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A NEW SEPERATION TECHNIQUE FOR METHOD DEVELOPMENT AND VALIDATION OF PIOGLITAZONE IN IT'S PURE AND PHARMACEUTICAL DOSAGE FORM BY USING HPLC

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ABSTRACT

The estimation of Pioglitazone was done by RP-HPLC. The assay of Pioglitazone was performed with tablets and the % assay was found to be 100.10 which show that the method is useful for routine analysis. Pioglitazone is a medication belonging to the thiazolidinedione class of drugs that are used as adjuncts to diet, exercise, and other diabetes medications to manage type 2 diabetes mellitus. Pioglitazone acts as a selective agonist at Peroxisome Proliferator Activated Receptor Gamma (PPARγ) in target tissues for insulin action such as adipose tissue, skeletal muscle, and liver. UV spectrum of 10 µg/ml Pioglitazone in diluents (mobile phase composition) was recorded by scanning in the range of 200nm to 400nm. the mobile phase was optimized to Acetonitrile: Phosphate buffer (pH 4.5) in proportion 50: 50 v/v respectively. Plot a graph of peak area versus concentration (on X-axis concentration and on Y-axis Peak area) and calculate the correlation coefficient. Acceptance Criteria: Correlation coefficient should be not less than 0.99. The robustness limit for mobile phase variation and flow rate variation are well within the limit, which shows that the method is having good system suitability and precision under given set of conditions.

Keywords: Pioglitazone, PPARγ and RP-HPLC.

INTRODUCTION

Pioglitazone is a medication belonging to the thiazolidinedione class of drugs that are used as adjuncts to diet, exercise, and other diabetes medications to manage type 2 diabetes mellitus. The thiazolidinedione class of medications exerts its pharmacological effect primarily by promoting insulin sensitivity and the improved uptake of blood glucose. Following entry into fat cell nuclei, pioglitazone selectively binds to the Peroxisome Proliferator-Activated Receptor Gamma (PPARγ). PPARs are ligand-activated transcription factors that are involved in the expression of more than 100 genes, and affect numerous metabolic processes, notably lipid and glucose homeostasis. PPARγ in particular is abundantly expressed in lipid cells (adipocytes), where it plays a central role in lipid production and regulation of lipid metabolism.

Mechanism of action

Pioglitazone acts as a selective agonist at Peroxisome Proliferator Activated Receptor Gamma (PPARγ) in target tissues for insulin action such as adipose tissue, skeletal muscle, and liver. Activation of PPAR-gamma receptors increases the transcription of insulin-responsive genes involved in the control of glucose production, transport, and utilization. In this way, pioglitazone both enhances tissue sensitivity to insulin and reduces the production of glucose via the liver (hepatic gluconeogenesis). Thus, insulin resistance associated with type 2 diabetes mellitus is improved without an increase in insulin secretion by pancreatic β cells.

Protein binding

Pioglitazone is extensively protein bound (> 99%) in human serum, principally to serum albumin. Pioglitazone also binds to other serum proteins, but with lower affinity.

Metabolism

Pioglitazone is extensively metabolized by hydroxylation and oxidation; the metabolites also partly convert to glucuronide or sulfate conjugates. Metabolites M-III and M-IV are the major circulating active metabolites in humans. The cytochrome P450 isoforms involved are CYP2C8 and, to a lesser degree, CYP3A4 with additional contributions from a variety of other isoforms including the mainly extrahepatic CYP1A1.

Following oral administration, approximately 15% to 30% of the pioglitazone dose is recovered in the urine. Renal elimination of pioglitazone is negligible, and the drug is excreted primarily as metabolites and their conjugates. It is presumed that most of the oral dose is excreted into the bile either unchanged or as metabolites and eliminated in the feces.

Affected organisms

Humans and other mammals.

EXPERIMENTAL METHODS

Table 1: Instruments used

SL.NO	INSTRUMENT	MODEL
1	HPLC	WATERS, software: Empower, 2695 separation module.2487 UV detector.
2	UV/VIS spectrophotometer	LABINDIA UV 3000+
3	pH meter	Adwa – AD 1020
4	Weighing machine	Afcoset ER-200A
5	Pipettes and Burettes	Borosil
6	Beakers	Borosil

Table 2: Chemical Used

SL.NO	Chemicals	Company Name
1	Pioglitazone	PHARMATRAIN
2	Water for HPLC	FINER chemical LTD
3	Methanol for HPLC	LICHROSOLV (MERCK)
4	Acetonitrile for HPLC	MOLYCHEM
5	KH2PO4	MERCK
6	NaOH	FINER chemical LTD

HPLC METHOD DEVELOPMENT

Wave length selection

UV spectrum of 10 µg/ml Pioglitazone in diluents (mobile phase composition) was recorded by scanning in the range of 200nm to 400nm. From the UV spectrum wavelength selected as 220 nm. At this wavelength both the drugs show good absorbance.

Mobile Phase Optimization

Initially the mobile phase tried was Methanol: Water, Methanol: 0.1% OPA, Acetonitrile: Phosphate buffer and Methanol: Phosphate buffer with various combinations of pH as well as varying proportions. Finally, the mobile phase was optimized to Acetonitrile: Phosphate buffer (pH 4.5) in proportion 50: 50 v/v respectively.

Optimization of Column

The method was performed with various columns like C18 column Phenomenex column, Inertsil ODS column and YMC column. Agilent (4.6 x 150mm, 5□m) was found to be ideal as it gave good peak shape and resolution at 1.0 ml/min flow.

OPTIMIZED CHROMATOGRAPHIC CONDITIONS

Instrument used :Waters HPLC with auto sampler and UV detector.
Temperature : Ambient
Column : Agilent (4.6 x 150mm, 5□m)
Buffer : Phosphate buffer
pH : 4.5
Mobile phase : Acetonitrile: Phosphate buffer (50:50)
Flow rate : 1 ml per min
Wavelength : 220 nm
Injection volume : 20 uL
Run time : 10 min.

PREPARATION OF BUFFER AND MOBILE PHASE

Preparation of Phosphate buffer

Take 3.4 gms of potassium di hydrogen ortho phosphate in 1000 ml of HPLC water, Ph was adjusted with NaOH up to 4.5. Final solution was filtered through 0.45 Membrane filter and sonicate it for 10 mins.

Preparation of mobile phase

Accurately measured 500 ml of Acetonitrile(50%) and 500 ml of above buffer (50%) were mixed and degassed in an ultrasonic water bath for 10 minutes and then filtered through 0.45 µ filter under vacuum filtration.

Preparation

The Mobile phase was used as the diluent.

ASSAY

Standard Solution Preparation

Accurately weigh and transfer 150 mg of Pioglitazone working standard into a 100 ml clean dry volumetric flask add about 50 ml of diluent and sonicate to dissolve it completely and make volume up to the mark with the same solvent. (Stock solution)
Further pipette 2.5 ml of the above stock solutions into a 25 ml volumetric flask and dilute up to the mark with diluent.
Further pipette 3 ml of the above stock solutions into a 10 ml volumetric flask and dilute up to the mark with diluent. (45 ppm Pioglitazone)

Sample Solution Preparation

Accurately weigh 20 tablets crush in motor and pestle and transfer equivalent to 150 mg (1200 mg of tablet power) of Pioglitazone sample into a 100 ml clean dry volumetric flask add about 50 mL of diluent and sonicate it up to 30 mins to dissolve it completely and make volume up to the mark with the same solvent. Then it is filtered through 0.45 micron injection filter. (Stock solution)
Further pipette 2.5 ml of the above stock solutions into a 25 ml volumetric flask and dilute up to the mark with diluent.
Further pipette 3 ml of the above stock solutions into a 10 ml volumetric flask and dilute up to the mark with diluent. (45 ppm Pioglitazone)

Procedure

Inject 20 µL of the standard, sample into the chromatographic system and measure the areas for Pioglitazone peaks and calculate the %Assay by using the formulae.

VALIDATION PARAMETERS

1. LINEARITY

Preparation of stock solution

Accurately weigh and transfer 150 mg of Pioglitazone working standard into a 100 ml clean dry volumetric flask add about 50 ml of diluent and sonicate to dissolve it completely and make volume up to the mark with the same solvent. (Stock solution)
Further pipette 2.5 ml of the above stock solutions into a 25 ml volumetric flask and dilute up to the mark with diluent.

Preparation of Level – I (15 ppm of Pioglitazone)

1 ml of above stock solutions has taken in 10 ml of volumetric flask, dilute up to the mark with diluent.

Preparation of Level – II (30 ppm of Pioglitazone)

2 ml of above stock solutions has taken in 10 ml of volumetric flask, dilute up to the mark with diluent.
Preparation of Level – III (45 ppm of Pioglitazone)
3 ml of above stock solutions has taken in 10 ml of volumetric flask, dilute up to the mark with diluent.
Preparation of Level – IV (60 ppm of Pioglitazone)
4 ml of above stock solutions has taken in 10 ml of volumetric flask, dilute up to the mark with diluent
Preparation of Level – V (75 ppm of Pioglitazone)
5 ml of above stock solutions has taken in 10 ml of volumetric flask, dilute up to the mark with diluent

Procedure
Inject each level into the chromatographic system and measure the peak area.
Plot a graph of peak area versus concentration (on X-axis concentration and on Y-axis Peak area) and calculate the correlation coefficient.
Acceptance Criteria: Correlation coefficient should be not less than 0.99.

2. PRECISION
Preparation of stock solution
Accurately weigh and transfer 150 mg of Pioglitazone working standard into a 100 ml clean dry volumetric flask add about 50 ml of diluent and sonicate to dissolve it completely and make volume up to the mark with the same solvent. (Stock solution)
Further pipette 2.5 ml of the above stock solutions into a 25 ml volumetric flask and dilute up to the mark with diluent.
Further pipette 3 ml of the above stock solutions into a 10 ml volumetric flask and dilute up to the mark with diluent. (45 ppm Pioglitazone)

Procedure
The standard solution was injected for six times and measured the area for all six. Injections in HPLC. The %RSD for the area of six replicate injections was found to be within the specified limits.
Acceptance Criteria: The % RSD for the area of six standard injections results should not be more than 2%.

3. INTERMEDIATE PRECISION/RUGGEDNESS
To evaluate the intermediate precision (also known as Ruggedness) of the method, Precision was performed on different day.
Preparation of stock solution
Accurately weigh and transfer 150 mg of Pioglitazone working standard into a 100 ml clean dry volumetric flask add about 50 ml of diluent and sonicate to dissolve it completely and make volume up to the mark with the same solvent. (Stock solution)
Further pipette 2.5 ml of the above stock solutions into a 25 ml volumetric flask and dilute up to the mark with diluent.
Further pipette 3 ml of the above stock solutions into a 10 ml volumetric flask and dilute up to the mark with diluent. (45 ppm Pioglitazone)

Procedure
The standard solutions prepared in the precision was injected on the other day, for six times and measured the area for all six injections in HPLC. The %RSD for the area of six replicate injections was found to be within the specified limits.
Acceptance Criteria: The % RSD for the area of six standard injections results should not be more than 2%.

4. ACCURACY
Preparation of Standard stock solution
Accurately weigh and transfer 150 mg of Pioglitazone working standard into a 100 ml clean dry volumetric flask add about 50 ml of diluent and sonicate to dissolve it completely and make volume up to the mark with the same solvent. (Stock solution)
Further pipette 2.5 ml of the above stock solutions into a 25 ml volumetric flask and dilute up to the mark with diluent.
Further pipette 3 ml of the above stock solutions into a 10 ml volumetric flask and dilute up to the mark with diluent. (45 ppm Pioglitazone)

Preparation of Sample solutions

For preparation of 50% solution (With respect to target Assay concentration)

Accurately weigh 20 tablets crush in motor and pestle and transfer equivalent to 75 mg (600 mg of tablet power) of Pioglitazone sample into a 100 ml clean dry volumetric flask add about 50 mL of diluent and sonicate it up to 30 mins to dissolve it completely and make volume up to the mark with the same solvent. Then it is filtered through 0.45 micron injection filter. (Stock solution)

Further pipette 2.5 ml of the above stock solutions into a 25 ml volumetric flask and dilute up to the mark with diluent.

Further pipette 3 ml of the above stock solutions into a 10 ml volumetric flask and dilute up to the mark with diluent. (22.5 ppm Pioglitazone)

For preparation of 100% solution (With respect to target Assay concentration):

Accurately weigh 20 tablets crush in motor and pestle and transfer equivalent to 150 mg (1200 mg of tablet power) of Pioglitazone sample into a 100 ml clean dry volumetric flask add about 50 mL of diluent and sonicate it up to 30 mins to dissolve it completely and make volume up to the mark with the same solvent. Then it is filtered through 0.45 micron injection filter. (Stock solution)

Further pipette 2.5 ml of the above stock solutions into a 25 ml volumetric flask and dilute up to the mark with diluent.

Further pipette 3 ml of the above stock solutions into a 10 ml volumetric flask and dilute up to the mark with diluent. (45 ppm Pioglitazone)

For preparation of 150% solution (With respect to target Assay concentration)

Accurately weigh 20 tablets crush in motor and pestle and transfer equivalent to 225 mg (1800 mg of tablet power) of Pioglitazone sample into a 100 ml clean dry volumetric flask add about 50 mL of diluent and sonicate it up to 30 mins to dissolve it completely and make volume up to the mark with the same solvent. Then it is filtered through 0.45 micron injection filter. (Stock solution)

Further pipette 2.5 ml of the above stock solutions into a 25 ml volumetric flask and dilute up to the mark with diluent.

Further pipette 3 ml of the above stock solutions into a 10 ml volumetric flask and dilute up to the mark with diluent. (67.5 ppm Pioglitazone)

Procedure

Inject the standard solution, Accuracy -50%, Accuracy -100% and Accuracy -150% solutions.

Calculate the Amount found and Amount added for Pioglitazone and calculate the individual recovery and mean recovery values.

Acceptance Criteria

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

5. ROBUSTNESS

As part of the Robustness, deliberate change in the Flow rate, Mobile Phase composition, Temperature Variation was made to evaluate the impact on the method.

A. The flow rate was varied at 0.8 ml/min to 1.2 ml/min.

Standard solution 45 ppm of Pioglitazone was prepared and analysed using the varied flow rates along with method flow rate.

On evaluation of the above results, it can be concluded that the variation in flow rate affected the method significantly. Hence it indicates that the method is robust even by change in the flow rate ±10%.

* Results for actual flow (1.0 ml/min) have been considered from Assay standard.

B. The organic composition in the Mobile phase was varied from 45% to 55%.

Standard solution 45 ppm of Pioglitazone was prepared and analysed using the varied Mobile phase composition along with the actual mobile phase composition in the method.

On evaluation of the above results, it can be concluded that the variation in 10%.

Organic composition in the mobile phase affected the method significantly. Hence it indicates that the method is robust even by change in the Mobile phase ±10%

* Results for actual Mobile phase composition (50:50 Acetonitrile: phosphate buffer pH 4.5) has been considered from Accuracy standard.

RESULTS AND DISCUSSION

SYSTEM SUITABILITY

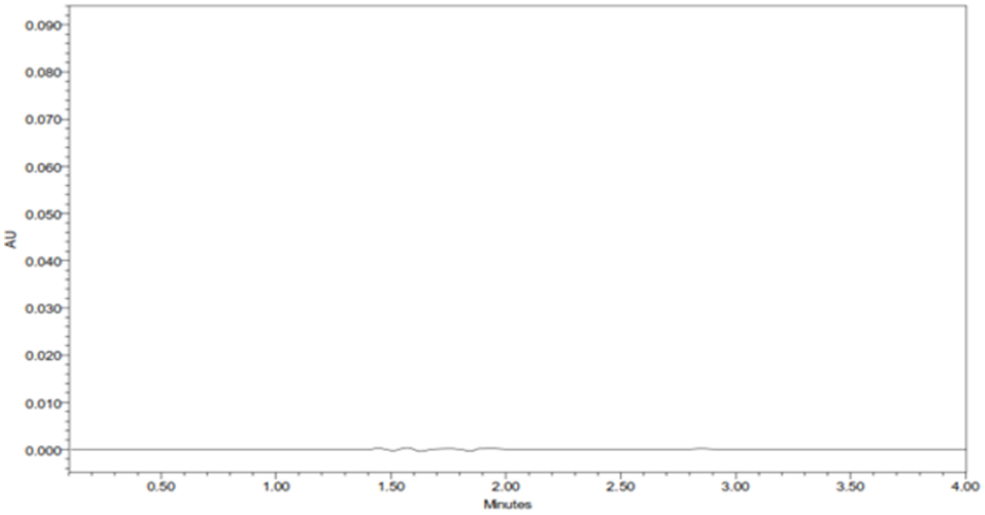

Fig. 1: Chromatogram for Blank

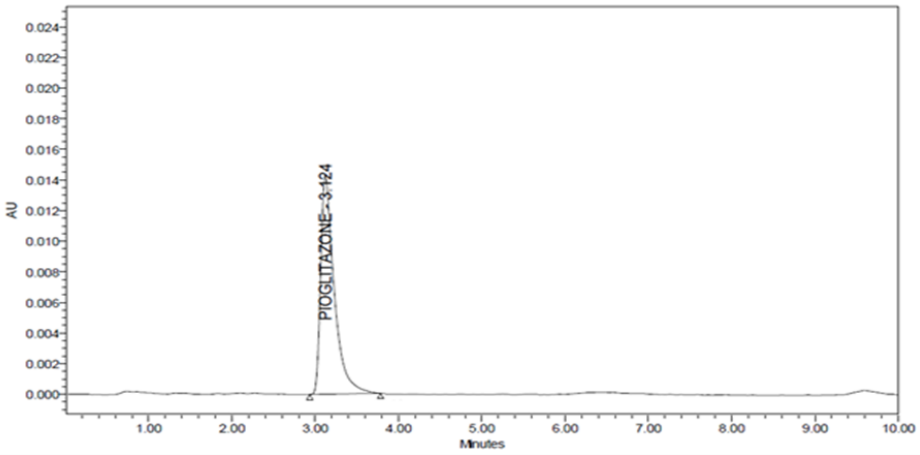

Fig. 2: Chromatogram for system suitability

Table 3: Results of system suitability parameters

S. NO.	NAME	RT(MIN)	AREA (µV sec)	Height (µV)	USP tailing	USP plate count
1	Pioglitazone	3.124	3584683	14422	1.13	3896.83

Acceptance criteria

- Theoretical plates must be not less than 2000.
- Tailing factor must be not more than 2.
- It was found from above data that all the system suitability parameters for developed method were within the limit.

ASSAY

Standard and sample solution injected as described under experimental work. The corresponding chromatograms and results are shown below.

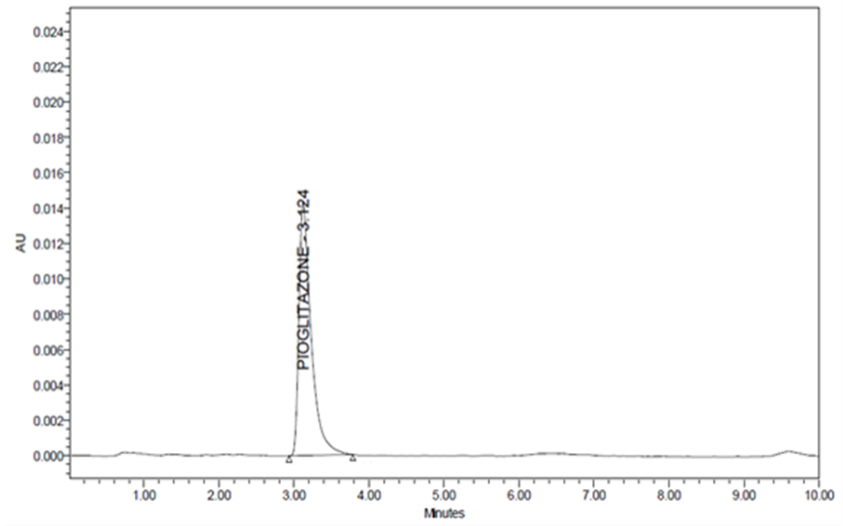

Fig. 3: Chromatogram for Standard

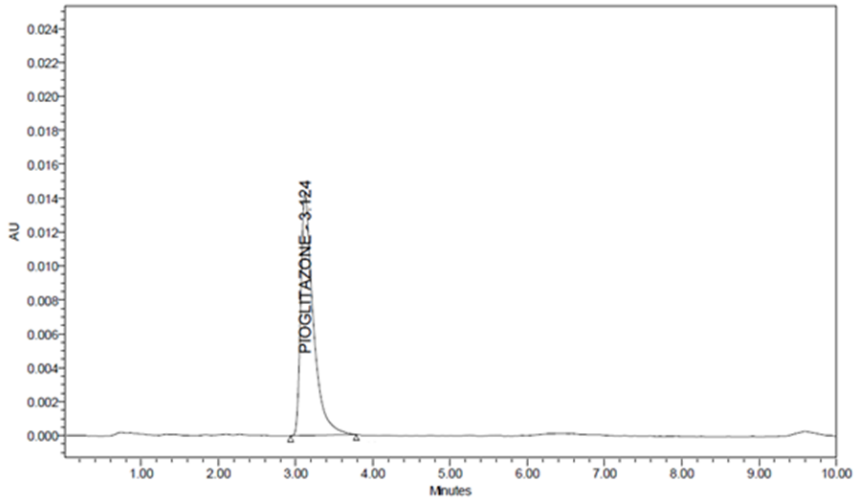

Fig. 4: Chromatogram for Sample

Formula for % Assay

$$\frac{Test\ Area}{Standard\ Area} * \frac{Standard\ Concentration}{Sample\ Concentration} * \frac{Percentage\ Purity\ of\ Drug}{100} * 100$$

$$\%\ Assay = \frac{3583009.3}{3572100.7} * \frac{45}{45} * \frac{99.8}{100} * 100 = 100.10$$

Table 4: Results of Assay for Pioglitazone

DRUG	LABEL CLAIM	% ASSAY
Pioglitazone	120	100.10

VALIDATION PARAMETERS

1. LINEARITY

The linearity range was found to lie from 15 µg/ml to 75 µg/ml of Pioglitazone and chromatograms are shown below.

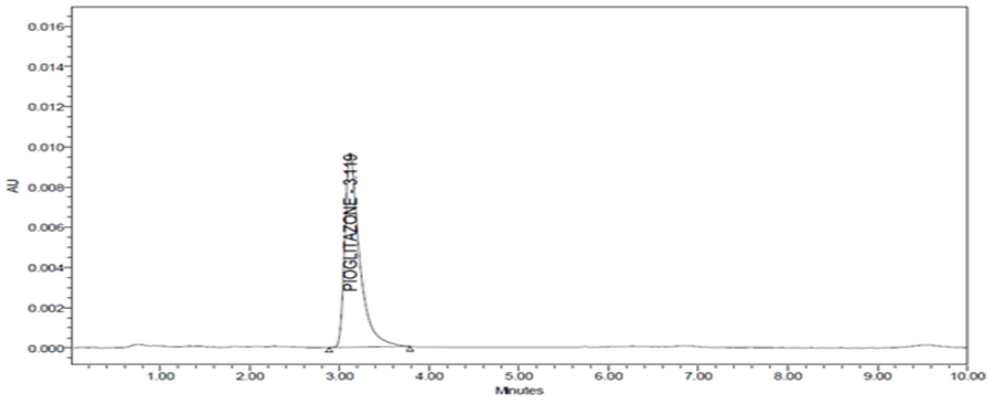

Fig. 5: Chromatogram for linearity-1

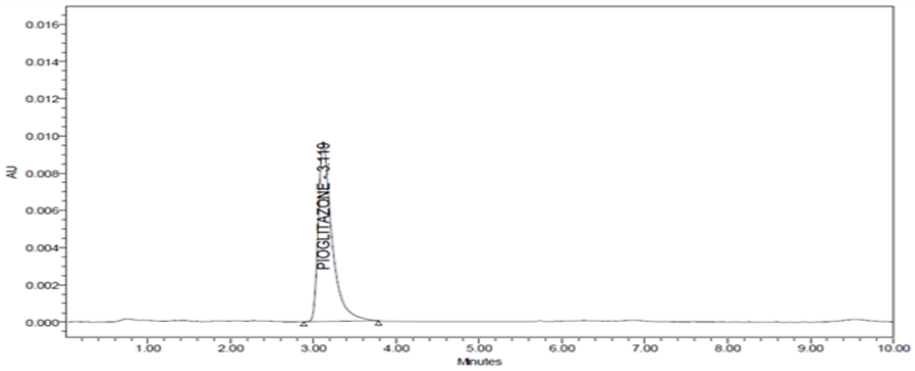

Fig. 6: Chromatogram for linearity-2

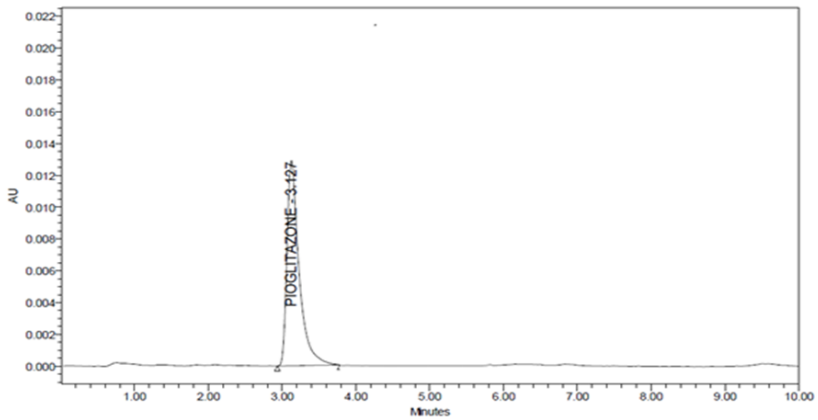

Fig. 7: Chromatogram for linearity-3

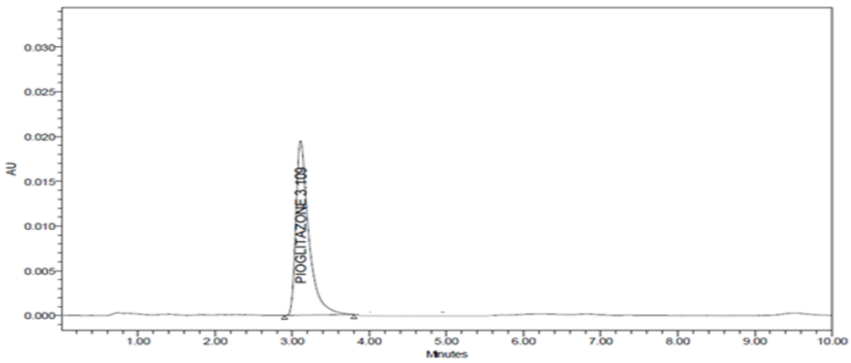

Fig. 8: Chromatogram for linearity-4

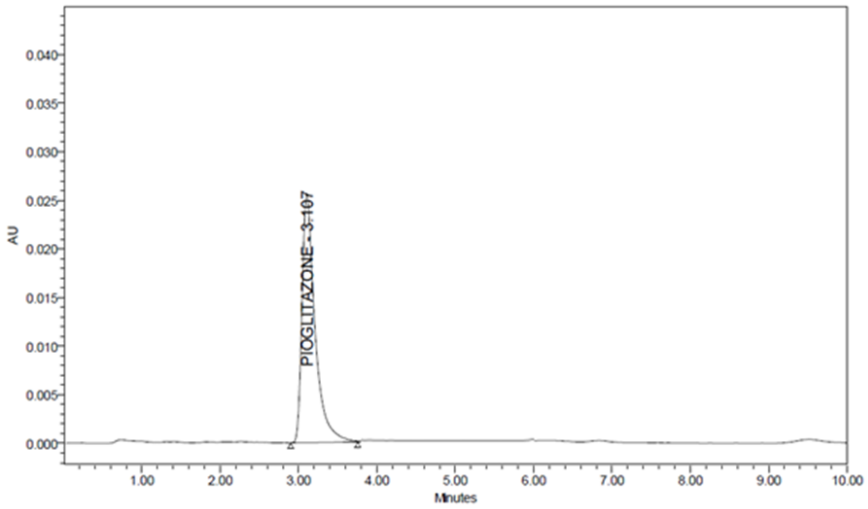

Fig. 9: Chromatogram for linearity-5

Table 5: Area of different concentration of Pioglitazone

S.NO	PIOGLITAZONE CONCENTRATION(ug/ml)	AREA
1	0	0
2	15	1259963
3	30	2458897
4	45	3574552
5	60	4863239
6	75	6133273

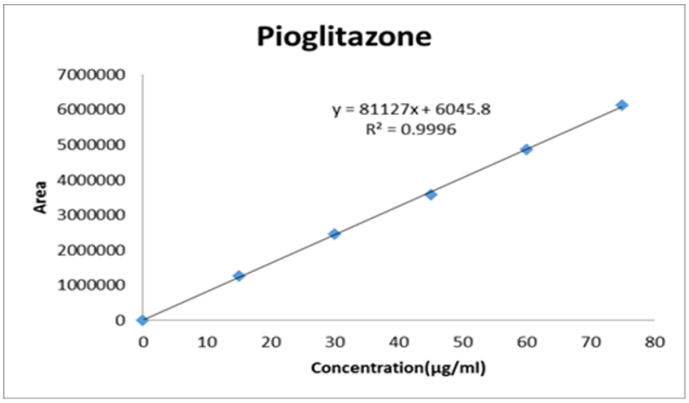

Fig. 10: Calibration graph for Pioglitazone

Table 6: Analytical performance parameters of Pioglitazone

Parameters	Pioglitazone
Slope(m)	81127
Intercept(c)	6045.8
Correlation Coefficient(R2)	0.99

2. PRECISION

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

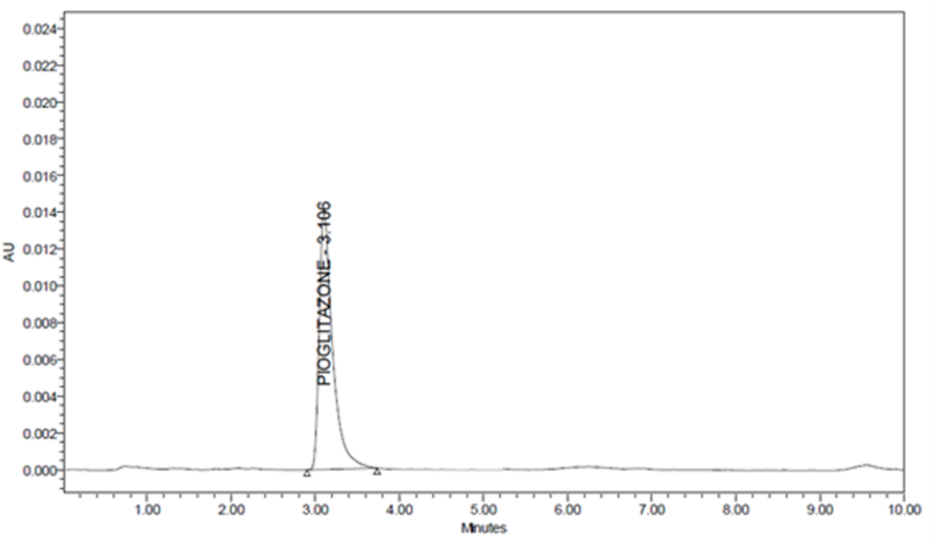

Fig. 11: Chromatogram for Precision -1

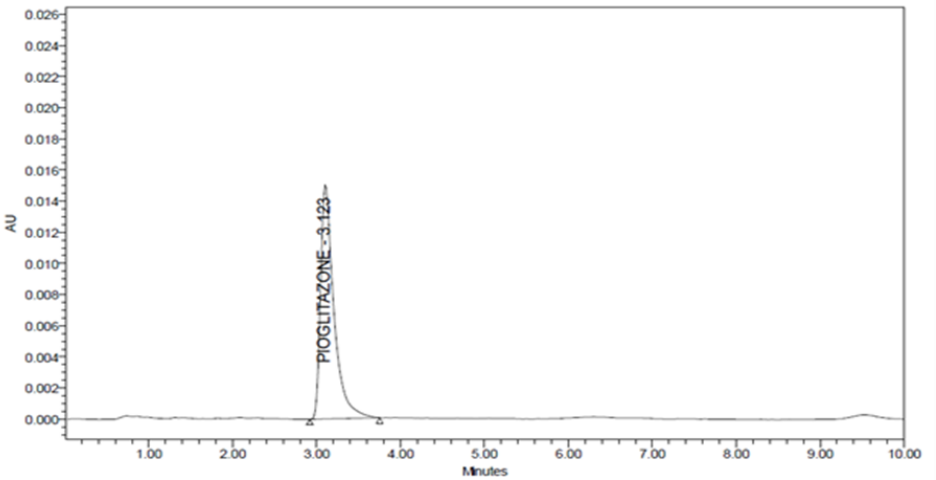

Fig. 12: Chromatogram for Precision -2

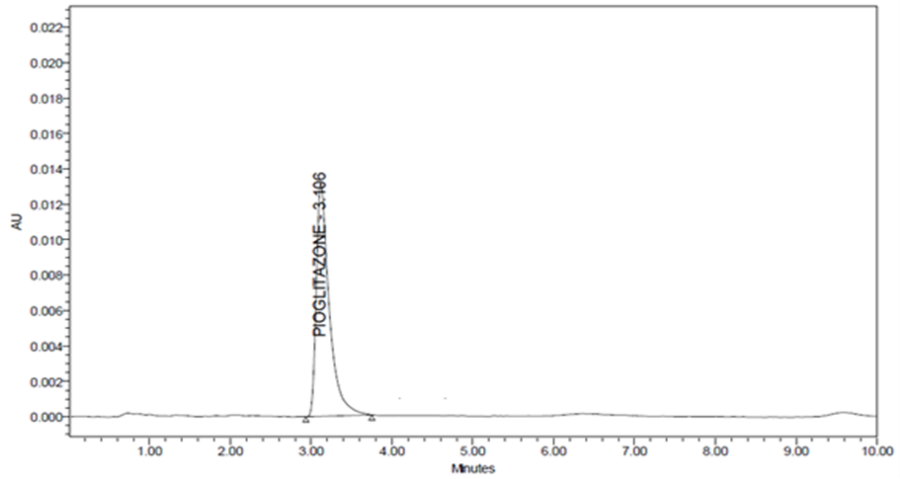

Fig. 13: Chromatogram for Precision -3

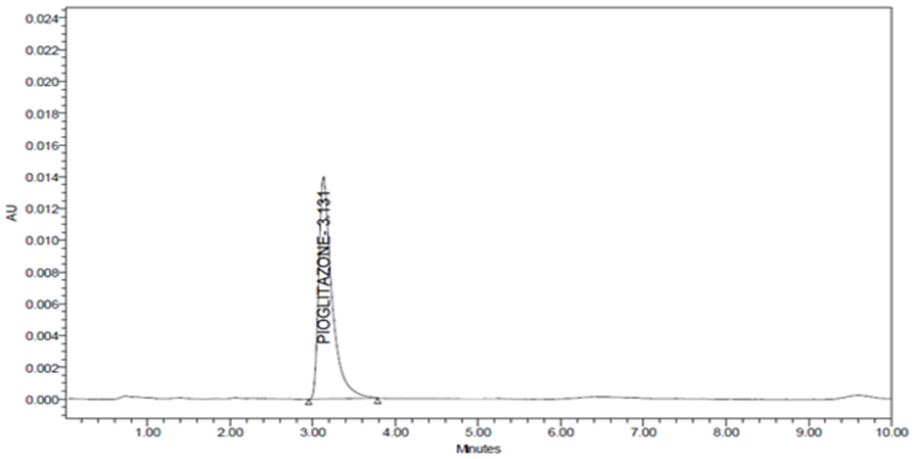

Fig. 14: Chromatogram for Precision -4

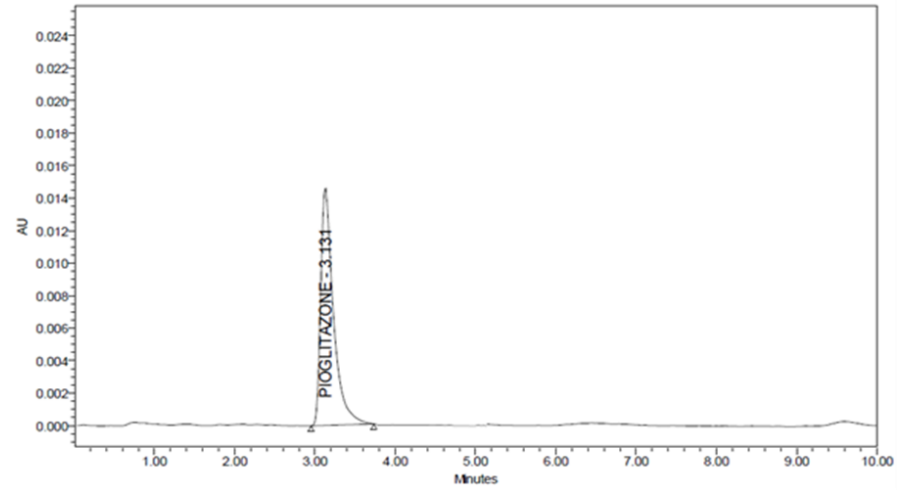

Fig. 15: Chromatogram for Precision -5

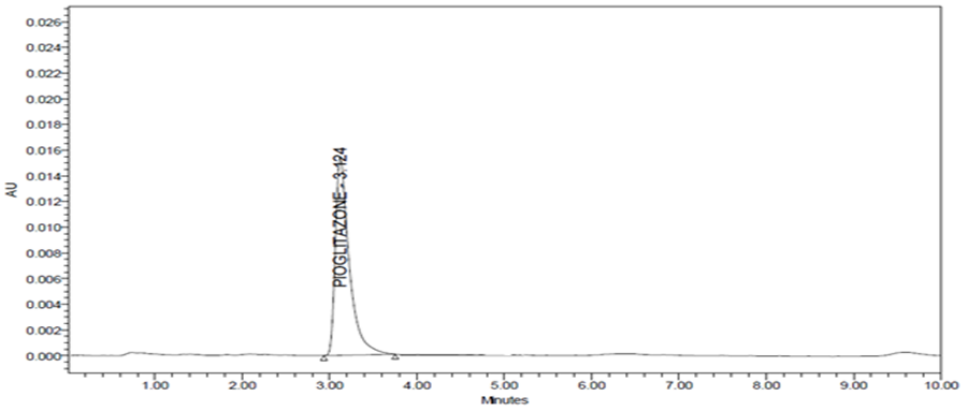

Fig. 16: Chromatogram for Precision -6

Table 7: % RSD FOR SAMPLE SOLUTION

INJECTION	Area
Injection-1	3592792
Injection-2	3599373
Injection-3	3524734
Injection-4	3547763
Injection-5	3588647
Injection-6	3588468
Average	3573629.5
Standard Deviation	30118.0
% RSD	0.8

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.

3. INTERMEDIATE PRECISION (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**.**

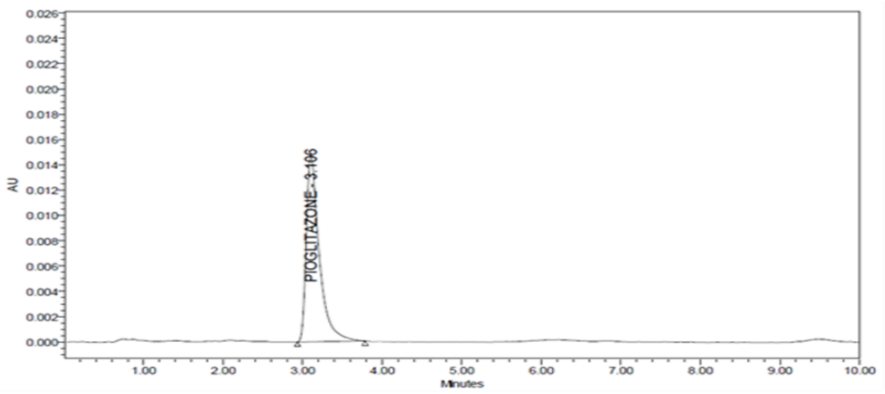

Fig. 17: Chromatogram for ID Precision -1

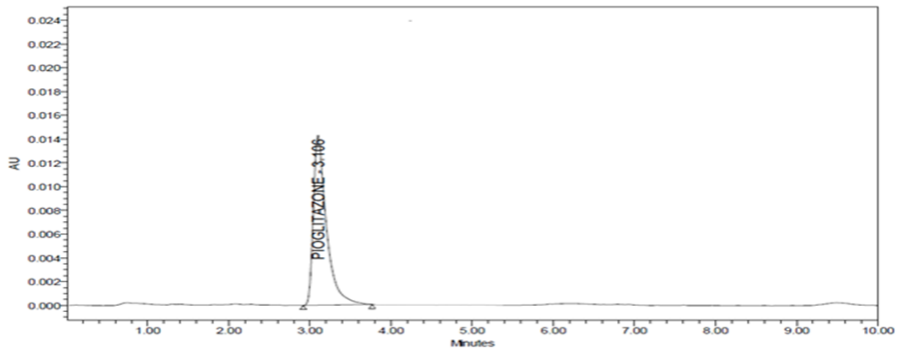

Fig. 18: Chromatogram for ID Precision -2

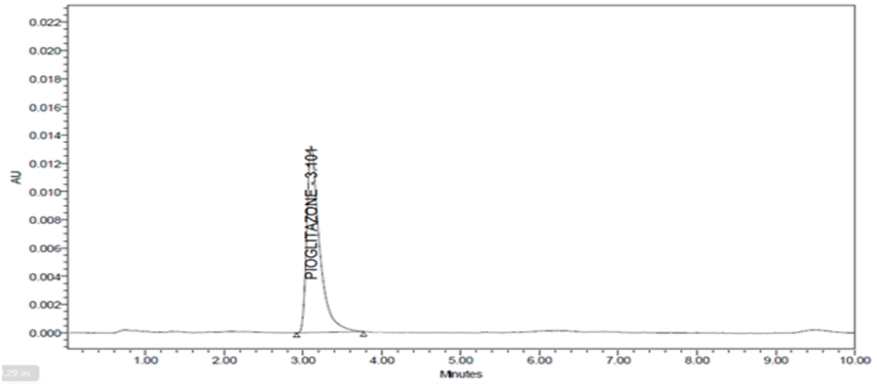

Fig. 19: Chromatogram for ID Precision-3

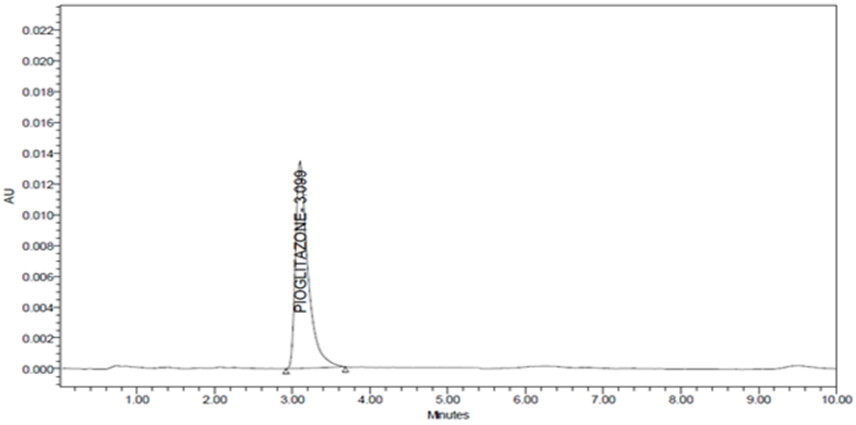

Fig. 20: Chromatogram for ID Precision-4

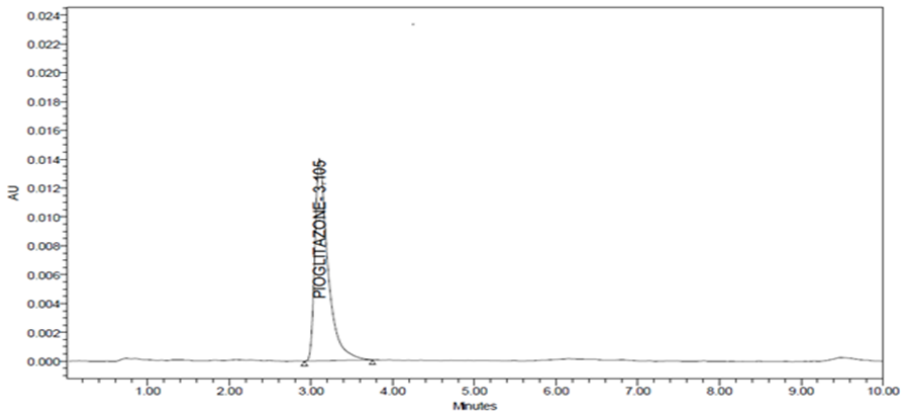

Fig. 21: Chromatogram for ID Precision -5

Table 8: Results of Intermediate precision for Pioglitazone

INJECTION	AREA
Injection-1	3594678
Injection-2	3548665
Injection-3	3547655
Injection-4	3522568
Injection-5	3564856
Injection-6	3555497
Average	3555653.2
Standard Deviation	23728.0
%RSD	0.7

Acceptance criteria

•%RSD of six different sample solutions should not more than 2.

•The %RSD obtained is within the limit, hence the method is rugged.

4. ACCURACY

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

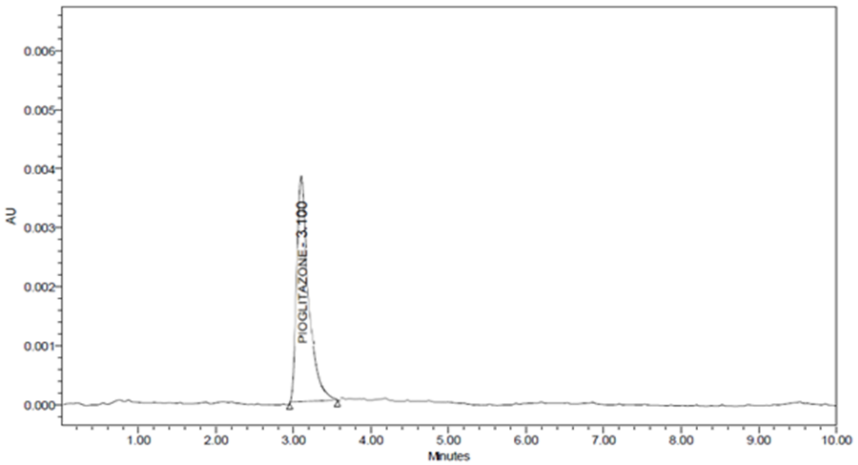

Fig. 22: Chromatogram for Accuracy 50%-1

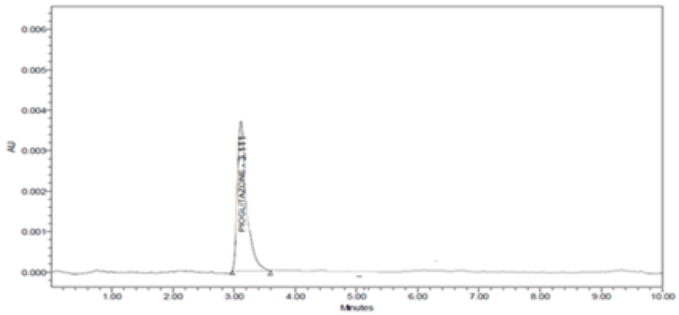

Fig. 23: Chromatogram for Accuracy 50%-2

5. ROBUSTNESS

The standard and samples of Pioglitazone were injected by changing the conditions of chromatography. There was no significant change in the parameters like resolution, tailing factor, asymmetric factor, and plate count.

Variation in flow

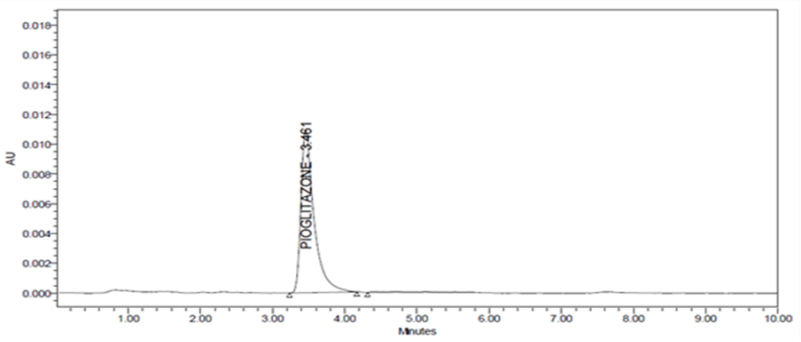

Fig. 24: Chromatogram showing less flow

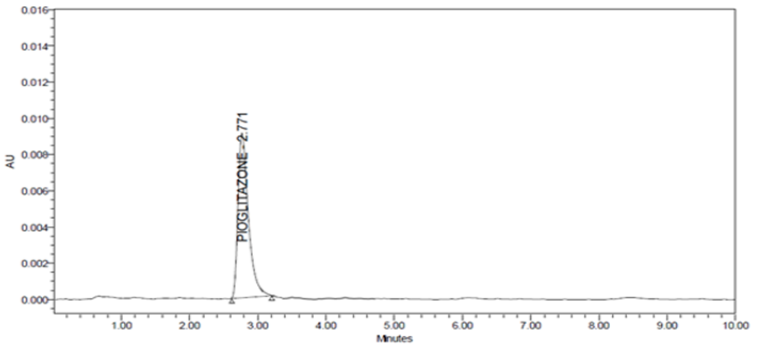

Fig. 25: Chromatogram showing more flow

Variation of mobile phase organic composition

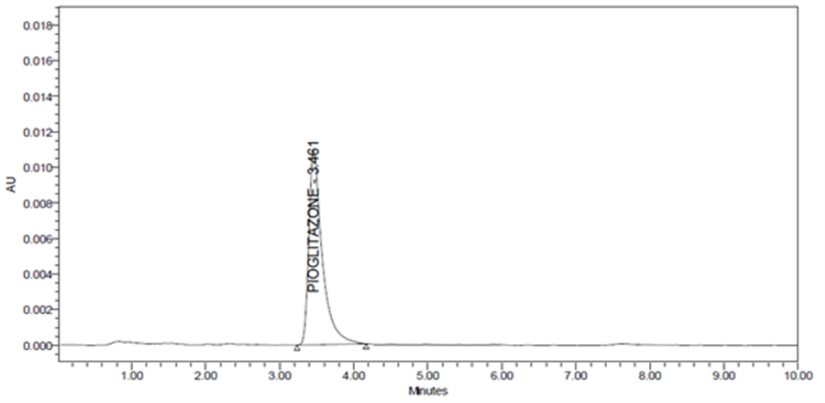

Fig. 26: Chromatogram showing less organic composition

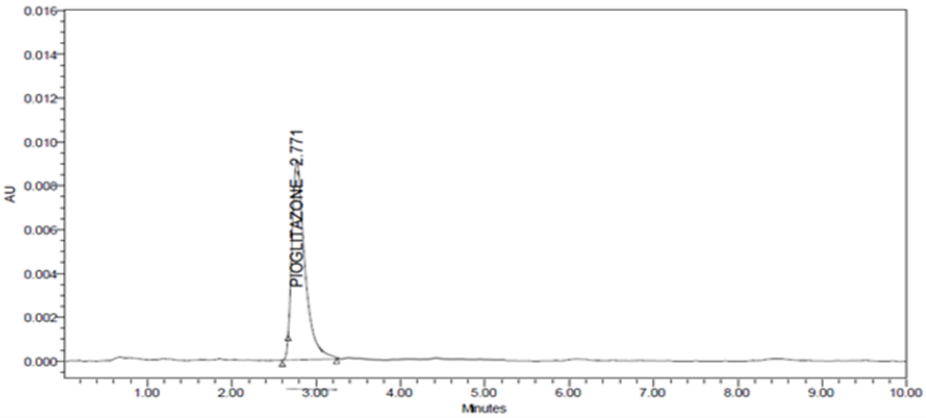

Fig. 27: Chromatogram showing less organic composition

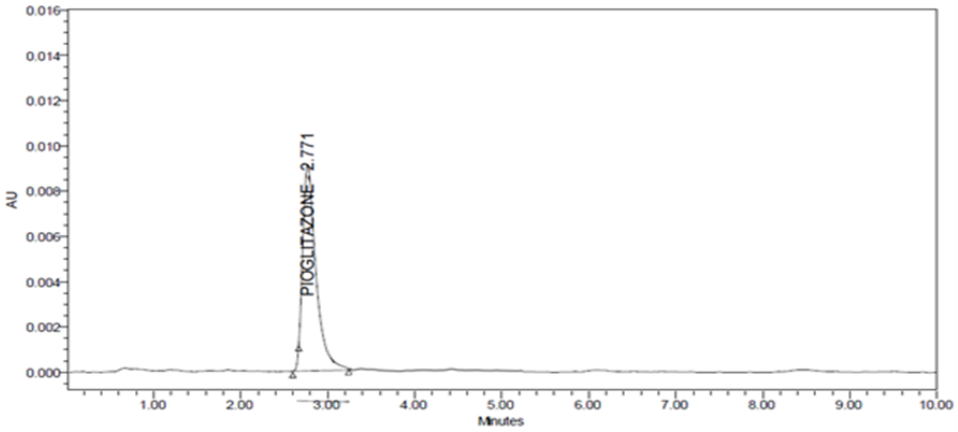

Fig. 28: Chromatogram showing more organic composition

CONCLUSION

The estimation of Pioglitazone was done by RP-HPLC.

The assay of Pioglitazone was performed with tablets and the % assay was found to be 100.10 which show that the method is useful for routine analysis.

The linearity of Pioglitazone was found to be linear with a correlation coefficient of 0.999, which shows that the method is capable of producing good sensitivity.

The acceptance criteria of precision is RSD should be not more than 2.0% and the method show precision 0.8 for Pioglitazone which shows that the method is precise.

The acceptance criteria of intermediate precision is RSD should be not more than 2.0% and the method show precision 0.7 for Pioglitazone which shows that the method is repeatable when performed in different days also.

The accuracy limit is the percentage recovery should be in the range of 98.0% - 102.0%. The total recovery was found to be 99.40% for Pioglitazone. The validation of developed method shows that the accuracy is well within the limit, which shows that the method is capable of showing good accuracy and reproducibility.

The robustness limit for mobile phase variation and flow rate variation are well within the limit, which shows that the method is having good system suitability and precision under given set of conditions.

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