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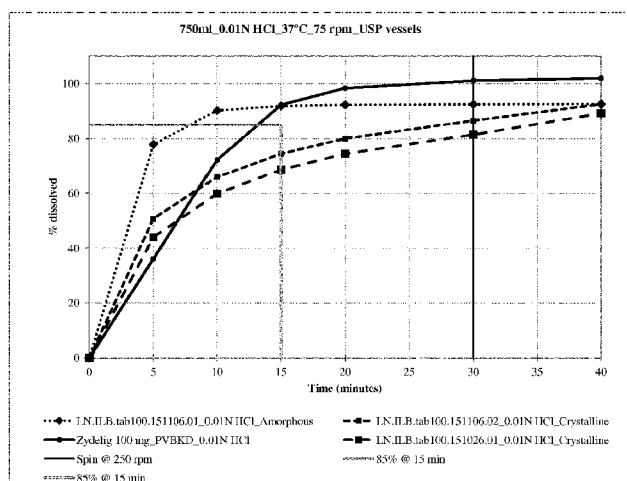
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(54) Title: PHARMACEUTICAL COMPOSITION COMPRISING IDELALISIB IN AMORPHOUS FORM

Figure 1: Dissolution in 0.01 N HCl (pH 2.0)

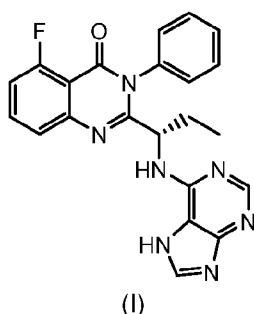


(57) Abstract: The present invention relates to a pharmaceutical composition comprising amorphous idelalisib, one or more dissolution modulating agents and one or more pharmaceutically acceptable excipients adapted to release at least 75% of idelalisib within 15 minutes when tested in a Paddle USP II dissolution apparatus at 75 rpm in 750 ml 0.01 N HCl (pH 2.0) at 37°C and not more than 50% of the idelalisib within 30 minutes when tested in a Paddle USP II dissolution apparatus at 75 rpm in 750 ml acetate buffer (pH 4.5) at 37°C.

PHARMACEUTICAL COMPOSITION COMPRISING IDELALISIB IN AMORPHOUS FORM

5 BACKGROUND OF THE PRESENT INVENTION

Idelalisib, chemically 5-fluoro-3-phenyl-2-[(1S)-1-(7H-purin-6-ylamino)propyl]-4(3H)-quinazolinone of formula (I),



is a pharmaceutically active compound used in the treatment of chronic lymphocytic
10 leukemia and non-hodgkin lymphoma. It is sold under the trade name Zydelig® by Gilead Sciences International. The compound was discovered by Icos Corporation and is disclosed in WO2005113556.

Idelalisib exhibits polymorphism. WO2013134288 discloses polymorphic forms I and II. In addition, five solvated forms of idelalisib are described. During drug development it has
15 been noted that the Zydelig® tablets contain a mixture of both forms I and II. Form I converts partly into form II during grinding and/or compression. Several experiments in WO2013134288 describe efforts to convert idelalisib form I into form II, but full conversion was not achieved. Neither do any of the described experiments prevent the formation of Form II during production of form I containing tablets.

20 In view of the prior art, there is still a need for finding alternative pharmaceutical compositions comprising a form of idelalisib with such a stability that it does not convert into

any other form under tableting or other stress conditions. The form of idelalisib present in the composition should be simple to prepare, easy to handle, suitable for use on commercial scale and the composition should release the idelalisib in a release profile similar to the marketed Zydelig® tablets (comprising crystalline idelalisib).

5

BRIEF DESCRIPTION OF THE PRESENT INVENTION

The present invention provides a pharmaceutical composition comprising amorphous idelalisib, one or more dissolution modulating agents and one or more pharmaceutically acceptable excipients adapted to release at least 75% of the idelalisib within 15 minutes when
10 tested in a Paddle USP II dissolution apparatus at 75 rpm in 750 ml 0.01 N HCl (pH 2.0) at 37°C and not more than 50% of the idelalisib within 30 minutes when tested in a Paddle USP II dissolution apparatus at 75 rpm in 750 ml acetate buffer (pH 4.5) at 37°C.

The dissolution modulating agents according to this invention are pharmaceutically acceptable excipients capable to modulate the drug dissolution rate acting as drug release
15 retardants particularly at pH 4.5 without delaying the drug release at pH 2.0.

The dissolution modulating agents of this invention are:

- Hydrophobic agents reducing the wettability of the idelalisib particles and subsequently the dissolution rate such as stearic acid, palmitic acid or their salts;
- Gel formers that retain the drug in the formulation, reducing the drug release rate
20 such as hydroxypropylmethylcellulose, carbomer, sodium alginate, or povidone;
- pH modifiers that generate a basic microenvironment, thereby reducing the solubility of idelalisib since idelalisib exhibits a pH dependent solubility being more soluble at acidic pHs, such as alkali or earth alkali salts of carbonate, hydrogencarbonate, hydroxide, citrate, acetate, phosphate, hydrogenphosphate.

Said pharmaceutical composition may be used as a medicament, particularly in the treatment of chronic lymphocytic leukemia and non-Hodgkin lymphoma.

BRIEF DESCRIPTION OF THE DRAWINGS

5 Figure 1: dissolution profiles for reference tablets comprising amorphous and crystalline idelalisib, and Zydelig® tablets tested in a Paddle USP II dissolution apparatus at 75 rpm in 750 ml 0.01 N HCl (pH 2.0) at 37°C.

 Figure 2: dissolution profiles for reference tablets comprising amorphous and crystalline idelalisib, and Zydelig® tablets tested in a Paddle USP II dissolution apparatus at
10 75 rpm in 750 ml acetate buffer (pH 4.5) at 37°C.

DETAILED DESCRIPTION OF THE PRESENT INVENTION

 The present invention provides a pharmaceutical composition comprising idelalisib in amorphous form, one or more dissolution modulating agents and one or more
15 pharmaceutically acceptable excipients including one or more dissolution modulators. Idelalisib was first disclosed in WO2005113556, methods of preparation described in WO2005113556 result in amorphous idelalisib.

 Idelalisib is sold in tablets under the brand name Zydelig®. Zydelig® tablets contain a mixture of two crystalline forms, named forms I and II. These two crystalline forms are
20 disclosed in WO2013134288.

 Since amorphous drugs have a higher solubility and show higher dissolution rates than their corresponding crystalline forms, they are frequently preferred. Often, a major drawback of amorphous drugs is that in most cases they exhibit worse physical and chemical stability than their crystalline equivalents. Drugs that can exist in either amorphous or crystalline form
25 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. In addition drugs in amorphous form are often hygroscopic and difficult to handle due to their bad flow properties.

Addition of crystallization inhibitors such as polymers to the drug to form amorphous molecular dispersions is a common method to minimize or prevent drug recrystallisation. In these amorphous molecular dispersions, it is believed that polymers can decrease the molecular mobility of the drug, therefore reducing the driving force for crystallization and improving the physical stability of amorphous drugs. Amorphous molecular dispersions are not only physically more stable than the free amorphous drugs, but in general they are also less hygroscopic and easier to process.

Surprisingly, it was discovered in our laboratory that idelalisib in free amorphous form is extremely stable. Moreover, the amorphous drug is not hygroscopic, has good physical properties and is easy to process. During stability studies no conversion into any crystalline form was observed even under stress conditions. X-ray powder diffraction analysis performed 2 months after storing the amorphous powder at 40°C/75% RH showed that the compound was still fully amorphous. Even after 3 days at 100°C, idelalisib remained completely amorphous and no significant degradation was observed.

At least a major portion of idelalisib is amorphous. The term “a major portion” of idelalisib means that at least 60% of the drug is in amorphous form, rather than a crystalline form. Preferably, idelalisib is for at least 80% in amorphous form. More preferably, idelalisib is “almost completely amorphous” meaning that the amount of idelalisib in amorphous form is at least 90% as measured by X-ray powder diffraction or any other standard quantitative measurement. Most preferably, idelalisib is in a completely amorphous form within the detection limits of the techniques used for characterization.

Idelalisib in amorphous form in accordance with the present invention advantageously is in the form of a free-flowing powder, with good handling properties, stable morphology

and is easily obtainable by common precipitation and evaporation processes. Some example processes for preparing idelalisib in amorphous form are described in reference examples 1 to 3.

Amorphous idelalisib is suitable to be used for the preparation of pharmaceutical compositions and it is sufficiently stable to be used in common tablet compositions without requiring stabilisation as a solid dispersion.

Reference examples 4 and 5 describe the preparation of tablets comprising idelalisib in amorphous (reference example 4) and crystalline (reference example 5) form. Amorphous Idelalisib compressed in tablets according to reference example 4 remains amorphous even after 6 months of storage.

Nevertheless despite the stability and suitability of amorphous idelalisib, immediate release tablets comprising 150 mg amorphous idelalisib show different release characteristics than immediate release tablets comprising 150 mg crystalline idelalisib (Zydelig®)

Figures 1 and 2 show the result of dissolution tests performed with tablets prepared according to reference examples 4 and 5 in comparison with Zydelig® when tested in a Paddle USP II dissolution apparatus at 75 rpm in 750 ml at 37°C at pH values 2.0 and 4.5.

To have similar bioavailability to the Zydelig® tablets already on the market, the tablets comprising amorphous idelalisib should release at least 75% of the idelalisib within 15 minutes when tested in a Paddle USP II dissolution apparatus at 75 rpm in 750 ml 0.01 N HCl (pH 2.0) at 37°C and not more than 50% of the idelalisib within 30 minutes when tested in a Paddle USP II dissolution apparatus at 75 rpm in 750 ml acetate buffer (pH 4.5) at 37°C.

It is clear from figure 1 that the amorphous idelalisib tablet of reference example 4 already meets the target criteria at pH 2.0, but that its release does not match the target profile at pH 4.5.

Surprisingly the problem was resolved by the addition of one or more dissolution modulating agents to the composition.

The dissolution modulating agents according to this invention are pharmaceutically acceptable excipients capable to modulate the drug dissolution rate by acting as drug release retardants particularly at pH 4.5 without delaying the drug release at pH 2.0.

The dissolution modulating agents of this invention are:

- Gel formers that retain the drug in the formulation, reducing the drug release rate such as hydroxypropylmethylcellulose, carbomer, sodium alginate, or povidone as shown in example 1. The high viscosity gel/liquid phase in the tablet area caused by these gel formers during dissolution hinders the diffusion of idelalisib out of the tablet area and thereby lowers the dissolution rate of idelalisib as present in such a tablet particularly at pH 4.5.
- Hydrophobic agents reducing the wettability of the idelalisib particles and subsequently the dissolution rate such as stearic acid, palmitic acid or their salt forms. In example 2 these hydrophobic agents are present intragranularly, where they are mixed with idelalisib before mixing with the other intragranular excipients to create a hydrophobic area around idelalisib reducing its wettability, as well as extragranularly, where they mainly act as lubricant.
- pH modifiers that generate a basic microenvironment, thereby reducing the solubility of idelalisib since idelalisib exhibits a pH dependent solubility being more soluble at acidic pHs, such as alkali or earth alkali salts of carbonate, hydrogencarbonate, hydroxide, citrate, acetate, phosphate, hydrogenphosphate.

As can be seen in figures 1 and 2, the difference between crystalline and amorphous idelalisib tablets in dissolution is larger at pH 4.5 than at pH 2.0 and the scale of dissolution modulation required is therefore larger at pH 4.5.

The solubility of idelalisib is pH dependent (below 0.1 mg/mL at pH 5-7 and above 1 mg/mL at pH 2 under ambient conditions). Addition of alkali or earth alkali salts such as those mentioned above as a pH modulator to the composition creates an increased pH microenvironment inside the tablet and modulates the release in a pH dependent manner. At low pH the influence of said alkali or earth alkali salts as a pH modulator is very limited maintaining the dissolution of idelalisib high. At pH 4.5, the increased pH microenvironment surrounding idelalisib has a stronger impact on the dissolution of idelalisib. It has been found that the effect of said alkali or earth alkali salts as a pH modifier on dissolution rate of amorphous idelalisib tablets is larger at pH 4.5 than at pH 2.0.

In a further embodiment the composition comprises a high load of amorphous idelalisib. Preferably the composition comprises at least 50% of amorphous idelalisib. More preferred at least 65% of amorphous idelalisib.

The composition further comprises pharmaceutically acceptable excipients. Examples of pharmaceutically acceptable excipients may include diluents, binders, disintegrants, lubricants, glidants, and colouring agents. The amount of additive employed depends upon various factors such as amount of active agent to be used.

Diluents may be selected from alumina, starch, kaolin, polacrillin potassium, powdered cellulose, microcrystalline cellulose, sugars such lactose, glucose, fructose, sucrose, mannose, dextrose, galactose, dextrans, dextrin; sugar alcohols such as mannitol, sorbitol, xylitol, lactitol, starch, calcium carbonate, calcium phosphate dibasic or tribasic, calcium sulphate or combinations thereof.

Binders may be selected from starches such as potato starch, wheat starch, corn starch; microcrystalline cellulose such as products known under the registered trademarks Avicel, Filtrak, Heweten or Pharmacel, combinations thereof and other materials known to one of ordinary skill in the art and mixtures thereof.

Disintegrants may be selected from low-substituted hydroxypropyl cellulose, e.g. L-HPC; cross-linked polyvinyl pyrrolidone (PVP-XL), e.g. Kollidon® CL and Polyplasdone® XL; cross-linked sodium carboxymethylcellulose, e.g. Ac-di-sol®, Primellose®; sodium starch glycolate, e.g. Primojel®; sodium carboxymethylcellulose; sodium carboxymethyl starch, e.g. Explotab®; ion-exchange resins, e.g. Dowex® or Amberlite®; microcrystalline cellulose, e.g. Avicel®; starches and pregelatinized starch, e.g. Starch 1500®, Sepistab ST200®; formalin-casein, e.g. Plas-Vita® and combinations thereof.

Lubricants may be selected from those conventionally known in the art such as magnesium, aluminum or calcium or zinc stearate, polyethylene glycol, glyceryl behenate, mineral oil, talc, sodium stearyl fumarate, stearic acid, vegetable oil such as hydrogenated vegetable oil and combinations thereof.

Glidants may be selected from silicon dioxide; magnesium trisilicate, talc and tribasic calcium phosphate, calcium silicate, magnesium silicate, colloidal silicon dioxide, silicon hydrogel.

Colouring agents may be selected from ferric oxide; pigments such as titanium dioxide. Colorants can also include natural food colours and dyes suitable for food, drug and cosmetic applications.

The amount of each type of excipient employed, e.g. glidant, binder, disintegrant, filler or diluent and lubricant may vary. Thus for example, the amount of glidant may vary within a range of 0.1 to 10% by weight, the amount of binder may vary within a range of from about 0.5 to 45% by weight, the amount of disintegrant may vary within a range of from 0.5 to 5% by weight, the amount of diluent may vary within a range of from 10 to 60% by weight; whereas the amount of lubricant may vary within a range of from 0.1 to 5.0% by weight.

The composition can be prepared by various methods known in the art such as by dry granulation, wet granulation or direct compression. The process of wet granulation includes aqueous and non-aqueous granulation.

The composition may further, be coated with a functional or non-functional coating.

5 The pharmaceutical 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 lymphocytic leukemia and non-Hodgkin lymphoma.

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

10

EXAMPLES

Reference example 1: Preparation of idelalisib in amorphous form

1.55 g of idelalisib was dissolved in 20 ml of dichloromethane and added drop wise to 60 ml of stirred n-heptane. A white precipitate was formed immediately. The solid was
15 isolated by filtration, washed with n-heptane and dried over night at ambient temperature under vacuum, affording idelalisib (1.53 g, 99% yield) as white powder.

The X-ray powder diffraction pattern of the isolated idelalisib showed that the compound was fully amorphous. X-ray powder diffraction analysis performed 2 months after storing the powder at 40°C/75% RH showed that the compound was still fully amorphous.
20 Idelalisib was still fully amorphous after 3 days in an oven at 100°C and no significant degradation was observed.

Reference example 2: Preparation of idelalisib in amorphous form

150 mg of idelalisib was dissolved in 10 ml methanol and the solution was stirred for 1 hour at ambient temperature. The solution was concentrated in vacuo and the resulting solid was dried under vacuum.

- 5 The X-ray powder diffraction pattern of the isolated idelalisib showed that the compound was fully amorphous.

Reference example 3: Preparation of idelalisib in amorphous form

100 mg of idelalisib was dissolved in 10 ml acetone. The solution was concentrated in vacuo and the resulting solid was dried under vacuum.

- 10 The X-ray powder diffraction pattern of the isolated idelalisib showed that the compound was fully amorphous.

Reference example 4: tablets comprising amorphous idelalisib

Ingredient	Amount (g)	Amount (%)
Intragranular		
Idelalisib (amorphous)	100	71.4
Microcrystalline cellulose	14.05	10.0
Hydroxypropylcellulose	2.8	2.0
Na starch glycollate	4.2	3.0
Extragranular		
Microcrystalline cellulose	14.05	10.0
Na croscarmellose	4.2	3.0
Mg stearate	0.7	0.5
<i>Total</i>	<i>140</i>	<i>100</i>

Idelalisib, microcrystalline cellulose and sodium starch glycolate were weighed, placed into a container and mixed for 1 minute at 600 rpm. Hydroxypropylcellulose is dissolved in water and added to the blend. Additional water is added if necessary. The granulate is dried in an oven at 50°C under vacuum for 3 hours. The granulate is sieved through a 0.71 mm mesh sieve. The extragranular microcrystalline cellulose and croscarmellose sodium are mixed with the granulate for 10 minutes to obtain a blend. Magnesium stearate is sieved through a 0.5 mm mesh sieve and mixed with the blend for 2 minutes. This final blend is compressed in a single punch excentric tablet press.

Reference example 5: tablets comprising crystalline idelalisib.

- 10 Tablets comprising crystalline idelalisib, were prepared according to the procedure as described in example 4 replacing amorphous idelalisib with crystalline idelalisib.

Example 1 - addition of gel forming agent

1a - HPMC

Ingredient	Amount (g)	Amount (%)
Intragranular		
Idelalisib (amorphous)	100	71.4
Microcrystalline cellulose	9.85	7.0
HPMC	7.0	5.0
Na starch glycolate	4.2	3.0
Extragranular		
Microcrystalline cellulose	14.05	10.0
Na croscarmellose	4.2	3.0
Mg stearate	0.7	0.5
Total core tablet	140	100

Ingredient	Amount (g)	Amount (%)
Cosmetic coating	4.2	3.0 of weight gain
<i>Total</i>	<i>144.2</i>	-

Process example by wet granulation approach:

Intragranular components are weighed, placed into a high shear granulator container and mixed. Water is added to the blend. The granulate is dried in fluid bed dryer. The granulate is sieved through a screen conical sieve. The extragranular components except Magnesium stearate are mixed with the dried granules in a free fall blender. Magnesium stearate is sieved through a 0.5 mm mesh sieve and mixed with the previous blend. This final blend is compressed in a rotary tablet press machine. The tablets are coated in a pan coater with a cosmetic coating.

Process example by dry granulation approach:

Intragranular components were weighed and mixed in suitable equipment. The blend is compacted in a roller compactor. The compacted powder is milled in a conical sieve to obtain granules with suitable particle size. The extragranular components except Magnesium stearate are mixed with the dried granules in a free fall blender. Magnesium stearate is sieved through a 0.5 mm mesh sieve and mixed with the previous blend. This final blend is compressed in a rotary tablet press machine. The tablets are coated in a pan coater with a cosmetic coating.

1b - 1d

Tablets are prepared as in example 1a but with HPMC replaced by carbomer, sodium alginate or povidone.

Example 2 - coating API with a hydrophobic compound*2a Magnesium stearate*

Ingredient	Amount (g)	Amount (%)
Intragranular		
Idelalisib (amorphous)	100	71.4
Magnesium stearate	7.0	5.0
Microcrystalline cellulose	7.0	5.0
Hydroxypropyl cellulose	2.8	2.0
Na starch glycollate	4.2	3.0
Extragranular		
Microcrystalline cellulose	14.05	10.0
Na croscarmellose	4.2	3.0
Mg stearate	0.7	0.5
Total core tablet	140	100
Cosmetic coating	4.2	3.0 of weight gain
<i>Total</i>	<i>144.2</i>	-

Process example by wet granulation approach:

- 5 Weigh idelalisib and hydrophobic compound and mix them in a high shear mixer or any other suitable equipment. Weigh the rest of intragranular components and add them over the previous mixture into a high shear mixer. Mix again and add water to the blend. The obtained granulate is dried in fluid bed dryer. The granulate is sieved through a screen conical sieve. The extragranular components except Magnesium stearate are mixed with the dried
- 10 granules in a free fall blender. Magnesium stearate is sieved through a 0.5 mm mesh sieve

and mixed with the previous blend. This final blend is compressed in a rotary tablet press machine. The tablets are coated in a pan coater with a cosmetic coating.

Process example by dry granulation approach:

Weigh idelalisib and hydrophobic compound and mix them in a high shear mixer or
 5 any other suitable equipment. Weigh the rest of intragranular components and mixed with the previous blend in suitable equipment. The blend is compacted in a roller compactor. The compacted powder is milled in a conical sieve to obtain granules with suitable particle size. The extragranular components except Magnesium stearate are mixed with the dried granules in a free fall blender. Magnesium stearate is sieved through a 0.5 mm mesh sieve and mixed
 10 with the previous blend. This final blend is compressed in a rotary tablet press machine. The tablets are coated in a pan coater with a cosmetic coating.

2b

Tablets are prepared as in example 2a but with magnesium stearate replaced by stearic
 15 acid.

Example 3 - addition of a pH modulator

Ingredient	Amount (g)	Amount (%)
Intragranular		
Idelalisib (amorphous)	100	71.4
Sodium bicarbonate	14.0	10.0
Hydroxypropyl cellulose	2.8	2.0
Na starch glycollate	4.2	3.0

Ingredient	Amount (g)	Amount (%)
Extragranular		
Microcrystalline cellulose	14.05	10.0
Na croscarmellose	4.2	3.0
Mg stearate	0.7	0.5
Total core tablet	140	100
Cosmetic coating	4.2	3.0 of weight gain
Total	144.2	-

Process example by wet granulation approach:

Weigh idelalisib, hydroxypropylcellulose and sodium starch glycolate, place in the high shear mixer and mix. Weigh the basic compound and dissolve in water. Add the solution over
5 the previous mixture into the high shear mixer. Additional water is added if necessary. The obtained granulate is dried in fluid bed dryer. The granulate is sieved through a screen conical sieve. The extragranular components except Magnesium stearate are mixed with the dried granules in a free fall blender. Magnesium stearate is sieved through a 0.5 mm mesh sieve and mixed with the previous blend. This final blend is compressed in a rotary tablet press
10 machine. The tablets are coated in a pan coater with a cosmetic coating.

Process example by dry granulation approach:

Intragranular components are weighed and mixed in suitable equipment. The blend is compacted in a roller compactor. The compacted powder is milled in a conical sieve to obtain granules with suitable particle size. The extragranular components except Magnesium
15 stearate are mixed with the dried granules in a free fall blender. Magnesium stearate is sieved through a 0.5 mm mesh sieve and mixed with the previous blend. This final blend is

compressed in a rotary tablet press machine. The tablets are coated in a pan coater with a cosmetic coating.

CLAIMS

1. A pharmaceutical composition comprising amorphous idelalisib, one or more dissolution modulating agents and one or more pharmaceutically acceptable excipients adapted to release at least 75% of idelalisib within 15 minutes when tested in a Paddle
5 USP II dissolution apparatus at 75 rpm in 750 ml 0.01 N HCl (pH 2.0) at 37°C and not more than 50% of the idelalisib within 30 minutes when tested in a Paddle USP II dissolution apparatus at 75 rpm in 750 ml acetate buffer (pH 4.5) at 37°C.
2. The composition according to claim 1 wherein the composition comprises at least 50% of amorphous idelalisib.
- 10 3. The composition according to claims 1 or 2, wherein the dissolution modulating agent is a hydrophobic compound.
4. The composition according to claims 3, wherein the hydrophobic compound is stearic acid or palmitic acid or a salt thereof.
5. The composition according to claims 1 or 2, wherein the dissolution modulating agent
15 is a gel former.
6. The composition according to claim 5, wherein the gel former is hydroxypropylmethyl-cellulose, carbomer, sodium alginate or povidone.
7. The composition according to claims 1 or 2, wherein the dissolution modulating agent is pH modifying agent.
- 20 8. The composition of claim 7, wherein the pH modifying agent is an alkali or earth alkali salt of carbonate, hydrogencarbonate, hydroxide, citrate, acetate, phosphate, hydrogenphosphate.
9. The composition according to claims 1 or 2, wherein the dissolution modulating agent is a combination of two or more of the hydrophobic compounds of claims 3 or 4, the
25 gel formers of claims 5 or 6 and the pH modifying agents of claims 7 or 8.

10. The composition according to claims 1 to 9 wherein the pharmaceutical composition is a tablet and the pharmaceutically acceptable excipients are one or more diluents, binders, disintegrants, lubricants, glidants, and colouring agents.
11. The composition according to claims 1 to 10 wherein the dissolution modulating agent
5 is intimately mixed with the amorphous idelalisib before mixing with the other excipients.
12. A composition according to any of claims 1 to 11 for use in the treatment of chronic lymphocytic leukemia and non-Hodgkin lymphoma

Figure 1: Dissolution in 0.01 N HCl (pH 2.0)

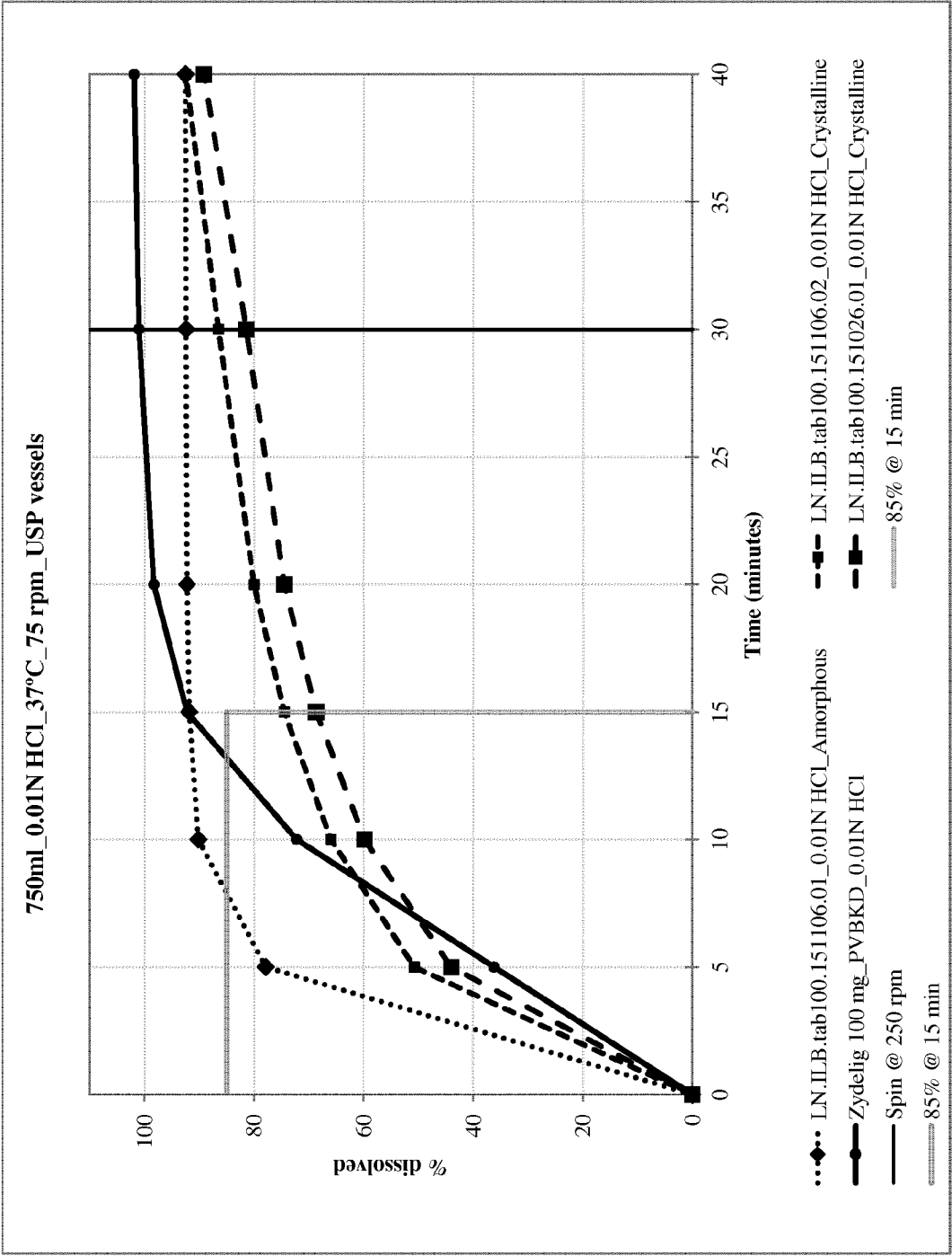
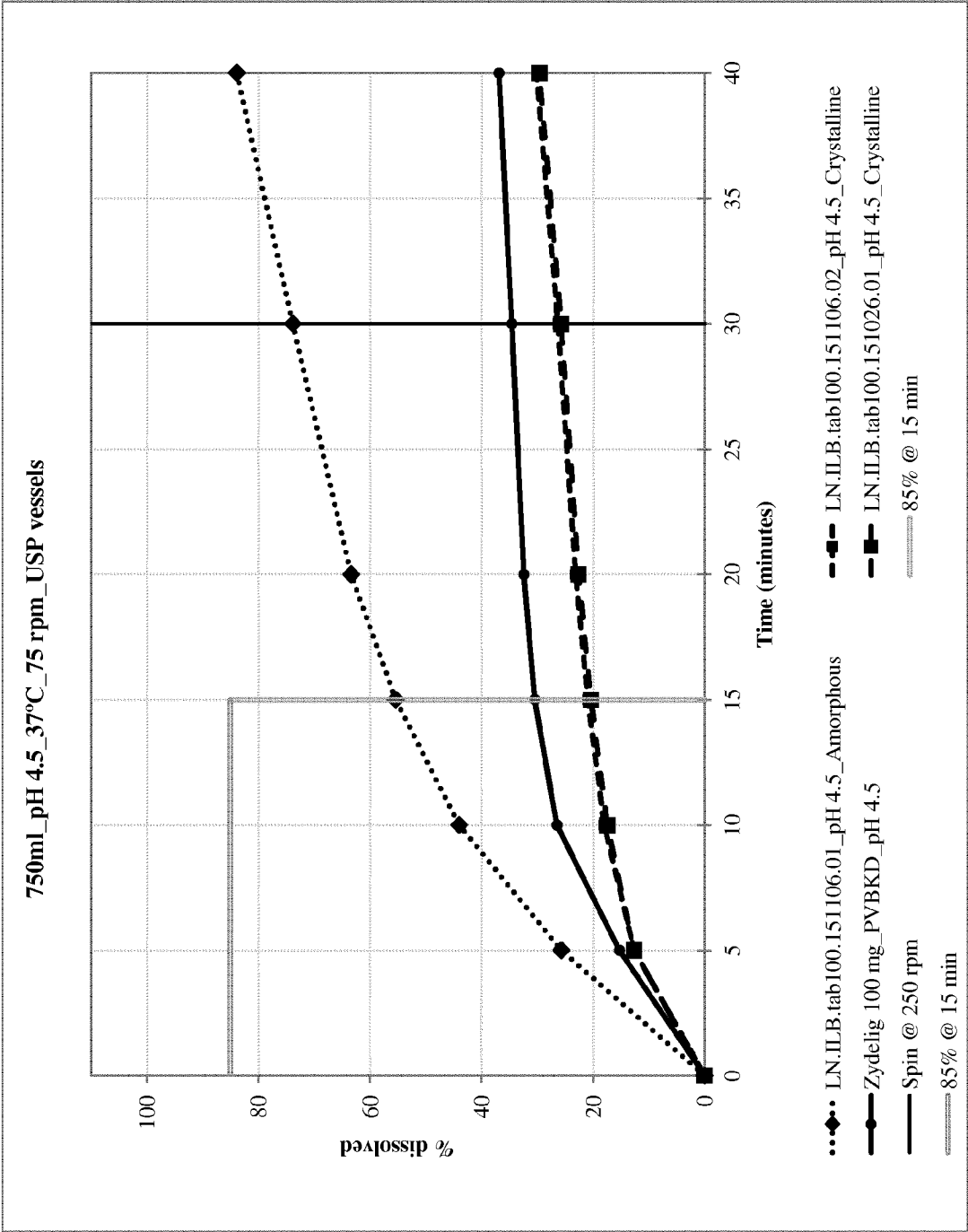


Figure 2: Dissolution in acetate buffer (pH 4.5)



INTERNATIONAL SEARCH REPORT

International application No
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A. CLASSIFICATION OF SUBJECT MATTER

INV. A61K9/20 A61K31/52
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, CHEM ABS 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 2015/092810 A2 (CADILA HEALTHCARE LTD [IN]) 25 June 2015 (2015-06-25)	1-12
Y	the whole document page 1, lines 4-6 page 2, lines 14-21 page 3, lines 20-23 page 8, lines 16-18 examples 4-6 claims 9-11,17 page 6, lines 5-14	1-12
X	EP 2 979 692 A1 (SANDOZ AG [CH]) 3 February 2016 (2016-02-03)	1-12
Y	the whole document paragraphs [0118], [0121], [0123], [0133], [0162] - [0163]; claim 7	1-12
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Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents :

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Date of the actual completion of the international search

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INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2016/053071

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
T	MILLER BARRY W ET AL: "FDA approval: idelalisib monotherapy for the treatment of patients with follicular lymphoma and small lymphocytic lymphoma.", CLINICAL CANCER RESEARCH : AN OFFICIAL JOURNAL OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH 1 APR 2015, vol. 21, no. 7, 1 April 2015 (2015-04-01), pages 1525-1529, XP55259037, ISSN: 1078-0432, DOI: 10.1158/1078-0432.CCR-14-2522 the whole document *Clinical Pharmacology"; page 1526, column 1 -----	1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2016/053071

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
W0 2015092810	A2	25-06-2015	NONE

EP 2979692	A1	03-02-2016	NONE
