(19) DANMARK

(10) DK/EP 3251660 T3

(12) Oversættelse af europæisk patentskrift

Patent- og Varemærkestyrelsen

(51) Int.Cl.: *A 61 K 9/20 (2006.01)* *A 61 K 31/4545 (2006.01)* *A 61 P 7/02 (2006.01)*

(45) Oversættelsen bekendtgjort den: **2019-11-25**

(80) Dato for Den Europæiske Patentmyndigheds bekendtgørelse om meddelelse af patentet: **2019-10-16**

(86) Europæisk ansøgning nr.: **17175788.3**

(86) Europæisk indleveringsdag: **2011-02-24**

(87) Den europæiske ansøgnings publiceringsdag: **2017-12-06**

(30) Prioritet: **2010-02-25 US 308056 P**

(62) Stamansøgningsnr: **15190823.3**

(84) Designerede stater: **AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HR HU IE IS IT LI LT LU LV MC MK MT NL NO PL PT RO RS SE SI SK SM TR**

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(54) Benævnelse: **APIXABANFORMULERINGER**

(56) Fremdragne publikationer:
WO-A1-2008/031782
WO-A1-2010/147978
US-A1- 2006 160 841

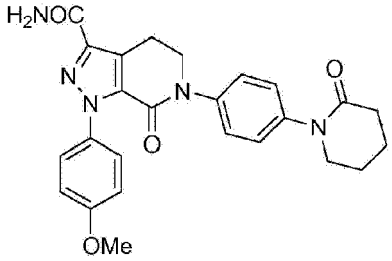
DESCRIPTION

FIELD OF THE INVENTION

[0001] This invention relates to apixaban tablets comprising crystalline apixaban particles having a maximum size cutoff, a process of their manufacturing and to said tablets for use in the treatment 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), 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. WO 2008/031782 A1 discloses a modified release pharmaceutical composition for oral administration comprising plural mini-tablets, comprising a therapeutically effective amount of a Factor Xa inhibitor.

[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), such as less than 50 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 tablet comprising a composition comprising up to 5 mg crystalline apixaban particles having a D_{90} less than 50 µm, as measured by laser light scattering, and further comprising a pharmaceutically acceptable diluent or carrier, wherein the composition is prepared using a dry granulation process. It is noted that 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 for use in the invention is D_{90} less than 50 µm, 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 that were determined using a laser light scattering technique.

[0008] The invention further provides the tablets as described above comprising a 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 the tablets according to the invention for use in the treatment of thromboembolic disorders.

[0010] The present invention also provides a dry granulation process for manufacturing apixaban tablets, wherein each tablet has a composition comprising up to 5 mg crystalline apixaban particles and a pharmaceutically acceptable diluent or carrier, comprising the steps of

1. (1) blending the raw materials required prior to granulation;
2. (2) granulating the raw materials from step (1) using a dry granulation process, wherein the apixaban particles have a D_{90} less than 50 µm as measured by laser light scattering;
3. (3) blending the sized granules from step (2) with extragranular raw materials;
4. (4) compressing the blend from step (3) into tablets; and

5. (5) film coating the tablets from step (4).

[0011] The tablets 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 that the 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 a dry granulation process, to achieve and maintain relatively fine particles to facilitate consistent in vivo dissolution.

[0012] In a relative bioavailability 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 a 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 is tested in vitro, preferably exhibit the following dissolution criteria. That is, the formulation exhibits dissolution properties such that 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 tablets, usually 6. The dissolution test is typically performed in an aqueous media buffered to a pH range (1 to 7.4) observed in the gastrointestinal tract and controlled at 37° C (±1°C), together maintaining a physiological 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 50 µm specified herein. However, if the mean size of the primary drug substance particles (i.e., apixaban) comprising the agglomerate is less than 50 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 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 tablets according to the invention comprise apixaban particles having a D_{90} less than 50 μm as measured by laser light scattering. 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. A tablet comprising a composition comprising crystalline apixaban particles having a mean particle size less than 50 μm, as measured by Malvern light scattering, and a pharmaceutically acceptable carrier exhibits 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; the tablets according to the invention comprise apixaban particles having a D_{90} less than 50 μm as measured by laser light scattering. 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.

DETAILED DESCRIPTION OF THE INVENTION

[0018] 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).

[0019] 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.

$Vm = V(\text{unit cell}) / (ZZ')$

[0020] 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

[0021] 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. Herein provided are processes that produce apixaban dosage forms with an ability to produce primary particles at the site of dissolution with a d90<89 µm; according to the invention the particles have a D_{90} less than 50 µm. Examples of such methods include dry granulation or wet-granulation by low or high-shear techniques, wherein the composition used in the tablets according to the invention is prepared using a dry granulation process.

[0022] The dry granulation process that produces crystalline apixaban particles having a mean particle size equal to or less than about 89 µm, with the proviso that the particles have a D_{90} less than 50 µm, is believed to be novel, and is accordingly provided as a further feature of the invention. Thus, the invention provides a process of manufacturing apixaban tablets, wherein each tablet has a composition comprising up to 5 mg crystalline apixaban particles and a pharmaceutically acceptable diluent or carrier, comprising the steps:

1. (1) Blend the raw materials required prior to granulation;
2. (2) Granulate the raw materials from step (1) using a dry granulation process, wherein the apixaban particles have a D_{90} less than 50 µm as measured by laser light scattering;
3. (3) Blend the sized granules from step (2) with extragranular raw materials;
4. (4) Compress the blend from step (3) into tablets; and
5. (5) Film coat the tablets from step (4).

[0023] Provided herein is a drug product manufacturing process, comprising the steps:

1. (1) Blend the raw materials, with apixaban of controlled particle size;
2. (2) Include intragranular portions of binder, disintegrant and other fillers in the mix from step (1);
3. (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 1.1 to 1.2 g/cm^3 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. (4) Blend the sized granules from step (3) and the extragranular disintegrant in a suitable blender;
5. (5) Delump the extragranular lubricant using a suitable screen/mill and blend with

granules from step (4);

6. (6) Compress the blend from (5) into tablets;
7. (7) Film coat the tablets from step (6).

[0024] According to the invention, the above dry granulation process including step (3a) is employed. The above alternative process using wet granulation step (3b) is not according to the invention.

[0025] 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 the air-jet milling process that is used to reduce the apixaban particle size to the desired size.

[0026] The amount of apixaban contained in the tablet of this invention will usually be between 2.5 and 5 mg, usually administered orally twice a day, although amounts outside this range but up to 5 mg, and different frequencies of administration are feasible for use in therapy as well. As previously mentioned, such tablet is 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.

[0027] 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.

[0028] 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.

[0029] 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 tests are included in this invention record and, unless otherwise specified, the results reported were averages of values from six tablets.

[0030] 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.

[0031] The invention is further exemplified and disclosed by the following examples:

[0032] Table 3 shows apixaban tablet compositions prepared using the inventive dry granulation process that were evaluated in bioequivalence (BE) study. Tablets comprising 20 mg of apixaban represent reference Examples.

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

[0033] Table 4 shows apixaban tablet compositions prepared using the comparative 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	5.00	60.00

Ingredients	Wet Granulation	
	5% w/w Drug Loaded Granulation (% w/w)	20 mg Tablet (mg/tablet)
Intragranular		
Cellulose		
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

[0034] 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 in 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

[0035] Table 6 and Table 6a provide the dissolution data from tablets made with different manufacturing processes (wet granulation (comparative process) and dry granulation (inventive process)) and drug substance different particle sizes. As shown in 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 in 30 minutes. Similar rank order of the dissolution rates was 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
Cmax (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)			

[0036] The results of clinical studies demonstrated that, for tablets with similar dissolution rates (89% and 86% in 30 min at 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% in 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 that the rate of absorption, as defined by Cmax, was lower for the slower dissolving tablet (77% in 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.

[0037] 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 in 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 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.

REFERENCES CITED IN THE DESCRIPTION

This list of references cited by the applicant is for the reader's convenience only. It does not form part of the European patent document. Even though great care has been taken in

compiling the references, errors or omissions cannot be excluded and the EPO disclaims all liability in this regard.

Patent documents cited in the description

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- US24512202A [0004]
- WO2008031782A1 [0004]
- US20060069258A1 [0018]
- US23551005A [0018]

Non-patent literature cited in the description

- **AMIDON, G. L. et al.**Pharmaceutical Research, 1995, vol. 12, 413-420 [0005]

APIXABANFORMULERINGER

PATENTKRAV

1. Tablet, der omfatter en sammensætning, der omfatter op til 5 mg krystallinske apixabanpartikler, der har en D_{90} mindre end 50 µm som målt ved spredning med laserlys og endvidere omfatter et farmaceutisk acceptabelt fortyndingsmiddel eller en farmaceutisk acceptabel bærer, hvor sammensætningen tilberedes ved hjælp af en tørgranuleringsproces.

2. Tablet som defineret i krav 1, hvor sammensætningen omfatter Form N-1 af apixaban.

3. Tablet som defineret i krav 1 eller 2, hvor partiklerne har en D_{90} mindre end 30 µm eller en D_{90} mindre end 25 µm som målt ved spredning med laserlys.

4. Tablet som defineret i et hvilket som helst af kravene 1 til 3, hvor mængden af apixaban, der er indeholdt i tabletten, er:

   (a) mellem 2,5 og 5 mg; eller

   (b) 2,5 mg eller 5 mg.

5. Tablet som defineret i et hvilket som helst af kravene 1 til 4, hvor formuleringen opviser opløsningsegenskaber således at en mængde af lægemidlet tilsvarende mindst 77% opløses inden for 30 minutter, hvor opløsningstesten udføres i et vandmedium, der er buffereret til et pH-interval 1 til 7,4 og kontrolleret ved 37°.

6. Tablet som defineret i krav 5, hvor

   (a) resultatet etableres som et gennemsnit af 6 tabletter; og/eller

   (b) opløsningstesten udføres i 900 mL af opløsningsmedium, der indeholder 0,05 M natriumfosfat ved et pH 6,8 med 0,05% SDS ved 37°C ved anvendelse av en USP apparat 2 (padler) ved en rotationshastighed af 75 rpm og mønstrene analyseres for apixaban ved HPLC ved 280 nm.

7. Tablet som defineret i et hvilket som helst af kravene 1 til 6 til anvendelse i behandling af en tromboembolisk sygdom.

8. Proces til fabrikation af apixabantabletter, hvor hver tablet har en sammensætning, der omfatter op til 5 mg krystallinske apixabanpartikler og et farmaceutisk acceptabelt fortyndingsmiddel eller en farmaceutisk acceptabel bærer, hvilken proces omfatter trinnene med:

   (1) blanding af råmaterialerne, der kræves, forud for granulering;

   (2) granulering af råmaterialerne fra trin (1) ved hjælp af en tørgranuleringsproces, hvor apixabanpartiklerne har en D_{90} mindre end 50 µm som målt ved spredning med laserlys;

   (3) blanding af de dimensionerede granulater fra trin (2) med ekstragranulære råmaterialer;

   (4) komprimering af blandingen fra trin (3) til tabletter; og

   (5) filmbelægning af tabletterne fra trin (4).

9. Proces ifølge krav 8, hvor formuleringen opviser opløsningsegenskaber således at en mængde af lægemidlet tilsvarende mindst 77% opløses inden for 30 minutter, hvor opløsningstesten udføres i et vandmedium, der er buffereret til et pH-interval 1 til 7,4 og kontrolleret ved 37°.

10. Proces ifølge krav 9, hvor

   (a) resultatet etableres som et gennemsnit af 6 tabletter; og/eller

(b) opløsningstesten udføres i 900 mL af opløsningsmedium, der indeholder 0,05 M natriumfosfat ved et pH 6,8 med 0,05% SDS ved 37°C ved anvendelse av en USP apparat 2 (padler) ved en rotationshastighed af 75 rpm og mønstrene analyseres for apixaban ved HPLC ved 280 nm.

11. Proces til fabrikation af apixabantabletter som defineret krav 8, hvilken proces omfatter trinnene med:

(1) blanding af råmaterialerne, med apixaban af kontrolleret partikelstørrelse;

(2) tilsætning af intragranulære portioner af et bindemiddel, et desintegrationsmiddel og andre fyldemidler til blandingen fra trin (1);

(3) granulering af materialerne fra trin (2) ved hjælp af en tørgranuleringsproces, der omfatter:

(a) fjernelse af klumper i et intragranulært smøremiddel ved hjælp af en passende sigte eller kværn;

(b) tilsætning af smøremidlet til blandingen fra trin (2) og blanding;

(c) komprimering af den smurte blanding til bånd med en tæthed, der ligger i intervallet fra 1,1 til 1,2 g/cm^3 og dimensionering af de komprimerede bånd ved hjælp af en trykvalse;

(4) blanding af de dimensionerede granulater fra trin (3) og det ekstragranulært disintegrationsmiddel i en passende blender;

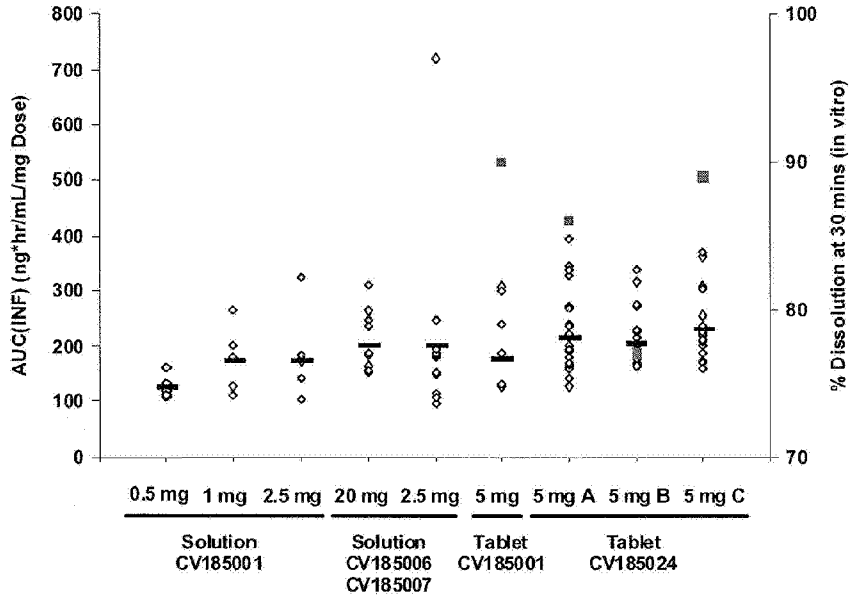
(5) fjernelse af klumper i det ekstragranulære smøremiddel ved hjælp af en passende sigte/kværn og blanding med granulaterne fra trin (4);

(6) komprimering af blandingen fra (5) til tabletter;

(7) filmbelægning af tabletterne fra trin (6).

DRAWINGS

Figure 1: Scatter Plot of Individual Dose-Normalized AUC(INF) Values for Solutions (CV185001, CV185006, and CV185007) and Tablets (CV185001 and CV185024)

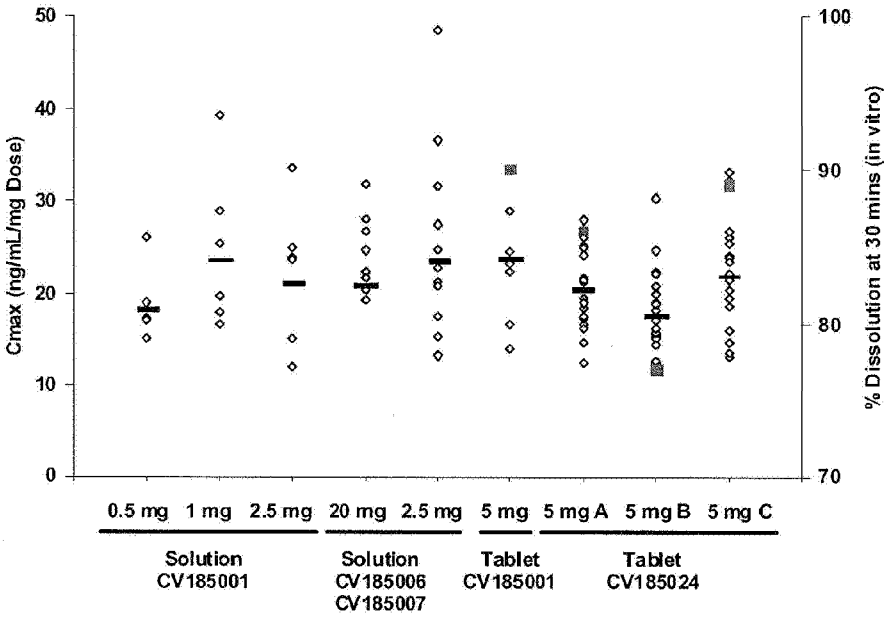


Source: CV185001, CV185006, CV185007, and CV185024 Clinical Study Reports

The solid line represents the geometric mean of AUC(INF) and the solid square represents the average %in-vitro dissolved at 30 minutes (using QC method in Table 1.2C). The X-axis represents the dose administered.

For CV185024, 5 mg A = Apixaban Phase 2 tablet (86% dissolution) 2x2.5 mg (reference formulation), 5 mg B = Apixaban Phase 2 tablet (77% dissolution) 2x2.5 mg, 5 mg C = Apixaban Phase 3 tablet (89% dissolution) 2x2.5 mg.

Figure 2: Scatter Plot of Individual Dose Normalized Cmax Values for Solutions (CV185001, CV185006, and CV185007) and Tablets (CV185001 and CV185024)



Source: CV185001, CV185006, CV185007, and CV185024 Clinical Study Reports

The solid line represents the geometric mean of Cmax and the solid square represents the average %in-vitro dissolved at 30 minutes (using QC method in Table 1.2C). The X-axis represents the dose administered.

For CV185024, 5 mg A = Apixaban Phase 2 tablet (86% dissolution) 2x2.5 mg (reference formulation), 5 mg B = Apixaban Phase 2 tablet (77% dissolution) 2x2.5 mg, 5 mg C = Apixaban Phase 3 tablet (89% dissolution) 2x2.5 mg.

Figure 3: Dissolution Rates of 2.5-mg Apixaban Tablets Using Drug Substance of Different Particle Size

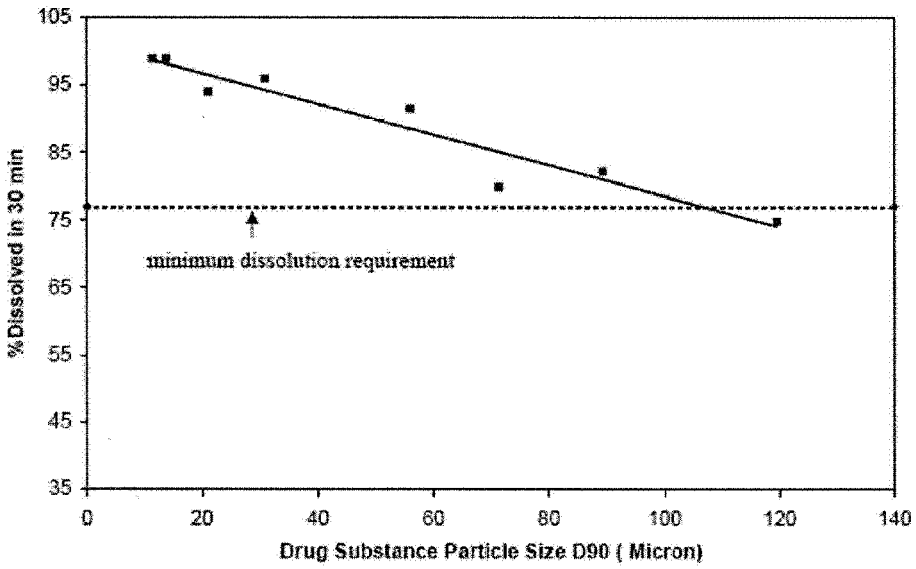


Figure 4: Dissolution Rates of 5-mg Apixaban Tablets Using Drug Substance of Different Particle Size