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Description

This invention relates to a novel controlled release pharmaceutical preparation and a method for producing the same.

One known type of controlled release formulation relies on the presence in the pharmaceutically active ingredient containing core of materials which in the presence of water or gastric fluid, form a gel-like complex of low solubility which retards the dissolution of the active ingredient out of the core. Such a tablet is described in US-A- 3458622. Such tablets suffer from the disadvantage that since little of the gummy complex is present initially, the active ingredient at or near the surface dissolves fairly rapidly and there is an initial surge wherein a relatively large amount of active ingredient is released in the beginning for a period of 1 hour.

An attempt to solve the initial surge problem is described in US-A-4252786 wherein a rupturable relatively water-insoluble water permeable film formed of a combination of hydrophobic and hydrophilic polymers over an insoluble swelling type delayed release matrix or core containing the active ingredient which core contains a blend of polyvinyl pyrolidone and a carboxy vinyl hydrophilic polymer is provided. Initially, while the film is intact, the release of the active ingredient is primarily controlled by diffusion of solvent and solute molecules through the film. As water or gastric fluid permeates through the film, the gummy complex forms and the slight swelling of the complex causes the film to rupture or erode.

US-A-4,610,870 describes a controlled release pharmaceutical formulation which undergoes substantially or approaches zero order release of active drug is provided, preferably in the form of a coated tablet, containing a core portion from which medicament, such as procainamide hydrochloride, is slowly released over a controlled length of time. The core also includes one or more hydrocolloid gelling agents having a viscosity of within the range of from about 10,000 to about 200,000 centipoises in 2% solution at 20 • C., such as hydroxypropylmethyl cellulose and/or methyl cellulose, one or more non-swellable binders and/or wax binders (where the medicament and/or hydrocolloid gelling agents are non-compressible), one or more inert fillers or excipients, one or more lubricants, and optionally one or more anti-adherents such as silicon dioxide and water. The above-described core is coated with a pharmaceutical coating composition containing a hydrophobic polymer and a hydrophilic polymer. Upon oral injection of the sustained release tablet, the tablet coating first slowly peels off up to hours after ingestion, leaving the core contents in contact with gastric fluid. Upon contact with gastric fluid, the core very slowly erodes; the outermost hydrocolloid particles hydrate and swell to form a gelatenous mass which acts as a protective barrier. Medicament is released by diffusion or leaching through the gel layer.

In another type of known pharmaceutical preparation, drug-containing cores are coated with compact films of hydrophobic polymeric substances.

Such preparations have advantages that they have excellent water resistance, light resistance, humidity resistance, abrasion resistance, storage stability, etc.

However, a preparation having a compact film of a hydrophobic substance has disadvantages in that it is slow in releasing rate of the inner drug and also that the drug cannot be completely released.

In other words, release of a drug is owing to the difference in concentration or osmotic pressure between the inside and outside of the preparation which is created by the dissolution of the drug to saturated concentration with digestive fluids having penetrated into the inside through the film. However, since the compact film of a hydrophobic substance scarcely has open space, permeation of the fluid into the film is slow, and even when an osmotic pressure difference enough to release the drug to outside may be created, the dissolution speed is not sufficient because of the small total area of the open space contributing to release.

In Australian Patent Application 43934/85A a method has been proposed in which particles of a water-soluble substance are embedded in the film of a hydrophobic polymeric substance so that the film may become porous in the digestive organs by dissolution and elimination of said water-soluble substance.

However, this method is still disadvantageous in that a special contrivance is required for embedding the water-soluble substance in the film, and in that it is necessary to use various additives such as dispersing agents, plasticizers, anti-aggregating agents, etc. which make the recipe complicated. Moreover, even if the film does become porous in the digestive organs, its porosity will be affected by the particle size of the water-soluble substance and the degree of dispersion of said substance in the film, and therefore the porosity cannot be accurately controlled.

The present inventors have studied intensively in order to enable release control while maintaining the advantages of a preparation having a compact film of a hydrophobic polymeric substance such as great physical strength, good storage stability, etc. As a result, the inventors have succeeded in forming a porous film of a hydrophobic polymeric substance on the surface of a core, and also found that a controlled release

pharmaceutical preparation having a desired dissolution rate can be obtained by controlling the porosity of the film.

According to the present invention, there is provided a controlled release pharmaceutical preparation, comprising a core containing a pharmaceutically active ingredient and coated with a porous film, characterised in that the porous film has a porosity as represented by the formula:-

$$1 - \frac{\text{(total weight of Film)/(total volume of film)}}{\text{(true specific gravity of film)}}$$

of 0.4 to 0.9 and is formed from a hydrophobic polymeric substance or a hydrophobic polymeric substance and a hydrophilic polymeric substance..

In the present invention, the core to be coated with the porous film is not particulary limited to specific form, but any of forms such as plain tablets, pills, granules, grains, etc. can be suitably used. However, it is preferable to use one granulated into granules, grains, etc., preferably one granulated into granules with an average particle size of about 300 μm to about 2000 μm, particularly about 500 μm to about 850 μm. The core of the present invention is not required to be hydrophobic, but both water-soluble core and water-insoluble core can be suitably used.

The core may contain a wide cariety of excipients including diluents, binders, lubricants, anti-aggregating agents, buffers, which are conventionally used in this field of art. For example, as the diluents, sugars such as sucrose, lactose, mannitol, glucose, etc., starch, crystalline cellulose, calcium phosphate, calcium sulfate, calcium lactate, etc. may be included; as the binders, polyvinyl alcohol, polyacrylic acid polymethacrylic acid, polyvinyl pyrrolidone, glucose, sucrose, lactose, maltose, sorbitol, mannitol, hydroxyethyl cellulose, hydroxypropylmethyl cellulose, hydroxypropyl cellulose, polyethylene glycols, gum arabic, gelatin, agar, starch, etc. As the lubricants and anti-aggregating agents, talc, magnesium stearate, calcium stearate, colloidal silica, stearic acid, waxes, hardened oil, polyethylene glycols, sodium benzoate, sodium laurylsulfate, magnesium laurylsulfate, etc. may be included. Furhter, as the buffers, organic acids such as fumaric acid, succinic acid, citric acid, malic acid and their salts may be included.

The hydrophobic polymeric substance constituting the porous film is not particularly limited, provided that it has film forming ability, and is insoluble in water, but soluble in a water-miscible organic solvent. Examples of such hydrophobic polymeric substance may include cellulose ether, cellulose ester, polyvinyl ester, acrylic acid type polymer having a quaternaly ammoniumalkyl group, etc. Specifically, there may be included, for example, ethyl cellulose, butyl cellulose, cellulose acetate, cellulose propionate; polyvinyl acetate, polyvinyl butyrate; Eudragit® RS (trade name of Röhm Pharma, chemical name: ethyl acrylate-methyl methacrylate-ethyl ammonium trimethyl chloride methacrylate copolymer), etc., and among them, preferable hydrophobic polymeric substances may include, for example, ethyl cellulose, butyl cellulose cellulose acetate, cellulose propionate or Eudragit® RS, etc. Among them, ethyl cellulose and cellulose acetate are particularly preferred, and most preferable is ethyl cellulose. Ethyl cellulose may be above all preferably a water-insoluble ethyl cellulose having, for example, an ethoxy content of about 40 to about 55%, particularly about 43% to about 51%, with a viscosity [viscosity measured at 5% ethyl cellulose concentration in toluene-ethanol (4:1) mixture at 25 °C] of about 4 to about 350 cP.

The porous film in the present invention may be, other than a porous film comprising only a hydrophobic polymeric substance, a porous film comprising a hydrophobic polymeric substance and a hydrophilic polymeric substance. In this case, as the hydrophilic polymeric substance, a water-soluble polymeric substance, an enteric polymeric substance, a gastric soluble polymeric substance, and a both gastric and enteric polymeric substance may be suitably used.

Examples of the water-soluble polymeric substance, may include polysaccharides optionally having sulfuric acid group such as pullulan, dextrin, alkali metal alginate, etc.; polysaccharides having a hydroxyalkyl group or a carboxyalkyl group such as hydroxypropyl cellulose, hydroxypropylmethyl cellulose, carboxymethyl cellulose sodium, etc.; methyl cellulose, polyvinyl pyrrolidone, polyvinyl alcohol or polyethylene glycol, etc. may be included. Among them, more preferable water soluble polymeric substances may include hydroxypropyl cellulose or polyethylene glycol.

As the enteric polymeric substance, a polymeric substance having film forming ability and being soluble in water of pH 5 or higher may be used, including, for example, (1) carboxyalkyl cellulose, (2) cellulose derivative having monoester bond of dibasic acid, (3) polyvinyl derivative having monoester bond of dibasic acid, (4) maleic acid-vinyl copolymer or (5) acrylic acid type polymer, etc. Specific examples of (1) may

include carboxymethyl cellulose; specific examples of (2) may include cellulose acetate phthalate, cellulose acetate succinate, methylcellulose phthalate, hydroxymethyl ethyl cellulose phthalate, hydroxypropylmethyl cellulose phthalate, hydroxypropylmethyl cellulose acetate succinate and the like; specific examples of (3) may include dibasic acid monoesters of vinyl polymers such as polyvinyl alcohol phthalate, polyvinyl butyrate phthalate, polyvinyl acetoacetal phthalate and the like; specific examples of (4) may include vinyl acetate-maleic anhydride copolymer, vinyl butyl ether-maleic anhydride copolymer, styrene-maleic acid monoester copolymer; and specific examples of (5) may include methyl acrylate-methacrylic acid copolymer, styrene-acrylic acid copolymer, methyl acrylate-methacrylic acid-octyl acrylate copolymer, Eudragit L and S (trade names of Rhom-Pharma, methacrylic acid-methyl methacrylate copolymer), etc. Among them, more preferable enteric polymeric substances are carboxylmethyl cellulose, hydroxypropyl methyl cellulose acetate succinate or Eudragit® L.

Further, as the gastric soluble polymeric substance, any polymeric substance soluble in water of pH 6 or lower and having film forming ability may be used, including, for example, (a) cellulose derivative having mono- or di-substituted amino group, (b) polyvinyl derivative having mono- or di-substituted amino group, (c) acrylic acid polymer having mono-substituted amino group, etc. Specific examples of (a) may include benzylaminomethyl cellulose, diethylaminomethyl cellulose, piperidyl ethyl hydroxyethyl cellulose, cellulose acetate diethylamino acetate, etc. Specific examples of (b) may include vinyldiethylamine-vinyl acetate copolymer, vinylbenzylamine-vinyl acetate copolymer, polyvinyl acetaldiethylaminoacetate, vinylpiperidyl-acetoacetalvinyl acetate copolymer, polydiethyl aminomethyl styrene, etc., and specific examples of (c) may include Eudragit® E (trade name of Rohm-Pharma, methyl methacrylate-butyl methacrylate-dimethylaminoethyl methacrylate copolymer), polydimethylaminoethyl methacrylate, etc. Among these, more preferable gastric soluble polymeric substances are polyvinyl acetal-diethylaminoacetate or Eudragit® E.

As the both gastric soluble and enteric polymeric substance, a polymeric substance having film forming ability and being soluble in water of pH 4.5 or lower and water of pH 6 or higher may be used, including vinylpyridine-acrylic acid type copolymer, carboxymethyl polysaccharide having mono- or di-substituted amino group or polyvinyl amino acid type derivative. Specific examples of vinylpyridine-acrylic acid type copolymer may include 2-methyl-5-vinylpyridine/methyl methacrylate/methacrylic acid copolymer, 2-methyl-5-vinylpyridine/methyl acrylate/methacrylic acid copolymer, 2-vinyl-5-ethyl pyridine/methacrylic acid/styrene copolymer, 2-vinyl-5-ethyl pyridine/methacrylic acid/methyl acrylate copolymer, 2-vinylpyridine/methacrylic acid/methyl acrylate copolymer, 2-vinylpyridine/methacrylic acid/acrylonitrile copolymer, etc. Specific examples of carboxymethyl polysaccharides having mono- or di-substituted amino group may include carboxymethyl piperidyl starch, carboxymethyl benzylaminocellulose, etc., and specific examples of polyvinyl amino acid type derivative may include poly-2-(vinylphenyl)glycine, N-vinylglycine-styrene copolymer, etc.

The combination of the hydrophobic polymeric substance and the hydrophilic polymeric substance is not particularly limited, but as preferable combination, a combination of a hydrophobic polymeric substance with a water soluble polymeric substance or an enteric polymeric substance may be included. As particularly preferable combination, a combination of ethyl cellulose with hydroxypropylcellulose, carboxymethylethyl cellulose or hydroxypropylmethyl cellulose acetate succinate may be employed. The ratio of the hydrophobic polymeric substance to the hydrophilic polymeric substance should be desirably about 0.05 to 0.5 part by weight of the hydrophilic polymeric substance per 1 part by weight of the hydrophobic polymeric substance.

The porous film comprising the hydrophobic polymeric substance or a combination of the hydrophobic polymeric substance and the hydrophilic polymeric substance has generally an appearance like sponge, and has regular or irregular pores of microscopic sizes, which are mutually communicated to each other.

The porosity of the porous film is represented by the formula (I):

$$1 - \frac{\text{(total weight of film)/(total volume of film)}}{\text{(true specific gravity of film)}}$$

In general, the porosity should be appropriately made a value of about 0.4 to 0.9, particularly 0.5 to 0.85.

The thickness of the film may be controlled by the amount of the hydrophobic polymeric substance relative to the core, and it is desirable that the hydrophobic polymeric substance should be used in an amount within the range from about 3 to 100 W/W%, particularly about 5 to 50 W/W% based on the core. When the hydrophobic polymeric substance is used in combination with the hydrophilic polymeric substance, the total amount of both polymeric substances should be desirably within the range mentioned above.

In the preparation of the present invention, by controlling adequately the thickness and the porosity, it is possible to make a preparation having a desired dissolution rate. For examle, when the pharmaceutically active ingredient contained in the core is a drug which is desired to exhibit pharmaceutical effect within a short period of time after administration, it is preferred to make the film thinner and the porosity thereof greater, while in the case of a drug which is desired to be released persistently for a prolonged period of time, it is preferred to make the film thicker and the porosity thereof smaller.

As the pharmaceutically active ingredient to be contained in said core, any drug capable of oral administration may be available without limitation at all. Examples of such pharmaceutically active ingredients may include vitamins, amino acids, peptides, chemotherapeutics, antibiotics, agents affecting respiratory organs, antitussive expectorants, antitumor agents, autonomic drugs, neuropsychotropic agents, muscle relaxants, drugs affecting digestive organs, antihistamic agents, antidotes, hypnotic sedatives, antiepileptics, antipyretic analgesic antiphlogistics, cardiotonics, antiarrhythmics, hypotensive diuretics, vasodilators, hypolipidemic agents, alimentary analeptics, anticoagulants, hepatics, blood sugar-lowering agents, hypotensive agents, etc.

The preparation of the present invention can be produced by spray coating a core containing a pharmaceutically active ingredient with a water-organic solvent mixture containing a hydrophobic polymeric substance or a mixture of a hydrophobic polymeric substance and a hydrophilic polymeric substance to form a porous film of said polymeric substance or substances on the surface of the core.

Preparation of a core can be practiced according to conventional methods as described in Remington's Pharmaceutical Science 17th ed., p.p. 1603 to 1632, p.p 1633 to 1643 (Mark Publishing Company, published in 1985). For example, the core can be prepared by mixing a pharmaceutical compound with a suitable excipient or excipients (i,e., diluents, binders, lubricants, etc.) and then granulation the mixture according to the wet extrusion granulating method, the rotating granulation method, the fluidized bed granulation method, etc. Alternatively, the core can be prepared according to the rotating granulation method, the pan coating method, the fluidized bed coating method, etc. in which a pharmaceutical compound or a mixture of the compound with an excipient or excipients is added little by little to inert carrier particles while spraying a solution of a binder dissolved in a suitable solvent such as water, lower alcohol (methanol, ethanol, propanol, isopropanol, butanol, etc.), lower alkanone (acetone, methyl ethyl ketone, etc.), chloroform, dichloromethane, dichloroethane or a mixture of these on the surface of inert carrier particles. In this case, as the inert carrier particles, for example, those prepared from sucrose, lactose, starch, crystalline cellulose, etc. may be suitably employed. Such carrier particles should preferably have an average particle size of about 300 μm to about 1500 μm.

In coating the core with a porous film, as the organic solvent which forms a solvent mixture together with water, any solvent which can dissolve the hydrophobic polymeric substance can be used without particular limitation, including, for example, lower alkanols such as methyl alcohol, ethyl alcohol, isopropyl alcohol, n-propyl alcohol, n-butyl alcohol, etc., lower alkanones such as acetone, methyl ethyl ketone, etc., acetonitrile and so on. Among these, more preferable solvent is lower alkanols, and particularly preferable solvents are ethyl alcohol and isopropyl alcohol. The mixing ratio of water and the organic solvent is suitably variable within the range of 9 to 0.5 volumes of the organic solvent per one volume of water, and the porosity of the porous film comprising the hydrophobic polymeric substance or the combination of the hydrophobic polymeric substance and the hydrophilic polymeric substance can readily be controlled by changing said ratio. The porosity of the porous film, as a general rule, becomes greater as the ratio of water in the water-organic solvent mixture is increased and smaller when the ratio of the organic solvent is increased.

The concentration of the hydrophobic polymeric substance in the water-organic solvent mixture should be preferably about 2 to 30 W/W%. Also, when a hydrophobic polymeric substance is used in combination with a hydrophilic polymeric substance, the total concentration of the both polymeric substances should be preferably within the above range.

Spray coating can be practiced according to conventional coating method. For example, it can be practiced easily by dissolving a hydrophobic polymeric substance or a combination of a hydrophobic polymeric substance and a hydrophilic polymeric substance in a water-organic solvent mixture, and spraying the resultant coating solution on the surface of a core according to the fluidized bed coating method, the pan coating method, etc. For example, according to the pan coating method, it is possible to practice the method by placing cores in a coating pan, spraying a water-organic solvent mixture containing a hydrophobic polymeric substance or a combination of a hydrophobic polymeric substance and a hydrophilic polymeric substance through a nozzle of a spray gun while rotating said coating pan, and then drying the coating.

At this time, if desired, talc, titanium dioxide, etc. may be also added as the anti-aggregating agent.

The thus-obtained pharmaceutical preparation of the present invention may be administered as such or said preparation can be also administered in the form of capsules filled with it when the preparation is in shape of granules.

The controlled release pharmaceutical preparation of the present invention is characterized in that it shows rapid stand-up of release. This is because, since the film is porous, digestive fluids penetrate into the inside of the preparation and dissolve the pharmaceutically active ingredient from the time immediately after administration. Besides, the preparation of the present invention is characterized in that the release rate can be readily controlled by changing the porosity of the film. For example, in the case where it is necessary to reduce the variation of blood level of the pharmaceutically active ingredient because the minimum therapeutically effective blood level of said active ingredient is close to the toxic blood level thereof, it is possible to minimize the variation between the highest and lowest blood cocentration thereof by making the porosity of the film smaller in order to exhibit the therapeutic effect of the active ingredient while keeping the blood level thereof lower than the toxic level. Further, in the case where the pharmaceutically active ingredient is desired to show long-lasting action, it is possible to release the active ingredient at a constant rate for a prolonged period of time by making the porosity of the film smaller. On the other hand, in the case where the active ingredient is desired to show quick action, it is possible to release the active ingredient from the time immediately after administration by making the porosity of the film greater.

Moreover, the pharmaceutical preparation having a porous film comprising a hydrophobic polymeric substance and a hydrophilic polymeric substance is effective to dissolve and release the pharmaceutical ingredient more quickly and within a shorter period of time after administration because the porosity of the film itself becomes further greater by dissolution of the hydrophilic substance constituting a part of the porous film.

Besides, the preparation of the present invention is not inferior at all with respect to humidity resistance, light shielding property, water resistance, abrasion resistance as compared with the known preparation having a compact film of a hydrophobic polymeric substance.

As described above, the preparation of the present invention is excellent in release control and at the same time, maintains the advantages possesed by the preparattion of the prior art as such.

Experimental examples

(1) Production of preparation:

One kg of Nonpareil (trade name of spherical granules of sucrose, manufactured by Freund) with particle sizes of 710 to 840 μm was placed and tumbled in a centrifugal fluidizing granulator (CF-360 EX Model, manufactured by Freund), and thereto was gradually added 1 kg of dilthiazem hydrochloride powder while spraying a water-ethanol solution (weight ratio = 3:1) containing 400 g of sucrose to cover it around Nonpareil. Subsequently, the dilthiazem hydrochloride granules obtained were sprayed with a coating solution of 300 g of ethyl cellulose (ethoxy content: 49.6%) dissolved in 2.7 kg of a water-ethanol mixture (weight ratio = 3:7, 2:8 or 1.5:8.5) while blowing warm air. By drying after spraying, dilthiazem hydrochloride containing preparations having porous ethyl cellulose films with different porosities, respectively, were obtained.

(2) Comparison of releasing rate:

For the respective preparations obtained as described above, the dissolution tests were practiced according to the dissolution test standard of the Paddle method specified in the 11th revised Japanese Pharmacopoeia.

(3) Results:

The dissolution percentage of the active ingredient (dilthiazem hydrochloride) is as shown in Table 1.

Table 1

Preparation (*1)	Porosity (*2)	dissolution percentage (%)		
		4 hours	10 hours	24 hours
A	0.83	34	77	100
B	0.54	20	53	86
C	0.42	17	34	52

(note):

*1; A - C show the following preparations:

A: preparation obtained by use of a water-ethanol mixture (3:7) as the solvent of the coating solution;

B: preparation obtained by use of a water-ethanol mixture (2:8) as the solvent of the coating solution;

C: preparation obtained by use of a water-ethanol mixture (1.5:8.5)) as the solvent of the coating solution;

*2: porosity was calculated according to the above formula (I).

As is apparent from the above Table 1, it can be seen that as the ratio of water in the water-ethanol mixture becomes smaller, the porosity of the film becomes smaller and a period of time to be required for dissolving 100% of the active ingredient become longer.

Example 1

500 g of Nonpareil with particle sizes of 710 to 840 μm were placed and tumbled in a centrifugal fluidizing granulator, and to this was gradually added 1 kg of theophylline (chemical name: 3,7-dihydro-1,3-dimethyl-1H-purine-2,6-dione) fine powder while spraying a solution of 270 g of sucrose dissolved in 145 ml of water to cover it around Nonpareil. Subsequently, 1 kg of the theophylline granules obtained was placed and tumbled in a centrifugal fluidizing granulator, and to this was sprayed a solution of 90 g of ethyl cellulose and 10 g of hydroxypropyl cellulose dissolved in 1.9 kg of a water-ethanol (3:7) mixture while blowing warm air. Subsequently, after drying, 1.1 kg of theophylline granules coated with a porous ethylcellulosehydroxypropylcellulose film were obtained.

The preparation obtained had a porous film of a porosity of 0.81.

Example 2

One kg of Nonpareil with particle sizes of 710 to 840 μm was placed and tumbled in a centrifugal fluidizing granulator, and to this was added gradually 1 kg of sodium salicylate powder while spraying 800 g of a water-ethanol mixture containing 400 g of sucrose to have it attached around Nonpareil. Subsequently, 500 g of the sodium salicylate granules obtained were placed in a fluidized bed coater and, under blow rotation with blowing of air, a mixture of 100 g of ethyl cellulose dissolved in 900 g of a water-ethanol (2:8) mixture added with 50 g of talc was sprayed thereon while blowing warm air. By drying after spraying, 600 g of sodium salicylate granules coated with a porous ethyl cellulose film were obtained. The preparation obtained had a porous film of a porosity of 0.68.

Example 3

1.33 kg of Nonpareil with particle sizes of 500 to 710 um were placed and tumbled in a centrifugal fluidizing granulator, and to this was gradually added a mixture of 1 kg of (+)-(2S,3S)-3-acetoxy-8-chloro-5-[2-(dimethylamino)ethyl]-2,3-dihydro-2-(4-methoxyphenyl)-1,5-benzodiazepine-4(5H)-one maleate fine powder and 1.67 g of succinic acid while spraying a solution of 652 g of sucrose dissolved in 1,957 g of a water-ethanol (3:1) mixture to cover it around Nonpareil. Subsequently, 2 kg of the granules obtained were placed and tumbled in a centrifugal fluidizing granulator, and a solution of 190 g of ethyl cellulose and 10 g of hydroxypropyl cellulose dissolved in 1.8 kg of a water-ethanol (3:7) mixture was sprayed thereon, while blowing warm air. Then, after drying, 2.2 kg of granules coated with a porous ethyl cellulose-hydroxypropyl cellulose film wereobtained.

The preparation obtained had a porous film of a porosity of 0.85.

Example 4

A mixture of 300 g of dilthiazem hydrochloride, 611 g of lactose and 150 g of corn starch was kneaded with 30 g of polyvinyl pyrrolidone and 100 ml of water, and the particles obtained were classified to obtain granules for tabletting. Then, to the granules were added 8 g of magnesium stearate, and the mixture was tabletted by a rotary system tabletting machine (RT F-9-2 Model, manufactured by Kikusui Seisakusho) to obtain tablets of 8 mm in diameter. The dilthiazem hydrochloride containing tablets obtained (500 g) were placed in a coating pan, and a water-ethanol (3:7) mixture containing 5 W/W% of ethyl cellulose was sprayed thereon at room temperature. Subsequently, after drying, tablets coated with a porous ethyl cellulose film were obtained.

The preparaton obtained had a porous film of a porosity of 0.67.

Example 5

500 g of theophylline granules (cores) obtained in the same manner as in Example 1 were placed in a centrifugal fluidizing granulator, and a solution of 50 g of ethyl cellulose dissolved in a water-isopropanol mixture (4:6) was sprayed thereon while blowing warm air. Subsequently, after drying, about 500 g of granules coated with a porous ethyl cellulose film were obtained.

The preparation obtained had a porous film of a porosity of 0.78.

Example 6

500 g of sodium salicylate granules (cores) obtained in the same manner as in Example 2 were placed in a fluidized bed coating device. 50 g of talc were added to a solution of 100 g of cellulose acetate in 900 g of a mixture of water-acetone (2:8), and the mixture was sprayed on the surface of granules while blowing warm air. By drying after spraying, 600 g of granules coated with a porous cellulose acetate film were obtained.

The granules obtained had a porous film of a porosity of 0.74.

Example 7

Example 1 was repeated except for using 100 g of cellulose acetate butyrate in place of cellulose acetate to obtain 600 g of granules coated with a porous cellulose acetate butyrate film.

The preparation obtained had a porous film of a porosity of 0.78.

Examples 8

One kg of the granules (cores) obtained in the same manner as in Example 3 was placed and tumbled in a centrifugal fluidizing granulator, and a solution of 95 g of ethyl cellulose and 5 g of polyvinyl pyrrolidone dissolved in 900 g of a water-ethanol (3:7) mixture was sprayed thereon while blowing warm air. By drying after spraying, 1.1 kg of granules coated with a porous ethyl cellulose-polyvinyl pyrrolidone film were obtained.

The preparation obtained had a porous film of a porosity of 0.81.

Example 9

Example 8 was repeated except for using 95 g ethyl cellulose and 5 g of polyethylene glycol to give 1.1 kg of granules coated with a porous ethyl cellulose-polyethylene glycol film.

The preparation obtained had a porous film of a porosity of 0.79.

Example 10

Example 8 was repeated except for using 95 g ethyl cellulose and 5 g of methyl cellulose to give 1.1 kg of granules coated with a porous ethyl cellulose-methylcellulose film.

The preparation obtained had a porous film of a porosity of 0.82.

Example 11

Example 8 was repeated except for using 95 g ethyl cellulose and 5 g of hydroxypropylmethyl cellulose to give 1.1 kg of granules coated with a porous ethyl cellulose-hydroxypropylmethyl cellulose film.

The preparation obtained had a porous film of a porosity of 0.76.

Example 12

Example 8 was repeated except for using 95 g ethyl cellulose and 5 g of hydroxypropyl cellulose acetate succinate to give 1.1 kg of granules coated with a porous ethyl cellulose-hydroxypropyl cellulose acetate succinate film.

The preparation obtained had a porous film of a porosity of 0.84.

Example 13

Example 8 was repeated except for using 95 g ethyl cellulose and 5 g of Eudragit L to give 1.1 kg of granules coated with a porous ethyl cellulose-Eudragit L film.

The preparation obtained had a porous film of a porosity of 0.79.

Claims

1. A controlled release pharmaceutical preparation, comprising a core containing a pharmaceutically active ingredient and coated with a porous film, characterised in that the porous film has a porosity as represented by the formula:-

$$1 - \frac{\text{(total weight of Film)/(total volume of film)}}{\text{(true specific gravity of film)}}$$

of 0.4 to 0.9 and is formed from a hydrophobic polymeric substance or a hydrophobic polymeric substance and a hydrophilic polymeric substance..

2. A preparation according to claim 2, characterised in that the porous film has a porosity of 0.5 to 0.85.

3. A preparation according to any of claim 1 or 2, characterised in that the porous film comprises 0.05 to 0.5 part by weight of hydrophilic polymeric substance per 1 part by weight of hydrophobic polymeric substance.

4. A preparation according to any of claims 1 to 3, characterised in that the hydrophobic polymeric substance is at least one selected from the group consisting of cellulose ether, cellulose ester, polyvinyl ester and an acrylic acid polymer having a quaternary ammonium alkyl group.

5. A preparation according to any of claims 1 to 4, characterised in that the hydrophilic substance is at least one selected from the group consisting of water soluble polymeric substances, enteric polymeric substances, gastric soluble polymeric substances and both gastric soluble and enteric polymeric substances.

6. A preparation according to claim 5, characterised in that the water-soluble polymeric substance is at least one selected from the group consisting of polysaccharides which optionally having sulfuric acid group, polysaccharides having hydroxyalkyl group, polysaccharides having carboxyalkyl group, methylcellulose, polyvinyl pyrrolidone, polyvinyl alcohol and polyethylene glycol; the enteric polymeric substance is at least one selected from the group consisting of carboxyalkyl cellulose, cellulose derivative having monoester bond of dibasic acid, polyvinyl derivative having monoester bond of dibasic acid, maleic acid-vinyl copolymer and acrylic acid type polymer; the gastric soluble polymeric substance is at least one selected from the group consisting of cellulose derivative having mono- or di-substituted amino group, polyvinyl derivative having mono- or di-substituted amino group and acrylic acid polymer having mono-substituted amino group; and both the gastic soluble and enteric polymeric substance is at least one selected from the group consisting of vinyl pyridine-acrylic acid type copolymer, carboxymethyl polysaccharides having mono- or di-substituted amino group and polyvinyl amino acid type derivative.

7. A preparation according to any of claims 1 to 6, characterised in that the porous film comprises ethyl cellulose and hydroxypropyl cellulose.

8. A preparation according to any of claims 1 to 7, characterised in that an organic acid is contained together with the pharmaceutical active ingredient in the core.

9. A preparation according to claim 8, characterised in that the organic acid is succinic acid.

10. A method for producing a controlled release pharmaceutical preparation, which comprises spray coating a core containing a pharmaceutically active ingredient with a water-organic solvent mixture containing a hydrophobic polymeric substance or a hydrophobic polymeric substance and a hydrophilic polymeric substance to form a porous film comprising said polymeric substance or substances on the surface of the core.

Patentansprüche

1. Pharmazeutische Zubereitung zur gesteuerten Freisetzung, welche einen Kern umfaßt, der einen pharmazeutisch wirksamen Bestandteil enthält und mit einem porösen Film überzogen ist, dadurch gekennzeichnet, daß der poröse Film eine durch die Formel

$$1 - \frac{\text{(Gesamtgewicht des Films)/(Gesamtvolumen des Films)}}{\text{(wahres spezifisches Gewicht des Films)}}$$

dargestellte Porosität von 0,4 bis 0,9 besitzt und aus einer hydrophoben Polymersubstanz oder einer hydrophoben Polymersubstanz und einer hydrophilen Polymersubstanz gebildet ist.

2. Zubereitung gemäß Anspruch 1, dadurch gekennzeichnet, daß der poröse Film eine Porosität von 0,5 bis 0,85 besitzt.

3. Zubereitung gemäß einem der Ansprüche 1 oder 2, dadurch gekennzeichnet, daß der poröse Film 0,05 bis 0,5 Gewichtsteile der hydrophilen Polymersubstanz auf 1 Gewichtsteil der hydrophoben Polymersubstanz umfaßt.

4. Zubereitung gemäß einem der Ansprüche 1 bis 3, dadurch gekennzeichnet, daß die hydrophobe Polymersubstanz wenigstens eine aus der aus einem Celluloseether, Celluloseester, Polyvinylester und einem Acrylsäurepolymer mit einer quaternären Ammoniumalkylgruppe bestehenden Gruppe ausgewählte ist.

5. Zubereitung gemäß einem der Ansprüche 1 bis 4, dadurch gekennzeichnet, daß die hydrophile Polymersubstanz wenigstens eine aus der aus wasserlöslichen Polymersubstanzen, magensaftresistenten Polymersubstanzen, magensaftlöslichen Polymersubstanzen und sowohl magensaftlöslichen als auch magensaftresistenten Polymersubstanzen bstehenden Gruppe ausgewählte ist.

6. Zubereitung gemäß Anspruch 5, dadurch gekennzeichnet, daß die wasserlösliche Polymersubstanz wenigstens eine aus der aus Polysacchariden mit gegebenenfalls einer Schwefelsäuregruppe, Polysacchariden mit einer Hydroxyalkylgruppe, Polysacchariden mit einer Carboxyalkylgruppe, Methylcellulose, Polyvinylpyrrolidon, Polyvinylalkohol und Polyethylenglykol bestehenden Gruppe ausgewählte ist; die magensaftresistente Polymersubstanz wenigstens eine aus der aus einer Carboxyalkylcellulose, einem Cellulosederivat mit einer Monoesterbindung einer dibasischen Säure, einem Polyvinylderivat mit einer Monoesterbindung einer dibasischen Säure, einem Maleinsäure-Vinylcopolymer und einem Polymer vom Acrylsäuretyp bestehenden Gruppe ausgewählte ist; die magensaftlösliche Polymersubstanz wenigstens eine aus der aus einem Cellulosederivat mit einer mono- oder disubtituierten Aminogruppe, einem Polyvinylderivat mit einer mono- oder disubstituierten Aminogruppe und einem Acrylsäurepolymer mit einer monosubtituierten Aminogruppe bestehenden Gruppe ausgewählte ist; und die sowohl magensaftlösliche als auch magensaftresistente Polymersubstanz wenigstens eine aus der aus einem Copolymer vom Vinylpyridin-Acrylsäuretyp, Carboxymethylpolysacchariden mit einer mono- oder disubtituierten Aminogruppe und einem Derivat vom Polyvinylaminosäuretyp bestehenden Gruppe ausgewählte ist.

7. Zubereitung gemäß einem der Ansprüche 1 bis 6, dadurch gekennzeichnet, daß der poröse Film Ethylcellulose und Hydroxypropylcellulose umfaßt.

8. Zubereitung gemäß einem der Ansprüche 1 bis 7, dadurch gekennzeichnet, daß eine organische Säure zusammen mit dem pharmazeutisch wirksamen Bestandteil in dem Kern enthalten ist.

9. Zubereitung gemäß Anspruch 8, dadurch gekennzeichnet, daß die organische Säure Bernsteinsäure ist.

10. Verfahren zur Herstellung einer pharmazeutischen Zubereitung zur gesteuerten Freisetzung, welche das Sprühbeschichten eines einen pharmazeutisch wirksamen Bestandteil enthaltenden Kerns mit einem Gemisch Wasser-organisches Lösungsmittel, welches eine hydrophobe Polymersubstanz oder eine hydrophobe Polymersubstanz und eine hydrophile Polymersubstanz enthält, unter Bilden eines porösen Films umfaßt, welcher die Polymersubstanz oder -substanzen auf der Oberfläche des Kerns enthält.

Revendications

1. Préparation pharmaceutique à libération réglée ou progressive de la substance active, qui comprend un noyau contenant un ingrédient pharmaceutiquement actif et enrobé d'un film poreux, caractérisée en ce que le film poreux possède une porosité telle que représentée par la formule suivante :

$$1 - \frac{\text{(poids total du film)/(volume total du film)}}{\text{(densité vraie du film)}}$$

de 0,4 à 0,9 et en ce qu'il est formé à partir d'une substance polymérique hydrophobe, ou d'une

substance polymérique hydrophobe et d'une substance polymérique hydrophile.

2. Préparation suivant la revendication 1, caractérisée en ce que le film poreux possède une porosité de 0,5 à 0,85.

3. Préparation suivant l'une quelconque des revendications 1 et 2, caractérisée en ce que le film poreux comprend de 0,05 à 0,5 partie en poids d'une substance polymérique hydrophile pour 1 partie en poids de substance polymérique hydrophobe.

4. Préparation suivant l'une quelconque des revendications 1 à 3, caractérisée en ce que la substance polymérique hydrophobe en est au moins une choisie dans le groupe formé par les éthers cellulosiques, les esters cellulosiques, les esters polyvinyliques et un polymère de l'acide acrylique comportant un radical alkylammonium quaternaire.

5. Préparation suivant l'une quelconque des revendications 1 à 4, caractérisée en ce que la substance hydrophile en est au moins une choisie dans le groupe formé par les substances polymériques solubles dans l'eau, les substances polymériques entériques, les substances polymériques solubles dans le suc gastrique et les substances polymériques à la fois solubles dans le suc gastrique et entérique.

6. Préparation suivant la revendication 5, caractérisée en ce que la substance polymérique soluble dans l'eau en est au moins une choisie dans le groupe formé par les polysaccharides qui possèdent un éventuel radical acide sulfurique, les polysaccharides qui possèdent un radical hydroxyalkyle, les polysaccharides qui possèdent un radical carboxyalkyle, la méthylcellulose, la polyvinylpyrrolidone, le poly(alcool vinylique) et le polyéthylèneglycol; la substance polymérique entérique en est au moins une choisie dans le groupe formé par une carboxyalkylcellulose, un dérivé de la cellulose possédant une liaison monoester d'acide dibasique, un dérivé polyvinylique possédant une liaison monoester d'acide dibasique, un copolymère vinylique de l'acide maléique et un polymère du type acide acrylique; la substance polymérique soluble dans le suc gastrique en est au moins une choisie dans le groupe formé par un dérivé de la cellulose possédant un radical amino monosubstitué ou disubstitué, un dérivé polyvinylique possédant un radical amino monosubstitué ou disubstitué et un polymère de l'acide acrylique possédant un radical amino monosubstitué; et la substance polymérique à la fois soluble dans le suc gastrique et entérique en est au moins une choisie dans le groupe formé par un copolymère de la vinylpyridine et de l'acide acrylique, des carboxyméthylpolysaccharides comportant un radical amino monosubstitué ou disubstitué et un dérivé du type polyvinylamino acide.

7. Préparation suivant l'une quelconque des revendications 1 à 6, caractérisée en ce que le film poreux comprend de l'éthylcellulose et de l'hydroxypropylcellulose.

8. Préparation suivant l'une quelconque des revendications 1 à 7, caractérisée en ce qu'elle contient un acide organique en même temps que l'ingrédient pharmaceutiquement actif dans le noyau.

9. Préparation suivant la revendication 8, caractérisée en ce que l'acide organique est l'acide succinique.

10. Procédé de production d'une préparation pharmaceutique à libération réglée ou progressive de la substance active, caractérisé en ce qu'il comprend l'enrobage par pulvérisation d'un noyau contenant un ingrédient pharmaceutiquement actif, par un mélange solvant constitué d'eau et d'un composé organique, contenant une substance polymérique hydrophobe, ou une substance polymérique hydrophobe et une substance polymérique hydrophile, afin de former un film poreux comprenant ladite substance polymérique ou lesdites substances polymériques sur la surface du noyau.

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