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- (71) **Applicant:** ZENTIVA K.S. [CZ/CZ]; U Kabelovny 130, 102 37 Praha 10 (CZ).
- (72) **Inventors:** SKARIA, Cyrus Victor; Paclo Colony 500/4, Bambolim, Goa 403 202 (IN). STOKROCKA, Malgorzata; Porebskiego 62/21, 80-180 Gdansk (PL).
- (74) **Agents:** JIROTKOVA, Ivana et al.; Rott, Ruzicka & Guttman, P.O. Box 44, 120 00 Praha 2 (CZ).
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(54) **Title:** DISPERSIBLE TABLETS CONTAINING DEFERASIROX

(57) **Abstract:** The present invention relates to dispersible tablets containing 4-[3,5-bis(2-hydroxyphenyl)-1H-[1,2,4]triazol-1-yl] benzoic acid (deferasirox), or its pharmaceutically acceptable salts or crystalline forms, and a combination of at least two disintegrants that have the same or different chemical composition and different average sizes of particles, the total amount of the disintegrant in the tablet being more than 35% by weight.



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Dispersible tablets containing deferasirox

Technical Field

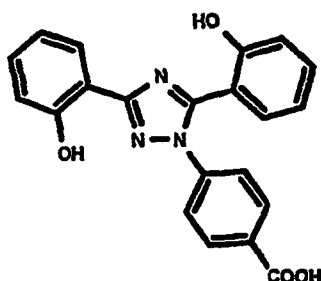
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The present invention relates to dispersible tablets containing 4-[3,5-bis(2-hydroxyphenyl)-1H-[1,2,4]triazol-1-yl]benzoic acid or its pharmaceutically acceptable salts or crystalline forms and a combination of at least two disintegrants that have the same or different chemical composition and a different average size of particles while the total amount of the disintegrant

10 in a tablet is more than 35% by weight.

Background Art

4-[3,5-bis(2-hydroxyphenyl)-1H-[1,2,4] triazol-1-yl]benzoic acid (also known as deferasirox)



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and its pharmaceutically acceptable salts and crystalline forms are described in the patent application WO97/049395A.

20 Deferasirox is an orally active iron chelator that is indicated for treatment of iron overload in patients with anemia treated by blood transfusions, in specific cases for beta thalassemia, thalassemia intermedia and for sickle cell anemia to reduce morbidity and mortality caused by iron, and is also used to treat haemochromatosis.

25 The patent application WO2004/035026A describes dispersible tablets containing 5 to 40% by weight of deferasirox or its pharmaceutically acceptable salts and at least one disintegrant in the amount of 10% to 35% by weight. The dispersible tablets are preferably prepared by wet granulation, which improves the physical characteristics of the drug, or the active substance, respectively, especially its poor flowability and sticking tendency. The description emphasizes

that even with the use of wet granulation the active component keeps sticking and is difficult to handle during tableting. This problem was solved by adding a lubricant to the tableting mixtures. However, the addition of a lubricant in amounts exceeding 0.2% by weight made the disintegration of dispersible tablets longer than 3 minutes. For this reason the lubricant is not added to the mixture, but is directly sprayed onto the punches of the tableting machine in amounts lower than 0.2% by weight in order to meet the requirement of the European Pharmacopoeia for disintegration, which should be shorter than 3 minutes.

It has been unexpectedly found out that dispersible tablets containing deferasirox, a combination of at least two disintegrants that have the same or different chemical composition and a different average size of particles, while the total amount of the disintegrant in a tablet is more than 35% by weight, and one or more pharmaceutically acceptable excipients have reduced the disintegration time of tablets and exhibited acceptable hardness and abrasion. In addition, a lubricant added in an amount of up to 2% by weight has no significant impact on the disintegration time of the tablet and improves processability of the active substance and excipients.

Disclosure of Invention

The present invention provides a dispersible tablet containing deferasirox, its pharmaceutically acceptable salts or crystalline forms, a combination of at least two disintegrants that have the same or different chemical composition and a different average size of particles, the total amount of the disintegrant in the a tablet being more than 35% by weight, and one or more pharmaceutically acceptable excipients.

In accordance with this invention the dispersible tablet contains a combination of at least two disintegrants that have the same or different chemical composition where the average particle size of the first disintegrant is less than 75 μm and the average particle size of the other disintegrant is more than 75 μm and less than 400 μm , preferably, the particle size of the first disintegrant is smaller than 50 μm , preferably smaller than 15 μm and the average particle size of the other disintegrant is from 100 μm to 400 μm , preferably from 110 μm to 140 μm .

The dispersible tablet contains deferasirox, its pharmaceutically acceptable salts or crystalline forms in an amount of from 15% by weight to 40% by weight. The tablet preferably contains 25 - 35% by weight of deferasirox, its pharmaceutically acceptable salt or crystalline form.

The dispersible table contains the first and second disintegrant in a total amount of from 40%
5 by weight to 58% by weight.

The ratio of the first and second disintegrant in the dispersible tablet is in the range from 1:2 to 1:15, preferably in the range from 1:3 to 1:13.

The first disintegrant with the particle size of less than 75 μm is crospovidone, sodium starch glycolate, corn starch, sodium crosscarmellose or low-substituted hydroxypropyl cellulose.

10 The average particle size of examples of suitable disintegrants is presented in the table below.

Disintegrant	Average particle size [μm]
Kollidon CL-F	20 - 40
Kollidon CL-SF	10 - 30
Kollidon CL-M	3 - 10
Polyplasdone XL-10	25-40
Crospopharm type B	30
Sodium starch glycolate	50
Corn starch	2-32
Sodium crosscarmellose (Aci-Di-Sol)	50
Low-substituted hydroxypropyl cellulose LH-22	45
Low-substituted hydroxypropyl cellulose LH-32	20

The other disintegrant exhibiting an average particle size of more than 75 μm and less than 400 μm is crospovidone. Examples of suitable variants of crospovidone with average particle
15 sizes are presented in the table below.

Disintegrant	Average particle size [μm]
Kollidon CL (BASF)	110-130
Polyplasdone XL (ISP)	110-140
Crospopharm type A	100

The dispersible tablet further contains one or more pharmaceutically acceptable excipients comprising fillers, wetting agents, glidants and lubricants.

5 Suitable fillers are microcrystalline cellulose, powdered cellulose, microcrystalline cellulose with added silicon dioxide, lactose, calcium carbonate, calcium hydrogen phosphate, calcium lactate, sugar alcohols and any mixtures thereof.

 Suitable wetting agents are sodium lauryl sulphate, polysorbates, poloxamer, quaternary ammonium salts or any combinations thereof.

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 Suitable glidants and lubricants are silicon dioxide, colloidal silicon dioxide, stearic acid, talc, magnesium trisilicate, stearates (e.g. magnesium stearate), behenates, fumarates, hydrogenated vegetable oil, hydrogenated castor oil or any combinations thereof.

15 The dispersible tablets preferably have a two-phase structure consisting of:

- a) an inner phase containing deferasirox, its pharmaceutically acceptable salts or crystalline forms, the first disintegrant, one or more pharmaceutically acceptable excipients and
- b) an outer phase containing the other disintegrant and one or more pharmaceutically acceptable excipients.

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 The average particle size of the first disintegrant is 75 μm , preferably less than 50 μm , most preferably less than 15 μm , and the average particle size of the other disintegrant is from 75 μm to 400 μm , preferably from 100 μm to 400 μm , most preferably from 110 μm to 140 μm .

25 In another variant the dispersible tablets have a two-phase structure consisting of:

- a) an inner phase containing deferasirox, its pharmaceutically acceptable salts or crystalline forms, the first disintegrant and a portion of the other disintegrant, one or more pharmaceutically acceptable excipients, and
 - b) an outer phase containing the remaining portion of the other disintegrant and one or more
- 30 pharmaceutically acceptable excipients.

The average particle size of the first disintegrant is 75 μm , preferably less than 50 μm , most preferably less than 15 μm and the average particle size of the other disintegrant is from 75 μm to 400 μm , preferably from 100 μm to 400 μm , most preferably from 110 μm to 140 μm .

- 5 According to the invention the dispersible tablets are prepared by dry granulation followed by compression of the granules into tablets.

The preparation method of the dispersible tablets consists of the following steps:

- 10 a) mixing deferasirox, its pharmaceutically acceptable salts or crystalline forms, with the first disintegrant and/or a portion of the other disintegrant and at least one pharmaceutically acceptable excipient,
- b) mixing the mixture produced in step a) with a portion of the lubricant,
- c) dry granulation of the mixture produced in step b),
- d) mixing the granules obtained in step c) with the other disintegrant, the remaining lubricant
- 15 and at least one pharmaceutically acceptable excipient,
- e) compressing the mixture obtained in step d) into tablets,
- f) compressing the mixture obtained in step e) to form a tablet.

In accordance with the invention the disintegration time of the dispersible tablets in aqueous solutions (e.g. in water) is shorter than 3 minutes.

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Examples

Dispersible tablets were prepared in the following way:

- 25 The constituents of the inner phase, deferasirox, crospovidone, microcrystalline cellulose, sodium lauryl sulphate and colloidal silicon dioxide were screened through a sieve with the mesh size of 1 mm and homogenized for 10 minutes. Then, magnesium stearate was added, the mixture was homogenized for 5 minutes and then it was compacted using a Gerteis roller compactor with a force of 1 – 10 kN/cm^2 , preferably 2 – 7 kN/cm^2 . The produced material strips were ground and the obtained granules were mixed with the constituents of the outer
- 30 phase, lactose and crospovidone, and homogenized for 10 minutes. Then, the remaining magnesium stearate was added and this mixture was homogenized for 5 minutes. The resulting granulate was compressed into tablets.

Example 1: Dispersible tablets with the disintegration time of 02:50 min.

Constituents		% by weight
Inner phase	Deferasirox	29.72
	Crospovidone (Kollidon CL-M)	8.92
	Microcrystalline cellulose (Avicel PH101)	5.94
	Sodium lauryl sulphate	0.44
	Colloidal silicon dioxide	0.18
	Magnesium stearate	0.42
Outer phase	Lactose	21.40
	Crospovidone (Polyplasdone XL)	32.69
	Magnesium stearate	0.30

Example 2: Dispersible tablets with the disintegration time of 00:46 min.

Constituents		% by weight
Inner phase	Deferasirox	29.72
	Crospovidone (Kollidon CL-M)	2.97
	Crospovidone (Polyplasdone XL)	8.92
	Microcrystalline cellulose (Avicel PH101)	5.94
	Sodium lauryl sulphate	0.44
	Colloidal silicon dioxide	0.18
	Magnesium stearate	0.42
Outer phase	Lactose	21.40
	Crospovidone (Polyplasdone XL)	29.72
	Magnesium stearate	0.30

5 **Example 3:** Effect of the amount of lubricant on the disintegration time of the tablet.

Dispersible tablets containing different amounts of magnesium stearate were prepared using the above mentioned preparation procedure.

Example 3a: Dispersible tablets containing 1% by weight of magnesium stearate:

Constituents		% by weight
Inner phase	Deferasirox	29.63
	Crospovidone (Kollidon CL-M)	2.96
	Crospovidone (Polyplasdone XL)	8.89
	Microcrystalline cellulose	5.93
	Sodium lauryl sulphate	0.44
	Colloidal silicon dioxide	0.18
	Magnesium stearate	0.41
Outer phase	Lactose	21.33
	Crospovidone (Polyplasdone XL)	29.63
	Magnesium stearate	0.60

Example 3b: Dispersible tablet formulation containing 1.5% by weight of magnesium stearate:

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Constituents		% by weight
Inner phase	Deferasirox	29.49
	Crospovidone (Kollidon CL-M)	2.95
	Crospovidone (Polyplasdone XL)	8.85
	Microcrystalline cellulose	5.90
	Sodium lauryl sulphate	0.44
	Colloidal silicon dioxide	0.18
	Magnesium stearate	0.41
Outer phase	Lactose	21.23
	Crospovidone (Polyplasdone XL)	29.49
	Magnesium stearate	1.06

Example 3c: Dispersible tablet formulation containing 1.99% by weight of magnesium stearate:

Constituents		% by weight
Inner phase	Deferasirox	29.33
	Crospovidone (Kollidon CL-M)	2.93
	Crospovidone (Polyplasdone XL)	8.80
	Microcrystalline cellulose	5.87
	Sodium lauryl sulphate	0.44
	Colloidal silicon dioxide	0.18
	Magnesium stearate	0.41
Outer phase	Lactose	21.12
	Crospovidone (Polyplasdone XL)	29.33
	Magnesium stearate	1.58

The results are summarized in the table below:

	Magnesium stearate [% by weight]	Disintegration time [mm:ss]
Example 2	0.72	00:46
Example 3a	1.01	01:32
Example 3b	1.47	01:27
Example 3c	1.99	01:25

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The results show that the amount of the lubricant does not have any critical impact on the disintegration time of the tablets if the tablets are produced in accordance with the invention, even tablets containing up to 2% by weight of the lubricant comply with the requirement for the disintegration time in accordance with the European Pharmacopoeia.

10

Claims

- 5 1. A dispersible tablet containing deferasirox, its pharmaceutically acceptable salts or crystalline forms, characterized in that it contains a combination of at least two disintegrants that have the same or different chemical composition and a different average size of particles and one or more pharmaceutically acceptable excipients, the first disintegrant having an average particle size smaller than 75 μm and the other disintegrant having an average particle size of from 75 μm to 400 μm and the total amount of the disintegrant in the tablet being more than 35% by weight.
- 10 2. The dispersible tablet according to claim 1, characterized in that it contains deferasirox, its pharmaceutically acceptable salts or crystalline forms in an amount of from 15 15% by weight to 40% by weight.
3. The dispersible tablet according to claim 2, characterized in that it contains the first and second disintegrants in a total amount of from 40% to 58% by weight.
- 20 4. The dispersible tablet according to claims 1-3, characterized in that the ratio between the first and second disintegrants is in the range of from 1:2 to 1:15.
5. The dispersible tablet according to claim 4, characterized in that the ratio between the first and second disintegrants is in the range of from 1:3 to 1:13.
- 25 6. The dispersible tablet according to claims 1-5, characterized in that the average particle size of the first disintegrant is less than 50 μm , preferably less than 15 μm .
7. The dispersible tablet according to claims 1-6, characterized in that the average particle size of the other disintegrant is in the range of from 100 μm to 400 μm , preferably from 110 μm to 140 μm .
- 30

8. The dispersible tablet according to claim 6, characterized in the first disintegrant is crospovidone, sodium starch glycolate, corn starch, sodium crosscarmellose or low-substituted hydroxypropyl cellulose.

5 9. The dispersible tablet according to claim 7, characterized in that the other disintegrant is crospovidone.

10. The dispersible tablet according to any one of the preceding claims, characterized in that the first disintegrant is crospovidone with an average particle size of less than 15 μm , and
10 the other disintegrant is crospovidone with an average particle size of from 110 μm to 140 μm .

11. The dispersible tablet according to any one of the preceding claims, characterized in that it has a two-phase structure consisting of:

- a) an inner phase containing deferasirox, its pharmaceutically acceptable salt or crystalline
15 form, the first disintegrant, one or more pharmaceutically acceptable excipients, and
b) an outer phase containing the other disintegrant and one or more pharmaceutically acceptable excipients.

12. The dispersible tablet according to claims 1-10, characterized in that it has a two-phase
20 structure consisting of:

- a) an inner phase containing deferasirox, its pharmaceutically acceptable salt or crystalline form, the first disintegrant and a portion of the other disintegrant, one or more pharmaceutically acceptable excipients, and
b) an outer phase containing the remaining portion of the other disintegrant and one or more
25 pharmaceutically acceptable excipients.

13. A method for the preparation of the dispersible tablet according to any one of the preceding claims, characterized in that it consists of:

- a) mixing deferasirox, its pharmaceutically acceptable salts or crystalline forms with the first
30 disintegrant, or the first disintegrant and a portion of the other disintegrant, and at least one pharmaceutically acceptable excipient,
b) mixing the mixture produced in step a) with a lubricant,
c) dry granulation of the mixture produced in step b),

- d) mixing the granules obtained in step c) with the other disintegrant and at least one pharmaceutically acceptable excipient,
- e) mixing the mixture obtained in step d) with a lubricant,
- f) compressing the mixture obtained in step e) to form a tablet.

INTERNATIONAL SEARCH REPORT

International application No
PCT/CZ2013/000138

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/00 A61K31/4196
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)

EP0-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2012/003987 A1 (RATIOPHARM GMBH [DE]; PAETZ JANA [DE]; RIMKUS KATRIN [DE]) 12 January 2012 (2012-01-12) page 1, line 1 - page 4, line 22 page 6, line 9 - line 22 page 9, line 28 - page 10, line 13 page 14, line 5 - page 15, line 11 claims 1, 2, 8, 9; examples 1, 1a, 1b -----	1-13
X	US 2009/142395 A1 (ZADOK URI [IL] ET AL) 4 June 2009 (2009-06-04) paragraph [0002] - paragraph [0003] paragraph [0013] - paragraph [0043] paragraph [0050] - paragraph [0051] paragraph [0066]; examples 1-48 claims 1, 23-32 ----- -/--	1-13

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

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

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

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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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

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Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040,
Fax: (+31-70) 340-3016

Authorized officer

González Ferreiro, M

INTERNATIONAL SEARCH REPORT

International application No
PCT/CZ2013/000138

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

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