(19) DANMARK

(10) DK/EP 3257500 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.: **17178613.0**

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

(87) Den europæiske ansøgnings publiceringsdag: **2017-12-20**

(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**

(73) Patenthaver: **Bristol-Myers Squibb Holdings Ireland Unlimited Company, Hinterbergstrasse 16, 6312 Steinhausen, Schweiz**
Pfizer Inc, 235 East 42nd Street, New York, NY 10017, USA

(72) Opfinder: **PATEL, Jatin, c/o Bristol-Myers Squibb Company, Route 206 and Province Line Road, Princton, NJ New Jersey 08543, USA**
FROST, Charles, c/o Bristol-Myers Squibb Company, Route 206 and Province Line Road, Princton, NJ New Jersey 08543, USA
JIA, Jingpin, c/o Bristol-Myers Squibb Company, Route 206 and Province Line Road, Princton, NJ New Jersey 08543, USA
VEMA-VARAPU, Chandra, c/o Bristol-Myers Squibb Company, Route 206 and Province Line Road, Princton, NJ New Jersey 08543, USA

(74) Fuldmægtig i Danmark: **Marks & Clerk (Luxembourg) LLP, 44 rue de la Vallée, B.P. 1775, L-1017 Luxembourg, Luxembourg**

(54) Benævnelse: **APIXABANFORMULERINGER**

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

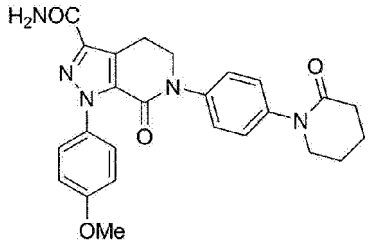
DESCRIPTION

FIELD OF THE INVENTION

[0001] This invention relates to apixaban compositions for tablets comprising crystalline apixaban particles having a maximum size cutoff, and to these compositions for use in treating thromboembolic disorders. The invention also relates to the process of manufacturing tablets having the above compositions.

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 oral modified release compositions comprising a plurality of mini-tablets comprising 5-10 mg of a Factor Xa inhibitor (such as apixaban). The mini-tablets are prepared by wet granulation. The dried granules are milled to achieve a D_{50} (median particle size) of 50 to 300 µm, for example 100-300 µm or 100-200 µm, they are combined with the remaining components, and they are compressed to tablets that are subsequently enteric coated. The enteric coat suitably comprises a surfactant (from 0.1 to 1% wt with respect to the total weight of the mini-tablet). The compositions are used for treating thromboembolism.

[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] The present invention provides a composition for tablets comprising crystalline apixaban particles having a mean particle size less than 89 µm and a D_{90} less than 89 µm as measured by laser light scattering, wherein the composition comprises up to 5 mg apixaban, a pharmaceutically acceptable diluent or carrier and a surfactant, wherein the surfactant is present in a concentration of 0.25% to 2% by weight and serves as a wetting aid for apixaban drug substance, wherein the composition is obtainable by a process comprising an air-jet milling process to reduce apixaban particle size to the desired size and dry granulation.

[0007] 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 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 according to the claims comprising crystalline apixaban particles having a D_{90} less than 89 µm as measured by laser light scattering method, and a pharmaceutically acceptable diluent or carrier. The apixaban particles in the composition have a D_{90} less than 89 µm. 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.

[0008] The range of particle sizes 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 that were determined using a laser light scattering technique.

[0009] The pharmaceutical composition of the invention further comprises 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.

[0010] The invention further provides the above composition for use in the treatment of thromboembolic disorders.

[0011] The present invention also provides a process of manufacturing apixaban tablets having a composition comprising crystalline apixaban particles having a mean particle size less than 89 µm and a D_{90} less than 89 µm as measured by laser light scattering, wherein the composition comprises up to 5 mg apixaban, a pharmaceutically acceptable diluent or carrier and a surfactant, wherein the surfactant is present in a concentration of 0.25% to 2% by weight and serves as a wetting aid for apixaban drug substance, wherein the process comprises the steps of:

1. (1) air-jet milling to reduce apixaban particle size to the desired size;
2. (2) blending raw materials prior to granulation;
3. (3) granulating the raw materials from step (2) using a dry granulation process;
4. (4) blending the granules obtained in the step (3) with extragranular raw materials;
5. (5) compressing the blend from the step (4) into tablets; and
6. (6) film coating the tablets from the step (5).

[0012] 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 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 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.

[0013] 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 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.

[0014] 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.

[0015] 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 89 µm specified herein. However, if the mean size of the primary drug substance particles (i.e., apixaban) comprising the agglomerate are less than 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.

[0016] 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.

[0017] "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.

[0018] 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 less than 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.

[0019] 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 embodiments, parts of embodiments, definitions, descriptions, and examples of the invention noted herein.

DETAILED DESCRIPTION OF THE INVENTION

[0020] 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).

[0021] 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

Form	N-1	H2-2
Solvate	None	Dihydrate
Sol.sites	None	$2H_2O$
Z' is the number of molecules per asymmetric unit. T(°C) is the temperature for the crystallographic data. Vm = V(unit cell) / (ZZ')		

[0022] 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

[0023] 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 dry granulation by low or high-shear techniques.

[0024] The dry granulation process that produces crystalline apixaban particles having a mean particle size less than 89 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 having a composition comprising crystalline apixaban particles having a mean particle size less than 89 µm and a D_{90} less than 89 µm as measured by laser light scattering, wherein the composition comprises up to 5 mg apixaban, a pharmaceutically acceptable diluent or carrier and a surfactant, wherein the surfactant is present in a concentration of 0.25% to 2% by weight and serves as a wetting aid for apixaban drug substance, wherein the process comprises the steps of:

1. (1) air-jet milling to reduce apixaban particle size to the desired size;
2. (2) blending raw materials prior to granulation;
3. (3) granulating the raw materials from step (2) using a dry granulation process;

4. (4) blending the granules obtained in the step (3) with extragranular raw materials;
5. (5) compressing the blend from the step (4) into tablets; and
6. (6) film coating the tablets from the step (5).

[0025] In another embodiment, the invention provides the above process comprising the steps of:

1. (1) air-jet milling to reduce apixaban particle size to the desired size;
2. (2) blending raw materials with apixaban of controlled particle size to form a mix;
3. (3) adding intragranular portions of a binder, a disintegrant and at least one filler to the mix from the step (2) to form a blend;
4. (4) granulating the materials from the step (3) using a dry 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 (3) 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/cm^3 and sizing the compacted ribbons using a roller compactor, and

5. (5) blending the granules obtained in the step (4) and an extragranular disintegrant in a blender;
6. (6) delumping an extragranular lubricant using a screen or mill and blending with granules from the step (5);
7. (7) compressing the blend from the step (6) into tablets; and
8. (8) film coating the tablets from the step (7).

[0026] 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 apixaban particle size to the desired size.

[0027] The amount of apixaban contained in a tablet 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 but up to 5 mg, and different frequencies of administration are feasible for use in therapy as well. As previously mentioned, such composition 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.

[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 nonlimiting examples:

[0033] Table 3 shows apixaban tablet compositions prepared using the 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

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

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 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

[0036] Table 6 and Table 6a provide the dissolution data from tablets made with different manufacturing processes (wet and dry granulation) 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. Tablets made by wet granulation represent reference Examples.

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% 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.

[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 µm 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 µm 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 µm particles shown below). Whilst dissolution rate at an apixaban particle size of 119 µm 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 µm. 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

- US6967208B **[0004] [0020] [0027]**
- US24512202A **[0004]**
- WO2008031782A1 **[0004]**
- US20060069258A1 **[0020]**
- US23551005A **[0020]**

Non-patent literature cited in the description

- **AMIDON, G. L. et al.**Biopharmaceutics Classification System (BCSPharmaceutical Research, 1995, vol. 12, 413-420 **[0005]**

APIXABANFORMULERINGER

PATENTKRAV

1. Sammensætning for tabletter, der omfatter krystallinske apixabanpartikler, der har en middelpartikelstørrelse mindre end 89 µm og en D_{90} mindre end 89 µm som målt ved spredning med laserlys, hvor sammensætningen omfatter op til 5 mg apixaban, et farmaceutisk acceptabelt fortyndingsmiddel eller en farmaceutisk acceptabel bærer og et overfladeaktivt middel, hvor det overfladeaktive middel er til stede i en koncentration på 0,25% til 2 vægtprocent og fungerer som befugtningsmiddel af lægemiddelsubstansen for apixaban, hvor sammensætningen kan opnås ved hjælp af en proces, der omfatter en luftstråle-fræsningsproces for at reducere apixabanpartikelstørrelsen til den ønskede størrelse og en tørgranuleringsproces.

2. Sammensætning som defineret i krav 1, hvor mængden af apixaban i tabletterne er 2,5 mg eller 5 mg eller mellem 2,5 og 5 mg.

3. Sammensætning som defineret i krav 1 eller 2, hvilken sammensætning omfatter krystallinske apixabanpartikler, der har en D_{90} mindre end 85 µm, krystallinske apixabanpartikler, der har en D_{90} mindre end 50 µm, krystallinske apixabanpartikler, der har en D_{90} mindre end 30 µm, eller krystallinske apixabanpartikler, der har en D_{90} mindre end 25 µm, som målt ved spredning med laserlys.

4. Sammensætning som defineret i et hvilket som helst af kravene 1 til 3, hvor sammensætningen omfatter Form N-1 af apixaban.

5. Sammensætning som defineret i et hvilket som helst af kravene 1 til 4, hvilken sammensætning omfatter fra 1 til 2 vægtprocent af det overfladeaktive middel.

6. Sammensætning som defineret i et hvilket som helst af kravene 1 til 5, hvor sammensætningen er en tablet, der 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°C.

7. Sammensætning som defineret i krav 6, 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.

8. Sammensætning som defineret i et hvilket som helst af kravene 1 til 6, hvor det overfladeaktive middel er natriumlaurylsulfate, natriumstearat, polysorbat 80 eller poloxamer.

9. Sammensætning som defineret i et hvilket som helst af kravene 1 til 8, hvor sammensætningen kan opnås ved hjælp af en proces, der omfatter trinnene med:

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

(2) granulering af råmaterialerne fra trin (1) ved hjælp af en tørgranuleringsproces;

(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).

10. Sammensætning som defineret i et hvilket som helst af kravene 1 til 9 til anvendelse i behandling af en tromboembolisk sygdom.

11. Proces til fabrikation af apixabantabletter, der har en sammensætning, der omfatter krystallinske apixabanpartikler, der har en middelpartikelstørrelse mindre end 89 µm og en D_{90} mindre end 89 µm som målt ved spredning med laserlys, hvor sammensætningen omfatter op til 5 mg apixaban, et farmaceutisk acceptabelt fortyndingsmiddel eller en farmaceutisk acceptabel bærer og et overfladeaktivt middel, hvor det overfladeaktive middel er til stede i en koncentration på 0,25% til 2 vægtprocent og fungerer som befugtningsmiddel af lægemiddelsubstansen for apixaban, hvor processen omfatter trinnene med:

(1) luftstråle-fræsning for at reducere apixabanpartikelstørrelsen til den ønskede størrelse;

(2) blanding af råmaterialer forud for granulering;

(3) granulering af råmaterialerne fra trin (2) ved hjælp af en tørgranuleringsproces;

(4) blanding af granulaterne opnået i trin (3) med ekstragranulære råmaterialer;

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

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

12. Proces til fabrikation af apixabantabletter ifølge krav 11, hvor processen omfatter trinnene med:

(1) luftstråle-fræsning for at reducere apixabanpartikelstørrelsen til den ønskede størrelse;

(2) blanding af råmaterialer med apixaban af kontrolleret partikelstørrelse for at danne en blanding;

(3) tilsætning af intragranulære portioner af et bindemiddel, et desintegrationsmiddel og mindst ét fyldemiddel til blandingen fra trin (2) for at danne en blanding;

(4) granulering af materialerne fra trin (3) ved hjælp af en tørgranuleringsproces;

hvor tørgranuleringsprocessen omfatter:

fjernelse af klumper i et intragranulært smøremiddel ved hjælp af en sigte eller kværn;

tilsætning af det intragranulære smøremiddel til blandingen fra trin (3) og blanding for at danne en smurt blanding;

komprimering af den smurte blanding til bånd med en tæthed, der ligger i et interval fra 1,1 til 1,2 g/cm^3 og

dimensionering af de komprimerede bånd ved hjælp af en trykvalse; og

(5) blanding af granulaterne opnået i trin (4) og et ekstragranulært disintegrationsmiddel i en blender;

(6) fjernelse af klumper i et ekstragranulært smøremiddel ved hjælp af en sigte eller kværn og blanding med granulater fra trin (5);

(7) komprimering af blandingen fra trin (6) til tabletter; og

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

13. Proces til fabrikation af apixabantabletter som defineret i krav 11 eller 12, hvor mængden af apixaban i tabletterne er 2,5 mg eller 5 mg eller mellem 2,5 og 5 mg.

14. Proces til fabrikation af apixabantabletter som defineret i et hvilket som helst af kravene 11 til 13, hvor tabletten 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°C.

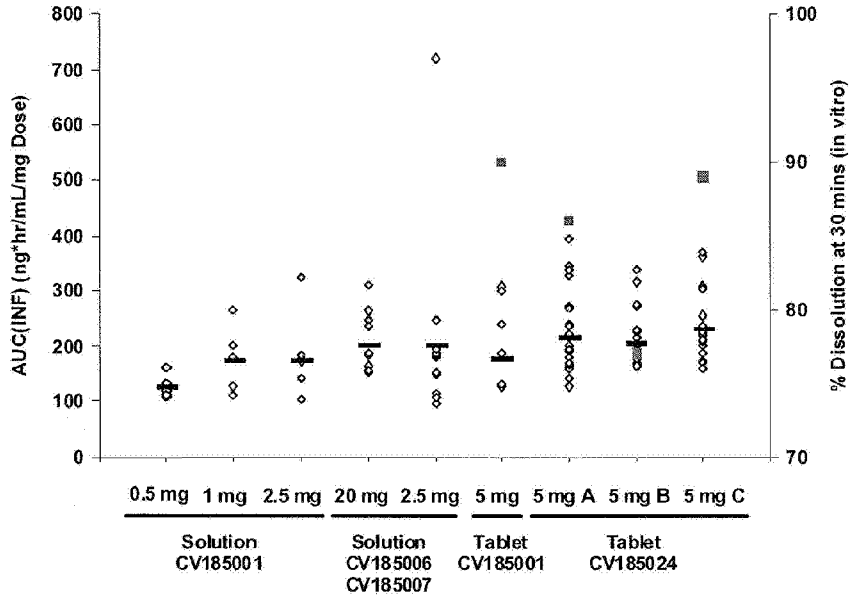
15. Proces til fabrikation af apixabantabletter som defineret i krav 14, hvor

(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.

DRAWINGS

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

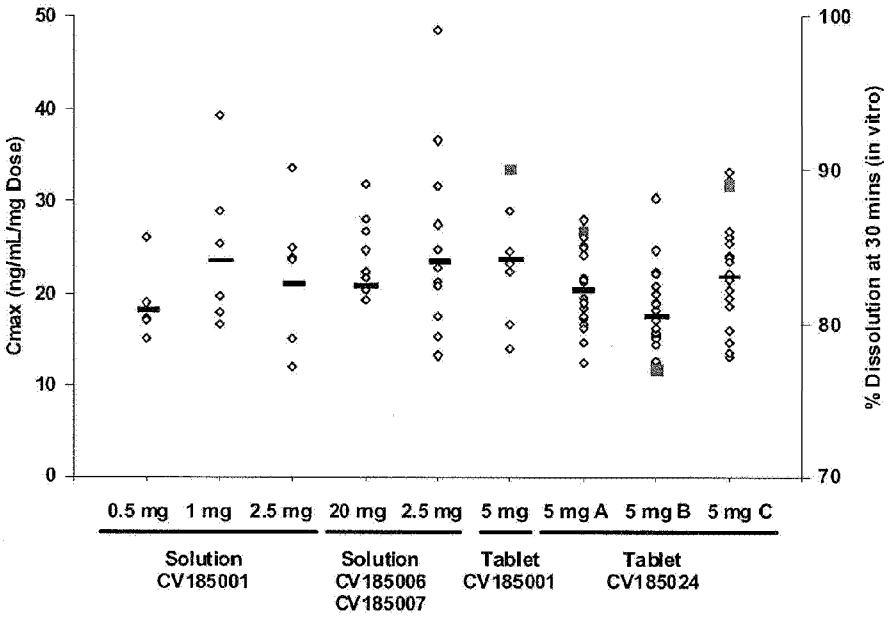


Source: CV185001, CV185006, CV185007, and CV185024 Clinical Study Reports

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

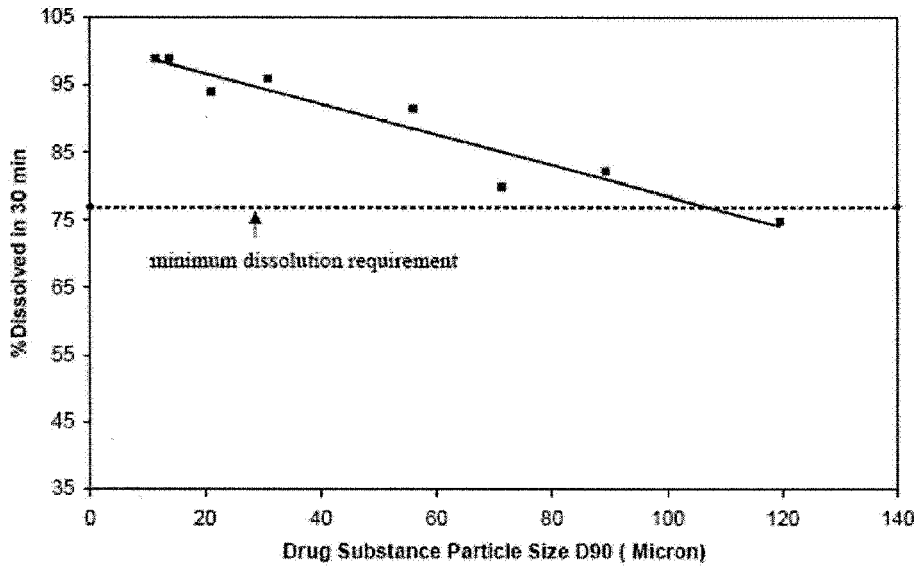


Figure 4: Dissolution Rates of 5-mg Apixaban Tablets Using Drug Substance of Different Particle Size