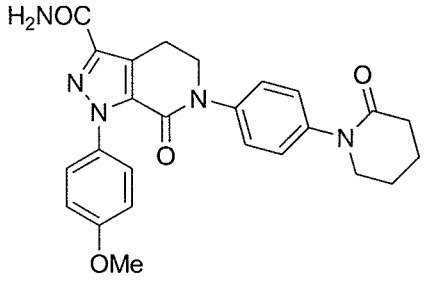
APIXABAN FORMULATIONS

FIELD OF THE INVENTION

[0001] This invention relates to apixaban pharmaceutical formulations comprising crystalline apixaban particles having a maximum size cutoff, and methods of using them, for example, for the treatment and/or prophylaxis of thromboembolic disorders.

BACKGROUND OF THE INVENTION

[0002] Apixaban is a known compound having the structure:



[0003] The chemical name for apixaban is 4,5,6,7-tetrahydro-1-(4-methoxyphenyl)-7-oxo-6-[4-(2-oxo-1-piperidinyl)phenyl]-1H-pyrazolo[3,4-c]pyridine-3-carboxamide (CAS name) or 1-(4-methoxyphenyl)-7-oxo-6-[4-(2-oxo-1-piperidinyl)phenyl]-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carboxamide (IUPAC name).

[0004] Apixaban is disclosed in U.S. Patent No. 6,967,208 (based on U.S. Application Serial No. 10/245,122 filed September 17, 2002), which is herein incorporated by reference in its entirety, has utility as a Factor Xa inhibitor, and is being developed for oral administration in a variety of indications that require the use of an antithrombotic agent.

[0005] The aqueous solubility (40 μg/mL at all physiological pH) of apixaban suggests that the tablets with less than 10 mg apixaban (dose/solubility ratio = 250 mL) should not demonstrate dissolution rate limited absorption since dissolution rate limitations are only expected when the dose/solubility ratio is greater than 250 mL. Based on this dose and solubility consideration, the particle size of the compound should not be critical for achieving consistent plasma profiles, according to the prediction based on the Biopharmaceutics Classification System (BCS; Amidon, G. L. et al., *Pharmaceutical Research*, 12: 413-420 (1995)). However, it was determined

that formulations that were made using a wet granulation process as well as those using large particles of apixaban drug substance resulted in less than optimal exposures, which can present quality control challenges.

SUMMARY OF THE INVENTION

[0006] Surprisingly and unexpectedly, it has been found that compositions for tablets comprising up to 5 mg, apixaban particles having a D_{90} (90% of the volume) less than 89 microns (μm) lead to consistent in-vivo dissolution in humans (at physiologic pH), hence, consistent exposure and consistent Factor Xa inhibition that will lead to consistency in therapeutic effect. Consistent exposure is defined as that where in-vivo exposure from tablets is similar to that from a solution and not affected by the differences in dissolution rates. The compositions were prepared using a dry granulation process. Accordingly, the invention provides a pharmaceutical composition comprising crystalline apixaban particles having a D_{90} equal to or less than about 89 μm as measured by laser light scattering method, and a pharmaceutically acceptable diluent or carrier. It is preferred that the apixaban particles in the composition have a D_{90} not exceeding 89 μm. It is noted the notation D_X means that X% of the volume of particles have a diameter less than a specified diameter D. Thus a D_{90} of 89 μm means that 90% of the volume of particles in an apixaban composition have a diameter less than 89 μm.

[0007] The range of particle sizes preferred for use in the invention is D_{90} less than 89 μm, more preferably D_{90} less than 50 μm, even more preferably D_{90} less than 30 μm, and most preferably D_{90} less than 25 μm. The particle sizes stipulated herein and in the claims refer to particle sizes were determined using a laser light scattering technique.

[0008] The invention further provides the pharmaceutical composition further comprising a surfactant from 0.25% to 2% by weight, preferably from 1% to 2% by weight. As regards the surfactant, it is generally used to aid in wetting of a hydrophobic drug in a tablet formulation to ensure efficient dissolution of the drug, for example, sodium lauryl sulfate, sodium stearate, polysorbate 80 and poloxamers, preferably sodium lauryl sulfate.

[0009] The invention further provides a method for the treatment or prophylaxis of thromboembolic disorders, comprising administering to a patient in need of such treatment or prophylaxis a therapeutically effective amount of a composition comprising crystalline apixaban particles having a D_{90} equal to or less than about 89 μm as measured by laser light scattering, and a pharmaceutically acceptable carrier.

[0010] The present invention also provides a dry granulation process for preparing a composition comprising crystalline apixaban particles having a D_{90} equal to or less than about 89 μm as measured by laser light scattering, and a pharmaceutically acceptable carrier.

[0011] The formulations of this invention are advantageous because, *inter alia*, as noted above, they lead to consistent human in-vivo dissolution. The invention is surprising in this respect, however, in that exposures are variable even though apixaban has adequate aqueous solubility that would allow the drug to dissolve rapidly. That is, one would expect dissolution rate for a drug that has high solubility (as defined by the Biopharmaceutical Classification System) would not be limited by the particle size. It has surprisingly been found, however, that the particle size that impacts apixaban absorption rate is about a D_{90} of 89 μm. Thus apixaban can be formulated in a composition having a reasonable particle size using dry granulation process, to achieve and maintain relatively fine particles to facilitate consistent in vivo dissolution.

[0012] In a relative bioavailabiltiy study where various apixaban formulations were evaluated, it was determined that formulations made using a wet granulation process resulted in lower exposures compared to the exposures obtained from a dry granulation process. Additionally, tablets made using larger particles (D_{90} of 89 μm) had lower exposures compared to tablets made using the same process but with particle size of D_{90} of 50 μm. In a dry granulation process, water is not used during manufacturing to develop granules containing apixaban and the excipients.

[0013] Formulations according to this invention, when dissolution tested in vitro preferably exhibit the following dissolution criteria. That is, the formulation exhibits dissolution properties such that, when an amount of the drug equivalent to 77% therein dissolves within 30 minutes. Usually the test result is established as an average for a pre-determined number of dosages (e.g., tablets, capsules, suspensions,

or other dosage form), usually 6. The dissolution test is typically performed in an aqueous media bufferred to a pH range (1 to 7.4) observed in the gastrointestinal tract and controlled at 37° C (±1°C), together maintaining a physilogical relevance. It is noted that if the dosage form being tested is a tablet, typically paddles rotating at 50 - 75 rpm are used to test the dissolution rate of the tablets. The amount of dissolved apixaban can be determined conventionally by HPLC, as hereinafter described. The dissolution (in-vitro) test is developed to serve as a quality control tool, and more preferably to predict the biological (invivo) performance of the tablet, where invivo-invitro relationships (IVIVR) are established.

[0014] The term "particles" refers to individual drug substance particles whether the particles exist singly or are agglomerated. Thus, a composition comprising particulate apixaban may contain agglomerates that are well beyond the size limit of about 89 μm specified herein. However, if the mean size of the primary drug substance particles (i.e., apixaban) comprising the agglomerate are less than about 89 μm individually, then the agglomerate itself is considered to satisfy the particle size constraints defined herein and the composition is within the scope of the invention.

[0015] Reference to apixaban particles having "a mean particle size" (herein also used interchangeably with "VMD" for "volume mean diameter") equal to or less than a given diameter or being within a given particle size range means that the average of all apixaban particles in the sample have an estimated volume, based on an assumption of spherical shape, less than or equal to the volume calculated for a spherical particle with a diameter equal to the given diameter. Particle size distribution can be measured by laser light scattering technique as known to those skilled in the art and as further disclosed and discussed below.

[0016] "Bioequivalent" as employed herein means that if a dosage form is tested in a crossover study (usually comprising a cohort of at least 10 or more human subjects), the average Area under the Curve (AUC) and/or the C_{max} for each crossover group is at least 80% of the (corresponding) mean AUC and/or C_{max} observed when the same cohort of subjects is dosed with an equivalent formulation and that formulation differs only in that the apixaban has a preferred particle size with a D_{90} in the range from 30 to 89 μm. The 30 μm particle size is, in effect, a standard against which other different formulations can be compared. AUCs are plots of serum

concentration of apixaban along the ordinate (Y-axis) against time for the abscissa (X-axis). Generally, the values for AUC represent a number of values taken from all the subjects in a patient population and are, therefore, mean values averaged over the entire test population. C.sub.max, the observed maximum in a plot of serum level concentration of apixaban (Y-axis) versus time (X-axis) is likewise an average value.

[0017] Use of AUCs, C_{max}, and crossover studies is, of course otherwise well understood in the art. The invention can indeed be viewed in alternative terms as a composition comprising crystalline apixaban particles having a mean particle size equal to or less than about 89 μm, as measured by Malvern light scattering, and a pharmaceutically acceptable carrier, said composition exhibiting a mean AUC and/or mean C_{max} which are at least 80% of the corresponding mean AUC and/or C_{max} values exhibited by a composition equivalent thereto (i.e., in terms of excipients employed and the amount of apixaban) but having an apixaban mean particle size of 30 μm. Use of the term "AUC" for purposes of this invention implies crossover testing within a cohort of at least 10 healthy subjects for all compositions tested, including the "standard" 30 μm particle size composition.

[0018] The present invention may be embodied in other specific forms without departing from the spirit or essential attributes thereof. Thus, the above embodiments should not be considered limiting. Any and all embodiments of the present invention may be taken in conjunction with any other embodiment or embodiments to describe additional embodiments. Each individual element of the embodiments is its own independent embodiment. Furthermore, any element of an embodiment is meant to be combined with any and all other elements from any embodiment to describe an additional embodiment. In addition, the present invention encompasses combinations of different embodiment, parts of embodiments, definitions, descriptions, and examples of the invention noted herein.

DETAILED DESCRIPTION OF THE INVENTION

[0019] As previously stated, apixaban in any form which will crystallize can be used in this invention. Apixaban may be obtained directly via the synthesis described in U.S. Pat. No. 6,967,208 and/or US20060069258A1 (based on U.S. Application Serial No. 11/235,510 filed September 26, 2005), herein incorporated by reference.

[0020] Form N-1 (neat) and Form H2-2 (hydrate) of apixaban may be characterized by unit cell parameters substantially equal to the following shown in Table 1.

Table 1

Form	N-1	H2-2
Solvate	None	Dihydrate
T	+22	+22
a(Å)	10.233(1)	6.193(1)
b(Å)	13.852(1)	30.523(1)
c(Å)	15.806(1)	13.046(1)
α,°	90	90
β,°	92.98(1)	90.95(1)
γ,°	90	90
V(Å^3)	2237.4(5)	2466.0(5)
Z'	1	1
Vm	559	617
SG	$P2_1/n$	$P2_1/n$
Dcalc	1.364	1.335
R	0.05	0.09
Sol.sites	None	2 H_2O

Z' is the number of molecules per asymmetric unit.

T(°C) is the temperature for the crystallographic data.

Vm = V(unit cell) / (ZZ')

[0021] Characteristic X-ray diffraction peak positions (degrees 2θ±0.1) at room temperature, based on a high quality pattern collected with a diffractometer (CuKα) with a spinning capillary with 2θ calibrated with a NIST suitable standard are shown in Table 2 below.

Table 2

Form N-1	Form H2-2
10.0	5.8
10.6	7.4
12.3	16.0
12.9	20.2
18.5	23.5
27.1	25.2

[0022] It will be appreciated by those skilled in the art of manufacturing and granulation processes that there are numerous known methods which can be applied to producing apixaban solid dosage forms. The feature of this invention, however, involves processes that produce apixaban dosage forms with an ability to produce primary particles at the site of dissolution with a d90<89 μm. Examples of such methods include as well as dry granulation or wet-granulation by low or high-shear techniques

[0023] The dry granulation process that produces crystalline apixaban particles having a mean particle size equal to or less than about 89 μm, is believed to be novel, and is accordingly provided as a further feature of the invention. Thus, the invention provides a drug product manufacturing process, comprising the steps:

(1) Blend the raw materials required prior to granulation;

(2) Granulate the raw materials from Step 1 using a dry or wet granulation process;

(3) Blend the sized granules from step 3 with extragranular raw materials;

(4) Compress the blend from Step 3 into tablets; and

(5) Film coat the tablets from step 4.

[0024] In another embodiment, the invention provides a drug product manufacturing process, comprising the steps:

(1) Blend the raw materials, with apixaban of controlled particle size;

(2) Include intragranular portions of binder, disintegrant and other fillers in the mix from step (1);

(3) Granulate the materials from step (2) using process (3a) or (3b):

(3a) DRY GRANULATION: Delump the intragranular lubricant using a suitable screen or mill. Add the lubricant to the blend from step (2)

and blend. Compact the lubricated blend to ribbons of density in the range of 1.0 to 1.2 g/cc and size the compacted ribbons using a roller compactor; or

(3b) WET GRANULATION: Wet granulate the composition from step (2) using water to a target end point and optionally, size the wet-granules by passing through a screen/mill. Remove water for granulation by drying in a convection oven or a fluid-bed dryer. Size the dried granules by passing through a screen/mill;

(4) Blend the sized granules from step (3) and the extragranular disintegrant in a suitable blender;

(5) Delump the extragranular lubricant using a suitable screen/mill and blend with granules from step (4);

(6) Compress the blend from (5) into tablets;

(7) Film coat the tablets from step (6).

[0025] In a preferred embodiment, a dry granulation process is employed.

[0026] In a preferred embodiment, the surfactant (SLS) in the composition serves as a wetting aid for inherently hydrophobic apixaban drug substance (contact angle=54° with water), further exacerbated as part of air-jet milling process that is used to reduce apixaban particle size to the desired size.

[0027] The amount of apixaban contained in a tablet, capsule, or other dosage form containing a composition of this invention will usually be between 2.5 and 5 mg, usually administered orally twice a day, although amounts outside this range and different frequencies of administration are feasible for use in therapy as well. As previously mentioned, such dosage forms are useful, *inter alia,* in the prevention and/or treatment of thromboembolic disorders, for example, deep vein thrombosis, acute coronary syndrome, stroke, and pulmonary embolism, as disclosed in U.S. Pat . No. 6,967,208.

[0028] As noted, average particle size can be determined by Malvern light scattering, a laser light scattering technique. In the examples below, the particle size for apixaban drug substance was measured using a Malvern particle size analyzer.

[0029] Upon measurement completion, the sample cell was emptied and cleaned, refilled with suspending medium, and the sampling procedure repeated for a total of three measurements.

[0030] The dissolution test is performed in 900 mL of dissolution medium at 37 °C, using USP Apparatus 2 (paddles) method at a rotation speed of 75 rpm. Samples are removed after 10, 20, 30, 45, and 60 minutes from test initiation and analyzed for apixaban by HPLC at 280 nm. 0.1 N HCl or 0.05 M sodium phosphate pH 6.8 with 0.05% SDS solution has been used as dissolution medium during formulation development. While both methods serve the purposes as quality control tests (with adequate discrimination ability), and in establishing IVIVR, the latter was preferred from the standpoint of method robustness. A role of SDS (surfactant) in the latter dissolution medium is as a wetting aid to facilitate complete dissolution of hydrophobic apixaban from tablets, rather than to increase the solubility of apixaban. Dissolution data from both the tests are included in this invention record and unless otherwise specified, the results reported were averages of values from six tablets.

[0031] Blood samples are drawn at predetermined time points following drug administration as specified in the clinical study protocol. Concentrations of the samples are measured using a validated analytical method (Liquid Chromatography with Tandem Mass Spectrometry). Individual subject pharmacokinetic parameters (eg, Cmax, AUC, T-HALF) are derived by non-compartmental methods using Kinetica® software from the time-concentration profiles.

[0032] The invention is further exemplified and disclosed by the following non-limiting examples:

[0033] Table 3 shows apixaban tablet compositions prepared using the drygranulation process that were evaluated in bioequivalence (BE) study.

Table 3

Ingredients	Dry Granulation	
	5% w/w Drug Loaded Granulation (% w/w)	20 mg Tablet (mg/tablet)
Intragranular		
Apixaban	5.00	20.00
Lactose Anhydrous	49.25	197.00
Microcrystalline Cellulose	39.50	158.00
Croscarmellose Sodium	2.00	8.00
Magnesium Stearate	0.50	2.00
Sodium Lauryl Sulfate	1.00	4.00
Extragranular		
Croscarmellose Sodium	2.00	8.00
Magnesium Stearate	0.75	3.00
Total	100.00 mg	400 mg
Film Coat	3.5	14.0
Total	103.5 mg	414 mg

[0034] Table 4 shows apixaban tablet compositions prepared using the wet granulation process that were evaluated in BE study.

Table 4

Ingredients	Wet Granulation	
	5% w/w Drug Loaded Granulation (% w/w)	20 mg Tablet (mg/tablet)
Intragranular		
Apixaban	5.00	20.00
Lactose Monohydrate	70.00	280.00
Microcrystalline Cellulose	5.00	60.00
Croscarmellose Sodium	2.50	10.00
Povidone	4.50	18.00
Purified Water	17.40	69.60
Extragranular		
Croscarmellose Sodium	2.50	10.00
Magnesium Stearate	0.50	2.09
Microcrystalline Cellulose	10.00	10.09
Total	100.00	400.00
Film Coat	3.5	14.0
Total	103.5 mg	414.0

[0035] Table 5 and Table 5a show the dissolution data that indicates that having a dry granulation process will result in faster dissolution compared to that from a wet granulation process. As shown in Table 5, the 20 mg tablets made using a dry granulation process had 79% apixaban dissolved in 30 minutes versus 62% apixaban dissolved at 30 minutes for the 20 mg tablets made using a wet granulation process. Dissolution test in 0.1N HCl also indicated a similar behavior of faster dissolution from tablets made using dry granulation process (58% in 30min), compared to wet granulation process (45% in 30min).

Table 5

Time (minutes)	% apixaban dissolved (USP II, 75 rpm, 0.05% SLS in 50mM phosphate, pH 6.8)	
	Wet Granulation 20 mg Tablets	Dry Granulation 20 mg Tablets
10	38	47
20	54	70
30	62	79
45	71	86
60	76	90
API Particle Size D_{90} (µm)	83.8	83.8

Table 5a

Time (minutes)	% apixaban dissolved (USP II, 75 rpm, 0.1N HCl)	
	Wet Granulation 20 mg Tablets	Dry Granulation 20 mg Tablets
10	30	41
20	39	52
30	45	58
45	51	64
60	56	68
90	64	74
API Particle Size D_{90} (µm)	83.8	83.8

[0036] Table 6 and Table 6a provides the dissolution data from tablets made with different manufacturing pprocesses (wet and dry granulation) and drug substance different particle sizes. As shown Table 6, apixaban tablets that had 77% dissolved in 30 minutes or 86% dissolved in 30 minutes both had AUC values that met

bioequivalence criteria (Confidence Interval between 80% to 125%) when compared to the tablets that had 89% dissolved at 30 minutes. Similar rank order of the dissolution rates were observed for these tablets (A, B & C) when tested in 0.1N HCl.

Table 6

Time (minutes)	% apixaban dissolved (USP II, 75 rpm, 0.05% SLS in 50mM phosphate, pH 6.8)		
	Wet Granulation 2 x 2.5 mg Tablets (A)	Wet Granulation 2 x 2.5 mg Tablets (B)	Dry Granulation 2 x 2.5 mg Tablets (C)
10	63	42	70
20	79	64	84
30	86	77	89
45	91	87	94
60	94	93	96
C_{max} (ng/mL)	101.8 (21)	87.8 (24)	108.3 (24)
AUC(INF) (ng*hr/mL)	1088 (32)	1030 (25)	1153 (26)

Geomean (CV%) are presented for Cmax and AUC(INF)

Table 6a

Time (minutes)	% apixaban dissolved (USP II, 75 rpm, 0.1N HCl)		
	Wet Granulation 2 x 2.5 mg Tablets (A)	Wet Granulation 2 x 2.5 mg Tablets (B)	Dry Granulation 2 x 2.5 mg Tablets (C)
10	44	25	56
20	62	43	71
30	72	54	79
45	80	66	85
60	84	74	88
AUC(INF) (ng*hr/mL)	1088 (32)	1030 (25)	1153 (26)

Geomean (CV%) are presented for Cmax and AUC(INF)

[0037] The results of clinical studies demonstrated that, for tablets with similar dissolution rates (89% and 86% at 30 min in pH 6.8 phosphate buffer containing 0.05% SLS), Cmax and AUC of the coated Phase 3 tablet (C) relative to the uncoated Phase 2 tablet (A), met bioequivalence criteria. Tablets with different dissolution rates (77% and 86% at 30 min) had similar AUCs, but did not meet equivalence criteria for Cmax. The lower boundary of the 90% confidence interval of ratio of

geometric mean Cmax was 0.788, indicating the rate of absorption, as defined by Cmax, was lower for the slower dissolving tablet (77% at 30 min). Since the oral bioavailability from these tablets is shown to be comparable to that from solution (see Figures 1 and 2 below), this dissolution rate (77% in 30min) is defined as the threshold for achieving consistent exposure.

[0038] Figures 3 and 4 illustrate the dissolution data that shows that while particle size impacts dissolution, controlling the particle size to less than 89 microns will result in a dissolution rate that will ensure consistent in-vivo exposures. As indicated in Figures 3 and 4, consistent exposures are expected once apixaban tablets have greater than 77% apixaban dissolved in 30 minutes. Since the tablets with 89 microns have >77% dissolved at 30 minutes, these tablets will also exhibit exposures that are equivalent to the exposures from tablets made with smaller particles (such as the tablets with 10 micron particles shown below). Whilst dissolution rate at an apixaban particle size of 119 microns is marginally greater than 77% in 30-min for the 5-mg apixaban tablets (Figure-4), the particle size threshold claimed is less than 89 microns. This allows for the typical variability (RSD=2 to 3%) in the dissolution results, such that the oral bioavailability from tablets consistently matches that from solution.

WHAT IS CLAIMED IS:

1. A composition comprising crystalline apixaban particles having a mean particle size equal to or less than about 89 μm and a pharmaceutically acceptable diluent or carrier.

2. A composition comprising crystalline apixaban particles having a mean particle size equal to or less than about 85 μm and a pharmaceutically acceptable diluent or carrier.

3. A composition as defined in claim 1 or claim 2, wherein said composition comprises Form N-1 of apixaban.

4. A composition as defined in claim 1, wherein particles with a D_{90} equal to or less than 89 μm.

5. A composition as defined in claim 2, wherein particles with a D_{90} equal to or less than 85 μm.

6. A composition as defined in any one of claims 1-5, wherein particles with a D_{90} equal to or less than 50 μm.

7. A composition as defined in any one of claims 1-5, wherein particles with a D_{90} equal to or less than 30 μm.

8. A composition as defined in any one of claims 1-5, wherein particles with a D_{90} equal to or less than 25 μm.

9. A composition as defined in claim 1 which exhibits an AUC and/or C_{max} that is at least 80% of the mean AUC and/or C_{max} observed for an equivalent formulation differing only in that the apixaban mean particle size is 89 μm.

10. A composition as defined in claim 1 which exhibits an AUC and/or C_{max} that is at least 80% of the mean AUC and/or C_{max} observed for an equivalent formulation differing only in that the apixaban mean particle size is 85 μm.

11. A composition as defined in any one of claims 1-10, further comprising:
from 1% to 2 % by weight of a surfactant.

12. A composition as defined in claim 11, wherein the surfactant is sodium lauryl sulfate.

13. A composition as defined in any one of claims 1-12 for use in treating a thromboembolic disorder.

14. Use of a composition as defined in any one of claims 1-12 in the treatment of a thromboembolic disorder.

15. Use of a composition as defined in any one of claims 1-12 in the preparation of a medicament for use in treating a thromboembolic disorder.

16. A process of manufacturing apixaban tablets having a composition as defined in any one of claims 1-12, comprising the steps of:

(1) blending raw materials prior to granulation;
(2) granulating the raw materials from the step (1) using a wet or dry granulation process;
(3) blending the granules obtained in the step (2) with extragranular raw materials;
(4) compressing the blend from the step (3) into tablets; and
(5) film coating the tablets from the step (4).

17. A process of manufacturing apixaban tablets having a composition as defined in any one of claims 1-12, comprising the steps of:

(1) blending raw materials with apixaban of controlled particle size to form a mix;

(2) adding intragranular portions of a binder, a disintegrant and at least one filler to the mix from the step (1) to form a blend;

(3) granulating the materials from the step (2) using a dry granulation process or a wet granulation process,

wherein the dry granulation process comprises:

delumping an intragranular lubricant using a screen or mill;

adding the intragranular lubricant to the blend from the step (2) and blending to form a lubricated blend;

compacting the lubricated blend to ribbons of density in a range of 1.1 to 1.2 g/cc and sizing the compacted ribbons using a roller compactor, and

wherein the wet granulation process comprises:

wet granulating the blend from the step (2) using water to a target end point and, optionally, sizing the wet-granules by passing through a screen or mill;

removing the water from the granulation by drying in a convection oven or a fluid-bed dryer; and

sizing the dried granules by passing through a screen or mill;

(4) blending the granules obtained in the step (3) and an extragranular disintegrant in a blender;

(5) delumping an extragranular lubricant using a screen or mill and blending with granules from the step (4);

(6) compressing the blend from the step (5) into tablets; and

(7) film coating the tablets from the step (6).

18. A process of manufacturing apixaban tablets according to claim 17, wherein the dry granulation process is used.