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Validated HPLC Method for Assay and Content Uniformity Testing of Roflumilast in Blend and Tablets

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Roflumilast is a selective enzyme inhibitor of phosphodiesterase-4. This drug is recommended for treatment of patients suffering from chronic-obstructive-pulmonary-disease with chronic-bronchitis. Roflumilast is not official in pharmacopoeia and the reported methods are having high chromatographic run times. A short run time HPLC method was developed for assay and content uniformity testing to determine the roflumilast in blend and tablets. The mobile phase consists of 10 mM sodium dihydrogen phosphate monohydrate buffer and acetonitrile in the ratio of 45:55 v/v. The HPLC method was developed using accucore-C18 150 × 4.6 mm, 4 µm column with a flow rate of 1.0 mL min^{-1}, 215 nm wavelength and 10 µL injection volume with run time of 5 min. The method linearity was proved between 5.02-40.17 µg mL^{-1} and obtained correlation-coefficient value is 1.0000. The mean recovery of roflumilast was 100.6%. The stability indicating nature was established and performed the validation by considering ICH Q2 (R1) recommendations.

Keywords: Roflumilast, Content uniformity, HPLC method.

INTRODUCTION

Roflumilast is a non-steroid, anti-inflammatory, enzyme inhibitor of phosphodiesterase-4 (PDE 4) and recommended to treat the patients who are suffering from chronic-obstructive-pulmonary disease (COPD) with exacerbation and chronic-bronchitis especially in adults [1]. The chemical name of roflumilast molecule is *N*-(3,5-dichloropyridin-4yl)-3-cyclopropylmethoxy 4-difluoromethoxybenzamide (Fig. 1, m.f. $C_{17}H_{14}N_2O_3Cl_2F_2$). Roflumilast tablets are available in the market with different trade names such as Daxas and Daliresp. Roflumilast is available as 500 µg tablets and administered as once daily oral dosage form.

Roflumilast drug substance is having impurities such as impurity-1 (3-cyclopropylmethoxy-4-difluoromethoxy benzoic acid, RFL-4), impurity-2 (3,5-dichloro-4-aminopyridine, DCPA), impurity-3 (*N*-(3,5-dichloro-pyridine-4yl)-3-cyclopropylmethoxy-4-difluoromethoxybenzamide *N*-oxide), impurity-4 (*N*-(pyridin-4-yl)-3-cyclopropyl-methoxy-4-difluoromethoxybenzamide), impurity-5 (*N*-(3-chloropyridin-4-yl)-3-cyclopropylethoxy-4-difluoromethoxybenzamide), impurity-6 (*N*-(3,5-dichloropyridin-4yl)-3-methoxy-4-difluoromethoxybenzamide), impurity-7 (3-cyclopropylmethoxy-*N*-(3,5-dichloropyridin-4-yl)-4-methoxybenzamide) and impurity-8 (3-cyclobutoxy-*N*-(3,5-dichloropyridine-4-yl)-4-difluoromethoxybenzamide, cyclobutane impurity) (API sources: Shasun and Interquim). The above mentioned impurities of roflumilast are considered for chromatographic separation from roflumilast peak in the present work.

From literature survey, it has been observed that roflumilast is not an official drug in the pharmacopoeia such as USP, Ph. Eur., BP, IP and JP. The analytical methods have been reported in the literature are having high chromatographic run times, which results in more organic solvent consumption and requires a lot of time to analyze the test sample in any pharma industry. It has been observed that the methods available in the literature are given for estimation of roflumilast by different instrumental techniques such as HPLC [2], HPTLC [3], UPLC

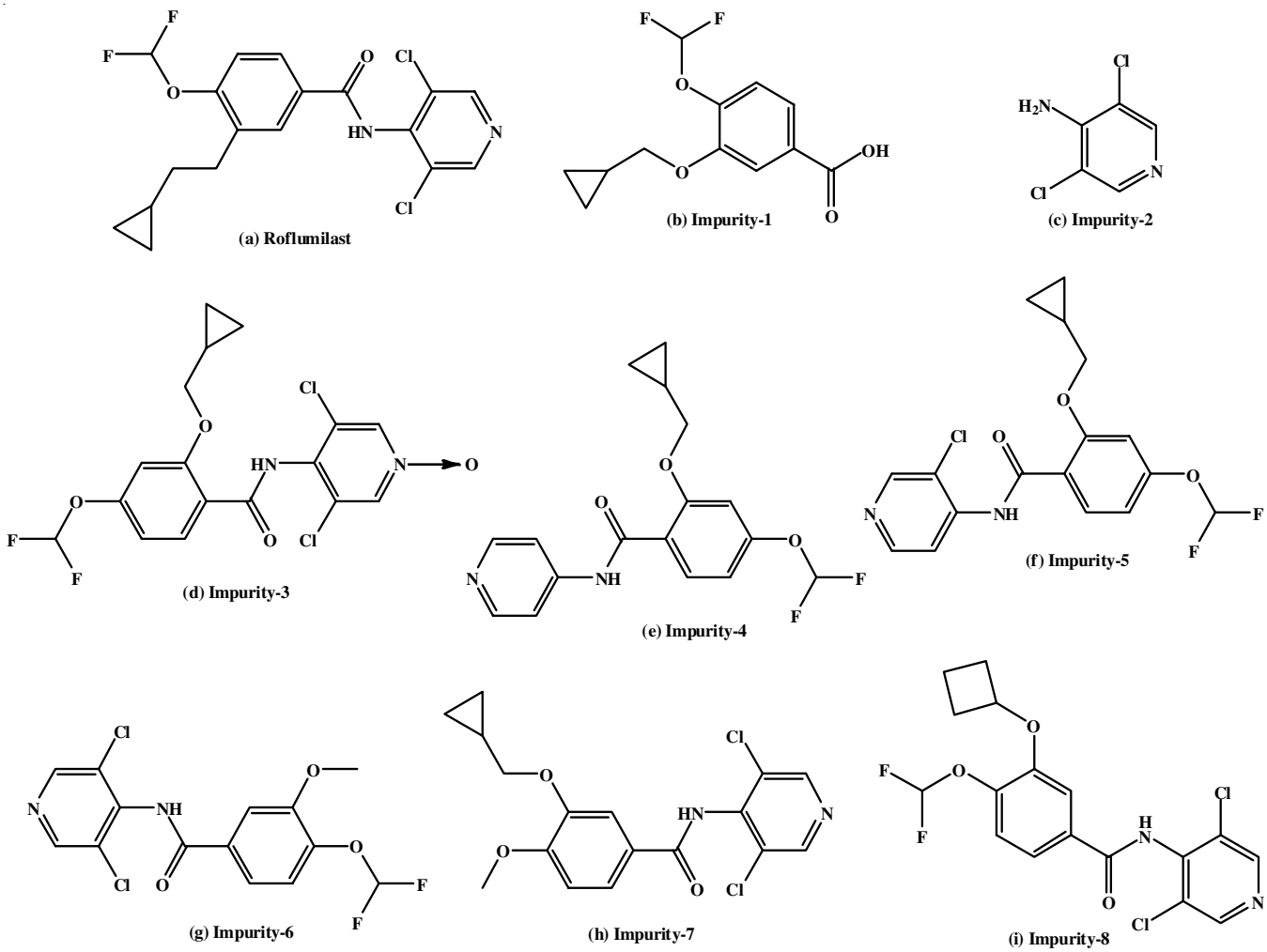

Fig. 1. Molecular structures of a) roflumilast b) imp-1 c) imp-2 d) imp-3 e) imp-4 f) imp-5 g) imp-6 h) imp-7 and i) imp-8

[4], electrophoresis [5], LC-MS [6] and UV [7]. The main objective of this study is to develop and validate the HPLC method with a short chromatographic run time for quantification of roflumilast in the presence of eight known impurities. Then, to demonstrate the stability indicating nature of the present method by performing forced degradation studies and method validation considering ICH Q2 (R1) recommendations. And also to develop a fast analytical method with a sharp chromatographic peak suitable for stability analysis of both tablet and blend samples.

EXPERIMENTAL

Sodium hydroxide, sodium dihydrogen phosphate monohydrate ($NaH_2PO_4 \cdot H_2O$), hydrochloric acid and ammonium acetate were purchased from Merck, India. HPLC grade organic solvents such as acetonitrile and methanol were also purchased from Merck, India. HPLC water for analysis was collected from Milli-Q water system of Merck, India. Roflumilast working-standard and roflumilast tablets were arranged by AET labs, India.

Instrumentation: HPLC instrument (Make: Waters), Waters Empower-3 chromatographic data operation software, Accucore XL column with 4.6 mm internal diameter (ID), 150 mm length, filled with octadecylsilyl solid core silica particles as a stationary phase having 4 m particle size and Zorbax XDB, 5µ, C18, 4.6 mm ID, 150 mm length columns were used for method development. Rotary shaker (RS 24BL, REMI), sonicator (PCI), vacuum filtration system (Millivac 230V, Millipore), analytical balance (XP205, Mettler Toledo), water bath (Metalab) were used during the present research work.

Chromatographic conditions: The chromatographic separation of roflumilast peak from the impurity peaks was achieved in the 4.6 mm ID, 150 mm length, 4 µ particle size accucore XL C18 HPLC column by using mobile phase, which consists of 10 mM $NaH_2PO_4.H_2O$ buffer and acetonitrile in the ratio of 45:55 v/v. The optimized chromatographic conditions such as UV-wavelength detection of 215 nm, an injection load of 10 µL, column compartment temperature of 30 ºC, mobile phase flow rate of 1.0 mL min^{-1} and chromatographic injection run time of 5 min were selected for quantification of roflumilast in blend and tablets. The pre-mixed solution containing 50 volumes of water and 50 volumes of acetonitrile was chosen as diluent for extraction and solubilization of roflumilast during preparation of test sample and standard solutions.

Standard and test sample preparations: About 50 mg of roflumilast working standard was weighed and transferred into a 200 mL dry volumetric-flask of class-A category. Solubilization of roflumilast substance was carried out by adding 140

mL of diluent and performed the ultra-sonication. The solution volume in the flask was made up to the mark with diluent and mixed to get uniform solution. The standard concentration of 25 μg mL^{-1} roflumilast was obtained by dilution of 5 mL of the above solution to 50 mL with diluent.

Test sample was prepared by taking pre-mixed tablet powder equivalent to 5 mg of roflumilast (10 tablets of 500 μg roflumilast or equivalent blend powder) into a 200 mL dry volumetric flask. Pipetted out 5 mL of 0.1 N HCl in same flask and performed the manual shaking for dispersion of the test sample. Sonicaion was done for 5 min to disperse the tablet powder. About 140 mL of diluent was added and performed the ultra-sonication for 10 min, followed by shaking for 10 min on a rotary-shaker at rotation speed of 150 rpm for complete extraction of roflumilast. The flask volume was made up to the mark with diluent and mixed to get the uniform solution. Filtered the sample solution into HPLC vial using 0.45 μ polyvinylidene difluoride (PVDF) membrane syringe-filter.

Solubility studies: Saturation solubility of roflumilast in water was performed to have a basic knowledge for selection of the diluent for sample preparation. A standard stock solution was prepared by taking 51.26 mg into a 100 mL volumetric flask and dissolved in a solvent mixture (water and acetonitrile 1:1 v/v). Diluted 5 mL of the above solution to 100 mL with solvent mixture and this solution was used as standard for solubility studies. About 50 mL of water was taken in a 100 mL volumetric flask. The roflumilast API sample was added in excess amount and flask shaking was done for 24 h at 37 ºC. The solution was filtered through 0.2 μ PVDF syringe filter and injected into the HPLC. The solubility of roflumilast in water was determined using area responses obtained from the standard and sample chromatograms. The solubility of roflumilast in organic solvents such as acetonitrile and methanol was determined, where, how much API goes into the solution to have a clear solution was evaluated by physical observation.

Sample preparations for method validation: The test preparations of sample and standard were done at the same concentration of 25 μg mL^{-1} roflumilast for specificity. Preparation of placebo solution was done similar to the sample preparation by using placebo without roflumilast. The impurity mix solution was prepared using imp-1, imp-2, imp-3, imp-4, imp-5, imp-6, imp-7 and imp-8 in the diluent at a concentration of 0.25 μg mL^{-1} of each impurity. Forced degradation study samples were prepared using test product and placebo in the presence of alkali, acid, water, peroxide and light. After exposure of the sample, the flask volume of each degradation sample was made up to the mark with diluent and mixed to get uniform solution. All the specificity and forced-degradation study samples were filtered using 0.45 μ PVDF membrane syringe filter and collected into HPLC vials. Injected the sample solutions into HPLC-PDA system by selecting a detector wavelength range of 200 nm to 400 nm for peak purity test. Extracted the chromatograms to demonstrate well separation of roflumilast peak from impurities and non-interference from impurity peaks, blank and placebo peaks at the chromatographic retention time of roflumilast peak.

To establish the linearity between detector response and concentration, the linearity stock was prepared using roflumilast drug substance with a concentration of 250 μg mL^{-1} roflumilast. The linearity test solutions were prepared at 20, 40, 50, 100 and 160% of roflumilast with respect to 100% sample concentration by dilution of 2, 4, 5, 10 and 16 mL of linearity stock to 100 mL using diluent, respectively. The final concentration range of linearity test for quantification analysis was 5-40 μg mL^{-1} of roflumilast. Established the linearity-plot between the concentration of roflumilast and chromatographic area response of the peak. The linearity of roflumilast using present method was verified by calculating regression-coefficient and correlation-coefficient.

Precision test was verified by executing six replicate preparations at a sample concentration of 25 μg mL^{-1} roflumilast using both tablets and blend samples. For demonstration of intermediate precision, precision samples were prepared in another day by different analyst on different HPLC system. The stock for accuracy samples was prepared at 835 μg mL^{-1} of roflumilast in diluent and labeled as accuracy stock. About 645 mg of placebo was weighed and taken into a 200 mL dry volumetric flask. The powder was dispersed by the addition of 0.1 N HCl (5 mL) followed by diluent (140 mL) and mixed. Pipetted out 6 mL of accuracy stock solution into the flask and applied the ultrasonication for 10 min. Flask shaking was done on a rotary shaker at 150 rpm for 10 min. Final flask volume was made up to the mark with diluent and mixed to get the final solution concentration of 25 μg mL^{-1} roflumilast (*i.e.* 100% level accuracy solution). Similarly, prepared the accuracy test solutions at 50 and 150% levels by spiking 3 mL and 9 mL of accuracy stock to get the final concentrations 12.5 μg mL^{-1}, 37.5 μg mL^{-1} of roflumilast, respectively. Filtration of accuracy test solutions was done using 0.45 μ PVDF syringe type filter and collected the samples into HPLC vials for analysis.

Method robustness was tested by small variation in the method parameters such as chromatographic flow rate 1.0 ± 0.1 mL min^{-1}, wavelength detection 215 ± 2 nm and mobile phase organic solvent composition 55 ± 5%. Filter interference study and solution stability were established on test samples.

RESULTS AND DISCUSSION

Method development: Solubility studies were performed and the obtained solubility results of rolflumilast in water, acetonitrile and methanol were 2.1, 500 and 250 μg mL^{-1}, respectively. Diluent was prepared by mixing 500 mL of water and 500 mL of acetonitrile in a beaker. The maximum spectral absorbance observed for roflumilast was 213 nm wavelength, hence 215 nm was chosen as UV detection wavelength for roflumilast. Method development trials were executed using Zorbax XDB, C18, 4.6 mm ID, 150 mm length, 5μ HPLC column with 20 mM ammonium acetate buffer (labeled as mobile phase-A) and acetonitrile (labeled as mobile phase-B). An injection volume of 20 μL with sample concentration of 10 μg mL^{-1} and mobile phase flow rate of 1.0 mL min^{-1} were used in the initial method optimization experiments. Sample solution injections were given into the HPLC chromatographic system using different solvent compositions, *i.e.* mobile phase-A and mobile phase-B in combinations of 60:40 v/v (T1), 50:50 v/v (T2), 40:60 v/v (T3) and 35:65 v/v (T4), and recorded the chromatograms for evaluation of system suitability parameters and peak shape.

The observed roflumilast peak symmetry factors for T1, T2, T3 and T4 experiments were 0.99, 1.03, 1.10 and 1.14, respectively. The sharp peak shape was observed in all the experiments and symmetry factor was below 1.5. The obtained retention times of roflumilast for T1, T2, T3 and T4 experiments were 14.565 min, 9.025 min, 4.447 min and 3.420 min, respectively. To achieve short retention time without any interference of blank peaks, experiment (T5) was executed using short dimension column *i.e*. Kinetex C18 75 mm length, 4.6 mm ID, 2.6µ, with a mobile phase consists of 10 mM sodium dihydrogen phosphate buffer and acetonitrile in the ratio of 45:55 v/v. The poor peak shape and peak tailing were observed using Kinetex HPLC column.

Further, experiments were conducted in the Accucore XL C18, 4.6 mm ID, 150 mm length, 4µ particle column. Sharp peak shape and complete resolution of all the impurities were achieved in the mobile phase composition containing 10 mM sodium dihydrogen phosphate monohydrate buffer and acetonitrile in the ratio of 45:55 v/v. The roflumilast peak was eluted at a retention time of 3.5 min in the chromatogram. Considering the elution of all the known impurities, the chromatographic run time was reduced to 5 min. The recovery of the sample was verified using a diluent composed of 500 mL of water and 500 mL of acetonitrile. The recoveries of roflumilast from tablet formulation was not achieved using as such diluent with sonication of sample solution. The recovery of roflumilast was achieved using addition of 5 mL of 0.1N HCl followed by sonication of 5 min to extract the drug from the sample matrix. The sample solution containing flask was made up to mark with diluent. The method validation was executed as per ICH Q2 (R1) recommendations for applicability of method to analyze the blend assay, blend content uniformity, tablets assay and tablet content uniformity.

Method validation

Specificity and forced degradation study: The specificity and forced degradation study samples were taken in HPLC vials and submitted the sequence of sample-set for injection into HPLC-PDA system and evaluated the test sample chromatograms. Non-interference of impurities, blank and placebo peaks was found at the chromatographic retention time of roflumilast peak in the sample chromatogram. The representative chromatograms of sample, standard, and the impurity spiked sample solutions are illustrated in Fig. 2. The retention time of each known impurity in the chromatogram was characterized by injecting individual impurity solutions and obtained chromatograms are illustrated in Figs. 3-5. Purity-threshold is greater than purity-angle for roflumilast peak in the chromatograms obtained with the acid, alkali, water, thermal, humidity, light and peroxide degradation samples (Table-1). Purity test for roflumilast peak was passed for all the stress samples generated from forced degradation studies. Hence, the present method proves the specificity and demonstrated the method capability to estimate the roflumilast in the stability samples.

Linearity: The linearity test solutions from 20 to 160% of target concentration were filled in HPLC vials and submitted the sample sequence into the HPLC system. Linearity plot between the concentration of roflumilast and detector area response from chromatographic data was studied. The obtained

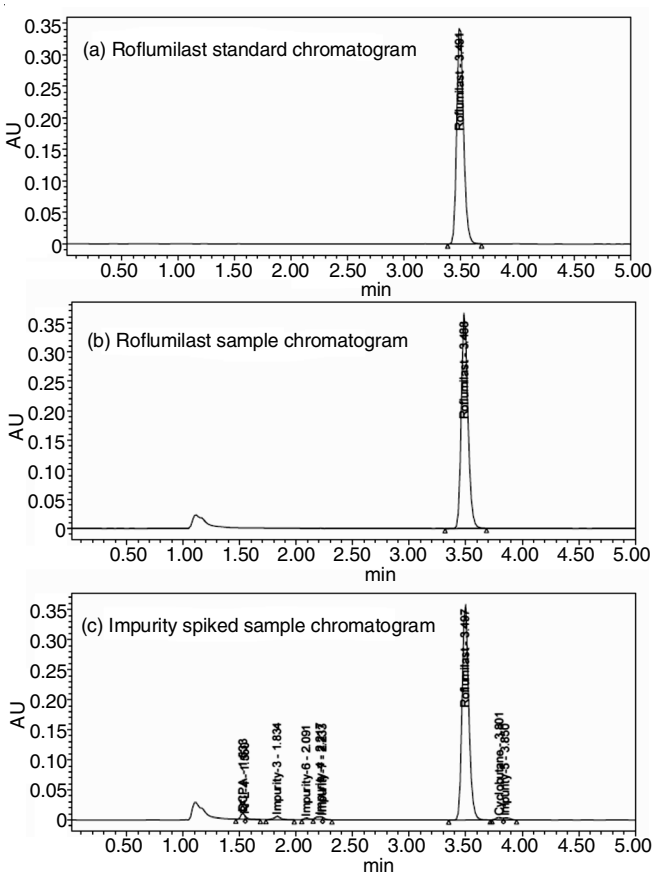

Fig. 2. Chromatograms of (a) standard solution (b) sample solution and (c) impurity spiked sample

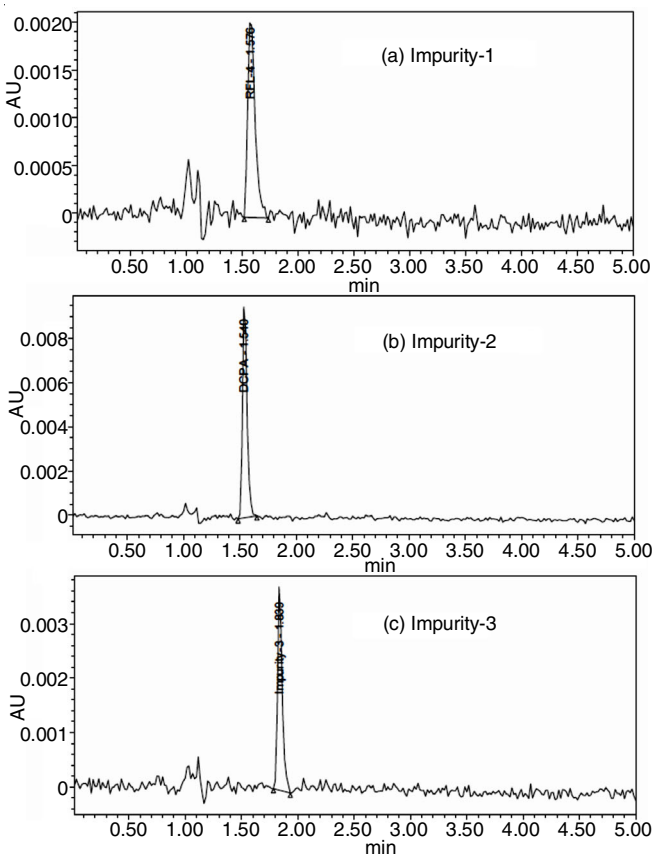

Fig. 3. Peak identification chromatograms of (a) impurity-1 (b) impurity-2 and (c) impurity-3

TABLE-1
RESULTS OF SPECIFICITY AND STRESS STUDY BY FORCED DEGRADATION

Name of the sample	Retention time (min)	Purity angle	Purity threshold	Peak purity
Roflumilast standard	3.491	0.135	0.305	Pass
Test sample	3.488	0.139	0.316	Pass
Acid degradation (0.1 N HCl, 60 °C, 3 h)	3.506	0.429	1.270	Pass
Alkali-degradation (0.1 N NaOH, 60 °C, 3 h)	3.508	0.362	1.030	Pass
Photo-degradation (200 watt hrs per square meter, 1.2 million lux hrs)	3.502	0.384	1.034	Pass
Thermal-degradation (60 °C, 3 h)	3.486	0.137	1.097	Pass
Humidity-degradation (80% RH, 5 days)	3.489	0.141	1.108	Pass
Water-degradation (Water, 60 °C, 3 h)	3.501	0.383	1.039	Pass
Oxidation with peroxide (5% H_2O_2, 3 h)	3.502	0.394	1.057	Pass

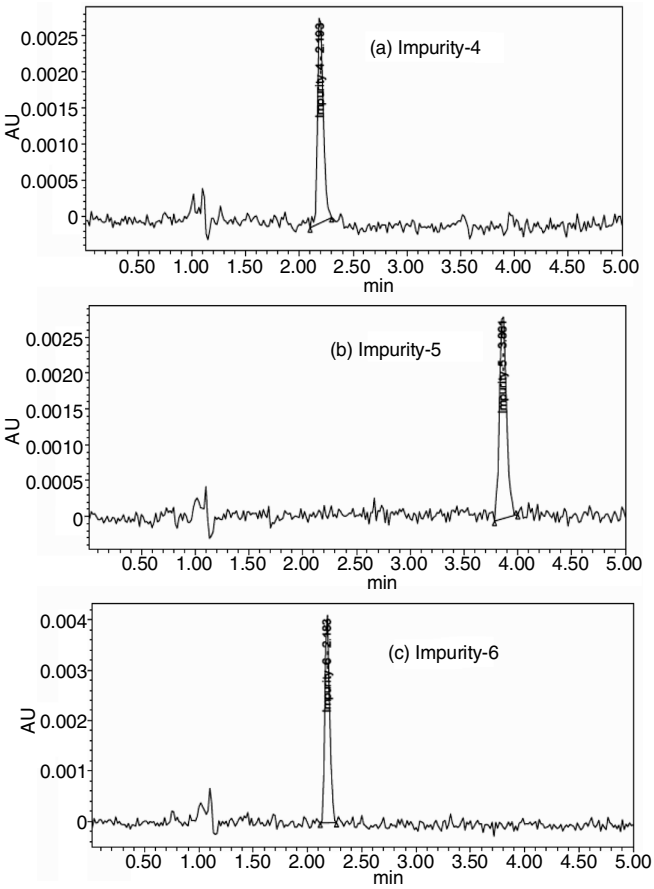

Fig. 4. Peak identification chromatograms of (a) impurity-4 (b) impurity-5 and (c) impurity-6

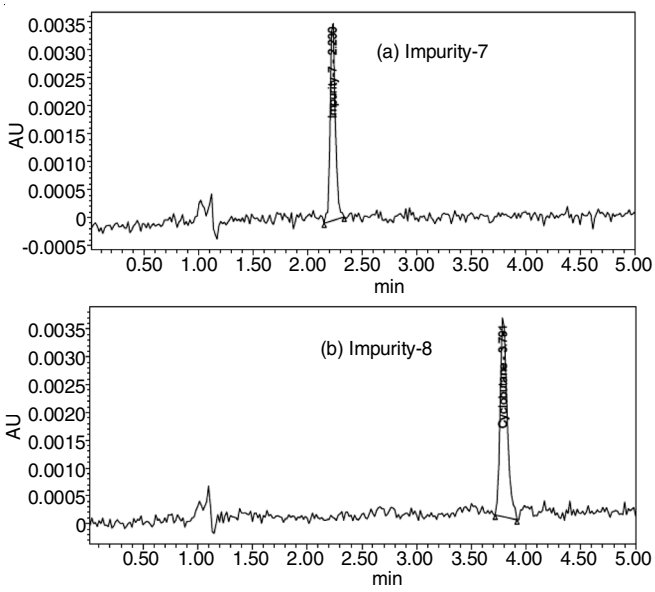

Fig. 5. Peak identification chromatograms of (a) impurity-7 and (b) impurity-8

correlation-coefficient and regression coefficient values are 1.0000 and 1.0000, respectively. The results indicate that the detector area response was linear within the selected range of concentration, *i.e.* 5 to 40 µg mL^{-1} of roflumilast, using present method of analysis. The summary of linearity and system suitability test finding are summarized in Table-2.

Precision: Repeatability of results using present analytical test method was studied by preparation of six replicate sample solutions and injected into the HPLC system. The %RSD results of repeatability-precision, intermediate precision and between analysts for blend samples were 0.38, 1.01 and 0.07, respectively. The %RSD results of precision-repeatability, intermediate precision and between two analysts precision for tablet samples were 0.65, 0.61 and 0.42, respectively. Since, %RSD results were within the acceptance criteria [8-11] (not more than 2.0), the present method is precise. The precision results for the assay and content uniformity analysis are provided in Table-3.

Accuracy: The extraction challenges of roflumilast were studied at 50, 100 and 150% with respect to target sample concentration by spiking known amount of roflumilast in the sample solution containing placebo. The recovery results were observed in the range of 99.0 to 101.7% with a mean recovery of 100.9%. The recovery values of roflumilast were well within the acceptance criteria [8-11], *i.e.* 98 to 102%. The results proved that the selected diluent and sample extraction procedure using the present method was capable to extract the roflumilast completely from the sample matrix. The recovery values at three concentration levels are shown in Table-4.

Robustness: Deliberate variations were done on the present method to demonstrate and prove the method robustness. The obtained roflumilast assay results demonstrated that no significant variation in final results takes place upon a slight change of detection wavelength, solvent composition of the mobile phase and pump flow rate. The analytical test solutions were stable for 48 h at room and refrigerator temperatures based on solution stability experiments. Filter interference was studied using a PVDF membrane syringe filter and obtained results demonstrated that PVDF membrane filter had no interference on roflumilast assay results upon filter saturation of minimum

TABLE-2
RESULTS OF SYSTEM SUITABILITY, LINEARITY AND ROBUSTNESS

Parameter	Acceptance criteria [8-11]	Results from the test		Remarks
		HPLC-1	HPLC-2	
% RSD of area response/5 injections	Not less than 2.0	0.29	0.69	Acceptable
Tailing	Not more than 2.0	1.23	1.28	Acceptable
USP plate count	Not less than 2000	12787	16868	Acceptable
Linearity results				
Type of test	Assay	Regression coefficient [R^2]		1.0000
Concentration of test sample (μg mL^{-1})	5.02 to 40.17	Slope		56435600.04
Correlation coefficient [R]	1.0000	Intercept		9057.75
Robustness results				
Parameter	Type of change	Assay results		Remarks
Solution stability	Initial	101.1		Stable for 48 hours
	After 48 h room temperature	101.1		
	After 48 h refrigerator	100.6		
Wavelength (215 ± 2 nm)	215	102.3		No significant variation in the results
	213	102.2		
	217	102.3		
Flow rate (1.0 ± 0.1 mL min^{-1})	1.0	99.5		
	0.9	98.4		
	1.1	99.1		
Mobile phase ratio (solvent A: solvent B, v/v)	45:55	100.9		
	40:60	100.1		
	50:50	100.1		
Filter study: PVDF membrane filter saturation	Centrifuged Sample	99.5		There was no filter interference. Hence, no variation in the results
	5 mL Saturation	99.8		
	10 mL Saturation	99.5		

TABLE-3
PRECISION-REPEATABILITY AND INTERMEDIATE PRECISION TEST RESULTS OF ASSAY AND CONTENT UNIFORMITY FOR BOTH BLEND AND TABLETS

Preparation	Blend assay (%)	Tablet assay (%)	Blend assay (%)	Tablet assay (%)
1	100.6	101.1	100.4	102.7
2	100.4	100.6	100.4	102.1
3	100.8	101.2	100.3	101.8
4	100.5	100.7	100.9	100.7
5	100.2	101.5	99.4	101.7
6	101.3	102.4	102.5	101.7
Mean	100.6	101.2	100.7	101.8
%RSD	0.38	0.65	1.01	0.61
Mean between two analyst values			100.7	101.5
%RSD between two analyst values			0.07	0.42
Content uniformity (CU) Results (%)			Blend CU	Tablets CU
			102.6	102.6
			102.4	101.8
			105.8	104.7
			102.8	101.6
			104.5	101.7
			103.6	103.0
			104.5	102.2
			104.3	101.3
			106.6	100.5
			102.2	101.9
		Mean	103.9	102.1
		%RSD	1.43	1.11

5 mL of sample solution through the filter. The robustness results are shown in Table-2.

TABLE-4
ACCURACY TEST RESULTS OF ROFLUMILAST

% Spiking w.r.t. sample concentration	Concentration (μg mL^{-1}, as roflumilast)		Recovery (%)
	Theoretical	Experimental	
50%-Test-1	12.69	12.75	100.5
50%-Test-2	12.85	12.82	99.8
50%-Test-3	14.31	14.45	101.0
50%-Test-4	12.97	13.06	100.7
50%-Tes-5	13.19	13.32	101.0
50%-Test-6	13.15	13.29	101.1
100%-Test-1	25.04	25.47	101.7
100%-Test-2	24.84	25.22	101.5
100%-Test-3	25.06	25.39	101.3
100%-Test-4	26.63	26.86	100.9
100%-Test-5	26.47	26.68	100.8
100%-Test-6	25.76	25.84	100.3
150%-Test-1	37.91	38.37	101.2
150%-Test-2	37.91	37.53	99.0
150%-Test-3	37.91	38.50	101.6
150%-Test-4	37.91	38.44	101.4
150%-Test-5	37.91	38.27	101.0
150%-Test-6	37.91	38.48	101.5
		Mean	100.9
		%RSD	0.67

Comparison of present developed method with reported literature methods: The reported analytical methods were available for estimation of roflumilast in different techniques such as HPLC, HPTLC, LC-MS, UPLC, electrophoresis and UV [2-7] (Table-5). The reported methods were having high chromatographic run times for analysis of roflumilast which

TABLE-5
COMPARISON OF REPORTED ANALYTICAL METHODS FOR ROFLUMILAST

Column, mobile phase, flow rate	Linear range, detection	Run time	Purpose	Ref.
Zorbax SB C18, 4.6 mm, 50 mm, 1.8 µ column, 5 mM ammonium formate buffer and acetonitrile with gradient method, flow rate 0.5 mL min^{-1}	15-225 µg mL^{-1}, HPLC-UV at 215 nm	13 min	Assay of bulk	[2]
Silica gel 60 F_{254}-TLC plate, toluene and ethylacetate (7:3 % v/v/)	0.6-2.6 µg per spot, HPTLC, 254 nm	Require more time	Assay of tablets	[3]
BEH C18 2.1 mm, 100 mm, 1.7 µ column, 20 mM KH_2PO_4, pH 6.0 buffer. Mobile phase - A buffer and methanol (90:10 v/v), mobile phase - B buffer and methanol (10:90 v/v), gradient, 0.4 0.5 mL min^{-1}	0.202 – 3.88 µg mL^{-1}, UPLC-UV at 220 nm	15 min	Assay and impurities of tablets	[4]
Fused silica, 50 cm, 75 µ i.d., 20 mmol L^{-1} $Na_2B_4O_7$ with 15% methanol	0.75-15 µg mL^{-1}, Electrophoresis, 200 nm	9 min	Assay of tablets	[5]
C18 column, 5 mM ammonium acetate buffer with 0.006% formic acid and acetonitrile with gradient program, 0.5 mL min^{-1}	0.1– 50 ng mL^{-1}, LC-MS/MS	–	Estimation in human plasma	[6]
0.2M Hydrochloric acid was used as solvent for estimation by UV spectrophotometric method	40 – 88 µg mL^{-1}, UV-248 nm	–	Estimation in human serum	[7]
Accucore C18 150x4.6 mm, 4 µm column, 10 mM $NaH_2PO_4.H_2O$ buffer and acetonitrile in the ratio of 45:55 v/v, 1.0 mL min^{-1}	5 – 40 µg mL^{-1}, HPLC-UV, 215 nm	5 min	For assay and content uniformity of both blend and tablets	Present method

would increase the consumption of organic solvents, equipment usage time and cost to the pharmaceutical industry. Whereas, the present method was developed in simple HPLC-PDA method with fast and short chromatographic run time of 5 min, which allows the minimum organic solvent consumption and fast analysis in the pharmaceutical industry. Solution stability of sample preparation was established for 48 h in the present method. Present method was evaluated for method recovery and repeatability studies for both blend and tablets.

Conclusion

A simple, specific, precise, good extraction and robust HPLC-PDA method was developed and validated for quantification of roflumilast in blend samples and tablets. The method development was done in HPLC with a fast and short chromatographic run time, which results in faster analysis in the present competitive pharma industry. Roflumilast peak was well separated from eight known impurities. Non-interference of blank, placebo and impurities upon chromatographic evaluation of forced-degradation samples revealed that the present quantification method is suitable for analysis of stability samples stored at accelerated and long term storage. The method was well demonstrated for ICH Q2 (R1) recommended validation parameters of linearity, specificity, precision-repeatability, accuracy, intermediate precision and robustness. In addition to roflumilast assay in bulk, blend and tablet formulations, the method can also be applied for testing of blend content uniformity, tablet content uniformity and estimation of drug released from a dosage form *in vitro* dissolution test.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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