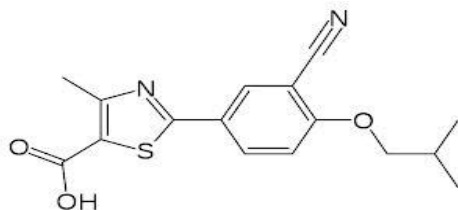


**Formulation and *In Vitro* Evaluation of solid dispersions of BCS Class II Drug Febuxostat by employing L-HPC**P.Tripura Sundari<sup>1\*</sup> and Krutika Lad<sup>2</sup><sup>1</sup>Department of Pharmaceutics, RBVRR women's college of Pharmacy, Osmania University, Hyderabad, India, 500027<sup>2</sup>Department Of Pharmaceutics, Shobhaben Pratapbhai Patel School of Pharmacy and Technology Management, NMIMS, Mumbai, India**\*Corresponding author e-mail:** [tripurakrishna@gmail.com](mailto:tripurakrishna@gmail.com)*Received on: 07-04-2016; Revised on: 14-06-2016; Accepted on: 28-06-2016***ABSTRACT**

Febuxostat (FBX) is a non purine selective inhibitor of xanthine oxidase/xanthine reductase. Because of low solubility the bioavailability of the drug is hampered, food also interferes with the absorption of drug and decreases the C<sub>max</sub> by 38-49%. In the category of poorly soluble drugs the change in surface area of the drug will show considerable changes in the solubility and dissolution of the drug. In the present study, the attempts were made to improve the bioavailability of FBX by solid dispersions technique by employing L-HPC as carrier molecules. Different ratios on weight basis were prepared viz 1:1, 1:2, 1:3, 2:1. These preparations were characterized in liquid state by phase solubility studies and in solid state by Differential scanning calorimetry (DSC), Fourier transform infrared spectroscopy (FTIR), Powdered X ray diffraction studies (PXRD) and Scanning electron microscopy (SEM). The aqueous solubility of FBX is favored by the presence of carrier polymer. Solid state characterization indicated that FBX was present as fine amorphous form in the carrier polymeric molecules. In contrast to the solution rate of pure FBX the dissolution of drug in carrier considerably improved the dissolution rate, this can be attributed to the increased wettability and dispersibility as well as decreased crystallinity and increased amorphous fraction of drug.

**Key words:** Febuxostat, solid dispersions, L-HPC, Phase solubility, drug release studies**INTRODUCTION**

Febuxostat is a non purine selective inhibitor of xanthine oxidase/xanthine reductase. The chemical name of febuxostat (FEB) is 2-[3-cyano-4-(2-methylpropoxy) phenyl]-4-methylthiazole-5-carboxylic acid.

**Fig.1: Molecular structure of Febuxostat**

It is indicated for the long-term management of hyperuricemia in patients with gout. It belongs to BCS class II with low solubility and high permeability. Because of low solubility the bioavailability of the drug is hampered and it also undergoes enzymatic degradation in intestine as well as in liver. Food interferes with the absorption of drug and decreases the C<sub>max</sub> by 38-49%. Thus, it has undesirable dissolution profile and poor bioavailability following oral administration. Poorly water soluble drugs present significant challenges during dosage form designing due to their inadequate solubilization in digestive fluids

Most of the newly discovered drugs receive little or

no aqueous solubility as a challenge for the successful formulation development and commercialization of new drugs in the pharmaceutical industry. The bioavailability of a drug is a function of dissolution rate of the drug which is controlled by the surface area of the drug. In the category of poorly soluble drugs the change in surface area of the drug will show considerable changes in the solubility and dissolution of the drug. Micronization, nanosuspensions, polymorphs, complexation, solid dispersions, prodrugs and salt formation can be employed to increase dissolution rate.

Among the various techniques of improving the surface area thus enhancing the solubility of drug substances, solid dispersion technique stands in the first row.

Chiou and Riegelman define solid dispersions as “the dispersion of one or more active ingredients in an inert carrier matrix at solid state”. Solid dispersions can be prepared by different methods using different water soluble carriers. These solid systems exhibit enhanced solubility and dissolution rate compared to the plain drug that may be attributed to the molecular/colloidal dispersion of drug in mixture, absence of aggregation of drug particles, particle size reduction, improved wettability and dispersibility and polymeric transformation of drug crystals. Enhancement of solubility may contribute directly to the improved bioavailability of poorly water soluble drugs.

The objectives of the current research investigation trials were to improve the dissolution rate of febuxostat by employing the solid dispersion technique. An attempt was made to improve the dissolution properties of febuxostat by preparing free flowing solid dispersions using L-HPC as carrier system. The prepared solid dispersions were characterized by fourier transform infra red spectroscopy (FTIR), differential scanning calorimetry (DSC), X-ray diffraction study (XRD).

#### **MATERIALS AND METHODS:**

The solid dispersions preparation required the following chemicals, Febuxostat (denoted as FBX) was generously donated by Sun Pharma Mumbai, L-HPC is procured from Loba chemicals, and all other chemicals used in the study are of pharmacopial grade.

**Phase solubility studies:** The phase solubility studies were conducted by using a simple technique, which involves the addition of excess amount of febuxostat (FBX) i.e. 100 mg in 25 ml of water containing different weights of Solubilizing agent i.e. L-HPC. The solutions were sonicated for 1 hr at

room temperature and maintained at 25<sup>0</sup>C for 48 hrs on an orbital shaker Orchid, Mumbai. The dispersions were filtered through a 0.22 μm nylon membrane filter. The filtrates were suitably diluted and analyzed spectrophotometrically (UV/Vis spectrophotometer, Perkin elmer), for the dissolved drug at 318 nm. All trials were performed in triplicate.

**Preparation of solid dispersions:** The solid dispersions of FBX employing L-HPC were prepared by using a simple method of solvent evaporation technique. The prepared solid dispersions were compared with pure FBX and the physical mixtures of drug and polymer.

**Solvent evaporation method:** Solid dispersions of the drug FBX in L-HPC in different weight ratios (1:1, 2:1, 1:2, 3:1 of L-HPC denoted as FBHPC 1:1, 2:1, 1:2, 3:1) were prepared by employing solvent evaporation method. The required amount of polymer was weighed and mixed with sufficient quantity of the solvent methanol to obtain a clear solution. In this solution the weighed quantity of drug was dispersed and the solution was triturated continuously till the entire solvent was evaporated. Then the mixture was further air dried for 24 hr to completely remove the solvent and pulverized and sifted through sieve no 60 to obtain the solid dispersions. Thus prepared solid dispersions were stored in a dessicator until further evaluation.

#### **Characterization of solid dispersions:**

##### **FTIR spectroscopy:**

A Perkin-Elmer Spectrum Rx 1 FTIR spectrometer was used for infrared analysis. Samples were prepared by KBr disc method (2 mg sample in 100 mg KBr) and examined in the transmission mode. A resolution of 4 cm<sup>-1</sup> was used and 64 scans were co-added for each spectrum over a frequency range of 4000–450 cm<sup>-1</sup>. The software used for the data analysis was Perkin-Elmer spectra MAX.

##### **DSC Analysis:**

Thermal analyses of prepared solid dispersions were performed in a Mettler Toledo, Switzerland differential scanning calorimeter with a thermal analysis controller. Samples were accurately weighed (5–8 mg) into aluminum pans and thermograms obtained at a heating rate of 10<sup>0</sup>C/min over a temperature range of 25–210<sup>0</sup>C.

##### **X-ray powder diffraction:**

Diffraction patterns were obtained on a Bruker AXS D8 DISCOVER INSTRUMENT (USA) modified for step-scan operations. Ni-filtered CuKα radiation was

produced with a Philips PW 1130/00 X-ray generator. Powder samples of solid dispersions were top loaded in a Philips PW 1066 (15/20 mm) flat sample holder. The patterns were collected with a voltage of 45 kV and a current of 32 mA in the angular range of 48B/2uB/758 in a step scan mode (step width 0.028, counting time 2 s/step) using the Philips PW 1710 microprocessor based control and measuring system.

**Scanning electron microscopy (SEM):** The SEM analysis was carried out using a scanning electron microscope. Prior to examination, samples were mounted on an aluminium stub using a double sided adhesive tape and then making it electrically conductive by coating with a thin layer of gold (approximately 20nm) in vacuum. The scanning electron microscope operated at an acceleration voltage of 15kV.

**Assay of solid dispersions:** The content of FBX in the prepared solid dispersions was determined using UV-VIS spectrophotometer. Solid dispersions equivalent to 10 mg drug were dissolved in methanol. 1ml of the stock solution was diluted to 10 ml with methanol which was further diluted with pH 6.0 buffer to give a final concentration of 10 µg/ml (10 ppm) solution. Percent drug content was calculated spectrophotometrically from the absorbance obtained at 318 nm.

**In vitro dissolution studies:** In vitro dissolution studies were carried out for pure drug, physical mixture and all the different solid dispersions prepared in USP type II dissolution test apparatus (Campbell Electronics, India) at 75 RPM in 900 ml of pH 6.0 Phosphate buffer. Forty milligrams of pure drug and an equivalent amount of solid dispersions and physical mixture were used for the dissolution studies. 10 mL of the aliquot was withdrawn at predetermined intervals and filtered using 0.45 mm nylon membrane (Pall Life Sciences, India). The required dilutions were made with pH 6.0 Phosphate buffer and the solution was analyzed for the drug content UV spectrophotometrically at 318 nm against pH 6.0 Phosphate buffer. An equal volume of the dissolution medium was replaced in the vessel after each withdrawal to maintain the sink condition. Three determinations were carried out for each formulation. From this, cumulative % of drug dissolved was calculated and plotted against function of time to study the pattern of drug release. Each test was performed in triplicate (n= 3), and calculated mean values of cumulative drug release were used while plotting the release curves.

**Tablet dosage form preparation:** Based on the results obtained from the drug release studies, the solid dispersions with better release profile were selected and prepared in the form of tablet dosage forms employing wet granulation technique.

**Stability studies:** Stability study was performed according to ICH guidelines for three months. Dissolution studies were carried out at the end of three months to check inhibition of reversal of FBX to crystalline form.

## RESULTS AND DISCUSSION

Fig. 2 shows the solubility phase diagram representing the effect of increasing the concentrations of L- HPC on the apparent solubility of FBX in water at 25°C. The aqueous solutions of L- HPC increased the solubility of FBX more when compared to pure drug. The polymers were selected for formulation of solid dispersions because of its higher molecular weight and better solubility of FBX in their aqueous solution.

**FTIR studies:** FTIR spectra of pure FBX, L- HPC and solid dispersions of FBX with L- HPC are shown in Fig 3 to 6. The spectra of Pure FBX presented characteristic peaks at 3450.40, 3533.40 cm<sup>-1</sup>(O,H stretching of free hydroxyl group), 2957.68 cm<sup>-1</sup> (C,H stretching of alkanes), 1670. cm<sup>-1</sup> (C,O stretching of carboxylic acid) 1592, 1580, 1455 cm<sup>-1</sup> (C,C stretching of aromatic ring), 1498.71, 1457.44, 1413.90 cm<sup>-1</sup> (C-H stretching of alkanes) respectively. The spectrum of L- HPC showed, among other important bands at 3416.22 cm<sup>-1</sup> (O,H stretching of free hydroxyl group) 2332.62 (aliphatic C-H stretching), 1622.05 cm<sup>-1</sup>(C=O of carbonyl group) 1096.60 cm<sup>-1</sup> (C-O stretching).

The characteristic peaks of FBX at 3450.40, 3533.40 cm<sup>-1</sup>(O, H stretching of acid), 2957.68 cm<sup>-1</sup> (C,H stretching of alkanes), 1592,1580,1455 cm<sup>-1</sup> (C,C stretching of aromatic ring) are disappeared in spectra of solid dispersions with L-HPC 1:2 ratio which indicates the trapping of FBX inside the matrix of L- HPC. In case of other ratios, 3450.40,3533.40 cm<sup>-1</sup> (O,H stretching of free hydroxyl group), 2957.68 cm<sup>-1</sup> (C,H stretching of alkanes), 1670.23 cm<sup>-1</sup> (C,O stretching of carboxylic group)1592, 1580,1455 cm<sup>-1</sup> (C,C stretching of aromatic ring), 1498.71, 1457.44, 1413.90 cm<sup>-1</sup> (C, H stretching of alkanes) are retained which shows that the trapping of the drug with the polymer matrix is incomplete.

**PXRD Studies:** The pure FBX, polymers PVP k30 and HPMC E15 and prepared solid dispersions of

carriers, physical mixtures were studied by XRD as shown in figure 7. PVP being amorphous did not show any sharp peaks. The powder diffraction patterns of pure FBX showed characteristic high-intensity diffraction peaks at  $2\theta$  values of 4.788, 6.857, 8.363, 11.79, 15.98, 16.78, 17.58, 20.001, 25.16 and 25.77 where as the Spectroscopy of L-HPC do not show any characteristic diffraction peaks. The high intensity diffraction peaks are very prominently preserved in case of physical mixtures, where as these characteristic peak intensities were drastically reduced in 1:2 ratio of drug and polymers owing to the complete encapsulation and amorphisation of drug. The findings of XRD are in line with that of DSC findings.

**DSC Analysis:** The DSC thermograms for pure FBX, Polymer and solid dispersions were shown in fig 8. The DSC thermogram of pure FBX shows the sharp endothermic peak at around 200-220°C, confirming the crystallinity of the drug. During scanning of L-HPC, a sharp endotherm with a peak of 208.84°C was observed. The DSC thermogram of the solid dispersion FBHPC in 1:2 ratio showed the presence of broaden peaks with no characteristic peaks of drug.

**Scanning Electron Microscopy (SEM):** SEM photomicrographs obtained for pure FBX, L-HPC and their physical mixtures and solid dispersions are shown in fig 9 in selected magnifications. From the photomicrograph of pure drug FBX, it is clear that the drug is present as needle shaped crystals. In the solid dispersion, drug particles were entrapped in the carrier matrix and the crystalline appearance of the drug was reduced and became more amorphous confirming the FTIR, XRD and DSC data analyses.

***In vitro* dissolution studies:**

Dissolution of pure FBX and all other prepared systems (solid dispersions and physical mixtures) were carried out in phosphate buffer of pH 6.0.  $DP_{45min}$ (Percent drug dissolved within 45 min) values were reported in table 1. From these data it is evident that the onset of dissolution of pure FBX is very low (8.29%). Dissolution profiles of pure FBX, its Physical mixtures and solid dispersions with L-HPC over a period of 45 min were shown in fig 10

respectively. It can be clearly observed that the dissolution rate of pure FBX is 41.8% in 45 min. solid dispersions FBHPC significantly enhanced the dissolution rate of FBX (100% release in 30 min) as compared to physical mixtures as well as pure FBX. Highest improvement was observed in solid dispersions of FBHPC 1:2 ratio.

**Drug content:** The percent drug content values of various solid dispersions prepared are given in Tables 2. There was no loss of drug during the preparation and all the solid dispersions contained the drug equal to the theoretical drug content based on the proportion of drug and carrier taken. Low s.d. and C.V. (<2.0) in the percent drug content values indicated that the drug content was uniform in a batch of solid dispersion in all the cases.

**Stability studies:** The solid dispersion FBHPC 1:2 was kept for stability studies and the preparation was evaluated for drug release studies after stability. As shown in fig 11 in the stability studies the formulation did not show any significant changes in the drug release profile which were also as per the DSC and XRD studies which prove that the drug had retained its amorphous form and did not convert into crystalline form upon storage

## CONCLUSION

Solid dispersions of FBX with L-HPC gave higher intrinsic dissolution rates. In contrast to physical mixture, FBX in the solid dispersions was present in amorphous form and was found to interact with L-HPC suggesting greater stability for the drug. The most important findings were that FBHPC 1:2 showed the best dissolution rate. The XRD, DSC, SEM studies of drug, carrier polymers and solid dispersions prepared indicated the entrapment of drug in carrier matrix. In these systems the drug carrier interactions were shown in FTIR. The results showed the suitability of carrier polymers in preventing crystallization of FBX. The increased dissolution rates in systems containing carrier polymers were due to surface tension lowering effect of polymers to the medium, resulting in the wettability of hydrophobic and BCS Class II drug like FBX and thus increase in dissolution rates.

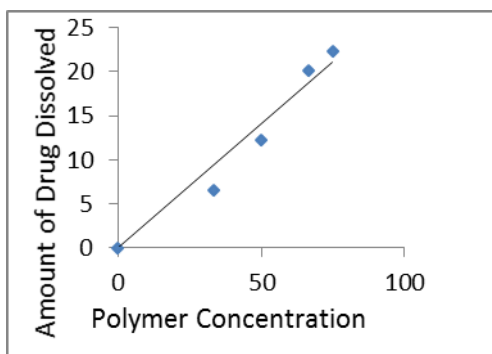


Fig2: Phase solubility studies of drug in Polymers

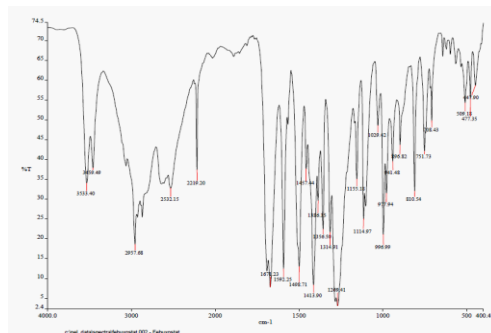


Fig 3: FTIR Spectra of Febuxostat

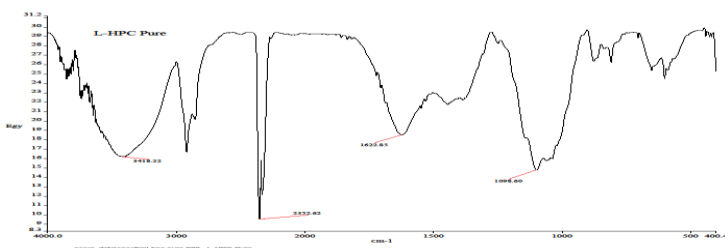


Fig 4: FTIR Spectra of L-HPC

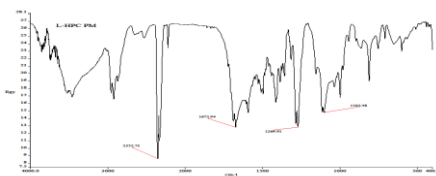


Fig 5: FTIR Spectra of Physical mixture(1:2 ratio)

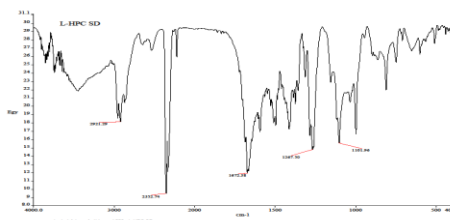


Fig 6: FTIR Spectra of Solid dispersions of FBX and L-HPC FBX and L-HPC (1:2 ratio)

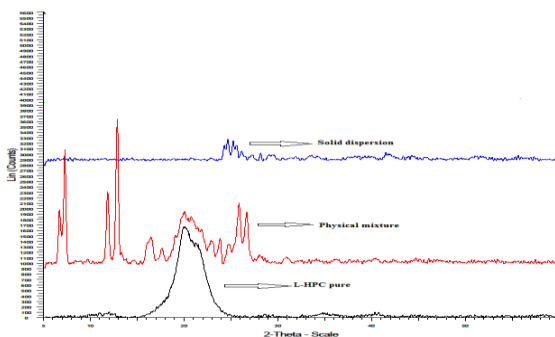


Fig 7: Overlying of Powder X-ray diffraction patterns of various compounds of L-HPC

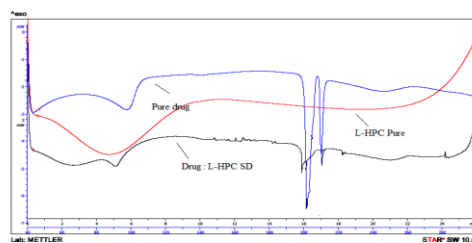


Fig 8: Overlying of DSC thermograms of various Solid dispersions of L-HPC

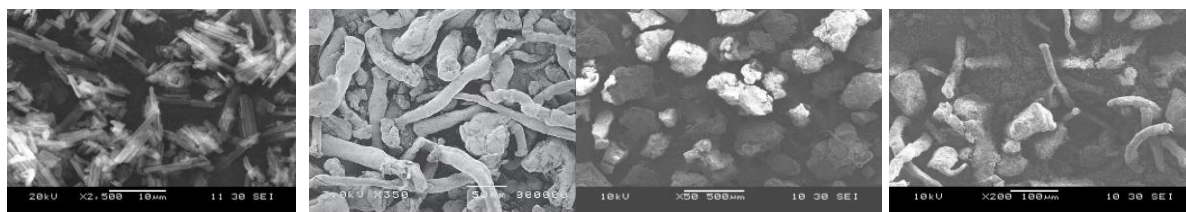


Fig 9: Scanning Electron Microscopy of Febuxostat, L-HPC, Solid dispersion of 1:2 ratio and Physical mixture of 1:2 ratio

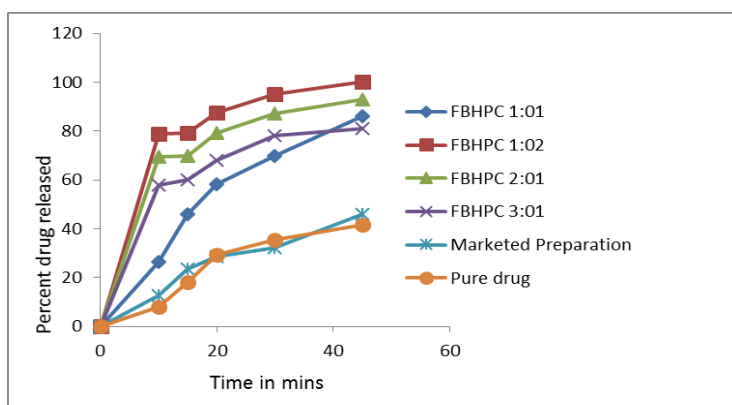


Fig 10: Drug release profiles of different ratios of solid dispersions with FBX and L-HPC, Pure drug and marketed preparation

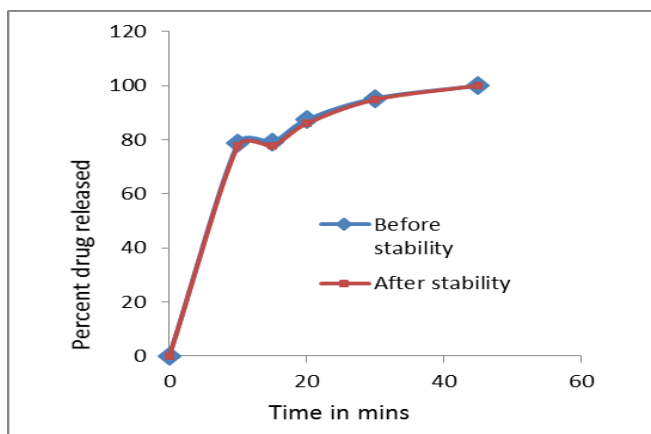


Fig: 11 Drug release profiles of selected solid dispersions before and after stability

Table No:1 Percent drug released from different ratios of solid dispersions prepared, marketed preparation and pure drug

Time (mins)	Percent Drug Released (n=3)					
	FBHPC 1:1	FBHPC 1:2	FBHPC 2:1	FBHPC 3:1	Marketed Preparation	Pure drug
10	26.64	78.73	69.50	57.85	12.6	8.16
15	46.08	79.05	70.70	60.23	23.5	18.23
20	58.32	87.36	79.26	68.02	28.5	29.34
30	70.0	95.28	87.00	78.26	32.4	35.61
45	86.20	100	92.80	81.00	45.8	41.8

Table No:2 Ratios of solid dispersions prepared and the drug content values

Ratios of solid dispersions prepared (Drug:Polymer)	Percent drug content
FBHPC1:1	100
FBHPC 2:1	100
FBHPC 3:1	97.30
FBHPC 1:2	100

Table No: 3 Percent drug release of the finalized formulations before and after stability

Time (Min)	Before stability	After stability
	FBHPC 1:2	FBHPC 1:2
10	78.73	77.7
15	79.05	77.62
20	87.36	85.9
30	95.28	94.8
45	100	100

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