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A VALIDATED STABILITY INDICATING RP-HPLC METHOD OF ESTIMATION OF PIOGLITAZONE HCL IN DOSAGE FORM

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ABSTRACT: This present study aims to develop an accurate, precise, and linear reverse-phase High-Performance Liquid Chromatographic (RP-HPLC) method for the estimation of Pioglitazone HCL in Pharmaceutical dosage form. **Method:** The chromatographic system employs a reverse-phase Hypersil BDS, C8 250 × 4.6 mm, 5 columns using 0.01M Potassium phosphate buffer and acetonitrile (40:60) as mobile phase, methanol as a diluent in isocratic mode. A flow rate of 1.0 ml/min was optimized with a detection wavelength at 225 nm. The retention time (R_t) was around 4.72 ± 0.2 min. **Results:** The method was validated with respect to specificity, selectivity, linearity, accuracy, precision, and robustness as per ICH guidelines. The assay method was observed linear in the concentration range of 0.079-0.318 mg/ml with a Correlation coefficient (r2) of 0.9999. The percentage recovery of active pharmaceutical ingredients from tablet dosage form ranged from 99.40-100.40%. Stress conditions of degradation in acidic, alkaline, peroxide, thermal, and UV radiation were studied.

INTRODUCTION: Pioglitazone HCl is an anti hyperglycaemic agent that, in the presence of insulin resistance, increases hepatic and peripheral insulin sensitivity, thereby inhibiting hepatic gluconeogenesis and increasing peripheral and splanchnic glucose uptake. It is a potent and highly selective agonist for the nuclear receptor, peroxisome proliferator-activated receptor gamma (PPAR- γ). PPARs are found in tissues like adipose tissues, skeletal muscle, and liver, which are critical to insulin action. Activation of (PPAR- γ) modulates the transcription of a number of insulin-responsive genes involved in the control of glucose and lipid metabolism [1, 2].

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It is administered orally; insoluble in water and ether; slightly soluble in acetone, acetonitrile, and alcohol; and soluble in dimethylformamide and dimethyl sulfoxide. It selectively stimulates the nuclear receptor peroxisome proliferator-activated receptor-gamma (PPAR-γ) and, to a lesser extent PPAR-α.

It modulates the transcription of the insulin-sensitive genes involved in glucose and lipid metabolism in the muscle, adipose tissue, and the liver. As a result, Pioglitazone HCl reduces insulin resistance in the liver and peripheral tissues, increases the expense of insulin-dependent glucose, decreases withdrawal of glucose from the liver, and reduces the quantity of glucose, insulin, and glycosylated hemoglobin in the bloodstream. It is not chemically or functionally related to the alpha-glucosidase inhibitors, the biguanides, or the sulfonylureas. It addresses the main patho-physiological defect, *i.e.*, insulin resistance, so it is used alone or in combination with insulin,

metformin, or a sulfonylurea (glimepiride and glibenclamide) as an agent to treat diabetes. It reduces peripheral and hepatic resistance to insulin, resulting in increased insulin-dependent glucose disposal and decreased hepatic glucose output.

Pioglitazone HCl is generally well tolerated, weight gain and oedema are the most common emergent adverse events, and there are no known drug interactions between Pioglitazone HCl and other drugs. Pioglitazone HCl was also effective in reducing some measures of cardiovascular risk and arteriosclerosis. Pioglitazone HCl thus offers an effective treatment option for the management of patients with type 2 diabetes. It is chemically (±) 5-[[4-[2-(5-Ethyl -2-pyridinyl) ethoxy] phenyl] methyl] -2, 4] thiazolidinedione monohydro-chloride.

Its molecular weight is $C_{19}H_{20}N_2O_3S$•HCl The molecular weight is 392.90 Da [3]. The influence of pioglitazone on DNA oxidative damage and metabolism of SOD (superoxide dismutase) was evaluated [4]. Effect of drug on lipid metabolism and glucose metabolism in type 2 diabetic patient showed a significant decrease in the plasma glucose level and improved tissue being sensitivity to insulin [5]. The solid pioglitazone dispersion study was developed, which proposed to improve the rate of dissolution and to develop tablets of pioglitazone with effective and fast dissolution characters [6]. Pioglitazone is an oral anti-hyperglycemic agent. It is used for the treatment of diabetes mellitus type 2. It selectively stimulates nuclear receptor pero-xisome proliferator-activated receptor gamma (PPAR-gamma). It was the tenth-best-selling drug in the U.S. in 20087. Attempts were made to study whether the usage of pioglitazone as an antidiabetic increases the risk of cancer.

This study revealed that the use of the drug did not show any significant risk in causing bladder cancer but is associated with the increase in the risk of prostate cancer and pancreatic cancer [8]. FDC (fixed-dose combination) of 15 mg of the drug pioglitazone and 850 mg of metformin was used for 24weeks in type 2 diabetic patients to study the anti-diabetic property and patients were not prescribed with or medicated with any diabetic drug [9]. Simultaneous estimation of drugs glimeperidine, pioglitazone HCl, and metformin HCI was done by using derivative spectro-photometry method [10]. Chromatographic separation was achieved on a C8 column. The mobile phase was methanol–water 45:55% (v/v) containing 0.2% (w/v) n-heptane sulfonic acid and 0.2% (v/v) triethylamine; the pH was adjusted to 3.0 with orthophosphoric acid. The flow rate was 1 mL min^{-1} and the photodiode-array detection wavelength was 267 nm [11].

Piogliptazone hydrochloride in the tablet form was analysed and validated by HPLC with C18 column, wave length 245 nm, mobile phase 50% of 10 mM phosphate buffer and 50% of acetonitrile. Recovery was more than 90% with LOD and LOQ value being 10 ng/ml and 2.5 ng/ml respectively. The linear regression coefficient being 0.992112.

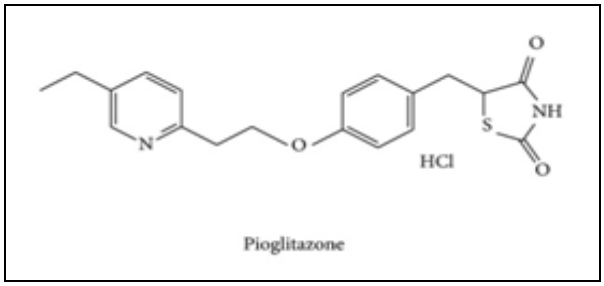

FIG. 1: STRUCTURE OF PIOGLITAZONE

The present study was aimed for establishing a simple, accurate, and rapid RP-HPLC method for determination of Pioglitazone in presence of its degradation products or other pharmaceutical excipients. The method was validated following analytical performance parameters suggested by ICH guidelines [13].

MATERIAL AND METHODS:

Chemicals and Reagents: The working standard of Pioglitazone was procured from PADM124 and the sample of Pioglitazone PIO/27030004. HPLC grade acetonitrile and methanol were purchased from Rankem. Milli Q water from Merck India Pvt. Ltd. Potassium dihydrogen phosphate obtained from S.D. Fine Chemicals Ltd.

Preparation of Solutions:

Standard Solution: Weigh accurately 100 mg of Pioglitazone HCl standard in a 50 ml volumetric flask. Add about 30 ml of Methanol and sonicate for 3 min. Dilute to volume with Methanol and mix. Dilute 5.0 ml of this solution to 50 ml Methanol.

Sample Solution: Weigh accurately 100 mg of Pioglitazone HCl sample in a 50 ml volumetric flask. Add about 30 ml of Methanol and sonicate for 3 min. Dilute to volume with Methanol and mix. Dilute 5.0 ml of this solution to 50 ml Methanol.

Procedure: Separately inject 10 µL of Standard and Sample solution into the chromatograph, record the chromatograms, and measure the area for the major peaks.

Apparatus and Chromatographic Conditions: The analytical technique was developed using Waters HPLC equipment, Model- HPLC-269, fitted with a Hypersil BDS C8 (250 × 4.6 mm, 5 µ). The mobile phase consisted of a mixture of 0.01M potassium dihydrogen phosphate buffer and acetonitrile in the ratio 40:60. The mobile phase was filtered through a 0.22-mm nylon filter and degassed using an ultrasonic bath sonicator for 30 min before running the experiment.

All experiments conducted on the HPLC were carried out in isocratic mode. Injection volume was 10 µL with a flow rate of 1.0 mL/min. The column temperature was maintained at 30 ºC and elution was monitored at 225 nm using a UV detector. All chromato-graphic data were acquired and processed with the Empower 3 software.

Validation of the Analytical Method: The developed method was validated as per the ICH guidelines for linearity, accuracy and precision, and specificity. Limit of detection (LOD) and limit of quantification (LOQ) were determined using the serial dilution method.

Linearity: Different aliquots of a standard solution of Pioglitazone was transferred into set of 50 ml volumetric flasks and diluted up to the mark with a diluent such that the final concentrations of Pioglitazone were in the linearity range of 0.08-40.32 mg/ml. Evaluation of the drug was performed with a PDA detector at 225 nm, and peak area was recorded. The response for the drug was linear and the regression equation was found to be y = 22750541, 96495x + 39279.17, and the correlation coefficient value of Pioglitazone was found to be 0.9999. The results showed that an excellent correlation exists between peak area and concentration of drug within the specified range.

Accuracy: Standard addition and recovery experiments were conducted to determine the accuracy of the method for the quantification of Pioglitazone in the drug product. The study was carried out in triplicate at 50, 100, and 150%.

The percentage recovery in each case was calculated. The percentage recovery ranges from 99.40-100.40%, and the mean recovery of Pioglitazone was 99.73% that shows there is no interference from excipients, and the lower values of %RSD of assay indicates the method is more accurate.

Precision: The precision was determined for Pioglitazone in terms of system precision, method precision, and intermediate precision. For system precision evaluation, a standard solution of fixed concentration was injected six times at different time intervals. Method precision was studied on six test solutions of the single batch were analyzed, the inter-day precision was studied by injecting the same concentration of the standard solution on consecutive days, and the %RSD for Pioglitazone was 0.0%, 0.3, and 1.1% (limit %RSD < 2.0%).

System Suitability: System suitability parameters like retention time, theoretical plates, and tailing factor were calculated and compared with standard values.

Robustness: The robustness of the method was determined by making slight changes in the chromatographic conditions like flow rate, detection wavelength, and organic phase in the mobile phase composition. It was observed that there were no marked changes in the chromato-grams, which demonstrated that the developed HPLC method is more robust.

Solution Stability: The stability of the solution under study was established by keeping the solution at room temperature for 24 h. The result showed no significant change in concentration and thus confirmed the stability of the drug in the solvent used for the analysis.

Forced Degradation Studies: Forced degradation study was carried out on Pioglitazone HCl. Conditions employed and the results obtained from forced degradation studies are summarized below.

Acid Degradation: The sample was separately treated with 10 mL of 4 N Hydrochloric acid at room temperature for 30 minutes. Cooled and neutralized with 10 mL of 4 N sodium hydroxide solution and further analyzed by the proposed method.

Base Degradation: The sample was separately treated with 10 mL of 4 N sodium hydroxide solutions at room temperature for 30 min. Cooled and neutralised with 10 mL of 4 N Hydrochloric acid. Further analysed by the proposed method.

Peroxide Degradation: Sample was separately treated with 5 mL of 30% v/v H_2O_2 at Room temperature for 30 min. Further analysed by the proposed method.

Thermal Degradation: Thermal degradation study was carried out by exposing the sample was subjected to thermal degradation by keeping at 105 °C for 48 h followed by analysis by the proposed method.

Humidity Degradation: Humidity degradation study was carried out by exposing the sample at 25 °C / 90% RH for 7 days.

Photolytic Degradation: Photolytic degradation study was carried out by exposing the sample to light providing an overall illumination of not less than 1.2 million lux hours and an integrated near ultraviolet energy of not less than 200-watt hours/square meter. The results obtained are given in **Table 3**. The chromatograms obtained are presented in a list of Annexures (D to I)

RESULTS AND DISCUSSION: In the present work a simple reverse-phase high-performance liquid chromatographic method has been developed, optimized and validated for the estimation of Pioglitazone in pharmaceutical formulations. Chromatographic separation was achieved on Hypersil BDS, C8 250 × 4.6 mm, 5 column using 0.01M Potassium dihydrogen phosphate buffer and acetonitrile (40:60) as mobile phase, methanol as a diluent in isocratic mode. Flow rate of 1.0 ml/min was optimized with detection wavelength at 225 nm. The retention time (R_t) was around 4.72 ± 0.2 min. The method was validated with respect to specificity, selectivity, linearity, accuracy, precision, and robustness as per ICH guidelines.

The assay method was observed linear in the concentration range of 0.079-0.318 mg/ml with a Correlation coefficient (r^2) 0.9999. The linearity and Chromatogram of Standard Chromatogram were shown in **Fig. 2** and **3**. The percentage recovery of active pharmaceutical ingredients from tablet dosage form ranged from 99.40-100.40%. The results were shown in **Tables 1** and **2**.

The %RSD for method precision and inter-day precision for Pioglitazone was found to be NMT 2, which indicates the method is precise. The results of precision studies were shown in **Tables 3** and **4**. A system suitability test was performed to evaluate the chromatographic parameters. The typical chromatograms of the degradation behavior of Pioglitazone in different stress conditions were shown from **Fig. 4** to **8**.

During the acidic and alkaline degradation, 24.5% and 18.1% were decomposed, respectively. Pioglitazone has undergone oxidative 2%, thermal 1.9%, and photostability was 4.5%. The results of the degradation studies were shown in **Table 5**. The summary of Validation parameters was shown in **Table 6**.

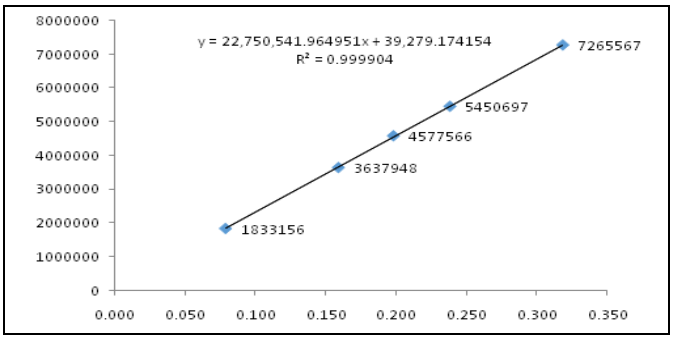

FIG. 2: LINEARITY GRAPH OF PIOGLITAZONE

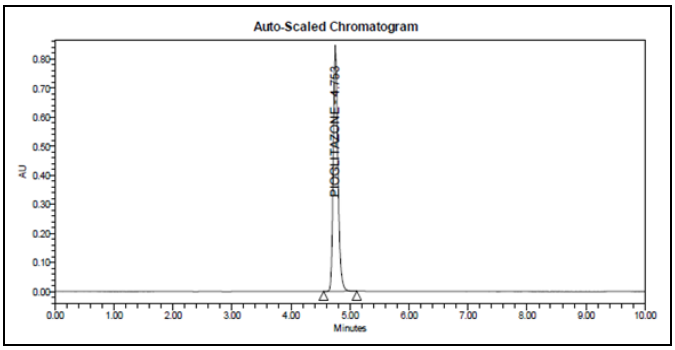

FIG. 3: CHROMATOGRAM OF STANDARD

PEAK RESULTS

S. no	Name	RT	Area	% Area	USP plate count	USP tailing
1	Pioglitazone	4.753	4579410	100.00	17675	1.2

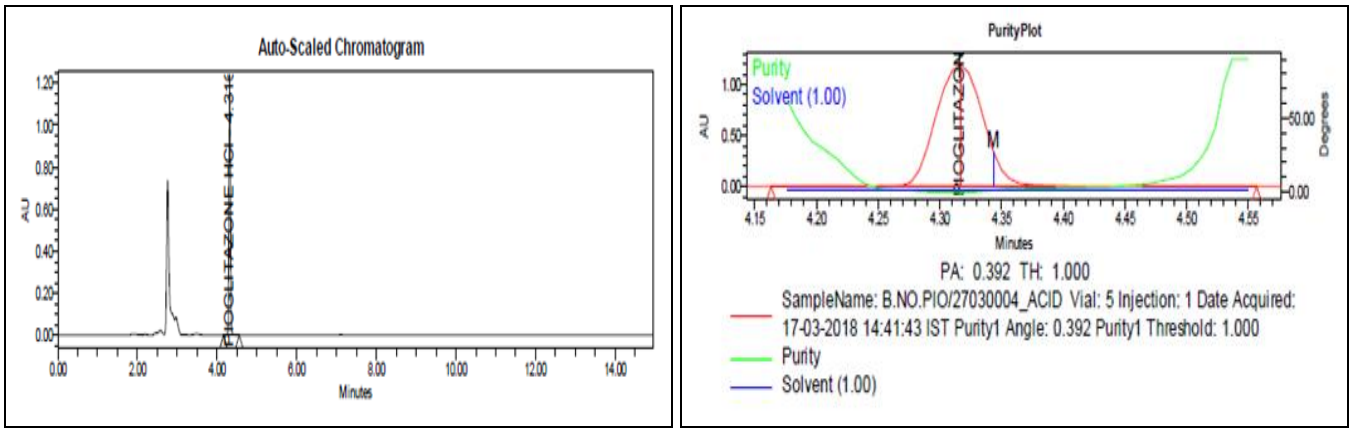

FIG. 4: CHROMATOGRAM OF ACID STRESSED SAMPLE (PURITY PLOT)

PEAK RESULTS

S. no.	Name	RT	Area	% Area	USP plate count	USP tailing	Purityl angle	Purityl threshoid
1	Pioglitazone HCI	4.316	3158776	100.0	59806	1.1	0.392	1.000

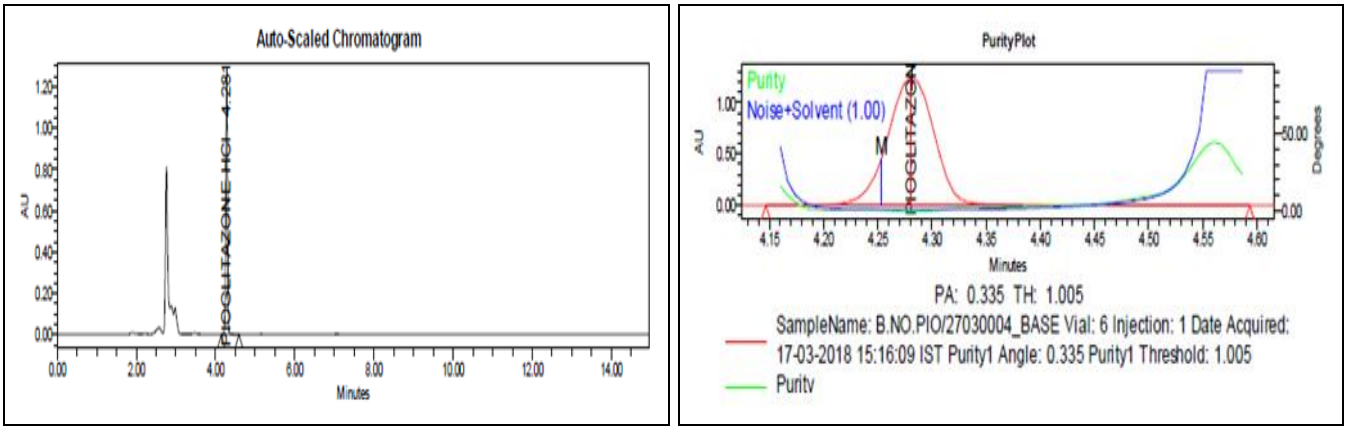

FIG. 5: CHROMATOGRAM OF BASE STRESSED SAMPLE (PURITY PLOT)

PEAK RESULTS

S. no.	Name	RT	Area	% Area	USP plate count	USP tailing	Purityl angle	Purityl threshoid
1	Pioglitazone HCI	4.281	3691701	100.00	49853	0.9	0.335	1.005

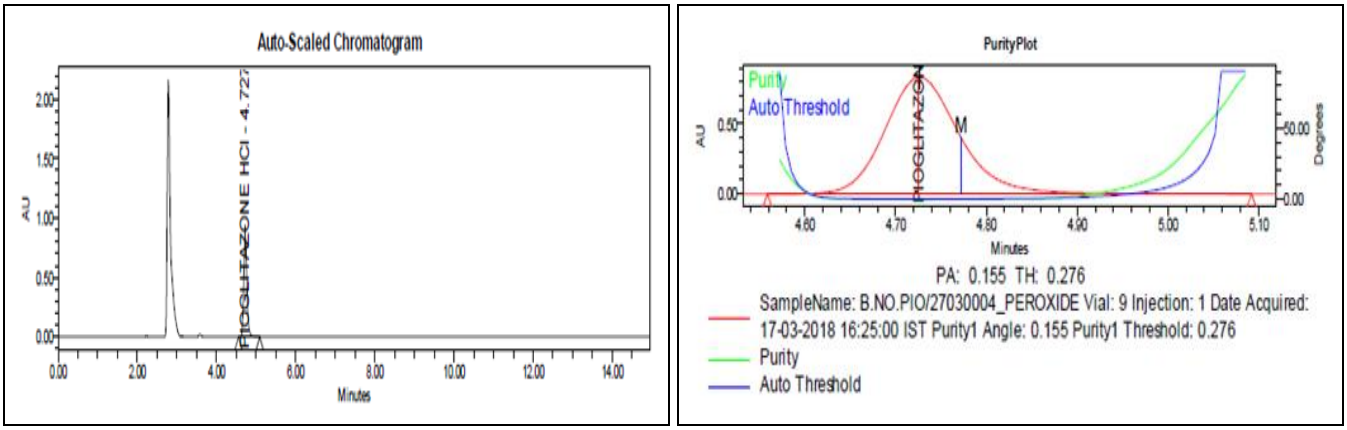

FIG. 6: CHROMATOGRAM OF OXIDATION STRESSED SAMPLE (PURITY PLOT)

PEAK RESULTS

S. no.	Name	RT	Area	% Area	USP plate count	USP tailing	Purityl angle	Purityl threshoid
1	Pioglitazone HCI	4.727	4714722	100.00	16727	1.2	0.155	0.276

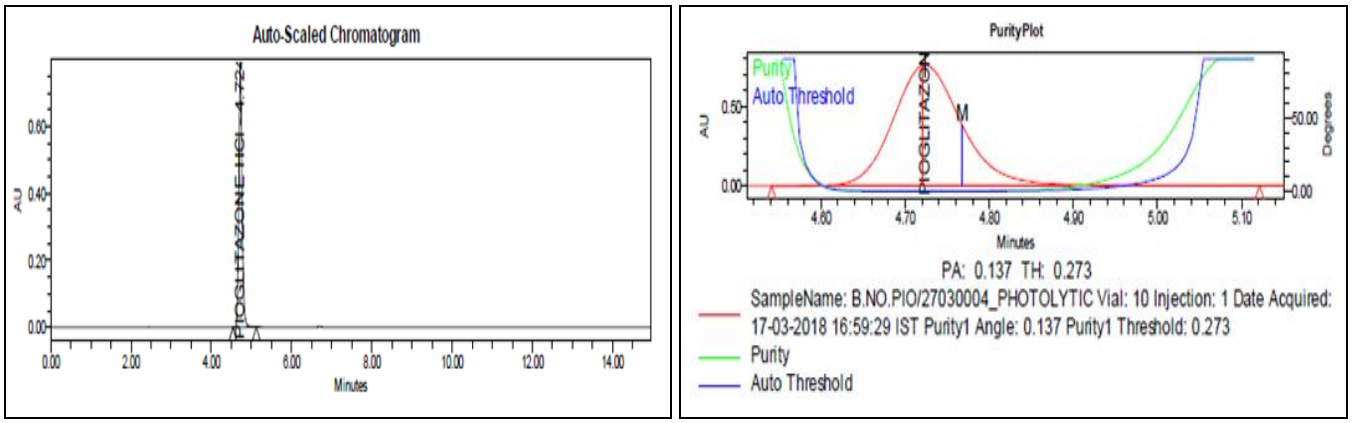

FIG. 7: CHROMATOGRAM OF PHOTOLYTIC STRESSED SAMPLE (PURITY PLOT)

PEAK RESULTS

S. no.	Name	RT	Area	% Area	USP plate count	USP tailing	Purityl angle	Purityl threshoid
1	Pioglitazone HCI	4.724	4312273	100.00	16717	1.2	0.137	0.273

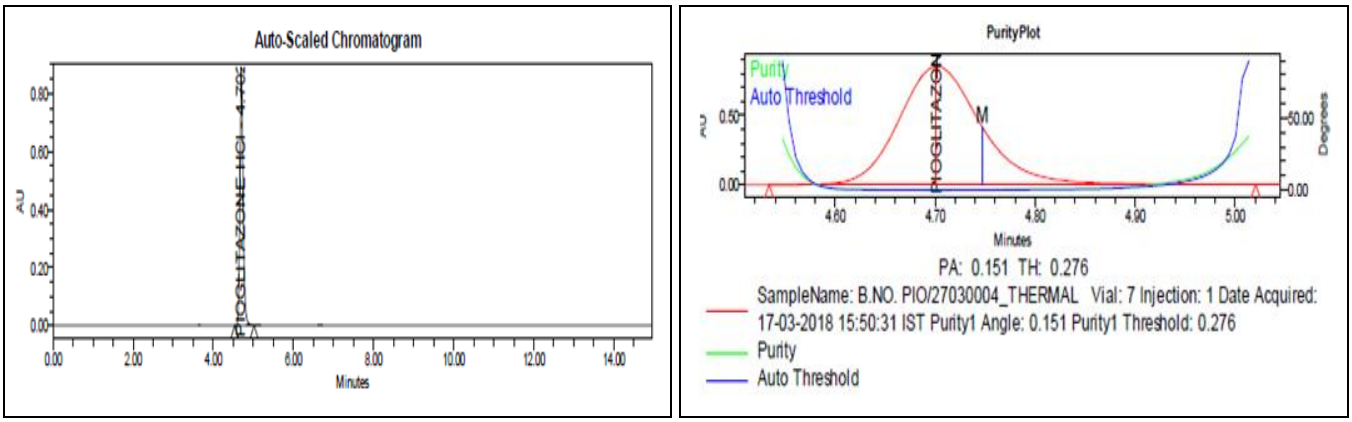

FIG. 8: CHROMATOGRAM OF THERMAL STRESSED SAMPLE (PURITY PLOT)

PEAK RESULTS

S. no.	Name	RT	Area	% Area	USP plate count	USP tailing	Purityl angle	Purityl threshoid
1	Pioglitazone HCI	4.702	4839019	100.00	16596	1.2	0.151	0.276

TABLE 1: LINEARITY OF STANDARD PIOGLITAZONE

S. no.	Level	Pioglitazone HCl Concentration (in mg)	Area	Mean Area
1	40%	0.079	1832362	1833156
			1833949	
2	80%	0.159	3639929	3637948
			3635967	
3	100%	0.198	4572379	4577566
			4582753	
4	120%	0.238	5452922	5450697
			5448472	
5	160%	0.318	7267528	7265567
			7263606	
		Correlation Coefficient (r)	0.999951977	
		Slope	22750541.96495	
		Intercept	39279.17415	
		% deviation of y-intercept	0.7	

TABLE 2: RESULTS OBTAINED FROM ACCURACY FOR PIOGLITAZONE HCL (% RECOVERY)

Accuracy Level	Amount added (mg)	Amount found (mg)	% Recovery		% RSD
			Individual	Mean	
Accuracy solution (50%)-1	49.719	49.623	99.8	100.4	0.5
Accuracy solution (50%)-2	49.749	50.145	100.8		
Accuracy solution (50%)-3	49.828	50.098	100.5		
Accuracy solution (100%)-1	99.339	98.757	99.4	99.4	0.3
Accuracy solution (100%)-2	99.418	99.146	99.7		
Accuracy solution (100%)-3	99.250	98.488	99.2		
Accuracy solution (150%)-1	149.028	147.627	99.1	99.4	0.4
Accuracy solution (150%)-2	148.909	148.564	99.8		
Accuracy solution (150%)-3	148.998	147.878	99.2		

TABLE 3: RESULTS OF SYSTEM PRECISION

Injection	Area of Pioglitazone HCl
1	4754547
2	4753954
3	4752729
4	4753630
5	4754631
6	4751478
Mean	4753495
SD	1206.744
% RSD	0.0

TABLE 4: RESULTS OBTAINED FROM SIX SAMPLE PREPARATIONS FROM METHOD PRECISION

S. no.	% Assay
1	99.3
2	98.8
3	99.1
4	99.1
5	99.3
6	98.7
Mean	99.1
SD	0.251
%RSD	0.3

TABLE 5: RESULTS OBTAINED FROM FORCED DEGRADATION STUDY

Mode of degradation	Condition	Purity Angle	Purity Threshold	Pioglitazone HCl	
				% Assay	% Degradation
Control	NA	0.149	0.275	98.1	NA
Acid stress	10 mL, 4 N HCl for 30 min. at RT	0.392	1.00	74.1	24.5
Humidity stress	25 °C/90% RH for NLT 7 days	0.165	0.281	97.6	0.5
Photolytic stress	1.2 million lux hrs / 200-watt hrs / square meter	0.137	0.273	93.7	4.5
Base stress test	10 mL, 4N NaOH for 30 mins. at RT	0.335	1.005	80.3	18.1
Oxidation stress	5 mL, 30% v/v H_2O_2 for 30 min at RT	0.155	0.278	96.1	2.0
Thermal stress	105 °C for 48 hours	0.151	0.276	96.2	1.9

TABLE 6: SUMMARY OF VALIDATION PARAMETERS

S. no.	Parameter	Experiment	Acceptance criteria	Results			
1	Specificity & Forced degradation	Blank, standard solution and test solution	There should not be any interfering peaks due to diluent at the retention time of Pioglitazone HCl peak. Peak purity angle should be less than Peak purity threshold of Pioglitazone HCl peak in standard, and test solution. There should be no tick mark in the purity flag column.	There is no interference due to diluent at the retention time of Pioglitazone HCl peak in standard and Sample Solution.			
				Name	Retention time (min) Pioglitazone HCl		
				Standard solution	4.726		
				Control sample	4.721		
				Name	Pioglitazone HCl		
				Sample	Purity Angle	Sample	Purity Angle
				Standard solution	0.158	Standard solution	0.158
				Test solution	0.149	Test solution	0.149

	Blank, standard solution, test solution and Stressed solutions	There should not be any interfering peaks due to diluent at the retention time of Pioglitazone HCl peak. Peak purity angle should be less than Peak purity threshold for Pioglitazone HCl peak in standard, test solution and stressed solution. There should be no tick mark in the purity flag column.	There is no interference due to diluent at the retention time of Pioglitazone HCl peak in standard and stressed solution			
			Name			
			Sample	Purity Angle	Sample	Purity Angle
			Standard	0.158	Standard	0.158
			Control Sample	0.149	Control Sample	0.149
			Acid Stress	0.392	Acid Stress	0.392
			Base Stress	0.335	Base Stress	0.335
			Oxidation stress	0.155	Oxidation stress	0.155
			Thermal stress	0.151	Thermal stress	0.151
			Photolytic stress	0.137	Photolytic stress	0.137
			Humidity stress	0.165	Humidity stress	0.165

CONCLUSION: The proposed stability-indicating HPLC method was validated as per ICH guidelines. The method was found to meet all the predetermined acceptance criteria. The validated HPLC method for Pioglitazone HCl is specific, stable, linear, accurate, precise, rugged, and robust. Based on the validation study results, it has been concluded that the HPLC method for Pioglitazone HCl is suitable for the intended purpose. At the same time, the chromatographic elution step is undertaken in a short time (< 5 min). There is no interference from any components of the pharmaceutical dosage form. The chromatograms of diluent (blank) indicate that there is no interference at the retention time Pioglitazone HCl peak.

The peak purity angle was less than the peak purity threshold, and there was no tick mark in the purity flag column for Pioglitazone HCl peak in all final stressed test solutions. The peak purity plot of stressed sample solutions indicates that Pioglitazone HCl peaks are homogeneous and have no co-eluting peaks ensuring the specificity of the method. Hence it can be successfully applied to perform the routine analysis of the drug in pharmaceutical formulations.

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CONFLICTS OF INTEREST: The authors declare no conflicts of interest.

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