The present invention relates to solid oral pharmaceutical compositions comprising ticagrelor or salt thereof. In particular, the present invention relates to a composition comprising ticagrelor or salt thereof in an amount less than 20 % of the weight of total composition, wherein the composition is devoid of water-insoluble fillers. The invention further relates to methods of reducing the rate of thrombotic cardiovascular events in patients with acute coronary syndrome (ACS) by using the composition ticagrelor or salt thereof.
**SOLID ORAL PHARMACEUTICAL COMPOSITIONS COMPRISING TICAGRELOR OR SALT THEREOF**

**Field of the Invention**

The present invention relates to solid oral pharmaceutical compositions comprising ticagrelor or salt thereof. In particular, the present invention relates to a composition comprising ticagrelor or salt thereof in an amount less than 20% of the weight of total composition, wherein the composition is devoid of water-insoluble fillers. The invention further relates to method of reducing the rate of thrombotic cardiovascular events in patients with acute coronary syndrome (ACS) by using the composition ticagrelor or salt thereof.

**Background of the Invention**

Ticagrelor is a P2Y12 platelet inhibitor that is used to reduce the rate of thrombotic cardiovascular events in patients with acute coronary syndrome (ACS) (unstable angina, non-ST elevation myocardial infarction, or ST elevation myocardial infarction). It is an inhibitor of platelet activation and aggregation mediated by the P2Y12 ADP-receptor.

Chemically it is \((1\,S,2\,S,3\,R,5\,S)-3-[7-\{[(1\,R,2\,S)-2-(3,4-difluorophenyl)\,\text{cyclopropyl}\,\text{amino}\}-5-(\text{propylthio})-3\text{H}-[1,2,3]\,-\text{triazolo}\,[4,5-d]\,-\text{pyrimidin-3-yl}]\,-5-\,(2-\text{hydroxyethoxy})\,\text{cyclopentane}\,-1,2\,-\text{diol}\). The empirical formula of ticagrelor is C23H28F2N6O4S and its molecular weight is 522.57. The chemical structure of ticagrelor is:
It appears as a white or off-white to pale pink crystalline powder which does not exhibit pH dependent solubility (aqueous solubility approx. 10 µg/mL at RT) and is defined as 'low solubility' under the Biopharmaceutics Classification System (BCS). Having also a low permeability, ticagrelor is a BCS class IV compound. Ticagrelor and its major metabolite reversibly interact with the platelet P₂Y₁₂ ADP-receptor to prevent signal transduction and platelet activation. Ticagrelor and its active metabolite are approximately equipotent.

Currently, ticagrelor is marketed in the US with a brand name Brilinta® as an immediate release tablet. It is used to reduce the rate of thrombotic cardiovascular events in patients with acute coronary syndrome (ACS).

PCT Application No. WO 2005/1 13006 discloses ticagrelor compositions in a general way, without specifying the excipients comprised therein.

PCT Application No. WO 2000/34283 discloses processes for the preparation of ticagrelor and related compounds, as well as their formulation in general terms with different pharmaceutical excipients.

U.S. Patent Application No. 2013/0131087 discloses composition of 90 mg ticagrelor and a means of releasing the said amount.

U.S. Patent No. 8,425,934 discloses compositions of ticagrelor comprising mixture of mannitol and dibasic calcium phosphate dihydrate, hydroxypropyl cellulose, sodium starch glycolate, and one or more lubricants.

As ticagrelor is a low soluble drug substance (not ionised in the physiological pH range) and exhibits a moderate intrinsic permeability, there is potentially a higher risk that changes in formulation such as nature and amount of excipients and processing parameters can affect drug release from the dosage form thereby may affect its clinical performance. This has to be taken into account during formulation development of BCS class IV drugs. Also, it is desirable ensure uniform and complete release of ticagrelor or salt thereof from the composition to avoid any variability in clinical performance.

Thus, there exists an enduring need to provide an improved formulation of ticagrelor or salt thereof having low drug load and which is devoid of water-insoluble fillers can address the aforesaid objective i.e. uniform and complete release as well as may exhibit excellent storage stability.

The inventors of the present invention tried to incorporate mostly water-soluble excipients and to keep low drug load in the composition so as to ensure immediate and complete release of ticagrelor. As fillers constitute major portion of the tablet composition, any water-insoluble filler in the composition is avoided. Further, as solubility of ticagrelor is not pH dependent, inventors of the present invention have avoided use of any pH modifying filler in the formulation.

To formulate a composition having low drug load, the inventors of the present invention have prepared a composition comprising low drug (ticagrelor or salt thereof) load i.e. less than 20 % of total weight of composition. In other words,
as the dose of ticagrelor is 90 mg, a composition with a total weight more than 450 mg is prepared.

The high excipient load may enable the production of solid oral pharmaceutical composition that releases its content completely and more uniformly. The total amount of excipients in a given unit dosage may be about 80% or more by weight based on the total weight of the tablet.

Inventors of the present invention have surprisingly found that it is possible to formulate a ticagrelor solid oral pharmaceutical composition having low drug load (less than 20%) that exhibits desired release profile, wherein the composition is devoid of any water-insoluble filler.

Accordingly, the present invention provides a solid oral pharmaceutical composition with low drug load comprising a pharmacologically effective amount of ticagrelor or salt thereof present in an amount of less than about 20%, wherein the formulation is devoid of any water-insoluble filler.

Summary of the Invention

In one general aspect, there is provided a solid oral pharmaceutical composition comprising ticagrelor or salt thereof with one or more pharmaceutically acceptable excipients, wherein the amount of ticagrelor is less than 20% by weight of the composition.

In another general aspect, there is provided a solid oral pharmaceutical composition comprising ticagrelor or salt thereof with one or more pharmaceutically acceptable excipients, wherein the composition is free of water-insoluble fillers.
In another general aspect, there is provided a solid oral pharmaceutical composition of ticagrelor or salt thereof, wherein the ratio of amount of ticagrelor to water-soluble fillers is 1:1.5 to 1:5.

In another general aspect, there is provided a solid oral pharmaceutical composition comprising ticagrelor or salt thereof with one or more pharmaceutically acceptable excipients, wherein all the excipients are water-soluble in nature.

In another general aspect, there is provided a solid oral pharmaceutical composition comprising ticagrelor or salt thereof, which composition is in the form of a tablet.

In another general aspect, there is provided a solid oral pharmaceutical composition comprising ticagrelor or salt thereof, which composition is in the form of a capsule.

The present invention also provides a tablet comprising:
(a) a pharmacologically effective amount of ticagrelor or salt thereof;
(b) at least one pharmaceutically acceptable excipient suitable for the preparation of tablets;
wherein the amount of ticagrelor or salt thereof is less than 20% when calculated as the percentage of the content in weight of the active moiety based on the total weight of the tablet;
wherein the tablet is free of water-insoluble fillers.

One or more pharmaceutically acceptable excipients may be present in the tablets, e.g. at least one filler, at least one binder, at least one disintegrant, at least one glidant, and at least one lubricant, and optionally a coating comprising film forming polymer.
In another general aspect, there is provided a solid oral pharmaceutical composition comprising ticagrelor or salt thereof with one or more pharmaceutically acceptable excipients, wherein the composition comprises at least 80% pharmaceutically acceptable excipients by weight of the composition.

The amount of water-soluble filler may vary within a range of from 5 to 90%, e.g. 10 to 80% and particularly 40 to 70% in weight based on the total weight of the composition.

According to the present invention, the amount of binder may vary within a range of from about 1 to 30%, preferably 1 to 20%, in particular 1 to 10% in weight based on the total weight of the composition.

The amount of disintegrant may vary within a range of from 5 to 20%, e.g. 10 to 15% in weight based on the total weight of the composition.

The amount of lubricant may vary within a range of from 0.1 to 5%, e.g. 0.5 to 2% in weight based on the total weight of the composition.

The amount of coating may vary from 1 to 10%, preferably from 1.5 to 2.5% in weight based on the total weight of the composition.

In a preferred aspect of the invention, there is provided a tablet comprising of one or more fillers in a total amount of about 5% to 90%, one or more binders in a total amount of about 1% to 20% in weight based on the total weight of the tablet, one or more disintegrants in a total amount of about 10% to 20% in weight based on the total weight of the tablet, and one or more lubricants in a total amount of about 0.5% to 2% in weight based on the total weight of the tablet, wherein the tablet is free of water-insoluble filler and wherein the amount of ticagrelor or salt thereof is less than 20% by weight of the total composition.
The absolute amounts of each excipient and the amounts relative to other excipients are similarly dependent on the desired properties of the tablet and may also be chosen by routine experimentation. For example, the solid oral pharmaceutical composition may be chosen to exhibit accelerated and/or delayed release of ticagrelor with or without quantitative control of the release of active agent. Preferably the solid oral pharmaceutical composition is chosen to exhibit immediate release of the ticagrelor.

In accordance with the present invention, it has now unexpectedly been found that stable and convenient tablets devoid of water insoluble fillers and comprising low load of ticagrelor are obtainable. Specifically, the tablets of the invention may be prepared by granulation, preferably wet-granulation, followed by compression methods.

It is a characteristic of the tablet according to the invention that it contains a low content of ticagrelor given the relatively high amount of excipients. This enables the production of tablets that releases its content completely and more uniformly. The total amount of excipients in a given unit dosage may be about 80% or more by weight based on the total weight of the tablet.

In another general aspect, the solid oral pharmaceutical composition retains at least 90% by weight of the total content of ticagrelor or salt thereof when stored at 40°C and 75% relative humidity over a period of at least 3 months.

In another general aspect, there is provided a process of preparing the solid oral pharmaceutical composition of ticagrelor or salt thereof, which process comprises steps of:
(a) mixing ticagrelor or salt thereof with one or more pharmaceutically acceptable excipients to form a dry powder blend;
(b) granulating the dry powder blend of step (a) to form granules;
(c) compressing granules obtained in step (b) to form a core; and
(d) filling one or more cores prepared in step (c) in a hard gelatin capsule shell; wherein the composition is devoid of water insoluble fillers; wherein the amount of ticagrelor or salt thereof is less than 20% by weight of the total composition.

In another general aspect, there is provided a process of preparing the composition of ticagrelor or salt thereof, which process comprises steps of:

(a) mixing ticagrelor or salt thereof with one or more pharmaceutically acceptable excipients to form a dry powder blend;
(b) granulating the dry powder blend of step (a) to form granules;
(c) compressing granules obtained in step (b) to form tablet; and
(d) optionally, coating the tablet prepared in step (c) with one or more film forming polymers;

wherein the composition is devoid of water insoluble fillers;
wherein the amount of ticagrelor or salt thereof is less than 20% by weight of the total composition.

Thus, inventors of the present invention have formulated a solid oral pharmaceutical composition devoid of water insoluble filler and having low drug load (less than 20%) to produce sufficiently small, and therefore, convenient to administer dosage form. A particular advantage of the composition is that it exhibits similar dissolution properties as compared to currently marketed ticagrelor tablets.

**Detailed Description of the Invention**

The term "ticagrelor" as used herein refers to ticagrelor base or its salt, solvates, prodrugs, hydrates, enantiomers or polymorphs thereof. Particularly, preferred salt of ticagrelor is ticagrelor base.
Suitable water soluble fillers include, but are not limited, dextrose, fructose, lactose, maltitol, maltodextrins, maltose, sorbitol, sucrose, xylitol, erythritol and the like.

Suitable binders include, but not limited to, microcrystalline cellulose, hydroxymethyl cellulose, hydroxypropylcellulose, starch (including corn starch and pregelatinized starch), gelatin, sugars (including sucrose, glucose, dextrose, lactose, and sorbitol), waxes, polyethylene glycol, natural and synthetic gums (e.g. acacia, tragacanth sodium alginate, celluloses, and Veegum), and synthetic polymers such as polymetacrylates and polyvinylpyrrolidone (povidone), ethylcellulose, hydroxyethyl cellulose, polyethylene oxide, mixtures thereof and the like.

Suitable disintegrants include, but not limited to, cross linked polyvinylpyrrolidone (crosplavidone, polyplasdone XL(R), kollidon CL(R)); starches such as maize starch and dried sodium starch glycolate; gums such as maize starch and dried sodium starch glycolate; gums such as alginic acid, sodium alginate, guar gum; croscarmellose sodium; cellulose products such as microcrystalline cellulose and its salts, microfine cellulose, low-substituted hydroxypropylcellulose, mixtures thereof and the like.

Suitable lubricants include, but not limited to sodium oleate, sodium stearate, sodium benzoate, sodium stearate, sodium chloride, stearic acid, sodium stearyl fumarate, calcium stearate, magnesium stearate, magnesium lauryl sulfate, sodium stearyl fumarate, sucrose esters or fatty acid, zinc, polyethylene glycol, talc, mixtures thereof and the like.

In an embodiment, a solid oral pharmaceutical composition comprising ticagrelor or salt thereof with one or more pharmaceutically acceptable excipients, wherein the amount of ticagrelor is less than 20% by weight of the composition.
In another embodiment, a solid oral pharmaceutical composition comprising ticagrelor or salt thereof with one or more pharmaceutically acceptable excipients, wherein the composition is free of water-insoluble fillers.

In another embodiment, a solid oral pharmaceutical composition of ticagrelor or salt thereof, wherein the ratio of amount of ticagrelor to water-soluble fillers is 1:1.5 to 1:5.

In another embodiment, there is provided a solid oral pharmaceutical composition comprising ticagrelor or salt thereof with one or more pharmaceutically acceptable excipients, wherein all the excipients are water-soluble in nature.

In an embodiment, a solid oral pharmaceutical composition comprising ticagrelor or salt thereof with one or more pharmaceutically acceptable excipients, wherein the amount of ticagrelor is less than 20% by weight of the composition and wherein the composition is free of water-insoluble fillers.

In another embodiment, the solid oral pharmaceutical composition comprising ticagrelor or salt thereof, wherein the composition is in the form of tablet.

In another embodiment, the solid oral pharmaceutical composition comprising ticagrelor or salt thereof, wherein the composition is in the form of capsule.

In another embodiment, the solid oral pharmaceutical composition comprises:
(a) a pharmacologically effective amount of ticagrelor or salt thereof; and
(b) at least one pharmaceutically acceptable excipient;
wherein the amount of ticagrelor or salt thereof, calculated as the percentage of the content in weight of the active moiety based on the total the composition, is less than 20%,
wherein the composition is free of water-insoluble fillers.
In another embodiment, the tablet comprises:
(a) a pharmacologically effective amount of ticagrelor or salt thereof; and
(b) at least one pharmaceutically acceptable excipient suitable for the preparation of tablets;
wherein the amount of ticagrelor or salt thereof, calculated as the percentage of the content in weight of the active moiety based on the total weight of the tablet, is less than 20%.
wherein the tablet is free of water-insoluble fillers.

In another embodiment, the solid oral pharmaceutical composition comprises of one or more filler in a total amount of about 5% to 90%, one or more binders in a total amount of about 1% to 20% in weight based on the total weight of the tablet, one or more disintegrants in a total amount of about 10% to 20% in weight based on the total weight of the tablet, and one or more lubricants in a total amount of about 0.5% to 2% in weight based on the total weight of the composition.

A solid bulk of granulate mass, which is necessary for manufacturing tablets, can be manufactured using two main processes, wet granulation or dry granulation. Tablets may also be manufactured using direct compression. Direct compression relates to the tableting process itself rather than preparation of the starting material.

In wet granulation, components are typically mixed and granulated using a wet binder. The wet granulates are then sieved, dried and optionally ground prior to compressing into tablets. Wet granulation is used extensively in the pharmaceutical industry although it has proven to be a difficult method, mainly because the liquids needed in the granule and tablet manufacturing process often have an adverse effect on the characteristics of the active pharmaceutical ingredients (APIs) and/or on the end product such as a tablet.
Dry granulation is usually described as a method of controlled crushing of precompacted powders densified by either slugging or passing the material between two counter-rotating rolls.

More specifically, powdered components that may contain very fine particles are typically mixed prior to being compacted to yield hard slugs which are then ground and sieved before the addition of other ingredients and final compression to form tablets. Because substantially no liquids are used in the dry granulation process, the issues related to wet granulation are avoided. Although dry granulation would in many cases appear to be the best way to produce products such as tablets containing APIs, it has been relatively little used because of the challenges in producing the desired kind of granules as well as managing the granulated material in the manufacturing process. Known dry granulation methods, as well as the known issues related to them are well described in scientific articles, such as the review article "Roll compaction / dry granulation: pharmaceutical applications" written by Peter Kleinebudde and published in European Journal of Pharmaceutics and Biopharmaceutics 58 (2004) at pages 317-326.

Direct compression is generally considered to be the simplest and the most economical process for producing tablets. However, it may only be applied to materials that do not need to be granulated before tableting. Direct compression requires only two principal steps; i.e., the mixing of all the ingredients and the compression of this mixture. However, direct compression is applicable to only a relatively small number of substances as the ingredients of the tablets often need to be processed by some granulation technique to make them compressible and/or for improving their homogeneity and flow-ability.

In another embodiment, the solid oral pharmaceutical composition retains at least 90% by weight of the total content of ticagrelor or salt thereof when stored at 40°C and 75% relative humidity over a period of at least 3 months.
It is also well known in the art that in order to get uniform tablets the bulk to be tableted should be homogeneous and should have good flow characteristics.

In another embodiment, the process of preparing the solid oral pharmaceutical composition of ticagrelor or salt thereof, which process comprises steps of:
(a) mixing ticagrelor or salt thereof with one or more pharmaceutically acceptable excipients to form a dry powder blend;
(b) granulating the dry powder blend of step (a) to form granules;
(c) compressing granules obtained in step (b) to form a core; and
(d) filling one or more cores prepared in step (c) in a hard gelatin capsule shell.

In another embodiment, the process of preparing the composition of ticagrelor or salt thereof, which process comprises steps of:
(a) mixing ticagrelor or salt thereof with one or more pharmaceutically acceptable excipients to form a dry powder blend;
(b) granulating the dry powder blend of step (a) to form granules;
(c) compressing granules obtained in step (b) to form tablet, and
(d) optionally, coating the tablet of step (c) with one or more film forming polymers.

In another embodiment, the process of preparing the composition of ticagrelor or salt thereof, which process comprises steps of:
(a) mixing ticagrelor, mannitol and dibasic calcium phosphate dihydrate and granulating with aqueous solution of hydroxypropylmethyl cellulose to form granules,
(b) compressing formed granules of step (a) to form a tablet, and
(c) optionally, coating the tablet formed in step (b) with one or more layers comprising hydroxypropylmethyl cellulose.
In another embodiment, the process of preparing the composition of ticagrelor or salt thereof, which process comprises steps of:
(a) mixing ticagrelor, mannitol and dibasic calcium phosphate dihydrate and granulated with aqueous solution of povidone to form granules,
(b) compressing formed granules of step (a) to form a tablet, and
(c) coating the tablet with one or more layers comprising hydroxypropyl methyl cellulose.

The invention further provides a method of treating multiple sclerosis by administering a solid oral pharmaceutical dosage form comprising ticagrelor or salt thereof of administering the solid oral composition of ticagrelor or salt thereof in accordance with the present invention.

The invention now will be described in particularity with the following illustrative examples; however, the scope of the present invention is not intended to be, and shall not be, limited to the exemplified embodiments below.
Example 1:

Table 1

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Ingredients</th>
<th>Quantity (mg/tab)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Intragranular</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Ticagrelor</td>
<td>90.0</td>
</tr>
<tr>
<td>2</td>
<td>Mannitol</td>
<td>189.0</td>
</tr>
<tr>
<td>3</td>
<td>Povidone</td>
<td>9.0</td>
</tr>
<tr>
<td></td>
<td><strong>Binder</strong></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Purified water</td>
<td>q.s.</td>
</tr>
<tr>
<td></td>
<td><strong>Extragranular</strong></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Sodium Starch Glycollate</td>
<td>9.0</td>
</tr>
<tr>
<td>6</td>
<td>Magnesium Stearate</td>
<td>3.0</td>
</tr>
<tr>
<td></td>
<td><strong>Core tab Total wt.</strong></td>
<td>300.0</td>
</tr>
<tr>
<td></td>
<td><strong>Coating</strong></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Opadry</td>
<td>6.0</td>
</tr>
<tr>
<td></td>
<td><strong>Total</strong></td>
<td>306.0</td>
</tr>
</tbody>
</table>

Process:

Intragranular materials were sifted through # 40 sieve and dry mixed in RMG. The dry blend was granulated using purified water to form wet mass. Thus formed wet mass was dries in fluidized bed dryer at 60°C till LOD of less than 2 % is achieved. Granules were sized through # 20 sieve. Dried and sized granules were mix for 2 min with extragranular material and lubricated with magnesium stearate in a blender. This lubricated blend was compressed using suitable tooling on compression machine to form tablets. The compressed tablets were coated using opadry dispersion in water using coating pan.
Example 2:

Table 2

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Ingredients</th>
<th>Quantity (mg/tab)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ticagrelor</td>
<td>90.0</td>
</tr>
<tr>
<td>2</td>
<td>Mannitol</td>
<td>379.0</td>
</tr>
<tr>
<td>3</td>
<td>Povidone</td>
<td>19.0</td>
</tr>
<tr>
<td>4</td>
<td>Purified water</td>
<td>q.s.</td>
</tr>
<tr>
<td>5</td>
<td>Sodium Starch Glycollate</td>
<td>9.0</td>
</tr>
<tr>
<td>6</td>
<td>Magnesium Stearate</td>
<td>3.0</td>
</tr>
<tr>
<td></td>
<td><strong>Core tab Total wt.</strong></td>
<td><strong>500.0</strong></td>
</tr>
<tr>
<td>7</td>
<td>Opadry</td>
<td>10.0</td>
</tr>
<tr>
<td></td>
<td><strong>Total</strong></td>
<td><strong>510.0</strong></td>
</tr>
</tbody>
</table>

Process:

Intragranular materials were sifted through # 40 sieve and dry mixed in RMG. The dry blend was granulated using purified water to form wet mass. Thus formed wet mass was dries in fluidized bed dryer at 60°C till LOD of less than 2 % is achieved. Granules were sized through # 20 sieve. Dried and sized granules were mix for 2 min with extragranular material and lubricated with magnesium stearate in a blender. This lubricated blend was compressed using suitable tooling on compression machine to form tablets. The compressed tablets were coated using opadry dispersion in water using coating pan.
Claims:
1. A solid oral pharmaceutical composition comprising ticagrelor or salt thereof and at least one pharmaceutically acceptable excipient, wherein ticagrelor is present in an amount less than 20% by weight based on the total weight of the composition.

2. The solid oral pharmaceutical composition of claim 1, wherein ticagrelor is present in an amount less than 10% by weight based on the total weight of the composition.

3. The solid oral pharmaceutical composition claim 1, wherein the composition is in the form of a tablet.

4. A solid oral pharmaceutical composition comprising ticagrelor or salt thereof with one or more pharmaceutically acceptable excipients, wherein the composition is free of water-insoluble fillers.

5. The solid oral pharmaceutical composition of claim 4, wherein the composition comprises of one or more water-soluble fillers.

6. The solid oral pharmaceutical composition of claim 5, wherein the ratio of amount of ticagrelor to water-soluble fillers is 1:1.5 to 1:5.

7. The solid oral pharmaceutical composition of claim 5, wherein the amount of water-soluble filler may vary within a range of from to 5 to 90%, e.g. 10 to 80% and particularly 40 to 70% in weight based on the total weight of the composition.

8. The solid oral pharmaceutical composition of claim 5, wherein the water-soluble filler is selected from dextrose, fructose, lactitol, lactose, L-hydroxypropyl-cellulose (low substituted), starches or modified starches.
(potato starch, wheat starch, corn starch, rice starch, pregelatinized maize starch), maltitol, maltodextrins, maltose, sorbitol, starch, sucrose, sugar, and xylitol, erythritol or mixture thereof.

9. The solid oral pharmaceutical composition of claim 4, wherein the composition is devoid of pH modifying filler.

10. The solid oral pharmaceutical composition of claim 4, wherein all the excipients are water-soluble.

11. The solid oral pharmaceutical composition claim 4, wherein the composition is in the form of a tablet.

12. A solid oral pharmaceutical composition comprising ticagrelor or salt thereof with one or more pharmaceutically acceptable excipients, wherein the amount of ticagrelor is less than 20% by weight of the composition and the composition is free of water-insoluble fillers.

13. The solid oral pharmaceutical composition claim 12, wherein the composition is in the form of a tablet.

14. The solid oral pharmaceutical composition of claim 1, 4 or 12, wherein the composition is in the form of a capsule.

15. The solid oral pharmaceutical composition of claim 3, wherein the weight of the tablet is more than 450 mg.

16. The solid oral pharmaceutical composition of claim 3, wherein the weight of the tablet is more than 1000 mg.
17. A process for preparation of solid oral pharmaceutical composition of claim 3 comprising steps of:
   (a) mixing ticagrelor or salt thereof with one or more pharmaceutically acceptable excipients to form a dry powder blend;
   (b) granulating the dry powder blend of step (a) to form granules;
   (c) compressing granules obtained in step (b) to form tablet; and
   (d) optionally, coating the tablet prepared in step (c) with one or more film forming polymers.

18. A process for preparation of solid oral pharmaceutical composition of claim 11 comprising steps of:
   (a) mixing ticagrelor or salt thereof with one or more pharmaceutically acceptable excipients to form a dry powder blend;
   (b) granulating the dry powder blend of step (a) to form granules;
   (c) compressing granules obtained in step (b) to form tablet; and
   (d) optionally, coating the tablet prepared in step (c) with one or more film forming polymers.

19. The solid oral pharmaceutical composition of any one of the claims 1 to 18, wherein the composition retains at least 90% by weight of the total content of ticagrelor or salt thereof when stored at 40°C and 75% relative humidity over a period of at least 3 months.

20. A method of treating acute coronary syndrome in a patient, said method comprising of administering the solid oral pharmaceutical composition according to any one of the claims 1 to 19.
INTERNATIONAL SEARCH REPORT
International application No
PCT/IB2015/050426

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/20 A61K31/519
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, EBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
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<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
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<tr>
<td>X</td>
<td>WO 2013/084089 AI (WOCKHARDT LTD [IN] ) 13 June 2013 (2013-06-13) page 19, paragraph 3 page 34, last paragraph - page 36, paragraph 1; example e 4</td>
<td>1-20</td>
</tr>
</tbody>
</table>

[X] Further documents are listed in the continuation of Box C.  [X] 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)
  "O" document referring to an oral disclosure, use, exhibition or other means
  "P" document published prior to the international filing date but later than the priority date claimed
  "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
  "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
  "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
  "&" document member of the same patent family

Date of the actual completion of the international search
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European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel: (+31-70) 340-2040, Fax: (+3 1-70) 340-3016 Toulaci s, C

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