Abstract:
The present invention relates to pharmaceutically acceptable complex formulae comprising complexes of Dabigatran, its esters, preferably Dabigatran etexilate, its salts, preferably 5 Dabigatran etexilate mesylate, or derivatives thereof and complexation agents and pharmaceutically accepted excipients, process for the preparation thereof and pharmaceutical compositions containing them. The complex formulae of the present invention have improved physicochemical properties and enhanced biological performance and are useful in the treatment and/or prophylaxis of diseases, in particular thrombotic diseases, stroke, cardiac infarction and/or atrial fibrillation and cardiac arrhythmia, as well as oncological diseases of any pathogenesis. More specifically, the complex of the present invention possesses increased apparent solubility in the whole physiologically relevant pH range resulting in increased absorption and higher overall bioavailability. This allows the reduction of dose which delivers significantly less anticoagulant to the GI tract. Furthermore, the complex composition of the present invention contains no tartaric acid or any other acid which further decreases the incidence of GI tract bleeding. This also makes the bioavailability of the compound independent of the way it is administered; the final dosage form is not sensitive to being broken, chewed, or opened. Overall, the complex Dabigatran composition of the present invention allows safer administration of a lower dose from the active ingredient.
COMPLEXES OF DABIGATRAN AND ITS DERIVATIVES, PROCESS FOR THE PREPARATION THEREOF AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

FIELD OF THE INVENTION

The invention is directed to a stable complex with increased apparent solubility and increased dissolution rate comprising as active compound Dabigatran, its esters, preferably Dabigatran etexilate, its salts, preferably Dabigatran etexilate mesylate, or derivatives thereof, which is useful in the treatment and/or prophylaxis of diseases, in particular thrombotic diseases, stroke, cardiac infarction and/or atrial fibrillation and cardiac arrhythmia, as well as oncological diseases of any pathogenesis. More specifically, the complex of the present invention possesses increased apparent solubility in the whole physiologically relevant pH range resulting in increased absorption and higher overall bioavailability. This allows the reduction of dose which delivers significantly less anticoagulant to the GI tract. Furthermore, the complex Dabigatran, its esters, preferably Dabigatran etexilate, its salts, preferably Dabigatran etexilate mesylate, or derivatives thereof of the present invention contains no tartaric acid or any other acid which further decreases the incidence of GI tract bleeding. This also makes the bioavailability of the compound independent of the way it is administered; the final dosage form is not sensitive to being broken, chewed, or opened. Overall, the complex Dabigatran, its esters, preferably Dabigatran etexilate, its salts, preferably Dabigatran etexilate mesylate, or derivatives thereof of the present invention allows safer administration of a lower dose from the active ingredient.

BACKGROUND OF THE INVENTION

Background Regarding Dabigatran

Dabigatran was discovered from a panel of chemicals with similar structure to benzamidine-based thrombin inhibitor a-NAPAP (N-alpha-(2-naphthylsulfonylglycyl)-4-amidinophenylalanine piperidide), which had been known since the 1980s as a powerful inhibitor of various serine proteases, specifically thrombin, but also trypsin. Addition of ethyl ester and hexyloxycarbonyl carbamide hydrophobic side chains led to the orally absorbed
prodrug. In order to improve the solubility of the prodrug its salts form was formulated as final drug product.

The chemical name for Dabigatran etexilate mesylate, is β-Alanine, N-[[2-[[4-[(hexyloxy)carbonyl]amino]iminomethyl]phenyl]amino]methyl]-1-methyl-1H-benzimidazol-5-yl]carbonyl]-N-2-pyridinyl-,ethyl ester, methanesulfonate. The empirical formula is C$_{34}$H$_{41}$N$_7$O$_5$·CH$_4$O$_9$S and the molecular weight is 723.86 (mesylate salt), 627.75 (free base). The structural formula is:

![](image)

Dabigatran etexilate mesylate is a yellow-white to yellow powder. A saturated solution in pure water has a solubility of 1.8 mg/mL. It is freely soluble in methanol, slightly soluble in ethanol, and sparingly soluble in isopropanol.

Based on these physicochemical and biopharmaceutical properties of Dabigatran etexilate mesylate and the clinical requirements for a reliable drug release a multilayer pellet was developed. Other formulation approaches were evaluated during early development, but were inferior to the selected formulation in terms of drug load, stability and *in vivo* performance.

The active substance is susceptible to hydrolysis in presence of humidity under acidic conditions. Batch analysis results confirm that alkyl methane sulfonates (genotoxic impurities) that could potentially be formed during manufacturing are not formed at detectable levels during the manufacturing of the finished product.

The 150 mg capsule (PRAXADA) for oral administration contains 172.95 mg Dabigatran etexilate mesylate, which is equivalent to 150 mg of Dabigatran etexilate, and the following pharmaceutically acceptable excipients: acacia, dimethicone, hypromellose, hydroxypropyl cellulose, talc, and tartaric acid. The capsule shell is composed of carrageenan, FD&C Blue No. 2 (150 mg only), FD&C Yellow No. 6, hypromellose, potassium chloride, titanium
dioxide, and black edible ink. The 75 mg capsule contains 86.48 mg dabigatran etexilate mesylate, equivalent to 75 mg dabigatran etexilate, and is otherwise similar to the 150 mg capsule.

PRAXADA should be swallowed as a whole with water, with or without food. Patients have to be instructed not to open the capsule as this may increase the risk of bleeding.

Dabigatran and its acyl glucuronides are competitive, direct thrombin inhibitors. Because thrombin (serine protease) enables the conversion of fibrinogen into fibrin during the coagulation cascade, its inhibition prevents the development of a thrombus. Both free and clot-bound thrombin and thrombin-induced platelet aggregation are inhibited by the active moieties.

Dabigatran etexilate mesylate is absorbed as the dabigatran etexilate ester. The ester is then hydrolyzed, forming dabigatran, the active moiety. Dabigatran is metabolized to four different acyl glucuronides and both the glucuronides and dabigatran have similar pharmacological activity. Pharmacokinetics described here refer to the sum of dabigatran and its glucuronides. Dabigatran displays dose-proportional pharmacokinetics in healthy subjects and patients in the range of doses from 10 to 400 mg.

The absolute bioavailability of dabigatran following oral administration of dabigatran etexilate is approximately 3 to 7%. Dabigatran etexilate is a substrate of the efflux transporter P-gp. After oral administration of dabigatran etexilate in healthy volunteers, C_{max} occurs at 1 hour post-administration in the fasted state. Co-administration of PRADAXA with a high-fat meal delays the time to C_{max} by approximately 2 hours but has no effect on the bioavailability of dabigatran; PRADAXA may be administered with or without food.

The oral bioavailability of dabigatran etexilate increases by 75% when the pellets are taken without the capsule shell compared to the intact capsule formulation. PRADAXA capsules should therefore not be broken, chewed, or opened before administration.

Dabigatran is approximately 35% bound to human plasma proteins. The red blood cell to plasma partitioning of dabigatran measured as total radioactivity is less than 0.3. The volume of distribution of dabigatran is 50 to 70 L. Dabigatran pharmacokinetics are dose proportional after single doses of 10 to 400 mg. Given twice daily, dabigatran's accumulation factor is approximately two.
Dabigatran is eliminated primarily in the urine. Renal clearance of Dabigatran is 80% of total clearance after intravenous administration. After oral administration of radiolabeled Dabigatran, 7% of radioactivity is recovered in urine and 86% in feces. The half-life of Dabigatran in healthy subjects is 12 to 17 hours.

After oral administration, Dabigatran etexilate is converted to Dabigatran. The cleavage of the Dabigatran etexilate by esterase-catalyzed hydrolysis to the active principal Dabigatran is the predominant metabolic reaction. Dabigatran is not a substrate, inhibitor, or inducer of CYP450 enzymes. Dabigatran is subject to conjugation forming pharmacologically active acyl glucuronides. Four positional isomers, 1-0, 2-0, 3-0, and 4-O-acylglucuronide exist, and each accounts for less than 10% of total Dabigatran in plasma.

The most commonly reported adverse reactions are bleedings occurring in total in approximately 16.5% in patients with atrial fibrillation treated for the prevention of stroke and systemic embolic events. A dose response with respect to bleeding was seen for Dabigatran etexilate. Major or severe bleeding may occur and, regardless of location, may lead to disabling, life-threatening or even fatal outcomes.

The European Medicines Agency has recommended updating the product information for the blood thinner PRAXADA, to give clearer guidance to doctors and patients on how to reduce and manage the risk of bleeding associated with the anticoagulant medicine. Bleeding is a well-known complication of all anticoagulant medicines and PRAXADA has therefore been kept under close review by the Agency's Committee for Medicinal Products for Human Use (CHMP) since its initial authorization (25 May 2012, EMA/337406/2012).

FDA has not changed its recommendations regarding PRAXADA. PRAXADA provides an important health benefit when used as directed. Healthcare professionals who prescribe PRAXADA should carefully follow the dosing recommendations in the drug label, especially for patients with renal impairment (when kidneys don't function normally) to reduce the risk of bleeding. Patients with atrial fibrillation should not stop taking PRAXADA without first talking to their healthcare professional. Stopping use of anticoagulant medications such as PRAXADA can increase the risk of stroke. Strokes can lead to permanent disability and death (FDA Drug Safety Communication of 12/19/2012).
The solubility of the Dabigatran ester is pH sensitive. Below pH 4.2 its solubility is actually appreciable. Above this pH it decreases rapidly reaching practically insoluble levels in the 6-7 pH range.

Dabigatran etexilate is available in capsule form (PRADAXA). It is formulated together with tartaric acid to reduce the variability of Dabigatran etexilate absorption, which is dependent on an acid environment. A Dabigatran etexilate coating is applied onto a tartaric acid core to form tiny pellets (~1mm diameter). A single capsule contains hundreds of these pellets, the exact number depending on the dose strength of the capsule. In this way, Dabigatran etexilate absorption is independent of gastrointestinal tract acidity and is not materially affected by co-administration of a proton pump inhibitor. The oral bioavailability of Dabigatran etexilate increases by 75% when the pellets are taken without the capsule shell compared to the intact capsule formulation. PRADAXA capsules should therefore not be broken, chewed, or opened before administration.

The low systemic oral bioavailability is attributed to the low solubility of the compound at physiologically relevant pH. The above formulation strategy ensures the absorption of the compound by creating a low pH milieu in the upper intestine (the first part of the duodenum) which dissolves the compound. At the lower parts of the GI track where pH is raised to the 6-7 range the compound precipitates. This creates a short window (around 0.5 h) for the compound to get absorbed.

As a result of this pH dependent solubility the absolute bioavailability of Dabigatran following oral administration of Dabigatran etexilate is approximately 3 to 7% even when using the above detailed formulation strategy. This makes it necessary to administer high doses which deliver substantial amount of tartaric acid and an anticoagulant to the GI tract. This results in GI tract bleeding as a very common adverse effect of the drug. The risk of major bleeds was similar with PRADAXA 150 mg and warfarin across major subgroups defined by baseline characteristics, with the exception of age, where there was a trend towards a higher incidence of major bleeding on PRADAXA (hazard ratio 1.2, 95% CI: 1.0 to 1.4) for patients ≥75 years of age. There was a higher rate of major gastrointestinal bleeds in patients receiving PRADAXA 150 mg than in patients receiving warfarin (1.6% vs. 1.1%, respectively, with a hazard ratio vs. warfarin of 1.5, 95% CI, 1.2 to 1.9), and a higher rate of any gastrointestinal bleeds (6.1% vs. 4.0%, respectively). It has been hypothesized that tartaric
acid may promote GI bleeding through caustic injury, this is likely to be the case because the anti-platelet medication Aggrenox® (aspirin and dipyridamole), which is formulated with similar amounts of tartaric acid, is also associated with increased GI bleeding.


DESCRIPTION OF THE INVENTION

Disclosed herein is a stable complex comprising as active compound chosen from Dabigatran, its salts or derivatives thereof; and at least one complexation agent chosen from polyvinylcaprolactam-polyvinyl acetate-polyethylene-glycol graft copolymers and poloxamers; polyvinylpyrrolidone; polyoxyglicerides; copolymers of vinylpyrrolidone and
vinyl-acetate; and poly(maleic acid-co-methyl-vinyl-ether); said complex characterized in that it possesses at least one of the following properties:

a) having a particle size in the range between 50 nm and 600 nm, preferably 50 nm and 300 nm;

b) is instantaneously redispersable in buffers in physiological pH range;

c) is stable in solid form and in colloid solution and/or dispersion;

d) exhibits pH independent PAMPA permeability in the physiological pH range

e) has a PAMPA permeability of at least 0.3*10^{-6} cm/s when dispersed in FaSSIF or FeSSIF biorelevant media;

f) is characterized by infrared (ATR) spectrum having main/characteristic absorption peaks at 1730 cm^{-1}, 1608 cm^{-1}, 1468 cm^{-1}, 1437 cm^{-1}, 1384 cm^{-1}, 1328 cm^{-1}, 1252 cm^{-1}, 1193 cm^{-1}, 1144 cm^{-1}, 1118 cm^{-1}, 1098 cm^{-1}, 1052 cm^{-1}, 993 cm^{-1}, 948 cm^{-1}, 888 cm^{-1}, 837 cm^{-1}, 811 768 cm^{-1}, 754 cm^{-1}, 704 cm^{-1}, 680 cm^{-1}, 632 cm^{-1}, 604 cm^{-1}, 567 cm^{-1}, 545 cm^{-1} and 524 cm^{-1}, preferably at 1730 cm^{-1}, 1608 cm^{-1}, 1437 cm^{-1}, 1328 cm^{-1}, 1118 cm^{-1}, 1098 cm^{-1}, and 754 cm^{-1}.

The invention is a complex formula having increased and pH independent permeability in the physiological relevant pH range and enhanced biological performance including higher $C_{\text{max}}$ and AUC, faster onset of action and decreased fed/fasted effect.

We have found that only selected combinations of complexation agents and pharmaceutically accepted excipients disclosed in the present invention result in a stable complex formula having improved physicochemical characteristics and enhanced biological performance.

The expression Dabigatran is generally used for Dabigatran, its esters, such as Dabigatran etexilate or its salts such as Dabigatran etexilate mesylate, Dabigatran etexilate methanesulphonate, Dabigatran etexilate bimesylate or derivatives of Dabigatran.

In an embodiment, said complexation agent is chosen from polyvinylcaprolactam-polyvinyl acetate-polyethylene-glycol graft copolymers and poloxamers; polyvinylpyrrolidone; polyoxyglicerides; copolymers of vinylpyrrolidone and vinyl-acetate; and poly(maleic acid-co-methyl-vinyl-ether).
In an embodiment, said complex further comprises at least one pharmaceutically acceptable excipient selected from the group of sodium-acetate, sodium-lauryl-sulfate, dioctyl sodium sulfosuccinate, cetylpyridinium chloride and sodium saccharine.

In an embodiment, said complex has a controlled particle size in the range between 50 nm and 600 nm. In an embodiment, said particle size is between 50 nm and 300 nm.

In an embodiment, said complex further comprises one or more additional active agents.

In an embodiment, said additional active agent is chosen from agents useful for the prophylaxis of diseases, in particular thrombotic diseases, stroke, cardiac infarction and/or atrial fibrillation and cardiac arrhythmia, as well as oncological diseases of any pathogenesis.

In an embodiment, said complex is orally available.

In an embodiment, said complex possesses at least two of the properties described in a) - f).

In an embodiment, said complex possesses at least three of the properties described in a) - f).

In an embodiment, said complex has an increased dissolution rate.

Further disclosed herein is a stable complex comprising an active compound selected from the group of Dabigatran, its salt, or derivatives thereof; at least one complexation agent chosen from polyvinylcaprolactam-polyvinyl acetate-polyethylene-glycol graft copolymers and poloxamers; polyvinylpyrrolidone; polyoxyglicerides; copolymers of vinylpyrrolidone and vinyl-acetate; and poly(maleic acid-co-methyl-vinyl-ether); and at least one pharmaceutically acceptable excipient chosen from sodium-acetate, sodium-lauryl-sulfate, dioctyl sodium sulfosuccinate, cetylpyridinium chloride and sodium saccharine; wherein said complex obtained via a mixing process.

In an embodiment, said complex is obtained via a continuous flow mixing process.

In an embodiment, a complex comprises a complexation agent and a pharmaceutically acceptable excipient in a total amount ranging from about 1.0 weight% to about 95.0 weight% based on the total weight of the complex.

In an embodiment, said complexation agent and pharmaceutically acceptable excipient comprise 50 weight% to about 95 weight% of the total weight of the complex.
Further disclosed herein is a process for the preparation of the complex, comprising the steps of mixing a solution of Dabigatran, its salt, or derivatives thereof; and at least one complexation agent chosen from polyvinylcaprolactam-polyvinyl acetate-polyethylene-glycol graft copolymers and poloxamers; polyvinylpyrrolidone; polyoxyglicerides; copolymers of vinylpyrrolidone and vinyl-acetate; and poly(maleic acid-co-methyl-vinyl-ether) in a pharmaceutically acceptable solvent with an aqueous solution containing and at least one pharmaceutically acceptable excipient chosen from sodium-acetate, sodium-lauryl-sulfate, dioctyl sodium sulfosuccinate, cetylpyridinium chloride and sodium saccharine.

In an embodiment, said process is performed in a continuous flow instrument.

In an embodiment, said continuous flow instrument is a microfluidic flow instrument.

In an embodiment, said pharmaceutically acceptable solvent is chosen from methanol, ethanol, i-propanol, n-propanol, acetone, acetonitrile, dimethyl-sulfoxide, or tetrahydrofuran, or combinations thereof.

In an embodiment, said pharmaceutically acceptable solvent and said aqueous solvent are miscible with each other.

In an embodiment, said aqueous solvent comprises 0.1 to 99.9% weight of the final solution.

In an embodiment, said aqueous solvent comprises 50 to 90% weight of the final solution.

In an embodiment, said aqueous solvent comprises 50 to 80% weight of the final solution.

In an embodiment, said aqueous solvent comprises 50 to 70% weight of the final solution.

In an embodiment, said aqueous solvent comprises 50 to 60% weight of the final solution.

In an embodiment, said aqueous solvent comprises 50 % weight of the final solution.

In an embodiment, a pharmaceutical composition comprising the complex together with pharmaceutically acceptable carrier.

In an embodiment, said composition is suitable for oral, pulmonary, rectal, colonic, parenteral, intracisternal, intravaginal, intraperitoneal, ocular, otic, local, buccal, nasal, or topical administration.
In an embodiment, said composition is suitable for oral administration.

In an embodiment, said complex is for use in the manufacture of a medicament for the treatment and/or prophylaxis of diseases, in particular thrombotic diseases, stroke, cardiac infarction and/or atrial fibrillation and cardiac arrhythmia, as well as oncological diseases of any pathogenesis.

In an embodiment, said complex is used for the treatment and/or prophylaxis of diseases, in particular thrombotic diseases, stroke, cardiac infarction and/or atrial fibrillation and cardiac arrhythmia, as well as oncological diseases of any pathogenesis.

In an embodiment, a method of treatment and/or prophylaxis of diseases, in particular thrombotic diseases, stroke, cardiac infarction and/or atrial fibrillation and cardiac arrhythmia, as well as oncological diseases of any pathogenesis comprises administration of a therapeutically effective amount of a complex or a pharmaceutical composition as described herein.

In an embodiment, a method for reducing the therapeutically effective dosage of Dabigatran compared to orally available formulations comprises oral administration of a pharmaceutical composition as described herein.

Further disclosed herein is a stable complex wherein said complex has a controlled particle size in the range between 50 nm and 600 nm; and wherein said complex is not obtained via a milling process or by high pressure homogenization process, encapsulation process and solid dispersion process, but it is obtained by a mixing process, preferable continuous flow mixing process.

In an embodiment, said particle size is between 50 nm and 300 nm.

In an embodiment, said complex shows reduced fed/fasted effect based on in vivo studies.

In an embodiment, said complex shows significantly improved exposure, earlier $t_{\text{max}}$, higher $C_{\text{max}}$ which will allow the oral administration and reduction of the dose.

In an embodiment, said complex has a faster onset of action compared to the marketed formulations.
In an embodiment, said complex is instantaneously redispersable in physiological relevant media.

In an embodiment, said complex is stable in solid form and in colloid solution and/or dispersion.

5 In an embodiment, said complex exhibits pH independent PAMPA permeability in the physiological pH range.

In an embodiment, said complex has a PAMPA permeability of at least $0.3 \times 10^{-6}$ cm/s when dispersed in FaSSIF or FeSSIF biorelevant media

In an embodiment, said complex is characterized by infrared (ATR) spectrum having characteristic absorption peaks at 1730 cm$^{-1}$, 1608 cm$^{-1}$, 1468 cm$^{-1}$, 1437 cm$^{-1}$, 1384 cm$^{-1}$, 1328 cm$^{-1}$, 1252 cm$^{-1}$, 1193 cm$^{-1}$, 1144 cm$^{-1}$, 1118 cm$^{-1}$, 1098 cm$^{-1}$, 1052 cm$^{-1}$, 993 cm$^{-1}$, 948 cm$^{-1}$, 888 cm$^{-1}$, 837 cm$^{-1}$, 811 768 cm$^{-1}$, 754 cm$^{-1}$, 704 cm$^{-1}$, 680 cm$^{-1}$, 632 cm$^{-1}$, 604 cm$^{-1}$, 567 cm$^{-1}$, 545 cm$^{-1}$ and 524 cm$^{-1}$, preferable at 1730 cm$^{-1}$, 1608 cm$^{-1}$, 1437 cm$^{-1}$, 1328 cm$^{-1}$, 1118 cm$^{-1}$, 1098 cm$^{-1}$, and 754 cm$^{-1}$.

15 In an embodiment, said complex has decreased incidence of GI tract bleeding adverse side effect when compared to the marketed form.

The complexation agents and pharmaceutically acceptable excipients of the Dabigatran complex formulae of the invention are selected from the group of pharmaceutically acceptable nonionic, anionic, cationic, ionic polymers, surfactants and other types of excipients. The complexation agents themselves or together with the pharmaceutically accepted excipients have the function to form a complex structure with an active pharmaceutical ingredient through non-covalent secondary interactions. The secondary interactions can form through electrostatic interactions such as ionic interactions, H-bonding, dipole-dipole interactions, dipole-induced dipole interactions, London dispersion forces, π-π interactions, and hydrophobic interactions. The complexation agents, pharmaceutically accepted excipients and active ingredients are selected from the group of complexation agents, pharmaceutically accepted excipients and active ingredients which are able to form such complex structures through non-covalent secondary interactions.
In some embodiments, the compositions may additionally include one or more pharmaceutically acceptable excipients, auxiliary materials, carriers, active agents or combinations thereof. In some embodiments, active agents may include agents useful for the treatment and/or prophylaxis of diseases, in particular thrombotic diseases, stroke, cardiac infarction and/or atrial fibrillation and cardiac arrhythmia, as well as oncological diseases of any pathogenesis.

Another aspect of the invention is the complex formulae of the Dabigatran with complexation agents and pharmaceutically acceptable excipients in which the complexation agents and pharmaceutically acceptable excipients preferably are associated or interacted with the Dabigatran especially as the results of the mixing process, preferably continuous flow mixing process. In some embodiment, the structure of the complex Dabigatran formula is different from the core-shell type milled particle, precipitated encapsulated particles, micelles and solid dispersions.

The pharmaceutical composition of the invention can be formulated: (a) for administration selected from the group consisting of oral, pulmonary, rectal, colonic, parenteral, intracisternal, intravaginal, intraperitoneal, ocular, otic, local, buccal, nasal, and topical administration; (b) into a dosage form selected from the group consisting of liquid dispersions, gels, aerosols, ointments, creams, lyophilized formulations, tablets, capsules; (c) into a dosage form selected from the group consisting of controlled release formulations, fast melt formulations, delayed release formulations, extended release formulations, pulsatile release formulations, and mixed immediate release and controlled release formulations; or (d) any combination of (a), (b), and (c).

The compositions can be formulated by adding different types of excipients for oral administration in solid, liquid, local (powders, ointments or drops), or topical administration, and the like.

The compositions can be formulated by adding different types of pharmaceutically acceptable excipients for oral administration in solid, liquid, local (powders, ointments or drops), or topical administration, and the like.

A preferred dosage form of the invention is a solid dosage form, although any pharmaceutically acceptable dosage form can be utilized.
Solid dosage forms for oral administration include, but are not limited to, capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active agent is admixed with at least one of the following excipients: (a) one or more inert excipients (or carriers), such as sodium citrate or dicalcium phosphate; (b) fillers or extenders, such as starches, lactose, sucrose, glucose, mannitol, microcrystalline cellulose and silicic acid; (c) binders, such as cellulose derivatives, alginates, gelatin, polyvinylpyrrolidone, sucrose and acacia; (d) humectants, such as glycerol; (e) disintegrating agents, such as crospovidon, sodium starch glycolate, effervescent compositions, croscarmellose sodium, calcium carbonate, potato or tapioca starch, alginic acid, certain complex silicates and sodium carbonate; (f) solution retarders, such as acrylates, cellulose derivatives, paraffin; (g) absorption accelerators, such as quaternary ammonium compounds; (h) wetting agents, such as polysorbates, cetyl alcohol and glycerol monostearate; (i) adsorbents, such as kaolin and bentonite; and (j) lubricants, such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, or mixtures thereof. For capsules, tablets, and pills, the dosage forms may also comprise buffering agents.

Besides such inert diluents, the composition can also include adjuvants, such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents.

Advantages of the complex Dabigatran formulae of the invention include, but are not limited to (1) physical and chemical stability, (2) instantaneous redispersibility, (3) stability in colloid solution or dispersion in the therapeutic time window, (4) increased solubility compared to the conventional Dabigatran formulation at physiologically relevant pH, (5) increased and pH independent permeability in the physiological relevant pH range, (6) possibility of dose reduction, (7) reduced GI tract bleeding adverse effect due to decreased anticoagulant dose and no strong acid necessary to be added to the formula and (8) good processability.

Beneficial features of the present invention are as follows: the good/instantaneous redispersibility of solid complex formulae of Dabigatran in water, biologically relevant media, e.g.: physiological saline solution, pH=2.5 HC1 solution, FessiF and FassiF media and gastro intestinal fluids and adequate stability in colloid solutions and/or dispersion in the therapeutic time window.

One of the preferred characteristics of the complex Dabigatran formulae of the present invention is their increased apparent solubility and pH independent increased permeability. In
some embodiments, the permeability of the complex Dabigatran formulae is at least $0.574 \times 10^{-6}$ cm/s, $0.376 \times 10^{-6}$ cm/s and $0.421 \times 10^{-6}$ cm/s in the 5-8.5 pH range, respectively.

Finally, the invention relates to a method for the treatment of a subject in need for the treatment and/or prophylaxis of diseases, in particular thrombotic diseases, stroke, cardiac infarction and/or atrial fibrillation and cardiac arrhythmia, as well as oncological diseases of any pathogenesisby administering to the subject an effective amount of the complex or the pharmaceutical composition according to the invention.

Another preferred characteristic of the complex Dabigatran formulae of the present invention relates to the enhanced pharmacokinetic performance of the complex Dabigatran formulae. The complex Dabigatran is available for absorption in the whole GI tract extending the window for absorption from 0.5 hour to 4-5 hours and allows safer administration of a lower dose from the active ingredient.

**BRIEF DESCRIPTION OF THE DRAWINGS**

**Figure 1.** shows complexation agent and pharmaceutically acceptable excipient screening for formula selection

**Figure 2.** shows particle size of the redispersed solid complex of the selected formula

**Figure 3.** shows SEM photos of complex Dabigatran (A) and placebo sample (B)

**Figure 4.** shows infrared (ATR) spectra of Crystalline Dabigatran etexilate (A), amorphous Dabigatran etexilate (B), complex Dabigatran exelate (C), placebo (D), Gelucire 44/14 (E), CPC (F) and Sacharine (G)

**Figure 5.** shows comparative PAMPA assays of complex Dabigatran formula and the marketed compound (Pradaxa)

**Figure 6.** shows pharmacokinetic properties of Dabigatran following the oral administration of Pradaxa (granules from the capsule) and complex Dabigatran Etexilate (dispersed in pH 8.5 Tris buffer) in rats in the fasted state at 3 mg/kg dose (n=4)
EXAMPLES

1. Selection of complexation agents and pharmaceutically accepted stabilizers for the production of complex Dabigatran formulae

Several pharmaceutically accepted complexation agents and pharmaceutically accepted excipients and their combinations were tested in order to select the formulae having instantaneous redispersibility as shown in Figure 1. One of the examples that displayed an acceptable level of redispersibility was selected for further analysis.

2. Process for producing stable colloid solution and or dispersion of solid complex Dabigatran formula

A colloid solution of Dabigatran complex formula with the optimal ratio of the pharmaceutically acceptable excipients of the present invention was prepared by continuous flow mixing in a flow instrument. As a starting solution, 200 mg Dabigatran etexilate and 600 mg polyoxygliceride (Gelucire 44/14) dissolved in 100 mL tetrahydrofuran was used. The prepared solution was passed into the instrument with 2 mL/min flow rate. Meanwhile, aqueous solvent containing 50 mg cetylpyridinium chloride and 250 mg sodium saccharine in 500 mL water was passed into the instrument with 8 mL/min flow rate, where Dabigatran formed complex Dabigatran composition. The colloid solution of the complex Dabigatran is continuously produced at atmospheric pressure. The produced colloid solution was frozen on dry-ice and then it was lyophilized using a freeze drier equipped with -110°C ice condenser, with a vacuum pump. Particle size of complex Dabigatran was measured in reconstituted colloid solution right after the lyophilisation. It was found to be 156 nm as shown in Figure 2.

3. Structural analysis

Morphology of complex Dabigatran etexilate of Example 2 was investigated using FEI Quanta 3D scanning electron microscope. The morphology of the complex of the present invention was compared to the placebo sample prepared in the lack of Dabigatran etexilate. Complex Dabigatran of the present invention consists of spherical particles. In the lack of the active compound, the pharmaceutically acceptable excipients do not form spherical particles as shown in Figure 3.
Structural analysis was performed by using Bruker Vertex 70 FT-IR spectrometer with Bruker Platinum diamond ATR unit. Continuous flow mixing of Dabigatran etexilate in the presence of selected complexation agents and pharmaceutically accepted excipients, such as polyoxgliceride (Gelucire 44/14), cetylpyridinium chloride and sodium saccharine resulted in a stable complex of Dabigatran as shown in Figure 4. In a preferred embodiment the complex or the pharmaceutical composition according to the invention characterized by at least one of the following characteristic infrared (ATR) peak at 1730 cm\(^{-1}\), 1608 cm\(^{-1}\), 1468 cm\(^{-1}\), 1437 cm\(^{-1}\), 1384 cm\(^{-1}\), 1328 cm\(^{-1}\), 1252 cm\(^{-1}\), 1193 cm\(^{-1}\), 1144 cm\(^{-1}\), 1118 cm\(^{-1}\), 1098 cm\(^{-1}\), 1052 cm\(^{-1}\), 993 cm\(^{-1}\), 948 cm\(^{-1}\), 888 cm\(^{-1}\), 837 cm\(^{-1}\), 811 768 cm\(^{-1}\), 754 cm\(^{-1}\), 704 cm\(^{-1}\), 680 cm\(^{-1}\), 632 cm\(^{-1}\), 604 cm\(^{-1}\), 567 cm\(^{-1}\), 545 cm\(^{-1}\) and 524 cm\(^{-1}\), preferable at 1730 cm\(^{-1}\), 1608 cm\(^{-1}\), 1437 cm\(^{-1}\), 1328 cm\(^{-1}\), 1118 cm\(^{-1}\), 1098 cm\(^{-1}\), and 754 cm\(^{-1}\).

4. Comparative in vitro PAMPA assays

PAMPA permeability measurements were performed as described by M. Kansi et al. (Journal of medicinal chemistry, 41, (1998) pp 1007) with modifications based on S. Bendels et al (Pharmaceutical research, 23 (2006) pp 2525). Sample containing the reference compound was a suspension of crystals visible by the naked eye, while samples of the novel complex were opalescent colloid solutions. Permeability was measured in a 96-well plate assay across an artificial membrane composed of dodecane with 20% soy lecithin supported by a PVDF membrane (Millipore, USA). The receiver compartment was phosphate buffered saline (pH 7.0) supplemented with 1% sodium dodecyl sulfate. The assay was performed at room temperature; incubation time was 1-24 hours. The concentration in the receiver compartment was determined by UV-VIS spectrophotometry (Thermo Scientific Genesys S10).

PAMPA permeability of complex Dabigatran formula of Example 2 was 0.574* 10\(^{-6}\) cm/s, 0.376* 10\(^{-6}\) cm/s and 0.421*10\(^{-6}\) cm/s when dispersed in a buffer pH 5.0, 6.5 or 8.5, respectively, while permeability of the marketed compound (Pradaxa) was 0.094* 10\(^{-6}\) cm/s, 0.060* 10\(^{-6}\) cm/s and 0.020* 10\(^{-6}\) cm/s when dispersed in the same buffers as shown in Figure 5.

5. Comparative in vivo study

The main objective of this study was the pharmacokinetic evaluation of a Dabigatran etexilate complex formulation following a single oral administration at 3 mg/kg dose to jugular vein
cannulated male Wistar rats. The mean metabolite, Dabigatran was measured in plasma using a reliable LC/MS6MS method.

The test item substance was formulated in 0.1M Tris buffer (pH=8.5). The test item was administered to the rats orally by gavage. The granules of the reference item were administered through a plastic gavage into the stomach of the rats. The granules were pushed out with the help of a mandrin then water was administered in a same amount as the test item administration amount.

Blood was collected in the following time points using sodium heparin as anticoagulant: 15m, 30m, 45m, 1h, 1.5h, 2h, 4h, 6h, and 8h. The plasma was separated and stored in an ultra-freezer (below -70°C) until analysis.

Dabigatran plasma kinetics showed high inter-individual variability after dosing the reference item. After dosing of the reference item the shape of the individual curves and the \( t_{\text{max}} \) values (0.25h - 4h) showed very high variability and the \( C_{\text{max}} \) values varied in a range (80.6 ± 37.0).

For the test item peak concentrations of Dabigatran occurred at 0.25h - 0.5h after administration in all the four rats. The average \( C_{\text{max}} \) value was 210 ± 154 ng/ml. The elimination of Dabigatran from the plasma was relatively fast: the mean half-life was 1.60 ± 0.291 h. The AUC_{\text{inf}} values were 470 ± 243 ng*h/ml. This total exposure of the complex formulation was compared to the AUC_{\text{inf}} value obtained for a reference formulation (Pradaxa) after administration of the same oral dose of Dabigatran etexilate. The AUC_{\text{inf}} of Pradaxa was 280 ± 93.7 ng*h/ml. The relative oral bioavailability \( (F_{\text{rel}}) \) of the investigated nano-formulation proved to be 168% (Figure 6).
Claims

1. A stable complex comprising as active compound selected from the group of Dabigatran, its esters, preferably Dabigatran etexilate, its salts, preferably Dabigatran etexilate mesylate, or derivatives thereof; and at least one complexation agent selected from the group of a polyvinylcaprolactam-polyvinyl acetate-polyethylene-glycol graft copolymers and poloxamers; polyvinylpyrrolidone; polyoxyglicerides; copolymers of vinylpyrrolidone and vinyl-acetate; and poly(maleic acid-co-methyl-vinyl-ether); said complex characterized in that it possesses at least one of the following properties:

   a) having a particle size in the range between 50 nm and 600 nm, preferably 50 nm and 300 nm;
   b) is instantaneously redispersable in buffers in physiological pH range;
   c) is stable in solid form and in colloid solution and/or dispersion;
   d) exhibits pH independent PAMPA permeability in the physiological pH range;
   e) has a PAMPA permeability of at least 0.3*10⁻⁶ cm/s when dispersed in FaSSIF or FeSSIF biorelevant media;
   f) is characterized by infrared (ATR) spectrum having main/characteristic absorption peaks at 1730 cm⁻¹, 1608 cm⁻¹, 1437 cm⁻¹, 1328 cm⁻¹, 1118 cm⁻¹, 1098 cm⁻¹, and 754 cm⁻¹;
   g) has reduced fed/fasted effect based on in vivo studies.
   h) has significantly improved exposure, earlier $t_{max}$, higher $C_{max}$ which will allow the oral administration and reduction of the dose.
   i) has a faster onset of action compared to the marketed formulations.

2. The complex according to Claim 1, wherein said complexation agent is selected from the group of polyvinylcaprolactam-polyvinyl acetate-polyethylene-glycol graft copolymers and poloxamers; polyvinylpyrrolidone; polyoxyglicerides; copolymers of vinylpyrrolidone and vinyl-acetate; and poly(maleic acid-co-methyl-vinyl-ether).

3. A complex according to Claims 1 or 2, wherein said complex further comprises at least one pharmaceutically accepted excipient selected from the group of sodium-lauryl-sulfate;
dioctyl sodium sulfosuccinate; cetylpyridinium chloride, sodium-acetate and sodium saccharine, preferably cetylpyridinium chloride and sodium saccharine.

4. The complex according to any of Claims 1 to 3, wherein said complex further comprises one or more additional active agents, preferable the additional active agent is selected from the group of agents useful for the treatment and/or prophylaxis of diseases, in particular thrombotic diseases, stroke, cardiac infarction and/or atrial fibrillation and cardiac arrhythmia, as well as oncological diseases of any pathogenesis.

5. The complex according to Claim 1, wherein said complex is orally bioavailable.

6. A stable complex according to any Claims 1 to 5 comprising an active compound selected from the group of Dabigatran, its esters, preferably Dabigatran etexilate, its salts, preferably Dabigatran etexilate mesylate, or derivatives thereof; at least one complexation agent selected from the group of a polyvinylcaprolactam-polyvinyl acetate-polyethylene-glycol graft copolymers and poloxamers; polyvinylpyrrolidone; polyoxyglicerides; copolymers of vinylpyrrolidone and vinyl-acetate; and poly(maleic acid-co-methyl-vinyl-ether), and at least one pharmaceutically accepted excipient chosen from the group of sodium-lauryl-sulfate; dioctyl sodium sulfosuccinate; cetylpyridinium chloride, sodium-acetate and sodium saccharine; wherein said complex obtained via a mixing process, preferable continuous flow mixing process, more preferable microfluidic flow mixing process.

7. A complex according to Claims 1 to 6 comprising complexation agents selected from the group of polyvinylcaprolactam-polyvinyl acetate-polyethylene-glycol graft copolymers and/or poloxamers and/or polyvinylpyrrolidone and/or copolymers of vinylpyrrolidone and vinyl-acetate and/or polyoxyglicerides and pharmaceutically accepted excipients selected from the group of sodium-acetate and/or sodium-lauryl-sulfate and/or dioctyl sodium sulfosuccinate and/or cetylpyridinium chloride and/or sodium saccharine in an amount ranging from about 1.0 weight% to about 90.0 weight % based on the total weight of the complex.

8. A process for the preparation of the complex according to Claims 1 to 6, comprising the steps of mixing a solution of Dabigatran, its esters, preferably Dabigatran etexilate, its salts, preferably Dabigatran etexilate mesylate, or derivatives thereof, and at least one
complexation agent selected from the group of polyvinylcaprolactam-polyvinyl acetate-polyethylene-glycol graft copolymers and/or poloxamers and/or polyvinylpyrrolidone and/or copolymers of vinylpyrrolidone and vinyl-acetate and/or polyoxyglicerides in a pharmaceutically acceptable solvent with an aqueous solution containing at least one pharmaceutically accepted excipient chosen from sodium-acetate, sodium-lauryl-sulfate, dioctyl sodium sulfosuccinate, cetylpyridinium chloride and sodium saccharine.

9. The process according to Claim 7, wherein said process is performed in a continuous flow instrument, preferable in microfluidic instrument.

10. The process according to Claims 7 or 8, wherein said pharmaceutically acceptable solvent is selected from the group of methanol, ethanol, isopropanol, n-propanol, acetone, acetonitrile, dimethyl-sulfoxide, tetrahydrofuran, and combinations thereof.

11. The process according to any of Claims 7 to 9, wherein the solvent and the aqueous solvent are miscible with each other and the aqueous solvent comprises 0.1 to 99.9% weight of the final solution.

12. A pharmaceutical composition comprising the complex according to any of Claims 1 to 6 together with pharmaceutically acceptable carrier.

13. A pharmaceutical composition according to Claim 11, wherein said composition is suitable for oral, pulmonary, rectal, colonic, parenteral, intracisternal, intravaginal, intraperitoneal, ocular, otic, local, buccal, nasal, or topical administration, preferable the composition is suitable for oral administration.

14. A complex according to any of Claims 1 or to 6 for use in the manufacture of a medicament for the treatment and/or prophylaxis of diseases, in particular thrombotic diseases, stroke, cardiac infarction and/or atrial fibrillation and cardiac arrhythmia, as well as oncological diseases of any pathogenesis.

15. The use of the complex according to any of Claims 1 or to 6 for the treatment and/or prophylaxis of diseases, in particular thrombotic diseases, stroke, cardiac infarction and/or atrial fibrillation and cardiac arrhythmia, as well as oncological diseases of any pathogenesis.
16. A method of treatment and/or prophylaxis of diseases, in particular thrombotic diseases, stroke, cardiac infarction and/or atrial fibrillation and cardiac arrhythmia, as well as oncological diseases of any pathogenesis comprising administration of a therapeutically effective amount of the complex according to any of Claims 1 to 6 or the pharmaceutical composition according to Claim 12 or 13.

17. A stable complex wherein said complex has a controlled particle size in the range between 50 nm and 600 nm, preferable the particle size is between 50 nm and 300 nm; and wherein said complex is obtained according to any of claims 7 to 11.
AMENDED CLAIMS
received by the International Bureau on 15.04.2015

1. A stable complex comprising a) as active compound selected from the group of Dabigatran, its esters, preferably Dabigatran etexilate, its salts, preferably Dabigatran etexilate mesylate; b) at least one complexing agent selected from the group of a polyvinylcaprolactam-polyvinyl acetate-polyethylene-glycol graft copolymers and poloxamers; polyvinylpyrrolidone; polyoxyglycerides; copolymers of vinylpyrrolidone and vinyl-acetate; and poly(maleic acid-co-methyl-vinyl-ether); c) at least one pharmaceutically accepted excipient selected from the group of sodium-lauryl-sulfate; dioctyl sodium sulfo succinate; cetylpyridinium chloride, sodium-acetate and sodium saccharine, wherein said complex is instantaneously redispersible in buffers in physiological pH range, and possesses at least one of the following properties:

a) has a particle size in the range between 50 nm and 600 nm, preferably 50 nm and 300 nm;
b) has a PAMPA permeability of at least 0.3*10^-6 cm/s when dispersed in FaSSIF or FeSSIF biorelevant media and exhibits pH independent PAMPA permeability in the physiological pH range;
c) is characterized by an infrared (ATR) spectrum having main/characteristic absorption peaks at 1730 cm^-1, 1608 cm^-1, 1468 cm^-1, 1437 cm^-1, 1384 cm^-1, 1328 cm^-1, 1252 cm^-1, 1193 cm^-1, 1144 cm^-1, 1118 cm^-1, 1098 cm^-1, 1052 cm^-1, 993 cm^-1, 948 cm^-1, 888 cm^-1, 837 cm^-1, 811 768 cm^-1, 754 cm^-1, 704 cm^-1, 680 cm^-1, 632 cm^-1, 604 cm^-1, 567 cm^-1, 545 cm^-1 and 524 cm^-1, using Bruker Vertex 70 FT-IR spectrometer with Bruker Platinum diamond ATR unit.

2. The complex according to Claim 1, wherein said complex is characterized by an infrared (ATR) spectrum having main/characteristic absorption peaks at preferably at 1730 cm^-1, 1608 cm^-1, 1437 cm^-1, 1328 cm^-1, 1118 cm^-1, 1098 cm^-1, and 754 cm^-1 using Bruker Vertex 70 FT-IR spectrometer with Bruker Platinum diamond ATR unit.

3. The complex according to Claim 1, wherein said complexing agent is selected from the group of polyvinylcaprolactam-polyvinyl acetate-polyethylene-glycol graft copolymers and poloxamers; polyvinylpyrrolidone; polyoxyglycerides; copolymers of vinylpyrrolidone and vinyl-acetate; and poly(maleic acid-co-methyl-vinyl-ether).

4. The complex according to Claims 1 to 3, wherein said complex comprises cetylpyridinium chloride and sodium saccharine.

AMENDED SHEET (ARTICLE 19)
5. The complex according to any of Claims 1 to 3, wherein said complex further comprises one or more additional active agents, wherein the additional active agent is selected from the group of agents useful for the treatment and/or prophylaxis of thrombotic diseases, stroke, cardiac infarction and/or atrial fibrillation and cardiac arrhythmia, as well as oncological diseases of any pathogenesis.

6. A stable complex according to any Claims 1 to 5 comprising an active compound selected from the group of Dabigatran, its esters, preferably Dabigatran etexilate, its salts, preferably Dabigatran etexilate mesylate; at least one complexing agent selected from the group of a polyvinylcaprolactam-polyvinyl acetate-polyethylene-glycol graft copolymers and poloxamers; polyvinylpyrrolidone; polyoxyglycerides; copolymers of vinylpyrrolidone and vinyl-acetate; and poly(maleic acid-co-methyl-vinyl-ether), and at least one pharmaceutically accepted excipient chosen from the group of sodium-lauryl-sulfate; dioctyl sodium sulfo succinate; cetylpyridinium chloride, sodium-acetate and sodium saccharine; wherein said complex obtained via a mixing process, preferable continuous flow mixing process, more preferable microfluidic flow mixing process.

7. A complex according to Claims 1 to 6 comprising complexing agents selected from the group of polyvinylcaprolactam-polyvinyl acetate-polyethylene-glycol graft copolymers and/or poloxamers and/or polyvinylpyrrolidone and/or copolymers of vinylpyrrolidone and vinyl-acetate and/or polyoxyglycerides and pharmaceutically accepted excipients selected from the group of sodium-acetate and/or sodium-lauryl-sulfate and/or dioctyl sodium sulfo succinate and/or cetylpyridinium chloride and/or sodium saccharine in a total amount ranging from 1.0 % by weight to 90.0 % by weight based on the total weight of the complex.

8. A process for the preparation of the complex according to Claims 1 to 6, comprising the steps of mixing a solution of Dabigatran, its esters, preferably Dabigatran etexilate, its salts, preferably Dabigatran etexilate mesylate, and at least one complexing agent selected from the group of polyvinylcaprolactam-polyvinyl acetate-polyethylene-glycol graft copolymers and/or poloxamers and/or polyvinylpyrrolidone and/or copolymers of vinylpyrrolidone and vinyl-acetate and/or polyoxyglycerides in a pharmaceutically acceptable solvent with an aqueous solution containing at least one pharmaceutically accepted excipient chosen from sodium-acetate, sodium-lauryl-sulfate, dioctyl sodium sulfo succinate, cetylpyridinium chloride and sodium saccharine.

9. The process according to Claim 7, wherein said process is performed in a continuous flow instrument, preferable in microfluidic instrument.
10. The process according to Claims 7 or 8, wherein said pharmaceutically acceptable solvent is selected from the group of methanol, ethanol, isopropanol, n-propanol, acetone, acetonitrile, dimethyl-sulfoxide, tetrahydrofuran, and combinations thereof.

11. The process according to any of Claims 7 to 9, wherein the solvent and the aqueous solvent are miscible with each other and the aqueous solvent comprises 0.1 to 99.9% weight of the final solution.

12. A pharmaceutical composition comprising the complex according to any of Claims 1 to 6 together with pharmaceutically acceptable carrier.

13. A pharmaceutical composition according to Claim 11, wherein said composition is suitable for oral, pulmonary, rectal, colonic, parenteral, intracisternal, intravaginal, intraperitoneal, ocular, otic, local, buccal, nasal, or topical administration, preferable the composition is suitable for oral administration.

14. A complex according to any of Claims 1 or to 6 for use in the manufacture of a medicament for the treatment and/or prophylaxis of diseases, in particular thrombotic diseases, stroke, cardiac infarction and/or atrial fibrillation and cardiac arrhythmia, as well as oncological diseases of any pathogenesis.

15. The complex according to any of Claims 1 or to 6 for use in the treatment and/or prophylaxis of diseases, in particular thrombotic diseases, stroke, cardiac infarction and/or atrial fibrillation and cardiac arrhythmia, as well as oncological diseases of any pathogenesis.

16. A method of treatment and/or prophylaxis of diseases, in particular thrombotic diseases, stroke, cardiac infarction and/or atrial fibrillation and cardiac arrhythmia, as well as oncological diseases of any pathogenesis comprising administration of a therapeutically effective amount of the complex according to any of Claims 1 to 6 or the pharmaceutical composition according to Claim 12 or 13.
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+ redispersable solid Dabigatran complex
- non-redispersable solid Dabigatran complex

Fig. 1
Fig. 5
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Fig. 6
**INTERNATIONAL SEARCH REPORT**

**A. CLASSIFICATION OF SUBJECT MATTER**

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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)

A61K

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

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

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**Further documents are listed in the continuation of Box C.**

**See patent family annex.**

* Special categories of cited documents:
  *A* document defining the general state of the art which is not considered to be of particular relevance
  *E* earlier application or patent but published on or after the international filing date
  *L* document which may throw doubt on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
  *O* of document referring to an oral disclosure, use, exhibition or other means
  *P* document published prior to the international filing date but later than the priority date claimed

**Date of the actual completion of the international search**

9 February 2015

**Date of mailing of the international search report**

18/02/2015

**Name and mailing address of the ISA/Authorized officer**

European Patent Office, P.B. 5618 Patentlaan 2
NL-2280 HV Rijswijk
Tel. (+31-70) 340-2040,
Fax (+31-70) 340-3018

Gomez Galardo S
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