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(71) Applicant: SYNTHON B.V. [NL/NL]; Microweg 22,
6545 CM Nijmegen (NL).

(72) Inventors: GARCIA JIMENEZ, Sonia; Synthon Hispania S.L., Castello 1, Poligono Las Salinas, 08830 Sant Boi de Llobregat (ES). ALVAREZ FERNANDEZ, Lisardo; Synthon Hispania S.L., Castello 1, Poligono Las Salinas, 08830 Sant Boi de Llobregat (ES). VELADA CALZADA, Jose; Synthon B.V., Microweg 22, 6545 CM Nijmegen (NL).

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(54) Title: PHARMACEUTICAL COMPOSITION COMPRISING AMORPHOUS DASATINIB

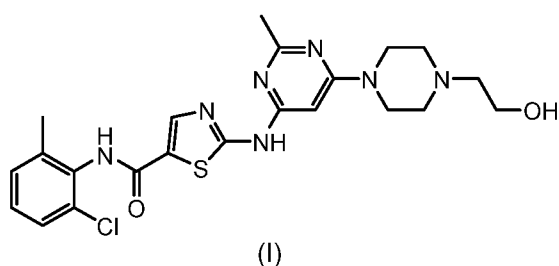
(57) Abstract: The present invention relates to a tablet composition comprising a solid dispersion of dasatinib and a polymer, wherein the composition is obtained by: (1) Dissolving dasatinib and the polymer in a solvent mixture comprising water, an alcohol and at least one molar equivalent of acid with respect to dasatinib at a temperature ranging from 45 to 70°C; (2) Adding the resulting solution to a diluent; (3) Evaporating the solvent; (4) Mixing the resulting blend with further excipients; (5) Compressing the final blend into tablets, what wherein the polymer is selected from polyvinylpyrrolidone, copovidone and hydroxypropyl cellulose. The invention further relates to the use of said tablet composition as a medicament, particularly in the treatment of chronic myeloid leukaemia (CML) and acute lymphoblastic leukaemia (ALL).



PHARMACEUTICAL COMPOSITION COMPRISING AMORPHOUS DASATINIB

5 BACKGROUND OF THE PRESENT INVENTION

Dasatinib, chemically *N*-(2-chloro-6-methylphenyl)-2-[[6-[4-(2-hydroxyethyl)-1-piperazinyl]-2-methyl-4-pyrimidinyl] amino]-5-thiazolecarboxamide of formula (I),



is a pharmaceutically active compound used for the treatment of adult patients with
10 chronic myelogenous leukaemia (CML) after imatinib treatment, Philadelphia chromosome-positive acute lymphoblastic leukaemia (ALL) and newly diagnosed Philadelphia chromosome positive (Ph⁺) chronic myelogenous leukaemia (CML) in the chronic phase.

Dasatinib was discovered by Bristol-Myers Squibb and is disclosed in EP1 169038.
Dasatinib is the active ingredient in the medicinal product sold under the brand name
15 Sprycel[®].

Several crystalline forms of dasatinib are known and described in literature.
WO2005077945 discloses a crystalline monohydrate of dasatinib and a butanol solvate of dasatinib. The marketed product Sprycel[®] contains the crystalline monohydrate of dasatinib.
WO2005077945 further discloses a crystalline ethanol solvate and two anhydrous forms of
20 dasatinib. Other forms of dasatinib are disclosed in WO2009053854, WO2010062715, WO2010067374, WO201 1095059 and WO2012014149. Some of the described forms do

contain unwanted solvents. Moreover, it was experienced in our laboratory that, especially under humid conditions, some of these forms are rather unstable.

Dasatinib monohydrate is a BCS class II compound, exhibiting low solubility and high permeability. Its low aqueous solubility affects the dissolution behavior of dasatinib monohydrate negatively.

The solubility of amorphous forms is higher compared to the solubility of crystalline forms, thus it would be desirable to have dasatinib available in amorphous form.

WO2009053854 provides processes to prepare amorphous dasatinib. WO2015049645

discloses processes to prepare several hydrated forms of amorphous dasatinib. CN104327067

provides a process to prepare amorphous dasatinib by dissolving the compound in a solvent/co-solvent system followed by spray-drying. However, amorphous dasatinib as such is not stable and therefore not suitable for use on pharmaceutical production scale.

WO2013105894 and WO2013105895 disclose pharmaceutical compositions comprising stable amorphous hybrid nanoparticles comprising dasatinib and a polymeric stabilizing and

matrix-forming component and processes to prepare them. The process to obtain said particles, involves the provision and mixing of several pressurized streams. Such a treatment could easily affect the physical stability of dasatinib and is moreover rather costly.

CN104367557 discloses a process to prepare solid dispersions comprising dasatinib and polyvinylpyrrolidone by dissolving dasatinib and the polymer in a mixture of methanol and

water followed by spray drying. Since the solubility of dasatinib in this solvent mixture is low, large amounts of solvent are used. The disclosed process is therefore not suitable for production on commercial scale.

Thus in view of the prior art cited above, there is still a need for stable pharmaceutical compositions with adequate dissolution comprising dasatinib, which are suitable for

production on commercial scale.

BRIEF DESCRIPTION OF THE PRESENT INVENTION

The present invention relates to a tablet composition comprising a solid dispersion of dasatinib and a polymer, wherein the composition is obtained by:

- (1) Dissolving dasatinib and the polymer in a solvent mixture comprising water, an alcohol and at least one molar equivalent of acid with respect to dasatinib at a temperature ranging from 45 to 70°C;
- (2) Adding the resulting solution to a diluent;
- (3) Evaporating the solvent;
- (4) Mixing the resulting blend with further excipients;
- (5) Compressing the final blend into tablets,

wherein the polymer is selected from polyvinylpyrrolidone, copovidone and hydroxypropyl cellulose.

Said tablet composition may be used as a medicament, particularly in the treatment of chronic myeloid leukaemia (CML) and acute lymphoblastic leukaemia (ALL).

DETAILED DESCRIPTION OF THE PRESENT INVENTION

Sprycel® contains the monohydrated form of dasatinib as disclosed in WO2005077945, the so-called form "H1-7". Dasatinib monohydrate is a very stable compound, but being a BCS class II compound, it exhibits low aqueous solubility which affects dissolution behavior.

Other forms of dasatinib have been disclosed in the prior art. Many of these forms are solvated forms of dasatinib and some of them do contain unwanted (*e.g.* toxic) solvents.

Moreover, some of the forms as disclosed in the prior art are rather unstable.

Various approaches to overcome the poor aqueous solubility of drug candidates have been investigated in drug research and development. Since the solubility of amorphous forms is higher compared to the solubility of crystalline forms, it would be desirable to have the

drug candidate available in amorphous form. However, drugs that can exist in either amorphous or crystalline form tend to crystallize over time when present in amorphous state because the crystalline form of the drug is a lower-energy state than the amorphous form.

One of the most successful strategies to improve the dissolution of poorly soluble drugs is the preparation of a solid dispersion. The term solid dispersion has been defined as a dispersion of one or more Active Pharmaceutical Ingredients (APIs) in an inert carrier or matrix at the solid state, prepared by a solvent or melting process or a combination of the two. Depending on the physical state of the carrier, which is crystalline or amorphous, the solid dispersions are divided into crystalline solid dispersions and amorphous solid dispersions respectively. Amorphous carriers used are mostly polymers. In amorphous solid dispersions, the API is dispersed in very small size and exists in supersaturated state in amorphous carriers because of forced degradation. The amorphous carriers can increase the wettability and dispersibility of drugs as well as inhibit the precipitation process of drugs when amorphous solid dispersions are dissolved in water. These properties along with the fast dissolution rate of amorphous carriers due to the low thermodynamic stability of amorphous state carriers, enhance the drug solubility and release rate. Despite the high active research interests, the number of marketed products arising from solid dispersion approaches is very low. This low number is mainly due to scale-up problems and physicochemical instability in the manufacturing process or during storage leading to phase separation and crystallization (Vo *et. al*, Eur. J. Pharm. Biopharm., 85 (2013) 799-813).

It is not self-evident that a given drug will form an amorphous solid dispersion with just any polymer, and that, even in the event the solid dispersion is formed, it will be stable over time. Factors playing a role herein are the physicochemical properties of both API and polymer, the ratio of API to polymer used and the technique used to prepare the solid

dispersion. Techniques to prepare solid dispersions often require very specific conditions for each combination of API and polymer.

In order to obtain tablet compositions comprising a solid dispersion of dasatinib and a polymer, exhibiting adequate dissolution and excellent long term stability, which are suitable for production on commercial scale, the use of several polymers has been investigated. Only some of them appeared to be suitable to be used in accordance with the present invention. Use of some of the polymers resulted in tablet compositions wherein dasatinib was present only partially in amorphous form. Other polymers did provide tablet compositions comprising solid dispersions wherein dasatinib was present in fully amorphous form, but wherein upon storage dasatinib converted into its crystalline form(s).

The process selected to prepare the tablet compositions of the present invention is the solvent evaporation method, because in this method problems related to decomposition, as frequently occurring in the melting method, are prevented. An important prerequisite of the solvent evaporation method is the sufficient solubility of the drug and the carrier in the solvent system. Finding a suitable non-toxic solvent is sometimes difficult because carriers are hydrophilic whereas drugs are hydrophobic.

The present invention provides a tablet composition comprising a solid dispersion of dasatinib and a polymer, wherein the composition is obtained by:

- (1) Dissolving dasatinib and the polymer in a solvent mixture comprising water, an alcohol and at least one molar equivalent of acid with respect to dasatinib at a temperature ranging from 45 to 70°C;
- (2) Adding the resulting solution to a diluent;
- (3) Evaporating the solvent;
- (4) Mixing the resulting blend with further excipients;
- (5) Compressing the final blend into tablets,

wherein the polymer is selected from polyvinylpyrrolidone, copovidone and hydroxypropyl cellulose.

The polymers to be used in accordance with the present invention are selected from polyvinylpyrrolidone (PVP), copovidone and hydroxypropyl cellulose. Commonly used
5 polymers like polyethylene glycol, Eudragit® and hydroxypropyl methylcellulose were found to be unsuitable to be used in the present invention for various reasons. Some of the polymers did not result in fully amorphous solid dispersions, while other polymers did give rise to amorphous solid dispersions but wherein dasatinib started to crystallize over time. Moreover, some polymers were found to be unsuitable to be used in accordance with the present
10 invention due to their solubility/gelling behavior in the solvent system. Polyvinylpyrrolidone is a particularly preferred polymer to be used in accordance with the present invention.

The weight ratio of dasatinib to polymer in the solid dispersion ranges from about 1:1 to about 1:6, preferably from 1:1 to 1:3.

The tablet composition of the present invention is obtained by dissolving, in the first
15 step of the process, dasatinib and the polymer in a solvent mixture. The non-toxic solvent mixture in accordance with the present invention comprises water, an alcohol and at least one molar equivalent of acid with respect to dasatinib. Both dasatinib and the polymer dissolve well in the solvent mixture upon heating at a temperature ranging from 45 to 70°C.

Preferably, the acid used in accordance with the present invention is a mineral acid. Most
20 preferably, the acid is hydrochloric acid. The amount of acid present in the solvent mixture may range. However, at molar ratios of acid to dasatinib below 1:1, dissolution is insufficient, while at too high ratios, gelling was observed. Preferably, the molar ratio of acid to dasatinib is ranging from 1:1 to 3:1. More preferably, the molar ratio of acid to dasatinib is ranging from 1:1 to 2:1. The alcohol used in the solvent mixture of the present invention is selected
25 from methanol, ethanol and isopropanol. Ethanol is a particularly preferred alcohol. The

volume ratio water to alcohol in the solvent mixture may vary, but is preferably ranging from 2:3 to 1:4. At these ratios, optimal solubility is achieved.

After the first step of dissolving dasatinib and the polymer in the solvent mixture, the resulting solution is added to a diluent. In a preferred embodiment of the present invention, the addition of the solution to the diluent is performed by spraying the solution over the diluent. The diluent to be used in accordance with the present invention may be any diluent known to a person of ordinary skill in the art. Particularly, the diluent to be used in accordance with the present invention is an inorganic diluent, polysaccharide, mono- or disaccharide or sugar alcohol. Microcrystalline cellulose is a particularly preferred diluent.

After the step of adding the solution, comprising of dasatinib and the polymer in the solvent mixture, to a diluent, the solvent is evaporated. The evaporation is carried out by techniques known to a person of ordinary skill in the art.

The resulting blend is then mixed with further excipients. The tablet compositions according to the present invention comprise, besides a diluent, further pharmaceutically acceptable excipients. The excipients to be used in accordance with the present invention are well known and are those excipients which are conventionally used by the person skilled in the art. The pharmaceutically acceptable excipients are chosen from one or more binders, disintegrants, glidants or lubricants. Most preferably, the further excipients are chosen from one or more disintegrants and one or more lubricants.

The disintegrant to be used in accordance with the present invention may be any disintegrant known to a person of ordinary skill in the art. Suitable disintegrants to be used in accordance with the present invention are selected from the group consisting of croscarmellose sodium, crospovidone or sodium starch glycolate. Croscarmellose sodium is a particularly preferred disintegrant.

The lubricant to be used in accordance with the present invention may be any lubricant known to a person of ordinary skill in the art. Magnesium stearate is a particularly preferred lubricant.

After mixing the blend, comprising of the solid dispersion of dasatinb and the polymer,
5 with further excipients, the final blend is compressed into tablets, using equipment and methods well-known in the art.

The tablet composition of the present invention exhibits excellent long term stability. Even after 3 months at 40°C/75% RH, no conversion into any crystalline form of dasatinib was observed. Moreover, the tablet composition of the present invention is cost effective and
10 very suitable for production on commercial scale.

The tablet composition of the present invention display dissolution behavior typical for immediate-release formulations. The composition of the present invention exhibits a dissolution rate of at least 85% in 15-30 minutes when tested in 500 ml 0.01 N hydrochloric acid pH 2.0 in a USP apparatus II at 75 rpm, 25°C.

15 The tablet composition in accordance with the present invention may be used as a medicament. The pharmaceutical composition typically may be used in the treatment of chronic myeloid leukaemia (CML) and acute lymphoblastic leukaemia (ALL).

The following examples are intended to illustrate the scope of the present invention but not to limit it thereto.

20

EXAMPLES

The tablets comprising a solid dispersion of dasatinib and a polymer were prepared by wet granulation and have the composition as given in table 1.

Table 1: tablet composition of tablets comprising a solid dispersion of dasatinib and a polymer

Component	Quantity (mg/tablet)	Weight%
<i>Intragranular components</i>		
Dasatinib	140.00	25.00
Polymer	140.00	25.00
Ethanol 96% (v/v):aqueous HCl (3M):water 60:5:35		
Microcrystalline cellulose	254.80	45.50
<i>Extragranular components</i>		
Croscarmellose sodium	22.40	4.00
Magnesium stearate	2.80	0.50
Total core tablet weight	560.00	100.00

87.5 g of the polymer was dissolved in a heated solution (60°C) of ethanol 96%

- 5 (v/v):aqueous hydrochloric acid (3M):water 60:5:35. 87.5 g of dasatinib was added. The total solution volume was 1250 ml. The resulting solution was added to 159.25 g of microcrystalline cellulose in a fluid bed dryer. The solvent was evaporated by using a top spraying/drying process. During spraying/drying the temperature was adjusted to 45-80°C, depending on the polymer used. The resulting blend was sieved through an appropriate mesh
- 10 size sieve. 14.00 g of croscarmellose sodium was sieved through a suitable mesh size sieve for deagglomeration and mixed with the blend. Magnesium stearate was sieved through an appropriate sieve to deagglomerate and mixed with the powder mix. The homogeneous powder obtained, was compressed using a rotating tablet press using appropriate punches. The tablets were stored at 40°C/75% RH (open dish).

Stability results :

Table 2: Stability results at 40°C/75% RH open dish for tablets comprising a solid dispersion of dasatinib:polyvinylpyrrolidone 1:1

Test	t= 0	t= 3 months	t= 6 months
XRPD	Amorphous	Amorphous	Amorphous
Impurities	Total: <0.05%	Total: 0.24%	Total: 0.31%

5 *Table 3: Stability results at 40°C/75% RH open dish for tablets comprising a solid dispersion of dasatinib:copovidone 1:1*

Test	t= 0	t= 3 months	t= 6 months
XRPD	Amorphous	Amorphous	Amorphous
Impurities	Total: <0.05%	Total: 0.06%	Total: 0.08%

Table 4: Stability results at 40°C/75% RH open dish for tablets comprising a solid dispersion of dasatinib:hydroxypropyl cellulose 1:1

Test	t= 0	t= 1 month	t= 3 months
XRPD	Amorphous	Amorphous	Amorphous
Impurities	Total: <0.05%	Total: 0.07%	Total: 0.09%

CLAIMS

1. A tablet composition comprising a solid dispersion of dasatinib and a polymer, wherein the composition is obtained by:
 - (1) Dissolving dasatinib and the polymer in a solvent mixture comprising water, an
5 alcohol and at least one molar equivalent of acid with respect to dasatinib at a temperature ranging from 45 to 70°C;
 - (2) Adding the resulting solution to a diluent;
 - (3) Evaporating the solvent;
 - (4) Mixing the resulting blend with further excipients;
 - 10 (5) Compressing the final blend into tablets,wherein the polymer is selected from polyvinylpyrrolidone, copovidone and hydroxypropyl cellulose.
2. The tablet composition according to claim 1, wherein the diluent is microcrystalline cellulose.
- 15 3. The tablet composition according to claim 1 or 2, wherein the polymer is polyvinylpyrrolidone.
4. The tablet composition according to any one of claims 1 to 3, wherein the weight ratio of dasatinib to polymer is ranging from 1:1 to 1:3.
5. The tablet composition according to any one of claims 1 to 4, wherein the alcohol is
20 selected from methanol, ethanol and isopropanol.
6. The tablet composition according to any one of claims 1 to 5, wherein the alcohol is ethanol.
7. The tablet composition according to any one of claims 1 to 6, wherein the volume ratio water to alcohol in the solvent mixture is ranging from 2:3 to 1:4.

8. The tablet composition according to any one of claims 1 to 7, wherein the molar ratio of acid to dasatinib is ranging from 1:1 to 3:1.
9. The tablet composition according to any one of claims 1 to 8, wherein the acid is a mineral acid.
- 5 10. The tablet composition according to any one of claims 1 to 9, wherein the acid is hydrochloric acid.
11. The tablet composition according to any one of claims 1 to 10, wherein the further excipients are chosen from one or more disintegrants and one or more lubricants.
12. The tablet composition according to any one of claims 1 to 11 exhibiting a dissolution
10 rate of at least 85% in 15-30 minutes when tested in aqueous hydrochloric acid pH 2.0 in a USP apparatus II at 75 rpm, 25°C.
13. The tablet composition according to any one of claims 1 to 12, for use as a medicament.
14. The tablet composition according to claim 13 for use in the treatment of chronic myeloid leukaemia (CML) and acute lymphoblastic leukaemia (ALL).

INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2016/081369

A. CLASSIFICATION OF SUBJECT MATTER
 INV. A61K9/14 A61K9/20 A61K31/00
 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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2014/343073 AI (DWIVEDI SHRI PRAKASH DHAR [IN] ET AL) 20 November 2014 (2014-11-20) page 1, paragraph 1 page 2, paragraph 18 page 3, paragraphs 19, 20, 25 page 4, paragraphs 65-67, 72, 77, 78, 79 page 6, paragraph 93-94 page 7, paragraph 104-105 page 7; example 2 -----	1-7 ,9-14
Y	CN 104 367 557 A (ZHEJIANG JIUZHOU PHARM CO LTD) 25 February 2015 (2015-02-25) page 1, paragraph 4 page 2, paragraph 13-34 page 3, paragraph 35-43 page 4; examples 5-9 pages 6-7; example 17 -----	1-7 ,9-14



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

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

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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

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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

Raposo, Antoni o

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2014343073	A1	20-11-2014	NONE

CN 104367557	A	25-02-2015	NONE
