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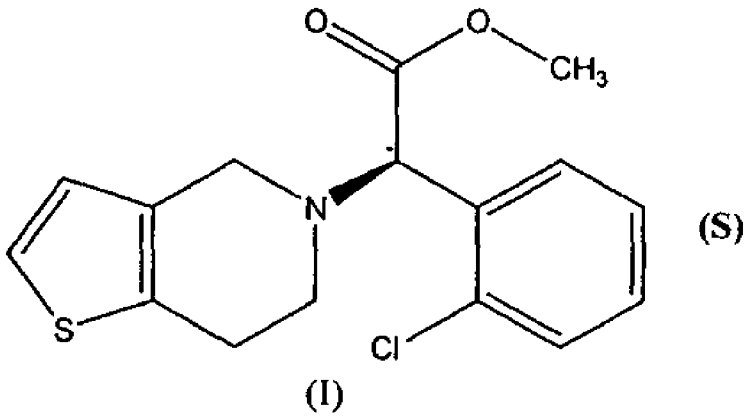
(54) **Title**: HIGHLY PURE SALTS OF CLOPIDOGREL FREE OF GENOTOXIC IMPURITIES



(I)

(57) **Abstract**: The present invention relates to substantially pure salts of clopidogrel of Formula (I) substantially free from genotoxic impurities. (I) wherein (S) represents a suitable organic or inorganic acid, which forms a salt with clopidogrel having less acidity.

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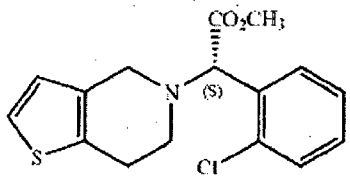
HIGHLY PURE SALTS OF CLOPIDOGREL FREE OF GENOTOXIC IMPURITIES

FIELD OF THE INVENTION

The invention relates to highly pure salts of clopidogrel substantially free of genotoxic impurities and processes for preparation thereof. The invention also relates to pharmaceutical compositions that include such highly pure salts of clopidogrel and use of said compositions for reducing atherothrombotic events and treating recent stroke or established peripheral arterial disease or acute coronary syndrome.

BACKGROUND OF THE INVENTION

Clopidogrel, methyl (+)-(S)-alpha.-(2-chlorophenyl)-6,7-dihydrothieno[3,2-c]pyridine-5(4H)-acetate of Formula (I) is an inhibitor of adenosine diphosphate (ADP)-induced platelet aggregation which is effective in treating peripheral arterial diseases such as stroke, thrombosis and embolism, as well as coronary arterial diseases, and myocardial infarction. Similar properties are displayed by the less potent racemic mixture (U.S. Patent No. 4,847,265).



Formula (I)

Clopidogrel is administered as its bisulfate (hydrogen sulfate) salt and is currently being marketed in the US as PLAVIX® tablets.

The enantiomer (S) clopidogrel is particularly preferred since it is the pharmaceutically active compound. The enantiomerically enriched compound can be prepared by means of enantioselective synthesis or starting from a racemic mixture of enantiomers in conjunction with a resolution process.

U.S. Patent No. 4,529,596 discloses thieno[3,2-c]pyridine derivatives including clopidogrel, which possess significant anti-aggregating and anti- thrombotic properties.

Various methods for preparing clopidogrel are described in literature, for example, in U.S. Patent Nos. 4,847,265, 5,204,469, 6,080,875, 6,495,691, 6,573,381, 6,635,763, 5,132,435, International (PCT) Patent Publication Nos. WO 2005/104663 and WO 2006/137628.

Various polymorphic forms of salts of clopidogrel are disclosed in European Patent Publication Nos. EP 1674468 A1, 1704152 A2, 1618113 A1 (clopidogrel hydrogen bromide) and International (PCT) Publication Nos. WO 2005/103059 (clopidogrel naphthalene-1,5-disulfonate), and U.S. Patent Publication No. 2005/0113406 (clopidogrel hydrogen chloride).

U.S. Patent No. 6,737,411 discloses the preparation of clopidogrel hydrogen sulfate.

International (PCT) Publication No. WO 2006/023676 discloses clopidogrel napsylate salt and a process for its preparation.

U.S. Patent application No. 2005/0203122 discloses clopidogrel besylate salt and its polymorphic form such as dioxane, and toluene solvate as well as crystalline anhydrous form thereof.

U.S. Patent application No. 2004/0132765 discloses various alkyl sulfuric acid salts of clopidogrel such as those of methyl sulfate, ethyl sulfate, propyl sulfate, isopropyl sulfate, butyl sulfate, sec-butyl sulfate, isobutyl sulfate or tert-butyl sulfate.

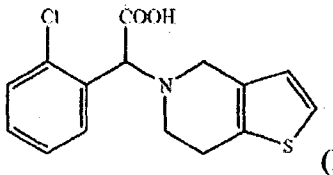
U.S. Patent No. 7,732,608 discloses various clopidogrel salts including clopidogrel besylate in crystalline and amorphous form, clopidogrel mesylate and clopidogrel para-toluenesulfonic acid salts in amorphous form.

European Patent No. EP 281459 B1 and U.S. Patent No. 4,847,265 disclose a number of acid addition salts of clopidogrel prepared using various inorganic or organic acids such as hydrochloride, hydrobromide, hydrogen sulfate, and taurocholate salts. However, it is also described that most of these salts are amorphous, hygroscopic and/or low melting, which are improper to use in pharmaceutical composition. Further, it is disclosed that hydrochloride and hydrobromide salts are highly hygroscopic under a condition of 60°C temperature and 75% relative humidity, resulting in a gum type or liquefied form.

It is known that synthetic compounds can contain extraneous compounds or impurities resulting from their synthesis or degradation. These can be unreacted starting materials, by-products of the reaction, products of side reactions, or degradation products. Generally, impurities in an active pharmaceutical ingredient (API) may arise from degradation of the API itself, or during the preparation of the API.

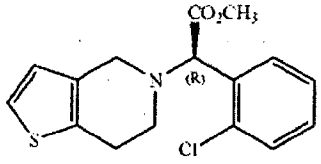
Clopidogrel being an oily substance, it is advantageous to convert to an acid addition salt for better handling and storage and therefore, its conversion to a salt form is almost unavoidable for stable storage. Clopidogrel has a methyl ester group as

evidenced from the structure of Formula (I). The ester group of clopidogrel is liable to hydrolysis to produce an impurity named clopidogrel free acid of Formula (II), which has no biological activity and needs to be monitored in the active substance as per pharmacopoeial specification. The main cause of generation of this impurity in clopidogrel is the hydrolysis of methyl ester under aqueous conditions during the processing.



(II)

Also, under moist and heat conditions, it can be transformed to the levorotatory isomer of Formula (III) having much less pharmacological activity. Accordingly, there has been a need to convert clopidogrel to a crystalline form which is very stable and easily purifiable, and for the purpose, it is common to make an acid addition salt using a pharmaceutically acceptable inorganic or organic acid.



(III)

In order to control the hydrolysis of ester, very mild bases like bicarbonates and controlled reaction conditions were employed in the art. Due to the poor solubility of either clopidogrel acid addition salt or clopidogrel free base in water, the process of breaking the salt in aqueous conditions were not effective or fast leading to larger reaction time which is detrimental to product purity. Thus, carrying out reactions at higher temperatures or for longer period lead to formation of acid impurity which necessitates extra purification resulting into yield losses and increase in number of operations that are not desirable for a practical process.

Furthermore, it is known that clopidogrel hydrogen sulfate employed in PLAVIX® (Sanofi-Synthelabo Inc.), a marketed tablet composition is also not sufficiently stable (H. Agrawal et al, Talanta, 61: 581-589, 2003). For example, it was reported that PLAVIX® is unstable under an accelerated test condition (40°C, 75% relative humidity, for 3 months), producing significant amounts of impurities (Y. Gomez et al, J. Pharm. Biomed. Anal. 34: 341-348, 2004).

Thus, clopidogrel salts obtained by the processes described in the prior art do not have satisfactory purity for pharmaceutical use. Unacceptable amounts of genotoxic impurities are generally formed along with clopidogrel salt. In addition, the process may involve the additional step of column chromatographic purifications. Methods involving column chromatographic purifications are generally undesirable for large-scale operations, thereby making the process commercially unfeasible.

Several generic versions of clopidogrel hydrochloride have recently become available throughout the world. However, some of these products have been reported to contain genotoxic impurities well beyond the TTC (threshold of toxicological concern) (A. Duguot et al., Core 7, Vascular Disease: Biology and Clinical Science, Session Title: Controversies in Antiplatelet Therapy, Annual Scientific Sessions of the American Heart Association).

Regulatory authorities worldwide require that drug manufacturers isolate, identify and characterize the impurities in their products. Furthermore, it is required to control the levels of these impurities in the final drug compound obtained by the manufacturing process and to ensure that the impurity is present at the lowest possible levels, even if structural determination is not possible. Due to the new requirements of Health Agencies on genotoxic compounds, the presence of genotoxic impurities make the use of such clopidogrel salts unsuitable for human if these contain impurities beyond set exposure limits. Thus, the active ingredient as well as pharmaceutical preparations made therefrom requires the presence of impurities well within the TTC limit in order to comply with regulatory guidance.

According to the ICH guidance (ICH Q3B) entitled "impurities in new drug products", the level of the impurities contained in the drug product should be carefully controlled and the upper level of the impurities should be determined and supported by adequate data in the dossier filed for registration of a new drug.

A major change in impurity testing involves a new regulatory guidance designed to tightly limit substances possessing potential for genotoxicity. The European Agency for the Evaluation of Medicinal Products (EMEA) provided guidance on genotoxic impurities. According to the guidelines, such genotoxic impurities exposure limit is set to 1.5 µg daily exposure limit in most pharmaceuticals based on a precedent application of the threshold of toxicological concern (TTC) concept to food additives and food contact materials.

Thus, residual impurities resulting from manufacturing and formulation or from degradation of clopidogrel salt, a subset of these impurities may present a potential for genotoxicity, which render inappropriate to use as an active principle in pharmaceutical preparations and therefore pose an additional safety concern to patients.

Hence, there exists a need to develop purified pharmaceutically acceptable salts of clopidogrel, and pharmaceutical compositions made therefrom which are substantially free of genotoxic impurities, which are acceptable for human use.

SUMMARY OF THE INVENTION

In one general aspect there are provided highly pure clopidogrel or salts thereof substantially free of genotoxic impurities.

In another general aspect there are provided pharmaceutical compositions comprising highly pure clopidogrel or salts thereof substantially free of genotoxic impurities.

In another general aspect there is provided highly pure clopidogrel besylate containing less than 20 ppm of genotoxic impurities.

In another general aspect there are provided pharmaceutical compositions comprising highly pure clopidogrel besylate containing less than 20 ppm of genotoxic impurities.

In another general aspect there is provided highly pure clopidogrel besylate containing less than 20 ppm of methyl besylate as genotoxic impurity.

In another general aspect there are provided pharmaceutical compositions comprising highly pure clopidogrel besylate containing less than 20 ppm of methyl besylate as genotoxic impurity.

In another general aspect there is provided a storage stable pharmaceutical composition comprising highly pure salts of clopidogrel containing less than 20 ppm of genotoxic impurities, wherein the composition retains at least 80% of the potency of clopidogrel or salts thereof after storage for at least three months at 40°C and 75% relative humidity.

In another general aspect there is provided a storage stable pharmaceutical composition comprising highly pure clopidogrel besylate containing less than 20 ppm of genotoxic impurities, wherein the composition retains at least 80% of the potency of clopidogrel besylate after storage for at least three months at 40°C and 75% relative humidity.

In another general aspect there is provided a storage stable pharmaceutical composition comprising highly pure salts of clopidogrel containing less than 20 ppm of genotoxic impurities, wherein the composition retains at least 80% of the potency of clopidogrel or acid addition salts thereof after storage for at least three months at 30°C and 60% relative humidity.

In another general aspect there is provided a storage stable pharmaceutical composition comprising highly pure clopidogrel besylate containing less than 20 ppm of genotoxic impurities, wherein the composition retains at least 80% of the potency of clopidogrel besylate after storage for at least three months at 30°C and 60% relative humidity.

In another general aspect there is provided a storage stable pharmaceutical composition comprising highly pure salts of clopidogrel containing less than 20 ppm of genotoxic impurities, wherein the composition retains at least 80% of the potency of clopidogrel or salts thereof after storage for at least three months at 25°C and 60% relative humidity.

In another general aspect there is provided a storage stable pharmaceutical composition comprising highly pure clopidogrel besylate containing less than 20 ppm of genotoxic impurities, wherein the composition retains at least 80% of the potency of clopidogrel besylate after storage for at least three months at 25°C and 60% relative humidity.

In another general aspect there is provided a storage stable pharmaceutical composition comprising highly pure salts of clopidogrel containing less than 20 ppm of genotoxic impurities, wherein the composition retains at least 80% of the potency of clopidogrel or salts thereof after storage for at least one year at room temperature.

In another general aspect there is provided a storage stable pharmaceutical composition comprising highly pure clopidogrel besylate containing less than 20 ppm of genotoxic impurities, wherein the composition retains at least 80% of the potency of clopidogrel besylate after storage for at least one year at room temperature.

In another general aspect there is provided a method of reducing of atherothrombotic events or treating recent stroke or established peripheral arterial disease or acute coronary syndrome comprising administering to human patient in need thereof a pharmaceutical composition comprising highly pure salts of clopidogrel containing less than 20 ppm of genotoxic impurities.

In another general aspect there is provided a method of reducing of atherothrombotic events or treating recent stroke or established peripheral arterial disease or acute coronary syndrome comprising administering to human patient in need thereof a pharmaceutical composition comprising highly pure clopidogrel besylate containing less than 20 ppm of genotoxic impurities.

In another general aspect there is provided a process for preparing highly pure salts of clopidogrel substantially free of genotoxic impurities, the process comprising:

a) reacting clopidogrel with an acid in one or more inert solvents;
b) crystallizing salt of clopidogrel;
c) removing residual acid;
d) isolating salt of clopidogrel, and
e) optionally, removing residual solvent to obtain the highly pure salt of clopidogrel.

In another general aspect there is provided a process for preparing highly pure salts of clopidogrel substantially free of genotoxic impurities, the process comprising:

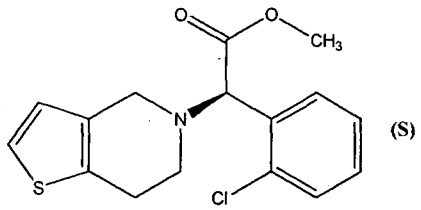
a) reacting clopidogrel with benzene sulfonic acid in one or more inert solvents;
b) crystallizing salt of clopidogrel;
c) removing residual acid;
d) isolating salt of clopidogrel, and
e) optionally, removing residual solvent to obtain the highly pure salt of clopidogrel.

BRIEF DESCRIPTION OF THE ACCOMPANYING DRAWINGS

Figure 1: Calibration curve of methyl besylate for concentration versus area

DETAILED DESCRIPTION OF THE INVENTION

The invention relates to substantially pure salts of clopidogrel of Formula (I) substantially free from genotoxic impurities.



(I)

wherein (S) represents a suitable acid.

In an embodiment, (S) represents an organic or inorganic acid, which forms a salt with clopidogrel having less acidity.

As used herein, the term "genotoxic impurities" refers to compounds that have the potential to damage DNA at any level of exposure, said damage leading/contributing to tumor development.

As used herein, the term "substantially free of genotoxic impurity" refers to the levels of potential genotoxic impurity which is less than threshold of toxicological concern (TTC), for example, less than 20 ppm. In particular, the impurity is less than 15 ppm.

The term "clopidogrel" used throughout the specification refers to not only clopidogrel per se, but also its pharmaceutically acceptable acid addition salts, pharmaceutically acceptable solvates, pharmaceutically acceptable hydrates, pharmaceutically acceptable enantiomers, pharmaceutically acceptable derivatives, pharmaceutically acceptable polymorphs and pharmaceutically acceptable prodrugs thereof. It is also possible to use salts of free base form of clopidogrel, including polymorphs, hydrates, solvates or amorphous forms.

The acid addition salts of clopidogrel include, but not limited to, hydrochloride, hydrobromide, hydroiodide, sulphate, hydrogensulphate, nitrate, phosphate, and organic acid addition salts such as mesylate, besylate, acetate, maleate, fumarate, citrate, oxalate, succinate, tartrate, malate, mandelate, methanesulfonate and p-toluenesulfonate. Most preferred salt is besylate.

The highly pure salt of clopidogrel has a purity of at least about 98% by HPLC. In particular, the purity is at least about 99%, for example, 99.9%.

Without being bound by any theory, it is believed that the potential genotoxic impurities may be like alkylated impurities in clopidogrel salt, which can be generated by degradation of clopidogrel upon storage. The clopidogrel salt is known to hydrolyze and generate degradants, for example a compound of Formula (II) and methanol. The residual methanol can internally react with residue of acid to generate corresponding alkylated impurities.

It is also believed that the potential genotoxic impurities can be generated in clopidogrel salt by internal reaction of clopidogrel salt or its residual degradants with residual solvent to generate potential genotoxic impurities.

In case of clopidogrel hydrochloride salt, the degradation of clopidogrel may result in clopidogrel acid of Formula (II) and methanol. The resultant residual methanol can react with residual hydrochloric acid to generate methyl chloride, which is a potential genotoxic impurity. For details, see the recent publication (A. Duguot et al.,

Core 7, Vascular Disease: Biology and Clinical Science, Session Title: Controversies in Antiplatelet Therapy, Annual Scientific Sessions of the American Heart Association). Interestingly and on similar lines, theoretically one can visualize the presence of extremely genotoxic substances such as dimethyl sulfate and mono-methyl sulfate in the samples of clopidogrel bisulfate as degradation products.

The inventors of the present invention have surprisingly found that clopidogrel is prone to hydrolysis when acid addition salt is formed by using acid, for example, a strong acid.

In another general aspect there is provided a process for preparing highly pure salts of clopidogrel substantially free of genotoxic impurities, the process comprising:

a) reacting clopidogrel with an acid in one or more inert solvents;
b) crystallizing salt of clopidogrel;
c) removing residual acid;
d) isolating salt of clopidogrel, and
e) optionally, removing residual solvent to obtain the highly pure salt of clopidogrel.

In general, acid include, but not limited to, hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, nitric acid, phosphoric acid, and organic acid such as methane sulfonic acid, benzene sulfonic acid, acetic acid, maleic acid, fumaric acid, citric acid, oxalic acid, succinic acid, tartaric acid, malic acid, mandelic acid, p-toluene sulfonic acid. Most preferred acid is benzene sulfonic acid.

In an embodiment, the invention provides a process for preparing highly pure clopidogrel besylate, the process comprising:

a) reacting clopidogrel with benzene sulfonic acid in one or more inert solvents;
b) crystallizing clopidogrel besylate;
c) removing residual benzene sulfonic acid;
d) isolating clopidogrel besylate; and
e) optionally, removing residual solvent to obtain highly pure clopidogrel besylate.

In one embodiment, the process disclosed herein or any of the process steps can be repeated any number of times until the substantial removal of the genotoxic impurity and to provide the desired purity of acid addition salt of clopidogrel.

The inventors have surprisingly found that when clopidogrel is reacted with acid in an inert solvent, preferably in anhydrous condition, the formed acid addition salt of clopidogrel is substantially free of genotoxic impurities.

Further, it was found that effective optimization of the molar ratio of acid may reduce the presence of free acid in the acid addition salt of clopidogrel. In Particular, the molar ratio of clopidogrel to acid used for preparing acid addition salt of clopidogrel may range from about 1:0.75 to about 1:1.25, respectively.

In an embodiment, the molar ratio of clopidogrel to benzene sulfonic acid used for preparing clopidogrel besylate is 1:0.99.

In accordance with the present invention, the reaction may be carried out in one or more inert solvents such that it does not react with benzene sulfonic acid to form potential genotoxic impurities. The inert solvent can be selected, but not limited to, from one or more of diethyl ether, diisopropyl ether, methyl tertiary butyl ether, tetrahydrofuran, acetone, methyl ethyl ketone, methyl isobutyl ketone, suitable alcohols selected from C_3-C_{12} alcohols which may be linear or branched, primary, secondary or tertiary alcohols such as n-propanol, isopropanol, 1-butanol, 2-butanol, isobutanol, t-butanol, 1-pentanol, 1-hexanol, 2-hexanol, 3-hexanol, isohexanol, 1-heptanol, 2-heptanol, 3-heptanol, 4-heptanol, octanol, isooctanol, decanol, and dodecanol.

The reaction may be carried out in substantially anhydrous condition so that water content of the reaction mass is such that the hydrolysis of clopidogrel base can be avoided.

The salt formation reaction may be carried out at ambient temperature to reflux temperature of inert solvent.

The acid addition salt of clopidogrel can be crystallized by various techniques known to a person skilled in the art, such as, cooling the reaction mass to room temperature or further cooling at a temperature in the range of from about 0°C to about 20°C to precipitate acid addition salt of clopidogrel or by addition of anti-solvent or by removing solvent or combination of one or more techniques to obtain acid addition salt of clopidogrel.

The obtained acid addition salt of clopidogrel may be mixed or slurried or washed or treated with a suitable solvent to remove residual acid and isolated by conventional methods such as filtration or centrifugation, optionally washed and dried, preferably under diminished pressure.

The residual solvent of the obtained acid addition salt of clopidogrel may be removed by any one of the following processes or combination thereof:

a) The residual water content of the clopidogrel is azeotropically removed by using non aqueous solvent such as toluene, xylene; or

b) drying the clopidogrel in tray dryer in presence of water adsorbent like phosphorus pentoxide, silica gel and anhydrous magnesium sulfate; or

c) drying the clopidogrel besylate under reduced pressure in vacuumed dryer or rotacone vacuum dryer or fluidized bed dryer.

The present invention further provides a pharmaceutical composition comprising clopidogrel besylate substantially free from genotoxic impurities.

The present invention further provides a process for preparing a pharmaceutical composition comprising clopidogrel besylate substantially free from genotoxic impurities.

In a further embodiment, the present invention provides a pharmaceutical composition comprising substantially pure acid addition salt of clopidogrel besylate which contains less than 20 ppm of genotoxic impurity.

The pharmaceutical composition may be developed in the form of powders, pellets, granules, beads, powder in capsule, pellets in capsule, granules in capsule, tablets, minitablets, minitablets in capsule, sachets, bilayered or multilayered tablets, films, patches, powder for suspension, or any suitable solid unit forms known to a person skilled in the art.

The pharmaceutical composition may be developed in the form suitable to provide modified, sustained, controlled, and delayed release of active by using various excipients and methods known to the person skilled in the art.

In an embodiment, the pharmaceutical composition may be developed in the form suitable for parenteral administration, pulmonary administration, dermal application and administration by rectal route.

The pharmaceutical compositions can be manufactured by various techniques or processes known to the person skilled in the art including direct compression, dry or wet granulation, slugging, fluidized bed granulation, melt extrusion, spray drying and solution evaporation, preferably the manufacturing process involves fluidized bed granulation technique.

The pharmaceutical composition may be coated with one or more release retarding agent and/or seal coated and/or film coated. The composition can be coated with ready colour mix systems (such as opadry colour mix systems).

Pharmaceutically acceptable excipients for use in the pharmaceutical composition comprise one or more diluents, binders, disintegrants, glidants, lubricants, sweeteners, surfactants, colorants and flavors.

Suitable diluents may include one or more of monosaccharides, disaccharides, polysaccharides and sugar alcohols such as arabinose, lactose, dextrose, sucrose, fructose, maltose, mannitol, erythritol, sorbitol, xylitol lactitol, and other bulking agents such as powdered cellulose, microcrystalline cellulose, sugar and derivatives thereof and the like.

Suitable binders may include one or more of methyl cellulose, hydroxypropyl cellulose (HPC), hydroxypropyl methyl cellulose (HPMC), sugars, starch, polyvinyl pyrrolidone (PVP), gelatin, gum Arabic, ethyl cellulose, polyvinyl alcohol, tragacanth, sodium alginate and equivalents thereof.

Suitable disintegrants may include one or more of croscarmellose sodium, crospovidone, sodium starch glycolate, corn starch, potato starch, maize starch and modified starches, calcium silicates, low substituted hydroxypropylcellulose, and the like.

Suitable lubricants and glidants may include one or more of stearic acid and its derivatives or esters like sodium stearate, magnesium stearate and calcium stearate and the corresponding esters such as sodium stearyl fumarate; talc, colloidal silicon dioxide, and the like.

Suitable sweeteners may include one or more of sucrose, dextrose, glucose, maltose, dextrins, D-tagatose, trehalose, dried invert sugar, fructose, levulose, galactose, corn syrup solids, and the like, alone or in combination. Other examples of sweeteners comprise sodium saccharin; aspartame; sugarless sweeteners including polyhydric alcohols such as sorbitol, mannitol, xylitol, glycerol, hydrogenated starch hydrolysates, maltitol, isomaltitol, erythritol, lactitol and the like.

Suitable flavors may include one or more of cinnamon, wintergreen, eucalyptus, spearmint, peppermint, menthol, anise as well as fruit flavors such as apple, pear, peach, strawberry, cherry, apricot, orange, watermelon, banana and the like; bean-derived flavors, such as coffee, cocoa and the like.

Suitable surfactants may include one or more of anionic, non-ionic and cationic surfactants.

Suitable polymers for sustained release may include one or more of hydrophilic and hydrophobic polymers.

The present invention further provides a method of reducing of atherothrombotic events like recent myocardial infarction and treating recent stroke or established peripheral arterial disease, acute coronary syndrome comprising

administering to human patient in need thereof a pharmaceutical composition comprising substantially pure acid addition salt of salt of clopidogrel.

The invention is further illustrated by the following examples which are provided to be exemplary of the invention and do not limit the scope of the invention. WO 2007/052300 further describes additional methodologies to make clopidogrel besylate in various solvents and reaction conditions.

In another general aspect there is provided a storage stable pharmaceutical composition comprising highly pure salts of clopidogrel containing less than 20 ppm of genotoxic impurities, wherein the composition retains at least 80% of the potency of clopidogrel or salts thereof after storage for at least three months at 40°C and 75% relative humidity.

In another general aspect there is provided a storage stable pharmaceutical composition comprising highly pure clopidogrel besylate containing less than 20 ppm of genotoxic impurities, wherein the composition retains at least 80% of the potency of clopidogrel besylate after storage for at least three months at 40°C and 75% relative humidity.

In another general aspect there is provided a storage stable pharmaceutical composition comprising highly pure salts of clopidogrel containing less than 20 ppm of genotoxic impurities, wherein the composition retains at least 80% of the potency of clopidogrel or acid addition salts thereof after storage for at least three months at 30°C and 60% relative humidity.

In another general aspect there is provided a storage stable pharmaceutical composition comprising highly pure clopidogrel besylate containing less than 20 ppm of genotoxic impurities, wherein the composition retains at least 80% of the potency of clopidogrel besylate after storage for at least three months at 30°C and 60% relative humidity.

In another general aspect there is provided a storage stable pharmaceutical composition comprising highly pure salts of clopidogrel containing less than 20 ppm of genotoxic impurities, wherein the composition retains at least 80% of the potency of clopidogrel or salts thereof after storage for at least three months at 25°C and 60% relative humidity.

In another general aspect there is provided a storage stable pharmaceutical composition comprising highly pure clopidogrel besylate containing less than 20 ppm of genotoxic impurities, wherein the composition retains at least 80% of the potency of

clopidogrel besylate after storage for at least three months at 25°C and 60% relative humidity.

In another general aspect there is provided a storage stable pharmaceutical composition comprising highly pure salts of clopidogrel containing less than 20 ppm of genotoxic impurities, wherein the composition retains at least 80% of the potency of clopidogrel or salts thereof after storage for at least one year at room temperature.

In another general aspect there is provided a storage stable pharmaceutical composition comprising highly pure clopidogrel besylate containing less than 20 ppm of genotoxic impurities, wherein the composition retains at least 80% of the potency of clopidogrel besylate after storage for at least one year at room temperature.

In another general aspect there is provided a method of reducing of atherothrombotic events or treating recent stroke or established peripheral arterial disease or acute coronary syndrome comprising administering to human patient in need thereof a pharmaceutical composition comprising highly pure clopidogrel besylate containing less than 20 ppm of genotoxic impurities.

While the present invention has been described in terms of its specific embodiments, certain modifications and equivalents will be apparent to those skilled in the art and are intended to be included within the scope of the present invention.

Example-1: Preparation of crystalline Clopidogrel Besylate

Clopidogrel base (1 mol) was dissolved in substantially anhydrous isopropyl alcohol at 50-55°C (500 ml, water 0.05 % and free from methanol). Benzene sulfonic acid (0.9 mol equivalent) was dissolved in isopropyl alcohol (480 ml, water 0.05 % and free from methanol) and was added to the solution of clopidogrel at 50-55°C. The reaction mixture was seeded with crystalline form of clopidogrel besylate and stirred at 20-30°C for 6 hrs. The mixture was further cooled to10-15°C and stirred for 10 minutes. The solid so obtained was filtered and washed with substantially anhydrous cold isopropyl alcohol. The solid salt was dried at about 50°C in a vacuum oven for 20-24 hrs to give crystalline clopidogrel besylate. M.P. 130-135°C.

Example-2: Preparation of crystalline Clopidogrel Besylate

Clopidogrel base (1 mol) was dissolved in substantially anhydrous isopropyl alcohol (500 ml, water 0.05 % and free from methanol) at 50-55°C. Benzene sulfonic acid (0.9 mol equivalent) was dissolved in substantially anhydrous isopropyl alcohol (480 ml, water 0.05 % and free from methanol) and was added to the solution of clopidogrel at 50-55°C and cooled to about 25-30°C. The reaction mixture was seeded

with crystalline form of clopidogrel besylate and was stirred at 25-30°C temperature for 1 hr. followed by further stirring at 25-30°C for 5 hrs for complete crystallization. The reaction mass was cooled to 10-15°C and stirred for 10 minutes .The solid was filtered and washed with substantially anhydrous cold isopropyl alcohol. The solid salt was dried at about 50°C in a vacuum oven for 20-24 hrs to give crystalline clopidogrel besylate. M.P. 130-135°C.

Example-3: Preparation of crystalline Clopidogrel Besylate

Clopidogrel base (1 mol) was dissolved in isopropyl alcohol (500 ml, water 0.05 % and free from methanol) at 50-55°C. Benzenesulfonic acid (0.9 mol equivalent) was dissolved in isopropyl alcohol (480 ml) and was added to the solution at 50-55°C. The reaction mass was cooled to 25-30°C stirred at 25-30°C temperature for 5 hrs. The reaction mass was further cooled to10-15°C and stirred for 10 minutes. The solid was filtered and washed with substantially anhydrous cold isopropyl alcohol. The solid salt was dried at about 50°C in a vacuum oven for 20-24 hrs to give crystalline clopidogrel besylate. M.P. 130-135°C.

Example-4: Preparation of crystalline Clopidogrel Besylate

Clopidogrel base (1 mol) was dissolved in isopropyl alcohol (500 ml, water 0.05 % and free from methanol) 50-55°C and cooled to 25-30°C. Benzene sulfonic acid (0.9 mol equivalent) was dissolved in isopropyl alcohol (480 ml) and was added to the solution at 25-30°C. The reaction mixture was cooled to 25-30°C. The reaction mixture was seeded with crystalline form of Clopidogrel besylate. The reaction mixture was stirred at 25-30°C temperature for 1 hr. and stirred further at 25-30°C for 5 hrs for complete crystallization. It was cooled to10-15°C and stirred for 10 minutes. The solid was filtered and washed with cold isopropyl alcohol. The solid salt was dried at about 50°C in a fludized bed drier for 10 hrs to give Clopidogrel besylate, which contain % water 0.3 %w/w and characterization data showed to be crystalline form. M.P. 132-135°C.

Preparation of Methyl benzenesulfonate:

Charge 3.4g NaOH pellets (3 mol eq.) to 8.5ml water (40% aq. NaOH sol.) in 50ml three neck round bottom, stirred well to dissolve it (temp. raises up to 50°C). Add 5 ml methanol in one lot at 25-30°C and cooled to < 0°C, charge drop wise benzenesulfonyl chloride 5g (1 mol eq.) through syringe and maintain temperature between -5°C to 0°C, stir for 3 hrs at -5°C to 0°C. The progress of reaction was monitored by TLC.

Charge 10 ml diethyl ether into reaction mixture, stirred for 5 min. organic layer separated dried and distilled to give 4.0 gm of pure methyl benzenesulfonate, sample analyzed for ^{1}H NMR & HPLC purity and was similar to market sample (Arti Drugs Ltd. B.No.MBS/12/01)

Analysis: - HPLC purity: 99.08%

Determination of genotoxic impurity Methyl Besylate in Clopidogrel Besylate as an API and in Tabs and demonstrating it absence:

As per the genotoxic impurity guideline, "Guideline on the limits of genotoxic impurities' (EMEA/CHMP/QWP/251344/2006), published in 2006" daily exposure of the genotoxic substances should not be more than 1.5 µg /person/day. Considering methyl besylate as genotoxic substance, its daily exposure should not be more than 1.5 µg/person/day. The Clopidogrel Besylate is available as 75 mg tablet. Considering daily dose of Clopidogrel Besylate 75 mg, the limit of methyl besylate in Clopidogrel Besylate tablet can be upto 20 ppm.

Method of Analysis:

The Clopidogrel Besylate (75 mg) was analyzed by reverse phase HPLC method for the determination of the content of methyl besylate using the Agilent 1100 series instrument equipped with UV detector. The HPLC grade acetonitrile was used for the sample preparation. The calibration curve was plotted with well characterized standard sample of the methyl besylate for the quantitative estimation using C_{18} (150 x 4.6 mm, 5 µm) column in gradient mode. The mobile phase consisting of 1.0 % thiethylamine in water with pH 3.0 adjusted by orthophosphoric acid and acetonitrile was used as an eluent at a flow rate of 1.0 mL/min. The detector was operated at 220 nm.

Standard Preparation:

Well characterized standard material of methyl besylate was used to prepare standard solutions of 0.5, 1, 5, 10, 20, 50 and 100 ppm of absolute concentration.

Sample Preparation:

1000 mg API or blend powder from crush tablets was dissolved in 5 mL acetonitrile and filtered through 0.45 um filter.

Results and Discussion:

The linearity was plotted for absolute standard concentration for 0.5, 1, 2, 10, 20, 50 and 100 ppm of methyl besylate with 0.999 correlation coefficient. The graph is

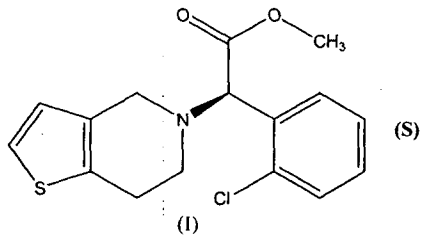
shown in figure 1. Based on linearity plot, it can be said that methyl besylate can be very well detected upto 0.5 ppm of absolute consetration

The API sample (Batch No. B925-SPP-46, manufactured in June 2008 and stored at RT and analyzed after 2 years and 8 months) and tablets samples (from Zydus France 75 mg, lot no. 01753 and Sandoz 75 mg, lot no. BA0994, prepared from Zydus Cadila's, Clopidogrel Besylate API) were tested using same method of analysis and there was no peak observed at the retention time (about 8.5 min) of methyl besylate. To confirm this observation, recovery experiment was done by spiking 5 µg methyl besylate in 1000 mg of clopidogrel besylate tablets. The peak of methyl besylate was very well detected. Therefore, it can be concluded that methyl besylate is not present in API as well as in Tablets (from Zydus France 75 mg, lot no. 01753 and Sandoz 75 mg, lot no. BA0994, prepared by Zydus Clopidogrel Besylate API). Please note that methyl besylate was absent in Zydus France tablets even after 2 years of storage at prescribed storage condition. Therefore, it can be concluded that the genotoxic impurity methyl besylate is virtually absent either in Zydus Cadila's API or in its Tablets or formulations, even after 2/3years of storage.

While the present invention has been described in terms of its specific embodiments, certain modifications and equivalents will be apparent to those skilled in the art and are intended to be included within the scope of the present invention.

We claim:

1. Substantially pure salts of clopidogrel of Formula (I) substantially free from genotoxic impurities.



(I)

wherein (S) represents a suitable organic or inorganic acid, which forms a salt with clopidogrel having less acidity.

2. Substantially pure salts of clopidogrel as claimed in claim 1 wherein said suitable organic or inorganic acid comprise of hydrochloride, hydrobromide, hydroiodide, sulphate, hydrogensulphate, nitrate, phosphate, mesylate, besylate, acetate, maleate, fumarate, citrate, oxalate, succinate, tartrate, malate, mandelate, methanesulfonate and p-toluenesulfonate.
3. Substantially pure salts of clopidogrel as claimed in claim 1 wherein said genotoxic impurity is of levels less than threshold of toxicological concern (TTC) which is less than 20 ppm.
4. Substantially pure salts of clopidogrel as claimed in claim 3 wherein said potential genotoxic impurity is alkylated impurities in clopidogrel salt.
5. A process for preparing highly pure salts of clopidogrel substantially free of genotoxic impurities, the process comprising:
   (a) reacting clopidogrel with an acid in one or more inert solvents;
   (b) crystallizing salt of clopidogrel;
   (c) removing residual acid;
   (d) isolating salt of clopidogrel, and
   (e) optionally, removing residual solvent to obtain the highly pure salt of clopidogrel.
6. The process as claimed in claim 5, wherein the acid include hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, nitric acid, phosphoric acid, and organic acid such as methane sulfonic acid, benzene sulfonic acid, acetic acid, maleic acid, fumaric acid, citric acid, oxalic acid, succinic acid, tartaric acid, malic acid, mandelic acid, p-toluene sulfonic acid.

7. The process as claimed in claim 5 wherein clopidogrel is reacted with acid in one or more of inert solvents in anhydrous condition to obtain clopidogrel besylate substantially free of genotoxic impurities.

8. A process for preparing highly pure clopidogrel besylate, the process comprising:
   (a) reacting clopidogrel with benzene sulfonic acid in one or more inert solvents;
   (b) crystallizing clopidogrel besylate;
   (c) removing residual benzene sulfonic acid;
   (d) isolating clopidogrel besylate; and
   (e) optionally, removing residual solvent to obtain highly pure clopidogrel besylate.

9. The process as claimed in claim 8 wherein said clopidogrel is reacted with benzene sulfonic acid in one or more of inert solvents in anhydrous condition to obtain clopidogrel besylate substantially free of genotoxic impurities.

10. The process as claimed in claim 8 or 9 wherein said inert solvent comprises one or more of diethylether, diisopropyl ether, methyl tertiary butyl ether, tetrahydrofuran, acetone, methyl ethyl ketone, methyl isobutyl ketone, C_3-C_{12} alcohols selected from linear or branched, primary or tertiary alcohols n-propanol, isopropanol, 1-butanol, 2-butanol, isobutanol, t-butanol, 1-pentanol, 1-hexanol, 2-hexanol, 3-hexanol, isohexanol, 1-heptanol, 2-heptanol, 3-heptanol, 4-heptanol, octanol, isooctanol, decanol, and dodecanol.

11. The process as claimed in claim 5 or 8 wherein crystallizing clopidogrel besylate includes at least one of the following (i) cooling the reaction mass to room temperature or (ii) cooling at a temperature in the range of from about 0°C to about 20°C or (iii) addition of anti-solvent or (iv) removing solvent or any combinations thereof.

12. The process as claimed in claim 5 or 8 wherein the residual solvent may be removed by any one of the following processes or combination thereof:
   (a) the residual water content of the clopidogrel is azeotropically removed by using non aqueous solvent such as toluene, xylene; or
   (b) drying the clopidogrel in tray dryer in presence of water adsorbent like phosphorus pentoxide, silica gel and anhydrous magnesium sulfate; or
   (c) drying the clopidogrel besylate under reduced pressure in vacuumed dryer or rotacone vacuum dryer or fluidized bed dryer.

13. A pharmaceutical composition comprising clopidogrel besylate substantially free from genotoxic impurities.

14. A pharmaceutical composition comprising substantially pure acid addition salt of clopidogrel besylate which contains less than 20 ppm of genotoxic impurity.

15. A storage stable pharmaceutical composition comprising highly pure salts of clopidogrel containing less than 20 ppm of genotoxic impurities, wherein the composition retains at least 80% of the potency of clopidogrel or salts thereof after storage for at least three months at 40°C and 75% relative humidity.

16. A storage stable pharmaceutical composition comprising highly pure clopidogrel besylate containing less than 20 ppm of genotoxic impurities, wherein the composition retains at least 80% of the potency of clopidogrel besylate after storage for at least three months at 40°C and 75% relative humidity.

17. A storage stable pharmaceutical composition comprising highly pure salts of clopidogrel containing less than 20 ppm of genotoxic impurities, wherein the composition retains at least 80% of the potency of clopidogrel or acid addition salts thereof after storage for at least three months at 30°C and 60% relative humidity.

18. A storage stable pharmaceutical composition comprising highly pure clopidogrel besylate containing less than 20 ppm of genotoxic impurities, wherein the composition retains at least 80% of the potency of clopidogrel besylate after storage for at least three months at 30°C and 60% relative humidity.

19. A storage stable pharmaceutical composition comprising highly pure salts of clopidogrel containing less than 20 ppm of genotoxic impurities, wherein the composition retains at least 80% of the potency of clopidogrel or salts thereof after storage for at least three months at 25° C and 60% relative humidity.

20. A storage stable pharmaceutical composition comprising highly pure clopidogrel besylate containing less than 20 ppm of genotoxic impurities, wherein the composition retains at least 80% of the potency of clopidogrel besylate after storage for at least three months at 25°C and 60% relative humidity.

21. A storage stable pharmaceutical composition comprising highly pure salts of clopidogrel containing less than 20 ppm of genotoxic impurities, wherein the composition retains at least 80% of the potency of clopidogrel or salts thereof after storage for at least one year at room temperature.

22. A storage stable pharmaceutical composition comprising highly pure clopidogrel besylate containing less than 20 ppm of genotoxic impurities, wherein the composition retains at least 80% of the potency of clopidogrel besylate after storage for at least one year at room temperature.

23. A method of reducing of atherothrombotic events or treating recent stroke or established peripheral arterial disease or acute coronary syndrome comprising administering to human patient in need thereof a pharmaceutical composition comprising highly pure clopidogrel besylate containing less than 20 ppm of genotoxic impurities.

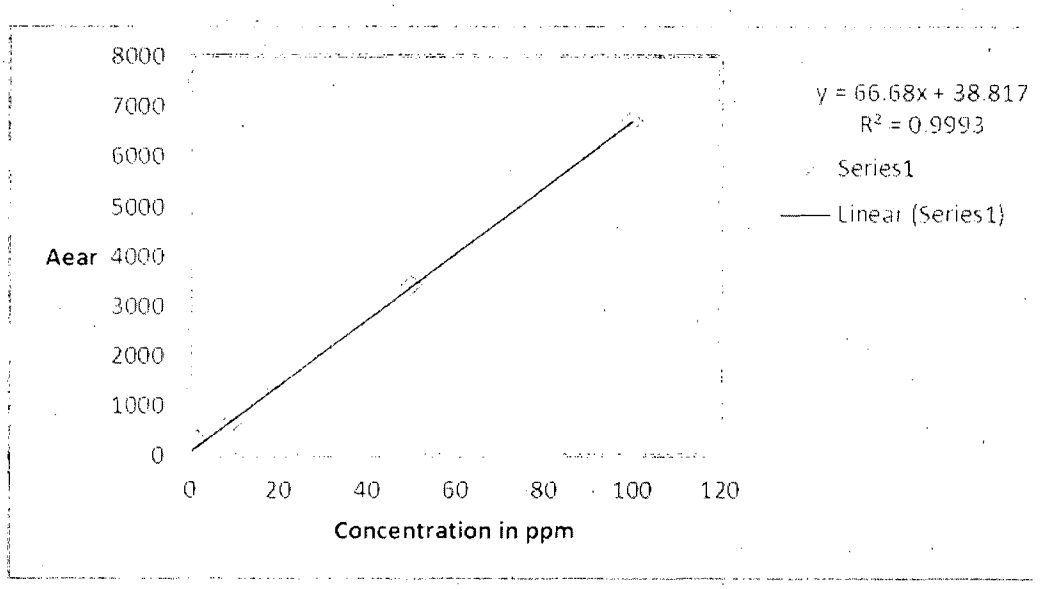


Figure 1: Calibration curve of methyl besylate for concentration versus area

INTERNATIONAL SEARCH REPORT

International application No
PCT/IN2012/000098

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D495/04 A61K31/4365 A61P9/10
ADD.

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 A61K A61P

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 practicable, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2007/052300 A2 (CADILA HEALTHCARE LTD [IN]; LOHRAY BRAJ BHUSHAN [IN]; LOHRAY VIDYA BHU) 10 May 2007 (2007-05-10) cited in the application the whole document	1-23
X	US 2005/203122 A1 (DOSER STEPHEN M [DE] ET AL) 15 September 2005 (2005-09-15) cited in the application the whole document	1-23
X	US 7 732 608 B2 (LOHRAY BRAJ B [IN] ET AL LOHRAY BRAJ BHUSHAN [IN] ET AL) 8 June 2010 (2010-06-08) cited in the application the whole document	1-23

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

☒ See patent family annex.

* Special categories of cited documents :

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"O" 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

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
16 August 2012	27/08/2012

Name and mailing address of the ISA/	Authorized officer
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Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IN2012/000098

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		US 2009221827 A1	03-09-2009
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		KR 20060013376 A	09-02-2006
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		WO 2004106344 A2	09-12-2004