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PREFORMULATION STUDIES OF FLUVASTATIN SODIUM WITH POLYVINYL PYROLLIDONE 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 pyrollidone 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 pyrollidone K-30, Polyethylene glycol 6000, Residue on ignition and loss on drying, Hygroscopicity

Introduction

Fluvastatin sodium (FSS) is 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 $C_{24}H_{25}FNNaO_4$ 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).

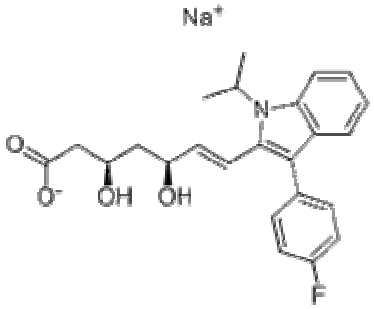

Fig. 1: Chemical Structure of Fluvastatin sodium.

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 pyrollidone K-30 (PVP K30) and polyethylene glycol 6000 (PEG 6000) (Alves-Silvaa *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 pyrollidone 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 sidewise 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:

$$\%\,\text{Loss on drying}\,(\%\text{LOD}) = \frac{W_2 - W_1}{W_2 - W_1} \times 100 \qquad (1)$$

Where, W_1 is weight of empty weighing bottle; W_2 is weight of bottle with FSS before drying and W_3 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:

$$\%\,\text{Residue on ignition} = \frac{W_2 - W_1}{W_3} \times 100 \qquad (2)$$

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 into exactly weighed dry plastic Petri dish (w_1), reweighed (w_2) and transferred into desiccators kept at 25°C ± 2°C temperature and 80 ± 2% RH for 24 hrs. Afterward, Petri dish was removed outside and reweighed (w_3). The % increase in weight ($W_{Ph.Eur}$) of FSS was calculated by following equation:

$$W_{Ph.Eur} = \frac{W_3 - W_2}{W_2 - W_1} \times 100 \qquad (3)$$

Hygroscopicity of FSS was estimated as declared in European Pharmacopoeia (Table 1) (Murikipudi *et al*., 2013; Mwesigwa *et al*., 2005).

Table 1: Material classification as per European Pharmacopeia Method.

Type of material	Standard weight gain (% w/w)
Non-hygroscopic	0-0.012
Slightly hygroscopic	0.2-2
Moderately hygroscopic	2-15
Very hygroscopic	More than 15

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:

$$\text{Partition coefficient}(P) = \frac{\text{amount of FSS in n-octanol}}{\text{amount of FSS in water}} \qquad (4)$$

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 hours. 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.

Descriptive term	Appropriate volume of solvent in milliliters per gram of solute
Very soluble	< 1
Freely soluble	1-10
Soluble	10-30
Sparingly soluble	30-100
Slightly soluble	100-1000
Very slightly soluble	1000-10000
Practically insoluble	>100000

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

X-ray diffraction pattern of NPH exhibited sharp crystalline peaks at 2θ =13.6°, 14.6°, 16.8°, 17.3°, 18.7°, 19.8°, 20.4°, 21.1°, 21.3°, 21.7°, 22.6°, 23.4°,25.1°, 28.1°, 29.4°, 33.9° and 43.9° which showed abundantly crystalline of FSS (Figure 2, Table 3).

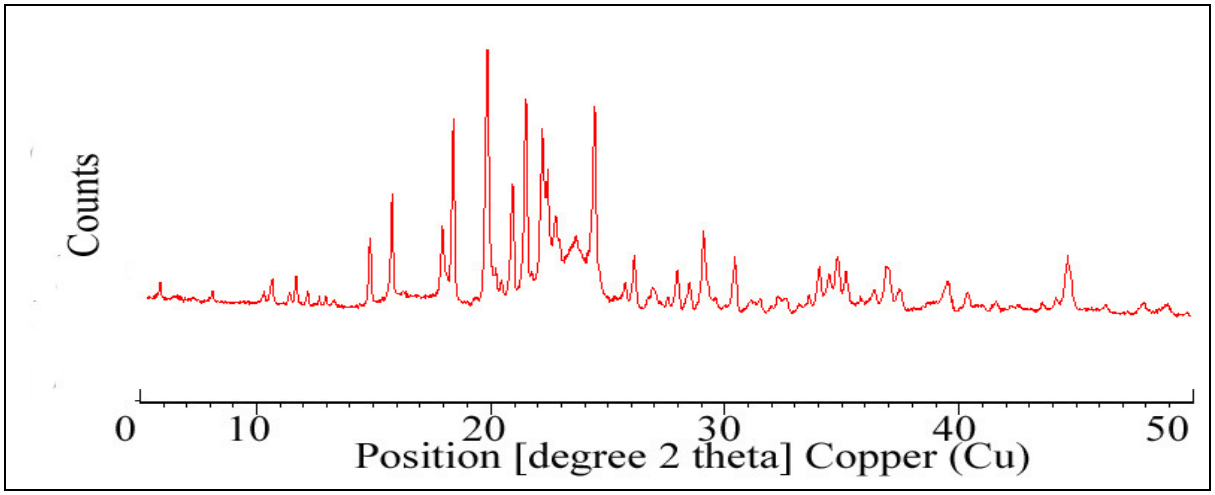

Fig. 2 : X-ray Diffraction Pattern of FSS.

Table 3: XRD Peaks of FSS.

Position at degree 2θ	d-spacing (A°)	Relative intensity (%)	Area (degree 2θ)
13.6980	6.45937	24.68	134.56
14.6534	6.04030	41.42	325.49
16.8530	5.25656	25.74	452.09
17.3050	5.12026	65.76	395.56
18.7760	4.72231	100.00	869.46
19.8656	4.46569	43.56	347.08
20.4459	4.34023	79.36	651.73
21.1636	4.19464	53.49	571.21
21.3910	4.15056	31.80	376.91
21.7672	4.07967	21.93	712.21
22.6191	3.92790	23.90	1186.60
23.4214	3.79513	71.07	693.03
25.1470	3.53849	17.36	112.06
28.1602	3.16633	25.82	242.80
29.4973	3.02578	18.66	131.62
33.9594	2.63772	18.82	202.09
43.9516	2.05844	21.33	333.26

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.

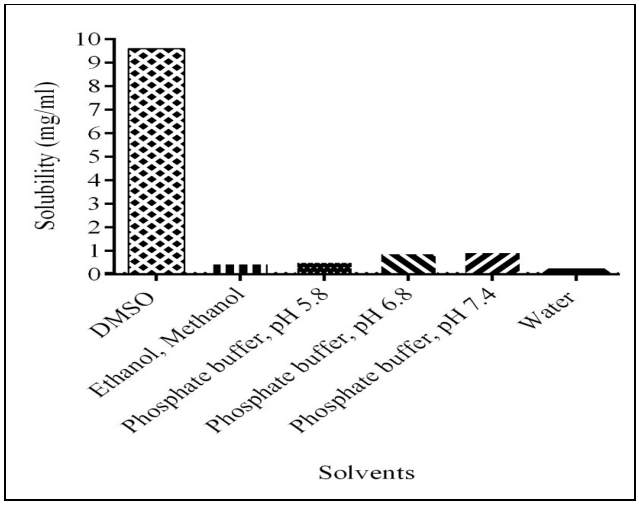

Fig. 3: Solubility of FSS in different solvents.

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).

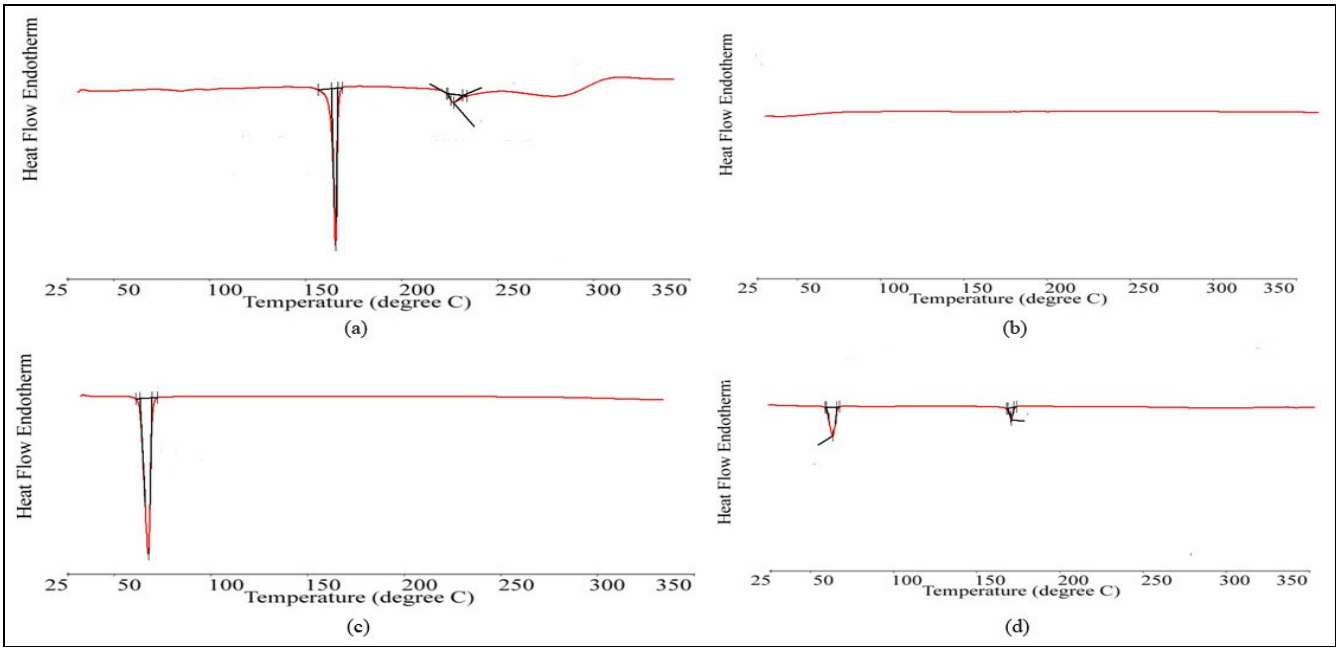

Fig. 4: DSC Curves of (a) FSS, (b) PEG 6000, (c) PVP K30 and (d) Physical Mixture of FSS, PEG 6000, PVP K30.

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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