Abstract: The present disclosure provides processes for the preparation of amorphous daclatasvir dihydrochloride. The present disclosure also provides processes for the preparation of amorphous solid dispersion of daclatasvir dihydrochloride in at least one pharmaceutically acceptable carrier. Suitable pharmaceutically acceptable carriers include, but are not limited to, PLASDONE™ S-630, polyvinylpyrrolidone K-30, β-cyclodextrin, and hydroxypropyl-β-cyclodextrin (HPBCD).
CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of the earlier filing date of Indian Provisional Patent Application No. 2562/MUM/2015 filed on July 03, 2015.

BACKGROUND OF THE INVENTION

FIELD OF THE INVENTION

The present invention relates to a process for the preparation of amorphous daclatasvir dihydrochloride. The present invention also relates to a process for the preparation of amorphous solid dispersion of daclatasvir dihydrochloride together with pharmaceutically acceptable carriers.

BACKGROUND OF THE INVENTION

Daclatasvir dihydrochloride is chemically named as methyl ((1S)-l-(((2S)-2-(5-(4’-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl-2-pyrrolidinyl)-lH-imidazol-5-yl)-4-biphenylyl)-lH-imidazol-2-yl)-lpyrrolidinyl)carbonyl)-2-methylpropyl) carbamate dihydrochloride and is represented by the following chemical structure:

![Chemical Structure of Daclatasvir Dihydrochloride]

Daclatasvir is disclosed in U.S Patent No. 8,329,159 B2, which is hereby incorporated by reference.

U.S. Patent Publication No. 2013/0172239 Al, which is hereby incorporated by reference, discloses an amorphous solid composition comprising an HCV inhibitor, a pharmaceutically acceptable hydrophilic polymer, and optionally a pharmaceutically acceptable surfactant.

The inventors of the present disclosure developed a process for the preparation of amorphous daclatasvir dihydrochloride and also a process for the preparation of amorphous solid dispersions of daclatasvir dihydrochloride together with pharmaceutically acceptable carriers.

SUMMARY OF THE INVENTION

In a first aspect, the present invention provides a process for the preparation of amorphous daclatasvir dihydrochloride that includes the steps of dissolving daclatasvir dihydrochloride in a solvent; and removing the solvent to obtain amorphous daclatasvir dihydrochloride. The solvent may be a polar solvent. Examples of suitable polar solvents include, but are not limited to, water, methanol, ethanol, isopropanol, isobutanol, acetone, ethyl acetate, acetonitrile, and mixtures thereof.

In another aspect, the present invention provides a process for the preparation of amorphous daclatasvir dihydrochloride that may include the steps of:

a) dissolving daclatasvir dihydrochloride in a first solvent;

b) removing the solvent from step (a);

c) adding a second solvent to the reaction mass obtained in step (b); and

d) isolating amorphous daclatasvir dihydrochloride.

The first solvent may be a polar solvent, and examples of suitable polar solvents include, but are not limited to, water, methanol, ethanol, isopropanol, isobutanol, acetone, ethyl acetate, acetonitrile, and mixtures thereof. The second solvent may be a non-polar solvent, with suitable non-polar solvents including, but not being limited to, isopropyl ether, methyl tert-butyl ether, tetrahydrofuran, heptane, hexane, cyclohexane, and mixtures thereof.

In another aspect, the present invention provides a process for the preparation of amorphous daclatasvir dihydrochloride that may include the steps of:

a) dissolving daclatasvir dihydrochloride in a solvent to form a first solution;

b) optionally suspending seeds of daclatasvir in an anti-solvent to get an anti-solvent solution;

c) adding the first solution to the anti-solvent solution; and

d) isolating amorphous daclatasvir dihydrochloride.
In these embodiments, the solvent may be a polar solvent, with suitable examples including, but not being limited to, methanol, ethanol, propanol, isopropanol, isobutanol, acetonitrile, dichloromethane, ethyl acetate, and mixtures thereof. The anti-solvent may be a non-polar organic solvent, such as, but not limited to, toluene, hexane, cyclohexane, methyl cyclohexane, heptane, pentane, methyl t-butyl ether, isopropyl ether, diethyl ether, and mixtures thereof.

In another aspect, the present invention provides a process for the preparation of amorphous daclatasvir dihydrochloride that may include the steps of:

a) dissolving daclatasvir dihydrochloride in a solvent to form a solution; and
b) adding anti-solvent to the solution and isolating amorphous daclatasvir dihydrochloride.

In these embodiments, the solvent may be a polar solvent, with suitable examples including, but not being limited to, methanol, ethanol, propanol, isopropanol, isobutanol, acetonitrile, dichloromethane, ethyl acetate, and mixtures thereof. The anti-solvent may be a non-polar organic solvent, such as, but not limited to, toluene, hexane, cyclohexane, methyl cyclohexane, heptane, pentane, methyl t-butyl ether, isopropyl ether, diethyl ether, and mixtures thereof.

In a fifth aspect, the present invention provides amorphous solid dispersions of daclatasvir dihydrochloride with a pharmaceutically acceptable carrier and methods for generating the same. Specifically, the present invention provides a process for the preparation of amorphous solid dispersion of daclatasvir dihydrochloride including the steps of:

a) dissolving daclatasvir dihydrochloride and pharmaceutically acceptable carrier in a solvent; and
b) removing the solvent to obtain amorphous solid dispersion of daclatasvir dihydrochloride.

The solvent used here may be a polar solvent, such as, but not limited to, water, methanol, ethanol, propanol, isopropanol, acetone, acetonitrile, dimethyl formamide, and mixtures thereof. A wide variety of pharmaceutically acceptable carriers may be employed within the scope of the present invention. Suitable examples include, but are not limited to,
PLASDONE™ S-630, polyvinylpyrrolidone K-30, β-cyclodextrin, and hydroxypropyl-β-cyclodextrin.

In yet another aspect, the present invention provides a process for the preparation of amorphous solid dispersion of daclatasvir dihydrochloride that may include the steps of:

a) dissolving daclatasvir dihydrochloride in water;
b) dissolving pharmaceutically acceptable carrier in water;
c) mixing the solutions obtained in step (a) and step (b); and
d) removing the water to obtain amorphous solid dispersion of daclatasvir dihydrochloride.

Generally, within the context of the present invention, solvent or water may be removed by methods well known in the prior art, such as distillation, spray drying, freeze drying, or by agitated thin film drier. Unless otherwise noted, the input daclatasvir dihydrochloride may be crystalline or amorphous and may be prepared by any prior-art process.

**BRIEF DESCRIPTION OF THE FIGURES**

Further aspects of the present disclosure together with additional features contributing thereto and advantages accruing there from will be apparent from the following description of embodiments of the disclosure which are shown in the accompanying drawing figures wherein:

**Figure 1** is an X-ray powder diffractogram of amorphous daclatasvir dihydrochloride;

**Figure 2** is an X-ray powder diffractogram of amorphous solid dispersion of daclatasvir dihydrochloride with Plasdone S-630;

**Figure 3** is an X-ray powder diffractogram of amorphous solid dispersion of daclatasvir dihydrochloride with polyvinylpyrrolidone K-30; and

**Figure 4** is an X-ray powder diffractogram of amorphous solid dispersion of daclatasvir dihydrochloride with β-cyclodextrin.

**DETAILED DESCRIPTION OF THE INVENTION**

The present invention generally provides for an amorphous form of daclatasvir dihydrochloride and methods of production thereof. Further, the present invention provides for amorphous solid dispersions of daclatasvir dihydrochloride together with
pharmaceutically acceptable carriers, and methods of production thereof. The amorphous daclatasvir dihydrochloride and amorphous solid dispersions of daclatasvir dihydrochloride with pharmaceutically acceptable carriers may be included in pharmaceutical dosage forms suitable for administration to patients in need thereof.

In one embodiment, the present disclosure relates to a process for the preparation of an amorphous form of daclatasvir dihydrochloride as characterized by the powder X-ray diffraction pattern (PXRD) as shown in FIG. 1. The PXRD measurements were carried out using PANalytical, X'Pert PRO powder diffractometer equipped with goniometer of ΘΘ configuration and X'Celerator detector. The Cu-anode X-ray tube is operated at 40kV and 30mA. The experiments were conducted over the 2Θ range of 2.0°-50.0°, 0.030° step size and 50 seconds step time.

In another embodiment, the present disclosure provides a process for the preparation of amorphous daclatasvir dihydrochloride that may include the steps of dissolving daclatasvir dihydrochloride in a solvent and removing the solvent to obtain amorphous daclatasvir dihydrochloride.

According to this embodiment, daclatasvir dihydrochloride is dissolved in a solvent. The input daclatasvir dihydrochloride may be crystalline or amorphous and may be prepared by any prior-art process. This dissolution step, as with dissolution steps disclosed elsewhere in the present application, may be conducted under a wide variety of conditions that would be well known to those having ordinary skill in the art. For example, large volumes of solvent held at room temperature may be effective to dissolve an appropriate mass of daclatasvir dihydrochloride. Alternatively, this step may be carried out at an elevated temperature so as to promote dissolution, e.g., about 60±5 °C. Within the context of the present disclosure, "about" means plus or minus 10% of the reported value. Following dissolution, the solution is cooled to about 25±5 °C. After that, the solvent is removed to yield amorphous daclatasvir dihydrochloride.

Within the context of this embodiment, the solvent may be a polar solvent. Examples of suitable polar solvents include, but are not limited to, water, methanol, ethanol, isopropanol, isobutanol, acetone, ethyl acetate, acetonitrile, and mixtures thereof. One of skill in the art will recognize numerous polar solvents that may be useful within the context of this embodiment.
Within the context of this embodiment, the solvent may be removed according to well-known techniques in the art, for example, distillation, evaporation, spray drying, freeze drying (i.e., lyophilization), or by agitated thin film drier.

Another embodiment of the present invention provides a process for the preparation of amorphous daclatasvir dihydrochloride that may include the steps of:

a) dissolving daclatasvir dihydrochloride in a first solvent;

b) removing the solvent from step (a);

c) adding a second solvent to the reaction mass obtained in step (b); and

d) isolating amorphous daclatasvir dihydrochloride.

According to this embodiment, daclatasvir dihydrochloride may be dissolved in a first solvent. The input daclatasvir dihydrochloride may be crystalline or amorphous and may be prepared by any prior-art process. This step may be carried out at an elevated temperature employed to promote dissolution, e.g., about 60+5 °C. Next, the first solvent may be removed, for example, by distillation, and a second solvent may be added to the reaction mixture. After that, the second solvent may be removed to yield amorphous daclatasvir dihydrochloride.

Within the context of this embodiment, the first solvent may be a polar solvent. Examples of suitable polar solvents include, but are not limited to, water, methanol, ethanol, isopropanol, isobutanol, acetone, ethyl acetate, acetonitrile, and mixtures thereof. One of skill in the art will recognize numerous polar solvents that may be useful within the context of this embodiment.

Within the context of the present disclosure, the second solvent may be a non-polar solvent. Examples of suitable non-polar solvents include, but are not limited to, isopropyl ether, methyl tert-butyl ether, tetrahydrofuran, heptane, hexane, cyclohexane, and mixtures thereof.

Within the context of this embodiment, the solvent may be removed according to well-known techniques in the art, for example, distillation, evaporation, spray drying, freeze drying, or by agitated thin film drier.

In another embodiment, the present invention provides a process for the preparation of amorphous daclatasvir dihydrochloride that may include the steps of:
a) dissolving daclatasvir dihydrochloride in a solvent;
b) optionally suspending seeds of amorphous daclatasvir in an anti-solvent to get an anti-solvent solution;
c) adding the first solution to the anti-solvent solution; and
d) isolating amorphous daclatasvir dihydrochloride.

According to the present disclosure daclatasvir dihydrochloride may be dissolved in solvent. The input daclatasvir dihydrochloride for this step may be crystalline or amorphous and may be prepared by any prior-art process. In particularly effective embodiments, the daclatasvir dihydrochloride solution may then be added to an anti-solvent solution optionally containing amorphous daclatasvir dihydrochloride seeds at room temperature. In other embodiments, the anti-solvent solution may be added to the daclatasvir dihydrochloride solution. Regardless of the order of addition, the addition may occur slowly and the resulting solution may be stirred or otherwise agitated until a solid product is generated. The obtained solid amorphous daclatasvir dihydrochloride may then be isolated, for example by filtration, distillation, evaporation, spray drying, freeze drying, or by agitated thin film drier, and dried.

Within the context of the present embodiment, the elevated temperature utilized during dissolution of daclatasvir dihydrochloride may range from room temperature to boiling temperature of the solvent, preferably the elevated temperature ranges from 40-75 °C depending on nature of solvent.

Within the context of the present embodiment, the solvent may be a polar solvent such as, but not limited to, water, methanol, ethanol, propanol, isopropanol, isobutanol, acetonitrile, dichloromethane, ethyl acetate, and mixtures thereof. The anti-solvent may be a non-polar organic solvent, such as, but not limited to, toluene, hexane, cyclohexane, methyl cyclohexane, heptane, pentane, methyl t-butyl ether, isopropyl ether, diethyl ether, and mixtures thereof.

In another embodiment, the present invention provides a process for the preparation of amorphous daclatasvir dihydrochloride that may include the steps of:

a) dissolving daclatasvir dihydrochloride in a solvent; and
b) adding anti-solvent and isolating amorphous daclatasvir dihydrochloride.
According to this embodiment, daclatasvir dihydrochloride may be dissolved in a solvent at elevated temperature. The input daclatasvir dihydrochloride may be crystalline or amorphous and may be prepared by any prior-art process. Next, the solvent may be removed by distillation or evaporation at elevated temperature, and the reaction mass may be cooled to 25±5 °C. In some embodiments, approximately 75% of the solvent is removed, while in other embodiments, the solvent is completely removed. In particularly effective embodiments, the daclatasvir dihydrochloride solution may then be added to an anti-solvent solution optionally containing amorphous daclatasvir dihydrochloride seeds at room temperature. In other embodiments, the anti-solvent solution may be added to the daclatasvir dihydrochloride solution. Regardless of the order of addition, the addition may occur slowly and the resulting solution may optionally be stirred or otherwise agitated until a solid product is generated. After that, the anti-solvent and any remaining solvent may be removed to yield amorphous daclatasvir dihydrochloride in solid form.

Within the context of this embodiment, the solvent may be a polar solvent such as, but not limited to, methanol, ethanol, propanol, isopropanol, isobutanol, acetonitrile, dichloromethane, ethyl acetate, and mixtures thereof. The anti-solvent may be a non-polar organic solvent, such as, but not limited to, toluene, hexane, cyclohexane, methyl cyclohexane, heptane, pentane, methyl t-butyl ether, isopropyl ether, diethyl ether, and mixtures thereof.

Within the context of the present embodiment, the elevated temperature utilized in this embodiment may range from room temperature to boiling temperature of the solvent, preferably the elevated temperature ranges from 40-75 °C depending on nature of solvent.

Within the context of this embodiment, the anti-solvent may be removed according to well-known techniques in the art, for example, distillation, evaporation, spray drying, freeze drying, or by agitated thin film drier.

In another embodiment, the present invention provides a process for the preparation of amorphous solid dispersion of daclatasvir dihydrochloride that may include the steps of:

a) dissolving daclatasvir dihydrochloride and at least one pharmaceutically acceptable carrier in a solvent; and

b) removing the solvent to obtain amorphous solid dispersion of daclatasvir dihydrochloride in the at least one pharmaceutically acceptable solvent.
According to this embodiment, daclatasvir dihydrochloride and one or more pharmaceutically acceptable carriers are dissolved in a solvent. The input daclatasvir dihydrochloride may be crystalline or amorphous and may be prepared by any prior-art process. Within the context of this embodiment, this dissolution step may be carried out at a temperature of about 25 °C to about 30 °C.

Within the context of the present embodiment, a wide range of pharmaceutically acceptable carriers may be employed. Examples of suitable pharmaceutically acceptable carriers include, but are not limited to, PLASDONE™ S-630, polyvinylpyrrolidine K-30, β-cyclodextrin, and hydroxypropyl -P-cyclodextrin (HPBCD). The pharmaceutically acceptable carriers may be included at a wide variety of concentrations relative to daclatasvir dihydrochloride, as would be recognized by one having ordinary skill in the art. The solvent employed may be, for example, a polar solvent. In some embodiments of the present invention, the solvent may be water miscible. Suitable polar solvents include, but are not limited to, water, methanol, ethanol, propanol, isopropanol, acetone, acetonitrile, dimethyl formamide, and mixtures thereof.

Next, the solvent may be removed, resulting in an amorphous solid dispersion of daclatasvir dihydrochloride in at least one pharmaceutically acceptable carrier. Within the context of the present embodiment, the solvent may be removed according to well-known techniques in the art, for example, distillation, evaporation, spray drying, freeze drying, or by agitated thin film drier.

Another embodiment of the present invention provides a process for the preparation of amorphous solid dispersion of daclatasvir dihydrochloride that may include the steps of:

a) dissolving daclatasvir dihydrochloride in water;
b) dissolving at least one pharmaceutically acceptable carrier in water;
c) mixing the solutions obtained in step (a) and step (b); and
d) removing the water to obtain amorphous solid dispersion of daclatasvir dihydrochloride in the at least one pharmaceutically acceptable solvent.

According to this embodiment, daclatasvir dihydrochloride and at least one pharmaceutical acceptable carrier are dissolved in water. The input daclatasvir dihydrochloride may be crystalline or amorphous and may be prepared by any prior-art process. Within the context of the present embodiment, the dissolution of daclatasvir
dihydrochloride may be carried out at a temperature of about 60 °C to about 65 °C. The input daclatasvir dihydrochloride may be crystalline or amorphous and may be prepared by any prior-art process.

Within the context of this embodiment, a wide range of pharmaceutically acceptable carriers may be employed. Examples of suitable pharmaceutically acceptable carriers include, but are not limited to, PLASDONE™ S-630, polyvinylpyrrolidine K-30, β-cyclodextrin, and hydroxypropyl -P-cyclodextrin (HPBCD). The pharmaceutically acceptable carriers may be included at a wide variety of concentrations relative to daclatasvir dihydrochloride, as would be recognized by one having ordinary skill in the art. The pharmaceutically acceptable carrier may also be dissolved in water. Within the context of the present embodiment, this dissolution may be carried out at a temperature of about 60 °C to about 65 °C.

Next, both solutions may be cooled and mixed together. The water may then be removed. Within the context of the present embodiment, mixing of both solutions may occur in any order. Within the context of the present embodiment, water may be removed according to well-known techniques in the art, for example, distillation, evaporation, spray drying, freeze drying, or by agitated thin film drier.

According to the present embodiment, starting material daclatasvir dihydrochloride may be crystalline or amorphous in nature and can be prepared as per the processes disclosed in the prior art, such as U.S. Patent No. 8,329,159 B2.

The amorphous solid dispersions of daclatasvir dihydrochloride with pharmaceutically acceptable solvents may be characterized by PXRD. FIG. 2 provides an exemplary PXRD of amorphous solid dispersion of daclatasvir dihydrochloride with PLASDONE™ S-630. FIG. 3 shows an exemplary PXRD of amorphous solid dispersion of daclatasvir dihydrochloride with polyvinylpyrrolidine K-30. Finally, FIG. 4 displays PXRD of amorphous solid dispersion of daclatasvir dihydrochloride with β-cyclodextrin.

Amorphous daclatasvir dihydrochloride disclosed herein may, in some embodiments, exhibit long-term physical and chemical stability. The physical and chemical stability of amorphous daclatasvir dihydrochloride was determined by storing the samples at 40 °C/75% relative humidity (RH) and at 25 °C/60% RH for two months. The samples
were tested for stability of amorphous form by PXRD analysis and for purity by HPLC analysis.

As an example, Table 1 below provides data collected on amorphous daclatasvir dihydrochloride. The stability data demonstrate that amorphous daclatasvir dihydrochloride displays no significant change in PXRD pattern and no significant change in purity for up to two months when stored at 25 °C/60% RH and 40 °C/75% RH.

**Table 1**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Amorphous form</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HPLC purity (%)</td>
</tr>
<tr>
<td>at 40 °C/75% RH</td>
<td></td>
</tr>
<tr>
<td>Initial</td>
<td>99.79</td>
</tr>
<tr>
<td>15 days</td>
<td>99.77</td>
</tr>
<tr>
<td>1 months</td>
<td>99.74</td>
</tr>
<tr>
<td>2 months</td>
<td>99.72</td>
</tr>
<tr>
<td>at 25 °C/60% RH</td>
<td></td>
</tr>
<tr>
<td>Initial</td>
<td>99.79</td>
</tr>
<tr>
<td>15 days</td>
<td>99.78</td>
</tr>
<tr>
<td>1 months</td>
<td>99.78</td>
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<tr>
<td>2 months</td>
<td>99.78</td>
</tr>
</tbody>
</table>

Amorphous solid dispersion of daclatasvir dihydrochloride with pharmaceutically acceptable carriers may exhibit long-term physical and chemical stability. By way of example, amorphous solid dispersions of daclatasvir dihydrochloride with PLASDONE™ S-630 (10% w/w), HPBCD (10% w/w), PVP K-30 (25% and 50% w/w) and β-cyclodextrin (10%, 25% and 50% w/w ratio) were evaluated by storing the samples at 40 °C/75% RH and at 25 °C/60% RH for two months. The samples were tested for stability of amorphous form by PXRD analysis and for purity by HPLC analysis.

As an example, Table 2 below provides data collected on amorphous solid dispersion of daclatasvir dihydrochloride with PLASDONE™ S-630 (10% w/w), and HPBCD (10% w/w). The stability data demonstrate that amorphous solid dispersions of daclatasvir dihydrochloride in these pharmaceutically acceptable carriers display no significant change in PXRD pattern and no significant change in purity for up to two months when stored at 25 °C/60% RH and 40 °C/75% RH.
As an example, Table 3 below provides data collected on amorphous solid dispersion of daclatasvir dihydrochloride with β-cyclodextrin (10%, 25%, and 50% w/w ratio). The stability data demonstrate that amorphous solid dispersion of daclatasvir dihydrochloride in β-cyclodextrin display no significant change in PXRD pattern and no significant change in purity for up to two months when stored at 25 °C/60% RH and 40 °C/75% RH.

### Table 2

<table>
<thead>
<tr>
<th>Condition</th>
<th>HPLC purity (%)</th>
<th>PXRD</th>
<th>HPLC purity (%)</th>
<th>PXRD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>at 40 °C/75% RH</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial</td>
<td>99.51</td>
<td>Amorphous</td>
<td>99.50</td>
<td>Amorphous</td>
</tr>
<tr>
<td>15 days</td>
<td>99.46</td>
<td>Stable</td>
<td>99.48</td>
<td>Stable</td>
</tr>
<tr>
<td>1 months</td>
<td>99.48</td>
<td>Stable</td>
<td>99.51</td>
<td>Stable</td>
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<tr>
<td>2 months</td>
<td>99.42</td>
<td>Stable</td>
<td>99.45</td>
<td>Stable</td>
</tr>
<tr>
<td><strong>at 25 °C/60% RH</strong></td>
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<td></td>
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<tr>
<td>Initial</td>
<td>99.51</td>
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<td>1 months</td>
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<td>99.54</td>
<td>Stable</td>
<td>99.55</td>
<td>Stable</td>
</tr>
</tbody>
</table>

### Table 3

<table>
<thead>
<tr>
<th>Condition</th>
<th>Amorphous solid dispersion with β-Cyclodextrin</th>
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<tbody>
<tr>
<td></td>
<td>10% w/w</td>
</tr>
<tr>
<td></td>
<td>HPLC purity (%)</td>
</tr>
<tr>
<td><strong>at 40 °C/75% RH</strong></td>
<td></td>
</tr>
<tr>
<td>Initial</td>
<td>&gt; 99</td>
</tr>
<tr>
<td>15 days</td>
<td>&gt; 99</td>
</tr>
<tr>
<td>1 months</td>
<td>&gt; 99</td>
</tr>
<tr>
<td>2 months</td>
<td>&gt; 99</td>
</tr>
<tr>
<td><strong>at 25 °C/60% RH</strong></td>
<td></td>
</tr>
<tr>
<td>Initial</td>
<td>&gt; 99</td>
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<tr>
<td>15 days</td>
<td>&gt; 99</td>
</tr>
<tr>
<td>1 months</td>
<td>&gt; 99</td>
</tr>
<tr>
<td>----------</td>
<td>------</td>
</tr>
<tr>
<td>2 months</td>
<td>&gt; 99</td>
</tr>
</tbody>
</table>

As an example, Table 4 below provides data collected on amorphous solid dispersion of daclatasvir dihydrochloride with PVP K-30 (25% and 50% w/w). The stability data demonstrate that amorphous solid dispersions of daclatasvir dihydrochloride with PVP K-30 display no significant change in PXRD pattern and no significant change in purity for up to two months when stored at 25 °C/60% RH and 40 °C/75% RH.
Table 4

<table>
<thead>
<tr>
<th>Condition</th>
<th>Amorphous solid dispersion with PVP K-30</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>25% w/w</td>
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<tr>
<td></td>
<td>HPLC purity (%)</td>
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<td>at 40 °C/75% RH</td>
<td></td>
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<tr>
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<td>&gt; 99</td>
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<tr>
<td>1 months</td>
<td>&gt; 99</td>
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<tr>
<td>2 months</td>
<td>&gt; 99</td>
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<tr>
<td>at 25 °C/60% RH</td>
<td></td>
</tr>
<tr>
<td>Initial</td>
<td>&gt; 99</td>
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<tr>
<td>15 days</td>
<td>&gt; 99</td>
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<tr>
<td>1 months</td>
<td>&gt; 99</td>
</tr>
<tr>
<td>2 months</td>
<td>&gt; 99</td>
</tr>
</tbody>
</table>

The amorphous daclatasvir dihydrochloride and amorphous daclatasvir dihydrochloride and a pharmaceutically acceptable excipient as disclosed herein may be included in pharmaceutical dosage forms for administration to patients in need thereof. Daclatasvir and its pharmaceutically acceptable salts are inhibitors of hepatitis C virus non-structural protein 5A (NS5A). Accordingly, the amorphous daclatasvir dihydrochloride and amorphous daclatasvir dihydrochloride and a pharmaceutically acceptable excipient as disclosed herein may be useful in treating hepatitis C infections in patients either alone or in combination with other active pharmaceutical agents. The amorphous daclatasvir dihydrochloride and amorphous daclatasvir dihydrochloride and a pharmaceutically acceptable excipient may be combined with additional pharmaceutically acceptable excipients in generating an oral dosage form, such as a tablet or capsule. Such excipients may include, but are not limited to, anhydrous lactose, microcrystalline cellulose, croscarmellose sodium, silicon dioxide, magnesium stearate, and Opadry green. The oral dosage form may include an effective amount of amorphous daclatasvir dihydrochloride and amorphous daclatasvir dihydrochloride and a pharmaceutically acceptable excipient, for example 30 milligrams, 60 milligrams, or 90 milligrams of daclatasvir dihydrochloride.

Certain specific aspects and embodiments of the present application will be explained in greater detail with reference to the following examples, which are provided
only for purposes of illustration and should not be construed as limiting the scope of the disclosure in any manner. Reasonable variations of the described procedures are intended to be within the scope of the present application. While particular aspects of the present application have been illustrated and described, it would be apparent to those skilled in the art that various other changes and modifications can be made without departing from the spirit and scope of the disclosure. It is therefore intended to encompass all such changes and modifications that are within the scope of this disclosure.

Example 1: Preparation of amorphous daclatasvir dihydrochloride.

Daclatasvir dihydrochloride (10 g) was dissolved in water (200 mL) at 25-30 °C. The clear solution was filtered through Hy-flo to remove any undissolved particulate. The Hy-flo was washed with 10 mL of water. The clear solution was then subjected to spray drying in a laboratory spray dryer (Model Buchi-290) with feed rate of the solution 5 mL/min and inlet temperature at 130 °C and with 100% aspiration to yield daclatasvir dihydrochloride amorphous form.

Yield: 5.3 g.

Example 2: Preparation of amorphous daclatasvir dihydrochloride.

Daclatasvir dihydrochloride (10 g) was dissolved in water (100 mL) at 60-70 °C. The resulting clear solution was cooled to room temperature and filtered through Hy-flo to remove any undissolved particulate. The Hy-flo was washed with 10 mL of water. The solution was then subjected to lyophilization in a laboratory lyophilizer (Model Virtis Advantage Plus) to yield daclatasvir dihydrochloride amorphous form.

Yield: 9.8 g.

Example 3: Preparation of amorphous daclatasvir dihydrochloride.

Daclatasvir dihydrochloride (1 g) was dissolved in water (20 mL) at 65+5 °C. The resulting clear solution was distilled completely under vacuum at 65+5 °C. Foamy solid was obtained. Heptane (2x30 mL) was added to the foamy solid and distilled completely under vacuum at 65+5 °C. The solid obtained was identified as daclatasvir dihydrochloride amorphous form.

Yield: 0.7 g.
Example 4: Preparation of amorphous daclatasvir dihydrochloride.

Daclatasvir dihydrochloride (1 g) was dissolved in methanol (50 mL) at 45+5 °C. The clear solution was cooled to room temperature and filtered through Hy-flo to remove any undissolved particulate. The Hy-flo was washed with 5 mL of methanol. The resulting clear solution was distilled completely under vacuum at 45+5 °C. To the resulting foamy solid, heptane (20 mL) was added and stirred for 30 minutes. The solid obtained was identified as daclatasvir dihydrochloride amorphous form. Yield: 0.8 g.

Example 5: Preparation of amorphous daclatasvir dihydrochloride.

Daclatasvir dihydrochloride (1 g) was dissolved in isobutanol (200 mL) and methanol (50 mL) solvent mixture at 45+5 °C and the resulting clear solution was cooled to 25+5 °C. In another flask, seeds (0.010 g) of amorphous form of daclatasvir dihydrochloride were suspended in methyl tert-butyl ether (400 mL). To this seed solution, the solution of daclatasvir dihydrochloride in methanol and isobutanol mixture was slowly added and maintained under agitation for 1-2 hours. The solid obtained was filtered, washed with methyl tert-butyl ether (10 mL), and suck-dried at 25+5 °C. The product obtained was identified as daclatasvir dihydrochloride amorphous form. Yield: 0.7 g.

Example 6: Preparation of amorphous daclatasvir dihydrochloride.

Daclatasvir dihydrochloride (20 g) was dissolved in water (150 mL) at 60 °C and cooled to 25 °C. The resulting clear solution was filtered through Hy-flo to remove any undissolved particulate and subjected to agitated thin film dryer (Flow rate: 15 mL/minute and inlet temperature 110 °C) to yield an amorphous form of daclatasvir dihydrochloride. Yield: 1.2 g.

Example 7: Preparation of amorphous daclatasvir dihydrochloride.

Daclatasvir dihydrochloride (10 g) was dissolved in methanol (200 mL) at 60 °C and the solvent was distilled by using rotary evaporator. Then, isopropyl ether (50 mL) was added to the reaction mass and distilled off completely, resulting in free powder. It was
further dried under vacuum at 25 °C for 15 hours. The product obtained was identified as an amorphous form of daclatasvir dihydrochloride.

Yield: 9 g.

**Example 8: Preparation of amorphous daclatasvir dihydrochloride.**

Daclatasvir dihydrochloride (10 g) was dissolved in methanol (100 mL) at 28+2 °C. The resulting clear solution was filtered through Hy-flo to remove any undissolved particulate. The clear solution was heated up to 45-50 °C and distilled out the solvent under vacuum till one quarter of the reaction mass remained. Then, methyl tert-butyl ether (50 mL) was added to the reaction mass and distilled out completely under vacuum. Reaction mass was cooled to 25+5 °C and methyl tert-butyl ether (50 mL) was added. That solution was stirred for 30 minutes. The resulting solid was filtered and washed with methyl tert-butyl ether (10 mL). That solid was dried under vacuum at 30 °C for 15 hours. The product obtained was identified as amorphous form of daclatasvir dihydrochloride.

Yield: 9.2 g.

**Example 9: Preparation of amorphous daclatasvir dihydrochloride.**

Daclatasvir dihydrochloride (10 g) was dissolved in methanol (100 mL) at 28+2 °C. The resulting clear solution was filtered through Hy-flo to remove any undissolved particulate. The resulting clear solution was heated up to 45-50 °C and the solvent distilled under vacuum till one quarter of the reaction mass remained. Then, isopropyl ether (50 mL) was added to the reaction mass and distilled out completely under vacuum. Reaction mass was cooled to 25+5 °C and isopropyl ether (50 mL) was added. The solution was stirred for 30 minutes. The resulting solid was filtered and washed with isopropyl ether (10 mL). That solid was dried under vacuum at 30 °C for 15 hours. The product obtained was identified as amorphous form of daclatasvir dihydrochloride.

Yield: 8.9 g.

**Example 10: Preparation of amorphous daclatasvir dihydrochloride.**

Daclatasvir dihydrochloride (20 g) was dissolved in methanol (200 mL) at 25-30 °C. Reaction mixture was filtered through Hy-flo to remove any undissolved particulate and the clear solution was subjected to spray drying in a laboratory spray dryer (Model Buchi, B-
290) with inlet temperature of 75 °C and flow rate of 20% to yield amorphous form of daclatasvir dihydrochloride.

Yield: 14.8 g.

Example 11: Preparation of amorphous daclatasvir dihydrochloride.

Daclatasvir dihydrochloride (1 g) was dissolved in methanol (10 mL) and ethyl acetate (10 mL) solvent mixture at 25-30 °C. Reaction mixture was heated to 60+5 °C and the solvent was distilled out completely by using rotary evaporator, resulting in free powder. The product obtained was identified as an amorphous form of daclatasvir dihydrochloride.

Yield: 1.9 g.

Example 12: Preparation of amorphous daclatasvir dihydrochloride.

Daclatasvir dihydrochloride (7.5 g) was dissolved in methanol (75 mL) at 25-30 °C. Reaction mixture was filtered through Hy-flo at the same temperature to remove any undissolved particulate and the clear solution was subjected to spray drying in a laboratory Spray Dryer (Model Buchi, B-290) with inlet temperature of 75 °C and flow rate of 20% to yield amorphous form of daclatasvir dihydrochloride.

Yield: 14.8 g.

Example 13: Preparation of amorphous daclatasvir dihydrochloride.

Daclatasvir dihydrochloride (2 g) was dissolved in methanol (20 mL) at 25-30 °C. The resulting clear solution was filtered through Hy-flo to remove any undissolved particulate. Methyl tert-butyl ether (10 mL) was added to the clear solution. Reaction mixture was heated to 40 °C and distilled out the solvent till one quarter of the reaction total mass remained by using rotary evaporator. Methyl tert-butyl ether (10 mL) was added to the reaction mass and distilled out solvent till one quarter of the total reaction mass remained. The product was filtered and dried under vacuum at 35 °C for 1 hour. The product obtained was identified as amorphous form of daclatasvir dihydrochloride.

Yield: 1.9 g.

Example 14: Preparation of amorphous solid dispersion of daclatasvir dihydrochloride.

Daclatasvir dihydrochloride (18 g) and PLASDONE™ S-630 (2 g) were dissolved in methanol (200 mL) at 25-30 °C. Reaction mixture was filtered through Hy-flo to remove
any undissolved particulate. The clear solution was subjected to spray drying in a laboratory spray dryer (Model Buchi, B-290) with inlet temperature of 75 °C and flow rate of 20% to yield premix amorphous form of daclatasvir dihydrochloride with 10% PLASDONE™ S-630 (w/w ratio).

Yield: 14.2 g.

Example 15: Preparation of amorphous solid dispersion of daclatasvir dihydrochloride.

Daclatasvir dihydrochloride (18 g) and hydroxypropyl -P-cyclodextrin (HPBCD) (2 g) were dissolved in methanol (200 mL) at 25-30 °C. Reaction mixture was filtered through Hy-flo to remove any undissolved particulate. The clear solution was subjected to spray drying in a laboratory spray dryer (Model Buchi, B-290) with inlet temperature of 75 °C and flow rate of 20% to yield premix amorphous form of daclatasvir dihydrochloride with 10% hydroxypropyl -P-cyclodextrin (HPBCD) (w/w ratio).

Yield: 14 g.

Example 16: Preparation of amorphous solid dispersion of daclatasvir dihydrochloride.

Daclatasvir dihydrochloride (9 g) was dissolved in water (150 mL) at 60 °C and cooled to 25 °C. In another flask, β-cyclodextrin (1 g) was dissolved in water (30 mL) at 60 °C and cooled to 25 °C. Both solutions were mixed and the resulting clear solution was filtered through Hy-flo at the same temperature to remove any undissolved particulate. The solution was then subjected to lyophilization in a laboratory lyophilizer (Model Heto Power Dry LL3000) to yield premix amorphous form of daclatasvir dihydrochloride with 10% β-cyclodextrin (w/w ratio).

Yield: 9 g.

Example 17: Preparation of amorphous solid dispersion of daclatasvir dihydrochloride.

Daclatasvir dihydrochloride (7.5 g) was dissolved in water (100 mL) at 60 °C and cooled to 25 °C. In another flask, β-cyclodextrin (2.5 g) was dissolved in water (85 mL) at 60 °C and cooled to 25 °C. Both solutions were mixed and the resulting clear solution was
filtered through Hy-flo at the same temperature to remove any undissolved particulate. The solution was then subjected to lyophilization in a laboratory lyophilizer (Model Heto PowerDry LL3000) to yield premix amorphous form of daclatasvir dihydrochloride with 25% β-cyclodextrin (w/w ratio).

Yield: 9.3 g.

**Example 18: Preparation of amorphous solid dispersion of daclatasvir dihydrochloride.**

Daclatasvir dihydrochloride (5 g) was dissolved in water (100 mL) at 60 °C and cooled to 25 °C. In another flask, β-cyclodextrin (5 g) was dissolved in water (100 mL) at 60 °C and cooled to 25 °C. Both solutions were mixed and the resulting clear solution was filtered through Hy-flo at the same temperature to remove any undissolved particulate. The solution was then subjected to lyophilization in a laboratory lyophilizer (Model Heto PowerDry LL3000) to yield premix amorphous form of daclatasvir dihydrochloride with 50% β-cyclodextrin (w/w ratio).

Yield: 8.5 g.

**Example 19: Preparation of amorphous solid dispersion of daclatasvir dihydrochloride.**

Daclatasvir dihydrochloride (7.5 g) was dissolved in water (100 mL) at 60 °C and cooled to 25 °C. In another flask, PVP K-30 (2.5 g) was dissolved in water (85 mL) at 60 °C and cooled to 25 °C. Both solutions were mixed and the resulting clear solution was filtered through Hy-flo at the same temperature to remove any undissolved particulate. The solution was then subjected to lyophilization in a laboratory lyophilizer (Model Heto PowerDry LL3000) to yield premix amorphous form of daclatasvir dihydrochloride with 25% PVP K-30 (w/w ratio).

Yield: 9.3 g.

**Example 20: Preparation of amorphous solid dispersion of daclatasvir dihydrochloride.**

Daclatasvir dihydrochloride (5 g) was dissolved in water (100 mL) at 60 °C and cooled to 25 °C. In another flask, PVP K-30 (5 g) was dissolved in water (100 mL) at 60 °C.
and cooled to 25 °C. Both solutions were mixed and the resulting clear solution was filtered through Hy-flo at the same temperature to remove any undissolved particulate. The solution was then subjected to lyophilization in a laboratory lyophilizer (Model Heto PowerDry LL3000) to yield premix amorphous form of daclatasvir dihydrochloride with 50% PVP K-30 (w/w ratio).

Yield: 9.1 g.
We claim:

1. A process for the preparation of amorphous daclatasvir dihydrochloride, comprising the steps of dissolving daclatasvir dihydrochloride in a solvent; and removing the solvent to obtain amorphous daclatasvir dihydrochloride.

2. The process according to claim 1, wherein the solvent is a polar solvent.

3. The process according to claim 2, wherein the polar solvent is selected from the group consisting of water, methanol, ethanol, isopropanol, isobutanol, acetone, ethyl acetate, acetonitrile, and mixtures thereof.

4. A process for the preparation of amorphous daclatasvir dihydrochloride, comprising the steps of:
   a) dissolving daclatasvir dihydrochloride in a first solvent;
   b) removing the solvent from step (a);
   c) adding a second solvent to the reaction mass obtained in step (b); and
   d) isolating amorphous daclatasvir dihydrochloride.

5. The process according to claim 4, wherein the first solvent is a polar solvent.

6. The process according to claim 5, wherein the polar solvent is selected from the group consisting of water, methanol, ethanol, isopropanol, isobutanol, acetone, ethyl acetate, acetonitrile, and mixtures thereof.

7. The process according to claim 4, wherein the second solvent is a non-polar solvent.

8. The process according to claim 7, wherein the non-polar solvent is selected from the group consisting of isopropyl ether, methyl tert-butyl ether, tetrahydrofuran, heptane, hexane, cyclohexane, and mixtures thereof.

9. A process for the preparation of amorphous daclatasvir dihydrochloride comprising the steps of:
   a) dissolving daclatasvir dihydrochloride in a solvent;
b) optionally suspending seeds of daclatasvir in an anti-solvent to get an anti-solvent solution;

c) adding the first solution to the anti-solvent solution; and

d) isolating amorphous daclatasvir dihydrochloride.

10. A process for the preparation of amorphous daclatasvir dihydrochloride comprising the steps of:

a) dissolving daclatasvir dihydrochloride in a solvent to form a solution;

b) adding an anti-solvent to the solution; and

c) isolating amorphous daclatasvir dihydrochloride.

11. The process according to claim 9 or 10, wherein the solvent is selected from the group consisting of methanol, ethanol, propanol, isopropanol, isobutanol, acetonitrile, dichloromethane, ethyl acetate, and mixtures thereof.

12. The process according to claim 9 or 10, wherein the anti-solvent is selected from the group consisting of toluene, hexane, cyclohexane, methyl cyclohexane, heptane, pentane, methyl t-butyl ether, isopropyl ether, diethyl ether, and mixtures thereof.

13. Amorphous solid dispersion of daclatasvir dihydrochloride with a pharmaceutically acceptable carrier.

14. The amorphous solid dispersion of claim 13, wherein the pharmaceutically acceptable carrier is selected from the group consisting of PLASDONE™ S-630, polyvinylpyrrolidone K-30, β-cyclodextrin, and hydroxypropyl -P-cyclodextrin.

15. A process for the preparation of amorphous solid dispersion of daclatasvir dihydrochloride, comprising the steps of:

a) dissolving daclatasvir dihydrochloride and pharmaceutically acceptable carrier in a solvent; and
b) removing the solvent to obtain the amorphous solid dispersion of daclatasvir dihydrochloride.

16. The process according to claim 15, wherein the solvent is selected from the group consisting of methanol, ethanol, isopropanol, acetone, acetonitrile, dimethyl formamide, and mixtures thereof.

17. A process for the preparation of amorphous solid dispersion of daclatasvir dihydrochloride, comprising the steps of:

   a) dissolving daclatasvir dihydrochloride in water;
   b) dissolving pharmaceutically acceptable carrier in water;
   c) mixing the solutions obtained in step (a) and step (b); and
   d) removing the water to obtain amorphous solid dispersion of daclatasvir dihydrochloride.

18. The process according to any one of the preceding claims, wherein the solvent or water is removed by distillation, spray drying, freeze drying, or by agitated thin film drier.
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Date of the actual completion of the international search: 27 September 2016

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Gregoi Tere, Ariane

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