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(54) **APIXABAN FORMULATIONS**

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FORMULATIONS D'APIXABAN

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(56) References cited:
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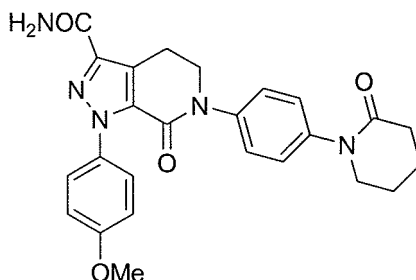
Description

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 $\mu\text{g/mL}$ 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 $89\text{ }\mu\text{m}$. 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 $89\text{ }\mu\text{m}$ means that 90% of the volume of particles in an apixaban composition have a diameter less than $89\text{ }\mu\text{m}$.

[0008] The range of particle sizes for use in the invention is D_{90} less than $89\text{ }\mu\text{m}$, more preferably D_{90} less than $50\text{ }\mu\text{m}$, even more preferably D_{90} less than $30\text{ }\mu\text{m}$, and most preferably D_{90} less than $25\text{ }\mu\text{m}$. 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 $89\text{ }\mu\text{m}$ and a D_{90} less than $89\text{ }\mu\text{m}$ 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) air-jet milling to reduce apixaban particle size to the desired size;
- (2) blending raw materials prior to granulation;
- (3) granulating the raw materials from step (2) using a dry granulation process;
- (4) blending the granules obtained in the step (3) with extragranular raw materials;
- (5) compressing the blend from the step (4) into tablets; and
- (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 $89\text{ }\mu\text{m}$. 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 $89\text{ }\mu\text{m}$) had lower exposures compared to tablets made using the same process but with particle size of D_{90} of $50\text{ }\mu\text{m}$. 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 ($\pm 1^\circ\text{C}$), 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 (in-vivo) performance of the tablet, where in-vivo-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 $89\text{ }\mu\text{m}$ specified herein. However, if the mean size of the primary drug substance particles (i.e., apixaban) comprising the agglomerate are less than $89\text{ }\mu\text{m}$ 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. $C_{\text{sub.max}}$, 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)
$\alpha, ^\circ$	90	90
$\beta, ^\circ$	92.98(1)	90.95(1)
$\gamma, ^\circ$	90	90
V(Å ³)	2237.4(5)	2466.0(5)
Z'	1	1
V _m	559	617
SG	P2 ₁ /n	P2 ₁ /n
D _{calc}	1.364	1.335
R	0.05	0.09

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(continued)

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

[0022] Characteristic X-ray diffraction peak positions (degrees $2\theta \pm 0.1$) at room temperature, based on a high quality pattern collected with a diffractometer (CuK α) 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 $d_{90} < 89 \mu\text{m}$. 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 $89 \mu\text{m}$ 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 $89 \mu\text{m}$ and a D_{90} less than $89 \mu\text{m}$ 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) air-jet milling to reduce apixaban particle size to the desired size;
- (2) blending raw materials prior to granulation;
- (3) granulating the raw materials from step (2) using a dry granulation process;
- (4) blending the granules obtained in the step (3) with extragranular raw materials;
- (5) compressing the blend from the step (4) into tablets; and
- (6) film coating the tablets from the step (5).

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

- (1) air-jet milling to reduce apixaban particle size to the desired size;
- (2) blending raw materials with apixaban of controlled particle size to form a mix;
- (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) 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;

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compacting the lubricated blend to ribbons of density in a range of 1.1 to 1.2 g/cm³ and sizing the compacted ribbons using a roller compactor, and

- (5) blending the granules obtained in the step (4) and an extragranular disintegrant in a blender;
- (6) delumping an extragranular lubricant using a screen or mill and blending with granules from the step (5);
- (7) compressing the blend from the step (6) into tablets; and
- (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, C_{max}, 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

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(continued)

Extragranular		
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

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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

(continued)

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)
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.

Claims

1. 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.
2. A composition as defined in claim 1, wherein the amount of apixaban in the tablets is 2.5 mg or 5 mg or between 2.5 and 5 mg.
3. A composition as defined in claim 1 or 2, comprising crystalline apixaban particles having a D_{90} less than 85 μm , crystalline apixaban particles having a D_{90} less than 50 μm , crystalline apixaban particles having a D_{90} less than 30 μm , or crystalline apixaban particles having a D_{90} less than 25 μm as measured by laser light scattering.
4. A composition as defined in any one of claims 1-3, wherein said composition comprises Form N-1 of apixaban.
5. A composition as defined in any one of claims 1-4, comprising from 1% to 2 % by weight of the surfactant.
6. A composition as defined in any one of claims 1-5, wherein the composition is a tablet which exhibits dissolution properties such that an amount of the drug equivalent to at least 77% dissolves within 30 minutes, wherein the dissolution test is performed in an aqueous media buffered to a pH range 1 to 7.4 and controlled at 37° C.
7. A composition as defined in claim 6, wherein
 - (a) the result is established as an average of 6 tablets; and/or
 - (b) the dissolution test is performed in 900 mL of dissolution medium containing 0.05 M sodium phosphate at

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pH 6.8 with 0.05% SDS at 37 °C using USP Apparatus 2 (paddles) at a rotation speed of 75 rpm and the samples are analyzed for apixaban by HPLC at 280 nm.

8. A composition as defined in any one of claims 1-6, wherein the surfactant is sodium lauryl sulfate, sodium stearate, polysorbate 80 or poloxamers.

9. A composition as defined in any one of claims 1 to 8, wherein the composition is obtainable by a process comprising the steps of:

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

10. A composition as defined in any one of claims 1-9 for use in treating a thromboembolic disorder.

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

12. A process of manufacturing apixaban tablets according to claim 11, wherein the process comprises the steps of:

- (1) air-jet milling to reduce apixaban particle size to the desired size;
- (2) blending raw materials with apixaban of controlled particle size to form a mix;
- (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) 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) blending the granules obtained in the step (4) and an extragranular disintegrant in a blender;
- (6) delumping an extragranular lubricant using a screen or mill and blending with granules from the step (5);
- (7) compressing the blend from the step (6) into tablets; and
- (8) film coating the tablets from the step (7).

13. A process of manufacturing apixaban tablets as defined in claim 11 or 12, wherein the amount of apixaban in the tablets is 2.5 mg or 5 mg or between 2.5 and 5 mg.

14. A process of manufacturing apixaban tablets as defined in one of claims 11 to 13, wherein the tablet exhibits dissolution properties such that an amount of the drug equivalent to at least 77% dissolves within 30 minutes, wherein the dissolution test is performed in an aqueous media buffered to a pH range 1 to 7.4 and controlled at 37° C.

15. A process of manufacturing apixaban tablets as defined in claim 14, wherein

- (a) the result is established as an average of 6 tablets; and/or
 (b) the dissolution test is performed in 900 mL of dissolution medium containing 0.05 M sodium phosphate at pH 6.8 with 0.05% SDS at 37 °C using USP Apparatus 2 (paddles) at a rotation speed of 75 rpm and the samples are analyzed for apixaban by HPLC at 280 nm.

Patentansprüche

1. Zusammensetzung für Tabletten, umfassend kristalline Apixaban-Teilchen mit einer durchschnittlichen Teilchengröße von weniger als 89 μm und einem D_{90} von weniger als 89 μm , wie gemessen durch Laserlichtstreuung, wobei die Zusammensetzung bis zu 5 mg Apixaban, ein pharmazeutisch verträgliches Verdünnungsmittel oder einen Träger und ein grenzflächenaktives Mittel umfasst, wobei das grenzflächenaktive Mittel in einer Konzentration von 0,25 Gew.-% bis 2 Gew.-% vorliegt und als ein Benetzungshilfsmittel für die Apixaban-Arzneimittelsubstanz dient, wobei die Zusammensetzung durch ein Verfahren erhältlich ist, das ein Luftstrahlmahlverfahren, um die Apixaban Teilchengröße zu der gewünschten Größe zu reduzieren und Trockengranulierung umfasst.
2. Zusammensetzung nach Anspruch 1, wobei die Menge an Apixaban, in den Tabletten 2,5 oder 5 mg, oder zwischen 2,5 mg und 5 mg beträgt.
3. Zusammensetzung nach Anspruch 1 oder 2, umfassend kristalline Apixaban-Teilchen mit einem D_{90} von weniger als 85 μm , kristalline Apixaban-Teilchen mit einem D_{90} von weniger als 50 μm , kristalline Apixaban-Teilchen mit einem D_{90} von weniger als 30 μm , oder kristalline Apixaban-Teilchen mit einem D_{90} von weniger als 25 μm , wie gemessen durch Laserlichtstreuung.
4. Zusammensetzung nach einem der Ansprüche 1 bis 3, wobei die Zusammensetzung die Form N-1 von Apixaban umfasst.
5. Zusammensetzung nach einem der Ansprüche 1 bis 4, umfassend von 1 Gew.-% bis 2 Gew.-% des grenzflächenaktiven Mittels.
6. Zusammensetzung nach einem der Ansprüche 1 bis 5, wobei die Zusammensetzung eine Tablette ist, die derartige Auflösungseigenschaften aufweist, dass sich eine Menge von mindestens 77% des Arzneimittels innerhalb von 30 Minuten auflöst, wobei der Auflösungstest in einem wässrigen Medium durchgeführt wird, das auf einen pH-Wert im Bereich von 1 bis 7,4 gepuffert wurde und bei 37°C belassen wird.
7. Zusammensetzung nach Anspruch 6, wobei
 - (a) das Ergebnis als Durchschnittswert aus 6 Tabletten bestimmt wird; und/oder
 - (b) der Auflösungstest in 900 mL eines Lösungsmittels durchgeführt wird, das 0,05 M Natriumphosphat bei pH 6,8 und 0,05 % SDS bei 37 °C enthält, wobei ein USP-Apparat 2 (Paddel) mit einer Drehzahl von 75 U/min verwendet wird und die Proben mittels HPLC bei 280 nm auf Apixaban hin analysiert werden.
8. Zusammensetzung nach einem der Ansprüche 1 bis 6, wobei das grenzflächenaktive Mittel Folgendes ist: Natriumlaurylsulfat, Natriumstearat, Polysorbat 80 oder Poloxamere.
9. Zusammensetzung nach einem der Ansprüche 1 bis 8, wobei die Zusammensetzung durch ein Verfahren erhalten wird, das die folgenden Schritte umfasst:
 - (1) Vermischen der notwendigen Rohmaterialien vor der Granulierung;
 - (2) Granulieren der Rohmaterialien aus Schritt (1) unter Verwendung eines Trockengranulierungsverfahrens;
 - (3) Vermischen der kalibrierten Granulate aus Schritt (2), mit extragranulären Rohmaterialien;
 - (4) Verpressen der Mischung aus Schritt (3) zu Tabletten; und
 - (5) Filmbeschichten der Tabletten aus Schritt (4).
10. Zusammensetzung nach einem der Ansprüche 1 bis 9, zur Verwendung bei der Behandlung einer thromboembolischen Erkrankung.
11. Verfahren zur Herstellung von Apixaban Tabletten, umfassend eine Zusammensetzung umfassend kristalline Api-

xaban-Teilchen mit einer durchschnittlichen Teilchengröße von weniger als 89 μm und einem D_{90} von weniger als 89 μm , wie gemessen durch Laserlichtstreuung, wobei die Zusammensetzung bis zu 5 mg Apixaban, ein pharmazeutisch verträgliches Verdünnungsmittel oder einen Träger und ein grenzflächenaktives Mittel umfasst, wobei das grenzflächenaktive Mittel in einer Konzentration von 0,25 Gew.-% bis 2 Gew.-% vorliegt und als ein Benetzungshilfsmittel für die Apixaban-Arzneimittelsubstanz dient, wobei das Verfahren die folgenden Schritte umfasst:

- (1) Luftstrahlmahlen, um die Größe der Apixaban-Teilchen zu der gewünschten Größe zu reduzieren,
- (2) Vermischen der Rohmaterialien vor der Granulierung,
- (3) Granulieren der Rohmaterialien aus Schritt (2) unter Verwendung eines Trockengranulierungsverfahrens
- (4) Vermischen der in Schritt (3) erhaltenen Granulate mit extragranulären Rohmaterialien;
- (5) Verpressen der Mischung aus Schritt (4) zu Tabletten; und
- (6) Filmbeschichten der Tabletten aus Schritt (5).

12. Verfahren zur Herstellung von Apixaban Tabletten nach Anspruch 11, wobei das Verfahren die folgenden Schritte umfasst:

- (1) Luftstrahlmahlen um die Größe der Apixaban-Teilchen zu der gewünschten Größe zu reduzieren,
- (2) Vermischen der Rohmaterialien mit Apixaban von kalibrierter Teilchengröße, um ein Gemisch zu bilden;
- (3) Hinzufügen von intragranulären Anteilen eines Bindemittels, eines Abbaumittels und mindestens eines Füllstoffs zu dem Gemisch aus Schritt (2), um eine Mischung zu bilden;
- (4) Granulieren der Materialien aus Schritt (3) unter Verwendung eines Trockengranulierungsverfahrens, wobei das Trockengranulierungsverfahren Folgendes umfasst:

Entklumpen eines intragranulären Schmiermittels unter Verwendung eines Siebes oder einer Mühle;
Hinzufügen des intragranulären Schmiermittels zu der Mischung aus Schritt (3) und Vermischen, um eine geschmierte Mischung zu bilden;
Verdichten der geschmierten Mischung zu Bändern mit einer Dichte in einem Bereich von 1,1 bis 1,2 g/cm³ und
Kalibrieren der verdichteten Bänder unter Verwendung eines Walzenverdichters, und

- (5) Vermischen der in Schritt (4) erhaltenen Granulate und eines extragranulären Abbaumittels in einem Mischer;
- (6) Entklumpen eines extragranulären Schmiermittels unter Verwendung eines Siebes oder einer Mühle und Vermischen mit Granulaten aus Schritt (5);
- (7) Verpressen der Mischung aus Schritt (6) zu Tabletten; und
- (8) Filmbeschichten der Tabletten aus dem Schritt (7).

13. Verfahren zur Herstellung von Apixaban Tabletten nach Anspruch 11 oder 12, wobei die Menge an Apixaban in den Tabletten 2,5 mg oder 5 mg, oder zwischen 2,5 mg und 5 mg beträgt.

14. Verfahren zur Herstellung von Apixaban Tabletten nach einem der Ansprüche 11 bis 13, wobei die Tablette, derartige Auflösungseigenschaften aufweist, dass sich eine Menge von mindestens 77% des Arzneimittels innerhalb von 30 Minuten auflöst, wobei der Auflösungstest in einem wässrigen Medium durchgeführt wird, das auf einen pH-Wert im Bereich von 1 bis 7,4 gepuffert wurde und bei 37°C belassen wird.

15. Verfahren zur Herstellung von Apixaban Tabletten nach Anspruch 14, wobei

- (a) das Ergebnis als Durchschnittswert aus 6 Tabletten bestimmt wird; und/oder
- (b) der Auflösungstest in 900 mL eines Lösungsmittels durchgeführt wird, das 0,05 M Natriumphosphat bei pH 6,8 und 0,05 % SDS bei 37 °C enthält, wobei ein USP-Apparat 2 (Paddel) mit einer Drehzahl von 75 U/min verwendet wird und die Proben mittels HPLC bei 280 nm auf Apixaban hin analysiert werden.

Revendications

1. Composition pour comprimés comprenant des particules cristallines d'apixaban ayant une taille moyenne inférieure à 89 μm et un D_{90} inférieur à 89 μm , tel que mesuré par diffusion de la lumière laser, dans laquelle la composition comprend jusqu'à 5 mg d'apixaban, un diluant ou support pharmaceutiquement acceptable et un tensioactif, le tensioactif étant présent à une concentration de 0,25% à 2% en poids et servant d'agent mouillant pour la substance

médicamenteuse d'apixaban, dans laquelle la composition peut être obtenue par un procédé comprenant un procédé de broyage à jet d'air pour réduire la taille des particules d'apixaban à la taille souhaitée et la granulation par voie sèche.

- 5 **2.** Composition selon la revendication 1, dans laquelle la quantité d'apixaban dans les comprimés est de 2,5 mg ou 5 mg ou entre 2,5 et 5 mg.
- 10 **3.** Composition selon la revendication 1 ou 2, comprenant des particules cristallines d'apixaban ayant un D_{90} inférieur à 85 μm , des particules cristallines d'apixaban ayant un D_{90} inférieur à 50 μm , des particules cristallines d'apixaban ayant un D_{90} inférieur à 30 μm , ou des particules cristallines d'apixabane ayant un D_{90} inférieur à 25 μm tel que mesuré par diffusion de la lumière laser.
- 15 **4.** Composition selon l'une quelconque des revendications 1 à 3, dans laquelle ladite composition comprend la forme N-1 d'apixaban.
- 20 **5.** Composition selon l'une quelconque des revendications 1 à 4, comprenant de 1% à 2% en poids du tensioactif.
- 25 **6.** Composition selon l'une quelconque des revendications 1 à 5, dans laquelle la composition est un comprimé qui présente des propriétés de dissolution telles qu'une quantité du médicament équivalente à au moins 77% se dissout en moins de 30 minutes, dans laquelle le test de dissolution est effectué dans un milieu aqueux tamponné à un pH compris entre 1 et 7,4 et maintenu à 37°C.
- 30 **7.** Composition selon la revendication 6, dans laquelle
 - 25 (a) le résultat est établi pour une moyenne de 6 comprimés; et/ou
 - (b) l'essai de dissolution est effectué dans 900 ml de milieu de dissolution contenant du phosphate de sodium 0,05 M à pH 6,8 avec 0,05% de SDS à 37°C en utilisant l'appareil USP 2 (à palettes) à une vitesse de rotation de 75 tours/min et en analysant les échantillons apixaban par HPLC à 280 nm.
- 35 **8.** Composition selon l'une quelconque des revendications 1 à 6, dans laquelle le tensioactif est le laurylsulfate de sodium, le stéarate de sodium, le polysorbate 80 ou des poloxamères.
- 40 **9.** Composition selon l'une quelconque des revendications 1 à 8, dans laquelle la composition peut être obtenue par un procédé comprenant les étapes consistant à:
 - 35 (1) mélanger les matières premières nécessaires avant la granulation;
 - (2) granuler les matières premières de l'étape (1) en utilisant un procédé de granulation à sec;
 - (3) mélanger les granulés calibrés de l'étape (2) avec des matières premières extragranulaires;
 - (4) comprimer le mélange de l'étape (3) en comprimés; et
 - 40 (5) pelliculer les comprimés obtenus à l'étape (4).
- 45 **10.** Composition selon l'une quelconque des revendications 1 à 9, destinée à être utilisée dans le traitement d'un trouble thromboembolique.
- 50 **11.** Procédé de fabrication de comprimés d'apixaban contenant une composition comprenant des particules d'apixaban ayant une taille moyenne inférieure à 89 μm et un D_{90} inférieur à 89 μm tel que mesuré par diffusion de la lumière laser, dans laquelle la composition comprend jusqu'à 5 mg d'apixaban, un diluant ou support pharmaceutiquement acceptable et un tensioactif, dans laquelle le tensioactif est présent à une concentration de 0,25% à 2% en poids et sert d'agent mouillant pour la substance médicamenteuse apixaban, dans laquelle le procédé comprend les étapes consistant à:
 - 55 (1) broyer par jet d'air pour réduire la taille des particules d'apixaban à la taille souhaitée;
 - (2) mélanger les matières premières avant la granulation;
 - (3) granuler les matières premières de l'étape (2) en utilisant un procédé de granulation à sec;
 - (4) mélanger les granules obtenus à l'étape (3) avec des matières premières extragranulaires;
 - (5) comprimer le mélange de l'étape (4) en comprimés; et
 - (6) filmer les comprimés de l'étape (5).

12. Procédé de fabrication de comprimés d'apixaban selon la revendication 11, dans lequel le procédé comprend les étapes de:

- (1) broyage par jet d'air pour réduire la taille des particules d'apixaban à la taille souhaitée;
- (2) mélange des matières premières avec de l'apixaban à granulométrie contrôlée pour former un mélange;
- (3) ajout des parties intragranulaires d'un liant, d'un désintégrant et d'au moins une charge au mélange de l'étape (2) pour former un mélange;
- (4) granulation des matériaux de l'étape (3) en utilisant un procédé de granulation à sec, dans laquelle le procédé de granulation à sec comprend:

- désagréger un lubrifiant intragranulaire en utilisant un tamis ou un broyeur;
- ajouter le lubrifiant intragranulaire au mélange issu de l'étape (3) et mélanger pour obtenir un mélange lubrifié;
- compacter le mélange lubrifié en rubans ayant une densité dans la plage de 1,1 à 1,2 et dimensionner les rubans compactés en utilisant un compacteur à rouleau, et

- (5) mélanger les granules obtenus à l'étape (4) et un désintégrant extragranulaire dans un mélangeur;
- (6) désagréger un lubrifiant extragranulaire en utilisant un tamis ou un broyeur et le mélanger avec les granules provenant de l'étape (5);
- (7) comprimer le mélange provenant de l'étape (6) en des comprimés; et
- (8) pelliculer le comprimé provenant de l'étape (7).

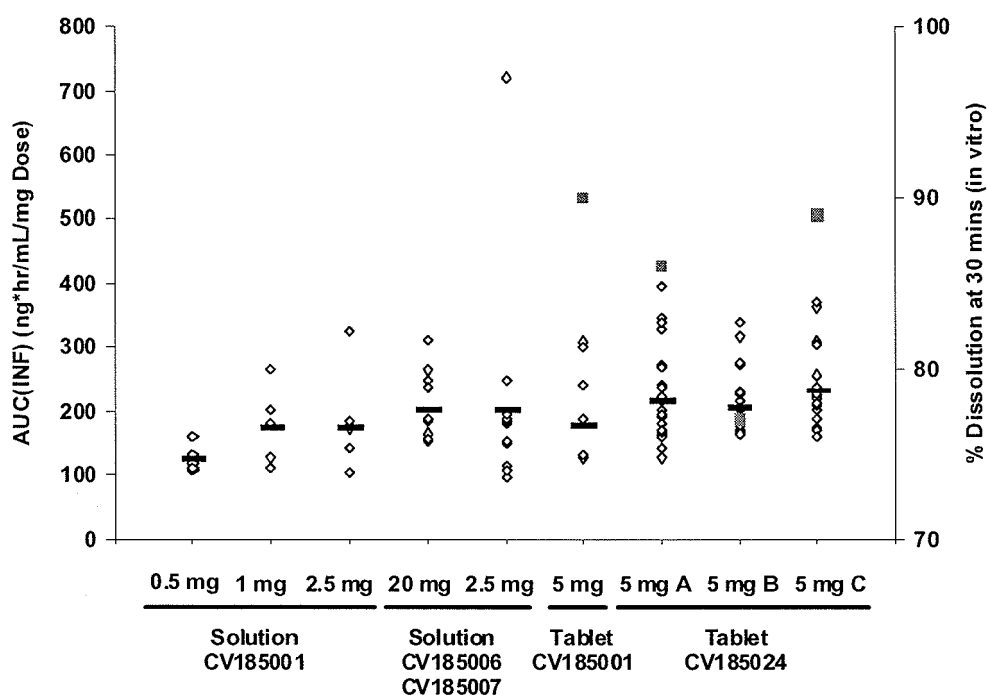
13. Procédé de fabrication de comprimés d'apixaban tels que définis dans les revendications 11 ou 12, dans lequel la quantité d'apixaban dans les comprimés est de 2,5 mg ou 5 mg ou entre 2,5 et 5 mg.

14. Procédé de fabrication de comprimés d'apixaban tels que définis dans l'une des revendications 11 à 13, dans lequel le comprimé présente des propriétés de dissolution telles qu'une quantité de médicament équivalente à au moins 77% se dissout en 30 minutes, l'essai de dissolution étant effectué dans un milieu aqueux tamponné à un pH situé dans l'intervalle de 1 et 7,4 et maintenu à 37°C.

15. Procédé de fabrication de comprimés d'apixaban selon la revendication 14, dans lequel

- (a) le résultat est établi en tant que moyenne de 6 comprimés; et/ou
- (b) l'essai de dissolution est effectué dans 900 ml de milieu de dissolution contenant du phosphate de sodium 0,05 M à pH 6,8 avec 0,05% de SDS à 37°C en utilisant un appareil USP 2 (à palettes) à une vitesse de rotation de 75 tours/min et les échantillons sont analysés pour la détermination de l'Apixaban par HPLC à 280 nm.

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

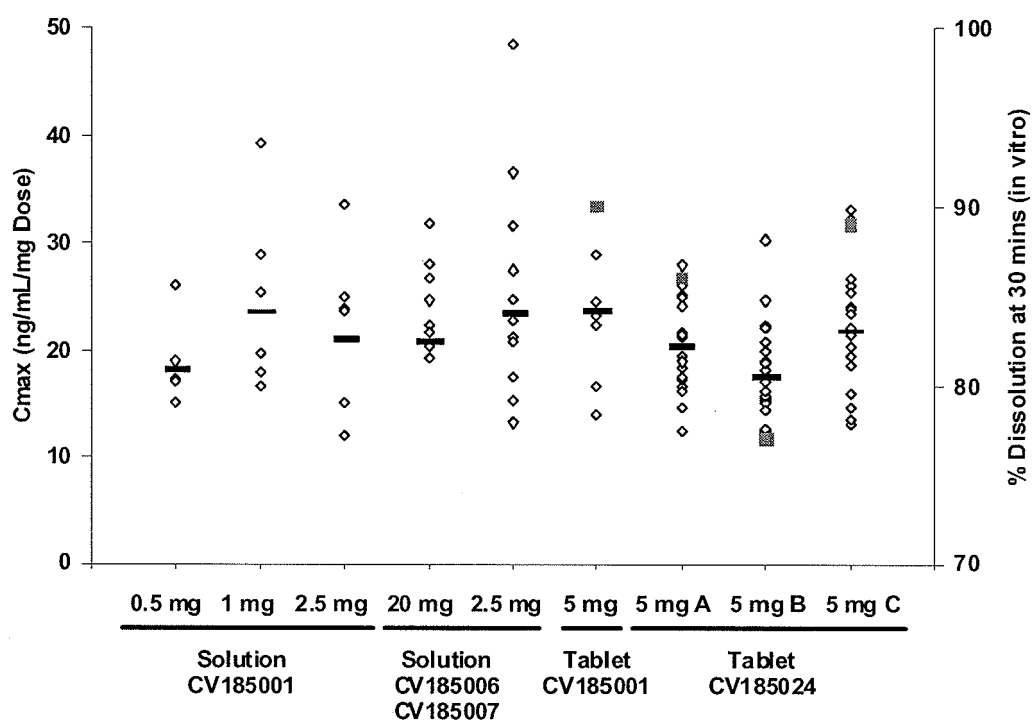


Source: CV185001, CV185006, CV185007, and CV185024 Clinical Study Reports

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

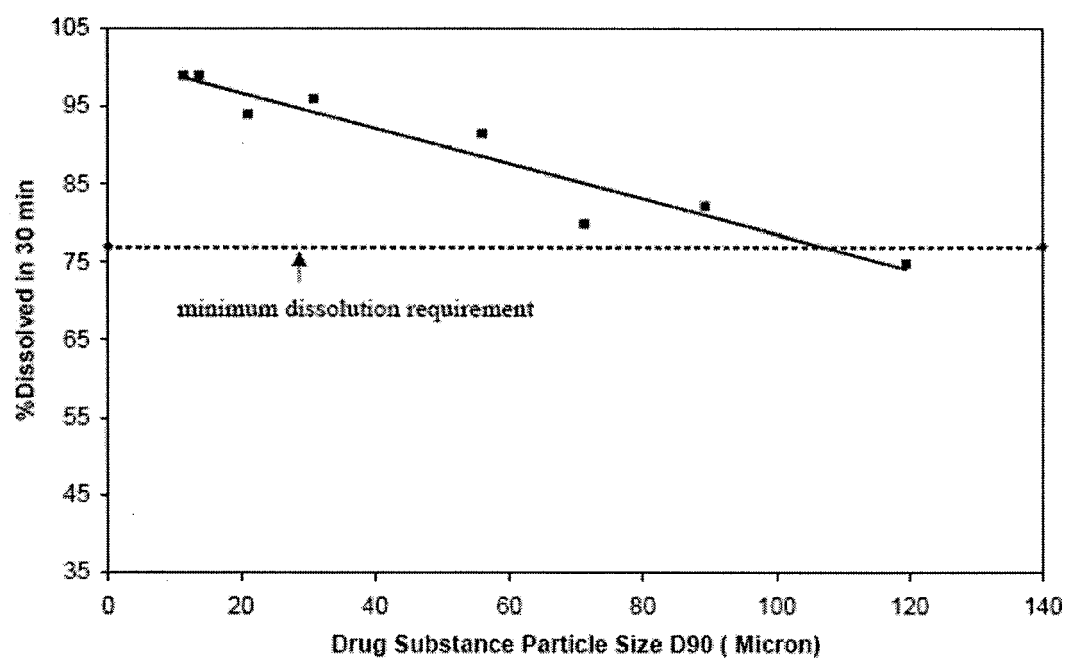
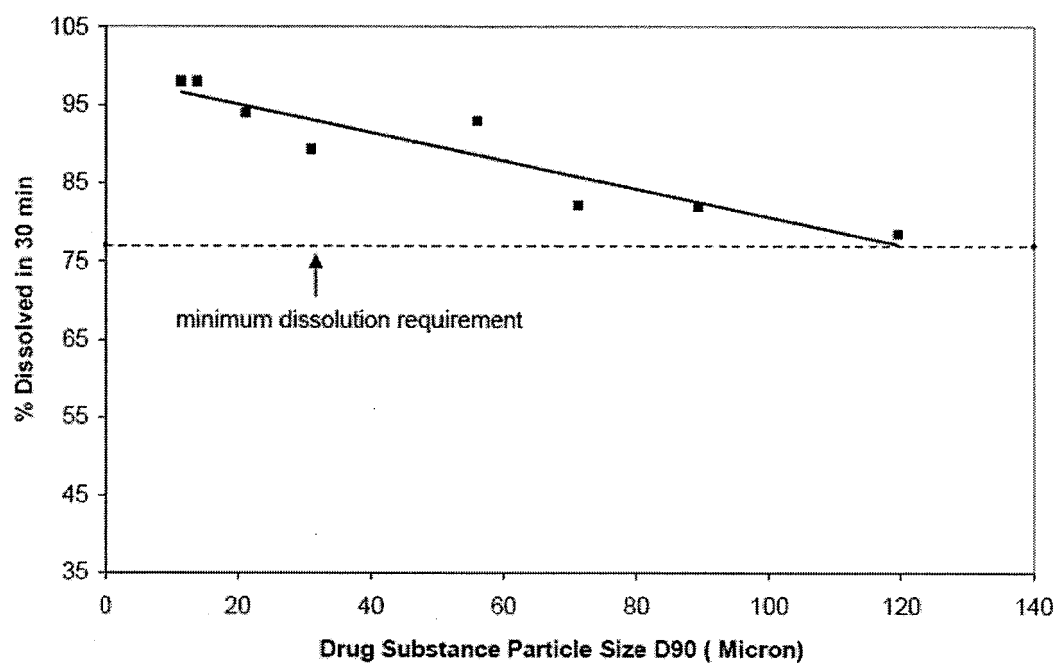


Figure 4: Dissolution Rates of 5-mg Apixaban Tablets Using Drug Substance of Different Particle Size



REFERENCES CITED IN THE DESCRIPTION

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Patent documents cited in the description

- US 6967208 B [0004] [0020] [0027]
- US 24512202 A [0004]
- WO 2008031782 A1 [0004]
- US 20060069258 A1 [0020]
- US 23551005 A [0020]

Non-patent literature cited in the description

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