Dabigatran Etexilate, Dabigatran Etexilate Mesylate and Processes for Preparation Thereof

Crystalline forms of Dabigatran Etexilate and Dabigatran Etexilate mesylate are described in the present application and processes for preparing the crystalline forms. The present invention also includes pharmaceutical compositions of such crystalline forms of Dabigatran Etexilate and Dabigatran Etexilate mesylate, methods of their preparation and the use of such crystalline forms in the treatment of a patient in need thereof.
SOLID STATE FORMS OF DABIGATRAN ETEXILATE, DABIGATRAN ETEXILATE MESYLATE AND PROCESSES FOR PREPARATION THEREOF

FIELD OF THE INVENTION

The invention relates to solid state forms of Dabigatran etexilate and Dabigatran etexilate mesylate, processes for preparing them, and pharmaceutical compositions thereof.

BACKGROUND OF THE INVENTION

Dabigatran etexilate mesylate has the chemical structure:

![Chemical Structure of Dabigatran Etexilate Mesylate]

Dabigatran etexilate mesylate has the chemical name, ethyl 3-\{[2-\{4-\{N'-[(hexyloxy)carbonyl]carbamimidoyl]phenyl)amino)methyl\} -1-methyl- 1H-benz-imidazol-5-yl)carbonyl\} (2-pyridinyl)amino\}propanoate mesylate salt. Dabigatran etexilate mesylate is an anticoagulant drug from the class of the direct thrombin inhibitors. Dabigatran etexilate mesylate is marketed under the trade name PRADAXA® by Boehringer Ingelheim.

Crystalline forms of Dabigatran etexilate are described in WO 2006/131491 and WO 2008/059029. Crystalline forms of Dabigatran etexilate mesylate are also disclosed in US 2005/0234104.

Polymorphism, the occurrence of different crystal forms, is a property of some molecules and molecular complexes. A single molecule, like Dabigatran etexilate mesylate, may give rise to a variety of polymorphic forms having distinct crystal structures and physical properties like melting point, powder X-ray diffraction (PXRD) pattern, infrared absorption fingerprint, and solid state NMR spectrum. One
polymorphic form may give rise to thermal behavior different from that of another polymorphic form. Thermal behavior can be measured in the laboratory by such techniques as capillary melting point, thermogravimetric analysis (TGA), and differential scanning calorimetry (DSC) as well as content of solvent in the polymorphic form, which have been used to distinguish polymorphic forms.

The difference in the physical properties of different polymorphic forms results from the orientation and intermolecular interactions of adjacent molecules or complexes in the bulk solid. Accordingly, polymorphs are distinct solids sharing the same molecular formula yet having distinct advantageous physical properties compared to other polymorphic forms of the same compound or complex.

One of the most important physical properties of pharmaceutical compounds is their solubility in aqueous solution, particularly their solubility in the gastric juices of a patient. For example, where absorption through the gastrointestinal tract is slow, it is often desirable for a drug that is unstable to conditions in the patient's stomach or intestine to dissolve slowly so that it does not accumulate in a deleterious environment. Different polymorphic forms or polymorphs of the same pharmaceutical compounds can and reportedly do have different aqueous solubilities.

The discovery of new polymorphic forms of Dabigatran etexilate and Dabigatran etexilate mesylate can provide new opportunities to improve the synthesis and the characteristics of the active pharmaceutical ingredient (API). Such discoveries can also enlarge the repertoire of materials that a formulation scientist has available for designing, for example, a pharmaceutical dosage form of a drug with a targeted release profile or other desired characteristic. Therefore, there is a need for additional solid state forms of Dabigatran etexilate mesylate.

**SUMMARY OF THE INVENTION**

In one embodiment, the invention encompasses novel solid state forms of Dabigatran Etexilate mesylate, referred to herein as forms A, B, C, D, G, H and III.

In another embodiment, the invention encompasses novel solid state forms of Dabigatran Etexilate, referred to herein as forms E, F, J, K and L.

In one embodiment the invention encompasses the use of any one, or a combination of the above described crystalline forms of Dabigatran etexilate for the preparation of Dabigatran etexilate mesylate.
In another embodiment the invention encompasses a process for preparing Dabigatran etexilate mesylate comprising preparing Dabigatran etexilate by the process of the present invention and converting it to Dabigatran etexilate mesylate.

In another embodiment the invention encompasses a pharmaceutical composition comprising any one, or a combination of the above described crystalline forms of Dabigatran etexilate or Dabigatran etexilate mesylate. This pharmaceutical composition may additionally comprise at least one pharmaceutically acceptable excipient.

In another embodiment the invention encompasses the use of any one, or a combination of the above described crystalline forms of Dabigatran etexilate or Dabigatran etexilate mesylate for the manufacture of a medicament.

In yet another embodiment the invention encompasses a method of treating or preventing blood clots in a patient suffering from, or susceptible to, the formation of blood clots, said method comprising administering a pharmaceutical composition comprising any one, or a combination of the above described crystalline forms of Dabigatran etexilate or Dabigatran etexilate mesylate.

**BRIEF DESCRIPTION OF THE FIGURES**

Figure 1 shows a PXRD pattern of crystalline Dabigatran etexilate mesylate designated form I.

Figure 2 shows a PXRD pattern of crystalline Dabigatran etexilate mesylate designated form A.

Figure 3 shows a TGA thermogram of crystalline Dabigatran etexilate mesylate designated form A.

Figure 4 shows a PXRD pattern of amorphous Dabigatran etexilate mesylate.

Figure 5 shows a PXRD pattern of crystalline Dabigatran etexilate mesylate designated form B.

Figure 6 shows a PXRD pattern of crystalline Dabigatran etexilate mesylate designated form C.

Figure 7 shows a PXRD pattern of crystalline Dabigatran etexilate mesylate designated form D.
Figure 8 shows a PXRD pattern of crystalline Dabigatran etexilate designated form E.

Figure 9 shows a PXRD pattern of crystalline Dabigatran etexilate designated form F.

Figure 10 shows a PXRD pattern of crystalline Dabigatran etexilate mesylate form G.

Figure 11 shows a DSC thermogram of crystalline Dabigatran etexilate mesylate form G.

Figure 12 shows a PXRD pattern of crystalline Dabigatran etexilate mesylate form H.

Figure 13 shows a PXRD pattern of crystalline Dabigatran etexilate designated form J.

Figure 14 shows a PXRD pattern of crystalline Dabigatran etexilate designated form K.

Figure 15 shows a PXRD pattern of amorphous Dabigatran etexilate.

Figure 16 shows a PXRD pattern of crystalline Dabigatran etexilate tetrahydrate.

Figure 17 shows a PXRD pattern of crystalline Dabigatran etexilate mesylate form III.

Figure 18 shows a DSC thermogram of crystalline Dabigatran etexilate mesylate form III.

Figure 19 shows a microscope image of crystalline Dabigatran etexilate mesylate form III.

Figure 20 shows a PXRD pattern of crystalline Dabigatran etexilate form L.

Figure 21 shows a DSC thermogram of crystalline Dabigatran etexilate Form L.

**DETAILED DESCRIPTION OF THE INVENTION**

The invention relates to solid state forms of Dabigatran etexilate and Dabigatran etexilate mesylate, processes for preparing them, and pharmaceutical compositions thereof.

A crystal form may be referred to herein as being characterized by graphical data substantially "as depicted in" a Figure. Such data include, for example, powder X-ray diffractograms, FTIR spectra and solid state NMR spectra. The skilled person...
will understand that such graphical representations of data may be subject to small variations, e.g., in peak relative intensities and peak positions due to factors such as variations in instrument response and variations in sample concentration and purity, which are well known to the skilled person. Nonetheless, the skilled person would readily be capable of comparing the graphical data in the Figures herein with graphical data generated for an unknown crystal form and confirm whether the two sets of graphical data are characterizing the same crystal form or two different crystal forms.

A crystal form (or polymorph) may be referred to herein as polymorphically pure, or substantially free of any other crystalline (or polymorphic) forms. As used herein in this context, the expression "substantially free" will be understood to mean that the crystalline form contains 20% or less, 10% or less, 5% or less, 2% or less, or 1% or less of any other form of the subject compound as measured, for example, by PXRD. Thus, polymorphs of Dabigatran etexilate mesylate described herein as substantially free of any other polymorphic forms would be understood to contain greater than 80% (w/w), greater than 90% (w/w), greater than 95% (w/w), greater than 98% (w/w), or greater than 99% (w/w) of the subject polymorphic form of Dabigatran etexilate mesylate. Accordingly, in some embodiments of the invention, the described polymorphs of Dabigatran etexilate mesylate may contain from 1% to 20% (w/w), from 5% to 20% (w/w), or from 5% to 10% (w/w) of one or more other crystal forms of Dabigatran etexilate mesylate.

As used herein, the term crystalline Dabigatran etexilate mesylate form I refers to a crystalline Dabigatran etexilate mesylate characterized by suitable analytical methods, such as: a PXRD pattern substantially as depicted in Figure 1 in combination with a melting point of $T_{mp} = 180^\circ C \pm 3^\circ C$ as determined by DSC, (evaluation by peak maximum, at a heating rate of 10$^\circ C$/min), or a combination thereof.

As used herein, the term crystalline Dabigatran etexilate tetrahydrate refers to a crystalline Dabigatran etexilate tetrahydrate characterized by suitable analytical, such as: a melting point of $T_{mp} = 90^\circ C \pm 5^\circ C$ as determined by DSC; a PXRD pattern substantially as depicted in Figure 16; or a combination thereof.

As used herein, unless stated otherwise, the PXRD measurements are taken using copper $K\alpha$ radiation wavelength 1.541 8A.
As used herein, the term "wet crystalline form" refers to a polymorph that was not dried using any conventional techniques to remove residual solvent.

As used herein, the term "dry crystalline form" refers to a polymorph that was dried using any conventional techniques to remove residual solvent.

A thing, e.g., a reaction mixture, may be characterized herein as being at, or allowed to come to "ambient temperature" or "room temperature," often abbreviated "RT." This means that the temperature of the thing is close to, or the same as, that of the space, e.g., the room or fume hood, in which the thing is located. Typically, room temperature is from about 15°C to about 30°C, or about 20°C to about 25°C.

A process or step may be referred to herein as being carried out "overnight." This refers to a time interval, e.g., for the process or step, that spans the time during the night, when that process or step may not be actively observed. This time interval is from about 8 to about 20 hours, or about 10-18 hours, typically about 16 hours.

As used herein, the term "absolute ethanol" refers to ethanol having 1% (weight/weight percentage) or less of water, or 0.5% or less of water, particularly, 0.25% or less of water, more particularly, 0.15% or less of water.

As used herein, and unless stated otherwise, the term "anhydrous" in relation to crystalline Dabigatran etexilate or Dabigatran etexilate mesylate relates to a crystalline Dabigatran etexilate or Dabigatran etexilate mesylate which contains not more than 1% (w/w), more preferably not more than 0.5% (w/w) of either water or organic solvents incorporated in the crystalline structure, as measured by TGA.

The term "solvate," as used herein and unless indicated otherwise, refers to a crystal form that incorporates a solvent in the crystal structure. When the solvent is water, the solvate is often referred to as a "hydrate." The solvent in a solvate may be present in either a stoichiometric or in a non-stoichiometric amount.

The present invention provides solid state forms of Dabigatran etexilate and Dabigatran etexilate mesylate. The solid state forms of the present invention have advantageous properties selected from at least one of: chemical purity, flowability, solubility, morphology or crystal habit, stability - such as storage stability, stability to dehydration, stability to polymorphic conversion, low hygroscopicity, and low content of residual solvents.

In one embodiment the invention encompasses crystalline Dabigatran etexilate mesylate, designated form A. Form A can be characterized by data selected from: a
PXRD pattern with peaks at 4.1, 6.1, 9.9 and 15.1 degrees 2-theta± 0.2 degrees 2-theta, a PXRD pattern substantially as depicted in Figure 2, and combinations thereof. The Dabigatran etexilate mesylate form A may be further characterized by data selected from: an X-ray powder diffraction pattern having additional peaks at 4.4, 8.1, 11.5, 13.2 and 18.0 degrees 2-theta± 0.2 degrees 2-theta; a TGA thermogram as depicted in Figure 3; and any combination thereof.

Alternatively Dabigatran etexilate mesylate form A can be characterized by a PXRD pattern with peaks at 3.4, 6.6, 9.9, 18.4, 19.2 and 23.2 degrees 2-theta.

In another embodiment, the invention encompasses polymorphically pure crystalline Dabigatran etexilate mesylate, designated Form B. Form B can be characterized by data selected from: a PXRD pattern with peaks at 4.0, 6.1, 15.1 and 18.0 degrees 2-theta ± 0.2 degrees 2-theta, a PXRD pattern substantially as depicted in Figure 5, and combinations thereof, wherein the polymorphically pure Dabigatran etexilate mesylate form B contains not more than about 20% by weight of crystalline Dabigatran etexilate mesylate form A. According to some embodiments, the polymorphically pure Dabigatran etexilate mesylate form B contains not more than about 10%, or not more than about 5%, or not more than about 1% by weight of crystalline Dabigatran etexilate mesylate form A.

Typically, the amount of Dabigatran etexilate mesylate form A in the crystalline Dabigatran etexilate mesylate form B of the present invention can be measured by PXRD using the peak at 4.4 degrees 2-theta ± 0.2 degrees 2-theta.

The polymorphically pure Dabigatran etexilate mesylate form B may be further characterized by an X-ray powder diffraction pattern having additional peaks at 8.1, 13.2, 21.1 and 22.2 degrees 2-theta± 0.2 degrees 2-theta.

Alternatively the polymorphically pure Dabigatran etexilate mesylate form B can be characterized by a PXRD pattern with peaks at 4.0, 6.1, 15.1 and 18.0 degrees 2-theta ± 0.2 degrees 2-theta, and also having one, two, three or four additional peaks selected from 8.1, 13.2, 21.1 and 22.2 degrees 2-theta ± 0.2 degrees 2-theta.

In yet another embodiment, the invention encompasses crystalline Dabigatran etexilate mesylate, designated Form C. Form C can be characterized by data selected from: a PXRD pattern with peaks at 3.4, 6.6, 9.9, 18.4, 19.2 and 23.2 degrees 2-theta.
± 0.2 degrees 2-theta, a PXRD pattern substantially as depicted in Figure 6, and combinations thereof.

In one embodiment, the invention encompasses crystalline Dabigatran etexilate mesylate, designated Form D. Form D can be characterized by data selected from: a PXRD pattern with peaks at 3.7, 7.3, 13.3 and 17.3 degrees 2-theta ± 0.2 degrees 2-theta, a PXRD pattern substantially as depicted in Figure 7, and combinations thereof.

The Dabigatran etexilate mesylate form D may be further characterized by an X-ray powder diffraction pattern having additional peaks at 12.0, 18.2, 20.3 and 21.1 degrees 2-theta ± 0.2 degrees 2-theta.

Alternatively Dabigatran etexilate mesylate form D can be characterized by a PXRD pattern with peaks at 3.7, 7.3, 13.3 and 17.3 degrees 2-theta ± 0.2 degrees 2-theta and also having one, two, three or four additional peaks selected from 12.0, 18.2, 20.3 and 21.1 degrees 2-theta ± 0.2 degrees 2-theta.

The present invention describes an amorphous Dabigatran etexilate mesylate. The amorphous Dabigatran etexilate mesylate can be characterized by a PXRD pattern substantially as depicted in Figure 4.

In one embodiment, the invention encompasses crystalline Dabigatran etexilate mesylate, designated Form G. Form G can be characterized by data selected from: a PXRD pattern with peaks at 4.5, 9.4, 11.1, 13.6 and 18.8 degrees 2-theta± 0.2 degrees 2-theta, a PXRD pattern substantially as depicted in Figure 10, and combinations thereof. The Dabigatran etexilate mesylate form G may be further characterized by a DSC thermogram substantially as depicted in Figure 11.

In addition, Dabigatran etexilate mesylate form G can be characterized by any combination of the above data.

In another embodiment, the invention encompasses crystalline Dabigatran etexilate mesylate, designated Form H, Form H can be characterized by data selected from: a PXRD pattern with peaks at 3.7, 7.3, 13.3, 17.3, 19.3 and 21.2 degrees 2-theta ± 0.2 degrees 2-theta, a PXRD pattern substantially as depicted in Figure 12, and combinations thereof.

In one embodiment, the invention encompasses crystalline Dabigatran etexilate mesylate, designated Form III. Form III can be characterized by a DSC thermogram having a melting point from 185°C to 190°C (peak maximum) in combination with data selected from: a PXRD pattern with peaks at 4.6, 9.7, 11.1,
17.8 and 22.3 degrees 2-theta ± 0.2 degrees 2-theta, a PXRD pattern substantially as depicted in Figure 17, and combinations thereof. The Dabigatran etexilate mesylate form III may be further characterized by data selected from: an X-ray powder diffraction pattern having additional peaks at 9.1, 13.6, 18.2, 23.0 and 25.3 degrees 2-theta ± 0.2 degrees 2-theta; a DSC thermogram substantially as depicted in Figure 18, and any combination thereof.

Alternatively Dabigatran etexilate mesylate form III can be characterized by the melting point from 185°C to about 190°C (peak maximum) in combination with a PXRD pattern with peaks at, 4.6, 9.7, 11.1, 17.8 and 22.3 degrees 2-theta; and also having one, two, three, four or five additional peaks selected from 9.1, 13.6, 18.2, 23.0 and 25.3 degrees 2-theta ± 0.2 degrees 2-theta.

Preferably, Dabigatran etexilate mesylate form III is an anhydrous form.

Crystalline Dabigatran etexilate mesylate form III has advantageous properties selected from at least one of: chemical purity, flowability, solubility, morphology or crystal habit, stability - such as storage stability, stability to dehydration, and stability to polymorphic conversion, low hygroscopicity, and low content of residual solvents. Particularly, the crystalline Dabigatran etexilate mesylate form III of the present invention has a high melting point (measured by DSC) and shows high thermal chemical stability. Particularly, Dabigatran etexilate mesylate form III of the present invention is chemically stable at the following conditions, for a period of at least a month:

<table>
<thead>
<tr>
<th>Desiccant presence</th>
<th>Temperature</th>
<th>Relative humidity (&quot;RH&quot;)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>25°C</td>
<td>60%</td>
</tr>
<tr>
<td>Yes</td>
<td>40°C</td>
<td>75%</td>
</tr>
<tr>
<td>Yes</td>
<td>50°C</td>
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</tr>
<tr>
<td>No</td>
<td>25°C</td>
<td>60%</td>
</tr>
<tr>
<td>No</td>
<td>40°C</td>
<td>75%</td>
</tr>
<tr>
<td>No</td>
<td>50°C</td>
<td>NA</td>
</tr>
</tbody>
</table>

NA – Not available

Crystalline Dabigatran etexilate mesylate form III of the present invention is also highly crystalline, has morphology of stick-like particles which possesses good filterability.
The above Dabigatran etexilate mesylate form III can be prepared by a process comprising crystallizing Dabigatran etexilate mesylate form III from a solvent selected from: alcohols, such as, for example, ethanol, propanol, isopropanol, 1-butanol and 2-butanol, or mixtures thereof with ethers such as, for example, t-butylmethyl ether, tetrahydrofuran (THF) or 2-methyltetrahydrofuran, or esters such as, for example, ethyl acetate or n-butyl acetate; and ketones such as, for example, acetone, methyl ethyl ketone (MEK) or methylisobutyl ketone, or mixtures thereof with ethers or esters.

Suitable solvents and solvent mixtures include, for example, 2-butanol, a mixture of absolute ethanol and 2-methyltetrahydrofuran, a mixture of 1-butanol and n-butyl acetate, a mixture of absolute ethanol and ethyl acetate, and a mixture of absolute ethanol and methyl isobutyl ketone.

The above process typically comprises dissolving Dabigatran etexilate mesylate in the above described solvents or solvent mixtures to obtain a solution, and cooling the solution to obtain a suspension from which Dabigatran etexilate mesylate precipitates.

The process can comprise dissolving Dabigatran etexilate mesylate in an alcoholic solvent, such as absolute ethanol, 2-butanol or 1-butanol, to obtain a first solution, adding a second solvent selected from: an ester, such as n-butyl acetate or ethyl acetate; an ether, such as 2-methyltetrahydrofuran; or a ketone such as methyl isobutyl ketone, acetone and MEK to form a mixture; and cooling the mixture to obtain a suspension from which Dabigatran etexilate mesylate form III precipitates.

The dissolution can be done while stirring. If necessary, to aid dissolution, stirring can be done while heating, for example to a temperature from about 40°C to about 60°C, or to about the reflux temperature of the solvent or solvent mixture.

Suitable cooling temperatures can vary, depending on the solvent system. The cooling is preferably to a temperature in which a suspension is formed and Dabigatran etexilate mesylate form III precipitates, for example a temperature from about 0°C to about room temperature.
After Dabigatran etexilate mesylate form III precipitates, it can be recovered. The recovery can comprise, for example, filtering and optionally washing and/or drying. Drying can be done under vacuum, for example at a temperature of about 40 to 60°C, preferably about 40°C

In one embodiment, the invention encompasses crystalline Dabigatran etexilate, designated Form E. Form E can be characterized by data selected from: a PXRD pattern with peaks 4.6, 8.6, 17.6 and 21.2 degrees 2-theta ± 0.2 degrees 2-theta, a PXRD pattern substantially as depicted in Figure 13, and combinations thereof.

The Dabigatran etexilate form E may be further characterized by an X-ray powder diffraction pattern having additional peaks at 13.8, 14.8, 20.5 and 22.7 degrees 2-theta ± 0.2 degrees 2-theta.

Alternatively Dabigatran etexilate form E can be characterized by a PXRD pattern with peaks at 4.6, 8.6, 17.6 and 21.2 degrees 2-theta ± 0.2 degrees 2-theta, and also having one, two, three or four additional peaks selected from 13.8, 14.8, 20.5 and 22.7 degrees 2-theta ± 0.2 degrees 2-theta. Form E can be an acetonitrile solvate.

In another embodiment, the invention encompasses crystalline Dabigatran etexilate, designated Form F. Form F can be characterized by data selected from: a PXRD pattern with peaks 4.6, 8.5, 9.4, 13.5, 17.3 and 18.5 degrees 2-theta ± 0.2 degrees 2-theta, a PXRD pattern substantially as depicted in Figure 9, and combinations thereof. The Dabigatran etexilate form F may be further characterized by an X-ray powder diffraction pattern having additional peaks at 10.4, 14.6, 22.7 and 26.4 degrees 2-theta ± 0.2 degrees 2-theta.

Alternatively Dabigatran etexilate form F can be characterized by a PXRD pattern with peaks at 4.6, 8.5, 9.4, 13.5, 17.3 and 18.5 degrees 2-theta ± 0.2 degrees 2-theta, and also having one, two, three or four additional peaks selected from 10.4, 14.6, 22.7 and 26.4 degrees 2-theta ± 0.2 degrees 2-theta.

In yet another embodiment, the invention encompasses crystalline Dabigatran etexilate, designated Form J. Form J can be characterized by data selected from: a PXRD pattern with peaks at 4.6, 8.5, 8.9, 13.6, 17.4, 22.7 and 27.6 degrees 2-theta ± 0.2 degrees 2-theta, a PXRD pattern substantially as depicted in Figure 13, and combinations thereof.
In another embodiment, the invention encompasses crystalline Dabigatran etexilate, designated Form K. Form K can be characterized by data selected from: a PXRD pattern with peaks at 4.6, 9.4, 12.1, 16.4, 20.4 and 26.7 degrees 2-theta ± 0.2 degrees 2-theta, a PXRD pattern substantially as depicted in Figure 14, and combinations thereof.

In yet another embodiment, the invention encompasses amorphous form of Dabigatran etexilate. The amorphous Dabigatran etexilate mesylate can be characterized by a PXRD pattern substantially as depicted in Figure 15.

The amorphous Dabigatran etexilate of the present invention has good solubility in common organic solvents, like alcohols, such as ethanol and methanol and ketones, like acetone, methyl ethyl ketone (MEK) etc. Moreover, the amorphous forms has low water content, of about 2% to 3% as measured by KF, thus it is stable towards degradation occurring in the presence of water. It can be used to prepare a pharmaceutical composition, or alternatively, to prepare Dabigatran etexilate having improved purity stability.

The present invention further describes crystalline Dabigatran etexilate, designated from Form L. Form L can be characterized by a DSC thermogram substantially as depicted in Figure 21 in combination with data selected from: a PXRD having peaks at 5.9, 11.8, 17.7, 19.9 and 26.5 degrees 2-theta ± 0.2 degrees 2-theta; a PXRD having peaks at 5.9, 11.8, 13.5, 15.1, 17.7, 19.9, 20.4, 21.5, 24.6, 25.2, 26.5 and 27.2 degrees 2-theta ± 0.2 degrees 2-theta and a PXRD substantially as depicted in Figure 20.

Alternatively Dabigatran etexilate form L can be characterized by a DSC thermogram substantially as depicted in Figure 21 in combination with PXRD pattern having peaks at 5.9, 11.8, 17.7, 19.9 and 26.5 degrees 2-theta ± 0.2 degrees 2-theta and also having one, two, three, four or five additional peaks selected from 13.5, 15.1, 20.4, 21.5, 24.6, 25.2 and 27.2 degrees 2-theta ± 0.2 degrees 2-theta.

Preferably, Form L can have a residual 2-butanol solvate content of about 9.17% (w/w), as measured by GC. Form L can be a 2-butanol solvate.

Crystalline Dabigatran etexilate form L has advantageous properties as described above. In particular, form L is chemically pure and it is stable to degradation occurring in the presence of water. It can be used to prepare a
pharmaceutical composition, or alternatively, to prepare Dabigatran etexilate having improved purity stability.

The above described solid state forms of Dabigatran etexilate can be used to prepare salts of Dabigatran etexilate, particularly Dabigatran etexilate mesylate.

The invention encompasses a process for preparing Dabigatran etexilate salt, preferably a mesylate salt, comprising preparing Dabigatran etexilate by the process of the present invention and converting it to Dabigatran etexilate salt, preferably a mesylate salt. The conversion can be done by any process known in the art. For example, the conversion can be done by reacting Dabigatran etexilate with an acid, preferably methanesulfonic acid.

The above described solid state forms of Dabigatran etexilate and Dabigatran etexilate mesylate can be used to prepare pharmaceutical compositions.

The present invention further encompasses 1) a pharmaceutical composition comprising any one or combination of solid state Forms, as described above, and at least one pharmaceutically acceptable excipient; 2) the use of any one or combination of the above-described solid state Forms, in the manufacture of a pharmaceutical composition; and 3) a method of treating or preventing blood clots in a patient suffering from or susceptible to the formation of blood clots. The pharmaceutical composition can be useful for preparing a medicament. The present invention also provides crystalline forms as described above for use as a medicament.

The present invention also describes a process for preparing Dabigatran etexilate mesylate form I. The process comprises crystallizing Dabigatran etexilate mesylate from a solvent selected from cyclohexanone, 1-pentanol, tetrahydrofuran, ethyl acetoacetate, 2-methoxyethyl ether and mixtures thereof. The crystallization comprises providing a solution of Dabigatran etexilate mesylate in one or more of the above described solvents and subsequently precipitating the crystalline form. The solution can be provided by combining Dabigatran etexilate mesylate and the solvent; and heating the combination to a temperature at which a solution is formed, for example from about 40° C up to about the reflux temperature of the solvent. Precipitation can be achieved by cooling and maintaining the solution, for example at room temperature, to obtain a suspension comprising the crystalline form. The obtained crystalline form can then be recovered from the suspension. The recovery can comprise, for example filtering the crystalline form and drying, for instance in a
vacuum oven, at a suitable temperature, e.g., about 40°C, for a suitable period, e.g., of about 2 hours.

Having described the invention with reference to certain preferred embodiments, other embodiments will become apparent to one skilled in the art from consideration of the specification. The invention is further defined by reference to the following examples describing in detail the preparation of the composition and methods of use of the invention. It will be apparent to those skilled in the art that many modifications, both to materials and methods, may be practiced without departing from the scope of the invention.

**PXRD method**

Samples, after being powdered using a mortar and pestle, were applied directly on silicon plate holder. The X-ray powder diffraction pattern was measured with Philips X'Pert PRO X-ray powder diffractometer, equipped with Cu irradiation source \( \lambda = 1.54184 \text{ Å} \), X'Celerator (2.022° 2\( \Theta \)) detector. Scanning parameters: angle range: 3-40 deg., step size 0.0167, time per step 37 s, continuous scan. A silicon (1 1 1) powder was added to all samples, except for amorphous Dabigatran etexilate mesylate, Dabigatran etexilate mesylate form A, form B, form G and form III; and Dabigatran etexilate forms J and K. Literature peak at about 28.45 degrees 2-\( \Theta \) (28.45 - theoretical value) represents silicon (1 1 1). No corrections were performed on the claimed peaks or on the presented diffractograms in the figures.

**TGA method**

TG analysis was performed under flow of nitrogen (60 ml/min) on TGA 2950 TA instrument, with heating rate of 10 °C/min. Standard platinum open pan was used, in temperature range from room temperature to 500°C. Sample mass was about 8-12 mg.

**DSC method**

DSC analysis was performed on Q 1000 MDSC TA instruments with a heating rate of 10 °C/min, under nitrogen flow of 50 ml/min. Standard aluminum, closed pan (with hole) was used. The sample mass was about 1-5 mg.
**EXAMPLES**

**Reference Examples**

**Dabigatran etexilate mesylate form I**

Dabigatran etexilate mesylate form I as used in the below described examples may be prepared according to US 2005/0234104 example 1, which is incorporated herein by reference.

**Preparation of Dabigatran etexilate mesylate form I according to US 2005/0234104 example 1:**

Ethyl 3-{[2-[[4-(hexyloxy carbonylamino)iminomethyl]phenylamino]methyl]-1-methyl-1H-benzimidazole-5-carbonyl]pyridin-2-ylamino|propionate | base (52.6 kg) (which has preferably been purified beforehand by recrystallization from ethyl acetate) is placed in an agitator apparatus which has been rendered inert and then 293 kg of acetone is added. The contents of the apparatus are heated to 40°C to 46°C with stirring. After a clear solution has formed, the contents of the apparatus is filtered into a second agitator apparatus through a lens filter and then cooled to 30°C to 36°C. 33 kg of acetone precooled to 0°C to 5°C, 7.9 kg of 99.5% methanesulfonic acid, and for rinsing another 9 kg of acetone are placed in the suspended container of the second apparatus. The contents of the suspended container are added in metered amounts to the solution of ethyl 3-{[2-[[4-(hexyloxy carbonylamino)iminomethyl]phenylamino]methyl]-1-methyl-1H-benzimidazole-5-carbonyl]pyridin-2-ylamino|propionate base at 26°C to 36°C within 15 to 40 minutes. Then the mixture is stirred for 40 to 60 minutes at 26°C to 33°C. It is then cooled to 17°C to 23°C and stirred for a further 40 to 80 minutes. The crystal suspension is filtered through a filter dryer and washed with a total of 270 L of acetone. The product is dried in vacuum at a maximum of 50°C for at least 4 hours. Yield: 54.5-59.4 kg; 90%-98% of theory based on ethyl 3-{[2-[[4-(hexyloxy carbonylanimo)iminomethyl]phenylamino]methyl]-1-methyl-1H-benzimidazole-5-carbonyl]pyridin-2-ylamino|propionate base.

**Dabigatran etexilate tetrahydrate**

Dabigatran etexilate tetrahydrate as used in the below described examples may be prepared according to US 2006/0276513 example 3, which is incorporated herein by reference.
Preparation according to US 2006/0276513 example 3:

3-[(2-

\{4-(Hexyloxy carbonylaniino-imino-memyl)-phenylamino\}-methyl} -1-lH-benzinidazole-5-carbonyl)-pyridin-2-yl-amrno\}-propionic acid ethyl ester base

(0.5 g) (Prepared as described in WO 98/37075) are dissolved in 5 ml of a mixture of acetone/water=80:20 at 60° C. with agitation. The solution was cooled to about 30° C and filtered through a filter, for example through a Sartorius Minisart Filter SRP 15 into a 10 ml glass vial, and the flask was sealed. The solution was then cooled in an ice/ethanol mixture to about-9° C. The substance began to crystallize out by itself.

After about 30 minutes in the ice bath, about 3 ml of a mixture of acetone and water (80:20) cooled to-9° C. were added, the mixture was agitated and then suction filtered through a filter, for example a Schleicher & Schiill round filter no. 595.

The collected material was rinsed with approximately another 5 ml of a mixture of acetone and water (80:20) cooled to-9° C. The substance filtered off was scraped off the round filter into a crystallizing dish and dried in the air at ambient temperature.

Examples

Example 1: Amorphous Dabigatran etexilate mesylate

The amorphous form was prepared by solid state dry grinding, as follows:
Dabigatran etexilate mesylate (Form I, 0.5g) was put in the agate container of a ball mill with 5 balls. The sample was ground at a speed rate of 600 rpm for 30 minutes and subjected to additional grinding at 700 rpm for another 30 minutes. The sample was then analyzed by PXRD and found to be an amorphous Dabigatran etexilate mesylate.

Example 2: Crystalline Dabigatran etexilate mesylate form A

Amorphous Dabigatran etexilate mesylate (about 0.5 g) was placed in a Petri dish at room temperature in a desiccator and exposed to 100% relative humidity (RH) for 30 days. After the 30 days, the sample was air dried for 3 hours. The sample was then analyzed by PXRD and TGA and the results are shown in figures 2 and 3, respectively.
Example 3: Crystalline Dabigatran etexilate mesylate form B

Amorphous Dabigatran etexilate mesylate (about 0.1 g) was slurried in 6 ml of water at room temperature for 24 hours. The slurry was filtered and the collected solid was air dried for 10 hours and then checked by PXRD.

Example 4: Crystalline Dabigatran etexilate mesylate form C

Dabigatran etexilate mesylate (Form I, 30 mg) was dissolved in 1-methyl-4-isopropylbenzol ("p-cymol") (3 ml) while heating. The solution was left at room temperature overnight to crystallize. The crystals were filtered off and were dried in a vacuum oven for 2 hours at 40°C and characterized by PXRD.

Example 5: Crystalline Dabigatran etexilate mesylate form D

Dabigatran etexilate mesylate (Form I, 30 mg) was dissolved in dimethyl sulfoxide (1 ml) at room temperature. The solution was left at room temperature overnight to crystallize. The crystals were filtered off and were dried in a vacuum oven for 2 hours at 40°C and characterized by PXRD.

Example 6: Crystalline Dabigatran etexilate form E

Amorphous Dabigatran etexilate (30 mg) was dissolved in acetonitrile (1 ml) at room temperature. The solution was left at room temperature overnight to crystallize. The crystals were filtered off and dried in a vacuum oven for 2 hours at 40°C. The crystals were characterized by PXRD.

Example 7: Crystalline Dabigatran etexilate form F

Amorphous Dabigatran etexilate (30 mg) was dissolved in butyl acetate (1 ml) while heating. The solution was left at room temperature overnight to crystallize. The crystals were filtered off and were dried in a vacuum oven for 2 hours at 40°C. The crystals were characterized by PXRD.

Example 8: Crystalline Dabigatran etexilate mesylate form G

About 0.2 g of amorphous Dabigatran etexilate mesylate, obtained by solid state grinding of crystalline form I, was exposed to a heptane atmosphere at room temperature for one month. Afterwards, the sample was characterized by PXRD.
Example 9: Crystalline Dabigatran etexilate mesylate form H

Dabigatran etexilate mesylate (Form I, 30 mg) was dissolved in pyridine (1 ml) at room temperature. The solution was left at room temperature overnight to crystallize. The crystals were filtered off and dried in a vacuum oven for 2 hours at 40°C. The crystals were characterized by PXRD.

Example 10: Crystalline Dabigatran etexilate form J

About 0.2 g of amorphous Dabigatran etexilate base, obtained by heating of tetrahydrate form of Dabigatran etexilate, was exposed to an atmosphere of anisole at room temperature for eight days. Afterwards, the sample was characterized by PXRD.

Example 11: Crystalline Dabigatran etexilate form K

About 0.2 g of amorphous Dabigatran etexilate base, obtained by heating of the tetrahydrate form of Dabigatran etexilate, was exposed to an atmosphere of 2-methyl-THF at room temperature for one month. Afterwards, the sample was characterized by PXRD.

Example 12: Crystalline Dabigatran etexilate mesylate form I

Dabigatran etexilate mesylate (30 mg) was dissolved in a solvent selected from list A (1 ml) while heating until a solution was formed. The solution was left at room temperature overnight to crystallize. The crystals were filtered off and dried in a vacuum oven for 2 hours at 40°C. List A: cyclohexanone, 1-pentanol, tetrahydrofuran.

Example 13: Crystalline Dabigatran etexilate mesylate form I

Dabigatran etexilate mesylate (30 mg) was dissolved in ethyl acetoacetate (2 ml) while heating until a solution was formed. The solution was left at room temperature overnight to crystallize. The crystals were filtered off and dried in a vacuum oven for 2 hours at 40°C.

Example 14: Crystalline Dabigatran etexilate mesylate form I

Dabigatran etexilate mesylate (30 mg) was dissolved in 2-methoxyethyl ether (3 ml) while heating. The solution was left at room temperature overnight to crystallize. The crystals were filtered off and dried in a vacuum oven for 2 hours at 40°C.
Example 15: Amorphous Dabigatran etexilate

Crystalline Dabigatran etexilate tetrahydrate (about 1 g) was dried at 50 °C at 10 mbar for 3 hours. The sample was characterized by PXRD.

Example 16: Crystalline Dabigatran etexilate mesylate form III

Dabigatran etexilate mesylate (2.00 g; form I) was dissolved in absolute ethanol (40 ml) while stirring at 40-45°C under nitrogen. 2-Methyltetrahydrofuran (80 ml) was added dropwise over 20 minutes. The resulting solution was cooled down to 35°C and additional 2-methyltetrahydrofuran (30 ml) was added dropwise. The solution was then cooled down to 25°C. Crystallization started at 25-30°C. The obtained suspension was stirred at 25°C for 2 hours and for an additional 45 minutes at 10-15°C. The obtained crystals were filtered off and dried in a vacuum oven for 2 hours at 40°C to afford 1.55 g of dabigatran etexilate mesylate (purity by HPLC: 99.6 area%). Samples were analyzed by PXRD and DSC, m.p. 188.1 °C.

Example 17: Crystalline Dabigatran etexilate mesylate form III

Dabigatran etexilate mesylate (0.40 g) was dissolved in 1-butanol (5 ml) while stirring at 80°C. The solution was then treated with active carbon NORIT SX-plus. The active carbon was then filtered off over diatomaceous earth. The filtrate was warmed up to 80°C and n-butyl acetate (10 ml) was added dropwise. The resulting solution was then cooled down to 20°C over 2 hours (crystallization started at 65-70°C). The resulting suspension was stirred at 20°C for an additional 30 minutes. The crystals were filtered off, washed with n-butyl acetate: 1-butanol mixture (2:1; 1.5 ml)) and dried for 80 hours at ambient temperature to afford 0.19 g of dabigatran etexilate mesylate (purity by HPLC: 99.3 area%). A sample was analyzed by PXRD and DSC, m.p. 186.7 °C.

Example 18: Crystalline Dabigatran etexilate mesylate form III

Dabigatran etexilate mesylate (2.00 g) was dissolved in absolute ethanol (40 ml) while stirring at 40-45°C under nitrogen. Ethyl acetate (100 ml) was added dropwise over 20 minutes. The resulting solution was then cooled down to 35°C and additional ethyl acetate (20 ml) was added dropwise. The solution was then cooled down to 25°C. Crystallization started at 25-30°C. The resulting suspension was stirred at 25°C for 2 hours and for an additional 30 minutes at 10-15°C. The crystals were
filtered off and dried in a vacuum oven for 2 hours at 40°C to afford 1.33 g of dabigatran etexilate mesylate (purity by HPLC: 99.7 area%). A sample was analyzed by PXRD and DSC, m.p. 189.1 °C.

**Example 19: Crystalline Dabigatran etexilate mesylate form III**

Dabigatran etexilate mesylate (2.00 g) was dissolved in absolute ethanol (40 ml) while stirring at 40-45°C under nitrogen. Methyl isobutyl ketone (120 ml) was added dropwise over 20 minutes. The resulting solution was then cooled down to 25-30°C, and additional methyl isobutyl ketone (10 ml) was added dropwise. The solution was then cooled down to 25°C. Crystallization started at 25-30°C. The resulting suspension was stirred at 25°C for 2 hours and for an additional 45 minutes at 10-15°C. The crystals were filtered off and dried in a vacuum oven for 2 hours at 40°C to afford 1.16 g of dabigatran etexilate mesylate (purity by HPLC: 99.7 area%). A sample was analyzed by PXRD and DSC, m.p. 189.7 °C.

**Example 20: Crystalline Dabigatran etexilate mesylate form III**

Dabigatran etexilate mesylate (2.00 g) was dissolved in absolute ethanol (40 ml) while stirring at 40-45°C under nitrogen. Ethyl acetate (100 ml) was added dropwise over 20 minutes. The resulting solution was then cooled down to 35°C and additional ethyl acetate (20 ml) was added dropwise. The solution was then cooled down to 25°C. Crystallization started at 25-30°C. The resulting suspension was stirred at 25°C for 2.5 hours and for an additional 30 minutes at 10-15°C. The crystals were filtered off to afford 1.39 g of wet dabigatran etexilate mesylate (purity by HPLC: 99.8 area%). A sample was analyzed by PXRD and DSC, m.p. 188.2 °C.

**Example 21: Crystalline Dabigatran etexilate mesylate form III**

Dabigatran etexilate mesylate (2.00 g) was dissolved in 1-butanol (40 ml) while stirring at 50-55°C under nitrogen. Ethyl acetate (40 ml) was added dropwise over 20 minutes. The resulting solution was then cooled down to 25°C. Crystallization started at 30-35°C. The resulting suspension was stirred at 25°C for 1.5 hour and for an additional 30 minutes at 10-15°C. The crystals were filtered off and dried in a vacuum oven for 2 hours at 40°C to afford 1.53 g of dabigatran etexilate mesylate (purity by HPLC: 99.7 area%). A sample was analyzed by PXRD and DSC, m.p. 188.4 °C.
Example 22: Preparation of Dabigatran etexilate mesylate form I

Step a: Preparation of Dabigatran etexilate, tetrahydrate

Ethyl 3-((4-carbamimidoylphenylamino)methyl)-1-methyl-N-(pyridin-2-yl)-1H-benzo[d]imidazole-5-carboxamido)propanoate hydrochloride salt (74.0 g, 0.14 mol) was dissolved in a mixture of water (1.17 L) and 2-methyl tetrahydrofuran ("2-MeTHF") (2.31 L) at 25 °C. The resulting solution was acidified to pH 3.5 using HCl (30 mL, 1.5 M). An aqueous solution of K$_2$CO$_3$ (52.7 g, 0.41 mol in 340 mL water) was added drop wise during half an hour. The resulting reaction mixture was stirred for 30 min at 25 °C. Hexilchloroformate ("HCF") (24.9 mL, 0.15 mol) was added dropwise during 10-15 min and the reaction mixture was stirred for 2 h at 25 °C (precipitation started approximately after 20 min and a suspension was formed). The resulting suspension is cooled to 0-5 °C and stirred for 1 h. The precipitate was filtered off, washed with water (200 mL) and ice cooled 2-MeTHF (200 mL). The obtained cake is dried at 40 °C/10 mbar /4h

Yield: 80.6 g (83%) Dabigatran etexilate tetrahydrate (HPLC: 99.63%; KF: 9.66%)

Step b: Preparation of Dabigatran etexilate mesylate form I

Dabigatran etexilate obtained according to step a (113.0 g, 161.45 mmol) was dissolved in 2-MeTHF (2.36 L) at 25 °C. Methanesulfonic acid (10.49 mL, 161.45 mmol) solution in 2-MeTHF (500 mL) was added drop wise to the solution of compound 1 in 2-MeTHF, at 25 °C during 60 minutes (precipitation started after approximately 20% of methanesulfonic acid was added). The resulting reaction mixture was stirred for 1 h at 25 °C. The precipitate was filtered off and washed with 2-MeTHF (300 mL). The solid was dried at 40 °C/100 mbar /4h.

Yield: 113 g (~ 97%) of Dabigatran etexilate mesylate form I (HPLC: 99.69%; PT: 13.1%)

Example 23: Preparation of Dabigatran etexilate mesylate form III

Step a: Preparation of Dabigatran etexilate, tetrahydrate

Ethyl 3-((4-carbamimidoylphenylamino)methyl)-1-methyl-N-(pyridin-2-yl)-1H-benzo[d]imidazole-5-carboxamido)propanoate hydrochloride salt (60.0 g, 0.11 mol) was dissolved in a mixture of water (330 mL) and acetone (980 mL) at 25 °C
(pH= 5.4). The resulting solution was acidified to pH 3.5 using HCl (14 ml, 1.5 M). An aqueous solution of K₂CO₃ (46.5 g, 0.34 mol in 165 ml water) was added dropwise during half an hour. The resulting reaction mixture was stirred for 15 min at 25 °C. HCF (20 ml, 0.12 mol) was added dropwise during 10-15 min and the reaction mixture was stirred for 2 h at 25 °C (precipitation started after approximately 1 h). The resulting suspension was cooled to 0-5 °C and stirred for 1 h. The precipitate was filtered, washed with acetone:water (1:1, 300 mL) and water (300 mL). The wet product was suspended in water (1.5 L) and the suspension was stirred for 1 h at 25 °C. The solid was filtered off, washed with water and dried at 30 °C/100 mbar.

Yield: 65.4 g (83%) Dabigatran etexilate, tetrahydrate (HPLC: 98.79%; KF: 11.7%)

Step b: Preparation of Dabigatran etexilate mesylate mesylate form III

Dabigatran etexilate obtained in step a (63.0 g, 87.5 mmol) was dissolved in 2-butanol (700 ml) while heating to 50 °C. The obtained solution was filtered and the filtrate was re-heated to 50 °C. Methanesulfonic acid (5.75 ml, 87.6 mmol) was added to the solution at 50 °C and the resulting reaction mixture was stirred for 1.5 h at 50 °C (precipitation started after approximately 45 min). The obtained suspension was cooled to 20 °C during 3 h and stirred for half an hour. The precipitate was filtered off and washed with 2-butanol (2x70 mL). The solid was dried at 40 °C/100 mbar.

Yield: 58 g (~ 91%) of Dabigatran etexilate mesylate mesylate form III (HPLC: 99.51%; KF: 12.99%)

Example 24: Preparation of crystalline Dabigatran etexilate form L

Dabigatran etexilate (tetrahydrate, 1.87 g) was dissolved in 2-butanol (19 ml) at 25 °C. The solution was stirred for 1 h and precipitation occurred. The precipitate was filtered off and washed with 2-butanol (7.5 mL). The solid was dried for 2 h at 40 °C/100 mbar.

Yield: 1 g (~ 57%) of Dabigatran etexilate form L (GC: 7.2% 2-butanol; KF: 0.6%). PXRD and DSC are shown in figures 20 and 21, respectively.
What is claimed is:

1. Crystalline Dabigatran Etexilate mesylate form III.

2. The crystalline Form III of claim 1, characterized by a DSC thermogram having a melting point from 185°C to 190°C (peak maximum) in combination with data selected from: a PXRD pattern with peaks at 4.6, 9.7, 11.1, 17.8 and 22.3 degrees 2-theta ± 0.2 degrees 2-theta, a PXRD pattern substantially as depicted in Figure 17, and combinations thereof.

3. The crystalline Form III of claim 2, further characterized by data selected from: a PXRD pattern having additional peaks at 9.1, 13.6, 18.2, 23.0 and 25.3 degrees two theta ± 0.2 degrees two theta; a DSC thermogram substantially as depicted in Figure 18; and combinations thereof.

4. The crystalline Form III of claim 1, characterized by a melting point from 185°C to about 190°C (peak maximum) in combination with a powder XRD pattern with peaks at 4.6, 9.7, 11.1, 17.8 and 22.3 degrees two theta ± 0.2 degrees two theta; and also having one, two, three, four or five peaks selected from 9.1, 13.6, 18.2, 23.0 and 25.3 degrees two theta ± 0.2 degrees two theta.

5. Crystalline Dabigatran Etexilate mesylate form G.

6. The crystalline Form G of claim 5, characterized by data selected from: a PXRD pattern with peaks at 4.5, 9.4, 11.1, 13.6 and 18.8 degrees 2-theta ± 0.2 degrees 2-theta, a PXRD pattern substantially as depicted in Figure 10, and combinations thereof.

7. The crystalline Form G of claim 6, further characterized by a DSC thermogram substantially as depicted in Figure 11.

8. Crystalline Dabigatran Etexilate form E.
9. The crystalline Form E of claim 8, characterized by data selected from: a PXRD pattern with peaks 4.6, 8.6, 17.6 and 21.2 degrees 2-theta ± 0.2 degrees 2-theta, a PXRD pattern substantially as depicted in Figure 8, and combinations thereof.

10. The crystalline Form E of claim 9, further characterized by an X-ray powder diffraction pattern having additional peaks at 13.8, 14.8, 20.5 and 22.7 degrees two theta ± 0.2 degrees two theta.

11. The crystalline Form E of claim 8, characterized by a powder XRD pattern with peaks at 4.6, 8.6, 17.6 and 21.2 degrees two theta ± 0.2 degrees two theta, and also having one, two, three or four peaks selected from 13.8, 14.8, 20.5 and 22.7 degrees two theta ± 0.2 degrees two theta.

12. Crystalline Dabigatran Etexilate form L.

13. The crystalline Form L of claim 12, characterized by a DSC thermogram shown in Figure 21 in combination with data selected from: a PXRD having peaks at 5.9, 11.8, 17.7, 19.9 and 26.5 degrees 2-theta ± 0.2 degrees 2-theta; a powder XRD having peaks at 5.9, 11.8, 13.5, 15.1, 17.7, 19.9, 20.4, 21.5, 24.6, 25.2, 26.5 and 27.2 degrees two theta ± 0.2 degrees two theta, a powder XRD substantially as depicted in Figure 20, and combinations thereof.

14. The crystalline Form L of claim 12, characterized by a DSC thermogram substantially as depicted in Figure 21 in combination with PXRD pattern having peaks at 5.9, 11.8, 17.7, 19.9 and 26.5 degrees 2-theta ± 0.2 degrees 2-theta and also having one, two, three, four or five additional peaks selected from 13.5, 15.1, 20.4, 21.5, 24.6, 25.2 and 27.2 degrees 2-theta ± 0.2 degrees 2-theta.

15. Amorphous Dabigatran Etexilate.

16. The amorphous Dabigatran Etexilate of claim 15, characterized by a PXRD pattern substantially as depicted in Figure 15.
17. The solid state forms of claim 8, or claim 12, or claim 15, for use in the preparation of Dabigatran Etexilate mesylate, solid state forms thereof, and formulations thereof.

18. A process for preparing Dabigatran etexilate mesylate comprising preparing Dabigatran etexilate in a solid state form selected from amorphous, Form E and Form L and converting it to Dabigatran etexilate mesylate.

19. The process of claim 18, comprising reacting said solid state form of Dabigatran etexilate with methanesulfonic acid.

20. A pharmaceutical composition comprising a solid state form according to any one of claims 1, 5, 8, 12, or 15; or any combination of said solid state forms, and at least one pharmaceutically acceptable excipient.

21. The crystalline form according to any one of claims 1, 5, 8, 12, or 15 for use in the manufacture of a pharmaceutical composition.

22. The crystalline form according to any one of claims 1, 5, 8, 12, or 15 for use in the manufacture of a pharmaceutical composition for treating or preventing blood clots in a patient suffering from, or susceptible to, the formation of blood clots.

23. A method of treating or preventing blood clots in a patient suffering from, or susceptible to, the formation of blood clots, comprising administering a pharmaceutical composition according to claim 20.
Figure 1: A PXRD pattern of crystalline Dabigatran etexilate mesylate designated form I.
Figure 2: A PXRD pattern of crystalline Dabigatran etexilate mesylate designated form A.
Figure 3: A Powder TGA thermogram of crystalline Dabigatran etexilate mesylate designated form A.
Figure 4: A PXRD pattern of amorphous Dabigatran etexilate mesylate.
Figure 5: PXRD pattern of crystalline Dabigatran etexilate mesylate designated form B.
Figure 6: A PXRD pattern of crystalline Dabigatran etexilate mesylate designated form C. (The peak at about 28.45 degrees 2-theta corresponds to silicon.)
Figure 7: A PXRD pattern of crystalline Dabigatran etexilate mesylate designated form D. (the peak at about 28.45 degrees 2-theta corresponds to silicon)
Figure 8: A PXRD pattern of crystalline Dabigatran etexilate designated form E. (The peak at about 28.45 degrees 2-theta corresponds to silicon.)
Figure 9: A PXRD pattern of crystalline Dabigatran etexilate designated form F. (The peak at about 28.45 degrees 2-theta corresponds to silicon)
Figure 10: A shows a PXRD pattern of crystalline Dabigatran etexilate mesylate form G.
Figure 11: A shows a powder DSC thermogram of crystalline Dabigatran etexilate mesylate form G.
Figure 12 shows a PXRD pattern of crystalline Dabigatran etexilate mesylate form H. (The peak at about 28.45 degrees 2-theta corresponds to silicon)
Figure 13 shows a PXRD pattern of crystalline Dabigatran etexilate designated form I.
Figure 14 shows a PXRD pattern of crystalline Dabigatran etexilate designated form K.
Figure 1.5 shows a PXRD pattern of amorphous Dabigatran etexilate. The peak at about 28-45 degrees 2-theta corresponds to silicon.
Figure 16 shows a PXRD pattern of crystalline Dabigatran etexilate tetrahydrate.
Figure 17 shows a PXRD pattern of crystalline Dabigatran etexilate mesylate form III.
Figure 18 shows a DSC thermogram of crystalline Dabigatran etexilate mesylate form III.
Figure 19 shows a microscope image of crystalline Dabigatran etexilate mesylate form III.

The image was recorded by OLIMPUS optical Microscop BX57.
Figure 20 shows a PXRD pattern of crystalline Dabigatran etexilate L.
Figure 21 shows a DSC thermogram of crystalline Dabigatran etexilate L.
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D401/12 A61P7/02

According to International Patent Classification (IPC) or to both national classification and IPC.

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal , CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
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Further documents listed in the continuation of Box C. | See patent family annex.

* Special categories of cited documents:

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<tr>
<td>&quot;E&quot;</td>
<td>Earlier document but published on or after the international filing date</td>
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<tr>
<td>&quot;L&quot;</td>
<td>Document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</td>
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<td>Document referring to an oral disclosure, use, exhibition or other means</td>
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Date of the actual completion of the international search: 6 October 2011

Date of mailing of the international search report: 03/01/2012

Name and mailing address of the ISA:
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk
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Authorized officer: Fanni Stefano
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<td>claims 35-36 f i g u r e 14</td>
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International application No.
PCT/US2011/049092

**INTERNATIONAL SEARCH REPORT**

**Box No. II** Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [ ] Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:

2. [ ] Claims Nos.: because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box No. III** Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

   Incompletely) 20-23 (partially)

**Remark on Protest**

- [ ] The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- [ ] The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- [ ] No protest accompanied the payment of additional search fees.

Form PCT/ISA/21 0 (continuation of first sheet (2)) (April 2005)
This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: Incompletely; 20-23(partially)

   Crystal line Dabigatran Etexilate mesylate Form III as defined in present claims 1 and 2, pharmaceutical compositions and medical uses thereof

2. claims: 5-7(completely); 20-23(partially)

   Crystal line Dabigatran Etexilate mesylate Form G as defined in present claims 5 and 6, pharmaceutical compositions and medical uses thereof

3. claims: 8-II (completely); 17-23(partially)

   Crystal line Dabigatran Etexilate mesylate Form E as defined in present claims 8 and 9, pharmaceutical compositions and medical uses thereof as well as the use of said form E in the preparation of Dabigatran Etexilate mesylate

4. claims: 12-14(completely); 17-23(partially)

   Crystal line Dabigatran Etexilate mesylate Form L as defined in present claims 12 and 13, pharmaceutical compositions and medical uses thereof as well as the use of said form L in the preparation of Dabigatran Etexilate mesylate

5. claims: 15, 16(completely); 17-23(partially)

   Amorphous form of Dabigatran Etexilate as defined in present claims 15 and 16, pharmaceutical compositions and medical uses thereof as well as the use of said amorphous form in the preparation of Dabigatran Etexilate mesylate
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