A61K 9/00 (2006.01)  A61K 9/20 (2006.01)
A61K 9/16 (2006.01)  A61K 31/506 (2006.01)

Title: PHARMACEUTICAL GASTRO-RETENTIVE SOLID ORAL DOSAGE FORM OF NILOTINIB

Abstract: The present invention relates to a pharmaceutical gastro-retentive solid oral dosage form comprising nilotinib as the active ingredient. The invention is further related to methods of preparing said dosage form.
PHARMACEUTICAL GASTRO-RETENTIVE SOLID ORAL DOSAGE FORM OF
NILOTINIB

Field of the Invention

The present invention relates to a pharmaceutical gastro-retentive solid oral dosage form comprising nilotinib as the active ingredient. The invention is further related to methods of preparing said solid oral dosage form.

Background of the Invention

Nilotinib was first disclosed in U.S. Patent No. 7,169,791. It is chemically described as 4-methyl-N-[3-(4-methyl-1H-imidazol-1-yl)-5-(trifluoromethyl)phenyl]-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]-benzamide and is an inhibitor of the protein tyrosine kinase (TK) activity of BCR-ABL.

U.S. Patent No. 8,293,756 discloses pharmaceutical compositions of nilotinib prepared by wet granulation.

Nilotinib is characterized as a Class IV compound according to the Biopharmaceutical Classification System (BCS), which means that it has low/moderate aqueous solubility and low permeability. The solubility of nilotinib at 25°C in aqueous solutions decreases strongly with increasing pH and it is practically insoluble at pH 4.5 and higher. This decrease in the solubility of nilotinib in environments with a pH of more than 1 leads to a decrease in the absorption of nilotinib. The poor water-solubility of nilotinib and its salts mean that they are difficult to formulate as oral delivery dosage forms with good bioavailability. Hence, there is a need to develop a pharmaceutical solid oral dosage form of nilotinib which has better solubility and bioavailability. In the present invention, the inventors have developed such a pharmaceutical oral solid dosage form of nilotinib.

Summary of the Invention

In one general aspect, the present invention provides a gastro-retentive solid oral dosage form which comprises nilotinib or a salt thereof, at least one rate controlling polymer, and other pharmaceutically acceptable excipients.

In an embodiment of the above aspect, the rate controlling polymer is a swelling agent.
In another embodiment of the above aspect, the dosage form may further comprise an acidifying agent.

In another embodiment of the above aspect, the dosage form may be administered once daily or twice daily.

In another embodiment of the above aspect, the dosage form is a tablet. The gastro-retentive action of the tablet is based on one or more mechanisms, for example, floatation, gas generation, or swelling.

In another embodiment of the above aspect, the dosage form may further comprise one or more osmogen agents.

In another embodiment of the above aspect, the other pharmaceutically acceptable excipients are selected from the group comprising diluents, matrix forming agents, disintegrants, binding agents, gas-generating agents, semi-permeable film-forming agents, glidants, and lubricants.

The details of the various embodiments of the invention are set forth in the description below. Other features and advantages of the invention will also be apparent from the description.

**Detailed Description of the Invention**

The term "gastro-retentive", as used herein, refers to a pharmaceutical dosage form which is capable of staying in the stomach for a prolonged period of time, preferably for a period longer than that of food, and therefore is capable of releasing the active ingredient in the stomach for a time period longer than when delivered as a conventional dosage form. The gastro-retentive time may be characterized by retention of the dosage form in the stomach for a period that is longer than the normal emptying time of the stomach, *i.e.*, longer than about 2 hours.

Several mechanisms for gastro-retentive action of the oral solid dosage form may be designed and developed by applying approaches which include low-density floating systems that cause buoyancy in gastric fluid; high-density sinking systems that are retained in the bottom of the stomach; mucoadhesive systems that cause bioadhesion to stomach mucosa; gas generation by the dosage form that causes buoyancy in gastric fluid; swelling of the dosage form beyond the size which can pass through the human pyloric sphincter of the stomach; and large sized dosage forms *per se* which may limit passing of
the dosage form through the pyloric sphincter. The diameter of the human pyloric sphincter is on an average 12 mm (±7mm) and therefore a dosage form larger than the pyloric diameter cannot pass through the stomach.

The term "solid oral dosage form", as used herein, includes tablets, mini-tablets, capsules, caplets, granules, beads, pellets, multiparticulates, spheroids, or combinations thereof. If the solid form is a tablet, the tablet can be of any suitable shape, such as round, spherical, oval, concave, bi-concave, hemispherical, or any polygonal shape, such as square, rectangular, pentagonal, hexagonal, and the like. The tablet may have a monolithic or a multilayer structure.

The term "rate-controlling polymer", as used herein, refers to polymers which are capable of controlling the release of the active ingredient from the dosage form. The polymer can control the release of the active ingredient by any mechanism, such as swelling, matrix forming, or film forming.

The term "swelling agent", as used herein, refers to polymers which are capable of absorbing water, resulting in physical swelling and expansion. The swelling of the polymer can be characterized by an increase in the dimensions of the dosage form in one or more directions. Preferred examples of swelling agents include, but are not limited to, hypromellose, methyl cellulose, hydroxypropyl cellulose, hydroxyethyl cellulose, carboxymethyl cellulose, guar gum, xanthan gum, tragacanth gum, carrageenan, pectin, egg albumin, chitosan, pectin, bovine serum albumin, microcrystalline cellulose, cross-linked carboxymethyl cellulose, cross-linked polyvinyl pyrrolidone, or a starch.

The term "acidifying agent", as used herein, refers to substances which are able to create an acidic pH environment within and around the dosage form and therefore increase the solubility and dissolution of the active ingredients which are soluble in acidic pH.

Preferred examples of acidifying agents include, but are not limited to, fumaric acid, citric acid, tartaric acid, amino acid, or lactic acid.

Preferred examples of osmogen agents include, but are not limited to, organic and inorganic compounds such as salts, acids, bases, chelating agents, sodium chloride, lithium chloride, magnesium chloride, magnesium sulfate, lithium sulfate, potassium chloride, sodium sulfite, calcium bicarbonate, sodium sulfate, calcium sulfate, calcium lactate, d-mannitol, urea, tartaric acid, raffinose, sucrose, alpha-d-lactose monohydrate, glucose, sorbitol, other similar or equivalent materials, and combinations thereof.
Preferred examples of diluents include, but are not limited to, calcium phosphate -
dibasic, calcium carbonate, lactose, glucose, microcrystalline cellulose, cellulose
powdered, silicified microcrystalline cellulose, calcium silicate, starch, starch
pregelatinized, and polyols such as mannitol, sorbitol, xylitol, maltitol, and sucrose.

The term "matrix forming agent", as used herein, refers to the pharmaceutical
agents which impart structural integrity and provide mechanical strength to the dosage
form, among other functions. Preferred examples of matrix forming agents include, but
are not limited to, hydroxypropyl methylcellulose (HPMC), acrylic acid polymers,
polyvinyl acetate (PVA), polyvinylpyrrolidone (PVP), cross-linked polyvinylpyrrolidone,
ethylcellulose, carbomer homopolymer (type A), and combinations thereof.

Preferred examples of disintegrants include, but are not limited to, cross-linked
cellulose, cross-linked polyvinylpyrrolidone (crospovidone), sodium starch glycolate,
polyvinylpyrrolidone (polyvidone, povidone), sodium carboxymethylcellulose, cross-
linked sodium carboxymethylcellulose (croscarmellose sodium), hydroxypropyl cellulose,
hydroxypropyl methylcellulose, xanthan gum, alginic acid, and soy polysaccharides.

Preferred examples of binding agents include, but are not limited to, starch,
pregelatinized starch, carboxymethyl cellulose, sodium cellulose, microcrystalline
cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, polyvinylpyrrolidone,
crospovidone, and combinations thereof.

Preferred examples of gas-generating agents include, but are not limited to, alkali
metal carbonates and bicarbonates such as sodium bicarbonate and calcium carbonate.
When gas-generating agents come in contact with water or stomach acid, they generate
gas bubbles which help keep the dosage form in a buoyant state and hence avoid its
passage through the stomach.

The term "semi-permeable film", as used herein, refers to a film allowing water or
solvent to pass through it, but is impermeable to the dissolved active ingredient and other
excipients, thereby preventing the passage of dissolved active ingredient and other
excipients through it. The semi-permeable film may include film-forming agents, for
example, polyvinylalcohol, hydroxypropyl starch, hydroxyethyl starch, hydroxypropyl
cellulose, hydroxypropyl methyl cellulose, hydroxypropyl methylcellulose phthalate,
hydroxypropyl methylcellulose acetate succinate, methyl cellulose, cellulose acetate, and
polyacrylic resin; pore-forming agents such as polyethylene glycol, hydroxypropyl
cellulose, micronized sugar, sodium chloride, mannitol, and sorbitol; or plasticizers such as triethyl citrate, castor oil, dibutyl sebacate, phthalates, polyethylene glycol, glycerol, and poloxamer; and combinations thereof.

Preferred examples of solvents used for preparing the coating solution of the semi-permeable film may include, but are not limited to, methylene chloride, isopropyl alcohol, acetone, propylene glycol, methanol, ethanol, chloroform, ether, water, and combinations thereof.

Preferred examples of glidants and lubricants may include, but are not limited to, sodium lauryl sulfate, talc, magnesium stearate, sodium stearyl fumarate, stearic acid, glycercyl behenate, hydrogenated vegetable oil, zinc stearate, and colloidal silicon dioxide.

The gastro-retentive solid oral dosage form of the present invention may be prepared by conventional processes of wet granulation, dry granulation, or direct compression. The processes may also involve coating of the dosage form with functional coatings such as a semi-permeable film coating.

The invention may be further illustrated by the following examples, which are for illustrative purposes only and should not be construed as limiting the scope of the invention in any way.

**EXAMPLES**

**Example 1: Density Based Gastro-Retentive Tablets**

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<th>Ingredients</th>
<th>Quantity (% w/w)</th>
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<tr>
<td>1</td>
<td>Nilotinib</td>
<td>50.00</td>
</tr>
<tr>
<td>2</td>
<td>Acidifying Agent (Fumaric acid, citric acid, tartaric acid, or amino acid)</td>
<td>5.00</td>
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<tr>
<td>3</td>
<td>Microcrystalline Cellulose</td>
<td>29.25</td>
</tr>
<tr>
<td>4</td>
<td>Hyromellose</td>
<td>10.00</td>
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<tr>
<td>5</td>
<td>Polyvinylpyrrolidone</td>
<td>2.50</td>
</tr>
<tr>
<td>6</td>
<td>Carbomer Homopolymer Type A</td>
<td>1.25</td>
</tr>
<tr>
<td>7</td>
<td>Colloidal Silicon Dioxide</td>
<td>1.00</td>
</tr>
<tr>
<td>8</td>
<td>Magnesium Stearate</td>
<td>1.00</td>
</tr>
</tbody>
</table>
Manufacturing Procedure:

1) Sift nilotinib, the acidifying agent, microcrystalline cellulose, hypromellose, polyvinylpyrrolidone, carbomer homopolymer type A, and colloidal silicon dioxide through a BSS #18 sieve.

2) Sift magnesium stearate through a BSS #60 sieve.

3) Blend the materials of step 1 in a low shear blender for 15 minutes.

4) Blend the materials of step 2 and step 3 in a low shear blender for 10 minutes.

5) Compress the blend of step 4 into tablets using suitable tooling.

Example 2: Gas Generating Gastro-Retentive Tablets

<table>
<thead>
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<th>S. No.</th>
<th>Ingredients</th>
<th>Quantity (% w/w)</th>
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</thead>
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<tr>
<td>1</td>
<td>Nilotinib</td>
<td>38.00</td>
</tr>
<tr>
<td>2</td>
<td>Acidifying Agent (Fumaric acid, citric acid, tartaric acid, or amino acid)</td>
<td>4.00</td>
</tr>
<tr>
<td>3</td>
<td>Sodium Bicarbonate</td>
<td>8.00</td>
</tr>
<tr>
<td>4</td>
<td>Microcrystalline Cellulose</td>
<td>10.00</td>
</tr>
<tr>
<td>5</td>
<td>Lactose Anhydrous</td>
<td>8.00</td>
</tr>
<tr>
<td>6</td>
<td>Xanthan Gum</td>
<td>30.00</td>
</tr>
<tr>
<td>7</td>
<td>Colloidal Silicon Dioxide</td>
<td>1.00</td>
</tr>
<tr>
<td>8</td>
<td>Magnesium Stearate</td>
<td>1.00</td>
</tr>
</tbody>
</table>

Manufacturing Procedure:

1) Sift nilotinib, the acidifying agent, sodium bicarbonate, microcrystalline cellulose, lactose anhydrous, xanthan gum, and colloidal silicon dioxide through a BSS #18 sieve.

2) Sift magnesium stearate through a BSS #60 sieve.

3) Blend the materials of step 1 in a low shear blender for 15 minutes.

4) Blend the materials of step 2 and step 3 in a low shear blender for 10 minutes.

5) Compress the blend of step 4 into tablets using a suitable tooling.
Example 3: Size Based Gastro-Retentive Osmotic Tablets

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Ingredients</th>
<th>Quantity (% w/w)</th>
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<tbody>
<tr>
<td>1</td>
<td>Nilotinib</td>
<td>46.40</td>
</tr>
<tr>
<td>2</td>
<td>Acidifying Agent (Fumaric acid, citric acid, tartaric acid, or amino acid)</td>
<td>11.60</td>
</tr>
<tr>
<td>3</td>
<td>Lactose Monohydrate</td>
<td>21.46</td>
</tr>
<tr>
<td>4</td>
<td>Sodium Chloride</td>
<td>5.80</td>
</tr>
<tr>
<td>5</td>
<td>Colloidal Silicon Dioxide</td>
<td>0.87</td>
</tr>
<tr>
<td>6</td>
<td>Magnesium Stearate</td>
<td>0.87</td>
</tr>
<tr>
<td>7</td>
<td>Hypromellose</td>
<td>3.00</td>
</tr>
<tr>
<td>8</td>
<td>Cellulose Acetate</td>
<td>9.90</td>
</tr>
<tr>
<td>9</td>
<td>Polyethylene Glycol</td>
<td>0.10</td>
</tr>
</tbody>
</table>

Manufacturing Procedure:

1) Sift nilotinib, the acidifying agent, sodium chloride, lactose monohydrate, and colloidal silicon dioxide through a BSS #18 sieve.

2) Sift magnesium stearate through a BSS #60 sieve.

3) Blend the materials of step 1 in a low shear blender for 15 minutes.

4) Blend the materials of step 2 and step 3 in a low shear blender for 10 minutes.

5) Compress the blend of step 4 into tablets using a suitable tooling.

6) Dissolve hypromellose in water.

7) Coat the tablets of step 5 with the solution of step 6.

8) Dissolve cellulose acetate and polyethylene glycol in an acetone and water mixture.

9) Coat the tablets of step 7 with the solution of step 8.

10) Cure the tablets of step 9 for a period of 24 hours at 40°C.

11) Drill the tablets of step 10 with one hole on one side or one hole on both sides using a laser beam to a particular diameter and depth.
Example 4: Gastro Floating Capsules

Manufacturing Procedure:

Preparation of Capsules:

1) Capsules may be prepared by any one of the following methods:

   a. Capsules may be filled with nilotinib.

   b. Capsules may be filled with nilotinib and lactose as granules or powder.

   c. Nilotinib and lactose mini-tablets may be filled into the capsules.

2) Prepare gelatin solution and use it to band seal the capsules of step 1.

Coating of Capsules:

3) Coat the capsules of step 2 with cellulose acetate or ethyl cellulose solution containing polyethylene glycol.

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Ingredients</th>
<th>Quantity (% w/w)</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>Nilotinib</td>
<td>70.0</td>
</tr>
<tr>
<td>2</td>
<td>Lactose Monohydrate</td>
<td>10.0</td>
</tr>
<tr>
<td>3</td>
<td>Gelatin/HPMC Capsule</td>
<td>10.0</td>
</tr>
<tr>
<td>4</td>
<td>Cellulose Acetate/Ethyl cellulose</td>
<td>9.0</td>
</tr>
<tr>
<td>5</td>
<td>Polyethylene Glycol</td>
<td>1.0</td>
</tr>
</tbody>
</table>
We Claim:

1. A gastro-retentive solid oral dosage form which comprises nilotinib or a salt thereof, at least one rate-controlling polymer, and other pharmaceutically acceptable excipients.

2. The gastro-retentive solid dosage form of claim 1, wherein the rate-controlling polymer is a swelling agent.

3. The gastro-retentive solid oral dosage form of claim 1, wherein the dosage form further comprises an acidifying agent.

4. The gastro-retentive solid oral dosage form of claim 1, wherein the dosage form is administered once daily or twice daily.

5. The gastro-retentive solid dosage form of claim 1, wherein the dosage form is a tablet.

6. The gastro-retentive tablet of claim 5, wherein the gastro-retentive action of the tablet is based on one or more mechanisms of floatation, gas generation, and swelling.

7. The gastro-retentive solid dosage form of claim 1, wherein the dosage form further comprises one or more osmogen agents.

8. The gastro-retentive solid dosage form of claim 1, wherein the other pharmaceutically acceptable excipients are selected from diluents, matrix forming agents, disintegrants, binding agents, gas-generating agents, semi-permeable film-forming agents, glidants, and lubricants.
**INTERNATIONAL SEARCH REPORT**

**International application No**

PCT/IB2014/061018

**A. CLASSIFICATION OF SUBJECT MATTER**

INV. A61K9/00  A61K9/16  A61K9/20  A61K31/506

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

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

A61K

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, WPI Data, BIOSIS, EMBASE

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

<table>
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<tr>
<th>Category</th>
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<td>X</td>
<td>WO 2011/048494 A2 (INTEC PHARMA LTD [I L]; NAVON NADAV [I L];) 28 April 2011 (2011-04-28) paragraphs [0011], [0012], [0016], [0027], [0036]; claim 40; examples 1-3; tables 4, 8, 10</td>
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<td>WO 2010/035273 A2 (INTEC PHARMA LTD [I L]; YISSUM RES DEV CO [I L]; FRIEDMAN MICHAEL [I L];) 1 April 2010 (2010-04-01) page 3, paragraphs 15, 17, 32-39, 49-87, 122; examples 1-5</td>
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* "A" document member of the same patent family

**Date of the actual completion of the international search**

15 July 2014

**Date of mailing of the international search report**

28/07/2014

**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**

Toulaci, C
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| X        | WO 02/102415 Al (BLUE CROSS LAB LTD [IN]; AVACHAT MAKARAND K [IN]; DHAMNE ABHIJT G [IN]) 27 December 2002 (2002-12-27)  
page 1, lines 4-11  
page 11, lines 5-17  
page 12, line 15 - page 15, line 2  
page 18, line 21 - page 19, line 5 | 1-8                   |
| X        | WO 01/37812 A2 (YISSUM RES DEV co [IL]; FRI EDMAN MICHAEL [IL]; KLAUSNER EYTAN [IL]; LA) 31 May 2001 (2001-05-31)  
page 1, lines 5-20  
page 8, lines 1-12  
page 11, lines 4-31  
page 12, lines 12-26  
page 17, lines 1-20  
examp les 1,2 | 1-8                   |
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