SOLID DISPERSION SYSTEMS OF POORLY WATER SOLUBLE DRUG FEBUXOSTAT: PREPARATION, CHARACTERIZATION AND OPTIMIZATION

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(Received 24 August 2022) (Accepted 15 September 2023)

ABSTRACT

Febuxostat is a poor soluble drug used in the management of hyperuricemia and gout. The present study aims at increasing the solubility of febuxostat by solid dispersion technique with the aid of various polymers (Beta cyclodextrin, Soluplus®, HPMC E5, and Kolliphor® P 407) in various drug: carrier ratios employing the solvent evaporation method. Solid dispersions were evaluated for physical appearance, percentage yield, drug content, saturation solubility and dissolution properties. Saturation solubility data of the study depict an increased solubility of the solid dispersion compared to the pure drug. In *in vitro* release profiles revealed that formulation SD20, having drug: Kolliphor® P 407 in 1:9 ratio exhibited highest dissolution rate. The powder X-ray diffraction study and scanning electron microscopy (SEM) exhibited a crystalline to an amorphous transformation in the solid dispersion. The study demonstrated that solid dispersions are a highly effective technique to increase solubility and bioavailability of febuxostat.

Keywords: Febuxostat (FBX), solid dispersion, hyperuricemia, gout, solvent evaporation, Kolliphor® P 407, solubility

INTRODUCTION

Poor solubility is a major challenge for the pharmaceutical industry as it affects dissolution rate and bioavailability of a drug[1]. Several factors like solubility, drug permeability, dissolution rate, presystemic first-pass metabolism and efflux mechanisms susceptibility are responsible for oral bioavailability of a drug[2]. Many drugs developed by applying combinatorial chemistry and high screening techniques encounter poor solubility problems[3]. The solid dispersion technique can help to resolve this problem. Amorphous solid dispersion formed by molecularly dispersing a drug in a polymeric matrix may lead to a decrease in particle size and increase in surface area, which results in enhancement of dissolution rates[4]. An amorphous solid does not require energy to break the crystal lattice, hence exhibiting a higher degree of solubility compared to a crystalline solid[5].

Febuxostat (FBX) is a selective potent, non-purine xanthine oxidoreductase inhibitor that lowers blood SUA levels[6]. Hyperuricemia, as termed when plasma or serum urate concentration is greater than 70 mg L^{-1}, is the primary risk for the progression of gout. The stages of progression of gout are gouty arthritis, tophaceous and nephrolithiasis[7]. Joints become stiff, swollen, red and incredibly painful due to the crystals deposited in the soft tissues, usually around joints. If gout is untreated, the disease can progress through four stages of gout; namely, asymptomatic (without symptoms) hyperuricemia, acute type, interval (intercritical) type and chronic tophaceous type[8].

Uricosuric agents are used to treat hyperuricemia and gout. The treatment mechanisms revolve around either increasing uric acid excretion or reducing the synthesis of uric acid[9].

Febuxostat is a weak acid, involved in purine catabolism. Being practically insoluble in water, its oral bioavailability is low[10]. Xanthine oxidoreductase (XOR) catalyzes hypoxanthine to xanthine and further catalyzes xanthine to uric acid. Febuxostat does not appear to inhibit other enzymes in the nucleotide catabolic pathways because the chemical structure of febuxostat does not resemble either purine or pyrimidine structures[11]. It is recommended in the treatment of symptomatic gout[12,13].

The present investigation aimed to formulate febuxostat solid dispersion (SD) using the solvent evaporation method.

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https://doi.org/10.53879/id.60.10.13648

MATERIALS AND METHODS

Materials

Febuxostat drug was kindly gifted by Watson Pharma Pvt. Ltd., Goa, India. The following polymers used in this study and their suppliers were Beta-cyclodextrin from Signet Excipients Pvt. Ltd., Mumbai, India, HPMC E5 from Molychem, Mumbai, India, Soluplus® and Kolliphor® P407 procured from BASF, Germany. All reagents used were of analytical grade.

Preformulation studies were performed on the drug to verify its identity, purity and nature.

Physicochemical characterization of drug

Appearance

The drug was observed visually for its appearance.

IR spectroscopy

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

Determination of λ_{max} and preparation of standard curve of febuxostat in 0.05M phosphate buffer pH 6 using UV spectroscopy

A standard solution of 1000 µg mL^{-1} and a working stock solution of 100 µg mL^{-1} of febuxostat (FBX) were prepared in methanol[14]. Further, diluting the working stock solution with 0.05 M phosphate buffer pH 6, a concentration equivalent to 4 µg mL^{-1} FBX solution was obtained and scanned in the range 200-400 nm on a UV spectrophotometer. The λ_{max} of the solution was determined using 0.05 M phosphate buffer pH 6.0 as blank[14].

Preparation of calibration curve

Solution with concentrations in the range of 2 to 10 µg mL^{-1} were prepared using working stock solution in phosphate buffer pH 6.0 as solvent. The absorbance was measured at 315 nm using 0.05 M phosphate buffer pH 6.0 as blank. A calibration curve was plotted of concentration (µg mL^{-1}) versus absorbance[15].

Preliminary solubility studies of febuxostat

Solubility analysis of pure drug febuxostat 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 h at room temperature of 25 °C. The resultant solution was taken out at 48 h and centrifuged at 2000 rpm for 15 min. Further, the supernatant was filtered and analysed under UV at λ_{max} 315 nm. The solvents used in the study were water, 0.1 N HCl and 0.05 M phosphate buffer pH 6.0 which is the OGD (Office of Generic Drugs) media for dissolution study and phosphate buffer pH 6.8[16].

Method of preparation of febuxostat solid dispersions (SD)

Following Tables I-IV depict solid dispersions of febuxostat prepared using various polymers in different ratios. 40 mg of febuxostat 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[17].

Table I: Formulation of febuxostat solid dispersion using β-cyclodextrin

Formulation code	SD1	SD2	SD3	SD4	SD5
Drug:carrier	1:1	1:3	1:5	1:7	1:9
Drug (mg)	40	40	40	40	40
β–cyclodextrin (mg)	40	120	200	240	360

Table II: Formulation of febuxostat solid dispersion using Soluplus®

Formulation code	SD6	SD7	SD8	SD9	SD10
Drug:carrier	1:1	1:3	1:5	1:7	1:9
Drug (mg)	40	40	40	40	40
Soluplus® (mg)	40	120	200	240	360

Table III: Formulation of febuxostat solid dispersion using HPMC E5

Formulation code	SD11	SD12	SD13	SD14	SD15
Drug:carrier	1:1	1:3	1:5	1:7	1:9
Drug (mg)	40	40	40	40	40
HPMC E5 (mg)	40	120	200	240	360

Table IV: Formulation of febuxostat solid dispersion using Kolliphor® P 407

Formulation code	SD16	SD17	SD18	SD19	SD20
Drug: carrier	1:1	1:3	1:5	1:7	1:9
Drug (mg)	40	40	40	40	40
Kolliphor®P 407 (mg)	40	120	200	240	360

EVALUATION OF SOLID DISPERSION

Physical appearance

All the solid dispersions were evaluated for physical appearance.

Percent practical yield

Solid dispersion was scraped and its practical yield (PY) was determined from the following equation:

$$PY\ (\%) = \frac{[\text{Practical mass (SD)}}{\text{Theoretical mass (Drug+ carrier)}]} \times 100 \quad ....(1)$$

Saturation solubility study

The saturation solubility study of solid dispersions (SD) was carried out by using the shake flask method. An excess quantity of drug-complex mixture equivalent to 20 mg of the drug was added to 10 mL of solvent in a screw cap glass vial. The vial was stoppered and the solution was vortexed for 2 min using a cyclomixer, and then shaken on a rotatory shaker for 2 days at 37 °C. The saturated solution was taken out at 48 h and centrifuged at 2000 rpm for 15 min. An aliquot of the supernatant was withdrawn and filtered, and absorbance was checked using a UV-Visible spectrophotometer. Concentration of drug in each solution was calculated[14]. The solvents used in the study were water, 0.1 N HCl and 0.05 M phosphate buffer pH 6.0 and phosphate buffer pH 6.8[13].

Drug content

The prepared febuxostat solid dispersion equivalent to 10 mg of the drug was weighed accurately and dissolved in 10 mL of methanol. Drug content was calculated by diluting the stock solutions with methanol, and analysed using a UV-Vis spectrophotometer at 315 nm[18].

$$\%\ \text{Drug content} = \frac{\text{Actual amount of drug in solid dispersion}}{\text{Theortical amount}} \times 100 \quad ....(2)$$

In vitro media dissolution studies[19]

In vitro dissolution in water, 0.1 N HCl, 0.05 M phosphate buffer pH 6.0, and phosphate buffer pH 6.8 was carried out for pure drug febuxostat and prepared solid dispersions. 40 mg of pure drug and solid dispersion equivalent to 40 mg of drug was used for dissolution studies; and were filled in empty tea bags and placed in the basket of dissolution apparatus. Dissolution studies were performed using USP type I, using rotating basket apparatus[20]. Dissolution was carried out for 1 h in 900 mL media and 75 rpm with sampling points at 5 min, 10 min, 15 min, 20 min, 30 min, 45 min and 60 min. Amount of drug released was calculated using UV spectroscopy[19].

X-ray diffraction (XRD) studies

Crystal characteristics of pure drug and solid dispersions were assessed by X-ray diffraction (XRD) studies using PANalytical X'pert Pro21.

Scanning electron microscopy

The shape and surface morphology of the optimised solid dispersions was examined using scanning electron microscopy (SEM) (JEOL (Japan) JSM 6100series).

RESULTS

The physicochemical characteristics of febuxostat drug are as tabulated in Table V.

Table V: Physicochemical characterization of drug

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 and soluble in dimethyl sulphoxide	Complies

FTIR spectroscopy

The FT-IR spectrum of the obtained drug samples were analysed against the reference standard FT-IR spectrum of febuxostat. The characteristic bands are depicted in Table VI. IR spectra of FBX and that of the drug polymer mixture are depicted Fig. 1 and Fig. 2. FTIR spectra of drug and solid dispersions indicate absence of interaction between drug and carriers.

Standard calibration of febuxostat in 0.05 M phosphate buffer pH 6

The λ_{max} of febuxostat was found to be 313.8 nm in 0.05M phosphate buffer pH 6.0 as depicted in Fig. 3. The linearity in 0.05 M phosphate buffer pH 6.0 is found in the range of 2-10 µg mL^{-1}, as depicted in Fig. 4.

Table VI: FT-IR characteristic bands

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

Preliminary solubility studies of febuxostat

Febuxostat showed highest saturation solubility in pH 6.8 phosphate buffer followed by 0.05 M phosphate buffer pH 6.0, 0.1 N HCl and water, as shown in Fig. 5.

The physical appearance, percent yield and drug content of all the solid dispersions prepared are depicted in Table VII. The dispersions varied from transparent gel to white granules in appearance, depending on the polymer and concentration. The febuxostat:β-cyclodextrin solid dispersions appeared as off white granular powder and the febuxostat:Soluplus® solid dispersion appeared as white granular powder in drug:carrier ratios of 1:1 and 1:3 respectively. In higher ratio, the dispersion forms a gel like appearance, thus affecting the yield. A similar phenomenon was observed with HPMC E5 and Kolliphor® P407 solid dispersions. Various appearances of the solid dispersions are depicted in Fig. 6.

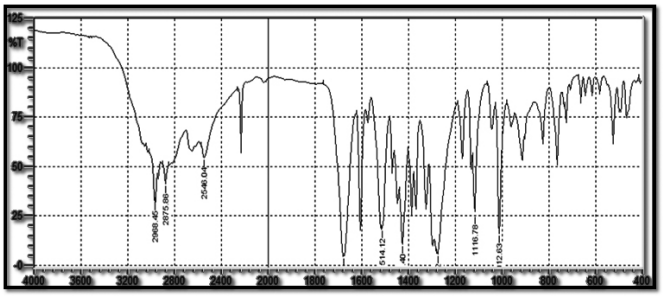

Fig. 1: FT-IR spectrum of febuxostat

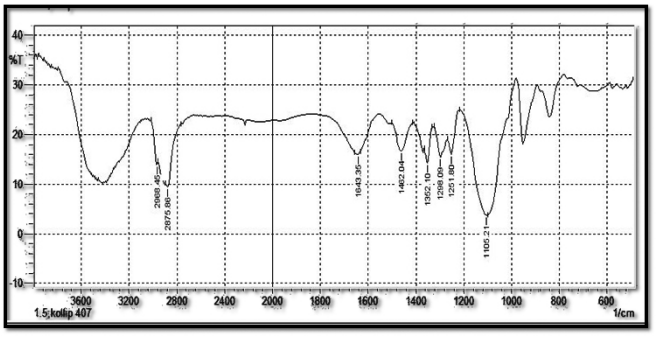

Fig. 2: FT-IR spectra of optimized solid dispersion SD18 indicating no significant change in chemical integrity of drug

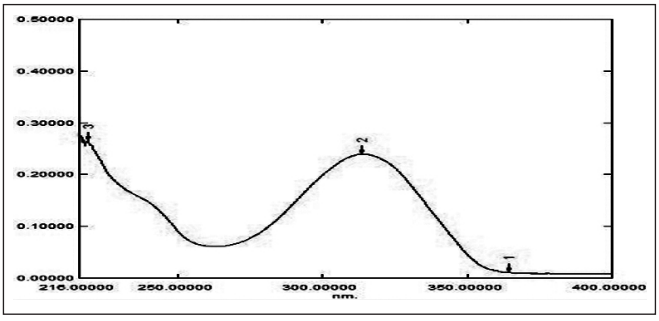

Fig. 3: UV spectrum of febuxostat in 0.05 M phosphate buffer pH 6.0

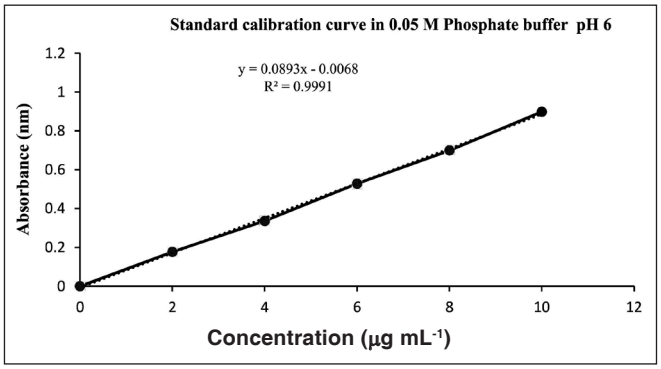

Fig. 4: Standard calibration curve of febuxostat in 0.05 M phosphate buffer pH 6.0 at 313.8 nm

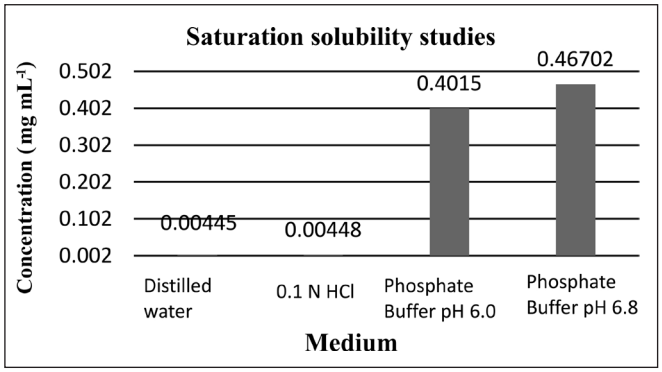

Fig. 5: Saturation solubility of pure drug

Saturation solubility studies

Solubility studies exhibited pH-dependant solubility, i.e. febuxostat showed greater solubility in pH 6.8 phosphate buffer media when compared to others. As observed from Fig. 7, solid dispersions with Kolliphor® P407 showed greater solubility when compared to other

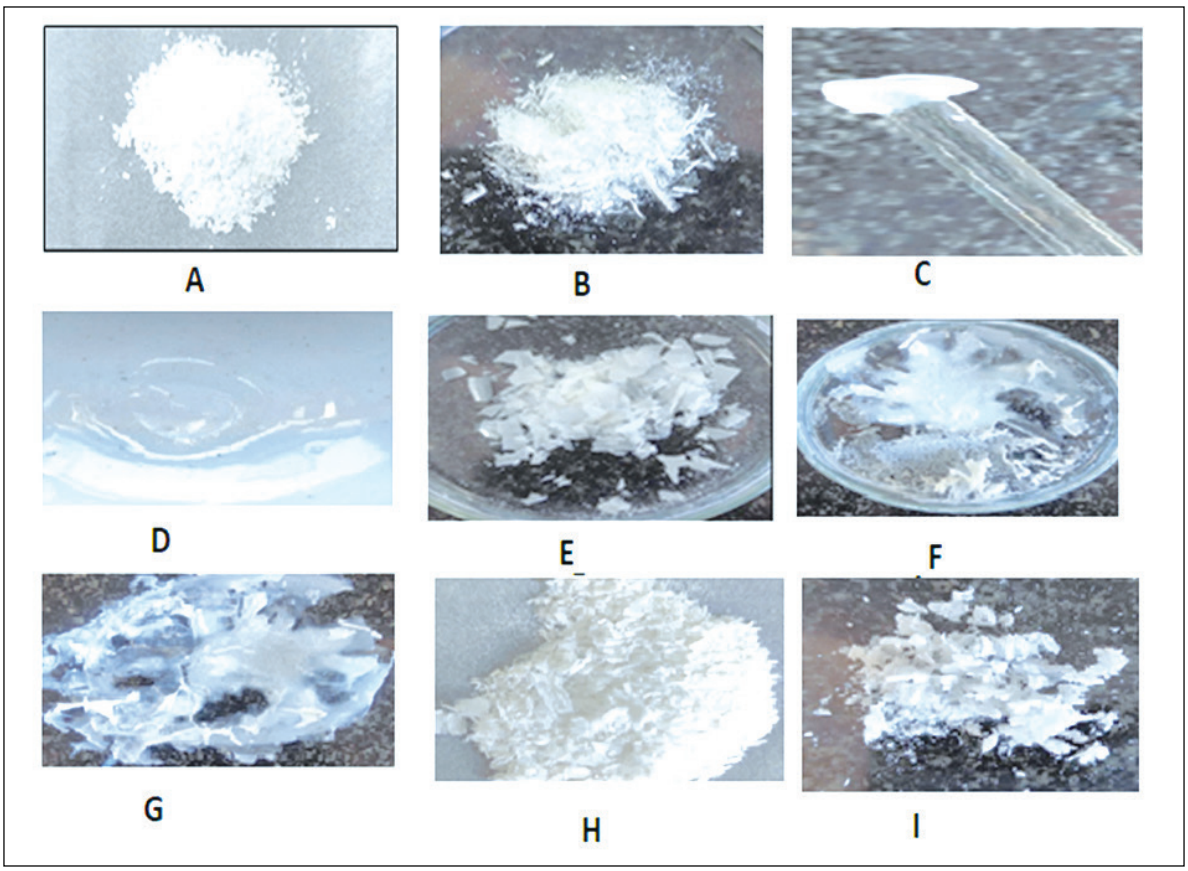

Fig. 6: (A) Drug:cyclodextrin (1:1) solid dispersion; (B) Drug:Soluplus®(1:3) solid dispersion; (C) Drug:Soluplus®(1:5) solid dispersion; (D) Drug:Soluplus®(1:10) solid dispersion; (E) Drug:HPMC E5(1:5) solid dispersion; (F) Drug:HPMC E5 (1:7) solid dispersion; (G) Drug:HPMC E5 (1:9) solid dispersion; (H) Drug:Kolliphor® P407 (1:5) solid dispersion; (I) Drug:Kolliphor® P407(1:9) solid dispersion

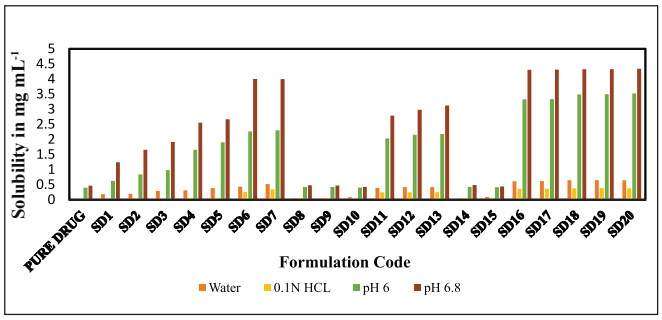

Fig. 7: Saturation solubility studies of febuxostat solid dispersions

carriers; the solubility also increased proportionally by increasing the polymer concentration.

Kolliphor® P 407 can act as a gelling agent at high concentrations, but it does not affect drug solubility from solid dispersions. From all the above formulations, SD20 showed the highest solubility in pH 6.8 phosphate buffer but with one limitation namely, that there was loss of drug, thereby giving less practical yield and drug content. Hence, solid dispersion SD 18, which exhibited better yield as well as good solubility, was chosen as optimized formulated solid dispersion.

In vitro multimedia studies of pure drug and solid dispersions

The dissolution studies of formulated solid dispersions in different media, indicated greater drug release in comparison to pure drug. The present work shows a higher dissolution rate of FBX solid dispersions with Kolliphor® P407 as compared to other polymers investigated. Figs. 8, 9 10 and 11 show the dissolution profiles of pure febuxostat drug and optimized solid dispersion SD18 in water, 0.1 N HCl (pH 1.2), 0.05 M phosphate buffer (pH 6.0) and phosphate buffer (pH 6.8). Optimized solid dispersion SD 18 exhibited a significant enhancement in dissolution rate in all the media under investigation when compared with the pure drug alone.

In water, a 20-fold increase in dissolution rate (53.77 ±1.10 vs 2.61 ±0.91 %) of optimized SD as compared to

the pure drug was observed in 60 min. In HCl, a 4-fold increase in dissolution rate (9.12 ± 2.34 vs. 2.90 ±1.83 %) of optimized SD 18 dispersion compared to the pure drug in 60 min was observed. Similarly, in 60 min, a 3-fold (80.63 ± 1.24 vs 34.73 ±0.87 %) and 2.4 -fold (93.33±2.34 vs. 38.34 ± 1.87 %) increase in dissolution of optimized SD was observed in pH 6.0 phosphate buffer and pH 6.8 phosphate buffer, respectively.

X-ray diffraction

The X-ray diffraction (XRD) scan of pure febuxostat exhibited highly sharp, intense peaks, indicating the

Table VII: Physical appearance, % yield and drug content of solid dispersion

Formulation code	Drug: Polymer	Physical appearance		Percentage yield	Drug content[a]
		Colour	Appearance	(%)	(%)
SD1	1:1	Off white	Powder (granular)	99.5	99.30 ± 0.89
SD2	1:3	Off white	Powder (granular)	98.7	98.74 ± 2.64
SD3	1:5	Off white	Powder (granular)	98	97.38 ±0.59
SD4	1:7	Off white	Powder (granular)	99.3	98.8 ±1.03
SD5	1:9	Off white	Powder (granular)	99.4	98.63 ± 1.08
SD6	1:1	Off white	Powder (granular)	99	99.3 ± 1.55
SD7	1:3	Off white	Powder (granular)	98	98.92±0.26
SD8	1:5	Transparent film	Gel formation	50	36.39±3.07
SD9	1:7	Transparent film	Gel formation	17.8	12.09±0.56
SD10	1:9	Transparent film	Gel formation	8.33	6.23±2.25
SD11	1:1	White	Powder flakes	98.2	98.77 ± 0.55
SD12	1:3	White	Powder flakes	99.4	98.93 ± 1.01
SD13	1:5	White	Powder flakes	98.6	99.56 ± 0.48
SD14	1:5	White + transparent	Powder flakes along with gel formation	53.57	43.36 ±3.07
SD15	1:9	White + transparent	White transparent film formation	52.7	40.46 ±0.15
SD16	1:1	Off white	Powder (granular)	99	99.83 ± 1.94
SD17	1:3	Off white	Powder (granular)	99.4	99.65 ± 3.86
SD18	1:5	Off white	Powder (granular)	99.6	101.11 ± 0.76
SD19	1:7	Off white	Powder (granular) + gel	71.4	67.37±3.46
SD20	1:9	Off white	Powder(granular) + gel	77.2	69.38±2.38

[a]*mean±SD, n = 3*

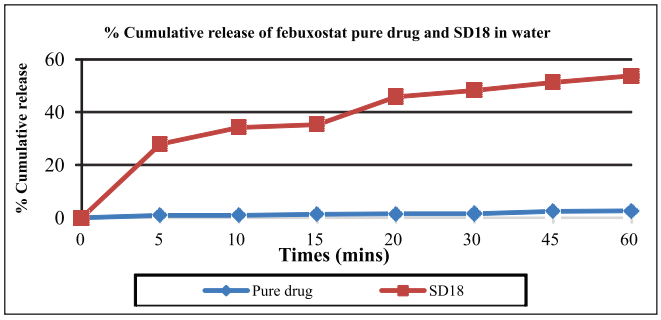

Fig. 8: *In vitro* drug release profile of febuxostat pure drug and solid dispersion SD18 in distilled water

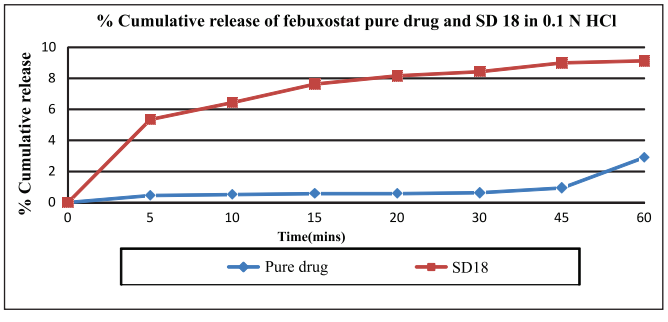

Fig. 9: *In vitro* drug release profile of febuxostat pure drug and solid dispersions SD18 in 0.1 N HCl

crystallinity of the drug as depicted in Fig. 12. The XRD pattern of SD18 showed less intense and denser peaks i.e. exhibited a halo pattern compared to pure drug, suggesting the desired decrease in crystalline

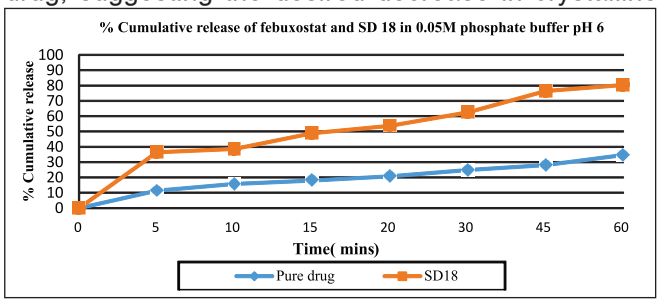

Fig. 10: *In vitro* drug release profile of febuxostat pure drug and solid dispersion SD 18 in 0.05 M phosphate buffer pH 6

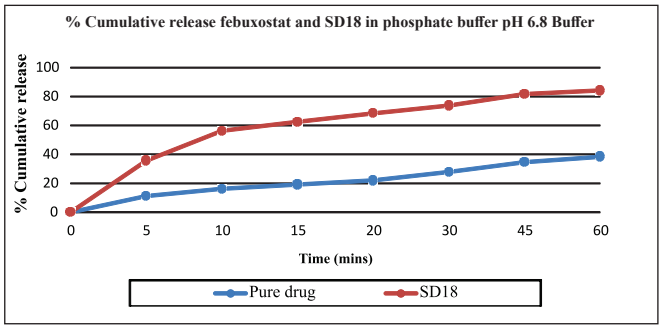

Fig. 11: *In vitro* drug release profile of febuxostat pure drug and solid dispersion SD18 in phosphate buffer pH 6.8

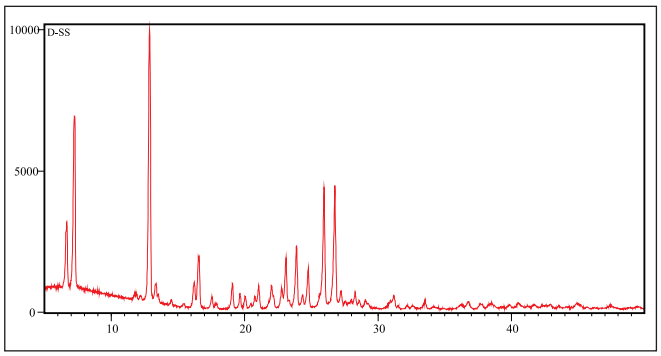

Fig. 12: XRD of pure drug febuxostat

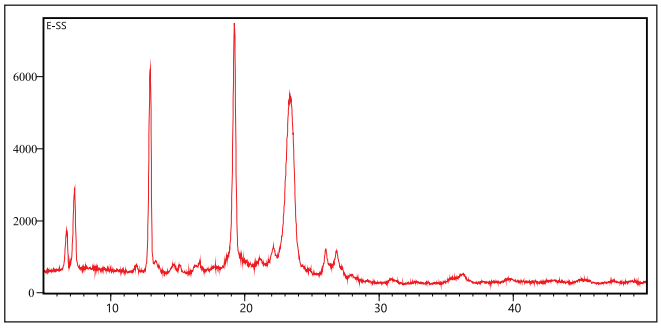

Fig. 13: XRD of solid dispersion 18

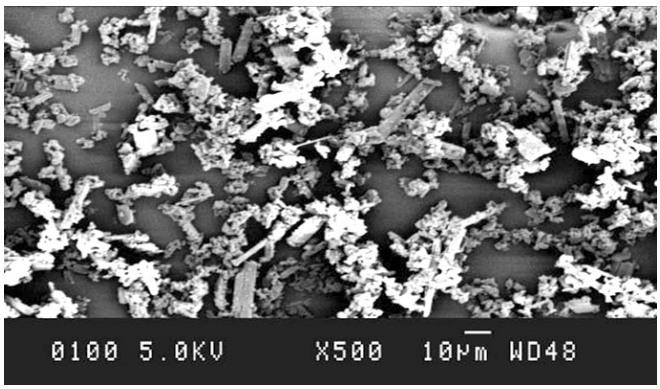

Fig. 14: SEM image of pure drug

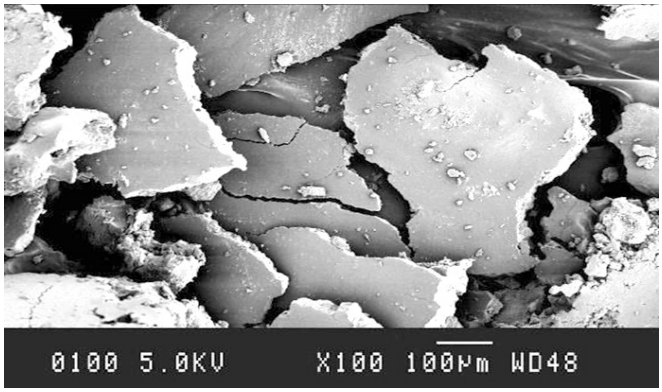

Fig. 15: SEM image solid dispersion SD 18

nature of the drug in its solid dispersion SD 18, as depicted in Fig. 13. Therefore, from the observation, it could be suggested that the febuxostat drug was converted to an amorphous form after dispersion into an inert carrier in a solid state formulation by solvent evaporation method.

Scanning electron microscopy

The drug crystals of febuxostat appeared to be agglomerated in bundles, rod-shaped, irregular in shape and size as in Fig. 14. In the case of solid dispersion, the drug surface appears more porous in nature. The drug in solid dispersion appeared to be embedded within the matrix of the polymer, as seen in Fig. 15. It could be concluded from SEM studies that the febuxostat solid dispersion exhibited an amorphous form, thus contributing to the improved dissolution rate of the drug.

DISCUSSION

It was confirmed from FT-IR studies that there was no interaction observed between the drug and the other excipients. Solubility studies of pure drug febuxostat exhibited higher solubility in DMF followed by DMSO, than in ethanol followed by methanol. Amongst the different

buffers, 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. 1:1, 1:3, 1:5, 1:7 and 1:9. Saturation solubility data established that the solubility of FBX increases with the use of polymers as carriers, which act as surface enhancers by decrease in particle size and the wetting of drug particles. Polymers showed higher solubility and dissolution in the order of - Kolliphor® P 407 > Soluplus® > β- cyclodextrin > HPMC E5. 0.1 N HCl (pH 1.2), water, phosphate buffer pH 6.8 and OGD medium 0.05M phosphate buffer pH 6.0 were the media used for dissolution studies. From the dissolution studies, it was found that there is a steady increase in dissolution of all formulations in all the studied media with an acceptable relative standard deviation. Solid dispersion SD 18 (1:5 drug Kolliphor® P407) was selected as an optimized formulation, which not only showed an increase in solubility but also an increase in *in vitro* dissolution rate compared to the pure drug. The XRPD study revealed the presence of an amorphous structure in the complexes prepared by a solvent evaporation method. SEM photographs indicate the reduction in the particle size after the dispersion of the drug in the carrier.

CONCLUSION

A large number of drugs that possess low solubility demand the development of technologies for enhancing drug solubility. The solvent evaporation process of solid dispersion is an excellent technique that provides an increase in the solubility of the poorly water soluble drug febuxostat.

ACKNOWLEDGEMENTS

The authors are thankful to CIL, Punjab University for carrying out XRD and SEM studies.

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