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(54) Title: THREE-PHASE PHARMACEUTICAL FORM WITH CONSTANT AND CONTROLLED RELEASE OF AMORPHOUS ACTIVE INGREDIENT FOR SINGLE DAILY APPLICATION

(57) Abstract

Described is a novel three-phase pharmaceutical form with constant and controlled release of an amorphous active ingredient stabilized with polymers for a single daily peroral application, which is especially suitable for active ingredients existing in amorphous form or in one or more polymorphous forms, which exhibit poor solubility in crystal form depending on the polymorphous form, particle size and the specific surface area of the active ingredient. The active ingredient can be used in its amorphous or any polymorphous form, which in the process of the preparation of the three-phase pharmaceutical form according to the invention is converted into the amorphous form. The three-phase pharmaceutical form with constant and controlled release of an amorphous active ingredient for a single daily peroral application contains a core consisting of a first and a second phase and a coating representing the third phase. In the first phase the three-phase pharmaceutical form contains an amorphous active ingredient, the water-soluble polymer polyvinylpyrrolidone and a cellulose ether as carriers of the amorphous active ingredient and simultaneously as inhibitors of its crystallization, a surfactant that improves the solubility of the active ingredient and promotes the absorption of the amorphous active ingredient from gastrointestinal tract, in the second phase it contains a cellulose ether and a mixture of mono-, di- and triglycerides as sustained release agents and the third phase is represented by a poorly soluble or gastro-resistant film coating, which in the first few hours after the application controls the release of the active ingredient and can consist of an ester of hydroxypropylmethylcellulose with phthalic anhydride or of a copolymerizate based on methacrylic acid and ethyl acrylate. Described is also a process for the preparation of this pharmaceutical form.

Exhibit 1022

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Three-phase Pharmaceutical Form with Constant and Controlled Release of Amorphous Active Ingredient for Single Daily Application

Technical Field of the Invention

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The invention belongs to the field of pharmaceutical industry and relates to a novel medicinal preparation with prolonged action for peroral application (sustained release tablets) based on a combination of an amorphous active ingredient, water-soluble polymer polyvinylpyrrolidone, cellulose ethers and a mixture of mono-, di- and triglycerides, an ester of hydroxypropylmethylcellulose with phthalic anhydride or a copolymer based on methacrylic acid and ethyl acrylate.

Particularly, the invention relates to a novel three-phase pharmaceutical form with a constant and controlled release of an amorphous active ingredient stabilized with polymers for a single daily peroral application such as tablets and capsules. A three-phase pharmaceutical form with constant and controlled release of an amorphous active ingredient for a single daily peroral application is especially suitable for active ingredients existing in amorphous form or in one or more polymorphous forms, which exhibit poor solubility in crystal form depending on the polymorphous form, particle size and specific surface area of the active ingredient. The active ingredient can be used in amorphous or any polymorphous form which is converted into the amorphous form during the manufacturing process of the three-phase pharmaceutical form of the invention. The three-phase pharmaceutical form with constant and controlled release of the amorphous active ingredient for a single daily peroral application contains a core consisting of a first and a second phase and a coating representing the third phase. The three-phase pharmaceutical form contains as the first phase an amorphous active ingredient, the water-soluble polymer polyvinylpyrrolidone and a cellulose ether as carriers of the amorphous active ingredient and simultaneously as inhibitors of crystallization of the amorphous active ingredient as well as a surfactant improving the solubility of the active ingredient and promoting the absorption of the amorphous active ingredient from the gastrointestinal tract; as the second phase it contains sustained-release agents such as cellulose ether and a mixture of mono-, di- and triglycerides, and the third phase is represented by a poorly soluble or gastro-resistant film coating, which in the first few hours after the application controls the release of the active ingredient and can consist of an ester of

hydroxypropylmethylcellulose with phthalic anhydride or of a copolymerizate based on methacrylic acid and ethyl acrylate.

Technical Problem

There exists a constant need to develop pharmaceutical forms in which solubility and dissolution rate of the active ingredient will be independent of its polymorphous form, crystallinity, particle size and specific surface area. Hitherto known pharmaceutical forms with prolonged release of the active ingredient containing a crystalline active ingredient in the pharmaceutical form have the essential disadvantage that, due to the presence of the crystalline active ingredient in several polymorphous modifications, the release rate of the active ingredient depends on the polymorphous modification, the crystal size and thus on the specific surface area of the active ingredient. The dissolution rate of a crystalline substance is not constant and it changes depending on various shapes and size distribution of the crystals of the active ingredient.

Prior Art

The use of cellulose ethers of various viscosities and molecular weights in the function of controlling the release rate has been known for a long time. In US patent 4,259,314 there is described a method for the preparation of a dry pharmaceutical preparation with controlled and sustained release, which is provided by a mixture of hydroxypropylmethylcellulose and hydroxypropylcellulose together with a hygroscopic active ingredient.

N.A. Shaikh, S.E. Abidi and L.H. Block (Drug Development and Industrial Pharmacy, 13 (8), 1345-1369 (1987)) studied the influence of the concentration of ethylcellulose in a pharmaceutical preparation on the release rate of the active ingredient (e.g. acetaminophen, theophyline). It was found that the higher is the viscosity of ethylcellulose the lower is the release rate of the active ingredient from a solid dispersion.

In US patent 4,389,393 there is described a carrier basis for active ingredients consisting of one or more hydroxypropylmethylcelluloses with various contents of methoxy or hydroxypropoxy groups and various average molecular weights, which combination gives a pharmaceutical preparation with sustained release.

In US patent 4,792,452 there is described a pharmaceutical form with a controlled release of the active ingredient (selected from the group of calcium antagonists) independently of the pH-value of the environment, which contains up to 45 wt.% of a polymer dependent of the pH value, which is an alginic acid salt e.g. sodium alginate, and a gelatinizing agent independent of the pH-value such as hydroxypropylmethylcellulose.

In WO 87/00044 there is described the use of bimodal hydroxypropylmethylcellulose in a carrier basis which together with the active ingredient gives a bimodal profile of the release of the active ingredient.

In WO 91/17743 a pharmaceutical preparation for a slow release of granules containing low and high viscous ethylcellulose is described.

In US patent 5,009,895 there is described a carrier basis in combination with an active ingredient (e.g. ibuprofen or its salt) that is formed and compressed in a solid pharmaceutical form with a sustained release of the active ingredient. The carrier basis contains two hydroxypropylmethylcelluloses of different viscosities in such a ratio that the release rate of the active ingredient is of zero order. In the pharmaceutical form there is also present polyvinylpyrrolidone (Povidon USP) acting as a binding agent.

In EP-A-596 203 there is described a pharmaceutical form containing solid particles, which is prepared by mixing an active ingredient (e.g. nifedipine) with a water-soluble melt consisting of two sorts of polymers with different viscosities (polymer A with a viscosity from 1000 to 120000 mPa.s, polymer B with a viscosity from 1 to 500 mPa.s) as a carrier.

A dosage form containing cellulose ethers with various molecular weights is described also in US patent 4,871,548.

In US patent 5,015,479, there is described a pharmaceutical preparation for a single daily application in the form of an adsorbate containing amorphous dihydropyridine (such as felodipine, nicardipine, nifedipine) and polyvinylpyrrolidone with average molecular weight above 55000 g/mol, whose role is to change the dissolution rate of dihydropyridine from cross-linked polyvinylpyrrolidone and to prevent the crystallization of dihydropyridine. Dihydropyridine and polyvinylpyrrolidone are adsorbed on cross-linked polyvinylpyrrolidone and mixed with a polymer which gelatinates in

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