PREFORMULATION STUDIES OF FLUVASTATIN SODIUM WITH POLYVINYL PYRROLLIDONE K-30 AND POLYETHYLENE GLYCOL 6000

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Abstract

The purpose of this pre-formulation work was to accomplish physicochemical characterization and compatibility analysis of fluvastatin sodium (FSS) with polyvinyl pyrrolidone K-30 (PVP K30) and polyethylene glycol 6000 (PEG 6000). Melting point, log P and hygroscopicity estimation of FSS was executed by capillary; shake flask and European Pharmacopeia method, respectively. Residue on ignition (% ROI) was determined according to ICH Q4B R1. Increase in weight of FSS was <0.2% which signified its non-hygroscopic nature. Melting point, log P, % loss on drying and % ROI of FSS was found 195 ± 5 °C, 3.9, 0.34 % (≤ 0.5%) and 0.03 % (≤ 0.1%), respectively. Abundant spiky crystalline peaks in x-ray diffraction pattern of FSS confirmed extremely crystalline nature of drug. FSS was found freely soluble in acetone, soluble in water, ethanol, methanol and phosphate buffer (pH 7.4) while very slightly soluble in chloroform and dichloromethane. Differential scanning calorimetry demonstrated compatibility of FSS with PEG 6000 and PVP K30.

Keywords: Pre-formulation, Fluvastatin sodium (FSS), Polyvinyl pyrrolidone K-30, Polyethylene glycol 6000, Residue on ignition and loss on drying, Hygroscopicity

Introduction

Fluvastatin sodium (FSS) is a cholesterol-reducing agent which acts by inhibition of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase (Ozkan et al., 2002; Larocque et al., 2010). Chemically, FSS is monosodium salt of (R,S-(E) (±)-7-(3-(4-fluorophenyl)-1-(1-methylethyl)-1H-indol-2-yl)-3,5-dihydroxy-6-heptenoic acid (Fig. 1). It is white crystalline powder with molecular formula and weight C_{25}H_{32}FNaO_{11} and 433.455 g/mol, respectively. FSS is subjected to extensive first pass metabolism in liver and bound to plasma proteins (~99%). It has plasma half-life of approximately 3 h with 40-60% bioavailability and an elimination half-life of about 1.2 hours. It is basic salt of acidic drug with pKa 4.56. It is drug of choice for treatment of hypercholesterolemia, a disease related to an increased risk of heart diseases (Tank et al., 2013; Plosker et al., 1996; Karavas et al., 2014).

Fig. 1: Chemical Structure of Fluvastatin sodium.

Pre-formulation is primary stage for stable, rationale, safe and effective product development of an active pharmaceutical ingredient (API). The purpose was examination of physicochemical properties of FSS and drug-excipients compatibility study of FSS with polyvinyl pyrrolidone K-30 (PVP K30) and polyethylene glycol 6000 (PEG 6000) (Alves-Silva et al., 2014; Sanghvi et al., 2009; Penumetcha et al., 2016; Krupa et al., 2014; Censi et al., 2014).

Materials and Methods

Materials

Fluvastatin sodium (CAS NO- 93957-55-2) was purchased from All Well Pharmaceuticals Company, Chandigarh. Polyvinyl pyrrolidone K-30 and polyethylene glycol 6000 were procured from Loba Chemicals Private Limited, Mumbai, India.

Determination of Physicochemical Characteristics of FSS

Melting Point Determination Using Capillary Method

A sufficient quantity of completely dried FSS was introduced into a capillary glass tube which formed a compact column of 4-6 mm height. Further, capillary tube was inserted into melting point apparatus (Perfit, India) along with calibrated thermometer (0-360°C) for determination of melting point. Temperature, at which drug substance coalesces and gets completely melted, was recorded as melting point of drug.

Loss on Drying (% LOD)

About 1-2 gm of FSS was transferred to dried weighing bottle. Drug was distributed to depth of 10 mm through gentle side wise shaking. Glass bottle was positioned in drying chamber; stopper was removed and positioned adjacent followed by drying at 105° for 3 hrs. Subsequently, glass bottle was cooled in desiccator and weighed again. % LOD was calculated using following formula:

\[
\% \text{Loss on drying (}\%\text{LOD}) = \frac{W_2 - W_1}{W_2} \times 100
\]

Where, \( W_1 \) is weight of empty weighing bottle; \( W_2 \) is weight of bottle with FSS before drying and \( W_1 \) is weight of bottle with FSS after drying (Chablani et al., 2011; Mohamed et al., 2012).

Residue on Ignition as Per ICH Q4B (R1)

Accurately weighed 1-2.5 gm of FSS was placed in crucible, and moistened with small amount of sulfuric acid. Subsequently, sample was ignited at low temperature until ignition and 1 ml of sulfuric acid was added followed by
slow heating till fruition of white fumes disappears. The crucible was ignited at 450-550 °C for 3 hrs into muffle furnace and allowed to cool in desiccators and weighed accurately (ICH Q4B R1). % ROI was determined using following formula:

\[ \% \text{Residue on ignition} = \frac{W_3 - W_1}{W_2 - W_1} \times 100 \]  

Where, \( W_1 \) - Weight of empty crucible; \( W_2 \) - Weight of crucible and residue after heating and \( W_3 \) - Sample weight.

### Hygroscopicity Assessment by European Pharmacopeia Method

Hygroscopicity is capacity of material to retain water molecules from contiguous atmosphere. Moisture sorption has been estimated gravimetrically by introducing pre-weighed material in closed desiccators filled with saturated solution of ammonium chloride. FSS (100-300 mg) was transferred to separating funnel containing 1:1 n-octanol and water which was placed on mechanical shaker for 4 hrs. Afterwards, funnel was allowed to stand for effective partitioning of FSS (Baka et al., 2008; Bharate et al., 2016). Samples were removed and investigated using UV spectroscopy. Partition coefficient of FSS was estimated by following equation:

\[ \text{Partition coefficient (Pr)} = \frac{\text{amount of FSS in n-octanol}}{\text{amount of FSS in water}} \]  

### Solubility Study by Equilibrium Solubility Method

The solubility of FSS was determined in HCl buffer (pH 2) and phosphate buffer (pH 5.8, 6.8 and 7.4). Accurately measured quantity of each solvent (10 ml) was placed in screw-capped glass vials followed by addition of excess drug. The glass vials were sealed and placed in orbital shaker (Remi, India) at 37 °C for 24 hrs. Afterwards, withdrawn aliquots were centrifuged, filtered, diluted and absorbance was recorded using UV-spectrophotometer for FSS quantification (Table 2) (Shete, et al., 2013; Dezani et al., 2013).

**Table 2: Values for Estimating Drug Solubility Based Upon USP Definition.**

<table>
<thead>
<tr>
<th>Descriptive term</th>
<th>Appropriate volume of solvent in milliliters per gram of solute</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very soluble</td>
<td>&lt; 1</td>
</tr>
<tr>
<td>Freely soluble</td>
<td>1-10</td>
</tr>
<tr>
<td>Soluble</td>
<td>10-30</td>
</tr>
<tr>
<td>Slightly soluble</td>
<td>30-100</td>
</tr>
<tr>
<td>Sparingly soluble</td>
<td>100-1000</td>
</tr>
<tr>
<td>Very slightly soluble</td>
<td>1000-10000</td>
</tr>
<tr>
<td>Practically insoluble</td>
<td>&gt;100000</td>
</tr>
</tbody>
</table>

### Drug-Polymer Compatibility investigation by Differential Scanning Calorimetric (DSC)

The thermal analysis of FSS, PVP K30, PEG 6000 and physical mixture (FSS: PVP K30: PEG 6000 in 1:1:1) was carried out on DSC 4000 Perkin Almer, Germany using Pyris Software. 5 mg samples were placed in an aluminum pan and heated over temperature range of 25-350 °C at constant rate of 20°C/min along with nitrogen purging at 100 mL/min (Choudhary et al., 2012; Dong et al., 2018).

### Results and Discussion

#### Physicochemical Characteristics of FSS

**Melting Point, % LOD and Residue on Ignition**

Melting point of FSS was found 195 ± 5 °C which was in compliance with theoretical value. % LOD of FSS was found 0.34 % of its weight after being dried at 105°C for three hours which was in conformity with the specification (% LOD ≤ 0.5%). The % residue on ignition of FSS was found 0.03 % which was in agreement with monograph limit (≤ 0.1%).

**Hygroscopicity and Partition Coefficient**

Percentage increase in weight of FSS estimated through European pharmacopeia method was <0.2% which specified its non-hygroscopic nature. Log P of FSS as estimated by shake flask method was found 3.9.

### Solid Form Identification Using X-Ray Diffraction Study

Solid form identification was executed employing powder x-ray diffraction (PXRD) pattern of FSS acquired on x-ray diffractometer (Xpert-Pro diffractometer) employing 1.54 A° CuKα and 1.39 A° CuKβ radiations. Data was assembled over an angular range from 5° to 50° at 2θ scale in continuous scan mode and rate 2°/min (Vippagunta et al., 2002).

#### Partition Coefficient (n-Octanol/Water) by Shake Flask Method

100 mg of FSS was transferred to separating funnel containing 1:1 n-octanol and water which was placed on mechanical shaker for 4 hrs. Afterwards, funnel was allowed to stand for effective partitioning of FSS (Baka et al., 2008; Bharate et al., 2016). Samples were removed and investigated using UV spectroscopy. Partition coefficient of FSS was estimated by following equation:

\[ \text{Partition coefficient} = \frac{\text{amount of FSS in n-octanol}}{\text{amount of FSS in water}} \]
Fig. 2: X-ray Diffraction Pattern of FSS.

Table 3: XRD Peaks of FSS.

<table>
<thead>
<tr>
<th>Position at degree 2θ</th>
<th>d-spacing (Å)</th>
<th>Relative intensity (%)</th>
<th>Area (degree 2θ)</th>
</tr>
</thead>
<tbody>
<tr>
<td>13.6980</td>
<td>6.45937</td>
<td>24.68</td>
<td>134.56</td>
</tr>
<tr>
<td>14.6534</td>
<td>6.04030</td>
<td>41.42</td>
<td>325.49</td>
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<tr>
<td>16.8530</td>
<td>5.25656</td>
<td>25.74</td>
<td>452.09</td>
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<tr>
<td>17.3050</td>
<td>5.12026</td>
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<td>18.7760</td>
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<td>19.8656</td>
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<td>20.4459</td>
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<tr>
<td>21.1636</td>
<td>4.19464</td>
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<td>23.4214</td>
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<td>28.1602</td>
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<td>33.9594</td>
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<td>202.09</td>
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<td>43.9516</td>
<td>2.05844</td>
<td>21.33</td>
<td>333.26</td>
</tr>
</tbody>
</table>

Solubility Study

Solubility of FSS estimated by equilibrium solubility method has been represented in Fig. 3. It was found that FSS was slightly soluble in dimethyl sulfoxide (DMSO) and very slightly soluble in ethanol, methanol and phosphate buffer, pH 5.8, 6.8 and 7.4. FSS was found practically insoluble in water.

Drug-Excipient Compatibility Study

Fig. 4 embodied the DSC thermograms of (a) FSS, (b) PVP K 30, (c) PEG 6000, and (d) physical mixture of FSS, PVP K 30 and PEG 6000. DSC thermograms of FSS revealed distinctive endothermic peak at 165.83 °C analogous to its melting point ($T_m$) which indicated significantly crystalline characteristics of drug (Figure 3a). No characteristic peak was observed in DSC thermogram of PVP K 30 indicating its amorphous nature (Figure 3b). PEG 6000 showed typical peak at 65.44°C (Figure 3c). The distinctive endothermic peaks of FSS and PEG 6000 were remarkably observed in physical mixtures which illustrated drug-polymer compatibility (Figure 3d) (Choudhary et al., 2012; Dong et al., 2018).
Conclusion

This study demonstrated that melting point, % LOD, residue on ignition and log P of FSS were 195 ± 5 °C, 0.34 % (≤ 0.5%), 0.03 % (≤ 0.1%) and 3.9 respectively. Research specified its non-hygroscopic and highly crystalline nature. FSS was found practically insoluble in water. Differential scanning calorimetry concluded compatibility of FSS with PEG 6000 and PVP K30.

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Conflict of interests:

Conflict of interest declared none.

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