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(54) Title: ORAL FORMULATIONS COMPRISING RIVAROXABAN

(57) Abstract: The present invention relates to an immediate release solid oral composition comprising rivaroxaban and one or more acceptable excipients manufactured by using optimised high- shear granulation process. More specifically, the invention relates to the oral pharmaceutical formulation comprising rivaroxaban and pharmaceutically acceptable excipients manufactured by using wet granulation method in which rivaroxaban is in non-hydrophilized form with an optimized kneading time from 30 seconds to 3 minutes.



WO 2020/101587 A1

ORAL FORMULATIONS COMPRISING RIVAROXABAN

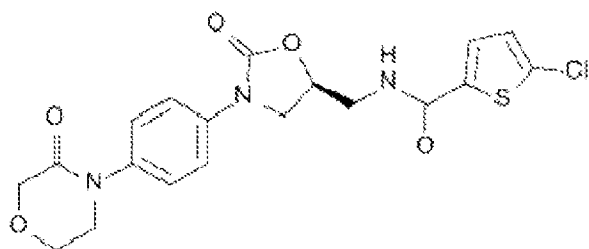
FIELD OF INVENTION

The present invention relates to a pharmaceutical composition, comprising rivaroxaban or a pharmaceutically acceptable salt thereof.

5 PRIOR ART

Rivaroxaban (5-chloro-N-[(5S)-2-oxo-3-[4-(3-oxomorpholin-4-yl)phenyl]oxazolidin-5-yl)methyl]thiophene-2-carboxamide) is a low molecular weight, orally administrable anticoagulant drug. Rivaroxaban is an anticoagulant and the first orally active direct factor Xa inhibitor. The pharmaceutical directly inhibits the active form of serine protease Factor Xa (FXa). Rivaroxaban can be used for the prevention and treatment of various thromboembolic diseases, in particular of deep vein thrombosis (DVT), pulmonary embolism (PE), myocardial infarct, angina pectoris, reocclusions and restenoses after angioplasty or aortocoronary bypass, cerebral stroke, transitory ischemic attacks, and peripheral arterial occlusive diseases.

Rivaroxaban was first disclosed in WO0147919, has the systematic name 5-chloro-N-[(5S)-2-oxo-3-[4-(3-oxomorpholin-4-yl)phenyl]-1,3-oxazolidin-5-yl)methyl]thiophene-2-carboxamide and the following chemical structure:



Formula

Three different polymorphic forms of rivaroxaban have been described in WO07039132.

US2007/0149522 relates to a synthesis method of 5-chloro-N-[(5S)-2-oxo-3-[4-(3-oxo-4-morpholinyl)-phenyl]-1,3-oxazolidin-5-yl]-methyl)-2-thiophene carboxamide using from 5-chlorothiophene-2-carbonyl chloride and (2S)-3-amino-propane-1,2-diol and 4-(4-aminophenyl)-3-morpholinone as starting materials.

WO2009023233 relates to novel compounds that are substituted oxazolidinones derivatives and pharmaceutically acceptable salts thereof. More specifically, this invention relates to novel oxazolidinone compounds that are derivatives of Rivaroxaban. The invention also provides pyrogen-free compositions comprising one or more compounds of the invention and a carrier, along with the use of the disclosed compounds and compositions in methods of treating diseases and condition that are beneficially treated by administering a selective inhibitor of factor Xa, such as Rivaroxaban.

WO2015155307 relates to a novel pharmaceutical composition comprising rivaroxaban or a pharmaceutically acceptable salt thereof in combination with a proton pump inhibitor for use in the anticoagulant treatment with preventing or reducing the risk of a gastrointestinal disorder.

WO2015169957 relates to a novel pharmaceutical composition comprising rivaroxaban or a pharmaceutically acceptable salt thereof in combination with a proton pump inhibitor for use in the anticoagulant treatment with preventing or reducing the risk of a gastrointestinal disorder.

WO2016131896 relates to a pharmaceutical combination comprising dronedarone or a pharmaceutically acceptable salt thereof in combination with rivaroxaban and at least one pharmaceutically acceptable excipient.

WO07039122 relates to rivaroxaban formulations comprising rivaroxaban in amorphous form or thermodynamically metastable crystal modification.

WO09049820 relates to rivaroxaban formulations comprising at least one solid substance at room temperature, the thermodynamically preferred crystalline form of rivaroxaban, cellulose and/or cellulose derivatives, as well as optionally a surface-active substance, wherein more than 50% of rivaroxaban in the formulation is in amorphous mixed phase as determined by X-ray diffractometry.

WO2005060940 relates to a method for production of a solid, orally administrable pharmaceutical composition comprising rivaroxaban in hydrophilized form. The wet granulation manufacturing method is disclosed by using fluidized-bed granulation. In the manufacturing method, first rivaroxaban is introduced into the wet granulation suspended in the granulation liquid. In the description part of the patent document it is discussed that since

rivaroxaban is a poor-water soluble drug, it should be dissolved in a suitable solvent for further processing and get a dosage form with good pharmaceutical properties.

WO2017021482 relates to an immediate release tablet comprising; rivaroxaban, a non-ionic surfactant and optionally one or more pharmaceutically acceptable excipients obtainable by
5 using a dry process.

W010146179 or W011042156 disclose hot melt rivaroxaban formulations. The use of hot melt process, coated granules, milling with excipients or microspheres formulations imply complex, lengthy and costly processes; therefore, they are not desirable.

10 Rivaroxaban is a pharmaceutical agent that is used to reduce stroke risk in nonvalvular atrial fibrillation. It helps reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation. It is also indicated for treating deep vein thrombosis and pulmonary embolism. It also reduces in the risk of recurrence of the same. Specifically, rivaroxaban is used for the prophylaxis of deep vein thrombosis after knee or hip replacement surgery which may lead to pulmonary embolism.

15 Rivaroxaban is an orally active factor Xa inhibitor marketed for the treatment or prevention of atherothrombotic events, prevention of venous thromboembolism, prevention of stroke and systemic embolism, treatment and prevention of deep vein thrombosis or treatment and prevention of pulmonary embolism. Rivaroxaban is marketed in 2.5, 10, 15 and 20 mg strengths immediate release tablets.

20 Rivaroxaban has poor water solubility (7 mg/L) and is thus difficult to incorporate into oral dosage forms that provide sufficient bioavailability of rivaroxaban following oral administration. There is thus a need to provide an improved process for the preparation of dosage forms of rivaroxaban with improved bioavailability of the rivaroxaban active ingredient.

25 Based on the information about the solubility of rivaroxaban wet granulation method is the preferred manufacturing method to achieve a solid dosage form with good pharmaceutical characteristics.

One process in wet granulation method is performed with high-shear granulator. A high-shear granulator consists of a cylindrical or conical mixing bowl, a three bladed impeller, a chopper,

an auxiliary chopper, a motor to drive the blades and a discharge pot. By either circulating hot or cool liquid or steam through the jacket, the mixing bowl is jacketed for heating or cooling the contents of the bowl as the case may be.

5 The present invention is an oral dosage form non-hydrophilized rivaroxaban with improved pharmaceutical characteristics by using high-shear granulation process as a part of wet granulation method.

SUMMARY OF INVENTION

10 The present invention relates to an immediate release solid oral composition comprising rivaroxaban and one or more acceptable excipients manufactured by using optimised high-shear granulation process.

Another object of the invention is the oral dosage form of the present invention for the treatment or prevention of atherothrombotic events, prevention of venous thromboembolism, prevention of stroke and systemic embolism, treatment and prevention of deep vein thrombosis or treatment and prevention of pulmonary embolism.

15 Another object of the invention is the oral dosage form comprising rivaroxaban in non-hydrophilized form which means rivaroxaban does not introduce into a solvent prior to further manufacturing processes. Manufacturing process without solvent has many challenges regarding rivaroxaban is poorly water-soluble drug. To overcome these problems some additional excipients should be used. In the present invention the excipients are selected
20 according to conventional manufacturing methods. Thus, critical manufacturing processes are improved.

Another object of the invention is to develop an oral dosage form with improved pharmaceutical properties. However, since the water-solubility of rivaroxaban is very low it is difficult to have an oral dosage form with improved bioavailability. Thus, critical
25 manufacturing processes are improved.

In another object of the embodiment, the pharmaceutically acceptable inert excipients comprise diluents, disintegrants, binders and solubilizers, lubricants, surfactants etc.

In yet another aspect of the embodiment, the granulation is wet granulation.

In yet another aspect of the embodiment, the granulation is high-shear granulation process.

The high-shear wet granulation process using high-shear granulator can be divided into 5 main stages includes;

1. Preparation of binder solution
- 5 2. Mixing the powders separately
3. Binder addition or addition of granulating liquid.
4. Wetting of powder and nucleation (kneeding)
5. Growth of granules and densification of the powder.

10 An advantage of high-shear granulation is that the process is completed within a short period of time. It does, however, need to be carefully controlled as the formulation can quickly progress from under- to overgranulated.

Kneading process is the part of granulation process after the completion of the addition of the binder solution. Kneading time is the critical parameter in wet granulation processes which determines the physical and chemical properties of the granule.

15 It is surprisingly found that solid oral dosage forms comprising non-hydrophilized rivaroxaban manufactured by using wet granulation especially high-shear granulation process has improved pharmaceutical properties through a specified kneading time in granulation step.

DETAILED DESCRIPTION OF THE INVENTION

20 The present invention provides a solid oral dosage form comprising non-hydrophilized rivaroxaban and pharmaceutically acceptable excipients manufactured by using a high-shear granulation process with a specified kneading time in granulation step. The rivaroxaban-containing particles of the present invention is easily incorporated into pharmaceutical dosage forms for oral administration to patients in need thereof.

25 At first, the manufacturing methods are investigated by using direct compression and slugging compression as the short and financially advantageous processes. The solid oral dosage forms are obtained and analysed for in-vitro dissolution. The parameters of dissolution analysis are defined as 900 ml pH 4.5 with 0.4% SLS, Pedal (USP App. II), 75 rpm.

Table 1: Dissolution results of drug products with dry manufacturing methods

Time, min.	Direct compression method	Slugging compression method
	Dissolution results, %	
5	33.5	28.4
10	49.7	46.4
15	59.5	55.8
20	65.6	62.1
30	73.5	70.5
45	80.4	77.6
60	86.5	82.0

Solid oral pharmaceutical dosage forms comprising rivaroxaban and pharmaceutically acceptable excipients manufactured by using the methods without a solvent is not convenient based on the dissolution results presented in the table 1.

- 5 Manufacturing method is determined as wet granulation method considering the dissolution results above. Particularly wetting stage is important as the rivaroxaban is a poor water-soluble drug. More particularly, granulation parameters should be optimized sensitively.

In one embodiment, the granulation process may result in enhanced granule consistency, improved workability of the final blend prior to solid oral dosage form. In this manufacturing process, rivaroxaban is dissolved in a solvent (hydrophilized) which means dosage form is expected to have improved dissolution results.

In an embodiment of the present invention, manufacturing steps are:

1. Rivaroxaban, surfactant and a specified amount of binder are dissolved in deionised water and mixed to obtain uniform solution.
- 15 2. Specified amount of filler, glidant, diluent and the remaining part of binder is mixed in a separate bowl.
3. The granulation solution prepared in step 1 is added on the powder mixture obtained in step 2 and granulation process is performed by using high-shear granulator.
4. Wet granules are dried to a specified moisture value and screened through a proper sieve.
- 20 5. Pharmaceutically acceptable amount of lubricant is added on the granules obtained in step 4 and mixed to obtain a uniform final blend.

6. Granules are used to get a pharmaceutically acceptable solid oral dosage forms.

In-vitro dissolution analysis is performed on solid oral dosage form in dissolution parameters defined above.

5 **Table 2:Dissolution results of drug product with wet granulation manufacturing method**

Time, min.	Formulation I
	Dissolution results, %
5	22.6
10	51.7
15	74.1
20	80.7
30	85.2
45	90.3
60	90.9

Unexpectedly, by using wet granulation method the dissolution results of the solid oral dosage form are not improved as intended.

In the details of the manufacturing method rivaroxaban is dissolved in deionized water with the pharmaceutically acceptable excipients. This process has various disadvantageous like, loss of solution comprising rivaroxaban, difficult to obtain a uniform blend. The blend obtained with wet granulation method was not uniform and its appearance was opaque which is not clear. Moreover, considering dissolution results it is recognized that dissolving rivaroxaban in binder solution makes a strong bound between rivaroxaban and binder which inhibits the release of rivaroxaban.

15 In another embodiment to overcome all the advantageous stated above, rivaroxaban is not dissolved in deionized water. Rivaroxaban is considered to be mixed with pharmaceutically acceptable excipients without a solvent which means it is in non-hydrophilized form.

In another embodiment of the present invention, manufacturing steps are:

1. Surfactant and a specified amount of binder are dissolved in deionised water and mixed to obtain uniform solution.
2. Specified amount of rivaroxaban, filler, glidant, diluent and the remaining part of binder is mixed in a separate bowl.
- 5 3. The granulation solution prepared in step 1 is added on the powder mixture obtained in step 2 and granulation process is performed by using high-shear granulator.
4. Wet granules are dried to a specified moisture value and screened through a proper sieve.
5. Pharmaceutically acceptable amount of lubricant is added on the granules obtained in step 4 and mixed to obtain a uniform final blend.
- 10 6. Granules are used to get a pharmaceutically acceptable solid oral dosage forms.

In-vitro dissolution analysis is performed on solid oral dosage form in dissolution parameters defined above.

Table 3: Dissolution results of drug product manufactured by using wet granulation manufacturing method

Time, min.	Formulation II
	Dissolution results, %
5	33.2
10	71.2
15	83.8
20	89.2
30	93.8
45	97.0
60	98.6

15

The dissolution results of the solid oral dosage forms obtained with the revised wet granulation method is as intended.

According to the present invention, a binder solution is added to the powder mixture of rivaroxaban and one or more pharmaceutically acceptable excipients, resulting in a granulation mixture. In particularly advantageous embodiments of the present invention, the binder solution is added to the blend with an optimized rate while the blend is subjected to high-shear granulation.

20

Within the context of the present invention, the binder may be, for example, hypromellose, cellulose or cellulose derivatives, povidone, starch, sucrose, polyethylene glycol, or mixtures thereof. The binder is dissolved in a solvent, for instance, water, an alcohol, or mixtures thereof. In particularly advantageous embodiments of the present invention, the binder solution is hypromellose dissolved in water.

In a preferred embodiment of the invention the filler is selected from the group consisting of lactose, microcrystalline cellulose, starch, pregelatinized starch, modified starch, calcium phosphate (dibasic and / or tribasic), calcium sulphate trihydrate or dihydrate, calcium carbonate, kaolin, cellulose, dextrose, dextrans, dextrin, sucrose, maltose, fructose, glucose, mannitol, maltol, sorbitol, xylitol, titanium dioxide (TiO₂) or the mixture thereof.

In a preferred embodiment of the invention the disintegrant is selected from the group consisting of calcium phosphate (dibasic and / or tribasic), sodium starch glycolate, croscopovidone, croscarmellose sodium and the mixture thereof.

In a preferred embodiment of the invention the surfactant is selected from the group consisting of alkylbenzene sulfonates, sodium lauryl sulphate, dialkyl sulfosuccinate, polyethylene glycol, sorbitan monoester, glycerol diester and the mixture thereof.

In a preferred embodiment of the invention the lubricant is selected from the group consisting of magnesium stearate, stearic acid, polyethylene glycol, sodium stearyl fumarate and the mixture thereof.

The critical step in the process of the present invention is the step 3, granulation step. Granulating the powder mixture with granulation or binder solution. In this step, kneading time after the completion of binder solution addition directly affects the physical and chemical properties of the granule. In the manufacturing methods of Formulation I and II, average kneading time in granulation was selected. However; granulation parameters should be optimised.

In the present invention, granulation method, kneading time in granulation step is optimised with multiple experiments. In these experiments, composition and manufacturing method for Formulation II are constant as defining the most proper granulation parameter; kneading time in granulation step.

Table 4: Optimization of Kneading Time through Formulation II by In-vitro Analysis

Time (min.)	Kneading time in Granulation Step			
	30 s.	1 min.	3 min.	5 min.
	In-vitro Dissolution Results in %			
5	41.9	38.6	30.1	38.8
10	77.9	82.2	69.4	58.4
15	88.2	92.0	86.7	65.2
20	91.0	94.8	89.1	69.6
30	94.1	97.8	92.0	74.9
45	96.2	99.8	93.7	80.3
60	97.1	101.0	94.6	83.5

Most proper dissolution results are obtained with a kneading time from 30 seconds to 3 minutes.

- 5 Further, Formulation II with optimized kneading time is subjected to bioequivalence study.

According to “Guideline on the Investigation on Bioequivalence” published by EMA, to establish bioequivalence of the test product with that of reference product, 90% Confidence Interval (CI) for the ratio (Test/Reference) of Least Square Means of the Ln transformed PK parameters (AUC_t and C_{max}) must fall between 80.00% to 125.00%.

10 Table 5: In-vivo

Pharmacokinetic Parameters	Test/Reference	90% CI Lower	90% CI Upper
Ln C_{max}	82.70%	70.45%	97.09%
Ln AUC_t	84.95%	78.31%	92.16%

**Bio-equivalence
study results**

15

PK parameters (AUC_t and C_{max}) are in line with the specifications based on Guideline on the Investigation on Bioequivalence.

- 20 Both in-vitro and in-vivo release profile of the drug comprising non-hydrophilized rivaroxaban and manufactured by wet granulation method in which high-shear granulator is used and the kneading time is optimized between 30 seconds to 3 minutes.

While the invention has been described with respect to the above specific embodiments, it should be recognized that various modifications and changes may be made to the invention by those skilled in the art which also fall within the scope of the invention as defined by the appended claims.

CLAIMS

1. An oral pharmaceutical formulation comprising rivaroxaban and pharmaceutically acceptable excipients wherein the dosage form is manufactured by using wet granulation method in which rivaroxaban is in non-hydrophilized form with an kneading time from 30
5 seconds to 3 minutes.
2. An oral pharmaceutical composition according to claim 1, the wet granulation method performed by using high-shear granulator.
3. An oral pharmaceutical composition according to claim 1, the composition is in the dosage form of tablet.
- 10 4. An oral pharmaceutical composition according to any of the preceding claims, wherein the pharmaceutically acceptable excipient is selected from the group comprising a lubricant, a binder, a disintegrant, a filler, a surfactant, lubricant and mixtures thereof.
- 15 5. An oral pharmaceutical composition according to claim 4, wherein binder is selected form the group comprising hypromellose, cellulose or cellulose derivatives, povidone, starch, sucrose, polyethylene glycol, or mixtures thereof.
6. An oral pharmaceutical composition according to claim 4, wherein disintegrant is selected form the group comprising calcium phosphate (dibasic and / or tribasic), sodium starch glycolate, croscopovidone, croscarmellose sodium and the mixture thereof.
- 20 7. An oral pharmaceutical composition according to claim 4, wherein filler is selected form the group comprising lactose, microcrystalline cellulose, starch, pregelatinized starch, modified starch, calcium phosphate (dibasic and / or tribasic), calcium sulphate trihydrate or dihydrate, calcium carbonate, kaolin, cellulose, dextrose, dextrans, dextrin, sucrose, maltose, fructose, glucose, mannitol, maltol, sorbitol, xylitol, titanium dioxide (TiO₂) or the mixture thereof.
- 25 8. An oral pharmaceutical composition according to claim 4, wherein surfactant is selected form the group comprising alkylbenzene sulfonates, sodium lauryl sulphate, dialkyl sulfosuccinate, polyethylene glycol, sorbitan monoester, glycerol diester and the mixture thereof.

9. An oral pharmaceutical composition according to claim 4, wherein surfactant is selected from the group comprising magnesium stearate, stearic acid, polyethylene glycol, sodium stearyl fumarate and the mixture thereof.

10. An oral pharmaceutical composition according to any of the preceding claims wherein it is indicated in the treatment of use as treatment to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation; for the treatment of deep vein thrombosis (DVT), pulmonary embolism (PE); for the reduction in the risk of recurrence of DVT and of PE; and for the prophylaxis of DVT, which may lead to PE in patients undergoing knee or hip replacement surgery.

11. Use of a pharmaceutical composition according to any of the preceding claims for producing a medicament for the prophylaxis and/or treatment of thromboembolic disorders.

12. Use of rivaroxaban for producing a solid, orally administrable pharmaceutical composition according to any of the preceding claims for the prophylaxis and/or treatment of thromboembolic disorders.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/TR2018/050699

A. CLASSIFICATION OF SUBJECT MATTER

A61K 31/5377 (2006.01)i; A61P 7/02 (2006.01)i; A61K 9/20 (2006.01)i; A61K 9/16 (2006.01)i

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B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

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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)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2017146709 A1 (MYLAN INC) 31 August 2017 (2017-08-31) Paragraph 23; examples 2,5; claim 1.	1-10
A	IN 781MUM2014 A (TORRENT PHARMACEUTICALS LTD) 25 September 2015 (2015-09-25) Claims 1,7,8.	1-10
A	WO 2010146179 A2 (KRKA TOVARNA ZDRAVIL D D NOVO MESTO) 23 December 2010 (2010-12-23) Page 17, lines 6-12; example 6	1-10



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:

- “A” document defining the general state of the art which is not considered to be of particular relevance
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Date of the actual completion of the international search

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/TR2018/050699

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: **11-12**
because they relate to subject matter not required to be searched by this Authority, namely:
(iv) methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).