AN IMPROVED PROCESS FOR PREPARATION OF PALIPERIDONE PALMITATE, AN ANTI-PSYCHOTIC AGENT

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ABSTRACT

An improved process for the preparation of Paliperidone palmitate, an anti-psychotic drug substance, with an overall yield of >87.0% (including purification) and >99.9% purity. Process optimization was done based on design of experiments (DOE) concept. Isolated product meets all regulatory requirements and quality target product profile (QTPP). Formation and control of all possible impurities are also addressed.

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INTRODUCTION

Paliperidone palmitate is an antipsychotic drug used for the treatment of schizophrenia. It is a prodrug of paliperidone. Paliperidone is known as 9-hydroxy risperidone and belonging to benzoisoxazol derivative and is the major metabolite of risperidone, which is approved for treatment of schizophrenia since 1994. Paliperidone palmitate is approved by the U.S. FDA in July 2009 in the brand name of INVEGA® SUSTENNA® developed by Janssen Pharmaceuticals, as the first once-monthly a new long-acting injection to treat schizophrenia and is now approved for more than 80 countries. The finished product is extended release suspension for injection containing 25 mg, 50 mg, 75 mg, 100 mg or 150 mg of Paliperidone, the active substance, in form of Paliperidone palmitate. Efficacy was established in four short-term studies and one longer-term study in adults. Paliperidone palmitate is chemically designated as (9RS)-3-[2-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)piperidin-1-yl][ethyl]-2-methyl-4-oxo-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidin-9-yl hexadecanoate. It is a selective monoaminergic antagonist having unique properties like high affinity to serotoninergic 5-HT2 receptor and dopamine D2 receptor. It binds to al-adrenergic receptor, and binds to histaminergic H1 receptor and a-adrenoceptor with a relatively low affinity. Paliperidone palmitate is a potent D2 antagonist and can improve positive symptoms of schizophrenia, but it may cause less motor function inhibition and catalepsy than classic antipsychotics. Its balanced antagonistic effects on serotonin and dopamine of central nervous system may reduce the possibility of occurrence of extra pyramidal side effects, and its therapeutic effects may be extended to negative symptoms and emotional symptoms of schizophrenia.

EXPERIMENTAL

1H NMR, 13CNMR and DEPT spectral data were performed in chloroform (CDCl3) at 500 MHz or 300 MHz spectrometer. The chemical shift values were reported on the δ scale in parts per million (ppm), downfield from tetramethylsilane (TMS, δ = 0.0) as an internal standard. Spin multiplicities are given as s (singlet), d (doublet), dd (doublet of doublet), t (triplet) and m (multiplet) as well as brs (broad). Coupling constants (J) are given in hertz. IR spectra were recorded in the solid state as KBr dispersion using a Perkin-Elmer PE SCIEX-API 2000, equipped with ESI source used online with a HPLC system after the ultraviolet (UV) detector. HPLC and GC Chromatographic purities were determined by using area normalization method. The thermal analysis was carried out on DSC Q 1000 TA. The thermogram was recorded from 30-250°C. The solvents and some reagents were used without purification.

Purification of hexadecanoic acid (Palmitic acid, 3)

Palmitic acid (20 kg, 0.078 kmol) was dissolved in n-heptane (100 L) at 40-45 °C and crystallized by slow cooling to 20-25 °C. The resultant reaction mixture was stirred for 4 h at 20-25 °C and crystallized solid filtered, washed with n-heptane (20 L) and dried it under vacuum at 40-50°C to furnish 12 kg (60%) of the title compound 3. Purity by GC: 99.88%; MR: 62.0-62.2 °C; IR (KBr, cm-1): 2954, 2917, 1703, 1311, 1295, 940, 720; 1H NMR (CDCl3, 300 MHz, δ ppm): 0.88 (t, 3H), 1.18 & 1.30 (m, 24H), 1.62 (q, 2H), 2.35 (t, 2H); MS m/z (ESI):255.0 [MH+].

Distillation of 2,2-Dimethylpropanoyl chloride (Pivaloyl chloride, 4)

Pivaloyl chloride (20 kg, 0.17 kmol) was subjected to vacuum fractional distillation using proper (1 foot in lab scale) distillation column. The first fraction (~10% of input) having low purity, distilling at < 65°C (vapour temperature) under reduced pressure (150-200 mmHg) was collected and discarded. Cooled the concentrated pivaloyl chloride (pot residue) to 25-30 °C and unload it to furnish 17.5 kg (87.5%) of the title compound 4. Purity by GC: 99.58%; Acetyl chloride content: 0.02%.

Preparation of (9RS)-3-[2-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)piperidin-1-yl][ethyl]-2-methyl-4-oxo-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidin-9-yl]hexadecanoate (Paliperidone palmitate, 1)

To a solution of palmitic acid (6.61 kg, 0.026 kmol) in dichloromethane (70 L) pivaloyl chloride (4.24 kg, 0.035 kmol) and N,N-dimethylaminopyridine (DMAP, 0.7 kg, 7% w/w) were added at 25-30 °C. The resultant mixture was stirred for 30 min. Paliperidone (10.0 kg, 0.024 kmol) was added at 25-30 °C followed by added triethylamine (5.93 kg, 0.059 kmol) was slowly in 30-40 min at 25-30 °C. The resultant mixture was stirred at 25-30 °C for 2 h. DM water (70 L) was added and stirred for 15 min. Separated the layers and organic layer was washed with DM water (2 x 70 L). Organic layer was evaporated by distilling dichloromethane completely under vacuum at 35-40 °C and stripped out with isopropyl alcohol (20 L) to remove traces of dichloromethane. Added isopropyl alcohol (2500 mL) and heated to 65-75 °C for 15-20 min to get clear solution, treated with carbon (10%), washed with isopropyl alcohol (100 mL). Crystallized the product by cooling the filtrate slowly to 25-30 °C and resultant reaction mixture was stirred at 25-30 °C for 4 h, filtered the solid, washed with isopropyl alcohol (2x10 L; 25-30 °C) to get Paliperidone palmitate. Crude (~ 16.5 kg). The crude product was again dissolved in isopropyl alcohol(250 L) and heated to 65-75 °C for 15-20 min to get clear solution, treated with carbon (5%), washed with isopropyl alcohol (10 L). Crystallized the product by cooling the filtrate slowly to 25-30 °C and resultant reaction mixture was stirred at 25-30 °C for 4 h, filtered the solid, washed with isopropyl alcohol (2x10 L; 25-30 °C) dried under vacuum at 50-60 °C to furnish 13.56 kg (87%) of the title compound 1. Purity by HPLC: 99.92%; IR (KBr, cm-1): 2919, 2850, 2798, 1736, 1651, 1540, 1413, 1273, 1158, 1123, 953, 836, 722; 1H NMR (CDCl3, 500 MHz, δ ppm): 0.88 (t, 3H), 1.26 (m, 20H), 1.32 (m, 4H), 1.67 (m, 2H), 1.91 (s, 1H), 2.00 (dd, 1H), 2.10 (m, 6H), 2.28 (m, 2H), 2.32 (s, 3H), 2.39 (t, 2H), 2.54 (t, 2H), 2.78 (m, 2H), 3.07 (m, 1H), 3.14 (m, 2H), 3.86 (m, 1H), 4.06 (m, 1H), 5.77 (t, 12H), 7.03-7.72 (m, 3H, Ar); 13C NMR (CDCl3, 300 MHz, δ ppm):14.5 (CH3), 18.4 (CH3), 21.8 (CH3), 23.1 (CH3), 24.3 (CH2), 25.4 (CH2), 26.0 (CH), 29.5 (CH2), 29.7 (CH3), 30.0 (7xCH3), 31.0 (CH2CH2), 32.3 (CH2), 34.8 (CH2), 35.0 (CH2), 42.7 (CH3), 53.8 (CH2CH2), 56.9(CH2CH3), 69.0(CH3), 97.8 (CH), 112.7
RESULTS AND DISCUSSION

Several reports are available in the literature regarding the various routes of synthesis, methodologies and processes that have been adopted for the preparation of Paliperidone palmitate. These processes have restricted application in the industry because of less overall yield, cumbersome workup process, difficult post-treatment and handling of excessive dehydrating reagents such as dicyclohexyl carbodiimide (DCC) and decomposition, removal of its byproducts dicyclohexyl urea (DCU). Initially process for preparation of paliperidone palmitate was developed by Janssen Pharmaceuticals and it was reported in the product patent of Paliperidone palmitate as described by following reaction scheme 1.

\[
\text{Scheme 1: Reported Synthetic route for Paliperidone palmitate.}
\]

In the above process dicyclohexyl carbodiimide (DCC) is used as dehydrating agent, it is very difficult to handle due to its hazardous nature, which is a potent allergen and a sensitizer, often causing skin rashes. Moreover, it is generating dicyclohexyl urea (DCU) as a by-product and it is difficult to remove from drug substance up to desired level. It is required additional purifications to reduce DCU from drug substance. Moreover, reaction is taking longer time (3 days) for esterification reaction by using DCC. It will result higher occupancy of the reactors and ultimately it will effect on the production cost.

Later on, new synthetic process was developed by Teva Pharmaceuticals. As per that process, paliperidone palmitate was prepared by following reaction scheme 2.

\[
\text{Scheme 2: Reported Synthetic route for Paliperidone palmitate.}
\]

This process has advantages of using non-hazardous materials. But during experimental study, it was observed that palmitoyl chloride converted into palmitic acid in aqueous basic medium. Ultimately it is required higher mole equivalents of palmitoyl chloride for convert Paliperidone into Paliperidone palmitate. The excess use of palmitoyl chloride effect on raw material cost of Paliperidone palmitate as well as require additional purification to remove palmitic acid from drug substance.

In another attempt, Paliperidone palmitate was prepared by esterification of Paliperidone by palmitic acid in tetrahydrofuran (THF) using pivaloyl chloride and triethylamine (TEA) as per following scheme 3.
Scheme 3: Reported Synthetic route for Paliperidone palmitate.

Above process have the advantages as use of molar quantity of palmitic acid but reaction is performed in THF, which is more costly and it has stringent ICH residual solvent limit (720 ppm) in the drug substance. This requires lengthy work-up process to remove the in-organic salt from the drug substance. Moreover, THF is costly solvent as compare to dichloromethane. In the view of high volume requirement, huge revenues associated with this molecule and disadvantages from the above reported processes, it is required to develop a new process for preparation of Paliperidone palmitate using non-hazardous raw materials and cheaper solvents with improved productivity timelines.

Following parameters were kept in criteria at the time of process development of Paliperidone palmitate for cost effective and safe process as per scheme 4.

1. Use of non- hazardous reagents which can handle safely and remove by-product easily from drug substance during workup.
2. Use of minimum amount of cost effective solvents and reagents to reduce the product cost.
3. Develop the effective process to reduce process time cycle as well as produce quality target product profile (QTPP).
Scheme 4: Re-designed Synthetic route for Paliperidone palmitate.

In the above route of synthesis of Paliperidone palmitate, Dichloromethane was selected as a solvent based on low cost to reduce the cost of solvent and higher solubility of Paliperidone palmitate in Dichloromethane. This will help to reduce inorganic salts by water washing to dichloromethane extract during workup. This process is not involve any hazardous chemical like DCC and reaction time is also very less (2 Hrs) as compare to reported reaction time (3Days). Isolation process is also short and very simple. Detail reaction mechanism of proposed route is described in Scheme 5.

Part-A: Formation of mixed anhydride (6)

\[
\begin{align*}
\text{H}_3\text{C} \quad &+ \quad \text{H}_3\text{C} \quad \text{COCl} \quad \text{DCM/TEA} \\
\text{25-30°C, 30 min} &\quad \quad \left[ \begin{array}{c}
\text{H}_3\text{C} \\
\text{H}_3\text{C} \\
\text{H}_3\text{C}
\end{array} \right]
\end{align*}
\]

\[
\begin{align*}
\text{O} \quad &+ \quad \left[ \begin{array}{c}
\text{H}_3\text{C} \\
\text{H}_3\text{C} \\
\text{H}_3\text{C}
\end{array} \right] \\
\text{DCM/TEA/ DMAP/} &\quad \quad \text{25-30°C, 2 h}
\end{align*}
\]
Part-B: Formation of intermediate 10

Part-C: Reaction of intermediate 10 with Alcohol 2

Scheme 5: Reaction mechanism of Paliperidone palmitate.

Quality of raw materials and reagent

To get the quality target product profile (QTPP), quality of raw materials and reagents have to fixed after finalization of route of synthesis based on science and quality risk management. Following are the major reagents for synthesis of Paliperidone palmitate.

Paliperidone

Paliperidone using for the preparation of Paliperidone palmitate is DMF grade and unknown impurities of Paliperidone are controlled in the specification of Paliperidone.
Palmitic acid

Palmitic acid (3) is available commercially, but quality is not as per process requirements. Actually, palmitic acid is isolated by extraction from palm oil as per reported literature. Palmitic acid (C-16) having higher (C-17 & C-18) and lower (C-12, C-14 & C-15) homologues as per literature. It was observed that palmitic acid having higher and lower homologues produce same level of higher and lower esters in Paliperidone palmitate ester due to same chemical properties. It is also very difficult to reduce from drug product during crystallization due to similar properties. Additional purification of drug product reduced the overall yield and increased the cost drastically. Therefore, high quality of palmitic acid is required for preparation of Paliperidone palmitate, which can be achieved by purification of palmitic acid. Experiments were carried out to identify the suitable solvent for purification of palmitic acid. Experimental data has been incorporated in table 1.

Table 1: Screening of solvents for purification of palmitic acid (3).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Tetra-decanoate (C₁₄)</th>
<th>Penta-decanoate (C₁₅)</th>
<th>Hexa-decanoate (C₁₆)</th>
<th>Hepta-decanoate (C₁₇)</th>
<th>Octa-decanoate (C₁₈)</th>
<th>YIELD (% w/w)¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>In put as such</td>
<td>0.43</td>
<td>0.08</td>
<td>98.66</td>
<td>ND</td>
<td>0.83</td>
<td>N/A</td>
</tr>
<tr>
<td>2</td>
<td>Methanol</td>
<td>0.11</td>
<td>ND</td>
<td>99.32</td>
<td>ND</td>
<td>0.58</td>
<td>0.75</td>
</tr>
<tr>
<td>3</td>
<td>Ethanol</td>
<td>0.07</td>
<td>ND</td>
<td>99.35</td>
<td>ND</td>
<td>0.49</td>
<td>0.34</td>
</tr>
<tr>
<td>4</td>
<td>Isopropyl alcohol</td>
<td>0.13</td>
<td>0.05</td>
<td>99.07</td>
<td>ND</td>
<td>0.63</td>
<td>0.91</td>
</tr>
<tr>
<td>5</td>
<td>Ethylacetate</td>
<td>0.08</td>
<td>ND</td>
<td>99.44</td>
<td>ND</td>
<td>0.48</td>
<td>0.57</td>
</tr>
<tr>
<td>6</td>
<td>o-Xylene</td>
<td>0.23</td>
<td>0.05</td>
<td>99.14</td>
<td>ND</td>
<td>0.58</td>
<td>0.49</td>
</tr>
<tr>
<td>7</td>
<td>Cyclohexane</td>
<td>0.14</td>
<td>ND</td>
<td>99.30</td>
<td>ND</td>
<td>0.48</td>
<td>0.24</td>
</tr>
<tr>
<td>8</td>
<td>n-Heptane</td>
<td>0.03</td>
<td>ND</td>
<td>99.88</td>
<td>ND</td>
<td>0.09</td>
<td>0.60</td>
</tr>
</tbody>
</table>

¹isolated yields of Palmitic acid

Based on experimental data (table-1), it was concluded the n-heptane is the best solvent to purify palmitic acid as compared to other solvents.

Pivaloyl chloride

Reaction was performed using purified palmitic acid and observed that two processes related impurities were formed. The structures of these impurities were confirmed by LC-MS data as Paliperidone acetate (8) and Paliperidone pivalate (9). These impurities were prepared as per scheme-6 and scheme-7. They were re-confirmed by HPLC spiking study also.

It was concluded that trace amount of acetyl chloride is present in commercially available pivaloyl chloride. Acetyl chloride can react with Paliperidone and form Paliperidone acetate (8) during preparation of Paliperidone palmitate. Based on experimental data, it was observed that the presence of 0.5% acetyl chloride in pivaloyl chloride leads to the formation of ~ 0.35% compound 8. To avoid the formation of 8, the content of acetyl chloride should control below 0.05% in the pivaloyl chloride by distilling forerun from commercial pivaloyl chloride. With this additional control of acetyl chloride in pivaloyl chloride, compound 8 was observed below 0.05% level in isolated product 1. Experimental data has been incorporated in table 2.

Table 2: Experimental data for correlation of 8.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Pivaloyl chloride</th>
<th>In-put Acetyl chloride in Pivaloyl chloride</th>
<th>Purity of isolated product (1)</th>
<th>Level of impurity (8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Before distillation²</td>
<td>0.50%</td>
<td>98.31%</td>
<td>0.35%</td>
</tr>
<tr>
<td>2</td>
<td>After distillation²</td>
<td>0.05%</td>
<td>98.49%</td>
<td>0.02%</td>
</tr>
</tbody>
</table>

²commercial source.

Process optimization and identification of critical attributes

After establishment of target product profile, route of synthesis, quality of raw material and reagents, it is require to design the manufacturing process, to identify and control critical attributes and process parameters using a quality risk management to produce consistent quality of drug substance over time. Following process parameters were screened to study the risk assessments.

Screening for different dilution of reaction in dichloromethane

Dichloromethane is using as a reaction solvent. It is require to evaluate the effect of dilution of reagents in the reaction time, impurity profile and quality of drug substance. Experimental data has been incorporated in table 3.
Table 3: Experimental data.

<table>
<thead>
<tr>
<th>Entry</th>
<th>DCM (vol)</th>
<th>Reaction time (h)</th>
<th>Paliperidone (2) Purity by HPLC (%)</th>
<th>Paliperidone palmitate (1) Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>15</td>
<td>6</td>
<td>5.79</td>
<td>92.28</td>
</tr>
<tr>
<td>2</td>
<td>10</td>
<td>6</td>
<td>1.46</td>
<td>96.29</td>
</tr>
<tr>
<td>3</td>
<td>7</td>
<td>2</td>
<td>0.06</td>
<td>96.34</td>
</tr>
<tr>
<td>4</td>
<td>5</td>
<td>2</td>
<td>nil</td>
<td>96.76</td>
</tr>
</tbody>
</table>

*a* it is reaction conversion during monitoring; *b* isolated yields of Paliperidone palmitate.

It was concluded that reaction is completed faster in lower concentrations as compared to higher concentrations but product is precipitated out during water washings where 5 volumes dichloromethane is used for the reaction. Based on experimental data (table 3) it was concluded that 7 volumes of dichloromethane (table 3, entry 3) is appropriate for esterification reaction.

Screening for molar ratio of pivaloyl chloride and triethylamine

During the study, it was found that the mole ratio of pivaloyl chloride and triethylamine have significant impact on formation of Paliperidone pivalate (9) impurity. 1.0 mole equivalents of pivaloyl chloride is required for esterification reaction to make mixed anhydride (6, scheme 4). So 1.0 mole equivalents of triethylamine is required for trapping hydrochloric acid obtained during formation of mixed anhydride 6. Mixed anhydride 6 react with paliperidone to form paliperidone palmitate and pivalic acid. Another mole equivalents of triethylamine is required for trapping pivalic acid byproduct obtained during esterification. Theoretically total 2.0 mole equivalents of triethylamine is require for esterification reaction. But reaction is not completed after 24 h also by using stoichiometry mole equivalents of both reagents. Experiments were carried out with different mole ratio of pivaloyl chloride and triethylamine. Experimental data has been incorporated in table 4.

Table 4: Experimental data.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Pivaloyl chloride (m/r)</th>
<th>Triethylamine (m/r)</th>
<th>Reaction time (h)</th>
<th>Paliperidone (2) Purity by HPLC (%)</th>
<th>Paliperidone palmitate (1) Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.0</td>
<td>2.0</td>
<td>20</td>
<td>9.30</td>
<td>89.68</td>
</tr>
<tr>
<td>2</td>
<td>1.1</td>
<td>2.0</td>
<td>24</td>
<td>4.09</td>
<td>94.93</td>
</tr>
<tr>
<td>3</td>
<td>1.2</td>
<td>2.0</td>
<td>6</td>
<td>5.06</td>
<td>93.69</td>
</tr>
<tr>
<td>4</td>
<td>1.3</td>
<td>2.5</td>
<td>6</td>
<td>5.79</td>
<td>91.00</td>
</tr>
<tr>
<td>5</td>
<td>1.5</td>
<td>2.5</td>
<td>6</td>
<td>0.57</td>
<td>97.62</td>
</tr>
<tr>
<td>6</td>
<td>2.5</td>
<td>3.5</td>
<td>6</td>
<td>0.04</td>
<td>92.03</td>
</tr>
</tbody>
</table>

*a* it is reaction conversion during monitoring; *b* isolated yields of Paliperidone palmitate.

From the above experimental data, it was concluded that 1.5 mole equivalents of pivaloyl chloride and 2.5 mole equivalents of triethylamine are optimal to result in Paliperidone palmitate (1) with minimum formation of Paliperidone pivalate (9). Further increasing the mole ratio beyond this limit proved futile as there was more formation of compound 9 levels and no significant reduction in the reaction time (table 4).

Screening for catalyst N,N-dimethylaminopyridine (DMAP)

N,N-dimethylaminopyridine (DMAP) is required to form an amide intermediate (10; Scheme 5, Part-B) as per Yamaguchi reaction. After optimizing pivaloyl chloride and triethylamine quantity, the magnitude of catalyst (DMAP) was studied in this esterification reaction. Experiments were carried out with different ratio of N,N-dimethylaminopyridine. Experimental data has been incorporated in table 5.

Table 5: Experimental data.

<table>
<thead>
<tr>
<th>Entry</th>
<th>DMAP (% w/w, w.r.t. paliperidone)</th>
<th>Reaction time (h)</th>
<th>Paliperidone (2) Purity by HPLC (%)</th>
<th>Paliperidone palmitate (1) Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0</td>
<td>24</td>
<td>98.53</td>
<td>0.87</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>6</td>
<td>11.04</td>
<td>88.27</td>
</tr>
<tr>
<td>3</td>
<td>5</td>
<td>6</td>
<td>7.70</td>
<td>91.50</td>
</tr>
<tr>
<td>4</td>
<td>7</td>
<td>6</td>
<td>0.57</td>
<td>97.62</td>
</tr>
<tr>
<td>5</td>
<td>10</td>
<td>6</td>
<td>0.61</td>
<td>98.49</td>
</tr>
</tbody>
</table>

*a* it is reaction conversion during monitoring; *b* isolated yields of Paliperidone palmitate.

From the above experimental data, it was concluded that 7% catalyst is required for esterification reaction to get maximum yield and desired quality of drug substance.
Isolation method of drug substance was simplified by washing reaction mass with water and evaporation of organic layer to get solid residue. Paliperidone palmitate crude was isolated by dissolving solid residue in isopropyl alcohol at higher temperature and precipitating by cooling followed by purification from isopropyl alcohol.

Three confirmation batches were carried out in the plant after optimizing the reaction. An improved process producing Paliperidone palmitate (1) with an overall yield of >87.0% (including purification) and >99.9% purity and meeting other quality parameters. Analytical results and yield have been incorporated in table 6.

| Table 6: Analytical results and yield of Paliperidone palmitate (1). |
|----------------------------------|-------------------|-----------------|-------------|-----------------|-----------------|
| Entry | Purity by HPLC (%) | RS by GC (ppm) | Yield (%) b | DSC (°C) | Minor Peak | Major Peak |
|-------|-------------------|----------------|-------------|-----------------|-----------------|
| 1     | 99.92             | Nil  d          | 22          | 87.0            | 108.35           | 116.63         |
| 2     | 99.93             | Nil  d          | 18          | 87.1            | 109.12           | 117.17         |
| 3     | 99.92             | Nil  d          | 14          | 87.1            | 108.15           | 116.61         |

*residual solvents; boverall yield; dnot detected.

Scheme 6: Synthetic route for Paliperidone acetate (8).

Scheme 7: Synthetic route for Paliperidone pivalate (9).

CONCLUSION
An improved process for the preparation of Paliperidone palmitate, an anti-psychotic drug substance, with an overall yield of >87.0% (including purification) and >99.9% purity. Process optimization was done based on design of experiments (DOE) concept. Isolated product meets all regulatory requirements and quality target product profile (QTPP). The process described in this article has certain advantages over the reported processes and also addressed formation and control of all the possible impurities.

Authors’ Statements
Competing Interests
The authors declare no conflict of interest.

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