

FORM 2

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COMPLETE SPECIFICATION

(See sections 10 & rule 13)

1. TITLE OF THE INVENTION

HYPROMELLOSE ACETATE SUCCINATE FOR USE AS HOT-MELT EXTRUSION CARRIER, HOT-MELT EXTRUSION COMPOSITION, AND METHOD FOR PRODUCING HOT-MELT EXTRUDATE

2. APPLICANTS (S)

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3. PREAMBLE TO THE DESCRIPTION

COMPLETE

The following specification particularly describes the invention and the manner in which it is to be performed.



TITLE OF THE INVENTION

HYPROMELLOSE ACETATE SUCCINATE FOR USE AS HOT-MELT EXTRUSION CARRIER, HOT-MELT EXTRUSION COMPOSITION, AND METHOD FOR PRODUCING HOT-MELT EXTRUDATE

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BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention relates to hypromellose acetate succinate (HPMCAS), a hot-melt extrusion composition comprising the HPMCAS, and a method for producing 10 a hot-melt extrudate.

2. Description of the Related Art

A method for producing a preparation by melt-extruding a mixture of a drug and a polymer under heating has recently attracted attentions.

For example, a solid dispersion obtained by solidifying a poorly water-soluble 15 drug and a polymer through a hot-melt extrusion exhibits improved biodegradability since the drug is, in an amorphous form, molecularly dispersed in the polymer carrier and apparent solubility of the drug is markedly improved. The hot-melt extrusion can be carried out without a solvent so that it can be applied to water-labile drugs. In the absence of solvent recovery, the hot-melt extrusion provides various advantages 20 including the advantages that concerns about safety or environment can be reduced, energy in a solvent recovery step can be saved, and the safety of workers can be improved. Further, different from a conventional batch production system, the hot-melt extrusion permits continuous production so that it has drawn attentions also from the standpoint of hourly productivity and consumption energy.

25 Examples of the polymer to be used for the hot-melt extrusion include



hypromellose acetate succinate (hereinafter also called “HPMCAS”) having four substituents in total introduced, more specifically, having two substituents, a methoxy group (-OCH₃) and a hydroxypropoxy group (-OC₃H₆OH) introduced into a cellulose skeleton to form ether structures and having two substituents, an acetyl group (-COCH₃) and a succinyl group (-COC₂H₄COOH) introduced to form ester structures.

With regard to an HPMCAS-containing solid dispersion obtained by the hot-melt extrusion method, there is, for example, proposed a method for producing a solid dispersion containing HPMCAS (commercially available “AS-LF” having a molar substitution of from 0.16 to 0.35 and an average particle size of 5 µm) and a poorly water-soluble drug through a hot-melt extrusion method in which water is added to the solid dispersion to reduce the glass transition temperature or softening temperature of the HPMCAS or the drug (WO2003/077827).

There is also proposed a method for producing a preparation comprising posaconazole, which is a poorly water-soluble drug, and a hydroxypropylmethyl cellulose derivative polymer having a particle size of from 0.2 to 1 µm through hot-melt extrusion in which the hydroxypropylmethyl cellulose derivative polymer is HPMCAS (commercially available “AS-MF” having a molar substitution of from 0.15 to 0.34 and an average particle size of 5 µm, or “AS-MG” having a molar substitution of from 0.15 to 0.34 and an average particle size of 1 mm) (JP 2011-516612T, which is a Japanese phase publication[¶] WO 2009/129300).

There is further proposed an enteric preparation in which a meltable substance such as hydrogenated castor oil is used as a binder and a core substance containing a pharmaceutical compound is coated with a film of an enteric substance having an average particle size of from 1 to 500 µm (JP04-290817A).



SUMMARY OF THE INVENTION

Commercially available HPMCAS having an average particle size of not more than 10 μm described in WO2003/077827 or JP 2011-516612T, however, has low flowability of powder owing to a small particle size and a high agglomeration property.

5 When a hot-melt extrudate is formed using a hot-melt extruder, a powder mixture of a drug and the above-mentioned HPMCAS is likely to form a bridge in the hopper of a feeder, thereby preventing constant feed and continuous operation. This results in reduction in uniformity of drug content and reduction in a weight ratio of the HPMCAS to the drug. The reason why the HPMCAS having such a small average particle size
10 has inevitably been used conventionally is that the HPMCAS is mainly used as an enteric coating agent and the HPMCAS in a finer powder form has been demanded in order to form a uniform film with a water-dispersible enteric coating agent. Commercially available HPMCAS having an average particle size of from 0.5 to 1.0 mm to be used for solvent coating is excellent in powder flowability. However, when
15 it is used for production of a solid dispersion with a hot-melt extruder, poor miscibility of the HPMCAS with a drug deteriorates the uniformity of the drug content in the resulting solid dispersion. The HPMCAS having a large average particle size has inevitably been used for solvent coating conventionally since a powder causing less dusting and easy to handle during preparation of a solution has been demanded.,

20 JP 04-290817A relates to a dry coating composition comprising HPMCAS for coating the periphery of a core substance containing a pharmaceutical compound. Accordingly, the drug is not molecularly dispersed in an amorphous form in an enteric substance.

With the foregoing in view, the invention has been made. An object of the
25 invention is to provide a hot-melt extrudate excellent in uniform miscibility between



HPMCAS and a drug, and a method for producing the hot-melt extrudate in which a powder can be fed smoothly for hot-melt extrusion, by using a hot-melt extrusion composition comprising a HPMCAS having an average particle size within a predetermined range.

5 With a view to achieving the above-mentioned object, the present inventors have carried out an intensive investigation. As a result, it has been found that by adjusting the average particle size of HPMCAS to fall within a predetermined range, the resulting HPMCAS can be fed smoothly, and a hot-melt extrudate having high uniformity of miscibility between the HPMCAS and a drug can be produced, leading to
10 the completion of the invention.

 In one aspect of the invention, there is provided hypromellose acetate succinate for use as a hot-melt extrusion carrier having a volume average particle size (D_{50}) as measured by dry laser diffraction of from 70 to 300 μm and a loose bulk density of from 0.25 to 0.40 g/cm^3 . In another aspect of the invention, there is also
15 provided a hot-melt extrusion composition comprising the hypromellose acetate succinate and a drug. In a further aspect of the invention, there is also provided a method for producing a hot-melt extrudate comprising the steps of: hot-melting a hot-melt extrusion composition comprising hypromellose acetate succinate having a volume average particle size (D_{50}) as measured by dry laser diffraction of from 70 to 300 μm
20 and having a loose bulk density of from 0.25 to 0.40 g/cm^3 and a drug at a hot-melt temperature equal to or higher than a melting temperature of the hypromellose acetate succinate, or at a hot-melt temperature equal to or higher than a temperature at which both the hypromellose acetate succinate and the drug become melt; and extruding the hot-melted composition.

25 According to the invention, powder feeding in hot-melt extrusion can be

carried out more smoothly than ever before, and owing to the improved miscibility with a drug, a hot-melt extrudate having a uniform drug content can be produced continuously.

5 DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

The invention will hereinafter be described more specifically.

HPMCAS has a volume-average particle size (D_{50}) of from 70 to 300 μm , preferably from 100 to 280 μm , more preferably from 100 to 200 μm . The volume-average particle size (D_{50}) is measured by using dry laser diffraction. When HPMCAS 10 has a volume-average particle size of less than 70 μm , it has low powder flowability so that it forms a bridge in the hopper of a feeder, thereby preventing the continuous operation. In addition, owing to deteriorated miscibility with a drug and deteriorated uniformity of drug content, the resulting solid preparation cannot have therein a necessary amount of the drug. Further, owing to a decrease in the weight ratio of the 15 HPMCAS to the drug, the drug does not become amorphous, thereby reducing the improvement of drug solubility. When HPMCAS has a volume-average particle size of more than 300 μm , a difference in the average particle size from the drug typically having an average particle size of from 1 to 50 μm , becomes too large, so that segregation occurs in the hopper and the drug content varies. As a result, owing to 20 deterioration in uniformity of drug content, the resulting solid preparation cannot have therein a necessary amount of the drug. When the particle size of HPMCAS is too large during hot-melting, the HPMCAS cannot be melted sufficiently, thereby reducing improvement of drug solubility.

The term “dry laser diffraction” means a method comprising the steps of 25 subjecting a powder sample blown by means of compressed air to a laser beam, and



measuring a diffraction intensity thereof to determine a volume-average particle size. For example, the method utilizes "Mastersizer" produced by Malvern Instruments, UK, or "HELOS" produced by Sympatec, Germany. According to description of, for example, "Kaitei Zoho Funtai Bussei Zusetsu" ("revised and enlarged edition of 5 Illustration of Powder Physical Properties") edited by The Society of Powder Technology, Japan and The Association of Powder Method Industry and Engineering, Japan, published by Nikkei Gijutsu Tosho, 1985, p88, the volume-average particle size is calculated based on the equation: $\{\Sigma(nD^3)/\Sigma n\}^{1/3}$ wherein D is a particle diameter, n is the number of particles having said particle diameter, and Σn is a total number of 10 particles. D_{50} means a particle size at 50% in the cumulative particle size distribution.

The loose bulk density of the HPMCAS is from 0.25 to 0.40 g/ml, preferably from 0.30 to 0.40 g/ml, more preferably from 0.33 to 0.38 g/ml. When HPMCAS has a loose bulk density of less than 0.25 g/ml, the HPMCAS becomes too light so that it forms a bridge in the hopper of a feeder, thereby preventing the continuous operation. 15 In addition, owing to deterioration in miscibility with a drug and deterioration in uniformity of drug content, the resulting solid preparation cannot have therein a necessary amount of the drug, and owing to a decrease in a weight ratio of the HPMCAS to the drug, the drug does not become amorphous, thereby reducing the improvement of drug solubility. When HPMCAS has a loose bulk density of more 20 than 0.40 g/ml, the HPMCAS becomes too heavy so that it causes segregation in the hopper and variation in drug content. In addition, the HPMCAS having an excessively high loose bulk density requires much time for hot-melting the HPMCAS, leading to insufficient melting of the HPMCAS and reduction of improvement of drug solubility.

The term "loose bulk density" means a bulk density in a loosely filled state 25 and the loose bulk density can be determined in the method comprising the steps of:

uniformly feeding a sample into a cylindrical vessel (made of stainless) having a diameter of 5.03 cm, a height of 5.03 cm and a volume of 100 ml through a Japan Industrial Standards (JIS) 22-mesh sieve having openings of 710 μm from 23 cm above the vessel; leveling off the top surface of the sample; and weighing the vessel filled with 5 the sample.

The degree of compaction of the HPMCAS is preferably from 15 to 40%, more preferably from 20 to 35% from the standpoint of flowability.

The term "degree of compaction" means a bulk-decreasing degree and can be calculated from the following equation:

10 Degree of compaction (%)

$$= [\{ (\text{tapped bulk density}) - (\text{loose bulk density}) \} / (\text{tapped bulk density})] \times 100$$

Herein, the term "tapped bulk density" means the bulk density measured after the sample is densely filled by tapping. The term "tapping" means an operation of dropping a vessel filled with a sample from a predetermined height in repetition to give 15 a light impact onto the bottom of the vessel, thereby filling the vessel with the sample densely. In practice, after the loose bulk density is measured by leveling off the top surface of the sample and then weighing the vessel filled with the sample, a cap is put on the vessel. The sample powder is added thereto until it reaches the upper end of the cap, and then tapped 180 times from a tapping height of 1.8 cm. After completion of 20 the tapping, the cap is removed and the top surface of the powder is leveled at the upper surface of the vessel. The bulk density in this state is designated as "tapped bulk density". The above-described measurement operation can be carried out using a powder tester "PT-S", produced by Hosokawa Micron Corporation.

The angle of repose of the HPMCAS is preferably from 30 to 45°, more 25 preferably from 30 to 40° from the standpoint of flowability. The angle of repose can

be determined by using a powder tester "PT-S" produced by Hosokawa Micron Corporation, allowing a sample powder to flow down from a height of 75 mm onto a disc-shaped stage being made of a metal and having a diameter of 80 mm until it makes a constant angle, and measuring an angle between the accumulated powder and the 5 stage. The smaller the angle becomes, the more excellent flowability the powder has.

The molar substitution degree of methoxy groups, which are substituents of the HPMCAS, is not particularly limited, but is preferably from 0.70 to 2.90, more preferably from 1.00 to 2.40, still more preferably from 1.4 to 1.9.

10 The molar substitution degree of hydroxypropoxy groups, which are substituents of the HPMCAS, is not particularly limited, but is preferably from 0.20 to 1.50, more preferably from 0.2 to 1.0, still more preferably from 0.40 to 0.90.

The molar substitution degree of acetyl groups, which are substituents of the HPMCAS, is not particularly limited, but is preferably from 0.10 to 2.50, more preferably from 0.10 to 1.00, still more preferably from 0.40 to 0.95.

15 The molar substitution degree of succinyl groups, which are substituents of the HPMCAS, is not particularly limited, but is preferably from 0.10 to 2.50, more preferably from 0.10 to 1.00, still more preferably from 0.10 to 0.60.

20 The contents of the substituents of the HPMCAS including the hydroxypropoxy group can be measured in accordance with the method described in "Hypromellose acetate succinate" of Official Monographs of the Japanese Pharmacopoeia, Sixteenth Edition, Supplement I.

The viscosity at 20°C of a 2% by weight aqueous dilute sodium hydroxide (0.1 mol/L NaOH) solution of the HPMCAS is preferably from 1.1 to 20 mPa·s, more preferably from 1.5 to 3.6 mPa·s. When the viscosity is less than 1.1 mPa·s, a shear 25 force may not be applied during hot-melt extrusion because of a too low melt viscosity,

which may cause idle running of a piston or screw, or may cause difficulty in extruding from a discharge port. When the viscosity is more than 20 mPa·s, the hot-melt extrusion composition comprising the HPMCAS may have a too high viscosity and an excessive torque may be applied to a piston or screw, which may prevent rotation of the 5 piston or screw, or may stop the machine for safety reasons. The viscosity can be measured in accordance with General Tests of HPMCAS in the Japanese Pharmacopoeia, Sixteenth Edition.

HPMCAS can be prepared using the method described in, for example, JP 54-061282A. Hypromellose also called "hydroxypropylmethyl cellulose" (hereinafter 10 also called "HPMC") and used as a raw material is dissolved in glacial acetic acid, and subjected to addition of acetic anhydride and succinic anhydride as esterifying agents and addition of sodium acetate as a reaction catalyst. The resulting mixture is allowed to react under heating. After completion of the reaction, a large amount of water is added to the reaction mixture to allow HPMCAS to precipitate. The precipitate thus 15 obtained is washed with water and then dried to obtain a granular dry product having a volume-average particle size of from about 0.5 to 2.0 mm.

The dry product thus obtained is ground in a grinder to obtain HPMCAS. Since the HPMCAS has a low softening temperature, an impact grinder having a 20 structure not easily causing an increase in the temperature of the ground product such as a jet mill, a knife mill or a pin mill is preferred.

The drug is not particularly limited as long as it is orally administrable. Examples of the drug include drugs for the central nervous system; drugs for the cardiovascular system; drugs for the respiratory system; drugs for the digestive system; antibiotics; antitussives/expectorants; antihistamines; analgesics, antipyretics and anti- 25 inflammatory drugs; diuretics; autonomic drugs; antimalarial drugs; antidiarrheal

agents; psychotropic drugs; and drugs of vitamins and derivatives thereof.

Examples of the drugs for the central nervous system include diazepam; idebenone; aspirin; ibuprofen; paracetamol; naproxen; piroxicam; dichlofenac; indomethacin; sulindac; lorazepam; nitrazepam; phenytoin; acetaminophen; 5 ethenzamide; ketoprofen; and chlordiazepoxide.

Examples of the drugs for the cardiovascular system include molsidomine; vincocetine; propranolol; methyldopa; dipyridamol; furosemide; triamterene; nifedipine; atenolol; spironolactone; metoprolol; pindolol; captopril; isosorbide nitrate; delapril hydrochloride; meclofenoxate hydrochloride; diltiazem hydrochloride; etilefrine 10 hydrochloride; digitoxin; propranolol hydrochloride; and alprenolol hydrochloride.

Examples of the drugs for the respiratory system include amlexanox; dextromethorphan; theophylline; pseudo-ephedrine; salbutamol; and guaiphenecin.

Examples of the drugs for the digestive system include benzimidazole-based drugs having anti-ulcer action such as 2-[(3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl)methylsulfinyl]benzimidazole and 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridyl)methylsulfinyl]benzimidazole; cimetidine; ranitidine; pirenzepine hydrochloride; pancreatin; bisacodyl; and 5-aminosalicylic acid.

Examples of the antibiotics include talampicillin hydrochloride; bacampicillin hydrochloride; cephaclor; and erythromycin.

20 Examples of the antitussives/expectorants include noscapine hydrochloride; carbetapentane citrate; dextromethorphan hydrobromide; isoaminile citrate; and dimemorfan phosphate.

Examples of the antihistamines include chlorpheniramine maleate; diphenhydramine hydrochloride; and promethazine hydrochloride.

25 Examples of the analgesics, antipyretics and anti-inflammatory drugs include

ibuprofen; diclofenac sodium; flufenamic acid; sulpyrine; aspirin; and ketoprofen.

Examples of the diuretics include caffeine.

Examples of the autonomic drugs include dihydrocodeine phosphate; dl-methylephedrine hydrochloride; atropine sulfate; acetylcholine chloride; and
5 neostigmine.

Examples of the antimalarial drugs include quinine hydrochloride.

Examples of the antidiarrheal agents include loperamide hydrochloride.

Examples of the psychotropic drugs include chlorpromazine.

Examples of the drugs of vitamins and derivatives thereof include Vitamin A;
10 Vitamin B1; fursultiamine; Vitamin B2; Vitamin B6; Vitamin B12; Vitamin C; Vitamin D; Vitamin E; Vitamin K; calcium pantothenate; and tranexamic acid.

According to the invention, in particular, use of the HPMCAS as a carrier for a poorly water-soluble drug can improve solubility of the poorly water-soluble drug. The term "poorly water-soluble drug" as used herein means a drug which is, in water,
15 "slightly soluble", "very slightly soluble", or "practically insoluble, or insoluble" described in the Japanese Pharmacopoeia, Sixteenth Edition. When 1 g or 1 mL of a drug in solid form is put in a beaker, the water is poured in the beaker, and the resulting mixture is vigorously shaken for mixing for 30 seconds at 5-minute intervals at 20±5°C, the term "slightly soluble" means the degree of dissolution in which water of from 100
20 mL to less than 1000 mL is required to dissolve the drug within 30 minutes. The term "very slightly soluble" means the degree of dissolution in which water of from 1000 mL to less than 10000 mL is required to dissolve the drug within 30 minutes in the same manner. The term "practically insoluble, or insoluble" means the degree of dissolution in which water of 10000 mL and more is required to dissolve 1 g or 1 mL of a
25 pharmaceutical in solid form within 30 minutes in the same manner.

In the above-mentioned pharmaceutical test, the dissolution of a poorly water-soluble drug means that it dissolves in water or becomes miscible with water, and as a result, fibers or the like are not present or if any, only a trace amount of them is present.

Specific examples of the poorly water-soluble drug include a zole-based 5 compounds such as itraconazole, ketoconazole, fluconazole, and metconazole; dihydropyridine-based compounds such as nifedipine, nitrendipine, amlodipine, nicardipine, nilvadipine, felodipine, and efonidipine; propionic acid-based compounds such as ibuprofen, ketoprofen, and naproxen; and indole-acetic acid-based compounds such as indomethacin and acemetacin; Additional examples include griseofulvin; 10 phenytoin; carbamazepine; and dipyridamole.

A weight ratio of the HPMCAS to the drug is not particularly limited. It is preferably from 1:0.01 to 1:100, more preferably from 1:0.1 to 1:10, still more preferably from 1:0.2 to 1:5 from the standpoint of storage stability in a morphized form.

According to the invention, the composition may further comprise an optional 15 additive such as a plasticizer or a surfactant in order to improve formability during hot-melt extrusion.

Examples of the plasticizer include acetone; higher alcohols including preferably C₁₀ to C₂₀ alcohols such as cetyl alcohol and stearyl alcohol; polyhydric alcohols including preferably diol, triol, tetraol, pentaol and hexaol such as mannitol, 20 sorbitol and glycerin; beeswax; triethyl citrate; alkylene glycols such as polyethylene glycol and propylene glycol; triacetin; dibutyl sebacate; glycerin monostearate; and monoglycerin acetate.

Examples of the surfactant include anionic surfactants such as sodium lauryl sulfate; nonionic surfactants such as diglycerides, poloxamers, polyoxyethylene sorbitan 25 fatty acid esters (Tween 20, 60, and 80), glycerin fatty acid esters, and propylene glycol

fatty acid esters; and natural surfactants such as lecithin and sodium taurocholate.

The composition comprises the plasticizer in an amount of preferably 30% by weight or less, and the surfactant in an amount of preferably 10% by weight or less, each on basis of the weight of the HPMCAS from the standpoint of storage stability.

5 The hot-melt extrudate may optionally comprise various additives ordinarily used in this field such as an excipient, a binder, a disintegrant, a lubricant, and an agglomeration preventive, so that the hot-melt extrudate can be used as an oral solid preparation such as a tablet, a granule, a fine granule, a capsule and a film formulation.

10 Examples of the excipient include a sugar such as sucrose, lactose, mannitol and glucose; starch; and crystalline cellulose. The excipient may be comprised in an amount of from 5 to 80% by weight by the solid preparation.

15 Examples of the binder include polyvinyl alcohol; polyacrylic acid; polyvinylpyrrolidone; hydroxyethyl cellulose; hydroxypropylmethyl cellulose; hydroxypropyl cellulose; macrogols; gum Arabic; gelatin; and starch. The binder may be comprised in an amount of from 0.5 to 5% by weight by the solid preparation.

20 Examples of the disintegrant include low-substituted hydroxypropyl cellulose carmellose or salts thereof; croscarmellose sodium; carboxymethyl starch sodium; crospovidone; crystalline cellulose; and crystalline cellulose carmellose sodium. The disintegrant may be comprised in an amount of from 1 to 10% by weight by the solid preparation.

25 Examples of the lubricant and the agglomeration additive include talc; magnesium stearate; calcium stearate; colloidal silica; stearic acid; waxes; hydrogenated oil; polyethylene glycols; and sodium benzoate. The lubricant and/or the agglomeration additive may be comprised respectively in an amount of from 0.1 to 5% by weight by the solid preparation.

The oral solid preparation thus obtained may comprise film coating with a water-soluble coating agent such as methyl cellulose or hypromellose, or enteric coating with an enteric coating agent such as hypromellose acetate succinate, hypromellose phthalate or a methacrylate acrylate copolymer.

5 Next, a method for producing a hot-melt extrudate will be described.

First, a hot-melt extrusion composition is prepared by mixing HPMCAS having a volume-average particle size (D_{50}) of from 70 to 300 μm and a loose bulk density of from 0.25 to 0.40 g/cm^3 , a drug and an optional component. The hot-melt extrusion composition thus obtained is charged in a hot-melt extruder from a hopper 10 thereof and extruded into a desired shape such as columnar or film shape as well as round or quadrangular shape, to obtain a hot-melt extrudate.

The hot-melt extruder is not particularly limited as long as it has a structure capable of heating the HPMCAS, a drug and others in the system for melting; kneading the resulting mixture with application of a shear force with a piston or screw to the 15 mixture; and then extruding the kneaded mixture from a die. In the standpoint of obtaining a more uniform extrudate, a twin-screw extruder is preferable. Specific examples include "Capilograph" (uniaxial piston extruder) produced by Toyo Seiki Seisaku-sho, "Nano-16" (twin-screw extruder) produced by Leistritz, and "MiniLab" (twin-screw extruder) and "PharmaLab" (twin-screw extruder) produced by 20 ThermoFisher Scientific.

The hot-melt temperature is not particularly limited. The hot-melt temperature is preferably a temperature at which the hot-melt extrusion composition is melted for smooth extrusion and degradation of the drug or polymer owing to heat can be avoided as much as possible. More specifically, when a solid dispersion is not 25 formed, the hot-melt temperature is preferably a temperature equal to or higher than the

melting temperature of the HPMCAS. When a solid dispersion is formed, the hot-melt temperature is preferably a temperature equal to or higher than the temperature at which both the HPMCAS and the drug become melt. Also when addition of the drug decreases the melting temperature of the HPMCAS, the hot-melt temperature is preferably equal to or higher than the temperature at which both the HPMCAS and the drug become melt.

5 More specifically, the hot-melt temperature is preferably from 50 to 250°C, more preferably from 60 to 200°C, still more preferably from 90 to 190°C. When the hot-melt temperature is less than 50°C, extrusion may become difficult to be carried out owing to insufficient melting. When the hot-melt temperature is higher than 250°C,

10 the molecular weight may be reduced owing to degradation of the HPMCAS or the drug, and deactivation may take place owing to hydrolysis of the substituents.

The hot-melt extrusion conditions are not particularly limited as long as they permit extrusion of a hot-melt extrusion composition having a viscosity of preferably from 1 to 100000 Pa·s during hot-melt extrusion. When a uniaxial piston extruder is used, an extrusion rate is preferably from 1 to 1000 mm/min, more preferably from 10 to 500 mm/min. When a twin-screw extruder is used, a screw rotation number is preferably 1 to 1000 rpm, more preferably 1 to 500 rpm. When the extrusion rate is less than 1 mm/min or the screw rotation number is less than 1 rpm, thermal degradation may occur owing to a long time of staying in the system. When the extrusion rate is more than 1000 mm/min or the screw rotation number is more than 1000 rpm, a hot-melt procedure at the kneading part may become insufficient so that a melt condition of the drug and the polymer in the hot-melt extrudate may not be uniform.

The hot-melt extrudate obtained by extrusion is cooled after a discharge port 25 of the die by natural air of room temperature (from 1 to 30°C) or by cooling air. In

order to minimize the thermal degradation of a drug, and in order to prevent recrystallization of a drug if the drug is an amorphized drug, the hot-melt extrudate is cooled to preferably 50°C or less, more preferably room temperature or lower (30°C or less) is desired.

5 The hot-melt extrudate after cooling may be optionally pelletized into pellets of from 0.1 to 5 mm by using a cutter, or the pellets thus obtained may be ground into granules or powders as particle size control. For grinding, an impact grinder such as a jet mill, a knife mill or a pin mill is preferred because the structure of the impact grinder is not likely to cause a temperature increase of the ground product. When the
10 temperature in the cutter or grinder becomes high, particles may adhere firmly to each other owing to thermal softening of the HPMCAS so that grinding under cooling air is preferred.

EXAMPLES

15 The invention will hereinafter be described specifically by Examples and Comparative Examples. However, it should not be construed that the invention is limited to or by Examples.

<Production of HPMCAS-7>

20 In a 50-L kneader, 12 kg of glacial acetic acid was placed, and 6 kg of hypromellose (HPMC) having a molar substitution degree of methoxy groups of 1.91 and a molar substitution degree of hydroxypropoxy groups of 0.24 was added into the kneader to dissolve the HPMC in the glacial acetic acid. To the resulting solution were added 3.5 kg of acetic anhydride, 1.2 kg of succinic anhydride and 2.9 kg of sodium
25 acetate, and the resulting mixture was allowed to react at 85°C for 5 hours. After

purified water (6.7 kg) was added to the reaction mixture and the resulting mixture was stirred, purified water was further added thereto to allow a HPMCAS in granular form to precipitate. A crude HPMCAS was collected by filtration. The crude HPMCAS was washed with purified water, dried, and then sieved through 10-mesh sieve having 5 openings of 1700 μm to obtain HPMCAS-7 having final water content of 1.2% by weight.

The content of each substituent of the resulting HPMCAS-7 was measured in accordance with the method described in the Japanese Pharmacopoeia, Sixteenth Edition, Supplement I. As a result, HPMCAS-7 was found to have methoxy content of 10 22.9% by weight (molar substitution degree of methoxy: 1.87), hydroxypropoxy content of 7.0% by weight (molar substitution degree of hydroxypropoxy: 0.24), acetyl content of 7.9% by weight (molar substitution degree of acetyl: 0.47), and succinyl content of 12.7% by weight (molar substitution degree of succinyl: 0.32).

HPMCAS-7 thus obtained had a volume-average particle size of 500 μm and 15 a loose bulk density of 0.420.

<Production of HPMCAS-1>

HPMCAS-7 was ground using a pin mill “100UPZ” produced by Hosokawa Micron Corporation at a feed rate of 20 kg/hr and a disc rotational speed of 1500 rpm to 20 obtain HPMCAS-1 having powder properties as shown in Table 1.

<Production of HPMCAS-2>

HPMCAS-7 was ground using a jet mill “CPY-2” produced by Nippon Pneumatic Mfg. Co., Ltd. at a feed rate of 20 kg/hr and a grinding pressure of 0.4 MPa 25 to obtain HPMCAS-2 having powder properties as shown in Table 1.



<Production of HPMCAS-3>

HPMCAS-7 was ground using a pin mill “100UPZ” produced by Hosokawa Micron Corporation at a feed rate of 20 kg/hr and a disc rotational speed of 1000 rpm to 5 obtain HPMCAS-3 having powder properties as shown in Table 1.

<Production of HPMCAS-4>

HPMCAS-7 was ground using a pin mill “100UPZ” produced by Hosokawa Micron Corporation at a feed rate of 20 kg/hr and a disc rotational speed of 500 rpm to 10 obtain HPMCAS-4 having powder properties as shown in Table 1.

<Production of HPMCAS—6>

HPMCAS-7 was ground using a jet mill “CPY-2” produced by Nippon Pneumatic Mfg. Co., Ltd. at a feed rate of 10 kg/hr and a grinding pressure of 0.5 MPa 15 to obtain HPMCAS-6 having powder properties as shown in Table 1.

<HPMCAS—5>

As HPMCAS-5, “Shin-Etsu AQOAT AS-MF” produced by Shin-Etsu Chemical Co., Ltd. having a volume-average particle size of about 5 μm was used as a 20 commercially available fine power of HPMCAS.

<Evaluation of Flowability of HPMCAS-1 to 7>

Measurement results of a loose bulk density, a tapped bulk density, a degree of compaction, and an angle of repose of each of the thus-obtained HPMCAS powders 25 by using a powder tester “PT-S” produced by Hosokawa Micron Corporation are shown

in Table 1. With respect to the degree of compaction and the angle of repose serving as an indicator of flowability, HPMCAS-1 to 4 exhibit lower values than those of HPMCAS-5 and 6, which suggests that HPMCAS-1 to 4 are superior in flowability.

5 Table 1

sample	volume-average particle size (μm)	loose density (g/cm^3)	bulk	degree of compaction	angle of repose ($^\circ$)
HPMCAS-1	76	0.326	28.2	38.7	
HPMCAS-2	105	0.384	20.2	36.4	
HPMCAS-3	163	0.336	20.6	36.2	
HPMCAS-4	271	0.394	22.9	35.1	
HPMCAS-5	5	0.230	47.0	55.0	
HPMCAS-6	21	0.278	39.8	42.5	
HPMCAS-7	500	0.420	10.0	35.0	

<Evaluation of Feed Rate of HPMCAS-1 to 7>

The 300g of each of HPMCAS-1 to 7 was introduced into a powder feed port of a single screw powder feeder having a screw diameter of 55 mm and a rotational speed of screw of 10 rpm, and a powder feed rate (g/min) at a discharge port was measured six times at intervals of 20 seconds. The above-mentioned operation was conducted three times and a coefficient of variation Cv [$\text{Cv} = (\text{standard deviation}/\text{average}) \times 100$] serving as an indicator of variation in feed rate was determined from an average of the feed rates measured 18 times in total and a standard deviation. The results are shown in Table 2.

HPMCAS-1 to 4 having lower Cv values than those of HPMCAS-5 to 7 are superior in flowability and superior in constant feeding of powder during hot-melt extrusion.



Table 2

sample	coefficient of variation Cv of feed rate of HPMCAS (%)
HPMCAS-1	4.2
HPMCAS-2	3.8
HPMCAS-3	4.3
HPMCAS-4	4.1
HPMCAS-5	12.0
HPMCAS-6	8.0
HPMCAS-7	6.5

<Evaluation of uniform miscibility of HPMCAS-1 to 7>

5 In a polyethylene bag were charged 30 g of vitamin C powder having an average particle size of 25 μm as a model drug and 90 g of each of HPMCAS-1 to 7. After shaken ten times with hands, the resulting mixture was placed in a powder feeder “Accurate” produced by KUMA Engineering Co., Ltd. and then discharged at a screw 10 rotational speed of 80 rpm. From the HPMCAS thus discharged, about 4 g was sampled nine times as time elapsed. From each of the fractions, 0.4 g was precisely weighed and vitamin C was extracted using purified water. After filtration through a membrane filter and dilution, an absorbance was measured using a UV spectrophotometer at a wavelength of 257 nm and an optical path length of 10 mm. A coefficient of variation Cv, $\text{Cv} = (\text{standard deviation}/\text{average}) \times 100$, was determined 15 from the vitamin C content in each of the fractions. The results are shown in Table 3. The values of the coefficient of variation for HPMCAS-1 to 4 are lower than those for HPMCAS-5 to 7, exhibiting that HPMCAS-1 to 4 are superior in miscibility during hot-melt extrusion.

Table 3

sample	coefficient of variation Cv of vitamin C content (%)
HPMCAS-1	5.2
HPMCAS-2	3.8
HPMCAS-3	4.3
HPMCAS-4	4.1
HPMCAS-5	7.0
HPMCAS-6	12.0
HPMCAS-7	10.6

<Examples 1 to 4 and Comparative Examples 1 to 2>

5 Preparation of Solid Dispersion

Hot-melt extrusion compositions were prepared by mixing each of HPMCAS-1(Example 1), HPMCAS-2 (Example 2), HPMCAS-3 (Example 3), HPMCAS-4 (Example 4), HPMCAS-7 (Comparative Example 1) with nifedipine as a poorly water-soluble drug in a mortar (at a HPMCAS: nifedipine mass ratio of 1:0.5). Hot-melt extrusion at 160°C of each of the resulting compositions was carried out using a hot-melt extrusion test apparatus “Capilograph” (uniaxial piston melt extruder) produced by Toyo Seiki Seisaku-sho, Ltd. having a die diameter of 1mm and a die height of 10 mm at an extrusion rate of 50 mm/min.

The resulting hot-melt extrudate was ground using a grinder “Wonder Blender WB-1”produced by Osaka Chemical Co., Ltd. at 20000 rpm, followed by filtration through a 30-mesh sieve. The powder thus obtained were subjected to the dissolution test described in the Japanese Pharmacopoeia, Sixteenth Edition.

A dissolution ratio (% by weight) of nifedipine eluted from 270 mg of the



resulting powder (corresponding to 90 mg of nifedipine) after 10 minutes was measured by using 900 ml of 2nd fluid having a pH value of 6.8 to be used in Disintegration Test of the Japanese Pharmacopoeia, Sixteenth Edition and a dissolution tester "NTR-6100A" produced by Toyama Sangyo Co., Ltd. at a paddle rotational speed of 100 rpm. The 5 amount of nifedipine was determined from the UV absorbance at 325 nm with an optical path length of 10 mm based on an absorbance calibration curve drawn at known concentrations in advance. The results are shown in Table 4. In Comparative Example 2, the same test was conducted on nifedipine bulk powder. The dissolution ratio after 10 minutes was measured because a maximum dissolution ratio is usually 10 observed after 10 minutes.

Table 4

	sample	dissolution ratio of nifedipine after 10 min (% by weight)
Example 1	HPMCAS-1	76.7
Example 2	HPMCAS-2	72.2
Example 3	HPMCAS-3	70.0
Example 4	HPMCAS-4	68.9
Comp. Ex. 1	HPMCAS-7	48.0
Comp. Ex. 2	nifedipine bulk powder	13.3

The powder obtained in each of Examples 1 to 4 showed marked 15 improvement in dissolution rate of nifedipine compared with the nifedipine bulk powder in Comparative Example 2. The powder obtained in Comparative Example 1 was inferior in dissolution improvement to those obtained in Examples 1 to 4. This is presumably because solubility was insufficient during hot-melt extrusion and formation of a solid dispersion was insufficient owing to a large particle size and a high loose bulk



density.

Powder X-ray diffraction analysis was carried out with respect to the powder obtained in each of Examples 1 to 4. Consequently, no crystal peak characteristic of nifedipine was observed. Thus, it is evident that in a solid dispersion obtained by hot-melt extrusion, nifedipine is dispersed in an amorphous form in the HPMCAS.

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CLAIMS

We Claim:

1. Hypromellose acetate succinate for use as a hot-melt extrusion carrier having a volume-average particle size (D_{50}) as measured by dry laser diffraction of from 70 to 300 μm and a loose bulk density of from 0.25 to 0.40 g/cm^3 .

2. The hypromellose acetate succinate for use as a hot-melt extrusion carrier according to claim 1, wherein the hypromellose acetate succinate has a degree of compaction of from 15 to 40%.

3. A hot-melt extrusion composition comprising the hypromellose acetate succinate as claimed in claim 1 or 2 and a drug.

4. The hot-melt extrusion composition according to claim 3, wherein the drug is a poorly water-soluble drug.

5. A method for producing a hot-melt extrudate, comprising the steps of:

hot-melting a hot-melt extrusion composition comprising hypromellose acetate succinate having a volume-average particle size (D_{50}) as measured by dry laser diffraction of from 70 to 300 μm and a loose bulk density of from 0.25 to 0.40 g/cm^3 and a drug at a hot-melt temperature equal to or higher than a melting temperature of the hypromellose acetate succinate, or at a hot-melt temperature equal to or higher than a temperature at which both of the hypromellose acetate succinate and the drug become melt; and

extruding the hot-melted composition.

6. The method for producing a hot-melt extrudate according to claim 5, wherein the hot-melt temperature is from 50 to 250°C.

ABSTRACT OF DISCLOSURE

Provided are a hot-melt extrudate excellent in uniform miscibility with a drug; and a method for producing a hot-melt extrudate capable of smoothly feeding a powder in hot-melt extrusion. More specifically, provided are hypromellose acetate succinate (HPMCAS) for use as a hot-melt extrusion carrier having a volume average particle size (D_{50}) of from 70 to 300 μm as measured by dry laser diffraction and a loose bulk density of from 0.25 to 0.40 g/cm^3 ; and a hot-melt extrusion composition comprising the HPMCAS and a drug. Also provided is a method for producing a hot-melt extrudate comprising the steps of: hot-melting the hot-melt extrusion composition at a hot-melt temperature equal to or higher than a melting temperature of the HPMCAS, or at a hot-melt temperature equal to or higher than a temperature at which both of the HPMCAS and the drug become melt; and extruding the hot-melted composition.

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