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Formulation Development of Immediate Release Tablets of Febuxostat using different hydrophilic polymers

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ABSTRACT
Febuxostat is a BCS class II molecule with low solubility and high permeability in aqueous fluids. Various methods to enhance the solubility of `Febuxostat were published in literature. In current investigation, we investigated the solubility of Febuxostat in different hydrophilic polymers. The selected polymers were used in a simple, economical, industrially feasible wet granulation technique. Cremophor RH40 and Tween 80 were selected based on solubility studies.F-MELT is a proprietary spray–dried powder of pharmaceutical excipients consisting of carbohydrates, inorganic ingredients and disintegrantsis used a diluent for granulation. Cremophor RH 40 and Tween 80 were used in ratio of 1:0.1; 1:0.2 and 1:0.3, singly and in combination. Granules made with Cremophor RH 40 and Tween 80 (1:0.2 and 1: 0.3 ratio) showed poor flow and sticking during compression. Based on the $t_{max}$of marketed Febuxostat tablets, 2.1 pH simulated gastric fluid was selected for dissolution studies.Tablets with both the polymers in the ratio of (1: 0.1:0.1) showed increased release profile when compared with marketed product. DSC graphs show a shift in melting point of Febuxostat and XRD results showed decrease in crystallinity when compared with pure Febuxostat API.
Keywords: Cremophor RH 40;Tween 80;Febuxostat; F-Melt.

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INTRODUCTION

One of the challenging requests of drug development is to enhance the dissolution behaviour of drugs that are poorly soluble drug in water. Various techniques such as complex formation with polymers, size micronization, solubilisation, modification of physical form, preparing a prodrugs, derivatization of drug and others have been used to improve the dissolution and bioavailability of drugs with low water solubility. Febuxostat is a nonpurine selective inhibitor of xanthine oxidase that works by non-competitively blocking the channel leading to the active site on xanthine oxidase. Xanthine oxidase is needed to successively oxidize both hypoxanthine and xanthine to uric acid. Febuxostat inhibits xanthine oxidase, thereby reducing production of uric acid. For treatment of hyperuricemia in patients with gout, Febuxostat is recommended at 40 mg or 80 mg once daily. According to the Biopharmaceutics Classification System Febuxostat is classified as a class 2 compound (low solubility, high permeability)[1-6]. Febuxostat is practically insoluble in water, which results in a low bioavailability following oral administration[7-10].The objective of this work was to increase the solubility and ultimately dissolution of Febuxostat by simple, economical and conventional wet granulation technique where Febuxostat is dispersed in a aqueous fluids containing wetting agent and a binder. Solid state characterizations were performed by differential scanning calorimetry (DSC) to determine the shift in melting point and X-ray diffraction of powder was done to demonstrate the crystallinity of the dispersions

MATERIAL AND METHODS

Materials:

Febuxostat was received as a gift sample from Glenmark Pharmaceuticals Limited, Mumbai.,Poloxamer 188, Cremophor RH40 was received as gift samples from BASF.Labrasol, and Transcutol HP were obtained from Gattefosse. Tween 80 was obtained as gift sample from Croda. HPC was obtained as gift sample from Ashland. F-Melt Type C was obtained as gift sample from Fuji Chemicals. Magnesium Stearate was obtained as gift sample from Roquette.

Determination of Febuxostat solubility in Solubilizers.

The solubility of Febuxostat in aqueous solutions with solubilizers (Transcutol HP , Cremophor-RH 40, Labrasol, Poloxamer188, Polysorbate 80 was determined by adding excess amount of Febuxostat into 50 mL solutions with solubilizers (5%, w/w) in tubes, the mixtures were stirred for 24hours at room temperature. After equilibrium, excess insoluble Febuxostat powder was removed by filtration. The solubilized Febuxostat contents in the solutions were quantified using an HPLC system equipped with a UV detector and reverse-phase C18 column.

Methods:

Manufacturing of Tablets

Table 1: Formulation compositions of Febuxostat Tablets

Ingredients (mg/tablet)	FB 4	FB 5	FB 6	FB 10	FB 11	FB12	FB16	FB18	FB20
Dry Mix									
F-Melt Type C	217.0	213.0	209.0	217.0	213.0	209.0	213.0	205.0	197.0
Binder solution									
Febuxostat	40.0	40.0	40.0	40.0	40.0	40.0	40.0	40.0	40.0
Cremophor RH40	-	-	-	4.0	8.0	12.0	4.0	8.0	12.0
Tween 80	4.0	8.0	12.0	-	-	-	4.0	8.0	12.0
Hydroxypropyl cellulose	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0
Purified Water	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Lubrication									
Magnesium Stearate	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0
Total	300.0	300.0	300.0	300.0	300.0	300.0	300.0	300.0	300.0

Manufacturing Process:

F-Melt Type C was sifted through #40 ASTM mesh. Hydroxypropyl cellulose was dissolved in purified water under stirring to form a clear solution. Tween 80 (for formulations FB 4,FB 5 and FB6), Cremophor RH 40(for formulations FB 10, FB11, FB12) and combination of Cremophor RH 40 and Tween 80 (for formulations FB16, FB18 and FB 20) were added into HydroxyPropyl cellulose binder solution and stirred to form a clear solution. Febuxostat was sifted through #40 ASTM and added to solutions of formulations (FB4 to FB 20) under stirring to form a uniform dispersion.The sifted F-Melt Type C was placed in a granulator and preheated at inlet temperature of 55°C ± 10°C till the product temperature 40 ± 10°C is achieved. Granulation was carried out on preheated F-Melt Type Cwith inlet temperature 55 ± 10°C and product temperature of 40°C ± 10°C. The wet granules are dried at inlet temperature at 60 ± 10°C and product temperature at 50 ± 10°C to get LOD below 1%.The dried granules were sifted through # 40 ASTM mesh and blended in a blender for 15 min at 10 rpm.Magnesium Stearate was sifted through 60 # ASTM mesh and added to blended granules and blended for 5 min at 10 rpm and compressed into tablets.

In vitro Dissolution studies:

Febuxostat is rapidly absorbed with t_{max} of 1.0-1.5 h.The t_{max} value indicates absorption takes place from stomach where the pH is 1.2.To mimic the gastrointestinal conditions for stomach SGF pH 2.1 (250 ml), Paddle-50 rpm, Time points- 5, 10, 15, 20, 30, 45, 60 was selected as dissolution medium.

Solid state characterization: Solid state characterization studies like Differential scanning calorimetry and X-ray diffraction (XRD) were carried out to check for the amount of crystallinity present in optimized formulation when compared with pure Febuxostat API.

Differential scanning calorimetry (DSC): The variation of melting point and crystal form of samples were demonstrated on a DSC instrument (STARe, Mettler Toledo Corporation, Switzerland). FXT and optimized formulation were weighed (2–5 mg) and heated in aluminum pans, respectively. The scanning rate was 10 °C/min and the temperature ranged from 20 °C to 300 °C.

X-ray diffraction (XRD): The X-ray diffraction pattern of Febuxostat API and optimized formulation was carried out using Empyrean- Expert XRD Diffractometer. The data was recorded at start 2θ of 2.0076 and end 2θ position of 39.9806 of the range inside copper target tube of X-ray at the step size of 0.0130.

RESULTS AND DISCUSSION

Selection of optimum solubiliser.

To find an appropriate solubilizer, the saturated solubility of Febuxostat was measured in different oils and surfactants. The experimental results confirmed that the used solubilizers increased the solubility of Febuxostat. In particular, the solubilities of Febuxostat in Tween 80 and Cremophor RH40 were found to be higher than solubilities of Febuxostat in Labrasol and Transcutol –P.

Table 2: Solubility studies of Febuxostat on aqueous solutions with various solubilizers.

Solubiliser	Saturation solubility (g/ml)	% Increase
Purified Water	13.3 ± 9.7	-
Tween 80	259.6 ±2.7	19.5
Labrasol	190.5± 6.4	14.3
Transcutol-P	53.3± 4.5	4.0
Poloxamer 188	49.1± 3.4	3.7
Cremophor RH 40	288.4± 2.1	21.6

Among all the solubilisers studied, Tween 80 and Cremophor RH 40 showed nearly 20% increase in Febuxostat solubility when compared with Febuxostat API alone. Hence both these solubilizers were selected to study their influence on dissolution enhancement of tablets.

Table 3: Physical Characterization of Febuxostat Formulations

Parameters	FB 4	FB 5	FB 6	FB 10	FB 11	FB12	FB16	FB18	FB20
Physical Properties of Lubricated Blend									
Bulk Density (g/ml)	0.51	0.52	0.50	0.51	0.52	0.55	0.51	0.38	0.39
Tapped Density (g/ml)	0.66	0.66	0.65	0.66	0.63	0.63	0.66	0.57	0.58
Compressibility Index (%)	29.41	26.92	30.00	29.41	21.15	14.55	29.41	50.00	48.72
Haunser ratio	1.29	1.26	1.30	1.30	1.27	1.14	1.29	1.50	1.48
Physical Properties of Tablet									
Hardness (N)	87 -91	79-88	82-92	75-86	78-85	71-80	65-70	66-75	70-76
Disintegration time (seconds)	69-78	69-85	78-88	68-79	78-84	74-85	71-82	102-120	104-130
Observation	No Sticking observed	No Sticking observed	No Sticking observed	No Sticking observed	No Sticking observed	No Sticking observed	No Sticking observed	Sticking observed during compression	Sticking observed during compression

Table 4 : Dissolution of Febuxostat Formulations

Time Points	Marketed Product (Uloric)	FB 4	FB 5	FB 6	FB 10	FB 11	FB12	FB16
5 minutes	14±5.5	9±4.6	13±4.2	18±3.9	16±5.1	15±4.1	17±5.6	24±5.3
10 minutes	19±3.1	19±1.2	20±1.3	24±2.1	23±3.1	22±3.2	26±2.3	32±3.1
15 minutes	24±1.2	25±1.5	26±1.8	33±3.0	30±2.9	28±2.8	33±2.1	40±2.0
20 minutes	29±1.2	30±1.8	32±2.0	40±1.5	35±2.8	34±3.6	38±2.5	46±2.5
30 minutes	37±1.8	38±2.0	42±1.4	51±2.1	42±2.8	43±2.1	47±2.1	55±3.0
45 minutes	48±2.4	48±2.6	54±1.9	61±2.0	51±3.2	54±2.2	57±2.0	65±2.0
60 minutes	57±2.0	55±2.4	62±3.1	68±2.0	58±2.0	62±2.3	64±2.1	72±2.5

DSC Interpretation: The various differential scanning calorimetric curves are shown in figure-4. In DSC thermo gram of Febuxostat a sharp endothermic peak is observed at 210.63 °C analogues to its melting point. Whereas in DSC thermo graph of optimized formulation, a significant reduction in height of an endothermic peak and heat of fusion was observed, which indicated a decrease in the crystallinity of Febuxostat? This physical state transformation results in higher water solubility and better dissolution behaviour.

Table 5: DSC curve interpretation

Parameter	Febuxostat API	Optimized Formulation (F16)
Peak Onset	210.63	167.68
Peak Height	-24 mW	-7 mW
Peak Area	-253.71 mJ	-88.20 mJ
Heat of fusion	-115.22 J/g	-41.45 J/g

Fig: 1: DSC graph of Febuxostat API

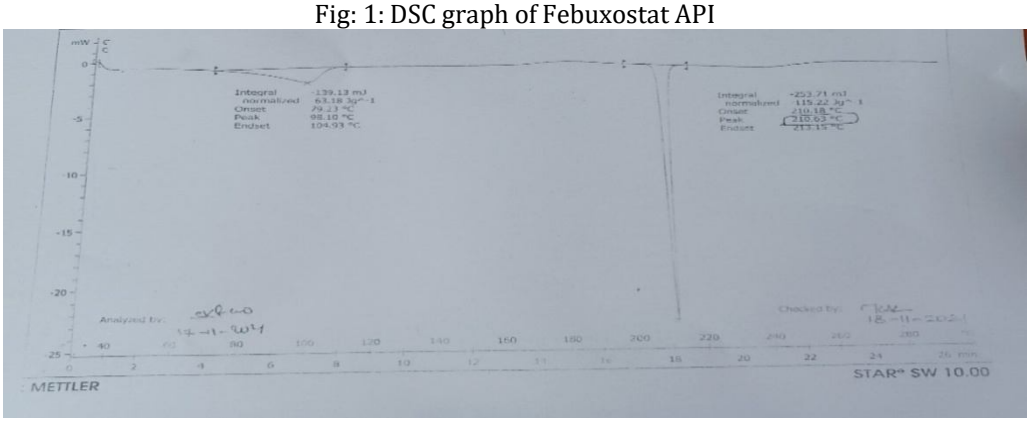
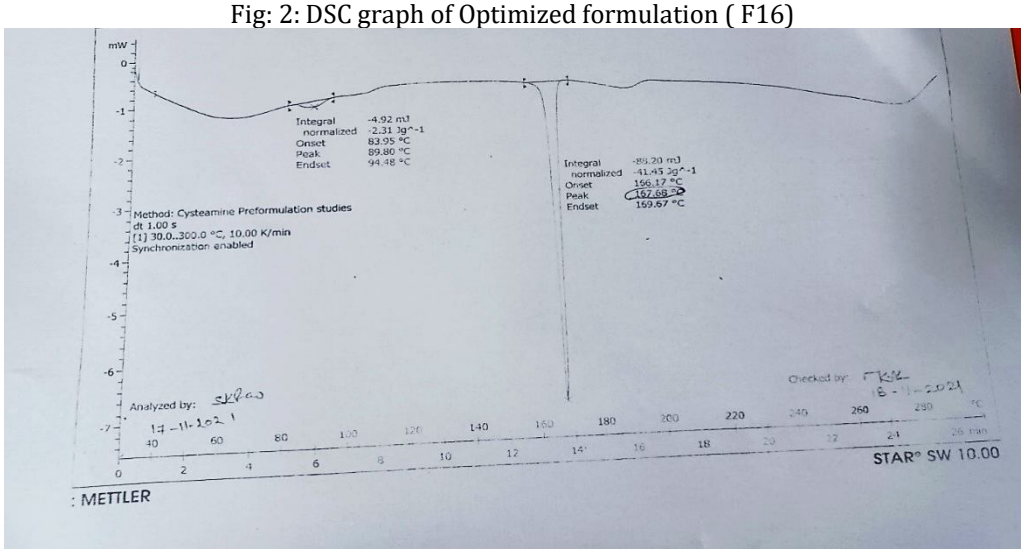


Fig: 2: DSC graph of Optimized formulation (F16)



X Ray Diffraction: The XRD scan of pure Febuxostat and optimized formulation are shown in Figures. 5. The XRD behaviour of pure Febuxostat illustrated strong and sharp peaks outlining well defined crystal structure; however the XRD pattern of optimized formulation depicted an observable decrease in number as well as magnitude of peaks compared to pure Febuxostat confirming the reduction in crystal behaviour or noticeable amorphization of dispersed drug.

Fig: 3: XRD graph of Febuxostat API

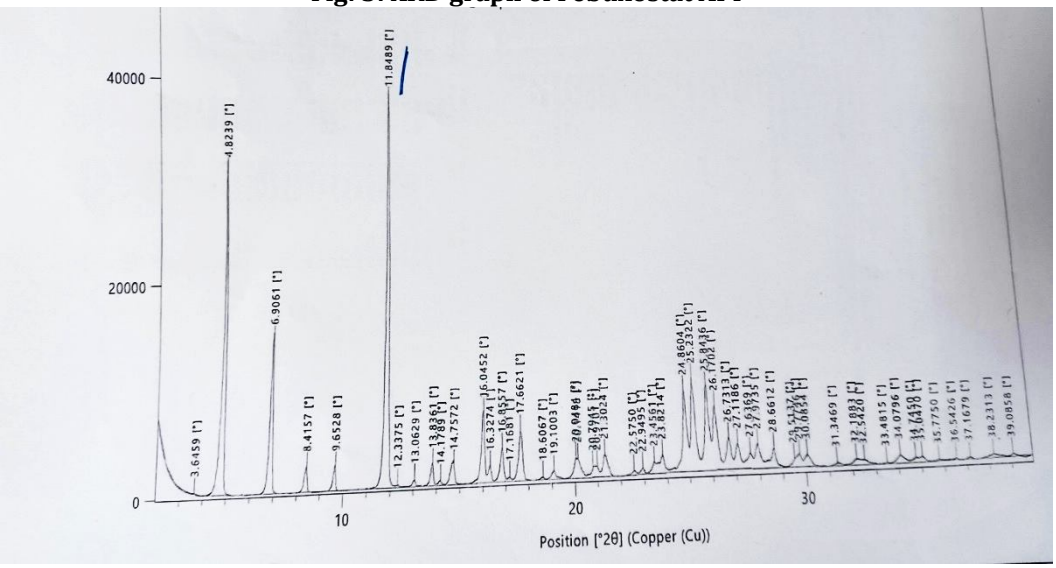
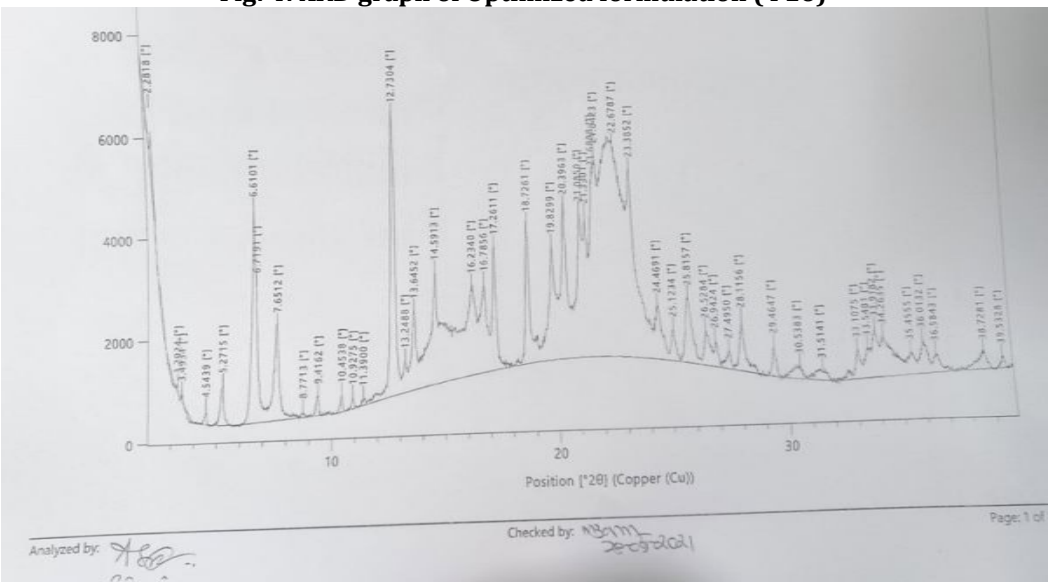


Fig: 4: XRD graph of Optimized formulation (F16)



CONCLUSION

The current investigation established an effective and easy method to formulate Febuxostat immediate release tablets with increased water solubility and dissolution. Febuxostat immediate release tablets were prepared by wet granulation technique using different Drug: Polymer ratio. Out of all the, the one with drug to polymer ratio of 1:0.1:0.1of Febuxostat, Cremophor RH 40 and Tween 80 was proved to have the best results in terms of dissolution. Optimized formulation showed increased dissolution of Febuxostat up to 72 % after 60 min. DSC thermo graph of optimized formulation , a significant reduction in height of an endothermic peak and heat of fusion was observed, which indicated a decrease in the crystallinity of Febuxostat.The XRD behaviour of pure Febuxostat illustrated strong and sharp peaks outlining well defined crystal structure; however the XRD pattern of optimized formulation depicted an observable decrease in number as well as magnitude of peaks compared to pure Febuxostat confirming the reduction in crystal behaviour or noticeable amorphization of dispersed drug.

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CONFLICT OF INTREST

The authors declare no conflict of interest.

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