liquid mixture as the solvent for granulation showed a superior extended-release property.

[0056] The results with the samples of Examples 11 and 12 are shown in FIG. 7, from which one can see that the samples of Examples 11 and 12 showed a superior extended-release property irrespective of whether the coating was applied or not.

[0057] The result with the sample of Comparative Example 1 is shown in FIG. 8. Commercially available asverin 20 tablets were used in Comparative Example 1.

[0058] Test 2: Dissolution Test Using Test Fluids with Different pHs

The tablets prepared in Examples 6, 7, 13 and 14 were checked for their dissolvability. In accordance with the dissolution test method (paddle method) specified in the Japanese Pharmacopoeia under the General Tests, Processes and Apparatus, 900 mL of the first fluid for dissolution test (pH 1.2; 2.0 g of sodium chloride was dissolved in 7.0 mL of hydrochloric acid and water to make 1000 mL) and 900 mL of the second fluid for dissolution test were used as the test fluids and dissolution tests were conducted at a rotation speed of 50 rpm by means of automatic sampling and automated absorbance measurement. From the obtained values of measurement, the percent dissolution at each sampling time was determined.

[0059] The result with the sample of Example 6 is shown in FIG. 9, from which one can see that the tablets prepared in Example 6 using different viscosities of hypromellose showed constant dissolution rates irrespective of the test fluid (pH).

[0060] The result with the sample of Example 7 is shown in FIG. 10, from which one can see that the tablets prepared in Example 7 using different viscosities of hypromellose showed constant dissolution rates irrespective of the test fluid (pH).

[0061] The result with the sample of Example 13 is shown in FIG. 11, from which one can see that the tablets prepared in Example 13 using different viscosities of hypromellose showed constant dissolution rates irrespective of the test fluid (pH).

[0062] The result with the sample of Example 14 is shown in FIG. 12, from which one can see that the tablets prepared in Example 14 using different viscosities of hypromellose showed constant dissolution rates irrespective of the test fluid (pH).

INDUSTRIAL APPLICABILITY

[0063] According to the present invention, the rate at which tipepidine dissolves in the stomach is controlled to enable its consistent and sustained release in the stomach and intestines, whereby tipepidine or pharmaceutically acceptable salts thereof can be provided as an extended-release preparation for oral administration.

CLAIMS

1. An extended-release oral solid composition comprising tipepidine or a pharmaceutically acceptable salt thereof as an active ingredient.
2. An extended-release oral solid composition of once- or twice-a-day dosage type comprising tipepidine or a pharmaceutically acceptable salt thereof as an active ingredient.
3. The composition as recited in claim 1 or 2 comprising tipepidine or a pharmaceutically acceptable salt thereof as an active ingredient, further comprising a water-soluble polymeric base.
4. The composition as recited in claim 3, wherein the water-soluble polymeric base is hypromellose or a carboxylvinyl polymer.
5. The composition as recited in claim 3, wherein the water-soluble polymeric base is hypromellose.
6. The composition as recited in claim 5, wherein the content of hypromellose ranges from 5 to 90 mass% of the composition.
7. The composition as recited in any one of claims 4 to 6, wherein hypromellose is a mixture of different viscosities of hypromellose.
8. The composition as recited in claim 7, wherein the mixture of different viscosities of hypromellose is a combination of at least one kind of hypromellose having a viscosity of 50 to 100 mPa•s and at least one kind of hypromellose having a viscosity of 4000 to 100000 mPa•s.
9. The composition as recited in claim 7, wherein the mixture of different viscosities of hypromellose is a combination of hypromellose having a viscosity of 100 mPa•s and at least one kind of hypromellose having a viscosity of 4000 to 15000 mPa•s.
10. The composition as recited in any one of claims 7 to 9, wherein the content of the mixture of different viscosities of hypromellose ranges from 5 to 45 mass% of the composition.
11. The composition as recited in any one of claims 7 to 9, wherein the content of the

mixture of different viscosities of hypromellose ranges from 10 to 30 mass% of the composition.

12. The composition as recited in any one of claims 7 to 11, wherein the different viscosities of hypromellose consist of the lower and higher viscosities that are mixed at a mass ratio ranging between 25:75 and 90:10.

13. The composition as recited in any one of claims 7 to 11, wherein the different viscosities of hypromellose consist of the lower and higher viscosities that are mixed at a mass ratio ranging between 25:75 and 80:20.

14. The composition as recited in any one of claims 7 to 11, wherein the different viscosities of hypromellose consist of the lower and higher viscosities that are mixed at a mass ratio ranging between 40:60 and 60:40.

15. The composition as recited in any one of claims 1 to 14, comprising granules further comprising an excipient.

16. The composition as recited in claim 15, wherein the granules are produced by wet or dry granulation.

17. The composition as recited in claim 16, wherein a solvent used in the wet granulation is one that consists of water and ethanol mixed at a mass ratio ranging between 100:0 and 20:80.

18. The composition as recited in claim 16, wherein a solvent used in the wet granulation is one that consists of water and ethanol mixed at a mass ratio ranging between 100:0 and 40:60.

19. The composition as recited in any one of claims 1 to 18, wherein the tipepidine or pharmaceutically acceptable salt thereof is tipepidine hibenstate.

20. The composition as recited in any one of claims 1 to 19, wherein the oral solid composition is selected from a tablet, a capsule or a granule.

21. The composition as recited in any one of claims 1 to 20 for preventing or treating cough, difficulty in phlegm expectoration, attention-deficit hyperactivity disorder, depression (including treatment-resistant depression), bipolar disorder, schizophrenia, anxiety disorder,

dementia, obsessive-compulsive disorder (including treatment-resistant obsessive-compulsive disorder), Parkinson's disease, dysuria, pain, dementia induced by β amyloid protein, or Alzheimer's disease.