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(54) **TABLETS FOR ORAL SUSPENSION CONTAINING RIVAROXABAN**

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(57) **ABSTRACT**

A tablet for oral suspension formulation suitable for reconstitution is disclosed. The tablet contains a disintegrant, a wetting agent, a lubricant and other excipients in selected amounts to provide fast disintegration and dissolution in water. Also disclosed is a method of treating a disease by administering to a subject in need thereof a tablet disclosed herein.

# TABLETS FOR ORAL SUSPENSION CONTAINING RIVAROXABAN

## FIELD OF THE INVENTION

**[0001]** This patent document discloses a novel formulation of rivaroxaban or its pharmaceutically acceptable salt, a method for its preparation and its use in medical therapy.

## BACKGROUND

**[0002]** Rivaroxaban is marketed in the United States by Janssen Pharmaceuticals, Inc., under the trade name XARELTO®, XARELTO is for the indication of reducing the risk of stroke and blood clots, treating blood clots in the veins, helping prevent blood clots, and also reducing the risk of serious heart problems, heart attack and stroke in people with coronary artery disease. XARELTO is an immediate release tablet. There are no liquid formulations of rivaroxaban commercially available and, as a result, pharmacists are often required to compound liquid formulations using crushed rivaroxaban tablets for pediatric patients and patients who cannot swallow tablets, for example, acutely ill medical patients who need medicine administered via an NG tube or gastric feeding tube. A need exists for an improved formulation of Rivaroxaban.

## SUMMARY

**[0003]** Tablets for oral suspension formulation described herein allows for convenient oral administration of Rivaroxaban. The formulation resolved the dose inaccuracy issue due to the crushed step and precipitation of big crushed particles in a suspension system, Furthermore, tablets for oral suspension do not require professionals to crush the tablet and can be dispersed in the vehicles to form suspension immediately before use, which is much convenient for patients and professionals. Moreover, the tablets for oral suspension formulation substantially improves the stability of the medication compared to the ready-to-use suspension.

**[0004]** An aspect of this patent document provides tablets for oral suspension formulation suitable for reconstitution with a pharmaceutically acceptable carrier to form a suspension. The formulation contains rivaroxaban or a pharmaceutically acceptable salt thereof, and excipients including for example disintegrant agent, lubricant, glidant, binder, wetting agent, and filler. The rivaroxaban tablets for oral suspension can disintegrate rapidly within about 3 minutes in 100 ml water at room temperature, and the reconstituted suspension can pass through mesh aperture of 710 μm, furthermore, the tablet provides an in vitro release of at least about 75% of the rivaroxaban within about 30 minutes under USP dissolution apparatus 2, in 900 ml of pH14.5 media (2.5 mg) or with 0.2% SLS (for 10 mg strength) or 0.4% SLS (for 15 mg and 20 mg strength) at 75 rpm stirring rate.

**[0005]** In some embodiments, rivaroxaban or a pharmaceutically acceptable salt is present ranging about 1 mg to about 50 mg in the tablet.

**[0006]** In some embodiments, rivaroxaban or a pharmaceutically acceptable salt is present ranging about 1% to about 30% in the tablet.

**[0007]** In some embodiments, the disintegrant agent is present ranging from about 5% to about 15% in the tablet.

**[0008]** In some embodiments, the ubricant is present ranging from about 0.5% to about 5% in the tablet.

**[0009]** In some embodiments, the glidant is present ranging from about 0.5% to about 3% in the tablet.

**[0010]** In some embodiments, the wetting agent is present ranging from about 0.1% to about 1% in the tablet.

**[0011]** In some embodiments, the binder is present ranging from about 1% to abort 8% in the tablet.

**[0012]** In some embodiments, the rivaroxaban or the pharmaceutically acceptable salt thereof and the wetting agent have a ratio ranging from about 20:0.1 to about 1:1 by weight.

**[0013]** In some embodiments, the rivaroxaban or the pharmaceutically acceptable salt thereof and the binder have a ratio ranging from about 20:0.5 to about 1:1 by weight.

**[0014]** In some embodiments, the disintegrant agent is selected from starch, crosslinked polyvinylpyrrolidone (crospovidone), crosslinked sodium carboxymethyl cellulose (croscarmellose sodium), the modified starch sodium starch glycolate and any combination thereof. In some embodiments, the disintegrant agent is crospovidone.

**[0015]** In some embodiments, the dosage form further contains a lubricant selected from the group consisting of magnesium stearate, stearic acid, sodium stearyl fumarate, and sodium lauryl sulfate, glyceryl palmitostearate, and any combination thereof. In some embodiments, the lubricant is sodium stearyl fumarate.

**[0016]** In some embodiments, the formulation further contains glidants including for example silicon dioxide, starch, talc and any combination thereof. In some embodiments, the glidant is silicon dioxide.

**[0017]** In some embodiments, the formulation further contains the wetting agent including for example sodium dodecyl sulfate (SDS) or sodium lauryl sulfate (SLS), poloxamers or pluronics, tween 80 and any combination thereof. In some embodiments, the wetting agent is sodium lauryl sulfate (SLS)

**[0018]** In some embodiments, the formulation further contains the binder including for example Polyvinylpyrrolidone (PVP), Hydroxypropyl methylcellulose (HPMC), hydroxypropyl cellulose (HPC) and any combination thereof. In some embodiments, the binder is Hydroxypropyl methylcellulose (HPMC).

**[0019]** In some embodiments, the formulation further contains a filler selected from the group consisting of sucrose, dextrose, mannitol, sorbitol, maltitol, starch, lactose, microcrystalline cellulose, and any combination thereof in about 10% to about 98% by weight of the tablet formulation. In some embodiments, the tiller is microcrystalline cellulose and lactose, with the ratio ranging from about 5:1 to about 1:5 by weight.

**[0020]** In some embodiments, the rivaroxaban or the pharmaceutically acceptable salt thereof has a D90 ranging from about 1 μm to about 50 μm prior to being mixed with the excipients.

**[0021]** In some embodiments, a dosage form can be manufacture via wet granulation, dry granulation, dry blending, melt granulation and fluid bed granulation approach. In some embodiments, a dosage form can be manufactured via wet granulation approach in high shear granulator.

**[0022]** In some embodiments, a dosage form can be manufacture via wet granulation by adding water in the powder in high shear granulator, the amount of water is 20% to 60% of that powder for granulation by weight.

**[0023]** In some embodiments, the rivaroxaban tablets for oral suspension can disintegrate rapidly within about 3

minutes in 100 ml water at room temperature, and the reconstituted suspension can pass through mesh aperture of 710 μm.

**[0024]** In some embodiments, the tablet provides an in vitro release of at least about 75% of the rivaroxaban within about 30 minutes under USP dissolution apparatus 2, in 900 ml of pH4.5 media (2.5 mg) or with 0.2% SLS (for 10 mg strength) or 0.4% SLS (for 15 mg and 20 mg strength) at 75 rpm stirring rate.

**[0025]** In some embodiments, the tablets for oral suspension formulation provides a release of rivaroxaban bioequivalent to XARELTO tablet of the same dose. In some embodiments, the suspension prepared from the tablet formulation provides a release of the rivaroxaban bioequivalent to a non-suspension dosage form (e.g. XARELTO tablet), which provides a therapeutically effective blood concentration of rivaroxaban.

**[0026]** Another aspect of the patent document provides a method of treating or prophylaxis or reducing the risk of a disease comprising administering the suspension described herein to a subject in need, wherein the disease is selected from the group consisting of stroke and systemic embolism in patients with nonvalvular atrial fibrillation, deep vein thrombosis (DVT), pulmonary embolism (PE), major cardiovascular events (cardiovascular (CV) death, myocardial infarction (MI) and stroke) in patients with chronic coronary artery disease (CAD) or peripheral artery disease (PAD).

## DETAILED DESCRIPTION

**[0027]** This document discloses a tablet formulation suitable for reconstitution with a pharmaceutically acceptable carrier to form a suspension oral dosage form of rivaroxaban. Advantages of the tablets for oral suspension formulation include avoiding tablet crushing, dose accuracy and better compliance for pediatric patients and patients who cannot swallow tablets in comparison with conventional immediate release non-suspension dosage forms.

**[0028]** Rivaroxaban is known as 5-chloro-N-[[(5S)-2-oxo-3-[4-(3-oxomorpholin-4-yl)phenyl]-1,3-oxazolidin-5-yl] methyl]thiophene-2-carboxamide. Rivaroxaban is insoluble in water. When crushed rivaroxaban tablets are simply added directly into water or other soft food, the compound tends to settle rapidly and cannot be easily redistributed and as such would potentially affect the dose accuracy delivered to a patient.

**[0029]** The tablets for oral suspension formulation disclosed herein effectively resolved the above issues. After reconstitution, the suspension enables easy and accurate dose for pediatric patients and patients who cannot swallow tablets, for example, acutely ill medical patients who need medicine administered via an NG tube or gastric feeding tube. Further, tablets for oral suspension formulation substantially improves the stability of the medication compared to the ready-to-use suspension. The table for oral suspension formulation described in this patent document are applicable to Rivaroxaban as well as salts, isomers, complexes, polymorphs, hydrates, esters and prodrugs thereof.

**[0030]** While the following text may reference or exemplify specific embodiments of a dosage form or a method of manufacturing the dosage from, it is not intended to limit the scope of the dosage form to such particular reference or examples. Various modifications may be made by those skilled in the art, in view of practical and economic considerations, such as the amount of individual excipients and the manufacturing condition.

**[0031]** The articles "a" and "an" as used herein refers to "one or more" or "at least one," unless otherwise indicated. That is, reference to any element or component of an embodiment by the indefinite article "a" or "an" does not exclude the possibility that more than one element or component is present.

**[0032]** The term "about" as used herein refers to the referenced numeric indication plus or minus 10% of that referenced numeric indication.

**[0033]** The term "active ingredient" or "active pharmaceutical ingredient" (API) refers to a compound (e.g. rivaroxaban) that can be used for treating a disorder or condition in a subject (e.g., a patient), or for preventing one or more symptoms of such disorder or condition in the subject.

**[0034]** The term "bioequivalence" or "bioequivalent" refers to two formulations, dosage forms, products, or compositions of an active ingredient having biological equivalence. It is generally considered bioequivalent if the 90% Confidence Interval ("CI") of the relative mean Cmax, AUC(0-t) and AUC(0-∞) of the test formulation to reference formulation (i.e., brand product) is within 80.0% to 125.0% in the fasting state of a tested subject.

**[0035]** The term "patient compliance" refers to the degree to which patient correctly follows medical advice.

**[0036]** The term "excipient" refers to any inert substance that may have specific functions to the active ingredient (e.g., filler agent, binder, lubricant, glidant). An excipient provides without limitation, bulk, consistency, stability, binding ability, lubrication, disintegrating ability, etc., to the formulation of an active ingredient. A "glidant" is a type of excipient. An excipient may function for multiple purposes.

**[0037]** The term "powder" as used herein refers to any composition or formulation which is dry and flowable. Non-limiting examples include granules, flakes, spheroids and other forms which can be readily prepared and mixed with an ingestible liquid to provide a desirable liquid suspension.

**[0038]** The term "wet granulation" refers to a process of using a liquid binder to lightly agglomerate the powder mixture.

**[0039]** The term "API" refer to active pharmaceutical ingredient, which is rivaroxaban or a pharmaceutically acceptable salt.

**[0040]** The term "release", "released", "releasing", and the like, when used in connection with a pharmaceutical compression or dosage form, refers to the process or the portion of the active ingredient that leaves the dosage form following contact with an aqueous environment. Unless otherwise indicated, the quantity of an active ingredient released from a dosage form is measured by dissolution testing in water as described in this invention. The results of the dissolution testing are reported as % (w/w) released as a function of time or as the release time. In some embodiments, complete release of an active ingredient occurs when at least 90% of the active ingredient has been released from the dosage form.

**[0041]** The term "immediate-release" refers to those which disintegration rapidly and/or get dissolved to release the medicaments or active ingredient.

**[0042]** The term "Cmax" or "peak plasma exposure", expressed in ng/mL, refers to the point of maximum concentration of drug in plasma.

**[0043]** The term "area under curve (AUC)" or "total plasma exposure", expressed in μg·hr/mL, refers to the total integrated area under plasma level time profile and expresses the total amount of the active ingredient that comes into systemic circulation after administration.

**[0044]** The term "D90" refers to the particle size corresponding to 90% of the cumulative undersize distribution by volume.

**[0045]** The term "pharmaceutically acceptable carrier" refers to an agent or a substance that enable an active ingredient or a composition thereof to be formulated as tablets, pills, dragees, capsules, liquids, gels, syrups, slurries, suspensions and the like, for administration to a subject in need. For example, the carrier can be water or an aqueous solution containing other excipients.

**[0046]** The term "subject" refers to a mammal, such as an animal or a human. Hence, the methods disclosed herein can be useful in human therapy and veterinary applications. In one embodiment, the subject is an animal. In another embodiment, the subject is a human.

**[0047]** The term "treat" or "treating" refers to attain or attaining a beneficial or desired result, such as a clinical result. In some embodiments, the beneficial or desired result is any one or more of the following: inhibiting or suppressing the onset or development of a condition, reducing the severity of the condition, reducing the number or severity of symptoms associated with the condition, increasing the quality of life of a patient suffering from the condition, decreasing the dose of another medication required to treat the condition, enhancing the effect of another medication a patient is taking for the condition, and prolonging the survival of a patient having the condition.

**[0048]** An aspect of the document provides tablets for oral suspension formulation suitable for reconstitution with a pharmaceutically acceptable carrier to form an oral suspension of rivaroxaban. The formulation includes:

**[0049]** Rivaroxaban, a pharmaceutically acceptable salt, an isomer, a complex, a polymorph, a hydrate, or an ester thereof:

**[0050]** Disintegrant agent present ranging from about 5% to about 15%

**[0051]** Lubricant agent present ranging from about 0.5% to about 5%

**[0052]** Glidant agent present ranging from about 0.5% to about 3%

**[0053]** Wetting agent present ranging from about 0.1% to about 1%

**[0054]** Binder present ranging from about 1% to about 8%

**[0055]** Filler ranging from about 10% to about 98% by weight

**[0056]** Wetting agent, having a ratio with rivaroxaban or the pharmaceutically acceptable salt ranging from about 20:0.1 to about 1:1 by weight.

**[0057]** Binder, having a ratio with rivaroxaban or the pharmaceutically acceptable salt ranging from about 20:0.5 to about 1:1 by weight.

**[0058]** In some embodiments. the pharmaceutically acceptable carrier is water or an aqueous solution containing one or more agents or excipients.

**[0059]** The rivaroxaban tablets for oral suspension can disintegrate rapidly within about 3 minutes (e.g. 160 seconds, 140 seconds, 120 seconds, 90 seconds, 60 seconds, or 30 seconds), within about 2 minutes (e.g. 100 seconds, 80 seconds. 60 seconds, or 30 seconds), or within about 1 minute (e.g. 30 seconds, 35 seconds, 40 seconds, 45 seconds, 50 seconds, or 55 seconds) in 100 ml water at room temperature, and the reconstituted suspension can pass through mesh aperture of 710 μm, furthermore, the tablet provides an in vitro release of at least about 75% of the rivaroxaban within about 30 minutes, within about 20 minutes, or within about 10 minutes under USP dissolution apparatus 2, in 900 ml of ph 4.5 media (2.5 mg) or with 0.2% SLS (for 10 mg strength) or 0.4% SLS (for 15 mg and 20 mg strength) at 75 rpm stirring rate.

**[0060]** In some embodiments, rivaroxaban or a pharmaceutically acceptable salt is present ranging from 1 mg to 50 mg. In some embodiments, the tablet includes 2.5-20 mg rivaroxaban or a pharmaceutically acceptable salt thereof.

**[0061]** In some embodiments, the rivaroxaban or a pharmaceutically acceptable salt is present ranging from about 1% to about 30%, from about 1.5% to about 25%, from about 1.8% to about 22%, or from about 2% to about 18% by weight.

**[0062]** In some embodiments, the disintegrant agent is present ranging from about 5% to about 15%, from about 5% to about 14%, from about 5% to about 13%, from about 6% to about 12%, from about 6% to about 11%, from about 6% to about 10% by weight.

**[0063]** In some embodiments, the lubricant agent is present ranging from about 0.2% to about 7%, from about 0.5% to about 5%, from about 1% to about 3%, from about 1.1% to about 2.5%, from about 1.3% to about 2.2% by weight,

**[0064]** In some embodiments, the glidant agent is present ranging from about 0.5% to about 3%, from about 0.6% to about 2%, from about 0.7% to about 1.5%, from about 0.8% to about 1.2% by weigh.

**[0065]** In some embodiments, the wetting agent is present ranging from about 0.1% to about 1.2%, from about 0.1% to about 1%, from about 0.2% to about 0.8%, from about 0.2% to about 0.6% by weigh.

**[0066]** In some embodiments, the binder is present ranging from about 1% to about 8%, from about 1% to about 3.5%, from about 1.5% to about 3.5%, from about 2% to about 3% by weigh.

**[0067]** In some embodiments, the rivaroxaban or the pharmaceutically acceptable salt thereof and the wetting agent have a ratio ranging from about 20:0.1 to about 1:1, from about 20:0.2 to about 2:1, from about 20:0.3 to about 3:1, from about 20:0.4 to about 4:1 by weight.

**[0068]** In some embodiments, the rivaroxaban or the pharmaceutically acceptable salt thereof and the binder have a ratio ranging from about 20:0.5 to about 1:1 by weight, from about 20:0.8 to about 1:1, from about 20:1 to about 1:1

**[0069]** In some embodiments, the disintegrant agent is selected from starch, crosslinked polyvinylpyrrolidone (crospovidone), crosslinked sodium carboxymethyl cellulose (croscarmellose sodium), the modified starch sodium starch glycolate and any combination thereof. In some embodiments, the disintegrant agent is crospovidone (Kollidon CL-F).

**[0070]** In some embodiments, the dosage form further contains a lubricant selected from the group consisting of magnesium stearate, stearic acid, sodium stearyl fumarate,

and sodium lauryl sulfate, glyceryl palmitostearate, and any combination thereof. In some embodiments, the lubricant is sodium stearyl fumarate.

**[0071]** In some embodiments, the formulation further contains glidants including for example silicon dioxide, starch, talc and any combination thereof. In some embodiments, the glidant is silicon dioxide.

**[0072]** In some embodiments, the wetting agent is selected sodium dodecyl sulfate (SLS) or sodium lauryl sulfate (SLS), poloxamers or pluronics, tween 80 and any combination thereof. In some embodiments, the wetting agent is sodium dodecyl sulfate (SLS).

**[0073]** In some embodiments, the binder is selected from Polyvinylpyrrolidone Hydroxypropyl methylcellulose (HPMC), hydroxypropyl cellulose (HPC) and any combination thereof. In some embodiments, the binder is Hydroxypropyl methylcellulose (HPMC).

**[0074]** In some embodiments, the formulation further contains a filler selected from the group consisting of sucrose, dextrose, mannitol, sorbitol, maltitol, starch, lactose, microcrystalline cellulose, and any combination thereof in about 10% to about 98%, from about 30% to about 95%, from about 45% to about 93%, from about 60% to about 90% by weight. In some embodiments, the filler is microcrystalline cellulose and lactose, with the ratio ranging from about 5:1 to about 1:5, from about 4:1 to about 1:2, from about 3:1 to about 1:1, from about 2:1 to about 1: 1 by weight.

**[0075]** In some embodiments, the tablet has an inner phase and an external phase. The inner phase includes rivaroxaban, hydroxypropyl methylcellulose, sodium lauryl sulfate, crosslinked polyvinylpyrrolidone (crospovidone), 70-95% of the total microcrystalline cellulose, and lactose monohydrate, while the external phase includes the remaining amount of microcrystalline cellulose, colloidal silicon dioxide and lubricant. In some embodiments, the ratio between the microcrystalline cellulose and the lactose monohydrate ranges from 1:1 to 2:1 or from 1.5-1.8:1 by weight. In some embodiments, substantially all of the lactose monohydrate is in the inner portion.

**[0076]** In some embodiments, the tablet by weight includes 1.0%-30.0% rivaroxaban, 1,0%-8.0% hydroxypropyl methylcellulose, 0.1-1% sodium lauryl sulfate, 5%-15. 0% crosslinked polyvinylpyrrolidone (crospovidone), 0.5%-3.0% colloidal silicon dioxide, 0.5%-5% lubricant (e.g. magnesium stearate or sodium stearvl fumarate), and filler (e.g. microcrystalline cellulose and the lactose monohydrate).

**[0077]** In some embodiments, the tablet by weight includes 1.5%-25.0% rivaroxaban, 1.0%-5.0% hydroxypropyl methylcellulose, 0.2-0.8% sodium lauryl sulfate, 6.0%12.0% crosslinked polyvinylpyrrolidone (crospovidone), 0.6%-2.0% colloidal silicon dioxide, 1.0%-3.0% sodium stearyl fumarate, and microcrystalline cellulose and the lactose monohydrate as filler.

**[0078]** In some embodiments, the tablet by weight includes 1.8%-22.0% rivaroxaban, 1.5%-3.5% hydroxypropyl methylcellulose, 0.2-0.8% sodium lauryl sulfate, 6.0%-12.0% crosslinked polyvinylpyrrolidone (crospovidone), 0.7%-4.5% colloidal silicon dioxide, 1.1%-2.5% sodium stearyl fumarate, and microcrystalline cellulose and the lactose monohydrate as filler.

**[0079]** In some embodiments, the tablet by weight includes 2.0%-18.0% rivaroxaban, 2.0%-3.0% hydroxypropyl methylcellulose, 0.2-0.6% sodium lauryl sulfate, 6.0%-10.0% crosslinked polyvinylpyrrolidone (crospovidone), 0.8%1.2% colloidal silicon dioxide, 1.3%-2.2% sodium stearvl fumarate, and microcrystalline cellulose and the lactose monohydrate as filler.

**[0080]** In some embodiments, the rivaroxaban or the pharmaceutically acceptable salt thereof has a D90 ranging from about 1 μm to about 50 μm, from about 2 um to about 40 um, from about 3 um to about 30 um, from about 4 um to about 20 um prior to being mixed with the excipients.

**[0081]** In some embodiments, a dosage form can be manufacture via wet granulation, dry granulation, dry blending, melt granulation and fluid bed granulation approach. In some embodiments, a dosage form can be manufactured via wet granulation approach in high shear granulator.

**[0082]** In some embodiments, a dosage form can be manufactured via wet granulation by adding from about 20% to about 60%, from about 30% to about 50% of water to the powder in high shear granulator.

**[0083]** The rivaroxaban tablets for oral suspension can disintegration rapidly within 3 minutes within about 2 minutes, within about 1 minutes when dispersing in the 100 ml water at room temperature.

**[0084]** The tablets for oral suspension formulation provide an in vitro release as measured by USP dissolution apparatus 2. In some embodiments, at least about 95%, at least about 90%, at least about 85%, at least about 80%, at least about 75%, at least about 65% or at least about 50% of 2.5 mg rivaroxaban is released in a pH4.5 medium within about 30 minutes, within about 20 minutes, within about 10 minutes at 75 rpm stirring rate

**[0085]** The tablets for oral suspension formulation provide an in vitro release as measured by USP dissolution apparatus 2. In some embodiments, at least about 95%, at least about 90%, at least about 85%, at least about 80%, at least about 75%, at least about 65% or at least about 50% of 10 mg rivaroxaban is released in a pH4.5 medium with 0.2% SLS within about 30 minutes, within about 20 minutes, within about 10 minutes at 75 rpm stirring rate

**[0086]** The tablets for oral suspension formulation provide an in vitro release as measured by USP dissolution apparatus 2. In some embodiments, at least about 95%, at least about 90%, at least about 85%, at least about 80%, at least about 75%, at least about 65% or at least about 50% of 15 mg or 20 mg rivaroxaban is released in a pH4.5 medium with 0.4% SLS within about 30 minutes, within about 20 minutes, within about 10 minutes at 75 rpm stirring rate

**[0087]** The tablets for oral suspension formulation can also provide a release of rivaroxaban bioequivalent to non-suspension formulation of rivaroxaban at the same dose. Examples of non-suspension formulation of rivaroxaban include rivaroxaban tablets. In some embodiments, the dose of rivaroxaban in the formulation is about 1 mg, 2.5 mg, 5 mg, 10 mg, 20 mg, 40 mg or 50 mg.

**[0088]** The suspension can be prepared from the above described tablets for oral suspension formulation by reconstitution or by mixing the necessary components in suitable means as long as the resulting suspension achieves a desirable profile for oral administration. For example, the suspension can be prepared by adding water to the above described tablets formulation containing suitable dosage of rivaroxaban or its salt and thoroughly mix the combined substances.

**[0089]** The tablets for oral suspension allow for accurate dose and easy administration. The tablets for oral suspension

formulation also have excellent stability compared to ready-to-use suspension. This is especially important for pediatric patients and patients who cannot swallow tablets, for example, acutely ill medical patients who need medicine administered via an NG tube or gastric feeding tube.

**[0090]** Another aspect of the patent document provides a method of preparing the above described formulation. The method generally includes:

Step 1 Dissolve wetting agent and partial binder (¼-½) in certain amount of water to form solution 1

Step 2 Pass internal phase excipient(including partial binder) through certain mesh and add them into high shear granulator

Step 3 Pre-mix the internal phase excipient before adding granulation liquid

Step 4 Add granulation fluid into excipient at certain speed while mixing

Step 5 After all the granulation liquid was added, the kneading step was added for certain time

Step 6 The wet mass pass through mill and then was dried in the fluid bed or oven under certain temperature

Step 7 The dried granule pass through mill with screen of certain orifice

Step 8 The screened granules mixed with external phase before compressed into tablets.

Step 9 The final blend was compressed into tablets of certain hardness.

**[0091]** In some embodiments, the tablet disclosed herein is prepared according to the following method:

Step 1 Dissolve sodium lauryl sulfate and ¼-½ of total amount of hydroxypropyl methylcellulose in water to form a solution;

Step 2 mix rivaroxaban, lactose monohydrate and the remaining amount of hydroxypropyl methylcellulose to obtain a mixture;

Step 3 pass the mixture of step 2 through mesh;

Step 4 mix the mixture of step 3 with 70-95% of microcrystalline cellulose and all crospovidone to prepare granules;

Step 5 add the solution from step 1 to the granules to obtain wet granules, dry the granules, and mix with lubricant and the remaining amount of microcrystalline cellulose, and colloidal silicon dioxide to obtain a blend, and compress the blend into tablets

**[0092]** In some embodiments, ¼ of the total amount of hydroxypropyl methylcellulose is used in step 1. In some embodiments, the particle size of crospovidone is Cl-F level.

**[0093]** Exemplary methods of preparation include dry powder blending, wet granulation, dry granulation by compaction/slugging, spray drying, hot melt extrusion, extrusion spheronization and fluidized bed granulation. As described above, in order to have good uniformity, the active ingredient and all the excipients in the powder formulation should have suitable particle size range and need to pass certain mesh before using, such as mesh 20, 40, 60, 80 or 100.

**[0094]** Another aspect of the patent document provides a method of treating or prophylaxis or reducing the risk of a disease comprising administering the suspension prepared from tablets described herein or the whole tablet to a subject in need, wherein the disease is selected from the group consisting of stroke and systemic embolism in patients with nonvalvular atrial fibrillation, deep vein thrombosis (DVT), pulmonary embolism (PE), major cardiovascular events (cardiovascular (CV) death, myocardial infarction (MI) and stroke) in patients with chronic coronary artery disease (CAD) or peripheral artery disease (PAD).

## EXAMPLES

### Example 1

**[0095]** Formulation compositions of rivaroxaban tablets with different types of disintegrants were prepared and shown in Table 1. The tablets were prepared by dry blend approach. The formulation with Kollidon CL-F has a short disintegration time.

TABLE 1

The composition of formulation with different types of disintegrants

| | 10 mg/tablet | | |
|---|---|---|---|
| Component | Formulation 1 | Formulation 2 | Formulation 3 |
| **Internal phase** | | | |
| Rivaroxaban | 10 | 10 | 10 |
| Croscarmellose Sodium | 10 | / | / |
| Sodium Starch Glycolate | / | 10 | / |
| Kollidon CL-F | / | / | 10 |
| Hypromellose | 1.5 | 1.5 | 1.5 |
| Microcrystalline Cellulose | 42.17 | 42.17 | 42.17 |
| Lactose Monohydrate | 33.73 | 33.73 | 33.73 |
| Colloidal Silicon Dioxide | 1.1 | 1.1 | 1.1 |
| Sodium Lauryl Sulphate | 0.5 | 0.5 | 0.5 |
| **External phase** | | | |
| Sodium Stearyl Fumarate | 2 | 9 | 2 |
| Microcrystalline Cellulose | 11.1 | 11.1 | 11.1 |
| Colloidal Silicon Dioxide | 1.1 | 1.1 | 1.1 |
| Total tablet weight | 113.2 | 113.2 | 113.2 |
| Disintegration time | 32 s | 28 s | 17 s |

### Example 2

**[0096]** The formulation with different levels of disintegrant (Kollidon CL-F) was prepared and shown in table 2.

TABLE 2

The composition of formulation with different levels of disintegrant

| | 10 mg/tablet | | |
|---|---|---|---|
| Component | Formulation 4 | Formulation 5 | Formulation 6 |
| **Internal phase** | | | |
| Rivaroxaban | 10 | 10 | 10 |
| Kollidon CL-F | 10 (8.8%) | 7 (6.18%) | 13 (11.5%) |
| Hypromellose | 1.5 | 1.5 | 1.5 |
| Microcrystalline Cellulose | 42.17 | 43.67 | 40.67 |
| Lactose Monohydrate | 33.73 | 35.23 | 32.23 |
| Colloidal Silicon Dioxide | 1.1 | 1.1 | 1.1 |

TABLE 2-continued

The composition of formulation with different levels of disintegrant

| Component | 10 mg/tablet Formulation 4 | Formulation 5 | Formulation 6 |
|---|---|---|---|
| Sodium Lauryl Sulphate | 0.5 | 0.5 | 0.5 |
| External phase | | | |
| Sodium Stearyl Fumarate | 9 | 2 | 2 |
| Microcrystalline Cellulose | 11.1 | 11.1 | 11.1 |
| Colloidal Silicon Dioxide | 1.1 | 1.1 | 1.1 |
| Total tablet weight | 113.2 | 113.2 | 113.2 |
| Disintegration time | 114 s | 108 s | 125 s |
| Dissolution (Q at 30 min) | 100.4% | 96.0% | 100.5% |

**[0097]** The process is as follows:

(1) Sodium Lauryl Sulphate and Hyprornellose were dissolved in water to form solution 1.

(2) The internal phase (Rivaroxaban, Lactose Monohydrate and Colloidal Silicon Dioxide) was mixed and sieved

(3) The above mixture was added into high sheer mixer and mixed for 3 min

(4) A wet granulation was carried out by adding solution 1 to the dry mixtures within 5 min.

(5) The wet granule was milled and dried in a fluid bed dryer

(6) The dry granule was milled and mixed with external phase

(8) The final blend was compressed into tablets with average hardness 40±5 N.

**[0098]** The disintegrant levels in the range 6.18% to 11.5% did not have any significant effect on the disintegration time and dissolution of tablet. However, the disintegration time of these formulation is too long (>100 s).

**[0099]** Formulation 4 were prepared with different processes as following:

Process 1: Half of binder was dissolved in granulation liquid while the other half was in the internal phase to form dry blend.

Process 2: All the of binder was in the internal phase to form dry blend.

Process 3: All the of binder was dissolved in granulation liquid.

TABLE 3

The process effect on tablet disintegration time and dissolution

| | Process 1 | Process 2 | Process 3 |
|---|---|---|---|
| Assay | 99.4% | 93.7% | 100.5% |
| Disintegration time | 33 s | 35 s | 114 s |
| Dissolution (Q at 30 min) | 99.7% | 92.9% | 100.4% |

**[0100]** Process 1 significantly shorten the integration time of the tablet compared to process 3 (33 s vs. 114 s). And the tablet with process 2 do not has an acceptable assay (93.7%).

Example 3

**[0101]** The formulation with different levels of binder (Hypromellose) was prepared and shown in table 4. The tablets were prepared by dividing binder into two parts, 0.75 mg binder was dissolved in granulation liquid and the rest binder was in the dry blend.

TABLE 4

The composition of formulation for different levels of binder

| Component | 20 mg/tablet Formulation 9 | Formulation 10 | Formulation 11 | Formulation 12 |
|---|---|---|---|---|
| Internal phase | | | | |
| Rivaroxaban | 20 | 20 | 2.0 | 20 |
| Kollidon CL-F | 10 | 10 | 10 | 10 |
| Hypromellose | 0 | 1 | 2 | 3.5 |
| Microcrystalline Cellulose | 40.74 | 40.26 | 39.65 | 38.74 |
| Lactose Monohydrate | 26.66 | 26.14 | 27.75 | 25.16 |
| Sodium Lauryl Sulphate | 0.6 | 0.6 | 0.6 | 0.6 |
| External phase | | | | |
| Sodium Stearyl Fumarate | 9 | 9 | 2 | 9 |
| Total tablet weight | 100 | 100 | 100 | 100 |
| Assay | 103.8% | 98.1% | 98.0% | 104.4% |
| Disintegration time (DT) | 22 s | 47 s | 62 s | 86 s |
| Dissolution (Q at 30 min) | 68.9% | 94.0% | 98.7% | 98.6% |

**[0102]** All the formulation has the acceptable DT (<90 s), and increasing binder amount in the formulation increase the disintegration time. However, without binder, formulation 9 does not have an acceptable dissolution profile (Q<75%). Therefore, the binder range in the formulation was between 1% -3.5%.

Example 4

**[0103]** The formulation with different ratio of filler (MCC and lactose monohydrate) was prepared and shown in table 5.

TABLE 5

The formulation composition of different ratio of MCC/Lactose Monohydrate

| | 20 mg/tablet | | | | |
|---|---|---|---|---|---|
| Component | Formulation 13 (1.96:1) | Formulation 14 (1.96:1) | Formulation 15 (1.54:1) | Formulation 16 (1:1) | Formulation 17 (1:1.54) |
| Internal phase | | | | | |
| Rivaroxaban | 20 | 20 | 20 | 20 | 20 |
| Kollidon CL-F | 10 | 10 | 10 | 10 | 10 |
| Hypromellose | 1 | 1 | 1 | 1 | 1 |
| Microcrystalline Cellulose(MCC) | 40.26 | 40.26 | 40.26 | 33.20 | 26.14 |
| Lactose Monohydrate | 26.14 | 26.14 | 26.14 | 33.20 | 40.26 |
| Sodium Lauryl Sulphate | 0.6 | 0.6 | 0.6 | 0.6 | 0.6 |
| External phase | | | | | |
| Sodium Stearyl Fumarate | 2 | 2 | 2 | 2 | 2 |
| Microcrystalline Cellulose | 11.1 | 11.1 | — | — | — |
| Colloidal Silicon Dioxide | — | 1.1 | — | — | — |
| Total tablet weight | 111.1 | 112.2 | 100 | 100 | 100 |
| Disintegration time (DT) | 52 s | 44 s | 64 s | 83 s | 103 s |
| Dissolution (Q at 30 min) | 99.25% | 99.25% | 98.0% | 97.3% | 95.6% |

**[0104]** The result showed external phase of MCC and Colloidal Silicon Dioxide (formulation 14) can shorten Disintegration time (44 s). The lower the ratio of MCC/Lactose Monohydrate, the longer DT is. The DT of tablet was 103 s when the MCC/Lactose ratio is 1:1.54 (formulation 17), which is not acceptable.

Example 5

**[0105]** The formulation with different types and levels of lubricant was prepared and shown in table 7. Magnesium Stearate is a hydrophobic lubricant and Sodium Stearyl Fumarate is a hydrophilic lubricant. The formulation 20 with Magnesium Stearate has a longer DT and the formulation with Sodium Stearyl Fumarate ranging 1.3%-2.2% do not show any difference in terms of DT and dissolution.

TABLE 6

The composition of different types and levels of lubricant

| | 10 mg/tablet | | | |
|---|---|---|---|---|
| Component | Formulation 20 | Formulation 21 | Formulation7 | Formulation 22 |
| Internal phase | | | | |
| Rivaroxaban | 10 | 10 | 10 | 10 |
| Kollidon CL-F | 10 | 10 | 10 | 10 |

TABLE 6-continued

The composition of different types and levels of lubricant

| | 10 mg/tablet | | | |
|---|---|---|---|---|
| Component | Formulation 20 | Formulation 21 | Formulation7 | Formulation 22 |
| Hypromellose E5 | 1.5 | 1.5 | 1.5 | 1.5 |
| Microcrystalline Cellulose | 42.17 | 42.17 | 42.17 | 42.17 |
| Lactose Monohydrate | 33.73 | 33.73 | 33.73 | 33.73 |
| Colloidal Silicon Dioxide | 1.1 | 1.1 | 1.1 | 1.1 |
| Sodium Lauryl Sulphate | 0.5 | 0.5 | 0.5 | 0.5 |
| External phase | | | | |
| Magnesium Stearate | 2 | / | / | / |
| Sodium Stearyl Fumarate | / | 1.5 | 2 | 2.5 |
| Microcrystalline Cellulose | 11.1 | 11.6 | 11.1 | 10.6 |
| Colloidal Silicon Dioxide | 1.1 | 1.1 | 1.1 | 1.1 |
| Total tablet weight | 113.2 | 113.2 | 113.2 | 113.2 |
| Disintegration time (DT) | 50 s | 31 s | 33 s | 31 s |
| Dissolution (Q at 30 min) | 100.4% | 101.1% | 99.7% | 98.8% |

Example 6

**[0106]** The formulation with different levels of Colloidal Silicon Dioxide was prepared and shown in table 6. All the formulations have acceptable DT, assay and dissolution profile. However, in the scale up, formulation 7 has a low assay (<90%) while formulation 23 without internal Colloidal Silicon Dioxide has a good assay (100.4%)

TABLE 7

The composition of different levels of Colloidal Silicon Dioxide

| | 10 mg/tablet | | | |
|---|---|---|---|---|
| Component | Formulation 7 | Formulation 18 | Formulation 19 | Formulation 23 |
| Internal phase | | | | |
| Rivaroxaban | 10 | 10 | 10 | 10 |
| Kollidon CL-F | 10 | 10 | 10 | 10 |
| Hypromellose E5 | 1.5 | 1.5 | 1.5 | 3 |
| Microcrystalline Cellulose | 42.17 | 42.72 | 42.44 | 42.17 |
| Lactose Monohydrate | 33.73 | 34.28 | 34.01 | 33.33 |
| Colloidal Silicon Dioxide | 1.1 | 0 | 0.55 | 0 |
| Sodium Lauryl Sulphate (SLS) | 0.5 | 0.5 | 0.5 | 0.5 |
| External phase | | | | |
| Sodium Stearyl Fumarate | 2 | 9 | 2 | 2 |
| Microcrystalline Cellulose | 11.1 | 11.1 | 11.1 | 11.1 |
| Colloidal Silicon Dioxide | 1.1 | 1.1 | 1.1 | 1.1 |
| Total tablet weight | 113.2 | 113.2 | 113.2 | 113.2 |
| Disintegration time (DT) | 33 s | 53 s | 45 s | 55 s |
| Dissolution (Q at 30 min) | 99.7% | 101.1% | 99.4% | 100.4% |

**[0107]** The process for formulation 23 is as following:
Step 1 Dissolve SLS and partial Hypromellose ES (¼) in certain amount of water to form solution 1
Step 2 Pass internal phase excipient through certain mesh and add them into high shear granulator
Step 3 Pre-mix the internal phase excipient before adding granulation liquid
Step 4 Add granulation fluid into excipient at certain speed while mixing
Step 5 After all the granulation liquid was added, the kneading step was added for certain time
Step 6 The wet mass pass through mill and then was dried in the fluid bed or oven under certain temperature
Step 7 The dried granule pass through mill with screen of certain orifice
Step 8 The screened granules were mixed with external phase before compressed into tablets.
Step 9 The final blend was compressed into tablets with average hardness 40±5 N

Example 7

**[0108]** The formulation with different strength of Rivaroxaban was prepared and shown in table 8. All the formulations have acceptable DT, assay and dissolution profile.

TABLE 8

The composition of formulation with different strength

| | mg/tablet | | | |
|---|---|---|---|---|
| Component | 2.5 | 10 | 15 | 20 |
| Internal phase | | | | |
| Rivaroxaban | 2.5 | 10 | 15 | 20 |
| Kollidon CL-F | 10 | 10 | 10 | 10 |
| Hypromellose | 3 | 3 | 3 | 3 |
| Microcrystalline Cellulose | 46.67 | 42.17 | 39.38 | 36.58 |
| Lactose Monohydrate | 36.33 | 33.33 | 31.12 | 28.92 |
| Sodium Lauryl Sulphate | 0.5 | 0.5 | 0.5 | 0.5 |
| External phase | | | | |
| Sodium Stearyl Fumarate | 2.0 | 2.0 | 2.0 | 2.0 |
| Microcrystalline Cellulose | 11.1 | 11.1 | 11.1 | 11.1 |
| Colloidal Silicon Dioxide | 1.1 | 1.1 | 1.1 | 1.1 |
| Total tablet weight | 113.2 | 113.2 | 113.2 | 113.2 |

**[0109]** While the invention has been disclosed in some detail by way of illustration and example for purposes of clarity of understanding, it is apparent to those in the art that various changes may be made and equivalents may be substituted without departing from the true spirit and scope of the invention. Therefore, the description and examples should not be construed as limiting the scope of the invention.

**1**. A tablet for oral suspension formulation, suitable for reconstitution with a pharmaceutically acceptable carrier to form a suspension, comprising

rivaroxaban or a pharmaceutically acceptable salt thereof, and

excipients comprising a disintegrant, a wetting agent, a hydrophilic lubricant and a binder;

wherein the excipients and their amounts in the tablet are so selected and configured that the tablet disintegrates within about 1 minute in 100 ml water at room temperature and a resulting suspension passes through mesh aperture of 710 μm, and the tablet provides an in vitro release of at least 75% of the rivaroxaban within about 30 minutes under United States Pharmacopeia (USP) dissolution apparatus 2, in 900 ml of pH 4.5 water medium comprising 0-0.4% sodium lauryl sulfate (SLS) at 75 rpm stirring rate,

wherein the disintegrant is crospovidone ranging from about 5% to about 15% by weight, the lubricant is sodium stearyl fumarate ranging from about 1% to about 3%, the binder ranges from 1% to about 3% by weight in the tablet,

wherein "about" as used herein includes the referenced numeric indication plus or minus 10% of that referenced numeric indication.

**2**. The tablet of claim **1**, wherein the rivaroxaban or the pharmaceutically acceptable salt is present in the amount ranging from about 1 mg to about 50 mg.

**3**. The tablet of claim **1**, wherein the disintegrant agent is present in the amount ranging from about 6% to about 10% in the tablet by weight.

**4**. (canceled)

**5**. The tablet of claim **1**, wherein the lubricant is present in the amount ranging from about 1.3% to about 2.2%.

**6**. The tablet of claim **1**, further comprising a glidant in the amount ranging from about 0.5% to about 3% in the tablet by weight.

**7**. The tablet of claim **6**, wherein the glidant is selected from the group consisting of silicon dioxide, starch and talc and any combination thereof.

**8**. The tablet of claim **1**, wherein the wetting agent of the tablet is present in the amount ranging from about 0.1% to about 1% in the tablet by weight.

**9**. The tablet formulation of claim **1**, wherein the binder is hypromellose.

**10**. (canceled)

**11**. The tablet of claim **1**, wherein the wetting agent is selected from the group consisting of sodium dodecyl sulfate (SDS), poloxamers, polysorbate 80 and any combination thereof.

**12**. The tablet of claim **1**, wherein the binder is selected from the group consisting of Polyvinylpyrrolidone (PVP), Hydroxypropyl methylcellulose (HPMC), hydroxypropyl cellulose (HPC) and any combination thereof.

**13**. The tablet of claim **1**, further comprising a filler comprising microcrystalline cellulose and lactose monohydrate, wherein the ratio between the microcrystalline cellulose and the lactose monohydrate ranges from about 1:1 to about 2:1 by weight.

**14**. (canceled)

**15**. The tablet of claim **1**, wherein the excipients and their amounts in the tablet are so selected that the tablet provides an in vitro release of at least 90% of the rivaroxaban within about 20 minutes under USP dissolution apparatus 2, in 900 ml of pH 4.5 water medium comprising 0-0.4% SLS at 75 rpm stirring rate.

**16**. The tablet of claim **1**, wherein the excipients and their amounts in the tablet are so selected that the tablet provides an in vitro release of at least about 90% of the rivaroxaban

within about 10 minutes under USP dissolution apparatus 2, in 900 ml of pH 4.5 water medium comprising 0-0.2% SLS at 75 rpm stirring rate, wherein the tablet comprises 2.5 or 10 mg of rivaroxaban.

**17**. The tablet of claim **1**, which is prepared according to the following:

(a) preparing a granulation liquid comprising the wetting agent and a first portion of the binder;

(b) mixing rivaroxaban or a pharmaceutically acceptable salt thereof with one or more excipients comprising a second portion of the binder and the disintegrant to prepare a dry mixture;

(c) mixing the granulation liquid and the dry mixture to obtain a wet granule and dry the wet granule to obtain a dry granule; and

(d) milling the dry granule and mixing the milled granule with an external phase comprising one or more additional excipients,

wherein the first portion of binder ranges from about ¼ to about ½ in the total amount of the binder.

**18**. The tablet of claim **17**, wherein the binder is hypromellose, the first portion is about ¼ of the total amount of the binder.

**19**. The tablet of claim **17**, wherein the granulation liquid of step (a) and the dry mixture of step (b) are substantially free from silicon dioxide.

**20**. A method of treating or reducing the risk of a disease comprising:

(a) preparing a suspension from the tablet of claim **1**; and

(b) administering the suspension to a subject in need thereof, wherein the disease is stroke or systemic embolism associated with nonvalvular atrial fibrillation, deep vein thrombosis (DVT), pulmonary embolism (PE), or myocardial infarction (MI) or stroke associated with with chronic coronary artery disease (CAD) or peripheral artery disease (PAD).

**21**. A method of preparing the tablet of claim **1**, comprising

(a) preparing a granulation liquid comprising a wetting agent and a first portion of binder;

(b) mixing rivaroxaban or a pharmaceutically acceptable salt thereof with one or more excipients comprising a second portion of the binder to prepare a dry mixture;

(c) mixing the granulation liquid and the dry mixture to obtain a wet granule and dry the wet granule to obtain a dry granule; and

(d) milling the dry granule and mixing the milled granule with one or more additional excipients,

wherein the first portion of binder ranges from about ¼ to about ½ in the total amount of the binder.

**22**. The tablet formulation of claim **1**, wherein the binder is present in the amount ranging from about 2% to about 3% by weight.

**23**. The tablet formulation of claim **1**, which is free from croscarmellose sodium.

**24**. The tablet formulation of claim **1**, which is free from magnesium stearate.

**25**. The tablet formulation of claim **1**, which is prepared by wet granulation.

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