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SOLUBILITY ENHANCEMENT STUDIES ON THE POORLY SOLUBLE DRUG FEBUXOSTAT

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ABSTRACT

Aim: Febuxostat (FBX) is a non purine selective inhibitor of xanthine oxidase/xanthine reductase. It belongs to BCS class II with low solubility and high permeability. Because of low solubility the bioavailability of the drug is hampered, food also interferes with the absorption of drug and decreases the Cmax by 38-49%. 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. **Materials and methods:** In the present study, the attempts were made to improve the bioavailability of FBX by solid dispersions technique by employing Soluplus as carrier molecule. Different ratios on weight basis viz 1:1, 1:2, 1:3, 2:1 coded as ($FBXS_1$, $FBXS_2$, $FBXS_3$, $FBXS_4$) with Soluplus were prepared. **Results and Discussion:** The drug release studies were characterized in liquid state by phase solubility studies and in solid state by Fourier transform infrared spectroscopy (FTIR), Differential scanning calorimetry (DSC), Powdered X ray diffraction studies (PXRD) and Scanning electron microscopy (SEM). The aqueous solubility of FBX was favored by the presence of carriers. Solid state characterization indicated that FBX was present as fine amorphous form in the carrier polymeric molecules. **Conclusion:** In contrast to the solution rate of pure FBX the drug in carriers 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.

KEYWORDS: Febuxostat, solid dispersions, Soluplus, Phase solubility, drug release

studies.

INTRODUCTION

Febuxostat denoted as FBX is a non purine selective inhibitor of xanthine oxidase/xanthine reductase. The chemical name of FBX is 2-[3-cyano-4-(2-methyl propoxy) phenyl]-4-methyl-1, 3-thiazole-5-carboxylic acid.

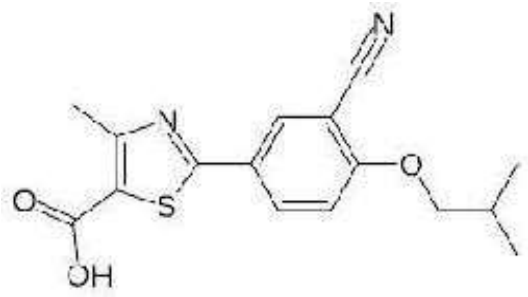


Fig.1: Molecular structure of Febuxostat

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 Cmax to 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[1] 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.[2] 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[3] 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[4] may contribute directly to the improved bioavailability of poorly water soluble drugs.

In the current research investigation[5] trials were made to improve the dissolution rate of FBX by employing the solid dispersion technique. An attempt was made to improve the dissolution properties of Febuxostat by preparing free flowing solid dispersions[6] using Soluplus 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, FBX was generously donated by Sun Pharma Mumbai, Soluplus was by were procured from Sigma Aldrich, Mumbai and all other chemicals used in the study are of pharmacopeial grade.

PHASE SOLUBILITY STUDIES

The phase solubility studies were conducted by using a simple technique, which involves the addition of excess amount of FBX i.e. 100 mg in 25 ml of water containing different weights of solubilizing agents i.e. Soluplus. The solutions were[7] sonicated for 1 hr at room temperature and maintained at 25^0C for 48 hrs on an orbital shaker Orchid, Mumbai. The dispersions were filtered[8] through a 0.22 µm nylon membrane filter. The filtrates were suitably diluted and analyzed, spectrophotometrically (UV/Vis spectrophotometer, Elico), for the dissolved drug at 318 nm. All trials were performed in triplicate.

PREPARATION OF SOLID DISPERSIONS

The solid dispersions of FBX employing Soluplus were prepared[9] 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 Soluplus in different weight ratios (1:1,1:2,1:3,2:1 of Soluplus coded as FBXS1, FBXS2, FBXS3, FBXS4) were prepared by employing solvent

evaporation method[10-13] The required amount of polymer Soluplus were weighed and mixed with sufficient quantity[14-16] of the solvent acetone 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 40 to obtain the solid dispersions. Thus prepared solid dispersions were stored in a dessicator until further evaluation.

CHARACTERIZATION OF SOLID DISPERSIONS

FTIR Spectroscopy

A Schimadzu P/N 206-73500-38 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−1 was used and 64 scans were co-added for each spectrum over a frequency range of 4000–450 cm−1. The software used for the data analysis was Perkin-Elmer spectra MAX.

DSC Analysis

Thermal analyses of prepared solid dispersions were performed in a DSC-60, SHIMADZU, 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 10^0C/min over a temperature range of 25–220^0C.

X-RAY POWDER DIFFRACTION

Diffraction patterns were obtained on a XRD-7000 X-RAY DIFFRACTIOMETER, SHIMADZU 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 (HITACHI S3700N). 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 acetone. 1ml of the stock solution was diluted to 10 ml with pH 6.0 Phosphate buffer which was further diluted to give a final concentration of 10 µ g/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 (Electrolab TDT-14L) 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 (Elico 191 SW) 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 direct compression technique using compression machine MINI Press.

Table No.1: Formulation of tablets using Soluplus

Ingredients	mg per tablet
Solid dispersions equivalent to 40mg of Febuxostat	120mg (FBXS2)
Crosspovidone	24mg
Magnesium stearate	3mg

Talc	3mg
Total tablet weight	150 mg

EVALUATION OF TABLETS: UNIFORMITY OF WEIGHT

Uniformity of weight was performed by randomly weighing 10 tablets individually and collectively on digital balance. Individual weight of tablets was determined from average weight of tablets.

TABLET HARDNESS

Hardness of tablet is defined as the force applied across the diameter of the tablet in order to break the tablet. Hardness of tablets was determined by using hardness tester. The harness of tablet was measured in terms of kg/cm^2.

TABLET THICKNESS

Thickness of tablets was performed using digital Vernier caliper. Thickness of tablet was determined by placing the tablet between two arms of Vernier caliper. Thickness of each tablet was measured in terms of mm.

TABLET DISINTEGRATION TIME

Tablet disintegration time was carried in triplicate (n=3) using tablet disintegration tester. Disintegration time for tablets was carried out in water maintained at 37+/- 0.5^0C. The time required for the tablet to disintegrate completely was reported in seconds.

ASSAY OF TABLETS

The content of Febuxostat in tablets was determined using UV-Visible spectrophotometer. 1 Tablet was crushed in a mortar pestle and powder equivalent to 10mg Febuxostat was dissolved in 10ml Acetone. 1mg of the stock solution was diluted to 10ml with Phosphate buffer (PH 6.0). It was further diluted to give a final concentration of 10 µg/ml (10 ppm) solution. Percent drug content was calculated spectrophotometrically from the absorbance obtained at 318nm.

IN VITRO DRUG RELEASE STUDIES

The dissolution rate of Febuxostat from tablets was measured in a dissolution test system using phosphate buffer PH 6.0 and USP apparatus II (paddle) method as specified in the OGD guidelines. The dissolution test tablets was carries out in triplicate (n=3). Bath temperature and paddle rotation speed were set at 37^0C and 75 rpm, respectively. Aliquots of

10 ml were withdrawn at 5, 10, 15, 20, 25, 30 and 45 minutes.1 ml from this was diluted to 10 ml with buffer solution. The amount of drug dissolved was assayed spectrophotometrically at 318 nm.

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: PHASE SOLUBILITY STUDIES

Fig. 2 shows the phase solubility diagram representing the effect of increasing the concentrations of Soluplus on the apparent solubility of FBX in water at 25^0C. The aqueous solutions of Soluplus increased the solubility of FBX more when compared to pure drug. The polymer was selected for formulation of solid dispersions because of its higher molecular weight and better solubility of FBX in its aqueous solution.

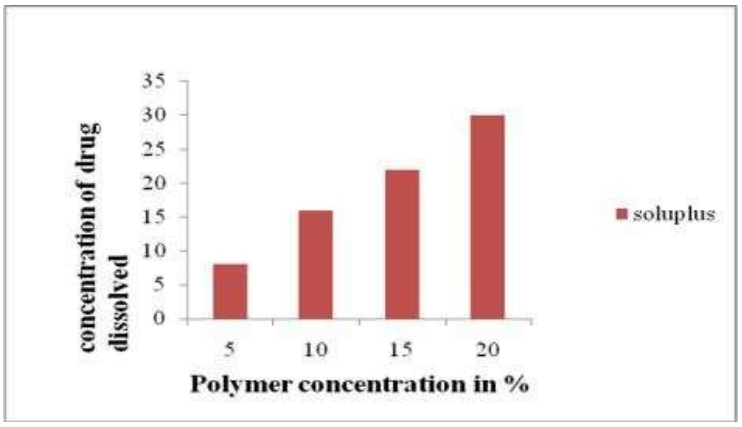


Fig 2: Phase solubility studies of drug in Polymers

FTIR STUDIES

FTIR spectra of solid dispersions of FBX with Soluplus is shown in Fig 3 to 6. The spectra of Pure FBX presented characteristic peaks at 3535.52, 3460.3, 3068.75 cm^{-1} (O- H stretching of free hydroxyl group), 2957.68 cm^{-1} (C-H stretching of alkanes), 1703.14, 1681, 1670 cm^{-1} (C-O stretching of carboxylic acid) 1510, 1577.7, 1425 cm^{-1} (C-C stretching of aromatic ring), 1469.71, 1498.44, 1298.09, 1282.66 cm^{-1} (C–H stretching of alkanes) respectively. The spectrum of Soluplus showed, among others important bands at 2927.9 cm^{-1} (C–H stretch) and 1629.85, 1701.22 cm^{-1} (C=O) a very broad band was also visible at 1240.23, 2858.51 cm^{-1} that was attributed to the presence of water, confirming the broad endotherm

detected in the DSC. The characteristic peaks of FBX at 2960.73, 3460.3, 3535.52, 3068 cm^{-1} (O- H stretching of acid), 2957.68 cm^{-1} (C- H stretching of alkanes), 1703.14, 1681, 1670 cm^{-1} (C- O stretching of carboxylic acid). 1510, 1577.7, 1425 cm^{-1} (C-C stretching of aromatic ring) are disappeared in spectra of solid dispersions with Soluplus (FBXS2) ratio which indicates the trapping of Febuxostat inside the matrix of Soluplus.

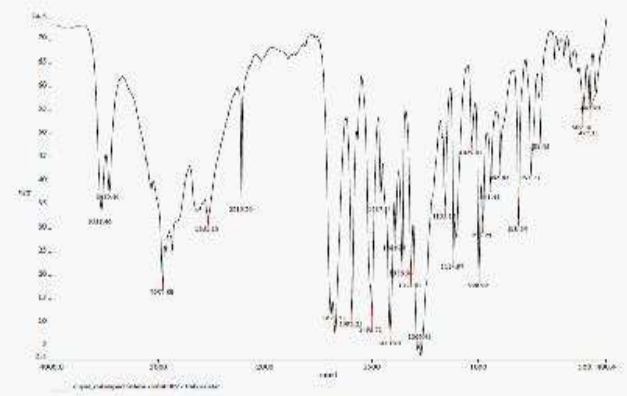


Fig 3: FTIR Spectra of Febuxostat

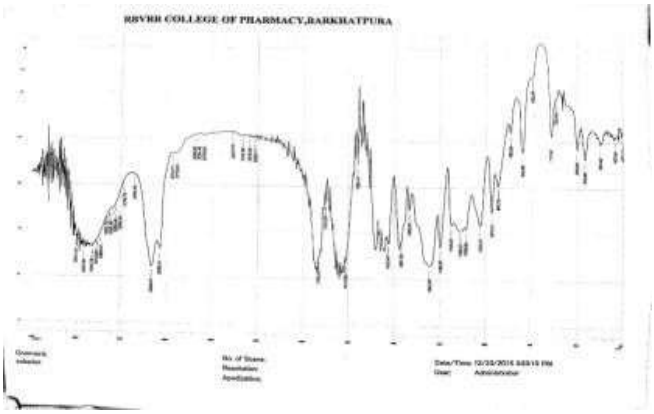


Fig 4: FTIR Spectra of Soluplus

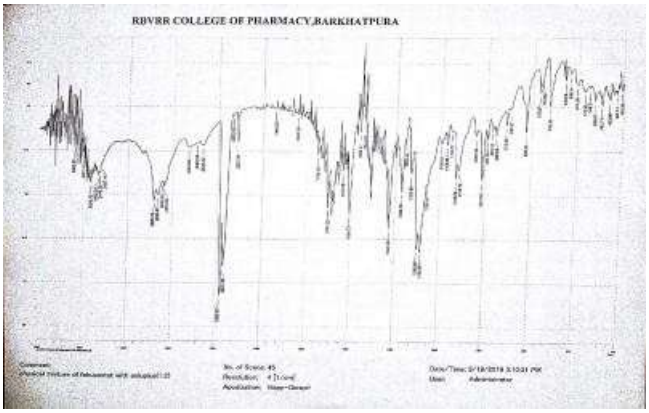


Fig 5: FTIR Spectra of PM (FBXSP2)

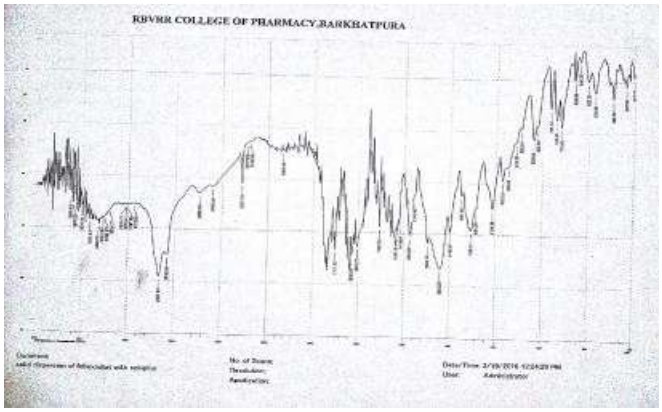


Fig 6: FTIR Spectra of SD (FBXS2)

PXRD STUDIES

The pure FBX, Soluplus, physical mixture and selected solid dispersions of carriers were studied by XRD as shown in figure 7. The powder diffraction patterns of pure FBX showed characteristic high-intensity diffraction peaks at 2θ 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 Soluplus do not show any characteristic diffraction peak. The high intensity diffraction peaks are very prominently preserved in case of physical mixtures, where as these characteristic peak intensities were drastically reduced in FBXS2 ratios 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.

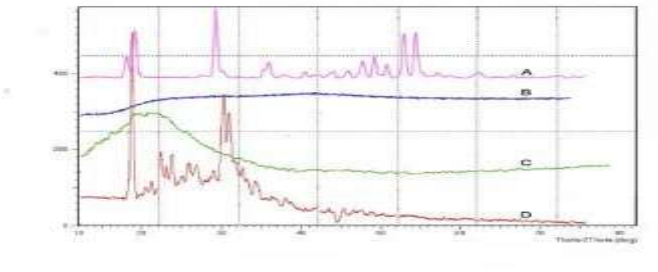


Fig 7: Overlaying of Powder X-ray diffraction Patternsof various compounds of soluplus.

(A) FBX, (B) Soluplus, (C) Solid dispersion (D) Physical mixture.

DSC Analysis

The DSC thermograms for pure FBX, Polymer, Physical mixture and selected solid dispersion were shown in fig 8. The DSC thermogram of pure FBX shows the sharp endothermic peak at around 200-220^{0}C, confirming the crystallinity of the drug. During

scanning of Soluplus, a broad endotherm ranging from 70 to 120^{0}C was observed. The DSC thermogram of the solid dispersion in FBXS2 ratio showed the presence of broaden peaks with no characteristic peaks of drug. Which means the drug is in the form of amorphous nature or in solid solution.

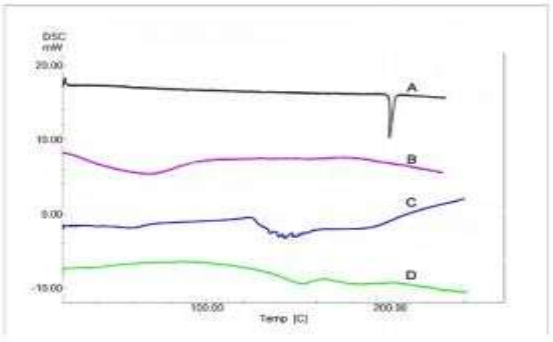
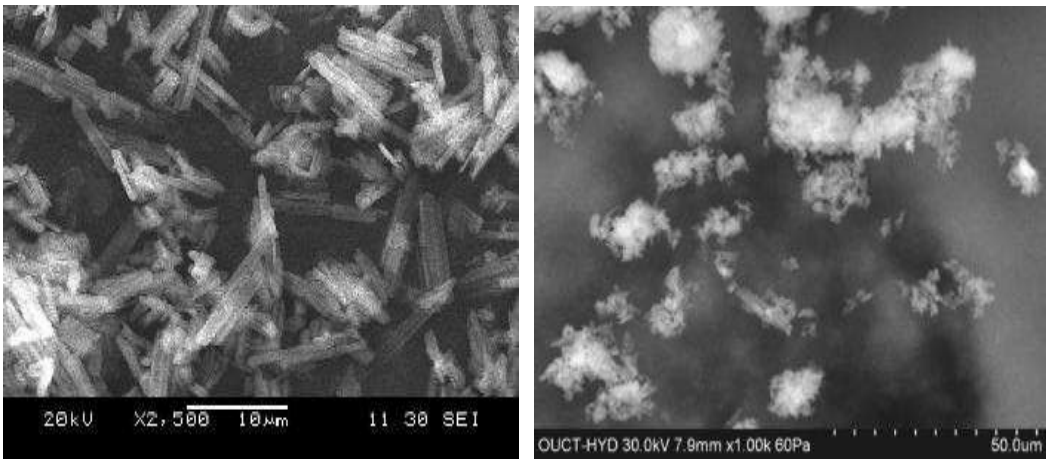


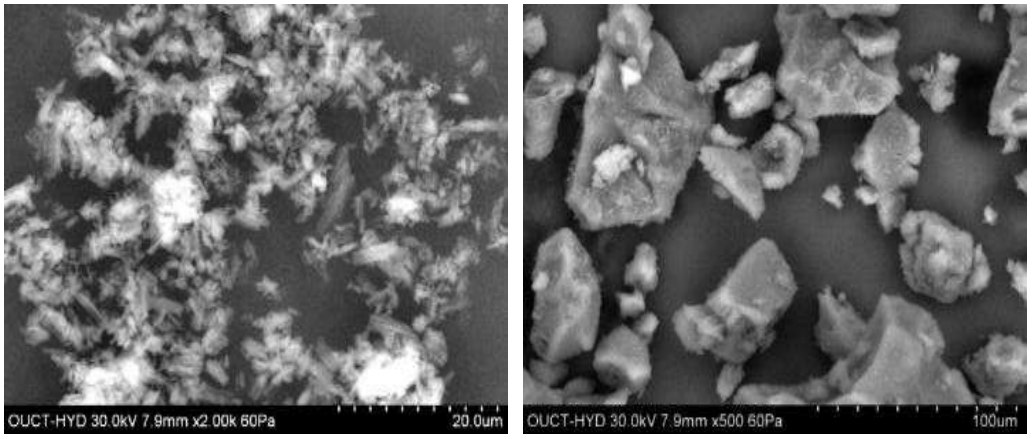
Fig 8: Overlaying of DSC thermograms of (A) FBX, (B) Soluplus, (C) Physical mixture, (D) solid dispersion

SCANNING ELECTRON MICROSCOPY (SEM)

SEM photomicrographs obtained for pure FBX, Soluplus, 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.



(A) **(B)**



(C) **(D)**

Fig 9: Scanning Electron Microscopy of (A) Febuxostat, (B) soluplus, (C) Physical mixture (FBXS2), (D) Solid dispersion (FBXS2).

Table 2: In-vitro drug release studies of various ratios of SDs and physical mixtures prepared using Soluplus

Time (min)	FBXS1	FBXS2	FBXS3	FBXS4	FBXSP1	FBXSP2	FBXSP3	FBXSP4
0	0	0	0	0	0	0	0	0
5	60.1±0.01	74.7±0.03	86.9±0.08	19.2±0.02	24.7±0.09	28±0.02	25±0.01	18.2±0.06
10	78.9±0.05	91.7±0.07	95.6±0.03	23.5±0.04	26±0.08	35±0.01	30±0.07	22±0.04
15	87.6±0.04	97.8±0.06	97.8±0.07	26.8±0.06	30±0.04	40±0.03	36±0.06	24±0.08
20	95.3±0.02	100±0.01	100±0.02	33±0.04	34±0.05	44±0.06	44±0.04	27±0.04
30	100±0.08	100±0.04	100±0.06	37.7±0.06	40±0.07	53±0.09	53±0.03	30±0.07
45	100±0.03	100±0.08	100±0.01	47±0.09	44±0.02	60.2±0.01	58±0.02	36±0.09

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 2 and From these data it is evident that the onset of dissolution of pure FBX is very low (5.3 ± 0.01%) and onset of drug release in solid dispersion ($FBXS_2$) is (74.7± 0.01%). Dissolution profiles of pure FBX, its Physical mixtures and solid dispersions with Soluplus over a period of 45 min were shown in fig 10. It can be clearly observed that the dissolution rate of pure FBX is 32% in 45 min. solid dispersions FBXS 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 $FBXS_2$.

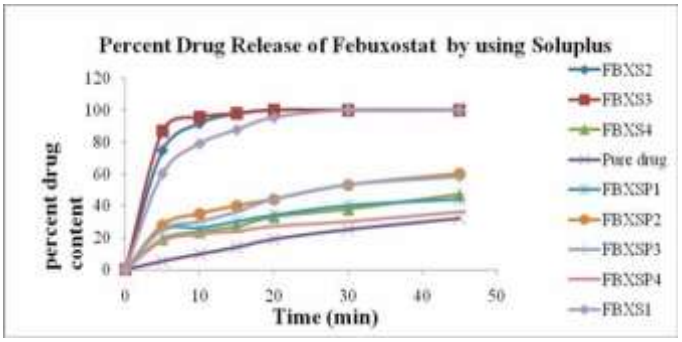


Fig 10: Drug release profiles of different ratios of solid dispersions and Physical mixtures of FBX and Soluplus, Pure drug and marketed preparation

DRUG CONTENT

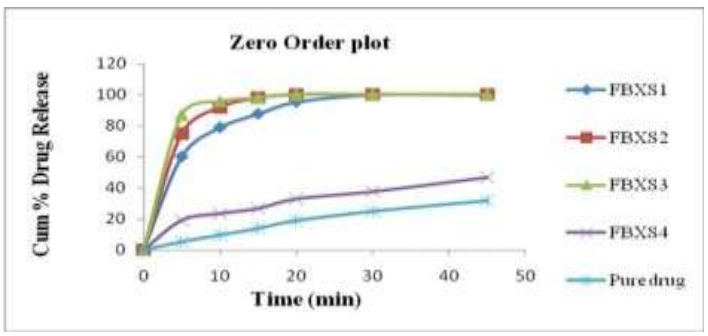
The percent drug content values of various solid dispersions prepared are given in Tables 3. There was no loss of drug during the preparation and all the solid dispersions contained the drug equal to the theoretical drug content based on the proportion of drug and carrier taken. Low s.d. and C.V. (<2.0) in the percent drug content values indicated that the drug content was uniform in a batch of solid dispersion in all the cases.

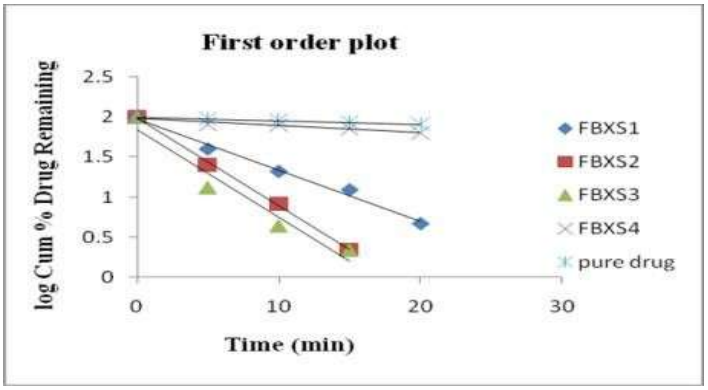
Table No: 3 Ratios of solid dispersions prepared and the drug content values

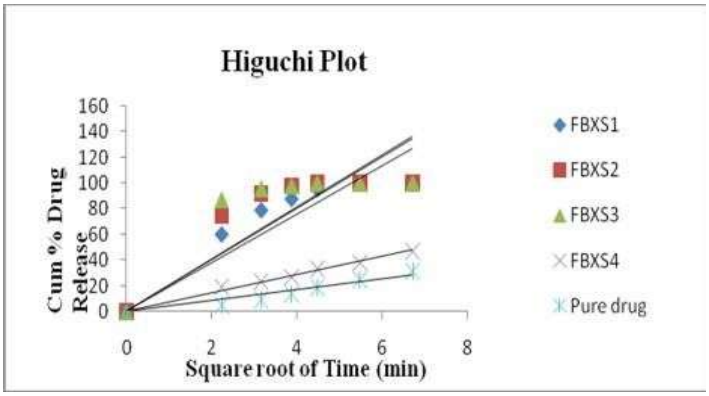
Ratios of solid dispersions prepared	Percent drug content
FBXS1	87.10
FBXS2	91.45
FBXS3	89.87
FBXS4	71.00

Table No.4: Correlation coefficient of solid dispersions and Febuxostat

Ratios of SDs	Zero Order plot r^2 values	First Order plot r^2 values	Higuchi plot r^2 values	Peppas plot 'n' values
FBXS1	**0.12**	**0.990**	**0.772**	**0.236**
FBXS2	**0.56**	**0.998**	**0.556**	**0.128**
FBXS3	**0.80**	**0.945**	**0.433**	**0.062**
FBXS4	**0.624**	**0.932**	**0.987**	**0.411**
Pure drug	**0.954**	**0.999**	**0.930**	**0.836**







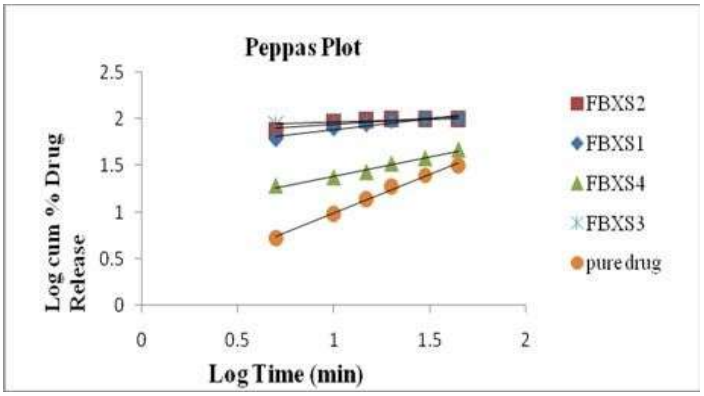


Fig 11: Kinetic representation of prepared solid dispersions and Febuxostat pure drug

Table No.5 Evaluation parameters for tablets

Parameters	Direct compression (Soluplus)
Weight variation	1.5mg
Hardness	3 kg/cm^2
Disintegration time	72 secs
In-vitro dissolution studies	100 + 0.01%

Table No.6: Tablet dissolution data of Febuxostat tablets prepared by employing SDs

Time (mins.)	Percent Febuxostat dissolved (X+ SD, n=3)			
	Pure drug	Direct compression	Marketed preparation	Physical mixture
0	0	0	0	0

5	5.3 ± 0.02	57.86± 0.07	12.6± 0.02	41.7± 0.06
10	9.7± 0.04	68.23± 0.04	23.5± 0.08	56.3± 0.01
15	14± 0.07	79.02± 0.06	25.12± 0.05	62.9± 0.04
20	19± 0.05	85.72± 0.05	28.5± 0.01	65± 0.03
30	25± 0.01	94.51± 0.03	32.4± 0.04	72.5± 0.08
45	32± 0.09	100± 0.01\	45.8± 0.07	78.9± 0.02

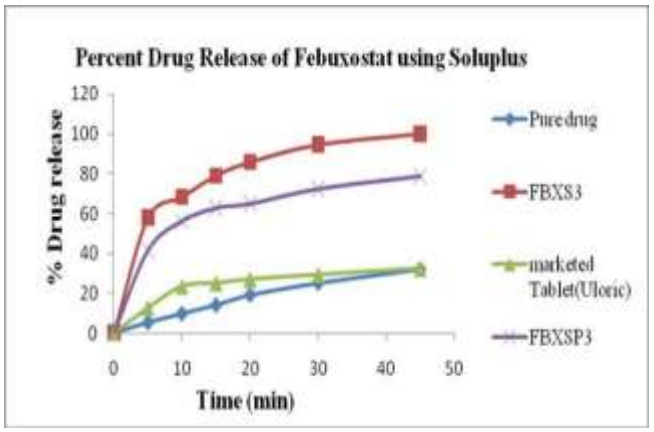


Fig 12: Comparative dissolution profile of FBX Tablets

SATBILITY STUDIES

The selected solid dispersions and formulated tablets, i.e. FBXS2 were kept for stability studies and the preparations were evaluated for drug release studies and other evaluation tests after stability. In the stability studies the formulations did not show any significant changes in the drug release profile which prove that the drug had retained its amorphous form and did not convert into crystalline form upon storage.

Table No.7: Percent drug release of the finalized formulations before and after stability

TIME (min)	Before stability FBXS2	After stability FBXS2	Before stability FBXS2 Tablets	After stability FBXS2 Tablets
0	0	0	0	0
5	74.7± 0.03	73.9± 0.08	57.86± 0.04	55.81± 0.09
10	91.7± 0.04	89.9± 0.02	68.23± 0.01	63.94± 0.04
15	97.8± 0.02	97.1± 0.01	79.02± 0.06	76.04± 0.05
20	100± 0.01	99.5± 0.05	85.72± 0.02	82.26± 0.01
30	100± 0.06	100± 0.04	94.51± 0.03	93± 0.02
45	100± 0.09	100± 0.07	100± 0.08	95.45± 0.08

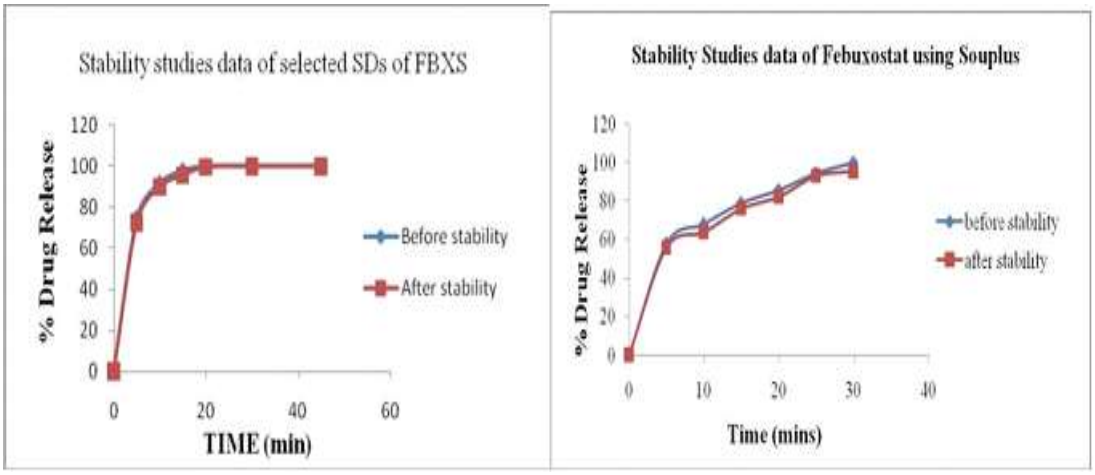


Fig 13: Drug release profiles of selected solid dispersions and prepared tablets before and after stability

CONCLUSION

In the present study, the drug Febuxostat was successfully prepared in the form of solid dispersions by employing Soluplus as carrier molecule. The solvent evaporation method can be used as a method for preparing solid dispersions. The prepared SDs showed better results in solubility and dissolution studies. The % drug dissolved from FBXS2 SDs is 100%, when compared to its physical mixture (60.2%) and the pure drug (32%). The assay of FBXS2 showed 91.45% of drug entrapment.

The prepared SDs were analysed by different instrumental methods like FTIR, DSC, XRD & SEM. Which revealed the entrapment of drug in polymer matrix and also there was improved amorphous nature of drug in SDs when compared to the crystalline nature in pure form.

The finalized ratios were compressed into tablet dosage forms by direct compression technique and were tested for different QC tests like weight variation hardness, thickness, disintegration, assay, in-vitro drug release studies. Drug release studies showed from FBXS2 is 100% of drug in 45 min. whereas the marketed preparations showed dissolution of 45.8% in 45 min.

The tablets prepared employing FBXS2were kept for stability studies at 40^0C, 75% RH for 3 months and were analysed at the end of 3 months for disintegration, dissolution and assay of drug. All the parameters were observed to be within limits indicating no significant change in tablet dosage form during stability period, which indicates that the drug was in entrapped condition during the storage also.

So the technique solvent evaporation can be employed to prepare Febuxostat solid dispersions and Soluplus can be successfully used as carrier molecule for this method. The SDs thus prepared showed increased solubility and dissolution parameters of the API.

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