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Formulation and Invitro evaluation of immediate release tablets containing febuxostat

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Abstract

In the present research work, Febuxostat Immediate Release Tablet was 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. From 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 were found to be within the limits. Among the formulation prepared the tablet containing 12mg of CCS shows 98.13% of the drug release within 45 min & follows first-order kinetics.

Keywords: Febuxostat, CCS, Lycoat, Crospovidone.

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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].

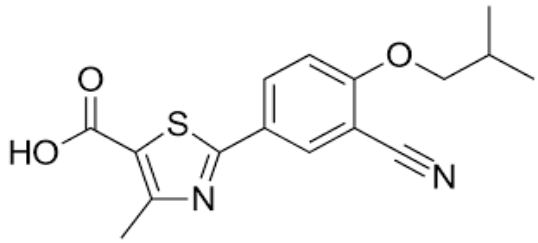

Fig 01: Chemical structure of Febuxostat

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]. In one form, the xanthine oxidoreductase enzyme is synthesized as xanthine dehydrogenase, exhibiting a very low reactivity with oxygen. However, under stress or disease conditions, such as ischemia-reperfusion injury and congestive heart failure, xanthine dehydrogenase can undergo the formation of intra-molecular disulfide bonds or proteolytic cleavage, which converts the enzyme to the second form, xanthine oxidase. Xanthine oxidase exhibits high reactivity with oxygen. Hyperuricemia is also associated with a number of disease conditions, such as renal injury and hypertension [1].

Hyperuricemia is defined as plasma or serum urate concentration greater than 70 mg/l (>420 μ mol/l) and is present in approximately 5% of the population in the world. Serum uric acid (sUA) is the primarily important risk factor for the development of gout. Sustained hyperuricemia is a risk factor for acute clinically

progressive stages of gout-like gouty arthritis, tophaceous gout and uric acid nephrolithiasis. Most patients with hyperuricemia will never have an attack of gout and remain untreated. In the Normative Aging Study, the 5-year cumulative risk of gout development in subjects with sUA levels >70 mg/l or >100 mg/l was 0.6% and 30.5%, respectively [5, 6]. The higher the sUA levels greater the likelihood of developing gout.

The available treatment option is uricosuric agent, increasing uric acid excretion and xanthine oxidoreductase inhibitor (Allopurinol and Febuxostat), reducing the synthesis of uric acid. Allopurinol has been shown to prevent renal injury and hypertension associated with hyperuricemia by inhibiting xanthine oxidoreductase; thus reducing uric acid levels. In contrast, it has been found that the extent of protection against renal injury and hypertension in subjects suffering from hyperuricemia is lower in subjects treated with the uricosuric agent benziodarone. Benziodarone does not inhibit xanthine oxidoreductase activity, but instead reduces plasma uric acid levels by increasing the excretion of uric acid in the kidney [7, 8]. Therefore, there is an unmet need for new dosage forms that not only reduce uric acid levels in hyperuricemic subjects, but are also capable of maintaining a high level of (namely, at least 80%) inhibition of xanthine oxidoreductase activity in order to protect subjects receiving these dosage forms throughout their treatment regimen (i. e., Dosing interval, which is typically twenty-four h) against increasing concentrations of oxygen free radicals.

Another treatment for hyperuricemia in patients with chronic gout is with the compound febuxostat, a non-purine inhibitor of xanthine oxidase [9, 10]. Febuxostat is marketed in various countries with different brand names as immediate release tablets. In the United States of America (USA), it is marketed by Takeda Pharmaceuticals as Uloric tablets 40 & 80 mg [11]. Extensive pharmacokinetic and pharmacodynamic data have established that maintaining a concentration of febuxostat in plasma over a prolonged period of time provides similar efficacy to treatment with high doses of the drug. Generally, these studies have shown that maintaining a febuxostat plasma concentration of 0.1 μg/ml is essential to provide 95% or greater inhibition of xanthine oxidase.

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 testapparatus from ElectrolabUSP EF2 ,Hydraulic press from Clit pilot press , Vernier caliper from Pico India Ltd , Tablet dissolutiontester (USPII) from Lab India DS8000 , Tap densitytester 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 pre requisite in development of any drug delivery system. Preformulation studies were performed on thed rug,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 Febuxo stat was accurately weighed and transferred into 10ml volumetric flask. It was dissolved and diluted to volumewith pH 6.8 phosphate buffer to give stock solution containing 1000 μg/ml. The standard stock solution was then serially diluted with pH 6.8 phosphate buffer to get 2to12μg/ml of Febuxostat. The absorbance of the solutionwere measured against pH 6.8 phosphate buffer asblank at 315 nm using UV visible spectrophotometer. The absorbance valueswereplotted againstconcentration (μg/ml) to obtain the standard calibration curve.

Solubility

Solubility of Febuxostat was determinedin Methanol, Ethanol, pH1.2,pH6.8andpH7.4phosphate buffers. Solubility studies were performed by taking excess amount of Febuxo statin different beakers containing the solvents. The mixtures were shaken for 24hrs atregular intervals. The solutions were filtered by using

whattmann's filter paper grade no.41. The filtered solutions were analyzed spectrophotometrically at315 nm.

Compatibility Studies

FTIR analysis

The drug-polymer interactions were studied by FTIR spectrometer, Shimadzu 8400 S. 2% (w/w) of the sample, with respect to a potassium bromide (KBr; SD Fine Chem. Ltd., Mumbai, India) was mixed with dry KBr. The mixture was ground into a fine powder using mortar and then compressed into a KBr discs in a hydraulic press at a pressure of 10000 PSI. Each KBr disc was scanned 10 times at a resolution of 2 cm–1 using Happ-Genzel apodization. The characteristic peaks were recorded

Formulation ofImmediate release Tablets of Febuxostat [18-27]

Formulation ofImmediate release tablets ofFebuxostat

The inner core tablets were prepared by using direct compression method as per the developed formulation table which was shown below. Accurately weighed amounts of Febuxostat, MCC, Crospovidone, CCS, Lycoat and Talc were dry blended for about 15min followed by addition of magnesium stearate. The mixture was then further blended for 10 min. Now the resultant powder blend was manually compressed using punching machine and finally the core tablet was obtained.

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.sterate	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 [20-37]

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

The weight of the tablet being made was routinely determined to ensure that a tablet contains the proper amount of drug.The USP weight variation test is done by weighing 20 tablets individually, calculating the average weight and comparing the individual weights to the average.The tablets met the USP specification that not more than 2 tablets are out sidethe percentage limits and no tablet differs by more than 2 times the percentage limit. USP official limits of percentage deviation of tablet are presented in the below table.

Table 02:Weight variation limits

Sr. No.	Average weight of tablet (mg)	Maximum % Difference allowed
1	130 orless	1
2	1	7
3	324<	5

2. Tablethardness

The resistance of tablets to shipping or breakage under conditions of storage, transport at ion and handling before usage depends on its hardness. The hardness of each batch of tablet was checke dby using Monsan to 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

Friability generally refers to loss in weight of tablets in the containers due to removal offines from the tablet surface. Friability generally reflects poor cohesion of tablet ingredients.

Method

20 tablets were weighed and the initial weight of these tablets was recorded and placed in Roche friabilat or and rotated at the speed of 25 rpm for 100 revolutions. Then tablets were removed from the friabilator,

dustedoff 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 × 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 Calipers. It was determined by checking the thickness often 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 powde requivalent to 25mg was weighed accurately and dissolvedin100 ml of buffer used. The solution was shaken thoroughly.The un dissolved matter was removed by filtration through Whattman'sfilter 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 Febuxostatin 6.8 phosphate buffer.

6. Disintegration time

Tablet disintegration is an important step in drug absorption. The test for disintegration was carried out in Electro lab USP disintegrationtest apparatus. It consists of 6 glass tubes which are 3 inches long, open at the top, and held againsta10 mesh screen, at the bottomend of the basket rackassembly. To test the disintegration time of tablets,one tablet was placed in each tube and the basket rack was positioned in a1litre 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 givenas below:

Procedure

Tablet was introduced into the vessels of theLab India DS-8000 USP dissolution test apparatus and the apparatus was setinmotion, 5ml of sample was withdrawn at regular intervals. Samples withdrawn were analyzed by UV spectro photometer for presence of drug using buffer solution as blank.

Drug Release Kinetics

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

It was determined as per standard procedure. The results are given in Table 3. Febuxostat was found to be soluble in 6.8pH buffer and soluble in methanol.

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

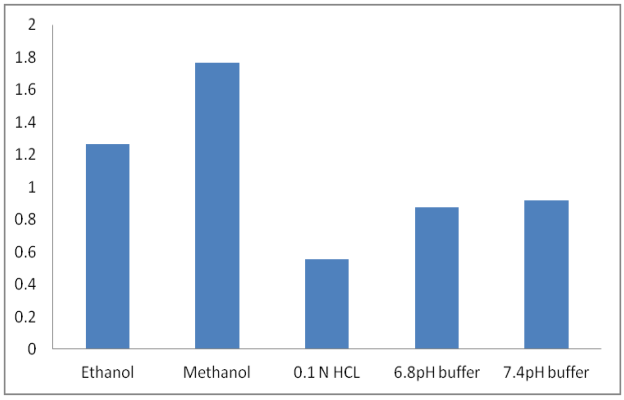

Fig 02: Solubility studies of Febuxostat in various solvents

Drug-Excipient compatibility studies

The IR spectrum of pure drug was found to be similar to the standard spectrum of Febuxostat. From the spectra of Febuxostat, combination of Febuxostat with polymers, it was observed that all characteristic peaks of Febuxostat were not altered and present without alteration in the combination spectrum, thus indicating compatibility of the drug and polymers. FTIR spectra of Febuxostat, and Optimized formulation are shown in Fig 03 and 04 respectively.

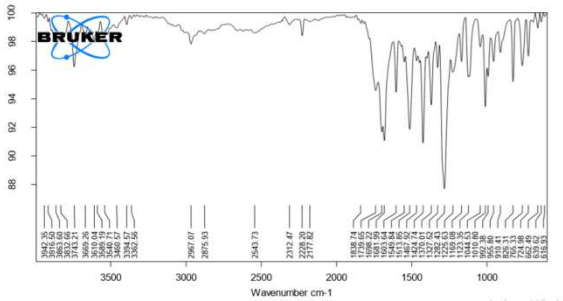

Fig 03: FTIR spectrum of Febuxostat

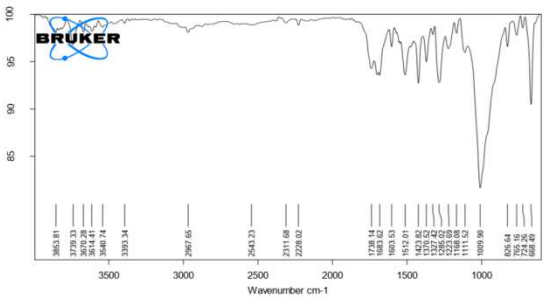

Fig 04: FTIR Spectrum of optimised formulation

Chemical interaction between drug and the polymeric material was studied by using FTIR. There was no difference between the IR patterns of Febuxostat, physical mixture of Febuxostat and Febuxostat optimized formulation.

λ_{max} Determination of Febuxostat

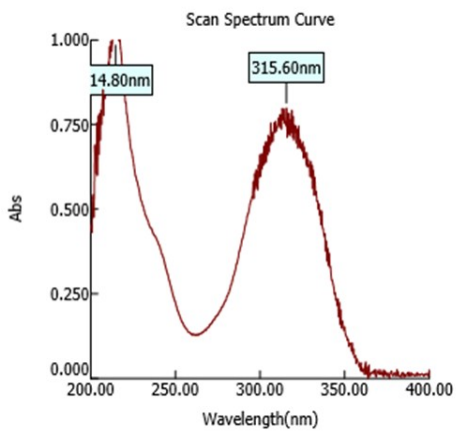

Fig 05: λ_{max} Determination of Febuxostat

Standard Calibration Curve

The standard calibration curve of Febuxostat was developed in pH 6.8 phosphate buffer. Two buffers were selected in order to mimic the in-vivo conditions of the GIT.

a. Standard Calibration Curve in 6.8 pH

Standard graph of Febuxostat showed linearity at the concentration range of 2-12µg with correlation coefficient of 0.999. Table 4 gives the data of the standard graph and Figure 6 shows the standard graph in pH 6.8.

Table 04: 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

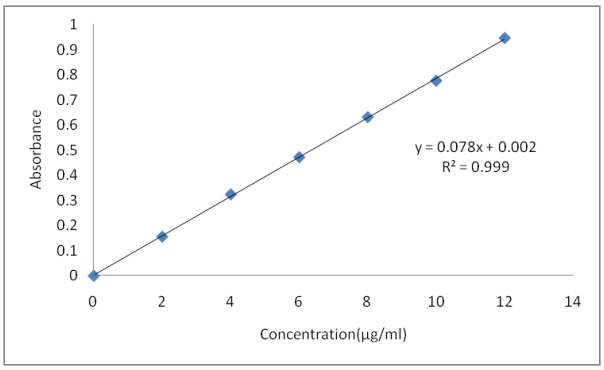

Fig 06: Standard Calibration Curve of Febuxostat in pH 6.8 at 315 nm

Flow Properties of Powder Blend

Table 05: Flow properties of powder blend

Formul	Angle of	Bulk Densi	Tapped Densit	Carr's	Hausner'
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

The angle of repose of different formulations was ≤ 29.84 which indicates that material had good flow property. So it was confirmed that the flow property of blends were free flowing. The bulk density of blend was found between 0.370g/cm^3 to 0.395g/cm^3.Tapped density was found between 0.451g/cm^3 to 0.475g/cm^3.These values indicate that the blends had good flow property. Carr's index for all the formulations was found to be between 15.25-18.53 and Hausner's ratio from 1.18-1.23 which reveals that the blends have good flow character.

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 06.

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

Hardness of the tablet was acceptable and uniform from batch to batch variation, which was found to be 3-5 kg/cm^2.All the formulations passed the weight variation test as the % weight variation was within the pharmacopoeial limits of the tablet weight. Friability values were found to be less than 1% in all the formulations F1 –F6 and considered to be satisfactory ensuring that all the formulations are mechanically stable. The drug content values for all the formulations (F1-F6) was found to be in the range of 95.04 – 99.43 %.

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	69.37	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

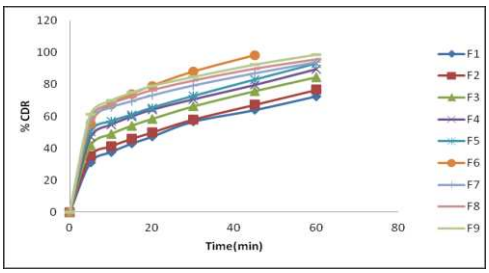

Fig 07: In vitro drug release of formulations F1-F9

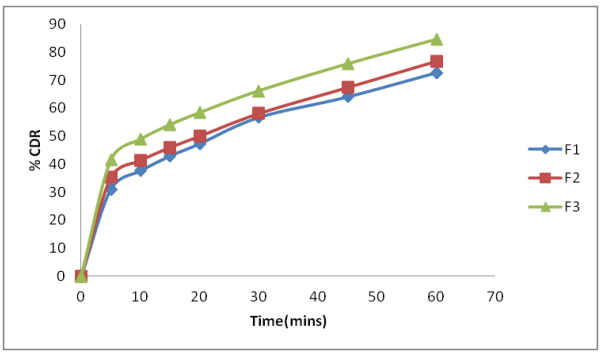

Fig 08: In vitro drug release of formulations F1-F3

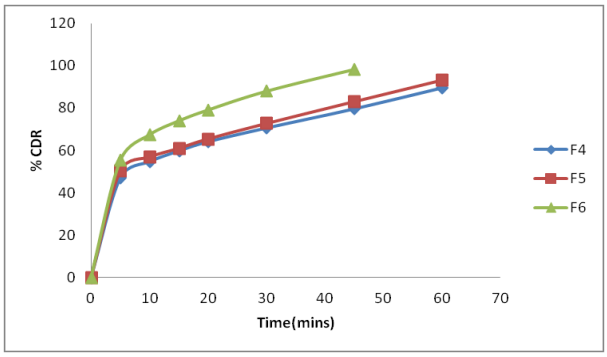

Fig 09: In vitro drug release of formulations F4-F6

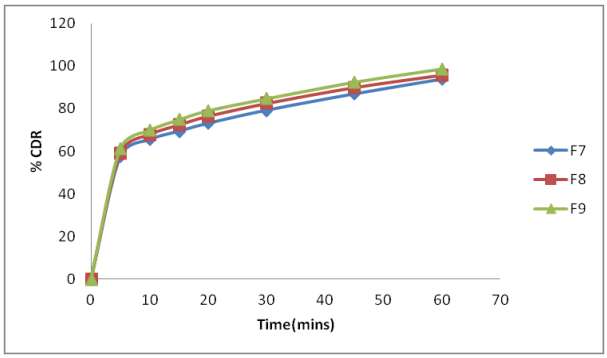

Fig 10: In vitro drug release of formulations F7-F9

From the in vitro drug release in studies it was observed that the formulations containing LYCOAT as a super disintegrant in different concentrations, reveals that the increased in the super disintegrant concentration decreases the drug release time and the F3 formulation containing LYCOAT 12mg shows maximum amount of drug release (76.68 %) at the end of 60mins.

Whereas formulations containing Crospovidone as a super disintegrant in different concentrations, reveals that the increased in the super disintegrant concentration decreases the drug release time and the F6 formulation containing Crospovidone with 12mg shows maximum amount of drug release (98.34%) at the end of 45mins.

Whereas formulations containing CCS as a super disintegrant in different concentrations, reveals that the increased in the super disintegrant 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 choosen 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.

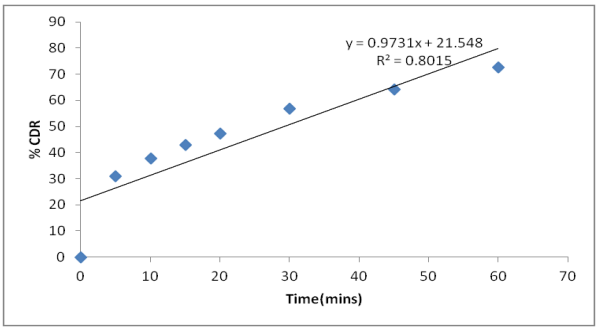

Fig 11: Zero order plot for optimized formulation F6

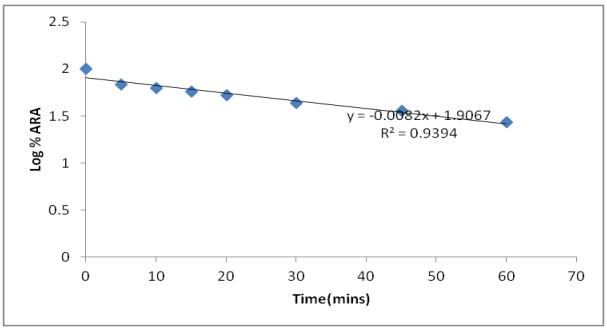

Fig 12: First order plot for optimized formulation F6

Summary and Conclusion

The present study is an attempt to select the best possible diluent - disintegrant combination to formulate 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. In all the formulations, Magnesium stearate and talc were used as lubricant and glidant respectively.The results of the drug – excipient compatibility studies revealed that there was no chemical interaction between the pure drug and excipients.Direct compression method was employed to formulate the tablets, because of its cost effectiveness and due to reduced number of manufacturing steps. The precompression parameters like bulk density, tapped density, Carr's index and angle of repose were determined. All the formulations showed acceptable flow properties.Thepostcompression parameters like the hardness, thickness, friability and weight variation, disintegration time, disintegration

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.

Author Contribution

All authors are Contributed Equally

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Conflict of Intrest

Authors are Declared no Conflict of Intrest

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