SOLUBILITY ENHANCEMENT STUDIES OF FEBUXOSTAT BY EMPLOYING GELUCIRE 50/13

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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, attempts were made to improve the bioavailability of FBX by solid dispersions technique by employing Gelucire 50/13 as carrier molecule. Different ratios on weight basis viz (1:1, 1:2, 2:1, 3:1, 4:1, 5:1, 6:1) coded as (FBXG1, FBXG2, FBXG3, FBXG4, FBXG5, FBXG6, FBXG7) with Gelucire 50/13 were prepared.

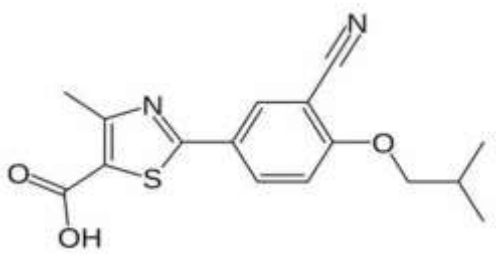
Results and Discussion: The drug release studies were characterized in liquid state by phase solubility studies and in solid state by Fourier transform infrared spectroscopy (FTIR), Differential scanning calorimetry (DSC), Powdered X ray diffraction studies (PXRD) and Scanning electron microscopy (SEM). 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, Gelucire 50/13, 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-methyl1, 3-thiazole-5-carboxylic acid.



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. Poor 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.

In the current research investigation 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 using Gelucire 50/13 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, Gelucire 50/13 was procured from Gattefosse and all other chemicals used in the study are of pharmacopeial grade.

SOLUBILITY STUDIES

The phase solubility studies were conducted by using a simple technique, which involves the addition of excess amount of FBX in 25 ml of water containing different weights of Solubilizing agent i.e. Polymer. The solutions were sonicated for 1 hr at room temperature and maintained at 25℃ 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, Elico), for the dissolved drug at 318 nm. All trials were performed in triplicate.

PREPARATION OF SOLID DISPERSIONS

The solid dispersions of FBX employing Gelucire 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 EVAOPORATION METHOD

Solid dispersions of FBX in Gelucire with different weight ratios 1:1, 1:2, 2:1, 3:1, 4:1, 5:1, 6:1 of Gelucire 50/13 coded as (FBXG1, FBXG2, FBXG3, FBXG4, FBXG5, FBXG6, FBXG7) were prepared by employing solvent evaporation method. The required amount of polymer Gelucire 50/13 were weighed and mixed with sufficient quantity 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 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 SHIMADZU 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.

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 methanol. 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 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 (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.

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

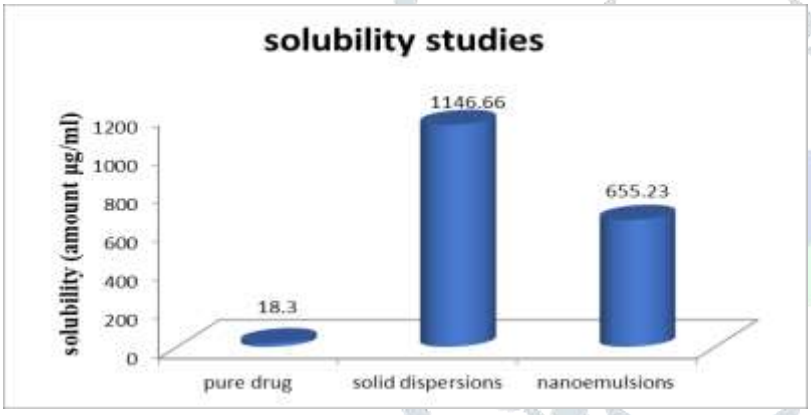
- Solubility studies

Solubility studies of different excipients used in formulations

Exicipient	Concentration of drug dissolved in (µg/ml)
Water	18.3
Gelucire	7866.66
Tween 80	755.14
Isopropyl myristate	134.33
Span 80	841.66

comparative studies of selected formulations with pure drug

Formulation	Concentration of drug dissolved(µg/ml)	No.of times increased compared to pure drug
Pure drug	18.3	-
Solid dispersions	1146.66	62.65
Nano emulsions	655.23	35.08

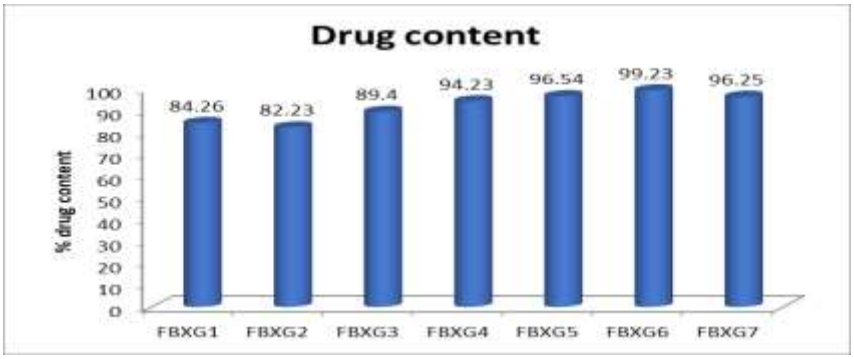


solubility studies of different formulations

1. Percent drug content (assay):

percent drug content of various SDs

S.NO	Prepared Solid Dispersions	Percent drug content
1	FBXG1	84.62
2	FBXG2	82.23
3	FBXG3	89.40
4	FBXG4	94.23
5	FBXG5	96.54
6	FBXG6	99.23
7	FBXG7	96.25



percent drug content of different formulations

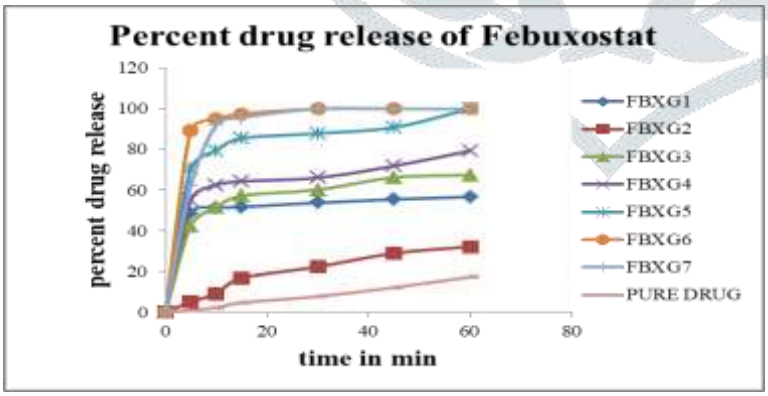
- The percent drug content of solid dispersions is mentioned in table 4.2.1. The drug content was calculated for all the prepared formulations and the values range from 84.26% to 99.23%. Among all FBXG6 formulation gave maximum drug content value of 99.23%.

2. In- vitro drug release studies

In-vitro drug release studies of various solid dispersions employing Gelucire 50/13 as carrier and pure drug

Time (min)	Percent drug release of solid dispersions (n=3)							Pure drug
	FBXG1	FBXG2	FBXG3	FBXG4	FBXG5	FBXG6	FBXG7	
5	48.75	5.12	42.5	55.27	70.5	89.37	61.87	0.86
10	51.18	9.15	51.5	62.5	79.5	95	91.87	2.25
15	51.75	16.75	57.25	64.25	85.5	97.5	95.62	4.68
30	53.81	22.37	60.25	66.11	87.9	100	100	7.72
45	55.5	29	66.25	71.94	90.9	-	-	12.18
60	56.68	32.25	67.5	79.35	100	-	-	17.28

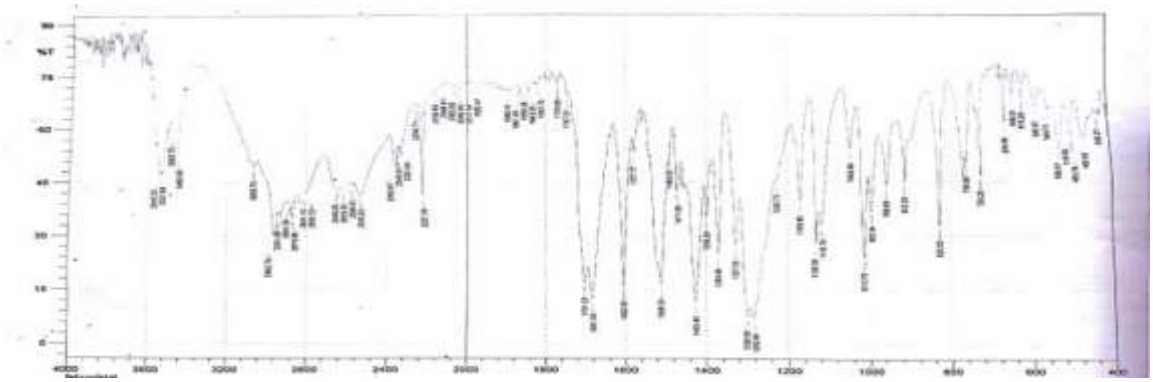
percent drug release of FBX SDs



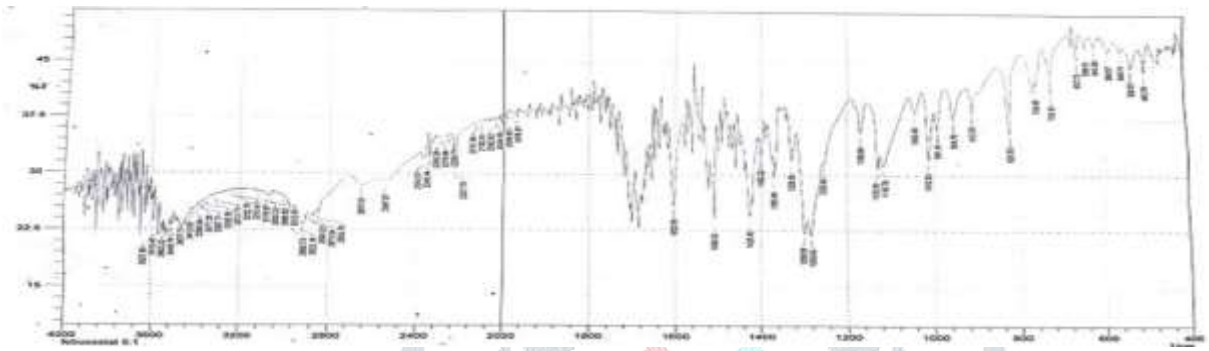
percent drug release

- In-vitro drug release of all the ratios were carried out in phosphate buffer pH 6.0. The percent drug dissolved for all the ratios ranged from 56.68% to 100%. Among all the ratio FBXG6 gave maximum drug release value of 100% in 30 min, hence this ratio was selected as the optimized ratio and further evaluation was done.

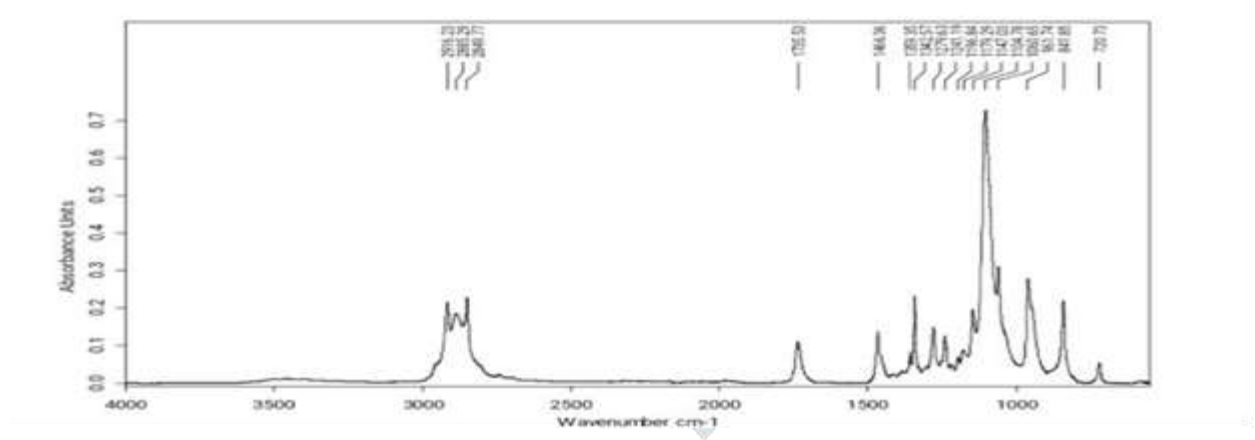
3. Fourier transform infrared spectroscopy (FTIR)



IR spectra of FBX



IR spectra of FBXG6



IR spectra of Gelucire 50/13

The FTIR spectra of pure drug, polymer and solid dispersion were performed. The spectra of pure drug presented characteristics peaks at

Characteristic peaks of FBX

Characteristics peaks	Functional groups
3543.23, 3460.30, 3068.75cm-1	O-H stretching of free hydroxyl group
2960.73cm-1	C-H stretching of alkanes

1701.22, 1681.93cm-1	C-O stretching of carboxylic acid
1577.7, 1508.33, 1425.40 cm-1	C-C stretching of aromatic ring

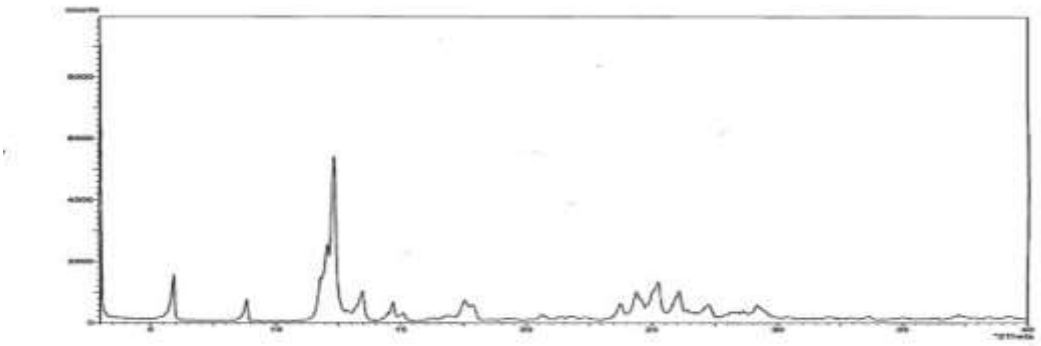
The spectra of Gelucire 50/13 showed important bands at

Characteristics peaks	Functional groups
2916.23cm-1	C-H stretch
1735.53cm-1	C=O
1104.78 cm-1	Broad band

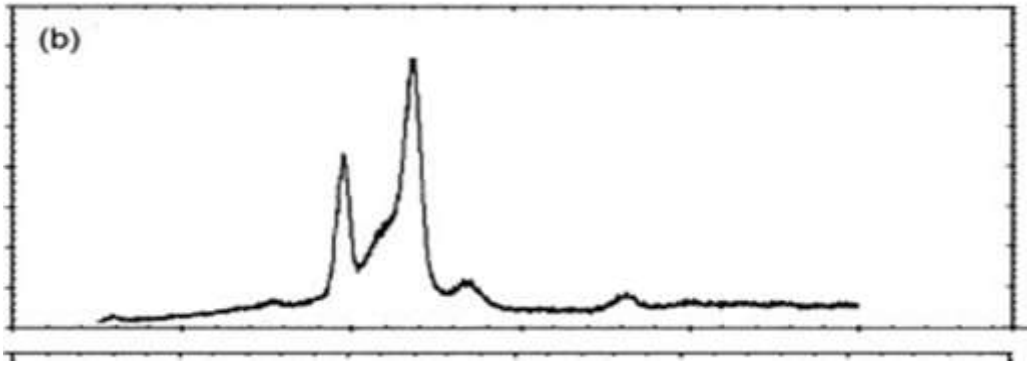
Characteristic peaks of Gelucire 50/13

The characteristic peaks of Febuxostat at 3460.30, 3068.75, 3527.80cm-1 (O-H) 2960.73cm-1 (C-H) 1602.85cm-1 (C-O) 1508.33, 1425.40cm-1 (C-C) are disappeared in spectra of solid dispersion which indicates tapping of Febuxostat in polymer matrix.

4. X-ray powder diffraction (PXRD)



Powder x-ray diffraction of febuxostat

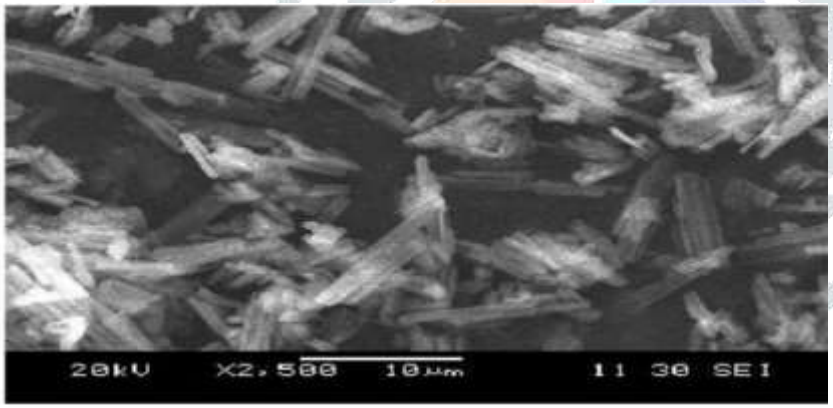


Powder x-ray diffraction of Gelucire 50/13

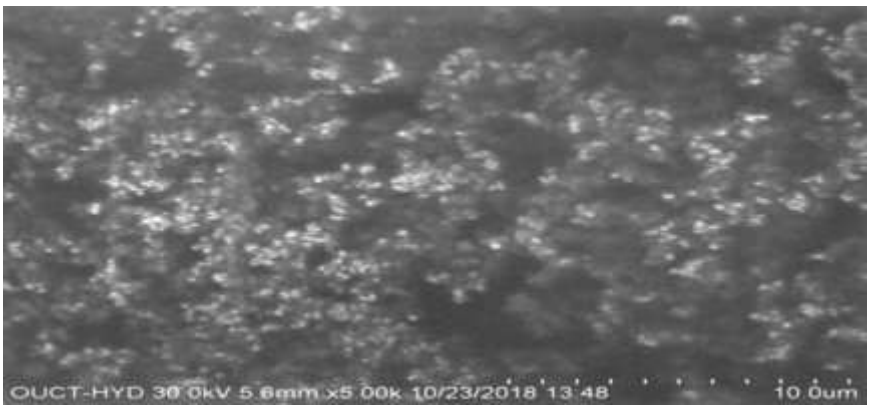
Powder x-ray diffraction of FBXG6

- The powder diffraction patterns of FBX showed characteristic high intensity diffraction peaks at 2ɵ values of 4.788, 6.788, 8.363, 11.79, 15.98, 16.78, 20.001, 25.16, 25.77.
- The powder diffraction pattern of pure Gelucire 50/13 shows only two sharp crystalline peaks at diffraction angles of 19.1and 23.1.
- The characteristics peaks intensities were drastically reduced in the prepared formulation owing to complete encapsulation and amorphisation of drug or reduction in crystallinity of drug which is responsible for increase in solubility of drug in formulation.

5. Scanning electron microscopy (SEM)



scanning electron microscopy of FBX



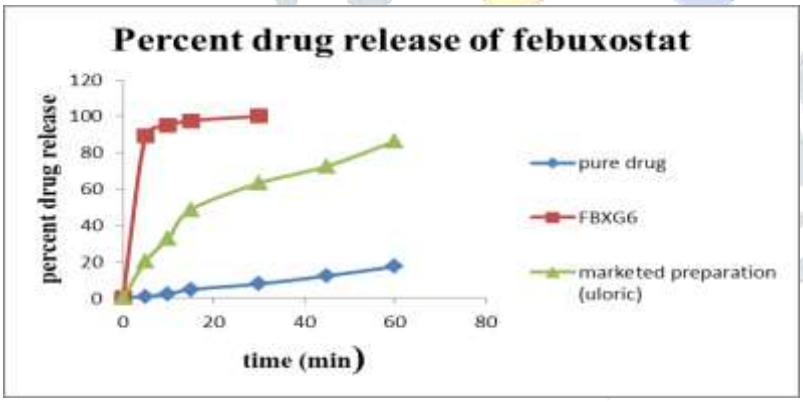
scanning electron microscopy of FBXG6

- The SEM photography also shows that the surface of the prepared formulation is more amorphous in nature which is responsible for the increase in solubility of drug. The results of SEM are in sync with XRD studies

❖ Dissolution profile of optimized formulations, pure drug and marketed preparation

TIME (in min)	PURE DRUG	SOLID DISPERSION (FBXG6)	MARKETED PREPARATIONS
5	0.86	89.37	20.2
10	2.25	95	32.8
15	4.68	97.5	48.6
30	7.72	100	63.10
45	12.18	--	72.5
60	17.28	--	86.2

comparison of dissolution profile with pure drug and marketed preparations



percent drug release of different formulations

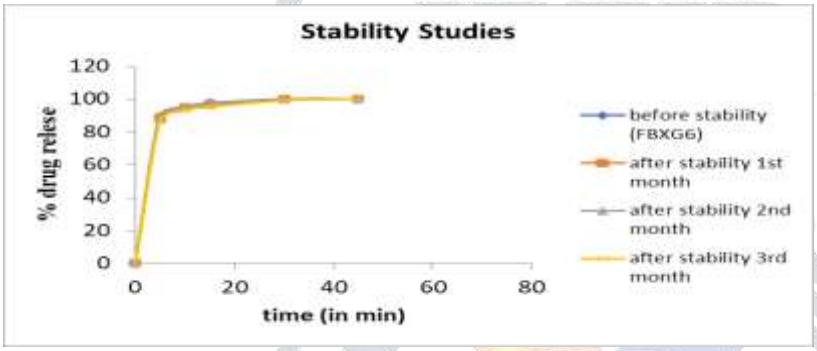
In the above table the prepared formulation was compared with the pure drug and marketed preparation. It was found that the marketed formulation gave 86.2% of drug release when compared with the prepared formulation 100% and pure drug 17.28% respectively.

❖ STABILITY STUDIES

The finalized solid dispersion (FBXG6) was kept for stability study and the preparation was evaluated for drug release studies.

Percent drug release of finalized formulation before and after stability

		After stability (FBXG4)		
Time (in min)	Before stability (FBXG6)	1st month	2nd month	3rd month
5	89.37	88.9	87.5	86.5
10	95	94.8	94,2	93.2
15	97.5	97	96.4	95.3
30	100	99.8	99.5	99.2
45	100	100	100	100
60	-	-	-	-



stability study of optimized solid dispersion of FBX

- The samples were analyzed periodically at the end of each month and the results obtained shows that no significant changes in the drug release profile. It means that the formulation is quite stable and did not change from amorphous to crystalline on standing. This can be further confirmed by instrumental analysis.

CONCLUSION

In the present study, the drug Febuxostat was successfully prepared in the form of solid dispersions by employing Gelucire 50/13 as carrier molecule. The solvent evaporation method can be used as a method for preparing solid dispersions. The prepared SDs showed better results in terms of solubility and dissolution studies. The % drug dissolved in SDs for FBXG6 is 100%, when compared to the pure drug is 17.28%. The assay of SDs of FBXP3 showed to be 99.23% of drug entrapment.

The prepared SDs were analyzed by instrumental analysis like FTIR, 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 stability studies were carried for SDs of optimized formulation (FBXG6), no significant changes has been observed during the stability period, which indicates that the formulations were stable for 3 months without any changes.

So the technique of solvent evaporation can be employed to prepare Febuxostat solid dispersions. Gelucire 50/13 can be successfully used as carrier molecule for this method. And this SDs thus prepared showed increased solubility and dissolution parameters of the API.

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