Abstract:

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The present invention relates to the preparation of stable pharmaceutical compositions containing prasugrel base and relevant excipients. The composition comprises at least one surfactant and optionally a cyclodextrine compound.


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Abstract: The present invention relates to the preparation of stable pharmaceutical compositions containing prasugrel base and relevant excipients. The composition comprises at least one surfactant and optionally a cyclodextrine compound.
STABLE PHARMACEUTICAL COMPOSITIONS CONTAINING PRASUGREL BASE

Field of invention
The present invention relates to the preparation of stable pharmaceutical compositions containing the active ingredient; prasugrel base and relevant excipients.

Background of the invention
Prasugrel, chemical name is 5-[2-Cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl acetate, is a platelet inhibitor having a molecular weight of 373,441. It is currently marketed in the world in cooperation with Eli Lilly and Company for acute coronary syndromes planned for percutaneous coronary intervention (PCI).

![Figure 1](image)

The compound having the figure 1 is known as prasugrel. Prasugrel and pharmacologically acceptable salts thereof are known to have a platelet aggregation-inhibiting action (particularly, an antithrombotic or anti-embolic agent). Prasugrel hydrochloride is a white solid, that is well soluble at pH 2, weakly soluble at pH 3 to 4, and is substantially insoluble at pH 6 to 7.5.

Prasugrel and its salts have stability problems about hydrolysis or oxidation during manufacturing and storage of the formulated drugs, because prasugrel's structure (EP 189601 9). Prasugrel is particularly unstable in the form of aqueous solutions, pH is critical for its stability. Optimum range for aqueous solutions of prasugrel is in the range of pH 4-6 at 25 °C.

Prasugrel can be affected from air and humidity in easily. When prasugrel is exposed to air and humidity, it degrades structurally and develops behavioral changes. Two main problems occur because of these changes. First one is stability of prasugrel products, including desired level and shelf life. Second one is prasugrel reacts the excipients in formulation. It results impurities in formulation and undesired components in formulation.

Prasugrel base very poorly soluble in water; maximum solubility in plain water is estimated to be about 20-50 \( \mu \text{M} \); buffers, serum, or other additives may increase or decrease the aqueous solubility.  

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Many patent publications are relevant to the preparation of prasugrel salts because the solubility of the base is very low on the other hand the salts are more stable. WO2011/092720 relates to pharmaceutical composition of prasugrel/its salts useful as tablet, comprises prasugrel hydrochloride, water insoluble dry binder, at least one diluent, at least one disintegrant, at least one lubricant, and composition is optionally coated with a film. WO2013/150322 relates to a quickly released stable oral pharmaceutical composition, comprises micronized prasugrel base, and starch or a starch derivative. EP2409701 relates to a pharmaceutical formulation which comprises granules of prasugrel hydrochloride, said granules comprising at least one coating layer containing pullulan. EP2409685 relates to an orally-disintegrating pharmaceutical formulation, comprising prasugrel or its derivative and one or more pharmaceutically acceptable excipient(s). WO2014/060560 describes to a solid oral composition comprises prasugrel free base and one or more pharmaceutically acceptable excipients. US2009/028136 relates to pharmaceutical formulations comprising prasugrel, including its salts, hydrates, solvates, polymorphs, and mixtures thereof and stabilizing agent e.g. sodium bisulfate.

Prasugrel is used in combination pharmaceutical formulation. US8569325 relates to composition for treating and preventing in which diseases of thrombus or embolus comprises prasugrel, aspirin and one or more pharmaceutically acceptable excipients.

**Summary of the invention**

Although there are no limitations for the usage of pharmaceutically acceptable salts of prasugrel, like its hydrogen chloride, hydrogen sulfate, maleate, mesylate, besylate, etc. in the present invention, the investigations leading to the present invention have been foremost concentrated on prasugrel in form of the free base as the active ingredient in the pharmaceutical formulations. This is the most challenging candidate, because it is considered as the most unstable form of prasugrel according to US Patent 6,693,115, and because its solubility is strongly dependent on pH.

In one aspect, the present invention is directed to the pharmaceutical composition comprising prasugrel base and pharmaceutically acceptable excipients, characterized in that at least one of the excipients is a surfactant.

Surfactant are used as wettability agent and solubilizing agents in poorly soluble drug products. They enhance the bioavailability of pharmaceutical compounds within the body by promoting more effective drug release.

Among preferred surfactants suitable for use in accordance with the present invention are included polyoxyethylene hardened castor oil, ethoxylated hydrogenated castor oil, glyceryl monostearate, sorbitan monostearate, sorbitan monopalmitate, sorbitan monolaurate,
polyoxyethylene polyoxypropylene block copolymers, polysorbate 80, sodium laurylsulfate, 
rrracrogols, sucrose esters of fatty acids and mixtures thereof.
More preferably, the surfactant is ethoxylated hydrogenated castor oil, polysorbate 80 and 
sodium laurylsulfate and mixtures thereof. Most preferably the surfactant is polysorbate 80 or 
mixture with sodium laurylsulfate or ethoxylated hydrogenated castor oil or mixture with sodium 
laurylsulfate.

Preferably, the amount of surfactant is in the range of about 0.1-5% by weight core tablet.
Ethoxylated hydrogenated castor oil (Polyoxyl 40 hydrogenated castor oil) and polysorbate 80 is 
known SEPITRAP as commercial name.

Two solubilizers specially selected for their solubilization efficacy: SEPITRAP 80, SEPITRAP 
4000. SEPITRAP 80 includes solubiiizer (polysorbate 80) and specific carrier in particular 
weight. SEPITRAP 4000 includes solubiiizer (Polyoxyl 40 hydrogenated castor oil) and specific 
carrier in particular weight.

SEPITRAP is a solubiiizer based on microencapsulate in powder form directly compressible.
SEPITRAP, for use in solid oral dosage forms such as tablets and capsules, is a functional 
exciipient designed especially to simplify the manufacture of dry forms. SEPITRAP improves the 
bioavailability of APIs with low solubility. SEPITRAP can be used in direct compression 
processes, without an intermediary wet granulation.

SEPITRAP has some advantages: improving bioavailability, increasing drug solubilisation 
and/or permeation; using less active pharmaceutical ingredient (API) for same efficiency. It has 
some properties about good ability to settle, particle size < 200pm, free flowing powder, 
solubilizing properties on poorly soluble API, effect of pH.

In another aspect, the present invention is directed to the pharmaceutical composition 
comprising prasugrel base and pharmaceutically acceptable excipients, characterized in that at 
least one of the excipients is a surfactant and additionally the composition comprises a 
cyclodextrine derivative. The pharmaceutical composition may comprise prasugrel base and 
cyclodextrine in the separate layers.
A preferred embodiment of the present invention is characterized in that prasugrel base 
granules comprise at least one coating containing cyclodextrine derivatives.
Cyclodextrins are wellknown compounds to improve the dissolution rate of drugs, in general. 
They are biodegradable compounds and are not toxic for pharmaceutical compositions.
Another embodiment of the present invention is characterized in that prasugrel base granules 
comprise at least one coating containing cyclodextrine with external phase of Sepitrap 80 or 
Sepitrap 4000 using wet granulation method.
In a preferred embodiment according to the present invention, the amount of cyclodextrine 
derivatives in said coating layer with respect to the total granule amount interval can be 
changed.
Cyclodextrins are cyclic oligosaccharides, which are composed of cyclic ct-(1→4) linked D-glucopyranose units. Cyclic oligosaccharides of cyclodextrins with six to eight units have been named α-, β- and γ-cyclodextrin, respectively. The number of units determines the size of the cavity which characterizes cyclodextrins and into which drugs may be included to form stable complexes. Cyclodextrine compounds are thus known complexing agents and have been previously used in the pharmaceutical field to form inclusion complexes with water-insoluble drugs and to thus solubilize them in aqueous media.

The complexes formed are, however, also stable in aqueous solution, so that the improvement in dissolution is accompanied by an increase in the saturation solubility of the drug. In another embodiment, the pharmaceutical composition comprises a film coating. The film coating may comprise specific moisture barrier compound. Film coating with specific moisture barrier system can be used in many manufacturing method. This barrier may consisting of Sepifilm LP and Opadry AMB.

Sepifilm LP is in granule form. It has advantages in a formulation process, for example, improving the stability of moisture-sensitive active ingredients, improving the stability of hygroscopic formulations and preventing degradation of tablets caused by ambient humidity. Its property is quick and easy dispersion in a composition. There are three types of Sepifilm LP according to its color: a) colorless film-coating, b) white film-coating, c) colored film-coating. Opadry AMB is a pigmented or white film coating system for the coating of oral solid-dosage forms that need to be protected from environmental moisture. This system provides fast hydration, excellent logo definition, smooth tablet finish, rapid equipment clean down with water. In another aspect, the manufacturing process of core tablet is direct compression or wet granulation process.

Direct compression (DC) is by far the simplest means of production of a pharmaceutical tablet. The term "direct compression" is defined as the process by which tablets are compressed directly from powder mixture of API and suitable excipients. No pretreatment of the powder blend by wet or dry granulation procedure is required. Three key factors for successful tableting are flow and compactability of the compression mix, and drug content uniformity in the mix and the final tablets. Some of advantages for direct compression method is cost effectiveness, stability, faster dissolution, less wear and tear of punches.

Direct compression involves comparatively few steps: i) Milling of drug and excipients, ii) Mixing of drug and excipients, iii) Tablet compression. Direct compression excipients mainly include diluents, binders and disintegrants.

Performing direct compression without any problems, it is considered two certain parameters: compactability and flow properties. Compatibility is critical, a conventional tablet must have enough hardness to withstand various stages in direct compression. Poor flow may result in difficulties for the compression, so flow properties must checked in direct compression.
Wet granulation, the process of adding a liquid solution to powders, is one of the most common ways to granulate. The process can be very simple or very complex depending on the characteristics of the powders, the final objective of tablet making, and the equipment that is available. This method can be used when powders are very fine, fluffy, will not stay blended, or will not compress. Wet granulation can be divided into three main processes of low shear, high shear, and fluid bed granulation.

Fluid bed granulation method has advantages in manufacturing pharmaceutical products. Fluid bed granules are homogeneous. All particles in the powder mix are sprayed evenly with liquid starting materials. The type of granulate (size, density, porosity) can be influenced over a wide range by the adjustment of various parameters.

One embodiment of the present invention is characterized in that prasugrel base granules with external phase of surfactant such as Sepitrap 80 or Sepitrap 4000 using direct compression method.

Method's steps are: i) blending drug and excipients. ii) mixing of drug with Sepitrap 80 or Sepitrap 4000 and excipients. iii) tablet compression stage.

After compressing tablet, film coating with specific moisture barrier is performed in the last stage of process. These coatings are a film-coating system to protect against moisture (Sepifilm LP and Opadry AMB as commercial name).

A further preferred embodiment according to the second present invention provides a method for preparing pharmaceutical granules in wet granulation, comprising the steps of

a. dissolving cyclodextrine derivatives in a proper solvent,
b. spray-coating the solution obtained above onto the granules comprising prasugreli or a pharmaceutically acceptable salt of prasugrel,
c. SEPITRAP 80 or SEPI TRAP 4000 is used as a solubilizer in external phase, and
d. film coating with specific moisture barrier compound is performed in the last stage of process.

Potential materials for increasing solubility: like HPC, PEG, beta-cyclodextrine, Sodium Laurylsulfate etc. can be used in wet granulation method.

The pharmaceutical composition is tablet or capsule for oral administration. It may be in the form of immediate release or in the form of prolonged release.

Detailed description of the invention

Present invention provides a pharmaceutical composition, which comprises of:

Prasugrel base,

with pharmaceutically acceptable excipients, which has an external phase of surfactant.

Present invention provides a pharmaceutical composition, which comprises of:

a) Prasugrel base,
b) cyclodextrine derivatives,
in combination with at least one pharmaceutically acceptable excipient, which has an external phase of surfactant.
A further preferred embodiment according to the second present invention provides a method for preparing pharmaceutical granules in wet granulation, comprising the steps of
a. dissolving cycloexetrine derivatives in a proper solvent,
b. spray-coating the solution obtained above onto the granules comprising prasugrel or a pharmaceutically acceptable salt of prasugrel,
c. surfactant such as Sepitrap 80 or Sepitrap 4000 is used as a solubilizer in external phase, and
d. film coating with specific moisture barrier compound is performed in the last stage of process.
In this invention, prasugrel granules and the other excipients can be used in the content of medications which are efficient in preventing or treating thrombosis and cardiovascular diseases.
One object of the present invention is to obtain a stable and coated granule with antithrombotic activity.
In a preferred embodiment, there are preferably one coating layers provided.
In this invention, the term "cycloexetrine" means a compound including, but not limited to: β-cyclodextrin, hydroxypip-cyclodextrin, sulfobutylether-cyclodextrin, random methylatedβ-cyclodextrin, dimethylp-cyclodextrin, trimethyl β-cyclodextrin, hydroxypropyl β-cyclodextrin, hydroxybutyl β-cyclodextrin, glucosy^-cyclodextrin, maltosy^-cyclodextrin, 2-O-methyl-β-cyclodextrin or a combination thereof and their pharmaceutically acceptable salts. By cyclodextrin compound, one means cyclodextrin as well as their pharmaceutically acceptable salts, enantiomeric forms, diastereoisomers and racemates.
As used herein the term "Prasugrel" means a compound including, but not limited to, the drug compound prasugrel, its pharmaceutical acceptable salts and their polymorphs and hydrates thereof.
The term granule, as used herein, means a powder, particle, or pellet form of prasugrel or a pharmaceutically acceptable salt of prasugrel.
The term "pharmaceutically acceptable salts" refers to salts including but not limited to, hydrohalides like hydrochloride; lower-alkyl sulfonic acid salts such as methanesulfonate, or ethanesulfonate; arylsulfonic acid salts such as benzene sulfonate or p-toluenesulfonate; inorganic acids such as nitrate, perchloric acid salt; organic acid salts such as acetate, fumarate, succinate, citrate, ascorbate, tartrate, oxalate or maleate; or an amino acid salts such as glycine salt, lysine salt, arginine salt, ornithine salt, glutamic acid salt or aspartic acid salt, preferably hydrohalides or organic acid salts, more preferably hydrochloride or maleate and most preferably hydrochloride.
In one embodiment, pharmaceutical composition may be formulated, for example, in the form of pharmaceutical compositions for oral administration such as granules, fine granules, powders, hard capsules, soft capsules, syrups, emulsions, suspensions, solutions and the like, or in the form for sublingual a buccal administration, or in the form of pharmaceutical compositions for parenteral administrations such as injections for intravenous, intramuscular, or subcutaneous administration, drip infusions, transdermal preparations, transmucosal preparations, nasal drops, inhalants, suppositories and the like. Injections or drip infusions may be prepared as powdery preparations such as in the form of lyophilized preparations, and may be used by dissolving just before use in an appropriate aqueous medium such as physiological saline.

The formulation according to the present inventions may be in the form of a tablet, dragee, capsule, caplet, orally-disintegrating tablet, film-coated tablet, enteric tablet, buccal tablet, sublingual tablet, chewable tablet, effervescent tablet, slow-release tablet, rapid-release tablet, modified-release tablet, delayed-release tablet, prolonged-release tablet, controlled-release tablet, sachet, granule, pilule, powder, pellet, suppository, pastille and similar solid oral dosage forms, or syrup, elixir, solution, suspension, drop (concentrated solution), potion, emulsion, ampoule, or similar liquid oral dosage forms. The preferred dosage form according to the present invention is the solid dosage form, preferably a tablet form.

In one embodiment, pharmaceutical composition may be developed in the form of a unit dosage form, such as tablet, minitablet, bilayer tablet, caplet, granules/pellets, and in the form of capsule or sachet filled with tablets, minitablets, granules/pellets.

Pharmaceutical composition of the present inventions may comprise one or more pharmaceutically acceptable excipient(s). Pharmaceutically acceptable excipients comprise, but are not limited to fillers, disintegrants, binders, lubricants, glidants, sweeteners, aromatic agents, preservatives, coloring agents, and the mixtures thereof, to facilitate the physical formulation of various dosage forms like orally disintegrating tablets, chewable tablets and suspensions (including dry powders or granules for suspension).

In one embodiment, pharmaceutical composition can be prepared by various formulation techniques known to the person skilled in the art, such as, but not limited to direct compression, wet or dry granulation,slugging, hot melt granulation, extrusion-spheronization, hot melt extrusion, fluidized bed granulation, extrusion, spray drying, spray coating, and solvent evaporation and the like.

In one embodiment, pharmaceutical composition may comprise single or plurality of multiple-compression tablets which are formed by two or more compression cycles. This results in a multiple-compression tablet which has at least two discrete layers defined by the presence of the said parts in the layer. A multiple-compression tablet can exist as, for example, a layered tablet, as a compression-coated tablet, or as an inlay tablet.
In one embodiment, a layered tablet is a tablet which is made up of two or more distinct cores of granulation compressed together with the individual layers lying one on top of another. In one embodiment, layered tablets are generally prepared by compressing a granulation onto a previously compressed granulation. The operation may be repeated to produce multilayered tablets of more than two layers.

In one embodiment, a compression-coated tablet is a tablet which is made up of an inner core and one or more outer core or coats wherein the inner core is completely surrounded by the outer coat or coats. These tablets have at least three discrete zones of components compressed together, i.e., an inner core, middle core, and an outermost coat. Such tablets also referred to as press-coat or dry-coated tablets are prepared by feeding a previously compressed inner core into a special tableting machine and compressing one or more other granulation coats around the preformed inner core. Instead of an inner core being completely surrounded by an outer coat, one surface of the inner core is exposed. These tablets have at least two cores of components compressed together, i.e., an inlay core and a base core. The preparation of inlay tablets is similar to the preparation of compression-coated tablets except that a surface of coating is eliminated. It will be within the pursuit of the skilled artisan to select any component or mixture thereof for preparing inlay core and base core.

The barrier layer may be formed by any method, including compression, molding, dipping, or spray coating.

Binders can be selected from the group, but are not limited to methylcellulose, sodium carboxymethylcellulose, calcium carboxymethylcellulose, ethyl cellulose, hydroxypropyl methylcellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, silicified microcrystalline cellulose (SMCC), polyvinyl pyrrolidone, gelatine, polyvinyl alcohol, acacia, tragacanth, guar, pectin, starch paste, pre-gelatinized starch, alginic acid, compressible sugar, liquid glucose, dextrates, dextrin, dextrose, maltodextrin, guar gum, magnesium aluminium silicate, polymethacrylates, sorbitol and other materials known to one of ordinary skill in the art. A preferred binder is hydroxypropyl methylcellulose. A mixture of binders may also be used. The binder is preferably used in an amount of from about 2 to about 15% by weight.

Diluents may be water-soluble or water insoluble. Diluents can be selected from the group, but are not limited to spray-dried or anhydrous lactose, sucrose, dextrose, starch, pre-gelatinized starch, mannitol, maltitol, sorbitol, xylitol, dextrin, cellulose derivatives including powdered cellulose, microcrystalline cellulose, dibasic calcium phosphate, tribasic calcium phosphate and calcium sulfate, kaolin, precipitated calcium carbonate, maltodextrin and other materials known to one of ordinary skill in the art. A preferred diluent is mannitol. A mixture of diluents may also be used. Mannitol is commercially available from under the brand name Pearlitol®. The diluent is preferably used in an amount of from about 10% to about 70% by weight.
Disintegrants can be selected from the group, but are not limited to alginic acid, carboxymethylcellulose calcium, carboxymethyl cellulose, carboxymethylcellulose sodium, cross-linked sodium carboxymethylcellulose, low substituted hydroxypropyl cellulose, colloidal silicon dioxide, croscarmellose sodium, crospovidone, guar gum, magnesium aluminium silicate, microcrystalline cellulose, methyl cellulose, polyvinylpyrrolidone, cross-linked polyvinylpyrrolidones, polacrifin potassium, starch, pregelatinised starch, sodium alginate, sodium lauryl sulphate, sodium starch glycoliate, crystalline cellulose, hydroxypropyl starch and other materials known to one of ordinary skill in the art. The combination of above-mentioned disintegrants can also be used. The preferred disintegrant is croscarmellose sodium. The disintegrant is preferably used in an amount of from about 5% to about 50% by weight.

Lubricants can be selected from the group, but are not limited to vegetable oils, such as hydrogenated vegetable oil or hydrogenated castor oil; polyethylene glycols, such as polyethylene glycol (PEG)-4000 and PEG-6000; stearic acid; derivatives of stearic acid, such as magnesium stearate, sodium stearate, calcium stearate, zinc stearate, glyceryl monostearate, glyceryl palmitostearate and sodium stearyl fumarate; mineral salts, such as talc; inorganic salts; organic salts, such as sodium benzoate, sodium acetate, sodium chloride and sodium oleate; and polyvinyl alcohols, microcrystalline cellulose, sodium lauryl sulphate, silica, colloidal silica, cornstarch, calcium silicate, magnesium silicate, silicon hydrogel and other materials known to one of ordinary skill in the art. The preferred lubricant is magnesium stearate. Preferably, lubricant is used in an amount from about 1 to about 5% by weight.

Glidants can be selected from the group, but are not limited to colloidal silicon dioxide, colloidal silica, cornstarch, talc, calcium silicate, magnesium silicate, magnesium trisilicate, amorphous silica, colloidal silicon, silicon hydrogel, powdered cellulose, silicon dioxide, talc, tribasic calcium phosphate and other materials known to one of ordinary skill in the art. Glidants are used in an amount from about 1 to about 30 percent by weight. Preferably, from about 5 to about 15 percent by weight.

Fillers can be selected from the group, but are not limited to calcium carbonate, calcium phosphate, calcium sulphate, carboxymethylcellulose calcium, carboxymethylcellulose sodium, compressible sugar, confectioner's sugar, dextrates, dextrin, dextrose, dibasic calcium phosphate dihydrate, dibasic calcium phosphate, fructose, glyceryl palmitostearate, glycine, hydrogenated vegetable oil-type 1, kaolin, lactose, maize starch, magnesium carbonate, magnesium oxide, maltodextrin, mannitol, microcrystalline cellulose, polymethacrylates, potassium chloride, powdered cellulose, pregelatinised starch, sodium chloride, sorbitol, starch, sucrose, sugar spheres, talc, tribasic calcium phosphate, and xylitol and other materials known to one of ordinary skill in the art.

Polymers can be selected from the group, but are not limited to hydroxypropylcellulose, hydroxypropyl cellulose, ethyl cellulose, hydroxypropylmethyl cellulose phthalate,
hydroxypropylmethyl cellulose acetate succinate, cellulose acetate phthalate; methacrylic polymers, aminoalkyl methacrylate copolymer, methacrylic acid copolymer (e.g. Eudragit®), polyvinyl acetate phthalate and polyvinyl alcohol (PVA). Plasticizer can be selected from the group, but are not limited to Acetylated monoglycerides, Triethyl citrate, Acetyl triethyl citrate, Tributyl citrate, Acetyl tributyl citrate, Triocetyl citrate, Acetyl triocyl citrate, Trihexyl citrate, Acetyl trihexyl citrate, Butyltri hexyl citrate, Trimethyl citrate, PEG, Epoxidized vegetable oils, Bis(2-ethylhexyl) adipate, Dimethyl adipate, Monomethyl adipate, Dioctyl adipate, Dibutyl sebacate, Tributyl sebacate, Dibutyl maleate, Diisobutyl maleate.

Surfactants can be selected from the group, but are not limited to, also polyoxyethylene hardened castor oil, Ethoxiated hydrogenated castor oil (Sepitrap 4000), glycercyl monostearate, sorbitan monostearate, sorbitan monopalmitate, sorbitan monolaurate, polyoxyethylene polyoxypropylene block copolymers, polysorbate 80 (Sepitrap 80), sodium laurylsulfate, macrogols, sucrose esters of fatty acids and other materials known to one of ordinary skill in the art. The preferred surfactant is sodium laurylsulfate. Preferably, surfactant is used in an amount of from about 0.1% to about 5% weight. A mixture of surfactants may also be used.

Dispersing agents or dispersants can be selected from the group, but are not limited to colloidal silicon dioxide, talc, magnesium stearate and titanium dioxide and other materials known to one of ordinary skill in the art. The preferred dispersing agent is colloidal silicon dioxide. Preferably dispersing agent is used in an amount of from about 1 to about 5 percent by weight.

As the "coating agents" used can be selected from the group, but are not limited to hydroxypropyl cellulose, hydroxyethyl cellulose, ethyl cellulose, talc, polyethylene glycol, titanium dioxide and color.

Sweeteners can be selected from the group, but are not limited to aspartame, saccharine; glucose, lactose, fructose and other sugars, and mannitol, sorbitol, xylitol, erythritol and other sugar alcohols, and the mixtures thereof.

Aromatic agents can be selected from the group, but are not limited to menthol, mint, cinnamon, chocolate, vanillin, and fruit extracts such as of cherry, orange, strawberry, grape, and the mixtures thereof.

Colorants, including, but not limited to Food, Drug, and Cosmetic (FD&C) dyes (e.g. FD&C blue, FD&C green, FD&C red, FD&C yellow, FD&C lake), ponceau, indigo Drug & Cosmetic (D&C) blue, indigotine FD&C blue, carmoisine indigotine (indigo Carmine); iron oxides (e.g. iron oxide red, yellow, black), quinoline yellow, flame red, brilliant red (carmine), carmoisine, sunset yellow, and the mixtures thereof.
Preservatives, including, but not limited to methylparaben and propylparaben and the salts thereof (e.g. sodium or potassium salts), sodium benzoate, citric acid, benzoic acid, butylated hydroxyioluene and butylated hydroxyanisole, and the mixtures thereof.

Preferably, flavoring agents for the composition of the present invention are black currant, sodium chloride, strawberry flavor, and peppermint flavor. Preferably, sweeteners for the composition of the present invention include sucralose, acesulfame potassium and aspartame. A combination of sweeteners and flavoring agents can also be used. Preferably, flavoring agents are used in an amount of from about 0.5 to about 5 percent by weight. Preferably, sweeteners are used in an amount of from about 1 to about 5 percent by weight.

Advantages

In these present inventions, it shows quick affect and efficiency. Direct compression, dry granulation and wet granulation can be used for this invention. This invention can include production method which is for increasing solubility. These methods can be spraying granulation from above and solid dispersion techniques.

The present inventions provide pharmaceutical formulations comprising prasugrel base characterized by 1) good stability, 2) to control / program the release of the active ingredient according to desired therapeutical needs, and 3) a simple and competitive manufacturing process.

The major subject of the present inventions are to provide a prasugrel formulation which has resistant against physical and enviromental conditions and also have a high bioavailability. Prasugrel base and salts are sensitive to moisture and oxygen content of the air.

In present inventions, the prasugrel formulations can be designed and processed in order to obtain pH-independent, fast or slow release drugs.

The coated granules surprisingly give results which are good dissolution rates and stability. Coating with cycloextrine of prasugrel granules and using Sepitrap 80 or Sepitrap 4000 can increase dissolution rates. Also it protects stability rates in composition. This step also avoids the aggregation of granules and any reduction in their flowabiliy. The flowability of the granules obtained is high, and their humidity-permeability is low.
Example 1

<table>
<thead>
<tr>
<th>Content</th>
<th>Unit Formula (mg/tablet)</th>
<th>Ratio</th>
<th>Theoretical Batch Formula (g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prasugrel Base</td>
<td>10.00</td>
<td>5.7%</td>
<td>14.00</td>
</tr>
<tr>
<td>Sepitrap 4000</td>
<td>10.00</td>
<td>5.7%</td>
<td>14.00</td>
</tr>
<tr>
<td>Mannitol 200 SD</td>
<td>93.00</td>
<td>56.9%</td>
<td>130.2</td>
</tr>
<tr>
<td>Hypromellose 3cP</td>
<td>3.50</td>
<td>2.0%</td>
<td>4.90</td>
</tr>
<tr>
<td>Ac-Di-Sol</td>
<td>8.75</td>
<td>5.0%</td>
<td>12.25</td>
</tr>
<tr>
<td>Avicel PH 112</td>
<td>48.00</td>
<td>27.4%</td>
<td>67.20</td>
</tr>
<tr>
<td>Magnesium Stearate</td>
<td>1.75</td>
<td>1.0%</td>
<td>2.45</td>
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<tr>
<td>Core Tablet weight</td>
<td><strong>175.00</strong></td>
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<td></td>
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</table>

Coating

<table>
<thead>
<tr>
<th></th>
<th>Unit Formula (mg/tablet)</th>
<th></th>
<th>Theoretical Batch Formula (g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opadry AMB</td>
<td>6.00</td>
<td></td>
<td>8.4</td>
</tr>
<tr>
<td>Water</td>
<td><strong>qs (54.00)</strong></td>
<td></td>
<td>75.6</td>
</tr>
</tbody>
</table>

Prasugrel, Mannitol (1/3), Hypromellose 3cP, Ac-Di-Sol and Sepitrap 4000 are sieved and mixed. Mannitol (2/3) and Avicel are added, mixed. Sieved Magnesium Stearate is added, mixed and compressed.

Example 2

<table>
<thead>
<tr>
<th>Content</th>
<th>Unit Formula (mg/tablet)</th>
<th>Ratio</th>
<th>Theoretical Batch Formula (g)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intragranular phase</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Mannitol 200 SD</td>
<td>94.68</td>
<td>52.31</td>
<td>213.03</td>
</tr>
<tr>
<td>Sodium Lauryl Sulfate</td>
<td>1.75</td>
<td>0.97</td>
<td>3.94</td>
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<td>9.86</td>
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<td><strong>Solution</strong></td>
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<td>Prasugrel Base</td>
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<td>Crospovidone, XL-10</td>
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<td>Avicel PH 112</td>
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<td>108.00</td>
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<td>Magnesium Stearate</td>
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<td><strong>Core tablet weight</strong></td>
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<td><strong>Coating</strong></td>
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<td>Water</td>
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Mannitol, Sodium lauryl sulphate, Crospovidon XL-10, Sepitrap 80 and PVPK30 are passed through 600µ screen and dry mix in High shear mixer. The mixture is granulated by Prasugrel base solution in acetone. Dry and sieve. Sieved Crospovidone XL-10 and Avicel PH 112 are added to dried granule and mixed. Sieved Magnesium Stearate is added, mixed, compressed and coated.
CLAIMS

1. A pharmaceutical composition comprising prasugrel base and at least one pharmaceutically acceptable excipient, characterized in that it comprises at least one surfactant.

2. A pharmaceutical composition according to claim 1, wherein the surfactant is selected from the group consisting of polyoxyethylene hardened castor oil, ethoxylated hydrogenated castor oil, glyceryl monostearate, sorbitan monostearate, sorbitan monopalmitate, sorbitan monolaurate, polyoxyethylene polyoxypropylene block copolymers, polysorbate 80, sodium lauryl sulfate, macrogols, sucrose esters of fatty acids and mixtures thereof.

3. A pharmaceutical composition according to claim 2, wherein the surfactant is selected from the group consisting of ethoxylated hydrogenated castor oil, polysorbate 80 and sodium laurylsulfate and mixtures thereof.

4. A pharmaceutical composition according to claim 2 and 3, wherein the surfactant is polysorbate 80 or mixture with sodium laurylsulfate.

5. A pharmaceutical composition according to claim 2 and 3, wherein the surfactant is ethoxylated hydrogenated castor oil or mixture with sodium laurylsulfate.

6. A pharmaceutical composition according to any one of the preceding claims, wherein the surfactant is used in an amount of from about 0.1% to about 5% by weight.

7. A pharmaceutical composition according to any one of the preceding claims, wherein it comprises a cyclodextrine derivative.

8. A pharmaceutical composition according to claim 7, wherein prasugrel base and cyclodextrine are in the separate layers.

9. A pharmaceutical composition according to any one of the preceding claims, wherein it comprises a film coating.

10. A pharmaceutical composition according to claim 9, wherein the film coating comprises specific moisture barrier compound.

11. A pharmaceutical composition according to any one of the preceding claims, wherein the manufacturing process of core tablet is wet granulation process.

12. A pharmaceutical composition according to any one of the preceding claims, wherein it is provided in the form of tablet or capsule.

13. Pharmaceutical composition according to according to claim 12, wherein it is provided in the form of immediate release.

14. A pharmaceutical composition according to claim 13, wherein it is provided in the form of prolonged release.
# INTERNATIONAL SEARCH REPORT

**International application No**

PCT/TR2015/00Q033

## A. CLASSIFICATION OF SUBJECT MATTER

INV. A61K9/00 A61K9/20 A61K31/4365

**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)

A61K

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

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

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<td>EP 2 409 685 A2 (SANOVEI I LAC SANAYI VE TICARET AS [TR]) 25 January 2012 (2012-01-25) page 4 - page 5; claims 1, 12, 16, 18</td>
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<td>WO 2011/036533 AI (GLENMARK PHARMACEUTICALS LTD [IN]; PATOLE PRASHANT [IN]; KHALI RATKAR-JO) 31 March 2011 (2011-03-31) page 11, line 11 - line 25; claim 1</td>
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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

Date of the actual completion of the international search

16 July 2015

Date of mailing of the international search report

24/07/2015

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel: (+31-70) 340-2040, Fax: (+31-70) 340-3016

Authorized officer

Kardas-Llorens, Eyup

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Form PCT/ISA/210 (second sheet) (April 2005)
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