manufactured by POWREX CORPORATION). The coating conditions were: inlet air temperature about 85°C, spray air pressure about 0.35 MPa, spray air volume about 100 Nl/min, inlet air volume about 1.5 m3/min, rotor rev rate about 550 rpm, spray rate about 18 g/min, spray position lower side. After the completion of coating, the obtained fine granules were then dried at 85°C for about 40 min in the tumbling fluidized bed coater and passed through a round sieve to give fine granules coated with intermediate layer with a particle size of 150 μm - 350 μm.

[Composition of fine granules coated with intermediate layer (~~110~~ 135 mg)]

fine granules containing a pharmaceutically active ingredient (Production Example 1)	85 mg
hypromellose	14 mg
low-substituted hydroxypropyl cellulose	10 mg
talc	6 mg
titanium oxide	6 mg
mannitol	14 mg
total	135 mg

[0034]

Production Example 4

Production of controlled release fine granules

Purified water (3474.5 g) was heated to 80°C, and polysorbate 80 (29.55 g), glycerol monostearate (73.87 g), triethyl citrate (246.5 g), yellow ferric oxide (2.373 g) and ferric oxide (2.373 g) were dispersed therein. The suspension was cooled to room temperature, and then ethyl acrylate/methyl methacrylate copolymer dispersion (Eudragit NE30D) (410.4 g) and citric acid (1.231 g) were added and the mixture was uniformly mixed. Furthermore, methacrylic acid/ethyl acrylate copolymer dispersion (Eudragit L30D-55) (3694 g) was added and the mixture was uniformly mixed to give a coating solution.

The fine granules coated with intermediate layer (1282.5 g)

ingredient obtained in Reference Example 17 was coated with an intermediate layer coating solution by using a tumbling fluidized bed coater (MP-10 TOKU-2 type, manufactured by POWREX CORPORATION), and then dried to give fine granules with the following composition. The intermediate layer coating solution was produced by dissolving hypromellose (TC-5E, 504 g) and mannitol (504 g) in purified water (5400 g), and dispersing titanium oxide (216 g), talc (216 g) and low-substituted hydroxypropyl cellulose (L-HPC-32, 360 g) in the obtained solution. The fine granules containing a pharmaceutically active ingredient (2550 g) obtained in Reference Example 17 were coated with a predetermined amount (6000 g) of the intermediate layer coating solution (7200 g) by using a tumbling fluidized bed coater (MP-10 TOKU-2 type, manufactured by POWREX CORPORATION). The coating conditions were: inlet air temperature about 85°C, spray air pressure about 0.35 MPa, spray air volume about 100 Nl/min, inlet air volume about 1.5 m3/min, rotor rev rate about 550 rpm, spray rate about 18 g/min, spray position lower side. After the completion of coating, the obtained fine granules were then dried at 85°C for about 4 0 min in the tumbling fluidized bed coater and passed through a round sieve to give fine granules coated with intermediate layer with a particle size of 150 μm - 350 μm.

[Composition of fine granules coated with intermediate layer (~~110~~ 135 mg)]

fine granules containing a pharmaceutically active ingredient (Reference Example 17)	85 mg
hypromellose	14 mg
low-substituted hydroxypropyl cellulose	10 mg
talc	6 mg
titanium oxide	6 mg
mannitol	14 mg
total	135 mg

Fig. 13.

[0110]

Experimental Example 14

A dissolution test (test method (3)) was performed for the formulations obtained in Examples 1 and 2, Reference Example 16 and Comparative Example 1. The results are shown in Fig. 14.

[0111]

Experimental Example 15

A dissolution test (test method (3)) was performed for the formulations obtained in Example 3, Reference Example 16 and Comparative Example 1. The results are shown in Fig. 15. [0112]

Reference Example 25

Production of granules containing a pharmaceutically active ingredient

Compound X (3645 g), magnesium carbonate (972 g), granulated sugar (2401 g) and low-substituted hydroxypropyl cellulose (L-HPC-32, 72 9 g) were thoroughly mixed to give a spray agent. Sucrose/starch spherical granules (Nonpareil 101, 2250 g) were supplied into a centrifugation rolling granulator (CF-600S, Freund Corporation) and coated with a predetermined amount (7173 g) of the above-mentioned spray agent (7747 g) while spraying a hydroxypropylcellulose (HPC-L, 27 g) solution (2 w/w%) to give granules containing a pharmaceutically active ingredient. The obtained granules containing a pharmaceutically active ingredient were dried in vacuo at 40°C for 16 hr, and passed through a round sieve to give granules with a particle size of 710 μm - 1400 μm.

The coating conditions were: spray air volume about 40 L/min, inlet air volume about 1.0 m3/min, spray rate ahout 60 g/min, rotor rev rate about 125 rpm.

[Composition of granules containing a pharmaceutically active ingredient (~~57.78~~63.0 mg)]

Sucrose/starch spherical granules (Nonpareil 101)	15.0 mg
compound X	22.5 mg
magnesium carbonate	6.0 mg
granulated sugar	14.82 mg
low-substituted hydroxypropyl cellulose	4.5 mg
hydroxypropyl cellulose	0.18 mg
total	63.0 mg

[0113]

Reference Example 26

Production of granules coated with intermediate layer

The granules containing a pharmaceutically active ingredient obtained in Reference Example 25 was coated with an intermediate layer coating solution by using a fluidized bed coater (FD-S2, manufactured by POWREX CORPORATION), and then dried to give fine granules with the following composition. The intermediate layer coating solution was produced by dissolving hypromellose (TC-5EW, 1135 g) in purified water (20420 g), and dispersing titanium oxide (679.7 g) and talc (455.0 g) in the obtained solution. The granules containing a pharmaceutically active ingredient (15120 g) obtained in Reference Example 25 were coated with a predetermined amount (19860 g) of the intermediate layer coating solution (22689.7 g) by using a fluidized bed coater (FD-S2, manufactured by POWREX CORPORATION). The coating conditions were: inlet air temperature about 60°C, spray air pressure about 0.5 MPa, spray air volume about 250 Nl/min, inlet air volume about 7 m3/min, spray rate about 70 g/min. After the completion of coating, the obtained granules were passed through a round sieve to give fine granules coated with intermediate layer with a particle size of 710 μm - 1400 μm. The obtained granules were dried in vacuo at 40°C for 16 hr.

[Composition of fine granules coated with intermediate layer (~~65~~ 70.88 mg)]

granules containing a pharmaceutically active ingredient

(Reference Example 25)	63.00 mg
hypromellose	3.94 mg
talc	1.58 mg
titanium oxide	2.36 mg
total	70.88 mg

[0114]

Reference Example 27

Production of controlled release granules

Polyethylene glycol 6000 (273.0 g) and polysorbate 80 (124.8 g) were dissolved in purified water (12600 g), and titanium oxide (273.0 g), talc (759.2 g) and methacrylic acid/ethyl acrylate copolymer dispersion (Eudragit L30D-55) (9126 g) were dispersed in the obtained solution, and uniformly mixed to give a coating solution. The granules coated with intermediate layer (15310 g) obtained in Reference Example 26 were coated with a predetermined amount (20200 g) of the aforementioned coating solution (23156.0 g) by using a fluidized bed coater (FD-S2, manufactured by POWREX CORPORATION). The coating conditions were: inlet air temperature 60°C, spray air pressure about 0.5 MPa, spray air volume about 250 Nl/min, inlet air volume about 7 m3/min, spray rate about 70 g/min. The obtained granules were passed through a round sieve to give controlled release granules with a particle size of 850 μm - 1400 μm. The obtained granules were dried in vacuo at 4 0°C for 16 hr.

[Composition of controlled release fine granules (~~79.92~~86.91 mg)]

fine granules coated with intermediate layer (Reference Example 26)	70.88 mg
methacrylic acid/ethyl acrylate copolymer	10.53 mg
polyethylene glycol 6000	1.05 mg
polysorbate 80	0.48 mg
titanium oxide	1.05 mg
talc	2.92 mg
total	86.91 mg

solution. The fine granules containing a pharmaceutically active ingredient (112.2 kg) obtained in Production Example 37 were coated with the intermediate layer coating solution (264 kg) by using a tumbling fluidized bed coater (MP-400, manufactured by POWREX CORPORATION). The coating conditions were: inlet air temperature about 75°C, spray air volume about 1100 Nl/min/gun, inlet air volume about 55 Nm3/min, rotor rev rate about 120 rpm, spray rate about 270 mL/min/gun, spray position lower side. After the completion of coating, the obtained fine granules were then dried at 85°C for about 20 min in the tumbling fluidized bed coater and passed through a round sieve to give the intermediate layer-coated fine granules with a particle size of 150 pm - 350 pm.

[Composition of fine granules coated with intermediate layer (~~110~~ 135 mg)]

fine granules containing a pharmaceutically active ingredient (Production Example 37)	85 mg
hypromellose	14 mg
low-substituted hydroxypropyl cellulose	10 mg
talc	6 mg
titanium oxide	6 mg
mannitol	14 mg
total	135 mg

[0118]

Production Example 39

Production of controlled release fine granules

Purified water (105.3 kg) was heated to 70°C, and polysorbate 80 (1.102 kg), glycerol monostearate (2.756 kg), yellow ferric oxide (0.08845 kg) and ferric oxide (0.08845 kg) were dispersed therein. The suspension was cooled to room temperature, and then ethyl acrylate/methyl methacrylate copolymer dispersion (Eudragit NE30D) (15.31 kg) and citric acid (0.046 kg) were added and the mixture was uniformly mixed. Furthermore, methacrylic acid/ethyl acrylate copolymer

tablet were 41 N and 30 seconds, respectively. The dissolution rate of the obtained tablet in O.1N HCl in 1 hour was 1.2%, showing superior acid resistance.

[0164]

experimental Example 22

A dissolution test (test method (2)) was performed for the formulations obtained in Examples 8 and 9. The results are shown in Fig. 22.

[Industrial Applicability]

[0165]

The orally disintegrating tablet of the present invention comprising fine granules including lansoprazole can suppress the dissolution of lansoprazole in the presence of acid, for example, in the stomach, to achieve a desired dissolution profile of lansoprazole. In addition, since the formulation can control the release of lansoprazole for a long time, a therapeutically effective concentration can be maintained for a prolonged time. Therefore administration frequency can be reduced, and an effective treatment with a small dose can be ensured, and effects such as reduction of side effects caused by the rise of blood concentration and the like can be achieved. Since the formulation shows superior disintegration property or dissolution property in the oral cavity, it is used for the treatment or prophylaxis of various diseases as a formulation conveniently taken by elderly persons and children even without water. In addition, since the fine granules including the pharmaceutically active ingredient having a size preventing dusty texture are blended, a formulation, which is smooth and comfortable in the mouth, can be provided.

~~[0166]~~

~~This application is based on a US provisional patent application No. 61/427,384, the contents of which are incorporated in full herein.~~

Claims

1. An orally disintegrating tablet comprising
(i) fine granules showing controlled release of a pharmaceutically active ingredient, which comprises fine granules containing a pharmaceutically active ingredient and a coating layer comprising a methacrylic acid/methyl acrylate/methyl methacrylate copolymer, wherein the fine granules containing a pharmaceutically active ingredient are coated with more than 80 wt% and not more than 300 wt% of the copolymer, relative to the fine granules containing a pharmaceutically active ingredient, and
(ii) fine granules showing controlled release of a pharmaceutically active ingredient, which comprises the pharmaceutically active ingredient and a coating layer comprising (a) an ethyl acrylate/methyl methacrylate copolymer, and (b) one or more kinds of polymers selected from the group consisting of methacrylic acid/ethyl acrylate copolymer, hypromellose phthalate, carboxymethylethylcellulose, polyvinyl acetate phthalate, hydroxypropyl methylcellulose acetate succinate and cellulose acetate phthalate, wherein the fine granules (i) and fine granules (ii) have an average particle size of not more than 500 μm, and the pharmaceutically active ingredient is lansoprazole or an optically active form thereof or a salt thereof.

2. An orally disintegrating tablet comprising
(i) fine granules showing controlled release of a pharmaceutically active ingredient, which comprises a pharmaceutically active ingredient and a coating layer comprising (a) a methacrylic acid/methyl acrylate/methyl methacrylate copolymer, and (b) one or more kinds of polymers selected from the group consisting of an ethyl acrylate/methyl methacrylate copolymer, polyvinyl acetate and ethylcellulose, and
(ii) fine granules showing controlled release of a