Research Article

SOLVENT EVAPORATION METHOD: A PROMISING SOLID DISPERSION METHOD USING BETA CYCLODEXTRIN POLYMER FOR ENHANCING SOLUBILITY OF POORLY SOLUBLE DRUG FEBUXOSTAT

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ABSTRACT

Febuxostat is nonpurine xanthine oxidase inhibitor used in treatment of hyperuricemia and gout. Due to its poor solubility, it has less bioavailability. Hence this problem is solved by formulating a solid dispersion using beta cyclodextrin (β-CD) polymer by solvent evaporation method. Beta cyclodextrin (β CD) was used in different drug: carrier ratios (1:2, 1:4, 1:6, 1:8, and 1:10). SE1, SE2, SE3, SE4,SE5 respectively. The effect of these polymers at different ratios on aqueous solubility was studied. Solid dispersion was evaluated for physical appearance, percentage yield, drug content, saturation solubility studies and dissolution studies, etc. Result of saturation solubility studies revealed increase in solubility of the solid dispersions compared to the pure drug. *Invitro* release profiles of all solid dispersion were evaluated and studied against pure febuxostat drug. Solid dispersion SE5, having drug:*β* CD(1:10 ratio) showed a higher dissolution rate.The powder X-ray diffraction study and Scanning electron microscopy (SEM) studies exhibited conversion of crystalline drug to an amorphous form of solid dispersion.The present study demonstrated that formulation of solid dispersion using *β* CD method is a highly the best technique for solubility enhancement of febuxostat drug.

Key words: Febuxostat (FBX), Solid Dispersion (SD), Beta cycodextrin (β CD), Active pharmaceutical ingredient (API) , Solvent evaporation method ,*Invitro* release profile ,X ray study(XRD), DMF (dimethyl formamide), DMSO (dimethyl sulfoxide)

INTRODUCTION

Febuxostat (FBX) chemically known as (2-[3-cyano-4-(2-methylpropoxy) phenyl]-4-methyl thiazole-5-carboxylic acid) is a selective potent, non-purine xanthine oxidoreductase inhibitor using in treatment of hyperuricemia and gout.[1] When (SUA) serum urate concentration is greater than >420 μ mol/l it is a clear indication of hyperuricemia. In women, about 1mg is slightly lower than in men. 500 -700 mg is the daily excretion of uric acid. [5]Gout is a systemic disease caused by the deposition of monosodium urate crystals (MSU) preferentially in the joint space and tissues thereby causing pain and inflammation.[6]

Beta cyclodextrin (β CD) is a cone-shaped, hydrophilic molecule. Being water soluble, and a variety of hydrophobic drug (poorly water soluble can be encapsulated in its non-polar cavity. Such a characteristic has been widely applied in the fields of drug-controlled release (CR), sustained release(SR) and immediate release formulations (IR).[7]β-CD is a cyclic derivative of starch prepared from partially hydrolyzed starch (maltodextrin) by an enzymatic process.

The solid dispersion technique can help in solving the problem of poor solubility and poor bioavailability. [8]Solid dispersion refers to a group of solid products consisting of at least two different components, generally a hydrophilic matrix and a hydrophobic drug. Advantage of preparing a solid dispersion is it not only increases porosity of

particles but also increases wettability with reduction in the particle size also there is conversion of crystalline drug into amorphous form.[10] There are various solid dispersion methods like fusion method, Solvent evaporation method, coprecipitation method,co-grinding method, melt evaporation method ,kneading method. All the different methods were tried out and among all solvent evaporation methods was found to give high yield and also there was no loss of product during formulation.

The present study aimed to formulate solid dispersion (SD) using beta cyclodextrin by solvent evaporation method.

MATERIALS AND METHODS

MATERIALS

Febuxostat was a gift sample from Watson Pharma Pvt Ltd (Verna, India).The polymer beta-cyclodextrin from Signet chemical company.(Mumbai, India) .All reagents are analytical grade.

To check the identity, purity and nature of the drug the pre-formulation test of the drug was carried out.

A. Physicochemical characterization of drug

1) Appearance.

The drug was observed visually.

2) IR spectroscopy.

To check the presence of characteristics of drug peaks and the purity of the drug IR study was carried out using the KBr pellet method.

3) Determination of λmax and Preparation of standard curve of febuxostat in 0.05M Phosphate buffer pH6

FBX standard solution of 1000 ug/ml and working stock solution of 100 ug/ml were prepared in methanol .[11] Further diluting the working stock solution with 0.05 M Phosphate buffer pH 6,a concentration equivalent to 4 ug/ml .Febuxostat solution was obtained and scanned in the range of 200-400 nm on UV spectrophotometer. The λmax of the solution was determined using 0.05 M Phosphate buffer pH 6 as blank.[12]

Preparation of calibration curve

From 100 ug/ml standard stock solution of methanol. FBX working stock solution was prepared of concentration 2, 4, 6,8 and 10 ug/ml respectively and made up to volume using phosphate buffer pH 6 as solvent. The absorbance was measured at 315 nm using 0.05M phosphate buffer pH 6 as blank. A calibration curve was plotted of concentration (µg/ml) versus absorbance.[12]

4) Preliminary solubility studies of Febuxostat

A solubility measurement of FBX was performed [9]. An excess amount of FBX was added to 25 ml of solvent in a screw-capped bottle and vortexed using cyclomixer for 48 hours at room temperature .The resultant solution was taken out at 48 hrs and centrifuged at 2000 rpm for 15 min. Subsequently, Whatman filter paper no 42 is used to filter the supernatant. Filtered solutions were analyzed under UV at λmax 315 nm. The solvent used in the study were water, 0.1 N HCl and 0.05 M phosphate buffer pH 6(OGD media) and phosphate buffer pH 6.8 [13].

5) Method of preparation of solid dispersion

Following tables1 depict dispersion of FBX (pure drug) in a beta cyclodextrin carrier in different ratios. 40 mg of drug was taken in the vial and 4 ml of ethanol was added to each. The febuxostat drug dissolved completely in ethanol to which the polymer solution was added and sonicated for 1 min. The solutions were allowed to evaporate completely until the dry solid mass was obtained and kept in a desiccator for further use . [14]

Table 1: Formulation of Febuxostat solid dispersion by changing the amounts of *β* cyclodextrin.

Formulation code	SE1	SE2	SE3	SE4	SE5
Drug: carrier	1:2	1:4	1:6	1:8	1:10
Drug (mg)	40	40	40	40	40
β cyclodextrin (mg)	80	160	240	320	400

Evaluation of solid dispersion

a) Physical appearance-

All prepared solid dispersions were evaluated for colour, appearance, percentage yield and drug content.

b) Percent practical yield

Solid dispersion was scraped and its practical yield (PY) was determined:

PY (%) = [Practical mass (SD)/Theoretical mass (Drug+ carrier)] ×100….(1)

c) Saturation Solubility study:

The saturation solubility study was performed by taking an excess amount of complex equivalent to 20 mg of drug was added to 10 ml of solvent in a screw cap glass vial. The vial is stoppered and the solution was vortexed for 2min using a cyclomixer and then shaken on a rotatory shaker for 2 days at 37° C. The saturated solution was taken out at 48 hrs and centrifuged at 2000 rpm for 15 min. An aliquot of the supernatant was then withdrawn and filtered through whatman paper 42. The filtrate

was diluted suitably if needed and absorbance was checked using a UV/Visible spectrophotometer. Concentration in each solution was calculated .[10] The solvent used in the study were water, 0.1 N HCl and 0.05 M phosphate buffer pH6 and phosphate buffer pH 6.8.[10]

Sr no	Property	Standard	Observation
1	Colour	White	Complies
2	Odour	Odourless	Complies
3	Nature	Crystalline	Complies
4	Solubility	Practically insoluble in water, slightly soluble in methanol, sparingly soluble in ethanol, soluble in dimethyl sulphoxide, freely soluble in N, N-dimethylformamide.	Complies

placed in the basket of dissolution apparatus. Dissolution studies were performed using USP type I, using rotating basket apparatus.[11] The volume of the dissolution medium was taken as 900 ml. The apparatus was rotated at 75 rpm. Dissolution was

f) XRD studies.

Crystal characteristics of pure drug and solid dispersions were evaluated by X-ray diffraction (XRD) studies, using Panlytical X' pert Pro[17].

g)Scanning electron microscopy

The shape and morphology of solid dispersion was examined using scanning electron microscopy (SEM) (JEOL Japan (JSM) 6100 series)

RESULT

Table 2: Physicochemical characterization of drug

2) FTIR spectroscopy

KBr pellet method was used to prepare pellets of the drug samples. The FT-IR spectrum of the obtained drug samples were compared with the reference standard FT-IR spectrum of Febuxostat.

d) Drug content

The prepared febuxostat solid dispersion equivalent to the drug (10mg) was weighed accurately and dissolved in 10 ml of methanol. Drug content was calculated by diluting the stock solutions with methanol and analyzed using a UV-Vis spectrophotometer at 315 nm [15].

$$\%Drug\ content = \frac{Actual\ amount\ of\ drug\ in\ solid\ dispersion}{Theortical\ amount} \times 100$$

e*) In-vitro* multimedia studies (16)

In vitro, multimedia dissolution studies of the pure drug febuxostat and optimised solid dispersions SE5 was carried out in 0.05M phosphate buffer pH 6. About 40 mg of pure drug and solid dispersion equivalent to 40 mg of drug was used for dissolution studies. FBX pure drug and the SE5 containing equivalent to 40 mg of the drug were filled in empty tea bags an

carried out for one hour with sampling points at 5 min, 10 min, 15 min, 20 min, 30 min, 45 min, and 60 min. A sample of 5ml was withdrawn at each time point for a period of 1 hour and replaced with a fresh dissolution medium. The drug released amount at a particular time point and at the end of the analysis was calculated by measuring absorbance using the appropriate blank solution and drug content was calculated using a calibration curve equation.[16]

I.R spectra of FBX and that with the polymer depicted in figure Fig.1 and Fig 2. Characteristic peaks were observed in the resultant spectra.

Table 3: FTIR characteristic bands

API	Aromatic C-H stretching	Aliphatic C–H Stretching	Nitrile $C\equiv$	Carboxylic acid	C-C stretching	C-O Stretching
Wave numbers (cm^{-1})	2968.45	2875.86	2263.34	1678.07	1514.12	1273.02

Figure 1: FTIR spectrum of febuxostat

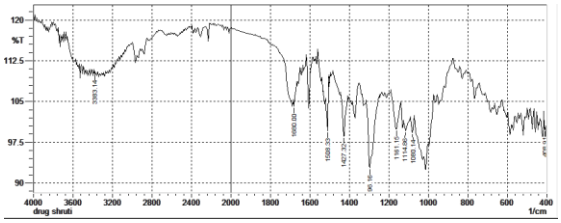


Figure 2: FTIR spectrum of β CD

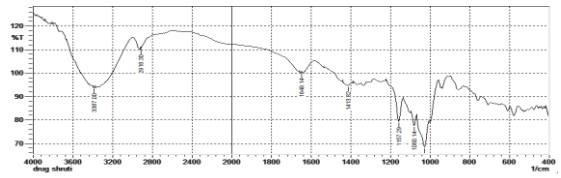
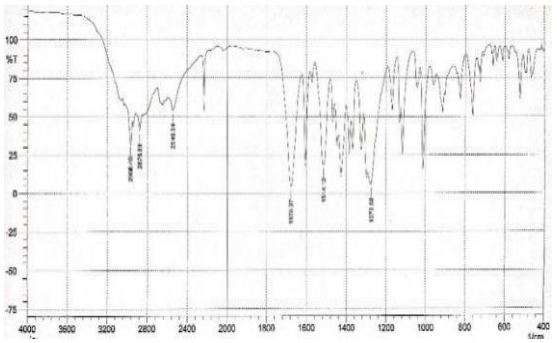


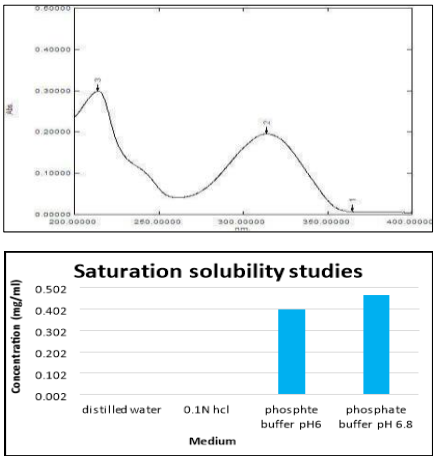
Figure 3: FTIR spectra of optimized solid dispersion SE 5 indicating no significant change in chemical integrity of drug



3) Standard calibration curve and scanning of Febuxostat in 0.05 M Phosphate buffer pH 6

The λmax of Febuxostat was found to be 313.8nm in 0.05M Phosphate buffer pH 6.

Fig4: UV Spectrum of febuxostat in 0.05 M Phosphate Buffer pH 6



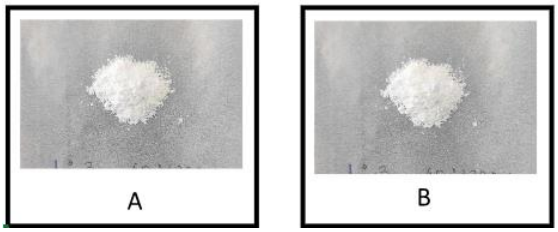
4)Preliminary solubility studies of Febuxostat

Febuxostat has shown highest saturation solubility in pH 6.8 phosphate buffer > 0.05 M phosphate buffer pH 6 > 0.1N HCl >water

Evaluation of solid dispersion

Table no 4: Physical appearance, % yield and drug content of solid dispersions

Formulation code	Drug: Polymer	Physical appearance		Percentage yield	Drug content n=3 S.D
		Colour	Appearance	(%)	(%)
SE1	1:2	Off white	Powder (granular)	99.5	99.30 ± 0.89
SE2	1:4	Off white	Powder (granular)	98.7	98.74 ± 2.64
SE3	1:6	Off white	Powder (granular)	98	97.38 ±0.59
SE4	1:8	Off white	Powder (granular)	99.3	98.8 ±1.03
SE5	1:10	Off white	Powder (granular)	99.4	98.63 ± 1.08



Saturation solubility study

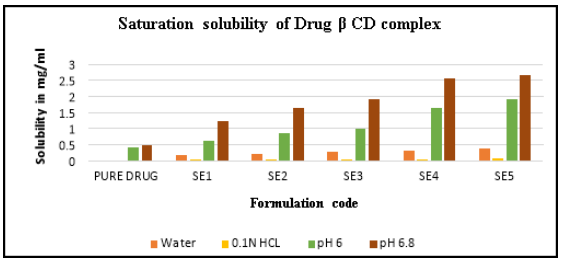


Fig 6: Saturation solubility studies of febuxostat solid dispersions

The saturation solubility studies were conducted in different buffers for all the prepared solid dispersions and compared with pure drug.

From the solubility studies, it was found that pure FBX showed greater solubility in 6.8 pH phosphate buffer when compared to others. From the results given in the table, SE5 showed greater solubility when compared to others, the solubility also increased proportionally by increasing the polymer concentration. SE5 showed the highest solubility in the 6.8 pH phosphate buffer. Hence solid dispersion SE5 gave better yield as well as good solubility so was chosen as optimized formulated solid dispersion for further formulation of the dosage form.

***Invitro* release studies of pure drug and optimised solid dispersion**

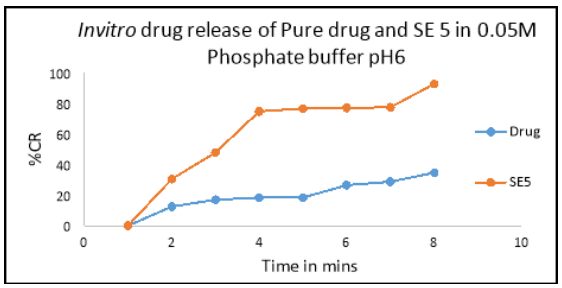


Fig 7: ***Invitro* drug releases vs time plots of Pure drug and solid dispersion SE 5 in 0.05M phosphate buffer pH 6**

According to the results obtained, solid dispersion SE 5 showed greater drug release as compared to pure drug. The above data displays the dissolution profiles of pure febuxostat drug and optimized solid dispersion SE 5 in 0.05 M phosphate buffer (pH 6). Optimized SE 5 exhibited a significant enhancement in dissolution rate when compared with the pure drug alone. In 0.05M phosphate buffer pH 6, a 4-fold increase in dissolution rate (92.88 ±1.10 vs 34.73 ±0.91 %) of optimized SE as compared to the pure drug in 60 min.

e) X-ray Diffraction

The X-ray diffraction (XRD) scan of pure FBX (Figure 8 A) showed highly sharp, intense, peaks indicating the crystalline nature of the drug. The XRD pattern of the solid dispersion SE5 (Fig 8 B) showed lesser intense and denser peaks compared pure drug indicating the decrease in crystallinity of the drug in its optimised formulation. Therefore from the observation, it could be suggested that the febuxostat drug was converted to an amorphous form after dispersion into an inner carrier in a solid state prepared solvent evaporation method.

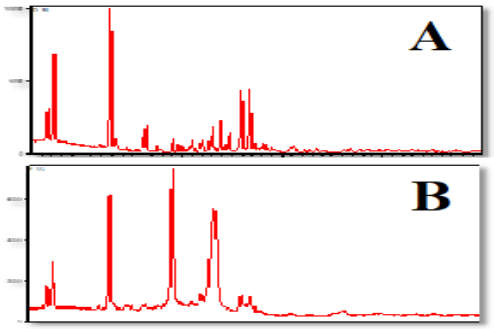


Fig 8: (A) XRD of Pure drug Febuxostat ; (B) XRD of solid dispersion SE 5

DISCUSSION

It was confirmed from FTIR studies that there was no interaction observed between the drug and the other excipients. Multimedia solubility studies were carried out for pure API FBX and it was found that it has higher solubility in DMF followed by DMSO than in ethanol following methanol. When different buffers were used it showed higher solubility in phosphate buffer pH 6.8. The solvent evaporation method was adopted to prepare complexes with different polymers in different ratios i.e. 1:2, 1:4, 1:6, 1:8, 1:10. Saturation solubility data demonstrate that the solubility of FBX increases with the use of polymers, which acts as surfactant enhancing a decrease in particle size and the wetting of drug particles. OGD medium 0.05M phosphate buffer pH 6 was also used as the medium of choice. Linearity in selected media was studied. From dissolution studies, it was found that there is a steady increase in dissolution of all formulations in all media with an acceptable relative standard deviation. Solid dispersion SE 5 (1:10 drug beta cyclodextrin complex) was selected as an optimized formulation which not only showed an increase in solubility but also an increase in *invitro* dissolution rate compared to pure drug. The XRPD study revealed the presence of an amorphous structure in the complexes prepared by a solvent evaporation method.

CONCLUSIONS:

The growing numbers of low solubility and high permeability drugs demand the development of technologies for enhancing drug solubility. The solvent evaporation method of solid dispersion provides an increase in the solubility of poorly water soluble drug FBX.

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