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Formulation and invitro evaluation of immediate release tablets containing febuxostat

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Abstract

Febuxostat Immediate Release Tablet were prepared by direct compression method using varying concentrations of Lycoat, Crospovidone & Croscarmellose sodium as disintegrants. The formulations prepared were evaluated for Precompression& post compression parameters. Form the drug excipient compatibility studies we observe that there are no interactions between the pure drug (Febuxostat) and optimized formulation (Febuxostat + excipients) which indicates there are no physical changes. Post compression parameters was found to be within the limits. Among the formulation prepared the tablet containing 12mg of CCS shows 98.45% of the drug release within 40 min & follows first order kinetics.

Introduction

Febuxostat, chemically 2-[3-cyano-4-(2-methylpropoxy) phenyl]-4-methylthiazole-5-carboxylic acid, is a potent, non-purine selective inhibitor of xanthine oxidoreductase. Febuxostat 40 and 80 mg once daily (QD) is approved in the United States and the United Kingdom for the chronic management of hyperuricemia in patients with gout [1, 2].

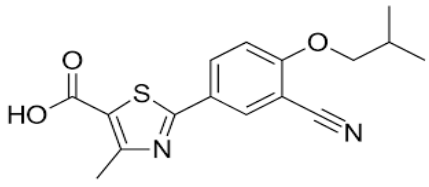

Fig 01: Chemical structure of Febuxostat

Gout is a disease that results from the deposition of urate crystals in synovial fluid and other tissues due to its saturation in blood. There are four clinical stages viz. asymptomatic hyperuricemia, acute gouty arthritis, inter-critical gout and chronic tophaceous gout [3].

Xanthine oxidoreductase enzyme can be present in two different isozymic forms [4]. Based on the literature review formulated and developed new methods for the drug and perform the evaluation by calculating the differencing parameters

Experimental work

Materials

Febuxostat from Spectrum labs ltd, Hyderabad, Lycoat , Crospovidone , Croscarmellose sodium from Signet Chemical Corp., Mumbai , Microcrystalline cellulose from Aurbindo Pharma Ltd., Hyd., talc and Magnesium sterate form SD Fine chem ltd.

Instruments

Digital balance form Essae-Teraoka ltd, DS-852j, Hardness tester from Monsanto, Friability test apparatus from Electrolab USP EF2, Hydraulic press from Clit pilot press, Vernier caliper from Pico India Ltd, Tablet dissolution tester (USPII) from Lab India DS8000, Tap density tester from K.E.India, UV Spectrophotometer from PG Instruments, T60, FTIR Spectrophotometer from Shimadzu -8400 S and pH meter from Hanna Instruments, Italy.

PREFORMULATION STUDIES [12-17]

It is one of the important prerequisite in development of any drug delivery system. Preformulation studies were performed on the drug, which included melting point determination, solubility and compatibility

studies.

Determination of UV spectrum of Febuxostat

10mg of Febuxostat was dissolved in 2-3ml of methanol then makeupto10ml with 6.8pH buffer so as to get a stock solution of 1000 µg/ml concentration. From the above stock solution pipette out 1ml of the solution and makeup the volume to 10ml using 6.8pH buffer to get the concentration of 100µg/ml concentration. From this stock solution pipette out 1ml of the solution and makeup the volume to 10ml using 6.8pH buffer to get the concentration of 10µg/ml concentration, this solution was scanned under UV Spectroscopy using 200-400nm.

Preparation of Standard Calibration Curve of Febuxostat in pH 6.8 phosphate buffer

10mg of Febuxostat was accurately weighed and transferred into 10ml volumetric flask. It was dissolved and diluted to volume with pH 6.8 phosphate buffer to give stock solution containing 1000µg/ml. The standard stock solution was then serially diluted with pH 6.8 phosphate buffer to get 2 to 12µg/ml of Febuxostat. The absorbance of the solution were measured against pH 6.8 phosphate buffer as blank at 315nm using UV visible spectrophotometer. The absorbance values were plotted against concentration (µg/ml) to obtain the standard calibration curve.

Solubility

Solubility of Febuxostat was determined in Methanol, Ethanol, pH 1.2, pH 6.8 and pH 7.4 phosphate buffers. The filtered solutions were analysed spectrophotometrically at 315 nm.

Compatibility Studies

FTIR analysis

The drug-polymer interactions were studied by FTIR spectrometer, Shimadzu 8400 S. 2% (w/w) of the sample, was mixed with dry KBr. done the analysis using the FTIR

Formulation of Immediate release Tablets of Febuxostat 18-27]

Formulation of Immediate release tablets of Febuxostat

Table 01: Formulation Table of Febuxostat IR Tablets

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Febuxostat	40	40	40	40	40	40	40	40	40
Lycoat	4	8	12	--	--	--	--	--	--
Crosspovidone	--	--	--	4	8	12	--	--	--
CCS	--	--	--	--	--	--	4	8	12
MCC	103	99	95	103	99	95	103	99	95
Mg.stearate	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Talc	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Total	150	150	150	150	150	150	150	150	150

Evaluation of IR Tablet [20-36]

Tablets were subjected to evaluation of properties including drug content uniformity, weight variation, tablet hardness, friability, and thickness, and in-vitro drug release with different media.

1. Weight variation

Table2: Weight variation limits

Sr. No.	Average weight of tablet (	Maximum % difference
1	130 or less	1
2	1	7
3	324<	5

2. Tablet hardness

The hardness of each batch of tablet was checked by using Monsanto hardness tester. The hardness was measured in terms of kg/cm^2. 3 tablets were chosen randomly and tested for hardness. The average hardness of 3 determinations was recorded.

3. Friability

20 tablets were weighed and the initial weight of these tablets was recorded and placed in Roche friabilator and rotated at the speed of 25 rpm for 100 revolutions. Then tablets were removed from the friabilator, dusted off the fines and again weighed and the weight was recorded. Percentage of friability of the tablets of a badge can be find by the following

Formula:

Percentage Friability = $W1 – W2/W1 \times 100$

Where,

W1 = weight of tablets before testing

W2 = weight of tablets after testing.

4. Tablet thickness

Thickness of the tablet is important for uniformity of tablet size. Thickness was measured using Vernier Callipers. It was determined by checking the thickness of ten tablets of each formulation.

5. Content Uniformity

The tablets were tested for their drug content uniformity. At random 20 tablets were weighed and powdered. The powder equivalent to 25 mg was weighed accurately and dissolved in 100ml of buffer used. The solution was shaken thoroughly. The un dissolved matter was removed by filtration through Whattman's filter paper No.41. The absorbance of the diluted solutions was measured at 315 nm. The concentration of the drug was computed from the standard curve of the Febuxostat in 6.8 phosphate buffer.

6. Disintegration time

Tablet disintegration is an important step in drug absorption. The test for disintegration was carried out in Electrolab USP disintegration test apparatus. It consists of 6 glass tubes which are 3 inches long, open at the top, and held against a 10 mesh screen, at the bottom end of the basket rack assembly. To test the disintegration time of tablets, one tablet was placed in each tube and the basket rack was positioned in a 1 litre beaker containing distilled water at 37°C ± 1°C such that the tablet remains 2.5 cm below the surface of the liquid. The time taken for the complete disintegration of the tablets was noted.

7. Invitro Dissolution time

In-vitro dissolution study of core and coated tablets of Febuxostat was carried out using Lab India DS8000 USP dissolution test apparatus. The details are given as below:

Tablet was introduced into the vessels of the Lab India DS-8000 USP dissolution test apparatus and the apparatus was set in motion, 5 ml of sample was withdrawn at regular intervals. Samples withdrawn were analysed by UV spectrophotometer for presence of drug using buffer solution as blank.

Drug Release Kinetics [37-41]

To examine the drug release kinetics and mechanism, the cumulative release data were fitted to models representing zero order (Q v/s t), first order [Log (Q0-Q) v/s t. In short, the results obtained from in vitro release studies were plotted in four kinetics models of data treatment as follows.

- Cumulative percentage drug release Vs. Time (zero order rate kinetics)
- Log cumulative percentage drug retained Vs. Time (first order rate kinetics)

Results and Discussion

Preformulation studies

Solubility

Table 03: Solubility studies of Febuxostat in various solvents

Solvent	Solubility (µg/mL)
Ethanol	1.264
Methanol	1.764
0.1 N HCL	0.557
6.8pH buffer	0.874
7.4pH buffer	0.917

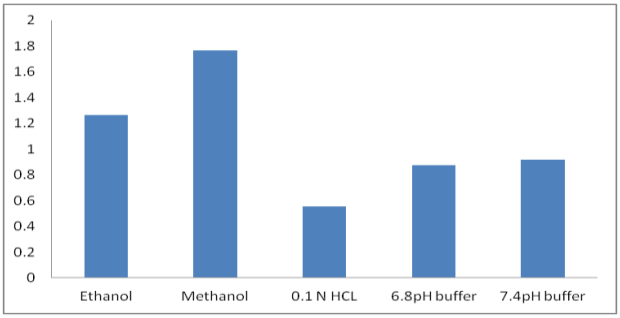

Fig 02: Solubility studies of Febuxostat in various solvents

Drug-Excipient compatibility studies

FTIR spectra of Febuxostat, and Optimized formulation are shown in Figure 3 and 4 respectively.

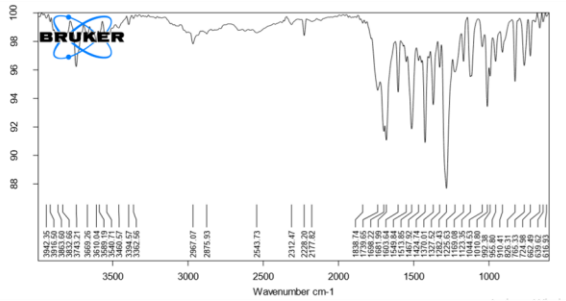

Fig 03: FTIR spectrum of Febuxostat

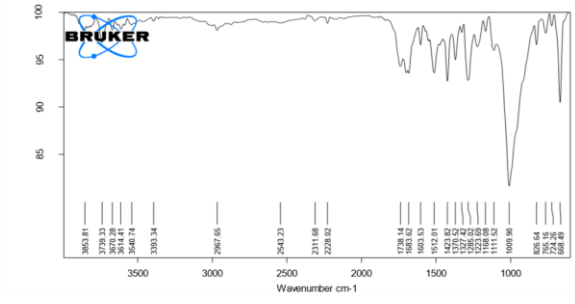

Fig 04: FTIR Spectrum of optimised formulation

λ_{max} Determination of Febuxostat

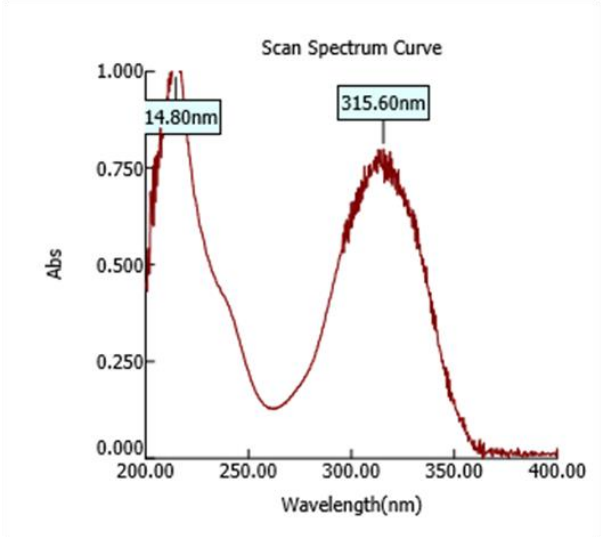

Fig 5: λ_{max} Determination of Febuxostat

Standard Calibration Curve

a. Standard Calibration Curve in 6.8 pH

Able 4: Data for calibration curve of Febuxostat in pH 6.8

Concentration (µg/ml)	Absorbance
0	0
2	0.156
4	0.324
6	0.472
8	0.631
10	0.776
12	0.946

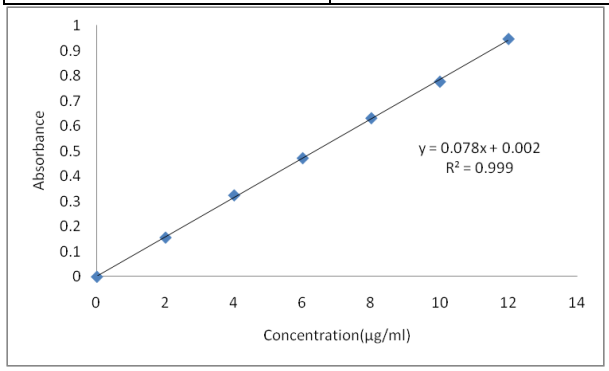

Figure 6 Standard Calibration Curve of Febuxostat in pH 6.8 at 315 nm

Flow properties of powder blend

Table 05: Flow properties of powder blend

Formulation Code	Angle of Repose±SD	Bulk Density (g/ml)±SD	Tapped Density (g/ml)±SD	Carr's Index. (%)±SD	Hausner's ratio±SD
F1	28.64±0.16	0.375±0.15	0.461±0.86	15.82±0.02	1.19±0.62
F2	27.49±0.24	0.377±0.23	0.465±0.24	17.53±0.52	1.20±0.59
F3	29.84±0.85	0.395±0.64	0.457±0.15	16.42±0.98	1.22±0.18
F4	26.59±0.63	0.371±0.78	0.471±0.39	18.53±0.36	1.18±0.63
F5	27.12±0.21	0.387±0.26	0.475±0.50	15.75±0.42	1.23±0.42
F6	29.46±0.14	0.389±0.94	0.469±0.16	17.88±0.15	1.21±0.15

Characterization of Tablets

Post Compression parameters

All the batches of tablet formulations were characterized for official evaluation parameters like Weight variation, Hardness, Friability, Tablet thickness and drug content and results are shown in the table.6

Table 06: Characterization Febuxostat Tablets

Formulation code	%Weight variation (mg)	Thickness (mm)	Diameter (mm)	Hardness	Friability (%)	Disintegrating time (sec)	Drug content (%)
F1	0.395	2.43	8.09	3.86	0.19	68.12	97.63
F2	0.498	2.54	8.10	3.56	0.34	56.15	96.43
F3	0.176	2.47	8.05	4.48	0.56	47.08	99.05
F4	0.765	2.52	8.11	3.97	0.65	61.58	96.04
F5	1.248	2.60	8.07	4.76	0.37	56.79	97.43
F6	0.687	2.59	8.06	3.45	0.85	44.16	95.04
F7	0.964	2.67	8.10	3.86	0.94	58.75	97.65
F8	1.508	2.71	8.09	5.08	0.39	39.49	99.43

F9	0.897	2.84	8.04	4.78	0.73	27.87	96.85

Dissolution studies of the tablets

The prepared tablets were subjected to dissolution studies in order to know the amount drug release.

Table 07: % Cumulative drug release of formulations F1-F9

Time (min)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
5	31.06	35.18	41.49	47.06	50.31	55.31	57.49	59.16	61.19
10	37.66	41.27	48.87	54.78	56.87	67.49	65.42	67.91	69.93
15	42.95	45.96	54.08	59.85	60.98	74.04	69.73	72.43	74.86
20	47.31	49.97	58.36	64.19	65.39	79.19	73.07	76.48	79.13
30	56.72	58.05	66.16	70.69	72.68	88.06	79.19	82.49	84.78
45	64.05	67.34	75.76	79.71	82.96	98.34	86.83	89.97	92.53
60	72.66	76.68	84.48	89.61	93.06		93.75	95.83	98.79

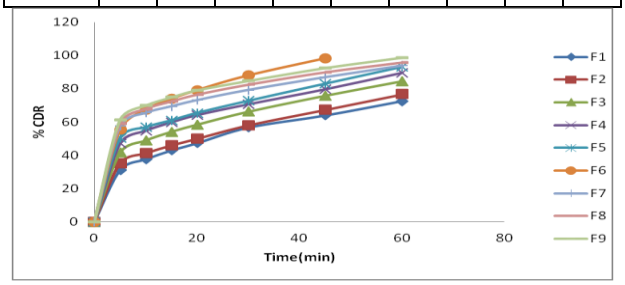

Fig 07: In vitro drug release of formulations F1-F9

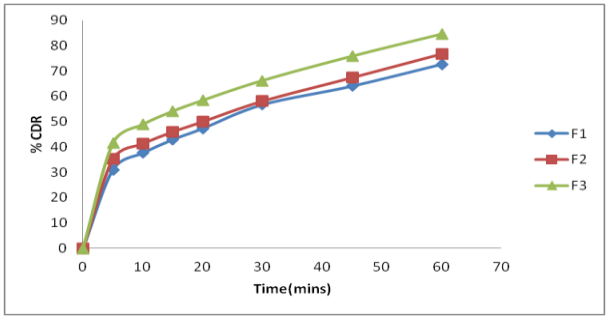

Fig 08: In vitro drug release of formulations F1-F3

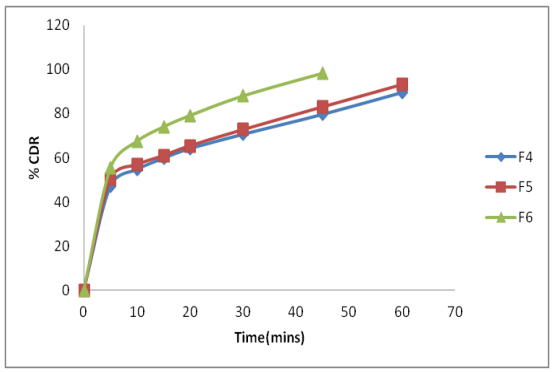

Fig 09: In vitro drug release of formulations F4-F6

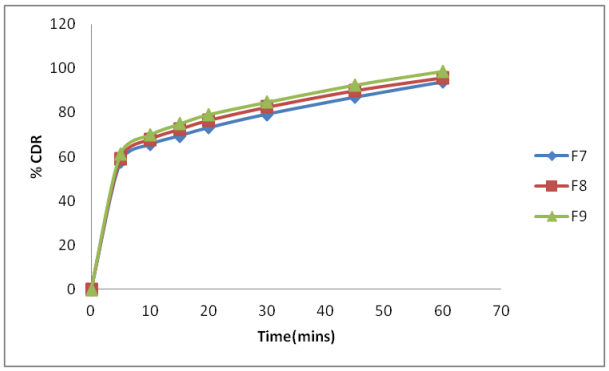

Fig 10: In vitro drug release of formulations F7-F9

Whereas formulations containing CCS as a super disintegrants in different concentrations, reveals that the increased in the super disintegrants concentration decreases the drug release time and the F9 formulation containing CCS with 12mg shows maximum amount of drug release (98.79%) at the end of 60mins.

So, F6 formulation containing 12mg of CCS shows max. Drug release within 45mins so that it is chosen as optimized formulation.

Release Kinetics

The drug release kinetics for the optimized formulation F6 followed the First order kinetics. The curves were in figure11, 12 respectively

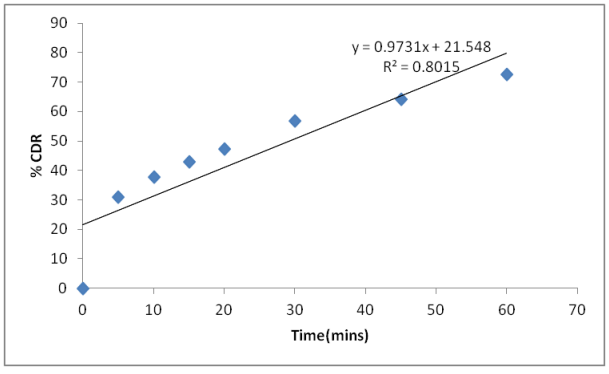

Figure 11 Zero order plot for optimized formulation F6

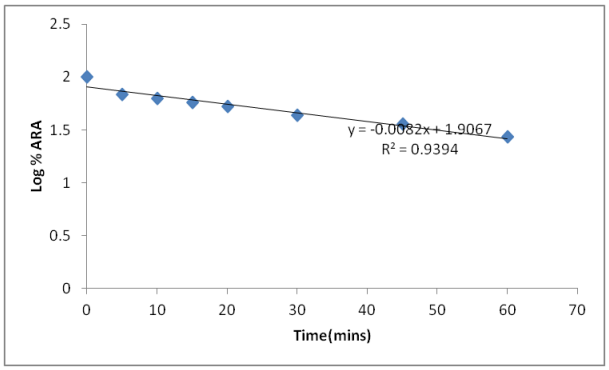

Figure 12: first order plot for optimized formulation F6

Summary and Conclusion

The present study is formulate the best formulation for Oral Immediate release tablets of Febuxostat, which disintegrates rapidly, thereby reducing the time of onset of pharmacological action. Lycoat, CCS and Crospovidone were used as disintegrants the post compression parameters like the hardness, thickness, friability and weight variation, disintegration time, disintegration n time in oral cavity and Invitro release were carried out and the values were found to be within IP limits. The percentage drug content of all the tablets was found to be between 72.66 – 98.79 % of Febuxostat, which was within the acceptable limits.

Among all the formulations F6 shows 98.34% drug release at the end of 45min. F6 contains CCS (12mg), it shows better % drug release when compared to other formulations. So F6 was considered as the optimized formulation. The drug release kinetics shows that the optimized formulation F6 follows First order drug release.

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