The invention relates to pharmaceutical compositions comprising clopidogrel or monobasic acid salts thereof in admixture with one or more hydrated excipients. The invention also relates to pharmaceutical compositions comprising clopidogrel or monobasic acid salts thereof which are free of any moisture scavenger. The invention also relates to processes for the preparation of such compositions.
Description

PHARMACEUTICAL COMPOSITIONS OF CLOPIDOGREL

[1] Field of the Invention
The invention relates to pharmaceutical compositions comprising clopidogrel or monobasic acid salts thereof in admixture with one or more hydrated excipients. The invention also relates to pharmaceutical compositions comprising clopidogrel or monobasic acid salts thereof which are free of any moisture scavenger. The invention also relates to processes for the preparation of such compositions.

[2] Background of the Invention
Clopidogrel is an inhibitor of ADP-induced platelet aggregation acting by direct inhibition of adenosine diphosphate (ADP) binding to its receptor and of the subsequent ADP-mediated activation of the glycoprotein GPIIb/IIIa complex. Chemically, it is (αS)-α-(2-chlorophenyl)-6,7-dihydrothieno[3,2-c]pyridine-5(4H)-acetic acid methyl ester. It is indicated for the reduction of atherothrombotic events in patients with history of recent myocardial infarction (MI), recent stroke, or established peripheral arterial disease and acute coronary syndrome.


[4] International (PCT) Publication No. WO2005048992 discloses compositions of clopidogrel, wherein the clopidogrel is in the form of coated particles mixed with anhydrous excipients along with moisture scavengers.


[8] Clopidogrel in a base or a monobasic acid salt form, such as mesylate, hydrochloride, hydrobromide, benzoate, salicylate, lactate, gluconate is known to exhibit difficulties in formulating solid stable dosage forms, owing to its hygroscopicity. The monobasic acid salts of clopidogrel are known to interact with certain formulation excipients and undergo degradation. The pharmaceutical compositions containing clopidogrel or monobasic acid salts thereof are not commercially available. To overcome such problems, usually the bisulphate salt of clopidogrel is used.

[9] During development of pharmaceutical formulations comprising clopidogrel hydrochloride, often drug tends to degrade even in the presence of a little moisture and thus
makes the drug unavailable in the plasma at the time of ingestion. Several references describe formulations, wherein the clopidogrel is either in the form of coated particles or mixed with anhydrous excipients along with moisture scavengers. Clearly, there is a need for improved compositions which are not only easy to prepare and does not utilize anhydrous excipients along with moisture scavengers but are also bioequivalent to the commercially available clopidogrel bisulphate tablets (Plavix®).

**Summary of the Invention**

[12] In one general aspect there is provided a pharmaceutical composition that includes clopidogrel or monobasic acid salts thereof, and one or more hydrated excipients.

[13] The term 'hydrated excipients' as used herein refers to sufficient amount of water present in them so as to get them in the hydrated state.

[14] Embodiments of the pharmaceutical composition may include one or more of the following features. The pharmaceutical composition may further include one or more pharmaceutically acceptable excipients. The pharmaceutically acceptable excipients may include one or more of fillers, binders, lubricants, glidants, disintegrants, and the like.

[15] In another general aspect there is provided a pharmaceutical composition that includes uncoated granules, particles or pellets of clopidogrel or monobasic acid salts thereof, wherein the composition is free of any moisture scavenger.

[16] The term 'moisture scavenger' as used herein refers to a substance which scavenges free moisture and prevents degradation or decomposition or sticking or hygroscopicity of the active ingredient.

[17] The term 'uncoated granules, particles or pellets of clopidogrel' as used herein refers to granules, particles or pellets of clopidogrel which are as such and not coated with any polymer.

[18] Embodiments of the pharmaceutical composition may include one or more of the following features. The pharmaceutical composition may further include one or more pharmaceutically acceptable excipients. The pharmaceutically acceptable excipients may include one or more of fillers, binders, lubricants, glidants, disintegrants, and the like.

[19] In another general aspect there is provided a pharmaceutical composition that includes clopidogrel hydrochloride and glyceryl behenate, wherein one or both of the rate and the extent of absorption of the clopidogrel hydrochloride is equal to or greater than that obtained by a clopidogrel bisulphate tablet marketed under the trade name Plavix®.

[20] In another general aspect there are provided processes for preparing pharmaceutical compositions that include clopidogrel or monobasic acid salts thereof. The process
includes: a) mixing and granulating clopidogrel or monobasic acid salts thereof with hydrated excipients; and b) converting the granules into a suitable dosage form.

Embodiments of the pharmaceutical composition may include one or more of the following features. The pharmaceutical composition may further include one or more pharmaceutically acceptable excipients. The pharmaceutically acceptable excipients may include one or more of fillers, binders, lubricants, glidants, disintegrants, and the like.

The details of one or more embodiments of the inventions are set forth in the description below. Other features, objects and advantages of the inventions will be apparent from the description and claims.

Description of drawings

Figure 1: Comparative in vivo area under the plasma concentration time profiles (AUC)

Detailed Description of the Invention

We have now discovered that clopidogrel or monobasic acid salts thereof, when mixed with hydrated excipients results in a composition which is stable that does not undergo degradation on storage. Further, we have discovered that a stable formulation of clopidogrel or monobasic acids salts thereof can be prepared without coating with any hydrophobic polymer. It was also found that a stable formulation can be prepared when the formulation does not contain any moisture scavenger. The inventors have surprisingly found that a stable formulation of clopidogrel or monobasic acid salts thereof can be prepared using glyceryl behenate in the formulation, which is bio-equivalent to clopidogrel bisulfate tablet dosage form commercially marketed under the trade name Plavix®.

The monobasic acid salts of clopidogrel can be selected from one or more of clopidogrel hydrochloride, clopidogrel hydrobromide, clopidogrel mesylate, clopidogrel besylate, clopidogrel salicylate, clopidogrel lactate or clopidogrel gluconate.

The hydrated excipients can be selected from one or more of microcrystalline cellulose such as Avicel PH 101, low substituted hydroxy propyl cellulose; high substituted hydroxypropyl cellulose, hydroxypropyl methyl cellulose, colloidal silicon dioxide and the like.

In general, the pharmaceutical compositions of the invention can be prepared by simple mixing, direct compression, dry granulation or wet granulation.

In one embodiment the pharmaceutical composition of clopidogrel or monobasic acid salts thereof may be prepared by compacting clopidogrel or monobasic acid salts thereof with pharmaceutically acceptable excipients optionally with lubricant. The aggregates thus obtained may be sized into granules or particles, which may be mixed
with other pharmaceutically acceptable excipients, may be formulated in suitable dosage form.

The pharmaceutical compositions may include one or more pharmaceutically acceptable excipients selected from fillers, binders, lubricants, glidants, disintegrants, and the like.

Suitable fillers may include one or more of lactose, microcrystalline cellulose, polyethylene glycols, mannitol, calcium phosphate, calcium sulfate, kaolin, dry starch, sorbitol, powdered sugar, prosolv, and the like.

Suitable disintegrants may include one or more of starch, croscarmellose sodium, crospovidone, sodium starch glycolate, hydroxypropylcellulose, and the like.

Suitable glidants may include one or more of colloidal silicon dioxide, talc or cornstarch, and the like.

Suitable lubricants comprises one or more of hydrogenated vegetable oil, hydrogenated castor oil, light mineral oil, glycerol monostearate, glycerol monobehenate, glyceryl behenate, glycercyl palmitostearate, and the like.

The pharmaceutical composition of the invention can be present in the form of granules, pellets, beads, spheroids, a tablet, a minitablet, a microtablet, a capsule, granules in a capsule, pellets in a capsule, minitablets in a capsule, or combinations thereof.

'Bioequivalence' is established by a 90% Confidence Interval (CI) of between 0.80 and 1.25 for both C_max and AUC under USFDA regulatory guidelines, or a 90% CI for AUC of between 0.80 to 1.25 and a 90% CI for C_max of between 0.70 to 1.43 under the European EMEA regulatory guidelines.

Bioequivalence studies were carried out between Plavix® and composition of the invention both in fed state and fasted state. The study was monitored in terms of C_max, AUC, Tmax achieved with the test product and reference product (Plavix®). Table 1 gives bioequivalence data of Plavix® and test product.

Each subject received a single dose of clopidogrel after starting breakfast. Wash out periods of one week separated doses.

Blood samples were collected prior to dosing (0 hour) and at 0.16, 0.33, 0.5, 0.75, 1.0, 1.25, 1.5, 1.75, 2.0, 2.5, 3.0, 3.5, 4.0, 6.0, 8.0, 12, and 16 hour after each dose. Plasma samples were assayed for clopidogrel using a validated high performance liquid chromatographic procedure. Values for clopidogrel pharmacokinetic parameters including observed C_{max}, AUC_{0-1} and AUC_{0-\infty}, were calculated using standard methods.

Table 1: Bioequivalence data with respect to Test (Composition of the invention) to reference (Plavix®) Ratios (T/R ratios) at 90% Confidence Interval (CI.)
The invention is further illustrated by the following examples which are provided merely to be exemplary of the invention and do not limit the scope of the invention. Certain modifications and equivalents will be apparent to those skilled in the art and are intended to be included within the scope of the invention.

Example 1: The composition of batches is provided in Table 1.

Table 1:

<table>
<thead>
<tr>
<th>Pharmacokinetic parameters</th>
<th>Ratio % (Test/Ref)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax</td>
<td>1. 81</td>
</tr>
<tr>
<td>AUC₀⁻&lt;sub&gt;t&lt;/sub&gt;</td>
<td>1. 35</td>
</tr>
<tr>
<td>AUC₀⁻&lt;sub&gt;∞&lt;/sub&gt;</td>
<td>1. 97</td>
</tr>
</tbody>
</table>

Procedure: Clopidogrel hydrochloride was mixed with microcrystalline cellulose, low substituted hydroxypropyl cellulose, colloidal silicon dioxide and glyceryl behenate in a double cone blender. The blend obtained was compacted using a roll compactor. The aggregates were sized into granules using oscillating granulator. The granules were mixed with low substituted hydroxypropyl cellulose, colloidal silicon dioxide, crospovidone, talc and lubricated with glyceryl behenate, hydrogenated castor oil in a double cone blender. The lubricated blend was finally compressed into tablets using a suitable tooling. The tablets were coated with aqueous dispersion of Opadry.
Example-2: The composition of the batches is provided in Table 2.

Table-2:

<table>
<thead>
<tr>
<th>S.No</th>
<th>Ingredients</th>
<th>% w/w</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>Intragranular</strong></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Clopidogrel Hydrochloride</td>
<td>15-40</td>
</tr>
<tr>
<td>2</td>
<td>Silicified microcrystalline cellulose</td>
<td>30-70</td>
</tr>
<tr>
<td>3</td>
<td>Low substituted HPC</td>
<td>5-10</td>
</tr>
<tr>
<td>4</td>
<td>Glyceryl Behenate</td>
<td>1-5</td>
</tr>
<tr>
<td></td>
<td><strong>Extragranular</strong></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Low substituted HPC (LH -11)</td>
<td>0.5-2.0</td>
</tr>
<tr>
<td>6</td>
<td>Silicified microcrystalline cellulose</td>
<td>5-10</td>
</tr>
<tr>
<td>7</td>
<td>Glyceryl Behenate</td>
<td>1-5</td>
</tr>
<tr>
<td>8</td>
<td>Hydrogenated Castor oil</td>
<td>1-5</td>
</tr>
</tbody>
</table>

Procedure: Clopidogrel hydrochloride was mixed with Prosolv, low substituted hydroxypropyl cellulose, and glycercyl behenate in a double cone blender and the blend was compacted using a roller compactor. The aggregates were sized into granules using oscillating granulator. The granules were mixed with Prosolv, low substituted hydroxypropyl cellulose and lubricated with glycercyl behenate, hydrogenated castor oil in a double cone blender. The lubricated blend was finally compressed into tablets using a suitable tooling. The tablets were coated with aqueous dispersion of Opadry.

While the 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 invention.
We Claim:

A pharmaceutical composition comprising clopidogrel or monobasic acid salts thereof and one or more hydrated excipients.

The pharmaceutical composition of claim 1, wherein the monobasic acid salt of clopidogrel comprises one or more of clopidogrel hydrochloride, clopidogrel hydrobromide, clopidogrel mesylate, clopidogrel besylate, clopidogrel salicylate, clopidogrel lactate and clopidogrel gluconate.

The pharmaceutical composition of claim 2, wherein the monobasic acid salt of clopidogrel is clopidogrel hydrochloride.

The pharmaceutical composition of claim 1, wherein the hydrated excipient comprises one or more of microcrystalline cellulose, low substituted hydroxypropyl cellulose, high substituted hydroxypropyl cellulose, hydroxypropyl methylcellulose and colloidal silicon dioxide.

The pharmaceutical composition of claim 1, wherein the composition is free of any moisture scavenger.

The pharmaceutical composition of claim 1 further comprises one or more pharmaceutically acceptable excipients comprising filler, binder, lubricant, glidant and disintegrand.

The pharmaceutical composition of claim 6, wherein the lubricant comprises one or more of hydrogenated vegetable oil, hydrogenated castor oil, light mineral oil, glycerol monostearate, glycerol monobehenate, glyceryl behenate, and glyceryl palmitostearate.

The pharmaceutical composition of claim 1, wherein the composition comprises one or more of granules, pellets, beads, spheroids, a tablet, a minitablet, a microtablet, a capsule, granules in a capsule, pellets in a capsule, microtablets in a capsule and minitablets in a capsule.

A pharmaceutical composition comprising uncoated granules, particles or pellets of clopidogrel or monobasic acid salts thereof, wherein the composition is free of any moisture scavenger.

The pharmaceutical composition of claim 9, wherein the monobasic acid salt of clopidogrel comprises one or more of clopidogrel hydrochloride, clopidogrel hydrobromide, clopidogrel mesylate, clopidogrel besylate, clopidogrel salicylate, clopidogrel lactate and clopidogrel gluconate.

The pharmaceutical composition of claim 10, wherein the monobasic acid salt of clopidogrel is clopidogrel hydrochloride.

The pharmaceutical composition of claim 9 further comprises one or more phar-
maceutically acceptable excipients comprising filler, binder, lubricant, glidant and disintegrant.

The pharmaceutical composition of claim 12, wherein the lubricant comprises one or more of hydrogenated vegetable oil, hydrogenated castor oil, light mineral oil, glycerol monostearate, glycerol monobehenate, glyceryl behenate, and glycercyl palmitostearate.

The pharmaceutical composition of claim 9 comprises one or more of granules, pellets, beads, spheroids, a tablet, a minitablet, a microtablet, a capsule, granules in a capsule, pellets in a capsule, microtablets in a capsule and minitablets in a capsule.

A pharmaceutical composition comprising clopidogrel hydrochloride and glycercyl behenate, wherein one or both of the rate and the extent of absorption of the clopidogrel hydrochloride is equal to or greater than that obtained by a clopidogrel bisulphate tablet marketed under the trade name Plavix®.

The pharmaceutical composition of claim 15 further comprises one or more pharmaceutically acceptable excipients comprising filler, binder, lubricant, glidant and disintegrant.

The pharmaceutical composition of claim 15 comprises one or more of granules, pellets, beads, spheroids, a tablet, a minitablet, a microtablet, a capsule, granules in a capsule, pellets in a capsule, microtablets in a capsule and minitablets in a capsule.

A process for preparing a pharmaceutical composition comprising clopidogrel or monobasic acid salts thereof, the process comprising:

(a) mixing and granulating clopidogrel or monobasic acid salts thereof with one or more hydrated excipients; and

(b) converting the granules into a suitable dosage form.

The process of claim 18, wherein the monobasic acid salts of clopidogrel comprises of clopidogrel hydrochloride, clopidogrel hydrobromide, clopidogrel mesylate, clopidogrel besylate, clopidogrel salicylate, clopidogrel lactate and clopidogrel gluconate.

The process of claim 19, wherein the monobasic acid salt of clopidogrel is clopidogrel hydrochloride.

The process of claim 18 further comprises one or more pharmaceutically acceptable excipients comprising filler, binder, lubricant, glidant and disintegrant.

The process of claim 21, wherein the lubricant comprises one or more of hydrogenated vegetable oil, hydrogenated castor oil, light mineral oil, glycerol monostearate, glycerol monobehenate, glyceryl behenate, and glycercyl palmitostearate.
The process of claim 18, wherein the hydrated excipient comprises one or more of microcrystalline cellulose, low substituted hydroxypropyl cellulose, high substituted hydroxypropyl cellulose, hydroxypropyl methylcellulose and colloidal silicon dioxide.

The process of claim 18, wherein the suitable dosage form comprises one or more of granules, pellets, beads, spheroids, a tablet, a minitablet, a microtablet, a capsule, granules in a capsule, pellets in a capsule, microtablets in a capsule and minitablets in a capsule.
FIGURE 1: COMPARATIVE AREA UNDER THE PLASMA CONCENTRATION TIME PROFILES

Untransformed Mean Plasma Concentration Time Curve

- Ref-B
- Test-A

Mean Plasma Concentration (ng/ml) vs Time (hr)