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(54) Title: SALTS OF N,N-DIMETHYLBIGUANIDE AND PREPARATION METHODS THEREOF

FIG. 1

(57) Abstract: The present invention provides novel metformin salts, method of preparing, and pharmaceutical compositions containing the same. The metformin sesquihydrochloride and metformin dihydrochloride according to the present invention has improved pharmacological effects as compared with metformin monohydrochloride and is capable of achieving a therapeutic purpose by administering a reduced amount of metformin. The metformin sesquihydrochloride and dihydrochloride has excellent physicochemical properties, such as solubility, stability, non-hygrosopic and good flow characteristics.

[Continued on next page]
SALTS OF N,N-DIMETHYLBIGUANIDE AND PREPARATION METHODS THEREOF

FIELD OF INVENTION
The present invention relates to salts of the anti-diabetic agent metformin, and more particularly to metformin sesquihydrochloride and dihydrochloride, preferably novel crystalline forms of metformin sesquihydrochloride and dihydrochloride.

BACKGROUND OF THE INVENTION
Metformin hydrochloride is described chemically as N,N-dimethylimidodicarbonimidicdiamide hydrochloride. The empirical formula of Metformin hydrochloride is C_{4}H_{11}N_{5}.HCl and its molecular weight is 165.62 g/mol. The molecular structure of Metformin hydrochloride is shown below:

It was first described in the scientific literature in J.Chem, Soc., 1922, 121, 1790. It is the only one available biguanide, most widely prescribed orally administered anti-diabetic drug for the treatment of type 2-diabetes. Metformin is also known by other name like 1,1-dimethylbiguanide.

The biguanide antihyperglycemic agent metformin is concurrently marketed in the USA in its mono hydrochloride salt form.

Metformin hydrochloride is a cohesive white powder which is highly soluble in water (>300 mg/ml at ambient temperature), has a hygroscopicity measured at 95% relative humidity/25°C of greater than 20% moisture uptake at 6 hours, and a high compaction susceptibility. Accordingly, handling of metformin hydrochloride in a pharmaceutical manufacturing facility could present problems especially in high humidity environments. Furthermore, formulation of the metformin hydrochloride in a controlled release system is exceedingly difficult due, at least in part, to its extremely high water solubility.

The currently marketed metformin hydrochloride salt has a pronounced saline, bitter taste. Accordingly, it is usually marketed as a coated tablet where the coating is designed to mask any unpleasant taste. However, where the metformin hydrochloride salt is in the form of scored divisible tablets, it will not usually have a coating or outer layer to mask the unpleasant taste.
PCT publication no 2010/146604 discloses a preparation of Metformin hydrochloride using hydrocarbon solvents, followed by treating with water and alcoholic solvents to get Metformin hydrochloride as a product.

Pharmaceutical Chemistry Journal, 1987, 21 (12), 892-894 discloses a preparation of Metformin hydrochloride by using n-butanol, followed by purification with isopropanol to obtain Metformin Hydrochloride as a final product with 65% yield.

Metformin is widely used in the treatment of diabetes across the globe. Various salt forms has been disclosed in the prior-art to enhance various physicochemical properties such as hygroscopicity, flow properties, taste, ability to develop into chewable tablets or liquids, improved drug delivery. Nevertheless no salt is able to achieve the desired properties.

In accordance with the present invention, novel crystalline form of metformin dihydrochloride is provided which retain equivalent antihyperglycemic activity compared to metformin hydrochloride, but which has improved handling properties as compared to metformin hydrochloride salt, including lower hygroscopicity and better flow properties as well as reduced compaction susceptibility and reduced corrosiveness such as to tablet tooling. The novel crystalline form of the invention also has improved taste properties as compared to the hydrochloride salt thus enhancing patient compliance, especially where the novel salts are in the form of scored tablets, chewable tablets or liquids.

Polymorphism, the occurrence of different crystal forms, is a property of some molecules and molecular complexes. A single molecule, like metformin may give rise to a variety of crystalline forms having distinct crystal structures and physical properties like melting point, x-ray diffraction pattern, infrared absorption fingerprint, and solid state NMR spectrum. One crystalline form may give rise to thermal behaviour different from that of another crystalline form.

The present invention relates to the solid state physical properties of metformin dihydrochloride and sesquihydrochloride.

The discovery of novel polymorphic forms of a pharmaceutically useful compound provides a new opportunity to improve the performance characteristics of a pharmaceutical formulation. It also enlarges the repertoire of materials that a formulation scientist has available for designing a pharmaceutical dosage form of a drug such as a targeted release profile or other
desired characteristic. Because of limited options, there is a need in the art for novel polymorphic forms of metformin and its pharmaceutically acceptable salts.

In accordance with the present invention, novel crystalline form of metformin sesquihydrochloride and dihydrochloride is provided which retain equivalent antihyperglycemic activity compared to metformin hydrochloride, but which has improved handling properties as compared to metformin hydrochloride salt, including lower hygroscopicity and better flow properties as well as reduced compaction susceptibility and reduced corrosiveness such as to tablet tooling. The novel crystalline form of the invention also has improved taste properties as compared to the hydrochloride salt thus enhancing patient compliance, especially where the novel salts are in the form of scored tablets, chewable tablets or liquids.

**SUMMARY OF THE INVENTION**

The main aspect of the present invention is salts of metformin sesquihydrochloride and dihydrochloride.

The second aspect of the present invention provides a novel crystalline form of sesquihydrochloride compound of formula I and dihydrochloride of formula II.

\[
\text{H}_2\text{N} \begin{array}{c}
\text{NH} \\
\text{NH} \\
\text{N} \text{CH}_3
\end{array} \begin{array}{c}
\text{NH} \\
\text{N} \text{CH}_3
\end{array} \cdot 1.5 \text{HCl}
\]

**Formula I**

\[
\text{H}_2\text{N} \begin{array}{c}
\text{NH} \\
\text{NH} \\
\text{N} \text{CH}_3
\end{array} \begin{array}{c}
\text{NH} \\
\text{N} \text{CH}_3
\end{array} \cdot 2\text{HCl}
\]

**Formula II**

The novel crystalline form of metformin sesquihydrochloride is characterised by the peaks at the diffraction angles 2-theta values at 12.7, 13.0, 17.6, 21.1, 22.3, 22.6, 26.2, 28.2 and 30.1 ± 0.2 degrees as shown in Fig 1.
In another aspect, the novel crystalline form of metformin dihydrochloride is characterised by the peaks at the diffraction angles 2-theta values at 7.3, 12.8, 13.0, 14.6, 20.1, 22.0, 22.4, 26.2 and 29.3 degrees ± 0.2° as shown in Fig 2.

Further, the novel crystalline form of metformin sesquihydrochloride can be characterized by a sharp endotherm at 213.46°C ± 2°C in the differential scanning calorimetry (DSC) as shown in Fig 3.

According, to yet another aspect of the present invention, the novel crystalline form of metformin dihydrochloride can be characterized by a small endotherm at 254.73 °C ± 2°C and a sharp exotherm at 255.18°C ± 2°C in the differential scanning calorimetry (DSC) as shown in Fig 4.

According to another aspect of the present invention there is provided a process for preparation of the novel crystalline form of metformin salts comprising:

i) treating Metformin or its hydrochloride salt with a solvent,

ii) adding hydrochloric acid to the mixture obtained in step (i),

iii) slurrying the reaction mass obtained in step (ii),

iv) optionally co-distilling with the same or another solvent and

v) isolating crystalline form of Metformin sesquihydrochloride or dihydrochloride.

According to another aspect of the present invention there is provided a process for preparation of the novel crystalline form of metformin salts comprising

i) treating dimethyl amine or its salt with 2-cyanoguanidine (DCDA) in a solvent at ambient to reflux temperature,

ii) cooling the reaction mass to ambient temperature and adding hydrochloric acid to the solution obtained in step (i),

iii) slurrying the reaction mass obtained in step (ii),

iv) optionally co-distilling with the same or another solvent and

v) isolating crystalline form of Metformin sesquihydrochloride and dihydrochloride.

**BRIEF DESCRIPTION OF THE DRAWINGS**

FIG.1 shows X-ray powder diffraction pattern of crystalline form of Metformin sesquihydrochloride.

FIG.2 shows X-ray powder diffraction pattern of crystalline form of metformin dihydrochloride.
FIG. 3 shows DSC thermogram of novel crystalline form of Metformin sesquihydrochloride.  
FIG. 4 shows DSC thermogram of crystalline form of metformin dihydrochloride.  
FIG. 5 shows IR spectrum of metformin sesquihydrochloride.  
FIG. 6 shows IR spectrum of metformin dihydrochloride.  
FIG. 7 shows mass spectrum of metformin sesquihydrochloride.  
FIG. 8 shows mass spectrum of metformin dihydrochloride.  
FIG. 9 shows $^1$H NMR of metformin sesquihydrochloride.  
FIG. 10 shows $^1$H NMR of metformin dihydrochloride.  
FIG. 11 shows $^{13}$C spectrum of metformin sesquihydrochloride.  
FIG. 12 shows $^{13}$C spectrum of metformin dihydrochloride.

**DESCRIPTION OF THE INVENTION**

The present invention provides metformin sesquihydrochloride and metformin dihydrochloride represented by formula I and formula II.

![Chemical Structure](image)

Formula I

![Chemical Structure](image)

Formula II

According to the present invention, the term “metformin sesquihydrochloride” is intended to encompass all of metformin sesquihydrochloride in the form of a crystal. Further, the present invention provides a method for preparing pure crystalline form of metformin sesquihydrochloride.

According to the present invention, the term “metformin dihydrochloride” is intended to encompass all of metformin dihydrochloride in the form of a crystal. Further, the present invention provides a method for preparing pure crystalline form of metformin dihydrochloride.
According to another aspect of the present invention there is provided a process for preparation of the novel crystalline forms of metformin salts comprising

i) Treating Metformin or its hydrochloride salt with a solvent,
ii) adding hydrochloric acid to the mixture obtained in step (i),
iii) slurrying the reaction mass obtained in step (ii),
iv) optionally co-distilling with the same or another solvent and
v) isolating crystalline form of Metformin sesquihydrochloride or dihydrochloride.

Metformin or Metformin monohydrochloride compound was mixed with water or other solvents like alochols, Toluene, Xylene, Dimethyl formamide, Methylene dichloride, Ethyl acetate in round bottomed flask and subsequently conc. Hydrochloric acid was added to the above reaction mixture. The resulting reaction mixture is distilled at ambient temperature, preferably at 40-80 °C under reduced pressure followed by co-distillation with n-butanol or alcoholic solvents, Toluene. The obtained residue is slurried with 30 g of n-butanol or other alcoholic solvents, Toluene, Ethyl acetate, filtered and dried to give pure crystalline form of metformin sesquihydrochloride.

The alcohols that are selected include methanol, ethanol, butanol, isopropyl alcohol, isoamylalcohol, more preferably n-butanol.

According to yet another aspect of the present invention there is provided a process for preparation of the novel crystalline forms of metformin comprising

i) treating dimethyl amine or its salt with 2-cyanoguanidine (DCDA) in a solvent at ambient to reflux temperature,
ii) cool to ambient temperature and adding hydrochloric acid to the solution obtained in step (i),
iii) slurrying the reaction mass obtained in step (ii),
iv) optionally co-distilling with the same or another solvent and
v) isolating crystalline form of Metformin sesquihydrochloride or dihydrochloride.

Treating dimethyl amine or its salt like hydrochloride (DMA HCl) with 2-cyanoguanidine (DCDA) in round bottomed flask in presence of alcoholic solvent or other solvents like toluene, xylene, dimethyl formamide, more preferably n-butanol at ambient to reflux temperature and cool to ambient temperature and adding subsequently conc. Hydrochloric acid or alcoholic HCl was
added to the above reaction mixture. The resulting reaction mixture was distilled at ambient
temperature, preferably at 40-80 °C under reduced pressure followed by co-distillation with n-
butanol or other alcoholic solvents, Toluene. The obtained residue was slurried with n-butanol or
other alcoholic solvents, Toluene, Ethyl acetate, filtered and dried to give pure crystalline form of
metformin sesquihydrochloride or dihydrochloride.

Alternatively, treating dimethyl amine in aqueous solution with 2-cyanoguanidine (DCDA) in
round bottomed flask in presence of alcoholic solvent or other solvents like toluene, xylene,
dimethyl formamide, more preferably n-butanol at ambient to reflux temperature and cool to
ambient temperature and adding subsequently conc. Hydrochloric acid or alcoholic HCl was
added to the above reaction mixture. The resulting reaction mixture was distilled at ambient
temperature, preferably at 40-80 °C under reduced pressure by co-distillation with n-butanol or
other alcoholic solvents, Toluene. The obtained residue was slurried with n-butanol or other
alcoholic solvents, Toluene, Ethyl acetate, filtered and dried to give pure crystalline form of
metformin dihydrochloride or sesquihydrochloride.

The process for the preparation of novel crystalline metformin sesquihydrochloride and
dihydrochloride form carried out in alcohols *i.e.* C$_1$-C$_5$ and mixtures thereof. The alcohols may be
preferably methanol, ethanol, Butanol, Isopropyl alcohol, Isoamylalcohol etc.

The salt produced is characterised by means of nuclear magnetic resonance, infrared
spectrometry, mass spectrometry, X-ray Diffraction and elemental analysis. The analysis of the
spectra indicated that the new salts produced is different from other metformin compounds.

The comparison of spectral data of Metformin monohydrochloride, sesquihydrochloride
and dihydrochloride is given below:

**Table 1.** Spectral data of Metformin sesquihydrochloride

<table>
<thead>
<tr>
<th>Test</th>
<th>IR(KBr)</th>
<th>1HNMR (d6-DMSO, 400 MHz)</th>
<th>13C NMR (d6-DMSO, 100 MHz)</th>
<th>Mass (GC MS, EI-m/z)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Result</td>
<td>3371, 3298, 3172, 1680, 1630, 1586, 1447, 1060 and 936cm$^{-1}$</td>
<td>δ 2.99 (s, 6H, -N(CH$_3$)$_2$), 7.49 (s, 4H), 8.01 (s, 2H) ppm</td>
<td>δ 38.3(-N(CH$_3$)$_2$), 156.5 and 157.2 ppm</td>
<td>129.8 (M$^+$H, 100%), 130.8 (M+H+H, 4%)</td>
</tr>
</tbody>
</table>
Table 2: Spectral data of Metformin Dihydrochloride

<table>
<thead>
<tr>
<th>Test</th>
<th>IR(KBr)</th>
<th>$^1$HNMR (d6-DMSO, 400 MHz)</th>
<th>$^{13}$C NMR (d6-DMSO, 100 MHz)</th>
<th>Mass (GC MS, EL-m/z)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Result</td>
<td>3305, 3190, 3008, 2769, 1681, 1631, 1591, 1083, and 1058 cm$^{-1}$</td>
<td>$\delta$ 3.05(s, 6H, - N(CH$_3$)$_2$), 8.37(s,4H, 9.07(s,2H) and 9.9(br-s,1H) ppm</td>
<td>$\delta$ 39.69 (- N(CH$_3$)$_2$, 152.82 and 155.58 ppm</td>
<td>129.8 (M$^+$H, 100%), 130.7(M+H+H, 4%)</td>
</tr>
</tbody>
</table>

Table 3: Spectral data of Metformin monohydrochloride

<table>
<thead>
<tr>
<th>Test</th>
<th>IR(KBr)</th>
<th>$^1$HNMR (d6-DMSO, 400MHz)</th>
<th>$^{13}$C NMR (d6-DMSO, 100MHz)</th>
<th>Mass (GC-MS, EL-m/z)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Result</td>
<td>3371, 3320, 3299, 3170, 2697, 1634, 1626, 1584, 1568, 1064, and 937 cm$^{-1}$</td>
<td>$\delta$ 2.94(s, 6H, - N(CH$_3$)$_2$), 6.86(s,4H, and 7.25(s,2H) ppm</td>
<td>$\delta$ 37.8(- N(CH$_3$)$_2$, 158.39, and 159.3 ppm</td>
<td>129.1 (M+H, 100%),</td>
</tr>
</tbody>
</table>

Further, Elemental analysis of Metformin sesquihydrochloride, dihydrochloride is differentiated from the Metformin monohydrochloride by elemental analysis data as shown below:

Table 4: Elemental analysis of Metformin sesquihydrochloride

<table>
<thead>
<tr>
<th>S.No</th>
<th>Element</th>
<th>Theory (%)</th>
<th>Found (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Carbon</td>
<td>26.13</td>
<td>25.94</td>
</tr>
<tr>
<td>2</td>
<td>Hydrogen</td>
<td>6.85</td>
<td>7.18</td>
</tr>
<tr>
<td>3</td>
<td>Nitrogen</td>
<td>38.09</td>
<td>38.18</td>
</tr>
<tr>
<td>4</td>
<td>Chloride</td>
<td>28.93</td>
<td>28.70</td>
</tr>
</tbody>
</table>
Table 5: Elemental analysis of Metformin dihydrochloride

<table>
<thead>
<tr>
<th>S.No</th>
<th>Element</th>
<th>Theory (%)</th>
<th>Found (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Carbon</td>
<td>23.77</td>
<td>23.50</td>
</tr>
<tr>
<td>2</td>
<td>Hydrogen</td>
<td>6.48</td>
<td>6.51</td>
</tr>
<tr>
<td>3</td>
<td>Nitrogen</td>
<td>34.66</td>
<td>34.64</td>
</tr>
<tr>
<td>4</td>
<td>Chloride</td>
<td>35.09</td>
<td>35.35</td>
</tr>
</tbody>
</table>

Table 6: Elemental analysis of Metformin monohydrochloride

<table>
<thead>
<tr>
<th>S.No</th>
<th>Element</th>
<th>Theory (%)</th>
<th>Found (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Carbon</td>
<td>29.0</td>
<td>28.8</td>
</tr>
<tr>
<td>2</td>
<td>Hydrogen</td>
<td>7.3</td>
<td>7.26</td>
</tr>
<tr>
<td>3</td>
<td>Nitrogen</td>
<td>42.3</td>
<td>42.13</td>
</tr>
<tr>
<td>4</td>
<td>Chloride</td>
<td>21.4</td>
<td>21.81</td>
</tr>
</tbody>
</table>

As polymorphic forms are most reliably characterized primarily by peak positions in the X-ray diffractogram, the polymorphs of the present invention have been characterized by powder X-ray diffraction spectroscopy which produces a fingerprint of the particular crystalline form. Measurements of 2θ values typically are accurate to within ± 0.2 degrees. All the polymorphs obtained in the present invention are stable, highly pure and with low amounts of residual solvents.

The novel crystalline form of metformin sesquihydrochloride has a XRD pattern with peaks 12.6, 13.0, 17.6, 21.1, 22.3, 22.6, 26.2, 28.2 and 30 ± 0.2° 2θ.

In another embodiment, the X-ray powder diffraction spectrum of novel crystalline form of metformin sesquihydrochloride is depicted in FIG. 1.

In an embodiment, the novel crystalline form of metformin sesquihydrochloride has a XRD pattern characterized with peaks at 2θ values as shown in the following Table 7
Table 7: PXRD data of Metformin sesquihydrochloride

<table>
<thead>
<tr>
<th>Index</th>
<th>Angle</th>
<th>Rel. Intensity %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>12.48</td>
<td>6</td>
</tr>
<tr>
<td>2</td>
<td>12.68</td>
<td>100</td>
</tr>
<tr>
<td>3</td>
<td>12.98</td>
<td>16</td>
</tr>
<tr>
<td>4</td>
<td>14.58</td>
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<td>5</td>
<td>16.91</td>
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<td>6</td>
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<td>7</td>
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<td>22</td>
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<tr>
<td>23</td>
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<td>24</td>
<td>32.80</td>
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<td>25</td>
<td>33.48</td>
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<td>26</td>
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<td>27</td>
<td>35.28</td>
<td>7</td>
</tr>
<tr>
<td>28</td>
<td>35.67</td>
<td>4</td>
</tr>
<tr>
<td>Index</td>
<td>Angle</td>
<td>Rel. Intensity %</td>
</tr>
<tr>
<td>-------</td>
<td>--------</td>
<td>------------------</td>
</tr>
<tr>
<td>1</td>
<td>7.32</td>
<td>17</td>
</tr>
<tr>
<td>2</td>
<td>12.88</td>
<td>25</td>
</tr>
<tr>
<td>3</td>
<td>13.01</td>
<td>40</td>
</tr>
<tr>
<td>4</td>
<td>14.63</td>
<td>35</td>
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<td>5</td>
<td>16.92</td>
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<td>6</td>
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<td>7</td>
<td>21.17</td>
<td>9</td>
</tr>
<tr>
<td>8</td>
<td>22.01</td>
<td>38</td>
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<td>11</td>
<td>26.44</td>
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<tr>
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<tr>
<td>14</td>
<td>29.48</td>
<td>6</td>
</tr>
<tr>
<td>15</td>
<td>30.11</td>
<td>7</td>
</tr>
</tbody>
</table>

The crystalline polymorph form of metformin dihydrochloride is characterized by PXRD pattern peaks at 7.3, 12.8, 13.01, 14.63, 20.1, 22.0, 22.4, 26.2, 28.7 and 29.3 ± 0.2° θ.

In another embodiment, the X-ray powder diffraction spectrum of novel crystalline form of metformin dihydrochloride is depicted in FIG. 2.

In an embodiment, the crystalline polymorph form of metformin dihydrochloride has a PXRD pattern with peaks at 2θ values as shown in Table 8.

**Table 8: PXRD data of Metformin dihydrochloride**
Further, the novel crystalline form of metformin sesquihydrochloride can be characterized by a sharp endotherm at 213.46 °C ± 2 °C in the differential scanning calorimetry (DSC) as shown in Fig 3.

Further, the novel crystalline form of metformin dihydrochloride can be characterized by a small endotherm at 254.17 °C ± 2 °C and a sharp exotherm at 255.18 °C ± 2 °C in the differential scanning calorimetry (DSC) as shown in Fig 4.

Further, the novel crystalline form of metformin sesquihydrochloride was analysed for hydrogen chloride content by potentiometric titration method using argentometric titration and documented the results as below. Theoretical value of Hydrogen chloride content in Metformin sesquihydrochloride *i.e* compound of formula I is 29.78 % as shown in table 9:

**Table 9: Hydrogen chloride content in Metformin sesquihydrochloride**

<table>
<thead>
<tr>
<th>S.No</th>
<th>Example</th>
<th>Hydrogen chloride content</th>
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<tr>
<td>1</td>
<td>1</td>
<td>29.43 %</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>29.30 %</td>
</tr>
</tbody>
</table>

Further, the novel crystalline metformin dihydrochloride form was analysed for hydrogen chloride content by potentiometric titration method using argentometric titration and documented the results as shown in table 10. Theoretical value of Hydrogen chloride content in crystalline metformin dihydrochloride is 36.13 %.

**Table 10: Hydrochloride content of Metformin dihydrochloride**

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<th>S.No</th>
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<td>36.05 %</td>
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<tr>
<td>2</td>
<td>9</td>
<td>35.92 %</td>
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One of the most important physical properties of pharmaceutical compounds is their solubility in aqueous solution and the present invention displays better solubility profile than what is known in the art. Different crystalline forms or polymorphs of the same pharmaceutical compound can (and reportedly do) have different aqueous solubility. The novel crystalline metformin sesquihydrochloride and dihydrochloride of the present invention has been subjected to solubility studies and is compared with the known metformin monohydrochloride in water solvent and the results are shown in table 11 and 12:

**Table 11:** Aqueous solubility profile of Metformin sesquihydrochloride

<table>
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<tr>
<th>S.No</th>
<th>Metformin monohydrochloride</th>
<th>Metformin sesquihydrochloride</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>415 mg/ml</td>
<td>590 mg/ml</td>
</tr>
</tbody>
</table>

**Table 12:** Aqueous solubility profile of Metformin dihydrochloride

<table>
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<tr>
<th>S.No</th>
<th>Metformin monohydrochloride</th>
<th>Metformin Dihydrochloride</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>415 mg/ml</td>
<td>1430 mg/ml</td>
</tr>
</tbody>
</table>

The above solubility study in water shows that Metformin sesquihydrochloride of the present invention has 1.42 times higher solubility than the known metformin monohydrochloride. This significant enhancement of solubility of Metformin sesquihydrochloride helps in improving the bioavailability of the metformin drug in the human body.

The above solubility study in water shows that metformin dihydrochloride form of the present invention has 3.45 times higher solubility than the known metformin monohydrochloride. This significant enhancement of solubility of Metformin dihydrochloride helps in improving the bioavailability of the metformin in the human body.

The novel crystalline metformin sesquihydrochloride and metformin dihydrochloride forms obtained according to the present invention is substantially free from other forms of metformin and its salt. "Substantially free" from other forms of metformin shall be understood to mean that the polymorphs of metformin contain less than 10%, preferably less than 5%, of any other forms of metformin and less than 1% of other impurities, water or solvates.
The novel metformin sesquihydrochloride and metformin dihydrochloride obtained according to the present invention are analysed for related substances by High Performance Liquid Chromatography (HPLC) and found to be greater than 99.9%.

In accordance with the present invention, novel salts of metformin sesquihydrochloride and dihydrochloride are provided which retain antihyperglycemic activity to metformin hydrochloride, have improved handling properties as compared to metformin hydrochloride salt, non-hygroscopic and have good flow characteristics. The novel crystalline forms of metformin sesquihydrochloride and dihydrochloride synthesized by the above mentioned process provides high yield and purity. The advantages of the process include simplicity, eco-friendliness and suitability for commercial use.

Hereinafter, embodiments of the present invention will be described in more detail with reference to the following examples. However, it should be understood that the following examples are provided only for illustrating the present invention and should not be construed as limiting the scope and spirit of the present invention.

Example 1: Preparation of novel Crystalline form of Metformin sesquihydrochloride

10g of Metformin hydrochloride and 150mL of water were mixed well in a 500 mL glass flask. 5.0g of concentrated hydrochloric acid was added to the above reaction mixture at a temperature in the range 25-40 ºC. The obtained reaction mass was stirred at same temperature preferably and completion of the reaction was monitored by HCl content. The resulting reaction mass was distilled off at ambient temperature, under reduced pressure, followed co-distillation with n-butanol. The obtained residue was slurried with 30g of n-butanol, filtered and dried to get pure crystalline form of Metformin sesquihydrochloride (11.0g).

Example 2: Preparation of novel crystalline form of metformin sesquihydrochloride

10 g of metformin and 100 ml of water were placed in a 250 ml round bottomed flask and then 15.0 g of conc. Hydrochloric acid was added to the above reaction mixture at a temperature in the range 25-40 ºC. The obtained reaction mixture was stirred at the same temperature and completion of the reaction was monitored by HCl content. The reaction mixture was distilled off at ambient temperature at 40-80 ºC under reduced pressure followed by co-distillation with toluene. The obtained residue was slurried with 30 g of toluene, filtered and dried to give crystalline form of metformin sesquihydrochloride (10.5 g).
Example 3: Preparation of novel Metformin sesquihydrochloride form

10g of Metformin hydrochloride and 100mL n-butanol are mixed well in a 250 ml glass flask. 6g of conc. hydrochloric acid in n-butanol is added to the above reaction mixture. The obtained reaction mixture was stirred at a temperature in the range 25-40°C. The obtained reaction mixture is stirred at the same temperature and completion of the reaction was monitored by HCl content. The resulting reaction mass was filtered and dried to get pure crystalline Metformin sesquihydrochloride (10.0g).

Example 4: Preparation of novel Metformin sesquihydrochloride form

10.01 g of 2-cyanoguanidine and 10.19 g of Dimethyl amine hydrochloride are added to 12 g of n-butanol in a 100 ml glass flask. The flask was equipped with cooling water condenser and the flask was allowed to reflux for 16 hr. The resulting reaction mass was cooled to ambient temperature, preferably 10-110°C and add 7.0g of concentrated hydrochloric acid was added to the above solution. Reaction mass was stirred at ambient temperature preferably at 0-40°C for 10 h. The resulting reaction mass was distilled off at ambient temperature, preferably 40-80°C under reduced pressure, and then co-distilled with 15g of n-Butanol. The obtained residue was slurried with 40g of n-butanol, filtered and dried to get pure crystalline Metformin sesquihydrochloride (21.0g).

Example 5: Preparation of novel Metformin sesquihydrochloride form

10.03 g of 2-cyanoguanidine and 10.20 g of Dimethyl amine hydrochloride were added to 12.5 g of Toluene in a 100 ml glass flask. The flask was equipped with cooling water condenser and the flask is allowed to reflux for 18 hr. The resulting reaction mass is cooled to ambient temperature, preferably 10-110°C and add 7.2g of concentrated hydrochloric acid was added to the above solution. Reaction mass is stirred at ambient temperature preferably at 0-40°C for 10 hr. The resulting reaction mass was distilled off at ambient temperature, preferably 40-80°C under reduced pressure, and then co-distilled with 15g of Toluene. The obtained residue was slurried with 40g of n-butanol, filtered and dried to get pure crystalline Metformin sesquihydrochloride (21.2g).

Example 6: Preparation of novel Metformin sesquihydrochloride form

100.02 g of 2-cyanoguanidine and 100.20 g of Dimethyl amine hydrochloride are added to 120 g of n-butanol in a 500 ml glass flask. The flask is equipped with cooling water condenser and the
flask is allowed to reflux for 18 hr. The resulting reaction mass was cooled to ambient temperature, preferably 10-110°C and add 60.0g of concentrated hydrochloric acid is added to the above solution. Reaction mass is stirred at ambient temperature preferably at 0-40°C for 8 h. The resulting reaction mass was distilled off at ambient temperature, preferably 40-80°C under reduced pressure, and then co-distilled with 100g of n-Butanol. The obtained residue was slurred with 410g of n-butanol, filtered and dried to get pure crystalline Metformin sesquihydrochloride (210.0g).

Example 7: Preparation of novel Metformin sesquihydrochloride form

10.04 g of 2-cyanoguanidine and 20.29 g of Dimethyl amine (40% in water) are added to 12 g of n-butanol in a 100 mL glass flask. The flask is equipped with cooling water condenser and the flask is allowed to reflux for 20 hr. The resulting reaction mass was cooled to ambient temperature, preferably 10-110°C and add 9.0g of concentrated hydrochloric acid was added to the above solution. Reaction mass is stirred at ambient temperature preferably at 0-40°C for 12 hr. The resulting reaction mass was distilled off at ambient temperature, preferably 40-80°C under reduced pressure, and then co-distilled with n-Butanol. The obtained residue is slurred with 40g of n-butanol, filtered and dried to get pure crystalline Metformin sesquihydrochloride (19.0g).

Example 8: Preparation of novel crystalline form of metformin dihydrochloride

10 gms of Metformin hydrochloride and 150 ml of water were placed in a 500 ml round bottomed flask and then 7.0 g of conc. Hydrochloric acid was added to the above reaction mixture at a temperature in the range 25-40 °C. The obtained reaction mixture was stirred at the same temperature and completion of the reaction was monitored by HCl content. The reaction mixture was distilled off at ambient temperature under reduced pressure followed by co-distillation with n-butanol. The obtained residue was slurred with 30 g of n-butanol, filtered and dried to give crystalline form of metformin dihydrochloride (11.5 g).
Example 9: Preparation of novel crystalline form of metformin dihydrochloride
10 g of metformin and 100 ml of water were placed in a 250 ml round bottomed flask and then 18.0 g of conc. Hydrochloric acid was added to the above reaction mixture at a temperature in the range 25-40 °C. The obtained reaction mixture was stirred at the same temperature and completion of the reaction was monitored by HCl content. The reaction mixture was distilled off at ambient temperature at 40-80 °C under reduced pressure followed by co-distillation with toluene. The obtained residue was slurried with 30 g of toluene, filtered and dried to give crystalline form of metformin dihydrochloride (12.0 g).

Example 10: Preparation of novel crystalline form of metformin dihydrochloride
10 g of metformin hydrochloride and 100 ml of n-butanol were placed in a 250 ml round bottomed flask and then 10.0 g of conc. Hydrochloric acid in n-butanol is added to the above reaction mixture. The obtained reaction mixture was stirred at same temperature and completion of the reaction mixture was monitored by HCl content. The resulting reaction mass was filtered and dried to get pure crystalline metformin dihydrochloride (11.0 g).

Example 11: Preparation of novel Metformin dihydrochloride form
10.0 g of 2-cyanoguanidine and 10.15 g of Dimethyl amine hydrochloride are added to 12 g of n-butanol in a 100 mL glass flask. The flask was equipped with cooling water condenser and the flask was allowed to reflux for 14 hr. The resulting reaction mass was cooled to ambient temperature, preferably 10-110°C and add 21.0g of concentrated hydrochloric acid was added to the above reaction mixture at a temperature in the range at 25-40°C. The obtained reaction mass was distilled off at same temperature, and completion of the reaction mixture was monitored by HCl content. The resulting reaction mixture was distilled off at ambient temperature under reduced pressure followed by co-distillation with n-butanol. The obtained residue was slurried with 45g of n-butanol, filtered and dried to get pure crystalline Metformin dihydrochloride (22.0g).

Example 12: Preparation of novel Metformin dihydrochloride form
10.2 g of 2-cyanoguanidine and 10.17 g of Dimethyl amine hydrochloride are added to 13 g of Xylene in a 100 mL glass flask. The flask was equipped with cooling water condenser and the flask was allowed to reflux for 18 hr. The resulting reaction mass was cooled to ambient temperature, preferably 10-110°C and add 22.0g of concentrated hydrochloric acid was added to
the above reaction mixture at a temperature in the range at 25-40°C. The obtained reaction mass was distilled off at same temperature, and completion of the reaction mixture was monitored by HCl content. The resulting reaction mixture was distilled off at ambient temperature under reduced pressure followed by co-distillation with n-butanol. The obtained residue was slurried with 47g of n-butanol, filtered and dried to get pure crystalline Metformin dihydrochloride (21.5g).

Example 13: Preparation of novel Metformin dihydrochloride form

10.02 g of 2-cyanoguanidine and 20.19 g of Dimethyl amine (40% in water) were added to 13 g of n-butanol in a 100 mL glass flask. The flask was equipped with cooling water condenser and the flask was allowed to reflux for 22 hr. The resulting reaction mass was cooled to ambient temperature, and 23.0g of concentrated hydrochloric acid was added to the above reaction mixture at a temperature in the range at 25-40°C. The obtained reaction mass was distilled off at same temperature, and completion of the reaction mixture was monitored by HCl content. The resulting reaction mass was distilled off at ambient temperature, under reduced pressure, and then co-distilled with n-Butanol. The obtained residue was slurried with 42g of n-butanol, filtered and dried to get pure crystalline Metformin dihydrochloride (19.2g).
Claims

1. A compound of formula I & II:

\[ \text{H}_2\text{N} - \text{NH} - \text{NH} - \text{N} - \text{CH}_3 \cdot 1.5 \text{HCl} \]

(I)

\[ \text{H}_2\text{N} - \text{NH} - \text{NH} - \text{N} - \text{CH}_3 \cdot 2\text{HCl} \]

(II)

2. A compound having a structure of formula I & II, wherein the said compounds are crystalline form.

3. The crystalline form of metformin sesquihydrochloride(I) as claimed in claim 2, having characteristic peaks in a PXRD diffraction pattern at 12.7, 13.0, 17.6, 21.1, 22.3, 22.6, 26.2, 28.2 and 30.1 ± 0.2°θ.

4. The crystalline form of metformin sesquihydrochloride(I) as claimed in claim 2, having characteristic peaks in IR at 3371, 3298, 3172, 1680, 1630, 1586, 1447, 1060 and 936 ±1 cm⁻¹.

5. The crystalline form of metformin sesquihydrochloride(I) as claimed in claim 2, exhibit DSC endotherm at 213.46°C ± 2°C.

6. The crystalline form of metformin dihydrochloride(II) as claimed in claim 2, having characteristic peaks in a PXRD diffraction pattern at 7.3, 12.8, 13.01, 14.63, 20.1, 22.0, 22.4, 26.2, 28.7 and 29.3 ± 0.2°θ.

7. The crystalline form of metformin dihydrochloride(II) as claimed in claim 2, having characteristic peaks in IR at 3305, 3190, 3008, 2769, 1681, 1631, 1591, 1083, and 1058 ± cm⁻¹.

8. The crystalline form of metformin dihydrochloride(II) as claimed in claim 2, exhibit DSC endotherm at 254.17°C ± 2°C and exotherm at 255.18°C ± 2°C.

9. The process for preparing the crystalline compounds of formula I & II of claim 1, comprising the following steps:

   i) Treating Metformin or its hydrochloride salt with a solvent,
   ii) adding hydrochloric acid to the mixture obtained in step (i),
   iii) slurrying the reaction mass obtained in step (ii),
iv) optionally co-distilling with the same or another solvent and
v) isolating crystalline sesquihydrochloride or dihydrochloride form of Metformin

10. The process for preparing the crystalline compound of formula I & II of claim 1, comprising the following steps

i) treating dimethyl amine or its salt with 2-cyanoguanidine (DCDA) in a solvent at ambient to reflux temperature,
ii) cool to ambient temperature and adding hydrochloric acid to the solution obtained in step (i),
iii) slurrying the reaction mass obtained in step (ii),
iv) optionally co-distilling with the same or another solvent and
v) isolating crystalline sesquihydrochloride or dihydrochloride form of metformin.

11. The process as claimed in claims 9 and 10, wherein the solvent is selected from water, alcohols, Toluene, Xylene, Dimethyl formamide, Methylene dichloride, Ethyl acetate or mixtures thereof.

12. The process as claimed in claim 11, wherein the alcohol is selected from methanol, ethanol, butanol, isopropyl alcohol, isoamylalcohol, more preferably n-butanol.

13. The process as claimed in claims 9 and 10, wherein the metformin sesquihydrochloride and metformin dihydrochloride compound has a purity of greater than 99 percent.

14. The process as claimed in claims 9 and 10, wherein the metformin sesquihydrochloride and metformin dihydrochloride compound has a purity of greater than 98 percent.

15. The process as claimed in claims 9 and 10, wherein the metformin sesquihydrochloride compound has a solubility of $590 \pm 10$ mg/ml.

16. The process as claimed in claims 9 and 10, wherein the metformin dihydrochloride compound has a solubility of $1430 \pm 10$ mg/ml.

17. The process as claimed in claims 9 and 10, wherein the content of dimethyl amine is less than 100 ppm, melamine and cyanoguanidine (DCDA) is less than 0.02%.
FIG. 6

![Graph showing wavenumbers and transmittance values.]

FIG. 7

![Graph showing intensity and m/z values.]


**INTERNATIONAL SEARCH REPORT**

**International application No**
PCT/IB2017/052654

### A. CLASSIFICATION OF SUBJECT MATTER

**INV.** C07C279/26

**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)

C07C

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, WPI Data, CHEM ABS Data

### C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
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<th>Category*</th>
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<td>WO 2010/146604 A2 (EXEMED PHARMACEUTICALS [IN]; PATEL PRANAV DUSHYANT [IN]; PATEL DINESH) 23 December 2010 (2010-12-23) cited in the application page 1, line 12 - page 2, line 15; claim 1</td>
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<td>Y</td>
<td>WO 99/29314 A1 (SQUIBB BRISTOL MYERS CO [US]) 17 June 1999 (1999-06-17) column 1, line 6 - line 42; claim 1</td>
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<td>Y</td>
<td>FR 2 796 551 A1 (LIPHA [FR]) 26 January 2001 (2001-01-26) page 1, line 5 - page 2, line 19; claim 1</td>
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<td>CN 106 008 277 A (LIAOCHENG UNIV) 12 October 2016 (2016-10-12) paragraph [0005]</td>
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  - "A" document defining the general state of the art which is not considered to be of particular relevance
  - "E" earlier application or patent but published on or after the international filing date
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- **"&"** document member of the same patent family

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

19 June 2017

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

27/06/2017

**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**

Seelmann, Ingo
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