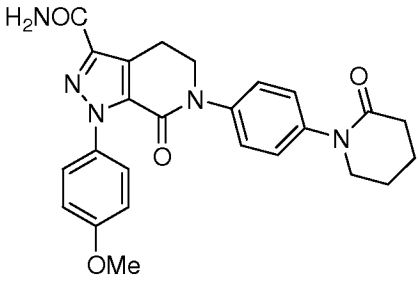
APIXABAN FORMULATIONS

FIELD OF THE INVENTION

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

BACKGROUND OF THE INVENTION

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



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

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

[0005] The aqueous solubility (40 µg/mL) 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 apixaban with large particles 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 85 microns (μm) exhibit 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. The compositions were prepared using a dry granulation process. Accordingly, the invention provides a pharmaceutical composition comprising crystalline apixaban particles having a D_{90} equal to or less than about 85 μm as measured by laser light distribution, and a pharmaceutically acceptable diluent or carrier. It is preferred that the apixaban particles in the composition have a D_{90} not exceeding 85 μm. It is noted the notation D_x means that X% of the volume of particles have a diameter less than a specified diameter D. Thus a D_{90} of 85 μm means that 90% of the volume of particles in an apixaban composition have a diameter less than 85 μm.

[0007] The range of particle sizes preferred for use in the invention is D_{90} less than 85 μm, more preferably D_{90} less than 50 μm, even more preferably D_{90} less than 30 μm, and most preferably D_{90} less than 25 μm. The particle sizes stipulated herein and in the claims refer to particle sizes were determined using a laser light scattering technique.

[0008] The invention further provides a method for the treatment or prophylaxis of thromboembolic disorders, comprising administering to a patient in need of such treatment or prophylaxis a therapeutically effective amount of a composition comprising crystalline apixaban particles having a D_{90} equal to or less than about 85 μm as measured by laser light scattering, and a pharmaceutically acceptable carrier.

[0009] The present invention also provides a dry granulation process for preparing a composition comprising crystalline apixaban particles having a D_{90} equal to or less

than about 85 μm as measured by laser light scattering, and a pharmaceutically acceptable carrier.

[0010] The formulations of this invention are advantageous because, *inter alia*, as noted above, they exhibit consistent human in-vivo dissolution. The invention is surprising in this respect, however, in that exposures are variable even though apixaban has adequate aqueous solubility that would allow the drug to dissolve rapidly. That is, one would expect dissolution rate for a drug that has high solubility (as defined by the Biopharmaceutical Classification System) would not be limited by the particle size. It has surprisingly been found, however, that the particle size that impacts apixaban absorption rate is about 85 μm. Thus apixaban can be formulated in a composition having a reasonable particle size using dry granulation process, to achieve and maintain relatively tiny particles to facilitate consistent in vivo dissolution.

[0011] In a relative bioavailabiltiy study where various apixaban formulations were evaluated, it was determined that formulations made using a wet granulation process resulted in lower exposures compared to the exposures obtained from a dry granulation process. Additionally, tablets made using larger particles (D_{90} of 85 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.

[0012] Formulations according to this invention, when dissolution tested in vitro preferably exhibit the following dissolution criteria. That is, the formulation exhibits dissolution properties such that, when an amount of the drug equivalent to 77% therein dissolves within 30 minutes. Usually the test result is established as an average for a pre-determined number of dosages (e.g., tablets, capsules, suspensions, or other dosage form), usually 6. The dissolution media is typically maintained at 37° C during the test. 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.

[0013] The term "particles" refers to individual particles whether the particles exist singly or are agglomerated. Thus, a composition comprising particulate apixaban may contain agglomerates that are well beyond the size limit of about 85 μm specified herein. However, if the mean size of the primary drug substance particles (i.e., apixaban) comprising the agglomerate are less than about 85 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.

[0014] 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.

[0015] "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 85 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.

[0016] Use of AUCs, C_{max}, and crossover studies is, of course otherwise well understood in the art. The invention can indeed be viewed in alternative terms as a composition comprising crystalline apixaban particles having a mean particle size

equal to or less than about 85 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.

[0017] The present invention may be embodied in other specific forms without departing from the spirit or essential attributes thereof. Thus, the above embodiments should not be considered limiting. Any and all embodiments of the present invention may be taken in conjunction with any other embodiment or embodiments to describe additional embodiments. Each individual element of the embodiments is its own independent embodiment. Furthermore, any element of an embodiment is meant to be combined with any and all other elements from any embodiment to describe an additional embodiment. In addition, the present invention encompasses combinations of different embodiment, parts of embodiments, definitions, descriptions, and examples of the invention noted herein.

DETAILED DESCRIPTION OF THE INVENTION

[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), herein incorporated by reference.

[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.

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