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(54) Title: PHARMACEUTICAL COMPOSITION COMPRISING ERLOTINIB HYDROCHLORIDE

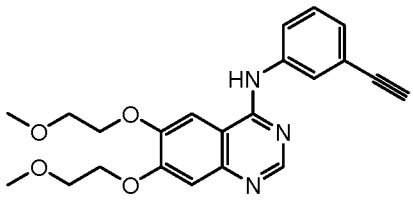
(57) Abstract: The present invention relates to a pharmaceutical composition comprising granules comprising erlotinib hydrochloride polymorph A and a water soluble binder selected from sodium carboxymethylcellulose and xanthan gum, exhibiting an in vitro release profile wherein on average from 10 to 30% of the erlotinib hydrochloride is dissolved within 15 minutes, from 20 to 40% within 30 minutes and from 30 to 60% within 60 minutes after placement of the composition in a dissolution test conducted using USP apparatus II at 75 rpm and a dissolution medium of 0.1 N HCl, pH 1.0 at 37°C. The invention further relates to the use of said compositions as a medicament, particularly in the treatment of non-small cell lung cancer and pancreatic cancer.

PHARMACEUTICAL COMPOSITION COMPRISING ERLOTINIB HYDROCHLORIDE

BACKGROUND OF THE INVENTION

The present invention relates to a pharmaceutical composition comprising erlotinib hydrochloride in its crystalline Form A.

Erlotinib, chemically [6,7-bis(2-methoxyethoxy)-quinazolin-4-yl]-(3-ethynylphenyl)-amine of formula (I)



(I).

is a compound that inhibits the human epidermal growth factor receptor tyrosine kinase, also known as EGFR-TK, that is critical for growth of malignant cells. EGFR overexpression is associated with disease progression, and reduced survival. Erlotinib acts by blocking tyrosine kinase activity of EGFR-TK, resulting in inhibition of the signaling pathway, and decreased growth of malignant tumors. Erlotinib is thus useful for the treatment of proliferative disorders such as cancers in humans. Erlotinib is marketed as its hydrochloride salt under such brand names as Tarceva® (OSI Pharmaceuticals, Inc.) for the treatment of certain lung cancers and pancreatic cancer.

WO9630347 teach quinazoline derivatives for treating hyperproliferative diseases such as cancers. Example 20 shows the formation of erlotinib free base and the subsequent conversion to the hydrochloride salt. Pharmaceutical compositions are only generically disclosed, there is not

one specific example. Neither is there any disclosure about polymorphism of erlotinib hydrochloride.

WO0134574 discloses the existence of two polymorphic forms of erlotinib hydrochloride which were designated as form A and B. Form B is thermodynamically more stable than form A. The document describes processes for producing each polymorph in an essentially pure form, and describes the use of the stable polymorph B form for treating hyperproliferative disorders, such as cancer. Pharmaceutical compositions are only generically disclosed.

WO2010086441 relates to a pharmaceutical composition comprising erlotinib hydrochloride and discloses pharmaceutical compositions comprising polymorph A of erlotinib hydrochloride and a hydrophilic excipient. According to the description, the addition of this excipient not only stabilises polymorphic form A, but it also increases the dissolution of the active pharmaceutical ingredient. According to the authors of WO2010086441, there is thus no requirement of providing the active pharmaceutical ingredient in a nanoparticulate form as was deemed necessary by the authors of WO2006110811.

WO2010086441 provides on page 6 a long list of suitable hydrophilic excipients, such as for example hydrophilic polymers. The hydrophilic polymer can have a weight average molecular weight in the range of about 1,000 g/mol to about 150,000 g/mol, preferably in the range of about 2,000 g/mol to about 90,000 g/mol. Microcrystalline cellulose is the preferred hydrophilic excipient. The amount of hydrophilic excipient to be used in accordance with WO2010086441 is in the range of about 10 wt.% to about 90 wt.%, most preferably in the range of about 50 wt.% to about 70 wt.% (see page 7). In the example on page 12, apart from microcrystalline cellulose also a surfactant, i.e. sodium lauryl sulphate, was included in the

formulation of form A. Repetition of the example cited in WO2010086441 showed that the obtained composition comprising erlotinib hydrochloride form A lacked long term stability.

WO2014118112 relates to pharmaceutical compositions suitable for administration of polymorphic form A of erlotinib hydrochloride, which exhibit improved stability upon long term storage, have a suitable release rate and which do not require the use of a surfactant. The compositions comprise, besides erlotinib hydrochloride form A, an effective amount of a carbomer. This amount of carbomer decreases the dissolution rate of the pharmaceutical composition and thereby compensates for the faster dissolving polymorph A resulting in a composition bioequivalent to commercial Tarceva®. The draw back of these compositions is that they are not robust, i.e. minor changes in the amount of carbopol used have a significant effect on the release rate.

Thus in view of the prior art, there is still a need for pharmaceutical compositions comprising erlotinib hydrochloride polymorph A exhibiting excellent long term stability and which are robust, bioequivalent to Tarceva®, cost effective, simple to prepare and suitable for use on a commercial scale.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1: Dissolution profiles in acidic media pH 1.0; Tarceva® versus the formulation of example 1

Figure 2: Dissolution profiles in acidic media pH 2.0; Tarceva® versus the formulation of example 1

BRIEF DESCRIPTION OF THE PRESENT INVENTION

The present invention relates to a pharmaceutical composition comprising erlotinib hydrochloride polymorph A, which is robust, bioequivalent to commercial Tarceva® and exhibits excellent long term stability.

In one aspect, the present invention relates to a pharmaceutical composition comprising granules comprising erlotinib hydrochloride polymorph A and a water soluble binder selected from sodium carboxymethylcellulose and xanthan gum exhibiting an *in vitro* release profile wherein on average from 10 to 30% of the erlotinib hydrochloride is dissolved within 15 minutes, from 20 to 40% within 30 minutes and from 30 to 60% within 60 minutes after placement of the composition in a dissolution test conducted using USP apparatus II at 75 rpm and a dissolution medium of 0.1 N HCl, pH 1.0 at 37ºC.

Preferably, the binder is sodium carboxymethylcellulose.

Preferably, the amount of binder in the pharmaceutical composition is from 0.1 to 5.0 wt.%. More preferably, the binder is sodium carboxymethylcellulose present in amount of 0.1 to 1.5 wt.%.

Preferably, the pharmaceutical composition is a tablet further comprising one or more pharmaceutically acceptable excipients selected from the group consisting of diluents, disintegrants and lubricants.

Preferably, the pharmaceutical composition contains at least one additional extragranular excipient.

Preferably, the pharmaceutical composition is packed in Triplex/Alu or Alu/Alu blister pack material.

In a second aspect, the invention relates to a process for preparing the granules comprising erlotinib hydrochloride polymorph A and a water soluble binder selected from sodium carboxymethylcellulose and xanthan gum by using a wet granulation process.

Preferably, the granulation solvent used in the wet granulation process is selected from the group consisting of water, acetone, ethanol, isopropanol or a mixture thereof.

In a third aspect, the invention relates to a process for preparing the pharmaceutical compositions comprising mixing the granules comprising erlotinib hydrochloride polymorph A and a water soluble binder selected from sodium carboxymethylcellulose and xanthan gum with one or more pharmaceutically acceptable excipients, followed by compression into tablets.

In a fourth aspect, the invention relates to a composition comprising erlotinib hydrochloride polymorph A and a water soluble binder selected from sodium carboxymethylcellulose and xanthan gum for use as a medicament, preferably in the treatment of proliferative disorders, particularly in the treatment of non-small cell lung cancer and pancreatic cancer.

DETAILED DESCRIPTION OF THE PRESENT INVENTION

The present invention relates to pharmaceutical compositions suitable for administration of polymorphic form A of erlotinib hydrochloride, which exhibit excellent stability upon long term storage and which are robust, bioequivalent to Tarceva®, cost effective, simple to prepare and suitable for use on a commercial scale.

Erlotinib hydrochloride can be synthesised using techniques well known in the art, e.g., as disclosed in WO9630347.

Polymorph A of erlotinib hydrochloride and a method for its preparation have been disclosed in WO0134574. 2-Theta values of characteristic peaks taken from the X-ray powder diffraction pattern of polymorph A of erlotinib hydrochloride and their relative intensities are summarised in Table 1 below (cf. Table 2 on page 17 of WO 0134574).

Table 1

Anode: Cu - Wavelength 1: 1.54056 Wavelength 2: 1.54439 (Rel Intensity: 0.500)

Range#1 - Coupled: 3.000 to 40.000 StepSize: 0.040 Step Time: 1.00

Smoothing Width: 0.300 Threshold: 1.0

2-Theta	I (rel)	2-Theta	I (rel)	2-Theta	I (rel)	2-Theta	I (rel)	2-Theta	I (rel)
5.579	100.0	13.340	1.7	19.517	4.8	24.594	8.2	30.673	3.5
6.165	3.9	15.135	2.1	21.152	4.7	25.398	9.3	32.759	3.7
7.522	1.5	15.534	2.3	21.230	4.4	26.173	6.0	34.440	1.8
8.006	1.2	16.193	2.4	22.360	4.7	26.572	5.3	36.154	1.3
8.696	1.4	16.991	3.6	22.703	12.4	27.080	4.2	37.404	2.2
9.841	13.1	18.447	3.5	23.502	24.2	29.240	7.1	38.905	1.7
11.251	7.8	18.862	12.2	24.175	8.8	30.007	3.0		

The XRPD pattern of form A as used or measured in the pharmaceutical compositions of the present invention substantially corresponds to that as disclosed for form A in WO0134574. "Substantially corresponds" is meant to cover variations/differences in the pattern that would be understood by a worker skilled in the art not to represent a difference in the crystal structure, but rather differences in the technique, equipment, sample preparation, impurities, etc.

The term "pharmaceutical composition" refers to single dosage forms, such as tablets, capsules, pellets, etc., as well as powders or granules which are used in the preparation of single dosage forms.

It is known from WO0134574, WO2010086441 and WO2014118112 that under conventional conditions polymorph A of erlotinib hydrochloride is thermodynamically unstable and converts into polymorph B. Experiments in our laboratory showed that the solubility of erlotinib hydrochloride polymorph A, especially at acidic pH values, is significantly higher when compared to polymorphic form B. From WO2010086441, it is known that the addition of hydrophilic excipients to a formulation comprising erlotinib hydrochloride polymorph A increases the dissolution of the pharmaceutical composition and, according to the authors, thereby making the use of erlotinib hydrochloride in nanoparticulate form redundant.

WO2014118112 shows that addition of a carbomer, instead of increasing, decreases the dissolution rate of the pharmaceutical composition comprising erlotinib hydrochloride polymorph A, making it possible to mimic the dissolution of the Tarceva® tablets containing the more stable, hence less soluble erlotinib hydrochloride polymorph B. However, the draw back of the compositions disclosed in WO2014118112 is that they are not robust, i.e. minor changes in the amount of carbopol used have a significant effect on the release rate.

In order to come to a more robust pharmaceutical composition which would still show excellent long term stability and which would also be bioequivalent to commercial Tarceva®, addition of water soluble binders to the composition in order to achieve a decrease in dissolution rate was studied. Many different water soluble binders were tested, a.o. hydroxypropyl methylcellulose, hydroxypropylcellulose, hydroxyethylcellulose, sodium alginate, xanthan gum and sodium carboxymethylcellulose. Some of the studied binders achieved an increase in dissolution rate, some did not have an effect at all or some just simply slowed down the release rate far too much.

Surprisingly, it was found that both sodium carboxymethylcellulose and xanthan gum were able to decrease the dissolution rate in such a way that the pharmaceutical compositions comprising the faster dissolving erlotinib hydrochloride polymorph A target in acidic media bioequivalence to commercial Tarceva® tablets containing the less soluble erlotinib hydrochloride polymorph B. In addition, it was found that the compositions of the present invention are very robust, i.e. minor changes in the amount of binder used do not have a significant effect on the release rate.

The pharmaceutical compositions of the present invention show excellent long term stability, meaning that in the pharmaceutical compositions erlotinib hydrochloride maintains its polymorphic form A even under storage conditions of 65% relative humidity and 30°C for at least 3 months, preferably for at least 12 months. Maintaining its polymorphic form A therefore means that polymorph A of erlotinib hydrochloride during storage is not converted into any other polymorph of erlotinib hydrochloride, in particular not into polymorph B.

The thermodynamic stability of polymorph A of erlotinib hydrochloride in the pharmaceutical composition of the present invention is confirmed by the stability data as provided in the examples section. Stability was tested for up to 3 months at 25°C/60% relative and humidity and 3 months 30°C/65% relative humidity. These data confirm that polymorph A of erlotinib hydrochloride is thermodynamically stable in the pharmaceutical composition of the present invention and in particular that polymorph A is not converted into polymorph B during long term storage.

The present invention relates to pharmaceutical compositions comprising granules comprising erlotinib hydrochloride polymorph A and a water soluble binder selected from sodium carboxymethylcellulose and xanthan gum exhibiting an *in vitro* release profile wherein

on average from 10 to 30% of the erlotinib hydrochloride is dissolved within 15 minutes, from 20 to 40% within 30 minutes and from 30 to 60% within 60 minutes after placement of the composition in a dissolution test conducted using USP apparatus II at 75 rpm and a dissolution medium of 0.1 N HCl, pH 1.0 at 37°C. Preferably, the water soluble binder is sodium carboxymethyl cellulose.

In order to provide a pharmaceutical composition having an optimal dissolution profile, it is preferred that the pharmaceutical composition is essentially free of polymorph B of erlotinib hydrochloride. Being essentially free of polymorph B means that polymorph B is present in the pharmaceutical composition of the present invention in an amount of less than 5 wt.%, preferably in an amount of less than 1 wt.%, each based on the total amount of erlotinib hydrochloride. Most preferably, the pharmaceutical composition of the present invention does not contain any polymorph B of erlotinib hydrochloride. Furthermore, it is preferred that the pharmaceutical composition does not contain any polymorph of erlotinib hydrochloride other than polymorph A. Thus, the pharmaceutical composition of the present invention preferably comprises erlotinib hydrochloride essentially only as polymorph A, i.e., at least 95 wt.% of the total amount of erlotinib hydrochloride in the pharmaceutical composition is present in polymorphic form A, preferably at least 99 wt.%. Most preferred, erlotinib hydrochloride is present in the pharmaceutical composition only in polymorphic form A.

The amount of water soluble binder is from 0.1 to 5.0 wt.%. Preferably, the water soluble binder is sodium carboxymethylcellulose present in an amount from 0.1 to 1.5 wt.%.

In one embodiment of the present invention, the pharmaceutical composition does not contain a surfactant, preferably it does not contain sodium lauryl sulphate.

The pharmaceutical compositions of the present invention may be formulated into various types of dosage forms, for instance as solutions or suspensions, or as tablets, capsules, granules, pellets or sachets for oral administration. A particularly preferred pharmaceutical composition is in the form of a solid oral dosage form, preferably tablets. The tablet is preferably a swallowable tablet. It may optionally be coated with a film coat comprising, in essence, any suitable inert coating material known in the art.

The pharmaceutical composition of the present invention comprises, in addition to the granules comprising erlotinib hydrochloride polymorph A and a water soluble binder selected from sodium carboxymethylcellulose and xanthan gum, one or more pharmaceutically acceptable excipients selected from the group consisting of diluents, disintegrants and lubricants.

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. Depending on the dosage form chosen for the pharmaceutical composition, the person skilled in the art will be able to select suitable pharmaceutically acceptable excipients. Preferably, the dosage form is an immediate release tablet.

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 and lactose are particularly preferred diluents.

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. Sodium starch glycolate 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.

In yet another embodiment of the present invention, the pharmaceutical composition of the present invention contains at least one additional extragranular excipient.

The granules, comprising erlotinib hydrochloride polymorph A and a water soluble binder selected from sodium carboxymethylcellulose and xanthan gum, can subsequently be mixed with one or more suitable diluents, disintegrants and lubricants, and the mixture can be compressed into tablets or filled into sachets or capsules of suitable size.

Since the present invention relates to the thermodynamically unstable polymorph A of erlotinib hydrochloride, the person skilled in the art would not contemplate the use of solvents in the manufacturing process because of expected conversion of the metastable polymorph A and would thus not choose wet granulation as the technique to prepare the granules of the current invention. This is supported by the examples presented in prior art documents WO2010086441 and WO2014118112 which teach that a dry process, e.g. dry granulation, is the method to be used in the preparation of compositions comprising the thermodynamically unstable erlotinib hydrochloride polymorph A.

Surprisingly, it was found that employing the wet granulation technique for the preparation of the granules of the present invention, comprising metastable erlotinib hydrochloride form A and a water soluble binder selected from sodium carboxymethylcellulose and xanthan gum, did result in stable pharmaceutical compositions, i.e. compositions free of polymorph B or any other

form of erlotinib hydrochloride. No conversion from polymorph A to any other polymorphic form was observed in time, even after long term storage. In general, the production costs of a wet granulation process are lower when compared to a dry granulation process. Another advantage of the wet granulation technique is that it is not relying on the intrinsic properties of the drug and excipients and that, in general, it is easier to obtain maximal tablet stability by using this method. Furthermore, from a safety perspective wet granulation is preferred over dry techniques in order to eliminate dust.

The process for preparing the granules comprising erlotinib hydrochloride polymorph A and a water soluble binder selected from sodium carboxymethylcellulose and xanthan gum is performed with a granulation solvent selected from the group consisting of water, acetone, ethanol, isopropanol or a mixture thereof. Preferably, the granulation solvent is water.

The particle size of the active pharmaceutical ingredient in the pharmaceutical composition of the present invention is not particularly limited. However, in view of the disadvantages associated with the preparation and handling of nanoparticles, it is preferred that the erlotinib hydrochloride in the pharmaceutical composition of the present invention has a D_{90} particle size of 5 µm or larger, preferably from 5 to 100 µm. D_{90} particle size means a particle size distribution where 90 vol.% of the total amount of erlotinib hydrochloride in the pharmaceutical composition has a particle size of 5 µm or larger, preferably from 5 to 100 µm, when measured by laser diffraction in wet state (sunflower oil:n-hexane 50:50) with a Malvern Laser Mastersizer 2000.

The pharmaceutical composition of the present invention can be formulated in any known manner, preferably as tablets, capsules, granules, pellets or sachets. The pharmaceutical composition may contain for example dosage amounts of 25, 50, 100 or 150 mg of erlotinib

(27.3, 54.6, 109.3 or 163.9 mg of erlotinib hydrochloride). Thus, the administered amount can be readily varied according to the individual patient's need, tolerance and safety.

The pharmaceutical compositions of the present invention are packaged in blister pack material. The blister pack materials to be used in accordance with the present invention may be any blister pack material known to a person of ordinary skill in the art. Suitable blister pack materials to be used in accordance with the present invention are selected from the group of PVC/Alu, Duplex/Alu, Triplex/Alu and Alu/Alu. To ensure protection of the compositions of the present invention from *e.g.* moisture and thereby preventing polymorphic conversions, Triplex/Alu and Alu/Alu are particularly preferred blister pack materials. After storage of the pharmaceutical compositions in these blister pack materials for 3 months at 30ºC/65% RH, XRPD analysis showed no reflections in accordance with erlotinib hydrochloride form B or any other polymorphic form of erlotinib hydrochloride other than form A.

The composition according to the present invention in accordance with the present invention may be used as medicament. The composition typically may be used in the treatment of proliferative disorders, particularly in the treatment of non-small cell lung cancer and pancreatic cancer.

The invention will be further described with reference to the following non-limiting examples.

EXAMPLES

Example 1: Tablets comprising erlotinib hydrochloride polymorph A

Tablet composition

	mg/tablet	%
150 mg strength		
Intragranular components		
Erlotinib hydrochloride form A	163.94	36.4
Lactose MH (Pharmatose 200M)	103.8	23.1
Microcrystalline cellulose (Vivapur 101)	30.2	6.7
Sodium Carboxymethylcellulose (Blanose 7HF)	5.1	1.1
Water	q.s.	
Extragranular components		
Microcrystalline cellulose (Vivapur 101)	102.0	22.7
Sodium starch glycolate (Glycolis)	36.0	8.0
Magnesium stearate	9.0	2.0
Uncoated tablet mass	*450.0*	*100.0*
Opadry white	22.5	5.0
Coated tablet mass	472.5	

Sodium carboxymethyl cellulose, microcrystalline cellulose and lactose are sieved. Erlotinib hydrochloride was added and the mixture was mixed in a granulator. Water was added to granulate. The wet granules obtained were sieved to de-agglomerate. The sieved granules were dried in a Fluid Bed until the required LOD was reached. The granules were sieved. Microcrystalline cellulose (extragranular) and sodium starch glycolate were sieved and mixed with the sieved granules in a blender. Magnesium stearate was sieved and mixed with the blend in a blender. The homogeneous blend obtained, was compressed under monitored humidity conditions on a rotary tabletting machine using appropriate punches. The tablets were coated

with an Opadry suspension. The tablets were packed in Alu/Alu blisters or any other suitable packaging material.

Dissolution profiles

Dissolution profiles were measured using the paddle method (USP apparatus II) in 1000 ml of acidic media (pH 1.0 (0.1 N HCl) or 2.0 (0.01 N HCl); 75 rpm; 37°C). Figure 1 shows the dissolution profiles at pH 1.0 for the marketed 150 mg Tarceva® tablet compared with the tablet of the present invention having a composition as described above. Figure 2 shows the dissolution profiles at pH 2.0 for the marketed 150 mg Tarceva® tablet compared with the tablet of the present invention having a composition as described above.

Stability data

	Triplex 120		Al/Al	
	30°C/65%RH	25°C/60%RH	30°C/65%RH	25°C/60%RH
t=0	**Form A**	**Form A**	**Form A**	**Form A**
t=1 months	**Form A**	**Form A**	**Form A**	**Form A**
t=2 months	**Form A**	**Form A**	**Form A**	**Form A**
t=3 months		**Form A**	**Form A**	**Form A**

In the above examples, the XRPD patterns were recorded on a Bruker-AXS D8 vario (Θ/2Θ geometry, reflection mode, Vantec PSD detector) at the following settings:

Start angle (2θ): 2.0 °

End angle (2θ): 35.0 °

Scan step width: 0.02 °

Scan step time: between 0.7-11.0 seconds

Radiation type:	Cu
Radiation wavelengths:	1.54060 Å ($K\alpha_1$), primary monochromator used
Exit slit:	6.0 mm
Focus slit:	0.2 mm
Divergence slit:	Variable (V20)
Antiscatter slit:	11.8 mm
Receiving slit:	20.7 mm

CLAIMS

1. A pharmaceutical composition comprising granules comprising erlotinib hydrochloride polymorph A and a water soluble binder selected from sodium carboxymethylcellulose and xanthan gum, said composition exhibiting an *in vitro* release profile wherein on average from 10 to 30% of the erlotinib hydrochloride is dissolved within 15 minutes, from 20 to 40% within 30 minutes and from 30 to 60% within 60 minutes after placement of the composition in a dissolution test conducted using USP apparatus II at 75 rpm and a dissolution medium of 0.1 N HCl, pH 1.0 at 37°C.
2. The composition according to claim 1, wherein the binder is sodium carboxymethylcellulose.
3. The composition according to claim 1 or 2, wherein the amount of binder is from 0.1 to 5.0 wt.%.
4. The composition according to any one of claims 1 to 3, wherein the binder is sodium carboxymethylcellulose present in an amount from 0.1 to1.5 wt.%.
5. The composition according to any one of claims 1 to 5, wherein the pharmaceutical composition is a tablet further comprising one or more pharmaceutically acceptable excipients selected from the group consisting of diluents, disintegrants and lubricants.
6. The composition according to any one of claims 1 to 6, with at least one additional extragranular excipient.
7. The composition according to any one of claims 1 to 7 packed in Triplex/Alu or Alu/Alu blister pack material.
8. A process for preparing the granules according to any one of claims 1 to 8, wherein said process is a wet granulation process.

9. A process according to claim 9, wherein a granulation solvent is used selected from the group consisting of water, acetone, ethanol, isopropanol or a mixture thereof.
10. A process according to claim 9 or 10, wherein water is used as granulation solvent.
11. A process for preparing the compositions according to any one of claims 1 to 8, further comprising mixing the granules comprising erlotinib hydrochloride polymorph A and a water soluble binder selected from sodium carboxymethylcellulose and xanthan gum with one or more pharmaceutically acceptable excipients, followed by compression into tablets.
12. The composition according to any one of claims 1 to 8 for use as a medicament.
13. The composition according to claim 13 for use in the treatment of proliferative disorders, particularly in the treatment of non-small cell lung cancer and pancreatic cancer.

FIGURE 1

Dissolution profiles in acidic media pH 1.0; Tarceva® versus the formulation of example 1

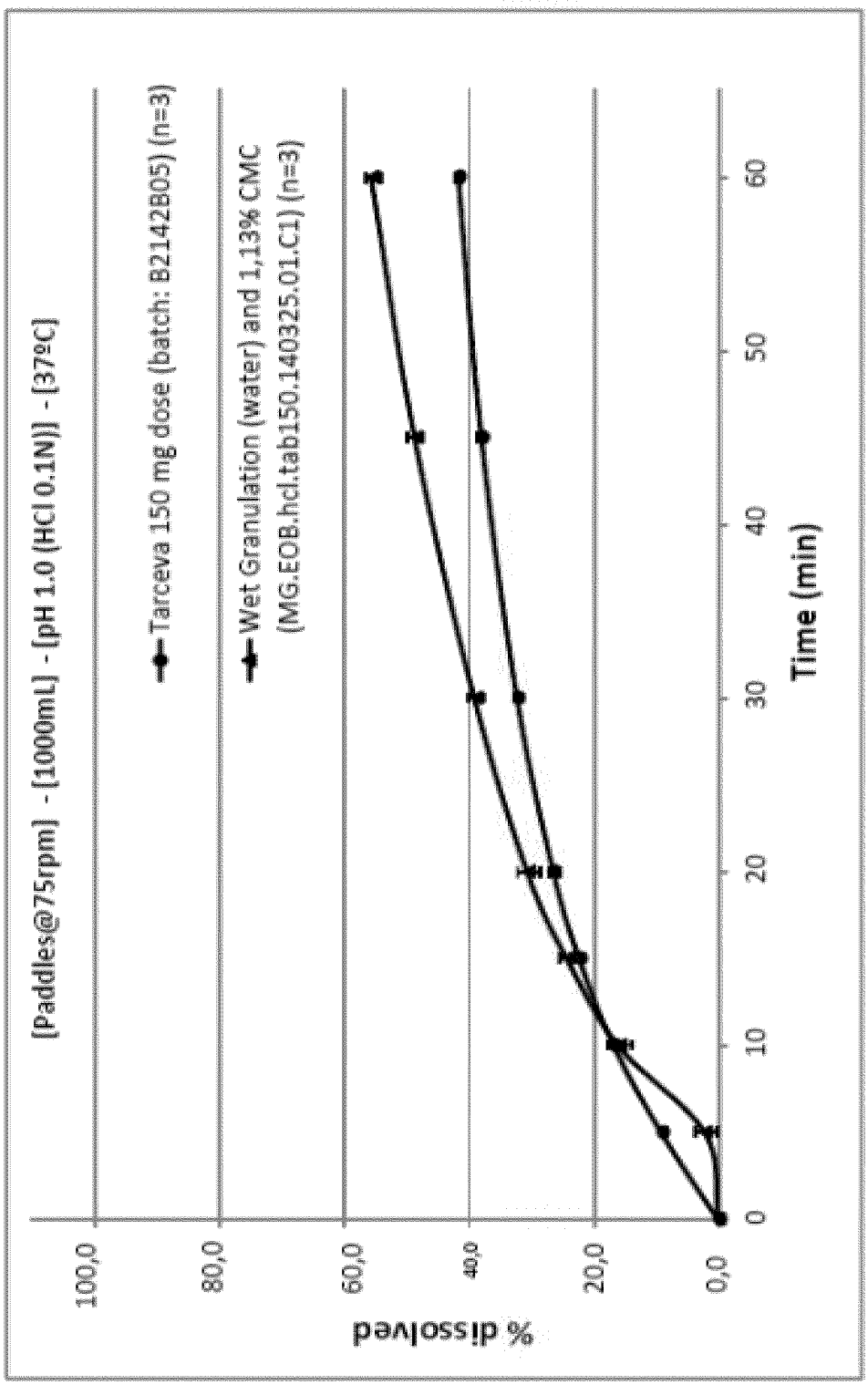
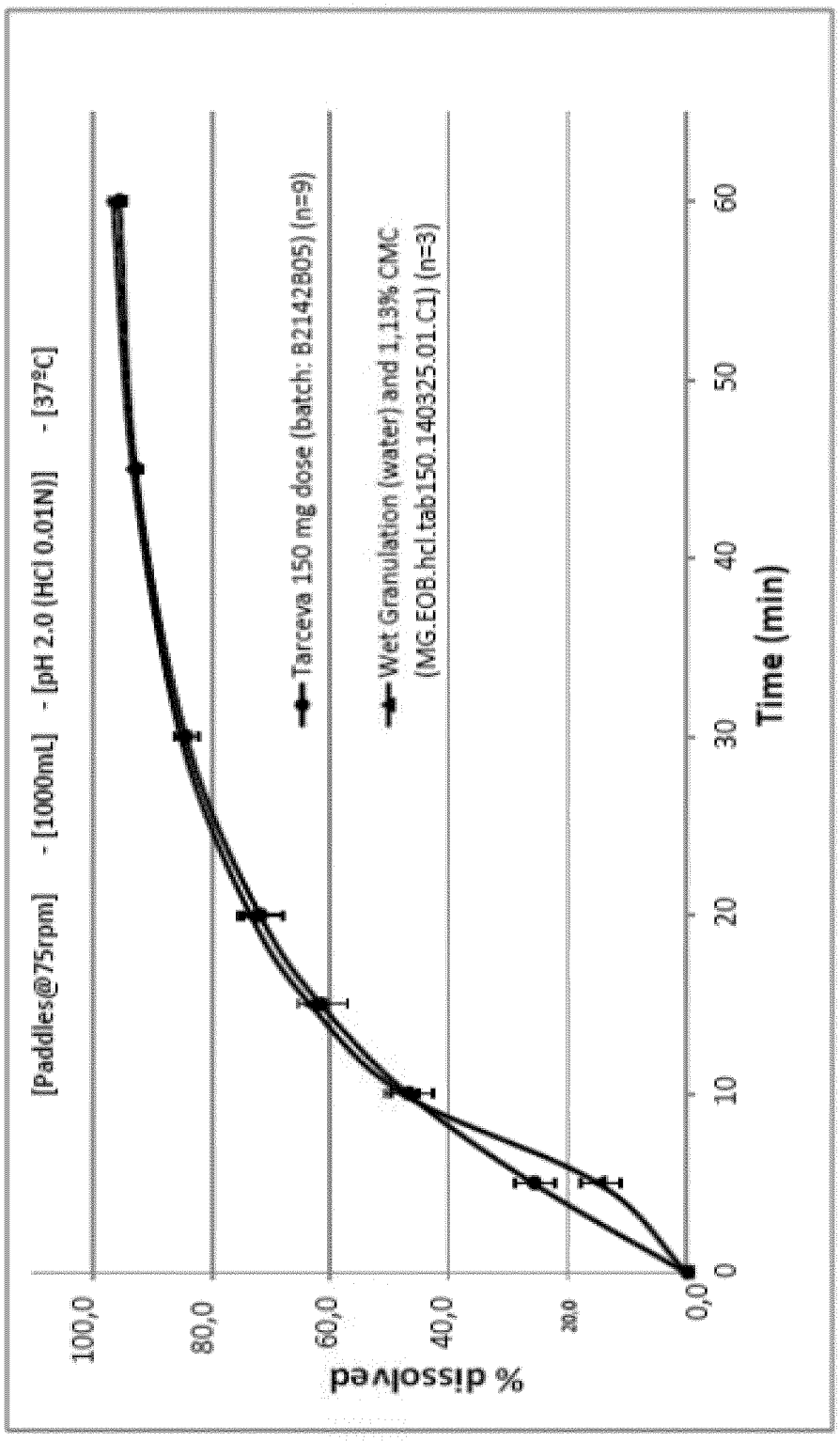


FIGURE 2

Dissolution profiles in acidic media pH 2.0; Tarceva® versus the formulation of example 1



INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2014/075788

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/20
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, CHEM ABS Data, EMBASE, WPI Data, BIOSIS, FSTA

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2014/118112 A1 (SYNTHON BV [NL]) 7 August 2014 (2014-08-07) cited in the application page 10, line 9 page 3, line 8 - line 14 examples	1-13
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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
30 January 2015	11/02/2015

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Schüle, Stefanie

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