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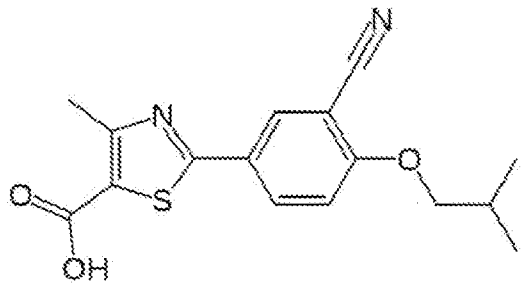
(54) Title: FORMULATIONS CONTAINING A SOLID SOLUTION OF FEBUXOSTAT

(57) Abstract: A pharmaceutical composition containing febuxostat as the active substance, characterised m that it comprises febuxostat in the form of a solid solution with a polymeric carrier with the particle size in the range of 1 to 1000 μτη, determined as the D90 value using the static light dispersion method, the microcrystalline cellulose filler and other pharmaceutically acceptable excipients.

Formulations containing a solid solution of febuxostat

Technical Field

The technical solution relates to pharmaceutical compositions containing febuxostat (2-(3-cyano-4-isobutyloxyphenyl)-4-methyl-5-thiazole-carboxylic acid) of formula I in the form of a solid solution.



(I)

Background Art

Febuxostat (2-(3-kyano-4-isobutyloxyphenyl)-4-methyl-5-thiazole-carboxylic acid) is well-known for its strong inhibition effects on xanthine oxidase and it is used as an active substance for the treatment of gout and hyperuricemia. Febuxostat and its effects were first described in the international application WO92/09279.

Febuxostat is currently available in the market in the form of coated tablets sold under the name Adenuric. These tablets contain 80 mg or 120 mg of febuxostat of the polymorphic form A. The tablet core consists of the active substance, lactose, microcrystalline cellulose, magnesium stearate, hydroxypropyl methyl cellulose, sodium salt of crosscarmellose and colloidal silicon dioxide. The tablet coating consists of polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc and pigment.

Febuxostat can form various crystalline structures. This phenomenon is called polymorphism and individual crystalline structures are called polymorphic forms. A great number of polymorphic forms of febuxostat have been described in the literature, but in the course of time most of them proved to lack thermodynamical stability and due to the influence of external conditions (e.g. being exposed to humidity) they are converted to another or other

polymorphic form(s). The international application WO99/65885 characterized the polymorphic forms A, B, C, D and G. These forms are distinctive with their characteristic X-ray powder diffraction peaks and specific absorption values in the infrared spectral analysis. The said application highlights the form A as the most suitable one for industrial application without this fact being specified in detail or supported by data.

Other polymorphic forms of febuxostat have been described in the documents WO2010144685A1 (forms F10, F1 and F2), WO2011080651A2 (forms R1, R2, R3, R4 and R5), WO2011107911A1 (form R), WO2011134101 (form N), WO2011161245 (forms I and II), WO2012038971 (form H1 and H2), WO2012168948 (forms H3 and H4), WO2012048861 (form III), WO2012056442 (forms VIII and IX), CN102093309 and CN102093308 (forms H, I and J), CN101386605 and CN101817801 (form K), CN101824007 and CN101891702 (form M), CN101824006 (form P), CN101824005 (form Q), CN101928260 (forms R, S and T), CN102070558 (L-shaped crystals), CN101805310 (crystal form delta), and further in the documents CN101525319, CN101768150, CN101671314, CN101857578, CN102127033 and CN101891703.

The international application WO03/082279 describes solid pharmaceutical formulations of febuxostat for oral administration, wherein febuxostat is present in a singlr crystalline form, namely form A. These pharmaceutical formulations can be prepared both by direct tabletting and with the use of dry granulation or wet granulation with water, ethanol and possibly solutions containing a binder. According to the authors of the application WO03/082279 form A was selected based on the application WO99/65885, where this form was preferred to forms B, C, D and G. Examples in WO03/082279 document that when pharmaceutical formulations were prepared with the other forms, conversion to other crystalline forms occurred.

The international application WO2012140632 describes amorphous solid dispersions of febuxostat, the term "solid dispersion" being explained as a system where febuxostat is dispersed in the form of small solid particles in a solid-state carrier. While the first aspect of the invention described in WO2012140632 are solid dispersions of febuxostat, the other aspect is a process of preparing an amorphous solid dispersion of febuxostat and a carrier comprising dissolution of febuxostat and the carrier (polyvinyl pyrrolidone) in a solvent and subsequent removal of the solvent from the solution.

An advantage of a solid solution of febuxostat in a polymer that is soluble in water is an increase of the dissolution rate, which leads to faster absorption into the patient's body, and increased biological availability of the active substance.

Disclosure of the technical solution

Febuxostat is a substance for the treatment of gout, which is poorly soluble in water and is easily subject to changes in its crystalline structure in the presence of water and atmospheric humidity. The technical solution provides formulations containing a solid solution of febuxostat and a polymeric carrier in the weight ratio of febuxostat to the polymeric carrier in the range of 1:3 to 3:2, including the limit values.

A "solid solution" means a chemically and physically homogeneous material, in which the molecules of the substance being dissolved are homogeneously dispersed among the molecules of the carrier substance (the substance forming a matrix of the solid solution) and in which no particles of the substance being dissolved can be detected by means of any method known from the state of the art (e.g. an optical and electron microscope, FTIR microscopy, X-ray analysis, NMR, DSC analysis).

An advantage of the solid solutions of febuxostat is stabilization and protection of febuxostat from the effects of atmospheric humidity. Another clear advantage of the solid solution of febuxostat is easier releasing into a solution, which increases biological compatibility of this active substance compared to its crystalline forms.

A solid solution of febuxostat can be prepared by melting of febuxostat with a polymeric carrier at a temperature of from 130 to 160°C, including the limit values, wherein the residence time of the melted mixture lies in the range of from 3 to 7 mins, incl. the limit values.

The ratio of febuxostat and the polymeric carrier influences the weight of the final dosage form. With regard to the subsequent use of the solid solution in the final dosage form it is necessary that the ratio of the active substance to the polymeric carrier be at least 1:3, in order

to keep the weight and thus size of the final dosage form to the minimum to make it as acceptable for the patients as possible.

The following list can be mentioned as polymeric carriers suitable for the preparation of solid solutions of febuxostat by melting, without the list limiting the scope of this technical solution: ethyl cellulose, polyethylene glycol, glycerine triacetate, polyethylene oxide, polymethacrylates, hydroxypropyl cellulose, hydroxypropyl methyl cellulose phtalate, cellulose acetate butyrate, polyvinyl alcohol, polycaprolactam, a copolymer of methacrylic acid with methyl methacrylate, a copolymer of polyvinyl caprolactam, polyvinyl acetate and polyethylene glycol, cellulose, polyvinyl pyrrolidone (povidone, PVP). One polymer or a mixture of more polymers can be used as the polymeric carrier.

One or more softeners can also be added to the melting mixture, namely in such a quantity to achieve the weight ratio of the polymeric carrier and softener of 1:0.6 at the most. Polyvinyl pyrrolidone (povidone, PVP), polyethylene oxide, polyethylene glycol, hydroxypropyl methyl cellulose, hydroxypropyl cellulose, a copolymer of polyvinyl pyrrolidone with vinyl acetate, ethyl cellulose, cellulose, polyvinyl caprolactam, polyvinyl acetate, butyl stearate, glycerol monostearate, stearyl alcohol, triethyl citrate, tributyl citrate, propylene glycol, mineral oil, diethyl phtalate, dibutyl phtalate and others can be used as the softeners.

Another possibility of preparing a solid solution of febuxostat involves spray drying of aqueous and organic solutions of a polymer and febuxostat. An advantage of this preparation method is easy control of the process parameters and the production rate. The produced particles have a narrow size distribution, which makes their further use for the preparation of solid drug forms easier. The drying rate and the size of drops at the beginning of drying proved to be important parameters.

As examples of suitable polymers for the preparation of solid solutions by spray drying from organic solvents the following substances can be mentioned for example: polyvinyl pyrrolidone, a copolymer of polyvinyl pyrrolidone and vinyl acetate, polyethylene glycol, polyethylene oxide, poly(butyl methacrylate), poly(methyl methacrylate), poly(ethyl methacrylate), poly(ethyl acrylate), poly(trimethylaminoethyl methacrylate) chloride and other

polymethacrylates, ethyl cellulose and other polymers soluble in organic solvents. A suitable polymer is polyvinyl pyrrolidone.

It is necessary to ensure, for use of the solid solution of febuxostat in a pharmaceutical formulation, that the size of the particles of the solid solution of febuxostat be in the range of from 1 to 1000 μm, preferably 5 to 500 μm, most preferably 5 to 250 μm, determined as the D90 value using the static light dispersion method. The D90 value indicates such a particle size that 90% by weight of all particles are smaller than this value. If particles of these sizes are not produced during the preparation process of the solid solution itself, e.g. by spray drying, these sizes can be achieved by crushing or grinding of the solid solution by means of a hammer mill, colloidal mill or ball mill.

A pharmaceutical formulation comprising the solid solution of febuxostat may be in the form of capsules or tablets or other known forms of pharmaceutical formulations for oral administration.

Pharmaceutical formulations of febuxostat in the form of a solid solution for oral administration comprise

- 10 to 70% by weight of a solid solution of febuxostat;
- 30 to 80% by weight of a filler (e.g. anhydrous and/or hydrated lactose, microcrystalline cellulose, sorbitol, mannitol, hydrates of calcium hydrogen phosphate and/or sucrose and/or any filler known from the prior art);
- disintegrants up to the concentration of 10% by weight (e.g. sodium salt of crosscarmellose, crosspovidone, starch, low substituted hydroxypropyl cellulose, colloidal silicon dioxide, sodium salt of carboxymethyl starch and/or any disintegrant known from the prior art);
- glidants up to the concentration of 10% by weight (e.g. colloidal silicon dioxide, magnesium carbonate, stearic acid or its salts such as magnesium stearate, sodium stearyl fumarate, magnesium palmitate, magnesium oleate, hydrogenated vegetable oil, hydrogenated castor oil, talc, macrogols (polyethylene glycols) of various molecular weights and/or any glidant known from the prior art);

- moisturizers up to the concentration of 7% (e.g. sodium stearyl fumarate, stearic acid or its salts such as magnesium stearate, calcium stearate, talc, anhydrous colloidal silicon dioxide and/or any moisturizer known from the prior art);
- or optionslly a binder up to the concentration of 8% by weight (e.g. povidone, copovidone, hydroxypropyl cellulose and/or hydroxyethyl cellulose and/or any binder known from the prior art).

Pharmaceutical formulations of febuxostat in the form of a solid solution for oral administration preferably comprise

- 15-20 % by weight of the active substance;
- 10-37% by weight of a polymeric carrier;
- 30-45% of microcrystalline cellulose;
- glidants, moisturizers, softeners and disintegrants up to the concentration of 15% by weight;
- colourants up to the concentration of 0.5 % by weight;
- coating agents up to the concentration of 5% by weight.

Pharmaceutical formulations of febuxostat in the form of a solid solution for oral administration can be further coated by means of common methods.

Example

Compound name	Quantity (kg / batch)	Function
Active substance		
Febuxostat	12.000	Active substance
Auxiliary substances		
Soluplus	24.000	Polymeric carrier
Microcrystalline cellulose	30.000	Filler
Sodium salt of crosscarmellose	3.000	Disintegrant
Colloidal silicon dioxide	0.600	Glidant
Sodium stearyl fumarate	1.500	Moisturizer
Hypromellose	1.103	Coating agent
Macrogol	0.177	Softener
Titanium dioxide	0.087	Colourant
Talc	0.014	Glidant
Yellow iron oxide	0.009	Colourant
Brown iron oxide	0.009	Colourant

A mixture of febuxostat with the polymer Soluplus (a copolymer of polyvinyl caprolactam with polyvinyl acetate and polyethylene glycol) was melted at 140°C in an extruder with screw feed of material. The residence time of the material in the extruder was 4 mins, the feed rate of the material inside the extruder was 5 cm/min. This experiment resulted in a melt comprising a solid solution of febuxostat in the polymer. The solid solution of febuxostat was ground to get the particle size of 230 μm. Absence of the crystalline form of febuxostat was confirmed by means of XPRD, NMR and DSC analyses. Stability of the solid solution was proved by exposure of the solution to 40°C and 75% relative humidity for one month.

Claims

1) A pharmaceutical composition containing febuxostat as the active substance, characterized in that it comprises febuxostat in the form of a solid solution with a polymeric carrier with the particle size in the range of 1 to 1000 μm, determined as the D90 value using the static light dispersion method, the microcrystalline cellulose filler and other pharmaceutically acceptable excipients.

2) The pharmaceutical formulation according to claim 1, characterized in that the polymeric carrier is a copolymer of polyvinyl caprolactam with polyvinyl acetate and polyethylene glycol.

INTERNATIONAL SEARCH REPORT

International application No
PCT/CZ2015/000146

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/14 A61K31/426
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data, BIOSIS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2012/140632 A1 (RANBAXY LAB LTD [IN]; KAUSHIK POONAM [IN]; THAIMATTAM RAM [IN]; PRASAD) 18 October 2012 (2012-10-18) cited in the application	1
Y	the whole document -----	2
Y	BASF: "Soluplus -Technical information", INTERNET CITATION, July 2010 (2010-07), pages 1-8, XP002666808, Retrieved from the Internet: URL:http://www.pharma-ingredients.basf.com/Statements/Technical%20Informations/EN/Pharma%20Solutions/03_090801e_Soluplus.pdf [retrieved on 2012-01-10] the whole document -----	2

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

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"P" document published prior to the international filing date but later than the priority date claimed

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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
9 March 2016	17/03/2016

Name and mailing address of the ISA/	Authorized officer
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/CZ2015/000146

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2012140632 A1	18-10-2012	AU 2012241378 A1	31-10-2013
		CA 2833101 A1	18-10-2012
		EP 2696854 A1	19-02-2014
		US 2015031732 A1	29-01-2015
		WO 2012140632 A1	18-10-2012