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Analytical Method Development and Validation by RP-HPLC for Simultaneous Estimation of Ketorolac and Febuxostat in Combined Tablet Dosage Form

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A B S T R A C T

A simple, Accurate, precise method was developed for the simultaneous estimation of the Ketorolac and Febuxostat in Tablet dosage form. Chromatogram was run through Inertsil C18 (4.6 x 150 mm, 5µm, Make: X Terra) or equivalent. Mobile phase containing methanol and phosphate buffer in the ratio of 60:40 was pumped through column at a flow rate of 1 ml/min. Buffer used at pH 3.5. Temperature was maintained at 30°C. Optimized wavelength for Ketorolac and Febuxostat was 292 nm. Retention time of Ketorolac and Febuxostat were found to be 4.981 min and 3.54 min. %RSD of the Ketorolac and Febuxostat were and found to be less than 2% respectively. %Recovery was found to be 97% and 103% for Ketorolac and Febuxostat respectively. LOD, LOQ values are obtained from regression equations of Ketorolac and Febuxostat was found to be within the limits respectively. The linearity range of Ketorolac and Febuxostat were found to be from 10-50 µg/ml of Ketorolac and 5-25µg/ml of Febuxostat. Linear regression coefficient was not more than 0.999.

Keywords: Ketorolac, Febuxostat, RP-HPLC

A R T I C L E I N F O

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1. Introduction

Ketorolac is a chemically named as 5-benzoyl-2, 3-dihydro-1H-pyrrolizine-1-Carboxylic acid [1]. Ketorolac is a nonsteroidal anti-inflammatory drug (NSAID) chemically related to indomethacin and tolmetin. Ketorolac tromethamine is a racemic mixture of [-]S- and [+]R-enantiomeric forms, with the S-form having analgesic activity. Its anti inflammatory effects are believed to be due to inhibition of both cylooxygenase-1 (COX-1) and cylooxygenase-2 (COX-2) which leads to the inhibition of prostaglandin synthesis leading to decreased formation of precursors of prostaglandins and thromboxanes from arachidonic acid [2].

The resultant reduction in prostaglandin synthesis and activity may be at least partially responsible for many of the adverse, as well as the therapeutic, effects of these medications [3]. Analgesia is probably produced via a peripheral action in which blockade of pain impulse generation results from decreased prostaglandin activity. However, inhibition of the synthesis or actions of other substances that sensitize pain receptors to mechanical or chemical stimulation may also contribute to the analgesic effect [4]. In terms of the ophthalmic applications of ketorolac - ocular administration of ketorolac reduces prostaglandin E2 levels in aqueous humor, secondary to inhibition of prostaglandin biosynthesis [5]. Febuxostat is a chemically named as 2-[3-cyano4-(2-methylpropoxy) phenyl] -4-methylthiazole-5-Carboxylic acid [6].

Febuxostat is a non-purine selective inhibitor of xanthine oxidizes. It works by non-competitively blocking the molybdenum pterin center, which is the active site on xanthine oxidase. Xanthine oxidase is needed to successively oxidize both hypoxanthine and xanthine to uric acid. Hence, febuxostat inhibits xanthine oxidase, therefore reducing production of uric acid [7]. Febuxostat inhibits both oxidized as well as reduced form of xanthine oxidase because of which febuxostat cannot be easily displaced from the molybdenum pterin site [8].

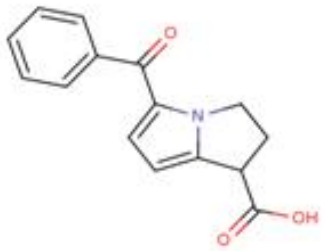


Figure 1: Structure of Ketorolac

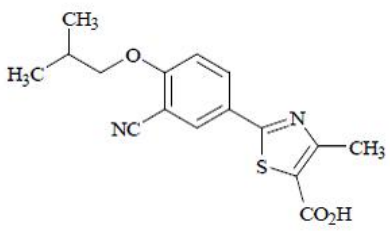


Figure 2: Structure of Febuxostat

2. Materials and Methods

Instruments Used

Table 1: Instruments used

S.No	Instrument	Model
1	HPLC	WATERS, software: Empower, 2695 separation module. 996 PDA detector
2	UV/VIS spectrophotometer	LABINDIA UV
3	pH meter	Lab India
4	Weighing machine	Sartorius
5	Pipettes and Burettes	Borosil
6	Beakers	Borosil

Chemicals Used

Table 2: Chemicals used

S.No	Chemical	Brand
1	Febuxostat	KP Labs
2	Ketorolac	KP Labs
3	KH_2PO_4	FINER chemical LTD
4	Water and Methanol for HPLC	LICHROSOLV (MERCK)
5	Acetonitrile for HPLC	Merck

HPLC Method Development

Mobile Phase Optimization:

Initially the mobile phase tried was methanol: Phosphate buffer pH 3.5 as well as varying proportions. Finally, the mobile phase was optimized to potassium dihydrogen phosphate with buffer (pH 3.5), Methanol 40: 60 v/v respectively [9].

Optimization of Column:

Optimization of Column:

The method was performed with various columns like C18 column, hypersil column, lichrosorb, and inertsil ODS column. Symmetry C8 (4.6 x 150 mm, 5µm, Make: XTerra) was found to be ideal as it gave good peak shape and resolution at 1.0 ml/min flow [10].

Optimized Chromatographic Conditions:

Instrument used : Waters HPLC with auto sampler and PDA Detector.
Temperature : Ambient
Column : Symmetry C8 (4.6 x 150mm, 5µm, Make: XTerra) or equivalent
Buffer : 7.0 grams of potassium dihydrogen ortho phosphate in1000 ml water pH adjusted with ortho phosphoaric acid.
pH : 3.5

Mobile phase : 40% buffer 60% Methanol
Flow rate : 1 ml per min
Wavelength : 292 nm
Injection volume : 20 µl
Run time : 8.0 min.

Optimized chromatogram is obtained by following conditions

Trial 1:

Column : Inertsil C18 (4.6 x 150mm, 5µm, Make: or equivalent
Buffer pH : 3.5
Mobile phase : 20% buffer 80% methanol
Flow rate : 1.0 ml per min
Wavelength : 292 nm
Temperature : ambient.
Run time : 10 min.

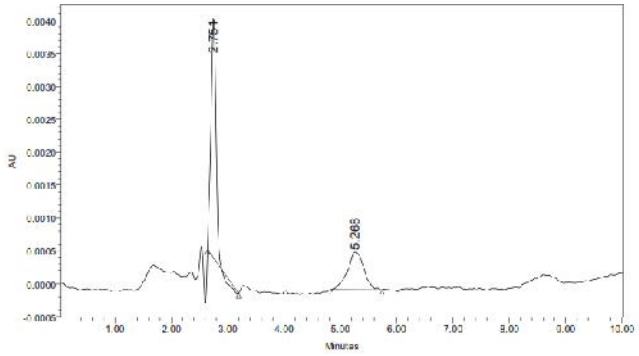


Figure 3: Chromatogram for trail 1

From the above chromatogram, it was observed that the Febuxostat peak was splitted but Ketorolac peak was not separated properly.

Trial 2:

Column : Symmetry C8 (4.6 x 150mm, 5µm, Make: XTerra) or equivalent
Buffer pH : 3.5.
Mobile phase : 30% buffer 70% acetonitrile
Flow rate : 1 ml per min
Wavelength : 292 nm
Temperature : ambient.
Run time : 10min.

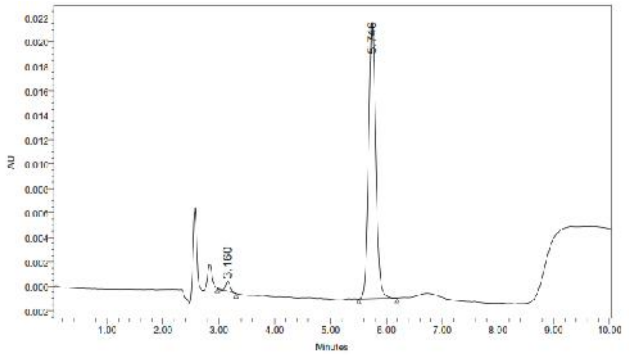


Figure 4: Chromatogram for trail 2

From the above chromatogram it was observed that the febuxostat and Ketorolac peaks are splitted [11].

Trial 3:

Column : Symmetry C8 (4.6 x 150mm, 5µm, Make: XTerra) or equivalent
Buffer pH : 3.5.
Mobile phase : 40% buffer 60% acetonitrile
Flow rate : 1.0 ml per min
Wavelength : 292 nm
Temperature : ambient.
Run time : 8.0 min.

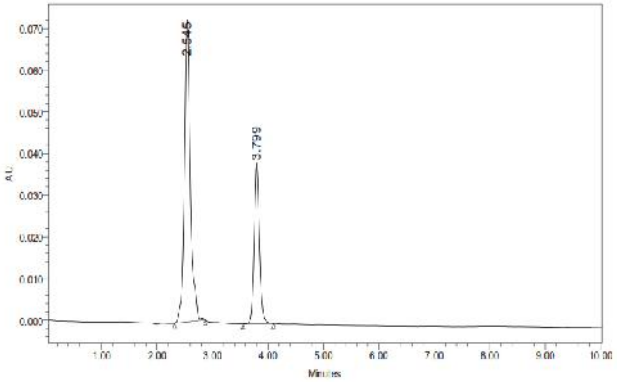


Figure 5: Chromatogram for trail 3

From the above chromatogram, it was observed that the Febuxostat and Ketorolac peaks are well separated but system suitability parameters are not obtained [12].

Trial 4:

Column : Symmetry C18 (4.6 x 150 mm, 5µm, Make: X Terra) or equivalent
Buffer pH : 3.5.
Mobile phase : 40% buffer 60% Methanol
Flow rate : 1.0 ml per min
Wavelength : 292 nm
Temperature : ambient.
Run time : 8.0 min.

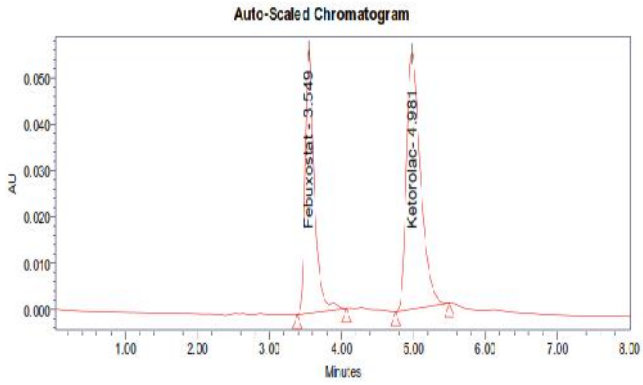


Figure 6: Chromatogram for optimization

Table 3: Chemicals used

Peak Results

	Name	RT	Area	Height	USP Resolution	USP Tailing	USP Plate Count	Injection
1	Febuxostat	3.549	508691	56817		1.42	3923	2
2	Ketorolac	4.981	747696	55296	4.79	1.46	3149	2

From the above chromatogram, it was observed that the Febuxostat and Ketorolac peaks are well separated and system suitability parameters are also obtained.

Preparation of buffer and mobile phase

Preparation of Phosphate buffer:

Accurately weighed 7.0 grams of KH_2PO_4 was taken in a 1000 ml volumetric flask, dissolved and diluted to 1000 ml with HPLC water and the volume was adjusted to pH 3.5 with Orthophosphoric acid [13].

Preparation of mobile phase:

Accurately measured 400 ml (40%) of above buffer and 600 ml of Methanol HPLC (60%) were mixed and degassed in an ultrasonic water bath for 10 minutes and then filtered through 0.45 µ filter under vacuum filtration [14].

Diluent Preparation: The Mobile phase was used as the diluent.

Validation Parameters:

Method Precision:

Preparation of Standard Solution:

Accurately weighed amount of 5 mg Febuxostat and 10 mg Ketorolac and Febuxostat were taken to a 10 ml cleaned and dried volumetric flask. This was then diluted with 7 ml of diluent and was sonicated [15]. The volume was made to 10 ml with the same solvent. This was marked and labeled as Stock solution. Further, an amount of 0.3 ml and Ketorolac and Febuxost at each was pipette from the above stock solution into a 10 ml volumetric flask and diluted up to the mark with diluents to get 15 µg/ml for febuxostat and 30 µg/ml for Ketorolac [16].

Preparation of Sample Solution:

Accurately weighed amount Equivalent to 5 mg and 10 mg of Febuxostat and Ketorolac and Febuxostat were taken to a 10 ml cleaned and dried volumetric flask. This was then diluted with 7 ml of diluent and was sonicated. The volume was made to 10 ml with the same solvent. This was marked and labeled as Stock solution [17]. Further, an amount of 0.3 ml and Ketorolac and Febuxostat each was pipette from the above stock solution into a 10ml volumetric flask and diluted up to the mark with diluents to get 30 µg/ml of and 15 µg/ml of Ketorolac and Febuxostat and febuxostat respectively [18]. The standard and sample solutions of 30 µg/ml of and 15 µg/ml of Ketorolac and Febuxostat were injected for three times.

Intermediate Precision/Ruggedness:

30 µg/ml of and 15 µg/ml of Ketorolac and Febuxostat of the above sample solution were injected for five times in five different days and peak areas were recorded.

Accuracy:

For accuracy determination, three different concentrations were prepared separately i.e. 50%, 100% and 150% for the analyte and chromatograms are recorded for the same.

Preparation Sample solutions:

Preparation of 50% solution (15 µg/ml of and 7.5 µg/ml of Ketorolac and Febuxostat):

About 5 mg of 2.5 mg of Ketorolac and Febuxostat were weighed and transferred to 10 ml volumetric flask, it was dissolved with diluent and the volume was made up to the mark with same solvent. Further 0.3 ml of above solution was diluted to 10 ml with the diluent to get 15 µg/ml of and 7.5 µg/ml of Ketorolac and febuxostat [19].

Preparation of 100% solution (30 µg/ml of and 15 µg/ml of Ketorolac and Febuxostat):

About 10 mg of 5 mg of Ketorolac and Febuxostat were weighed and transferred to 10 ml volumetric flask, it was dissolved with diluent and the volume was made up to the mark with same solvent. Further 0.3 ml of above solution was diluted to 10 ml with the diluent to get 30 µg/ml of and 15 µg/ml of Ketorolac [20].

Preparation of 150% solution (45 µg/ml of and 22.5 µg/ml of Ketorolac and febuxostat):

About 15 mg of 7.5 mg of Ketorolac and Febuxostat were weighed and transferred to 10 ml volumetric flask, it was dissolved with diluent and the volume was made up to the mark with same solvent. Further 0.3 ml of above solution was diluted to 10 ml with the diluent to get 45 µg/ml of and 22.5 µg/ml of Ketorolac [21]. These solutions were filtered through 0.45µ membrane and then each concentration; three replicate injections were made under the optimized conditions. Recorded the chromatograms and measured the peak responses.

Linearity:

Preparation of sample stock solution:

About 10 mg of and 5 mg of Ketorolac and Febuxostat samples was weighed in to 10 ml volumetric flask, it was dissolved with diluent and the volume was made up to the mark with same diluent (1000 µg/ml of and 500 µg/ml of Ketorolac)[22].

Preparation of Level – I (10 µg/ml of & 5 µg/ml of Ketorolac and Febuxostat)

0.1 ml of stock solution had taken in 10 ml of volumetric flask diluted up to the mark with diluent.

Preparation of Level – II (20 µg/ml of &10 µg/ml of Ketorolac and Febuxostat)

0.2ml of stock solution had taken in 10ml of volumetric flask diluted up to the mark with diluent.

Preparation of Level – III (30 µg/ml of & 15 µg/ml of Ketorolac and Febuxostat)

0.3 ml of stock solution had taken in 10 ml of volumetric flask diluted up to the mark with diluent.

Preparation of Level – IV (40 µg/ml of & 20 µg/ml of Ketorolac and Febuxostat)

0.4 ml of stock solution had taken in 10 ml of volumetric flask diluted up to the mark with diluent.

Preparation of Level – V (50 µg/ml of & 25 µg/ml of Ketorolac and Febuxostat)

0.5 ml of stock solution had taken in 10 ml of volumetric flask diluted up to the mark with diluent. 10 µl of each of Ketorolac and Febuxostat Levels were injected in triplicate and recorded the peak response.

Limit of Detection (for Ketorolac):

Preparation of 30 µg/ml solution:

Pipette 0.3 ml of the stock solution into a 10 ml volumetric flask and dilute up to the mark with diluent.

Preparation of 0.58% solution At Specification level (0.017 µg/ml solution):

pipette 1 ml of the stock solution into a 10 ml volumetric flask and diluted up to the mark with diluent. Further Pipette 0.58 ml of 1 µg/ml solution into a 10 ml of volumetric flask and dilute up to the mark with diluent.

Limit of Quantification:

Preparation of 30 µg/ml solution:
Pipette 0.3 ml of the stock solution into a 10 ml volumetric flask and diluted up to the mark with diluent.
Preparation of 1.95% solutions At Specification level (0.058 µg/ml solution):
Pipette 1ml of the stock solution into a 10 ml volumetric flask and diluted up to the mark with diluent.
Further Pipette 1.95 ml of 1 µg/ml solution into a 10 ml of volumetric flask and diluted up to the mark with diluents
Limit of Detection: (for Febuxostat)
Preparation of 15 µg/ml solution: Pipette 0.3 ml of the above stock solution into a 10 ml volumetric flask and diluted up to the mark with diluents [23].
Preparation of 0.6% solution At Specification level (0.009 µg/ml solution):
Pipette 1 ml of the above stock solution into a 10 ml volumetric flask and diluted up to the mark with diluent
Further Pipette 0.6 ml of 1 µg/ml solution into a 10 ml of volumetric flask and diluted up to the mark with diluent.
Limit of Quantification:
Preparation of 15µg/ml solution:
Pipette 0.3 ml of the above stock solution into a 10 ml volumetric flask and diluted up to the mark with diluents [24].
Preparation of 2.15% solution At Specification level (0.03 µg/ml solution):
Further pipetted 1ml of the above stock solution into a 10 ml volumetric flask and diluted up to the mark with diluent.
Pipetted 2.15 ml of 1 µg/ml solution into a 10 ml of volumetric flask and diluted up to the mark with diluent.
Robustness:
The analysis was performed in different conditions to find the variability of test results. The following conditions are checked for variation of results. .
Preparation of sample solution (30 µg/ml of 15 µg/ml of Ketorolac)
About 10 mg of and 5 mg of Ketorolac and Febuxostat were weighed and transferred to 10 ml volumetric flask, it was dissolved with diluent and the volume was made up to the mark with same solvent. Further 0.3 ml of above solution was diluted to 10 ml with the diluent to get 30µg/ml of 15 µg/ml of Ketorolac and Febuxostat [25].
Effect of Variation of flow:
The sample was analyzed at 0.8 ml/min and 1.2 ml/min instead of 1.0 ml/min, remaining conditions are same. 10 µl of the above sample was injected twice and chromatograms were recorded
Effect of Variation of mobile phase organic composition:
The sample was analyzed by variation of mobile phase i.e. phosphate buffer: Methanol was taken in the ratio 45: 55 and 70:30 instead of 40:60, remaining conditions are same. 10 µl of the above sample was injected twice and chromatograms were recorded.

3. Results and Discussion

Validation Parameters:
Precision:
Precision of the method was carried out for both sample and standard solutions as described under experimental work. The corresponding chromatograms and results are shown below.

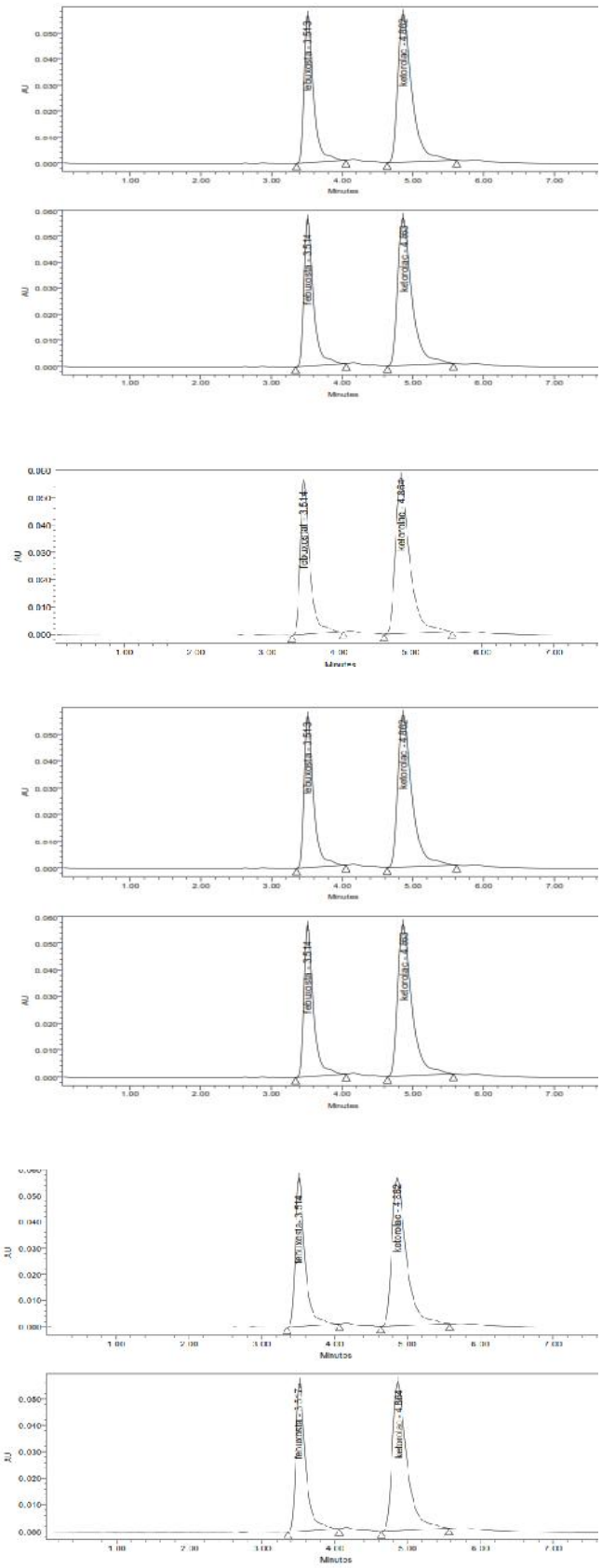


Figure 7: Chromatograms for precision injection -1 to 5.

Table 4: Results of method precession for ketorolac

	Peak Name	RT	Area (µV*sec)	Height (µV)	USP Plate Count	USP Tailing
1	ketorolacl	3.517	520512	55970	3743.5	1.5
2	ketorolac	3.514	521717	56909	3777.3	1.5
3	ketorolac	3.513	521646	57014	3776.0	1.5
4	ketorolac	3.514	522710	56972	3822.2	1.5
5	ketorolac	3.514	523284	56798	3770.1	1.5
Mean			522013.9		3777.8	1.5
Std. Dev.			1057.0			
% RSD			0.2			

Table 5: Results of method precession for febuxostat

Peak Name: febuxostat

	Peak Name	RT	Area (µV*sec)	Height (µV)	USP Plate Count	USP Tailing	USP Resolution
1	febuxostat	4.864	787229	56504	3081.3	1.6	4.5
2	febuxostat	4.864	789890	56992	3144.1	1.6	4.5
3	febuxostat	4.863	790187	56962	3118.1	1.6	4.5
4	febuxostat	4.862	791763	56934	3147.3	1.6	4.5
5	febuxostat	4.862	794118	57105	3101.8	1.6	4.5
Mean			790597.2		3118.5	1.6	4.5
Std. Dev.			2553.9				
% RSD			0.3				

Acceptance criteria:

- %RSD for sample should be NMT 2
- The %RSD for the standard solution is below 1, which is within the limits hence method is precise.

Intermediate Precession (ruggedness)

There was no significant change in assay content and system suitability parameters at different conditions of ruggedness like day to day and system to system variation.

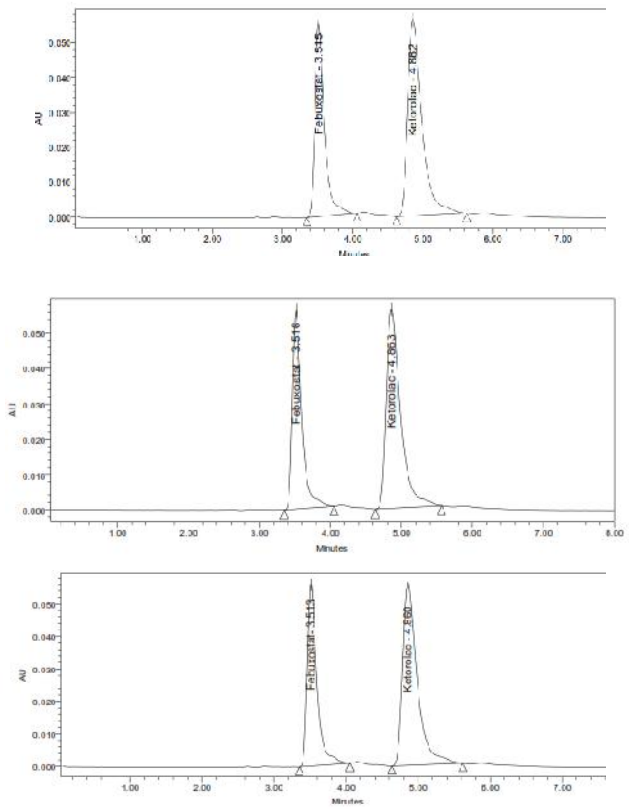


Figure 8: Showing results for intermediate precision injections 1-3

Table 6: Results of Intermediate precision for Febuxostat

Peak Name: Febuxostat

	Peak Name	RT	Area (µV*sec)	Height (µV)	USP Plate Count	USP Tailing	USP Resolution
1	Febuxostat	4.863	790742	56569	3075.9	1.6	4.5
2	Febuxostat	4.860	794791	56512	3043.2	1.7	4.5
3	Febuxostat	4.862	796445	56415	3029.9	1.6	4.4
Mean			793992.9		3049.7	1.6	4.5
Std. Dev.			2934.1				
% RSD			0.4				

Table 7: Results of Intermediate precision for Febuxostat

Peak Name: Ketorolac

	Peak Name	RT	Area (µV*sec)	Height (µV)	USP Plate Count	USP Tailing
1	Ketorolac	3.513	521817	56358	3704.2	1.6
2	Ketorolac	3.515	522684	56384	3696.0	1.5
3	Ketorolac	3.516	522921	56456	3716.3	1.5
Mean			522473.9		3705.5	1.6
Std. Dev.			581.3			
% RSD			0.1			

Acceptance criteria:

- %RSD of five different sample solutions should not more than 2
- The %RSD obtained is within the limit, hence the method is rugged.

Accuracy:

Sample solutions at different concentrations (50%, 100%, and 150%) were prepared and the % recovery was calculated.

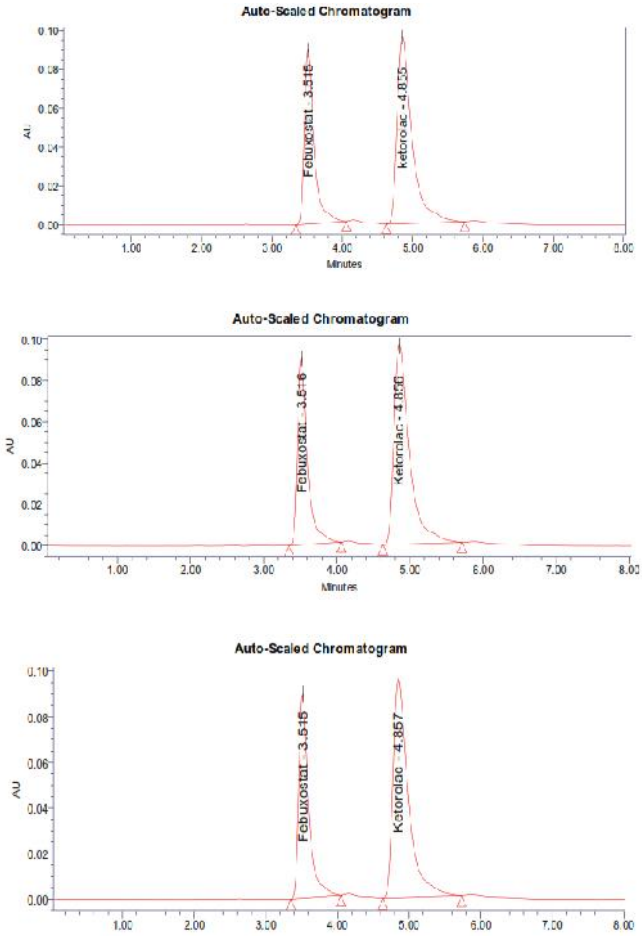


Figure 9: Chromatograms showing accuracy 50%: 1 to 3.

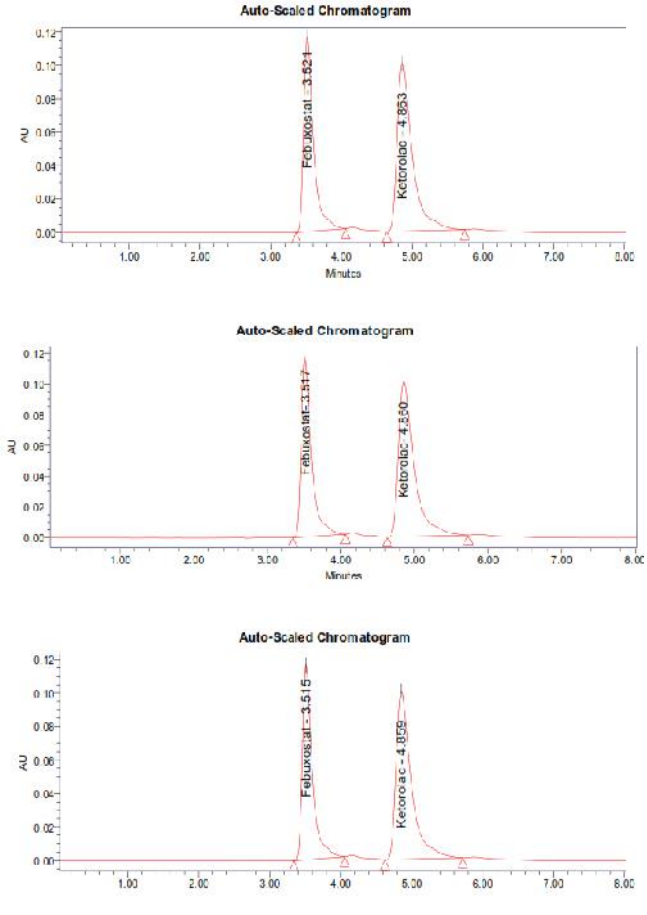


Fig 10: Chromatograms showing accuracy 100%: 1 to 3.

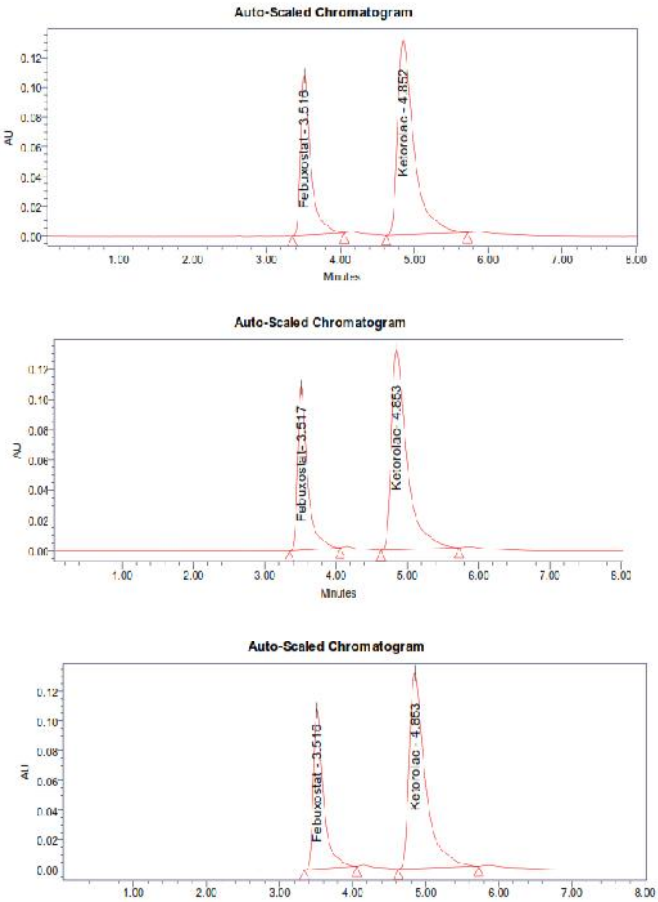


Fig 11: Chromatograms showing accuracy 150%: 1 to 3.

Table 8: Accuracy (recovery) data for Febuxostat

%Concentration	Area	Amount present (mg)	Amount Found (mg)	% Recovery	Mean Recovery
50%	852858	2.5	2.52	101.2%	100.7%
100%	1119197	5	4.99	99.9%	
150%	1038553	7.5	7.50	101.0%	

Acceptance Criteria: The % Recovery for each level should be between 98.0 to 102.0%.

Table 9: Accuracy (recovery) data for Ketorolac

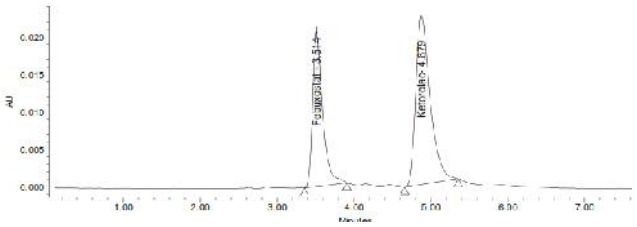
%Concentration	Area	Amount present (mg)	Amount Found (mg)	% Recovery	Mean Recovery
50%	1424941	5	5.01	100.4%	100.8%
100%	1499296	10	10.02	100.5%	
150%	2021862	15	15.86	101.4%	

Acceptance Criteria: The percentage recovery was found to be within the limit (97-103%).

The results obtained for recovery at 50%, 100%, 150% are within the limits. Hence, method is accurate

Linearity:

The linearity range was found to lie from 10 µg/ml to 50 µg/ml of Ketorolac, 5 µg/ml to 25 µg/ml of Febuxostat and chromatograms are shown below.



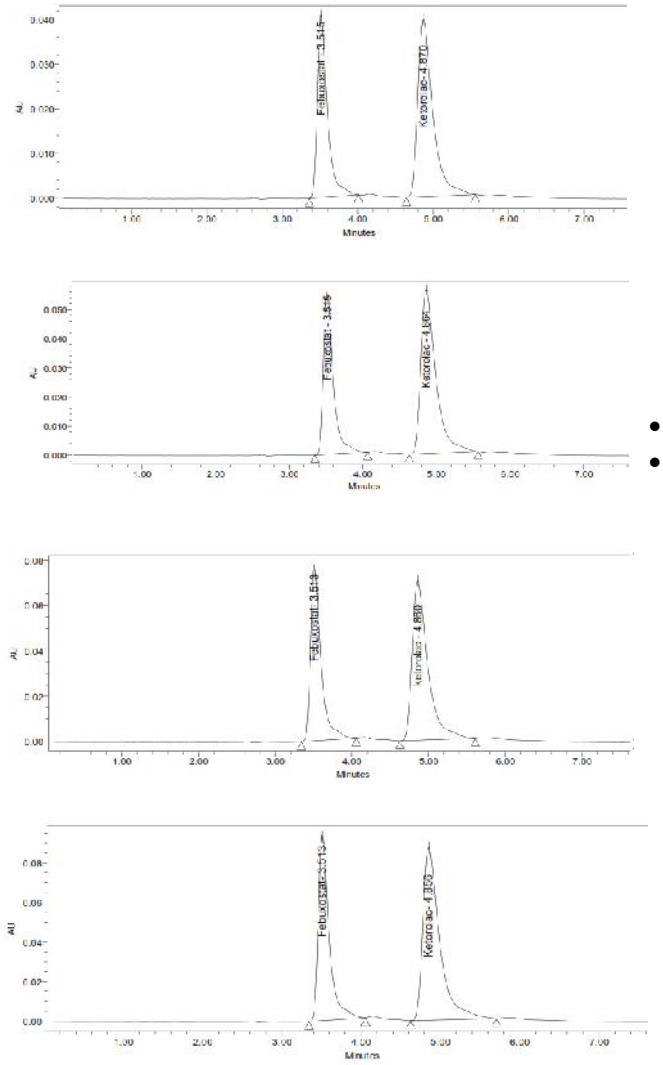


Figure 12: Chromatogram for linearity concentration of Level 1 to Level 5

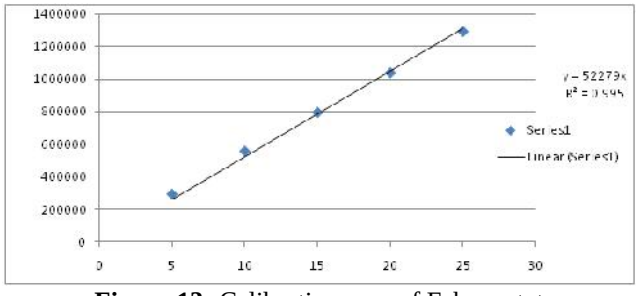


Figure 13: Calibration cure of Febuxostat

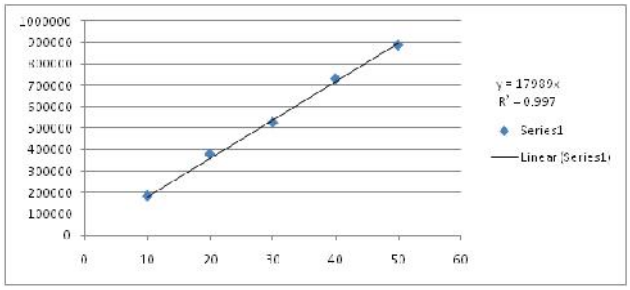


Figure 14: Calibration cure of Ketorolac

Table 10: Analytical performance parameters of Febuxostat and ketorolac

Parameters	Febuxostat	Ketorolac
Slope (m)	52279	17989
Intercept (c)	53592	50245
Correlation coefficient (R^2)	0.995	0.997

Acceptance criteria: Correlation coefficient (R^2) should not be less than 0.999**.** The correlation coefficient obtained was 0.999 which is in the acceptance limit. The linearity was established in the range of 10% to 50% of Ketorolac and 5% to 25% of Febuxosta

4. Conclusion

High performance liquid chromatography is at present one of the most sophisticated tool of the analysis. The estimation of ketorolac and febuxostat was done by RP-HPLC. The Phosphate buffer was p^H 3.5 and the mobile phase was optimized with consists of methanol: Phosphate buffer mixed in the ratio of 60:40 % v/ v. A C_8 column C8 (4.6 x 150mm, 5µm, Make: XTerra) or equivalent chemically bonded to porous silica particles was used as stationary phase. The solutions were chromatographed at a constant flow rate of 1.0 ml/min. the linearity range of Ketorolac and febuxostat were found to be from 10-50 µg/ml of ketorolac and 5-25µg/ml of febuxostat. Linear regression coefficient was not more than 0.999. The values of % RSD are less than 2% indicating accuracy and precision of the method. LOD and LOQ were found to be within limit. The results obtained on the validation parameters met ICH and USP requirements .it inferred the method found to be simple, accurate, precise and linear. The method was found to be having suitable application in routine laboratory analysis with high degree of accuracy and precision.

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