RESEARCH ARTICLE

Simple, Rapid, Economic and Stability Indicating Method for Propranolol Hydrochloride and Flunarizine Tablets by RP-HPLC

Mashru C[1], Somaiya C[2], Joshi K[3], Dhalani J[1*]

[1]*School of Science, RK University, Rajkot-360020, Gujarat, India*
[2]*Department of Chemical Science, Parul Institute of Applied Sciences, Parul University, Vadodara-391760, Gujarat, India*
[3]*Department of Chemistry, D K V Arts and Science College, Pandit Nehru Marg, Jamnagar-361008, Gujarat, India*

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ABSTRACT
Simple, sensitive, precise, accurate, economic, and stability demonstrating high performance liquid chromatography method created and confirmed for the simultaneous evaluation of propranolol hydrochloride and flunarizine in drug substance and combined dosage form. The optimum separation was accomplished on symmetry ODS (75 x 4.6) mm, 5µm stationary phase. The mobile phase consists 550 ml of phosphate buffer pH 2.5 and 450 ml of acetonitrile at isocratic rate of 1.0 ml minute^{-1}. Method was validated at 240 nm and 10µl injection volume. Retention time for propranolol hydrochloride and flunarizine were achieved at 0.8 and 2.4 minutes respectively. The recommended method was linear from 1µg/mL to 7.5 µg/mL for flunarizine and from 2µg/mL to 15 µg/mL for propranolol hydrochloride. The proposed method is able to detect 0.1 µg/mL of both flunarizine and propranolol hydrochloride and able to quantify 0.2 µg/mL of both the drug substance. System suitability, linearity, recovery, filter compatibility, repeatability, intermediate precision, specificity, and solution stability criteria were taken into consideration while validating the recommended method. At the benchtop, the sample solution remained stable up to 40 hours and the standard solution up to 42 hours.
Keywords*:* Propranolol hydrochloride, Flunarizine dihydrochloride, RP-HPLC, Validation, Force degradation.
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INTRODUCTION

Propranolol, known chemically as (RS)-1-(isopropyl amino)-3-(1-naphthyloxy) propan-2-ol[1] (Fig 1), functions as a beta-adrenergic receptor that is non-selective, preventing the effect of epinephrine and norepinephrine on β1 and β2 receptors. Its primary applications include treating hypertension, migration prevention, myocardial infarction, angina pectoris, and cardiac arrhythmias as well as managing anxiety, glaucoma, hyperthyroidism, tremor, pheochromocytoma, and paediatric migraines[2]. The drug's impacts encompass decreased heart rate and cardiac output, extended AV nodal conduction time, reduced blood flow in most vascular regions, elevated plasma renin activity, inhibited lipolysis, increased triglycerides, and slightly reduced HDL cholesterol[3]. Daily dosages can range from 0.5 to 1 g for extended periods[4]. Potential adverse reactions include hypoglycaemia, bronchoconstriction, thrombocytopenic and non-thrombocytopenic purpura, skin rashes, hallucinations, drowsiness, and paraesthesia[5]. Flunarizine dihydrochloride, a calcium channel blocker with the chemical formula $C_{26}H_{26}F_2N_2$ and molecular weight of 404.495 g/mol[6], is a fluorine-containing derivative of cinnarizine dihydrochloride (fig 2). [Trans-1-cinnamyl-4-(4, 4-difluorobenzenhydryl) piperazine dihydrochloride] is another name for this compound. Its main purpose is to avoid migraines. It demonstrates antihistaminic, sedative, and antidepressant effects within the CNS[7]. Moreover, it proves beneficial in treating epilepsy, vascular disorders, and conditions affecting cerebral and peripheral blood vessels[8,9]. Its physiological action involves reducing arterial and arteriolar smooth muscle contractions by limiting the intracellular calcium accumulation caused by cerebral hypoxia. Multiple studies have documented its remarkable capacity to decrease the frequency of both classic and common migraine attacks by up to 90%. It is also effective in preventing complex conditions like childhood hemiplegic migraine[10-12]. The compound appears as a powdery white substance that dissolve in various solvents, including DMSO, ethanol, and a chloroform-methanol mixture[11,12]. It's effectiveness and wide-ranging applications, Flunarizine dihydrochloride has been the subject of extensive scientific investigation in the medical field. This medication combination is commercially available for managing hypertension. A particular dose formulation (40 mg Propranolol HCl and 10 mg Flunarizine) has been sanctioned for preventing migraines[13-16]. The literature review shows that UV, HPLC, HPTLC, and GC methods can measure propranolol in single or combined formulations[17]. For Flunarizine hydrochloride, the European and British Pharmacopoeias suggest potentiometric titration with sodium hydroxide and

**Author for Correspondence: jayesh.dhalani@rku.ac.in*

mention UV-spectrophotometry, spectrophotometry, liquid chromatography, HPTLC, and HPLC. These methods evaluate FLN hydrochloride's efficacy alone or with other drugs[14,17].

MATERIALS AND METHODS

Chemicals and Reagents

Flunarizine dihydrochloride (FLN) and Propranolol hydrochloride (PRH) reference standard were standardized against IP reference standard. Tablets named Migon Plus was purchase from local market. Potassium dihydrogen phosphate anhydrous AR (Finar, Ahmedabad), Orthophosphoric acid (Spectrochem) and triethylamine (Spectrochem) were used.

Instrumentation and Chromatographic Condition

Chromatographic system equipped with Quaternary Gradient pump, Waters alliance HPLC system (E2695), consist of UV-VIS Detector (2489) or PDA detector (2998) fitted with Symmetry C18 (75 x 4.6 x 5µm) column. Empower 3.8.0 software was use to interpretation of chromatograms. The mobile phase degassed by sonication using ultrasonic bath (Microclean-109). Analytical balance sartorius (Model No. Secura 225D) used for weighing standard and sample. Merck Millipore assembly (FOSB49200) used to get milli q water used for mobile phase and diluent preparation. Mettler Toledo (Model No. 7 direct SD 50) pH meter used to measure pH of the mobile phase. To prepare phosphate buffer, 2.72 gm monobasic potassium phosphate was dissolve in a thousand millilitres of water. Then added triethylamine (1 millilitre) in it and dilute phosphoric acid was used to get the pH down to 2.5. 55 volumes of filtered buffer solution and 45 volumes of acetonitrile mixed, and degassed. The experiment performed utilizing 5µm column of Symmetry C18 (75 mm x 4.6 mm) at a flow rate of 1.0 ml/ min. 40°C is the column temperature. Chromatography run with 10µl injection volume at 220 nm detection wavelength. Chromatography run for 4 minutes.

Preparation of Diluent

450 mL of acetonitrile and 550 mL of water were degassed and used as a diluent.

Standard Solution

59 mg of Flunarizine dihydrochloride and 200 mg of Propranolol hydrochloride standard were weigh in suitable graduated flask. Add dilute, dissolve completely, make up with diluent and further dilute to achieve 20 ppm of Propranolol hydrochloride and 5 ppm of Flunarizine.

Sample Solution

Crushed tablets into a fine power. Weighing the tablet powder, we transferred it to a 200 mL graduated flask. Added diluent into it and sonicate with ultrasound. Make up and finally dilute to a suitable volume to achieve 20 ppm of Propranolol hydrochloride and 5 ppm of Flunarizine

Development Trials and Optimization of Chromatographic Condition

Development and optimization of the method was to get proper peak shape, resolution and consistent retention time of the analyte peak. Different C_{18} columns were evaluate for stationary phase optimization. Symmetry column was selected for its better peak shape and reproducible retention time. For optimization of phosphate buffer, different trial of phosphate buffer with different pH taken. The pH of the buffer solution 2.5 was finalize to fulfil system suitability criteria. For composition of buffer solution and acetonitrile, different trials performed. Lower solvent ratio effect on retention time and tailing factor of Flunarizine peak. Hence, for the mobile phase, 55 volumes of pH 2.5 buffer and 45 volumes of acetonitrile have been finalized. Initially column temperature was set at 25°C, but due to improper peak shape and higher tailing factor, higher column temperature applied. At 40°C, peak shape of both analytes found satisfactory. Detector wavelength was optimized by scanning both component between 200-400 nm.

Method Validation[18-25]

The proposed method has been verified to meet the requirements of the International Conference on Harmonization (ICH).

System Suitability

System appropriateness factor was analysed in order to assess system performance. Five replicate injections of standard preparations were made in order to assess the precision of the system. Percentage RSD and asymmetry were interpreted.

Specificity

Peak purity profiling studies used to determine the method's specificity. The purity of the drug was determined by examining the spectrum at the beginning, middle, and end of the peak. Using software, the peak purity was determined for both standard solution and sample solution. Further, the interference of diluent and excipient peak was monitor with analyte peak.

Linearity

The method's linearity illustrated by preparing standard solution at 1, 2.5, 5, 6 and 7.5 µg/ml for Flunarizine and 2, 5, 10, 12, 15 µg/ml for Propranolol hydrochloride. Single injection of each solution was injected in to the chromatography, as mentioned above. Peak area vs. concentration of FLN and PRH plotted on calibration graphs, and the regression equation was calculated. The calibration graphs for FLN and PRH plotted over five different linear concentrations, ranging from 1 to 7.5 µg ml^{-1} for FLN and 2 to 15 µg ml^{-1} for PRH.

Filter Compatibility Study

Filter selection is a very important in estimation of drug product. To select a suitable filter, filter compatibility has been performed on sample solution. Sample solution was prepared as per proposed method. It divided in three parts. One part use for centrifuge the solution at 3500 RPM. Second part filtered using PVDF 0.45µm syringe filter, discarding fist five mL of the filtrate. Third part filtered with syringe filter 0.45µm Nylon. Results obtained from PVDF syringe filter and nylon syringe filter, compared with results of centrifuge.

Accuracy

To confirm the accuracy of the method, at four different levels (25%, 50%, 100% and 150%), a known quantity of FLN and PRH drug substance were added to the placebo mixture and the same procedure was carried out as per sample preparation. At each level, analysis carried out in triplicate.

Table 1: Results of System suitability

Parameter	FLN	PRH	Acceptance criteria
Tailing factor	1.2	1.3	Not more than 2.0
% RSD (Area)	0.2	0.3	Not more than 2.0%

Table 2: Results of filter compatibility study

	FLN (%)	%Difference	PRH (%)	%Difference
Centrifuge	99.6	-------	100.1	-------
0.45 µm PVDF	99.6	0.0	100.6	0.5
0.45 µm Nylon	99.2	0.4	99.6	0.5

Precision

The precision of the method was evaluated by preparing six sample solutions. The results, shown in the table 5 and 6, demonstrated that the developed method was precise with a %RSD of less than ±2.0%. Intra-day and inter-day precision were assessed using six replicates preparations. Both intra-day and inter-day precision limits were found to be well within acceptable limits, with deviations of less than ±2%. These findings confirm that the developed method is precise, meeting the required performance criteria.

Robustness

The test solution was tested with minor but significant changes to the analytical parameters, including flow rate (± 10%), buffer pH (± 0.50), solvent composition in the mobile phase (± 5%), wavelength (± 2nm), and column temperature (± 5°C), in order to assess the robustness of the method. In each of the aforementioned circumstances, five replicate injections of the standard solution and duplicate injections of the sample solution were made. Percentage assay computed in relation to the corresponding standard solution.

Stability of Analyte in Solution

To demonstrate the stability of the analyte in solution, the standard and sample solutions were produced as described above. At each 4-hour interval, same solutions of standard and sample injected into the chromatography. For standard solution, percentage RSD evaluated with initial injected replicate injections of standard solution. For sample solution, percentage assay was calculated and evaluated against initial assay of the drug product.

Sensitivity

To identify the minimum concentration of drug substances that can be reliably detected (LOD) and quantified (LOQ), a range of progressively diluted standard solutions was prepared, starting from a higher concentration and decreasing incrementally. These solutions were analysed using the HPLC system, and the signal-to-noise ratio (S/N) was calculated for each injection. The LOD was established at the concentration where the S/N ratio was approximately 3:1, while the LOQ was defined at the concentration with an S/N ratio of around 10:1, ensuring reliable detection and quantification.

Table 3: Results of accuracy for Flunarizine

S. No.	Recovery set No.	% Recovery	Average (%)	% RSD
1	25% (Preparation-1)	99.4	100.0	0.7
	25% (Preparation-2)	99.8		
	25% (Preparation-3)	100.8		
2	50% (Preparation-1)	99.3	99.7	0.4
	50% (Preparation-2)	99.6		
	50% (Preparation-3)	100.1		
3	100% (Preparation-1)	100.7	100.5	0.2
	100% (Preparation-2)	100.3		
	100% (Preparation-3)	100.5		
4	150% (Preparation-1)	99.5	99.8	0.5
	150% (Preparation-2)	99.5		
	150% (Preparation-3)	100.3		

Table 4: Results of accuracy for Propranolol hydrochloride

S. No.	Recovery set No.	% Recovery	Average (%)	% RSD
1	25% (Preparation-1)	100.8	100.9	0.2
	25% (Preparation-2)	100.8		
	25% (Preparation-3)	101.2		
2	50% (Preparation-1)	100.1	100.5	0.4
	50% (Preparation-2)	100.7		
	50% (Preparation-3)	100.8		
3	100% (Preparation-1)	100.9	100.5	0.3
	100% (Preparation-2)	100.5		
	100% (Preparation-3)	100.2		
4	150% (Preparation-1)	100.5	100.5	0.2
	150% (Preparation-2)	100.3		
	150% (Preparation-3)	100.7		

Forced Degradation Study

To demonstrate that the suggested approach is stable and that no degradation product interferes with the analyte peak, a force degradation analysis was performed.

Sample Preparation (Acid Degradation)

Tablet powder containing 20 mg of Flunarizine was weighed and transferred to a 200 mL volumetric flask. 150 mL of diluent and 5 mL of 0.1N Hydrochloric acid were added. The sample was stored at room temperature for 35 hours. After 35 hours, 5 mL of 0.1N sodium hydroxide solution was added to neutralize the mixture. The solution was sonicated to achieve proper solubility of drug. The

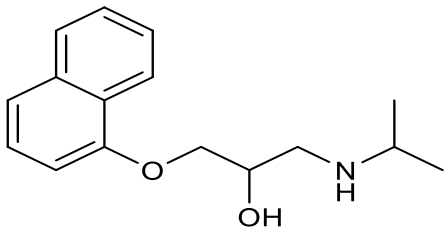

Figure 1: Structure of propranolol

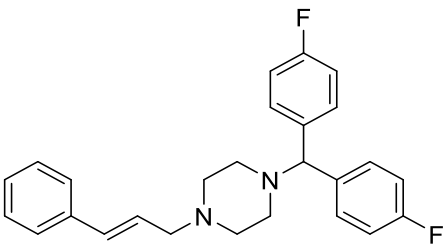

Figure 2: Structure of flunarizine

solution was made to the mark using diluent. Dilute 5 mL of the solution to 100 mL with diluent and filter through a 0.45µm PVDF syringe filter, discarding the first 5 ml of filtrate.

Sample Preparation (Base Degradation)

Tablet powder containing 20 mg of Flunarizine was weighed and transferred to a 200 mL volumetric flask. 150 mL of diluent and 5 mL of sodium hydroxide solution were added. The sample was stored at room temperature for 35 hours. After 35 hours, 5 mL of 0.1N hydrochloric acid solution was added to neutralize the mixture. The solution was sonicated to achieve proper solubility of drug. The solution was made to the mark using diluent. Dilute 5 mL of the solution to 100 mL with diluent and filter through a 0.45µm PVDF syringe filter, discarding the first 5 ml of filtrate.

Sample Preparation (Oxidative Degradation)

Tablet powder containing 20 mg of Flunarizine was weighed and transferred to a 200 mL volumetric flask. 150 mL of diluent and 5 mL of 3% H_2O_2 solution were added. The sample was stored at room temperature for 35 hours. After 35 hours, the solution was sonicated to achieve proper solubility of drug. The solution was made to the mark using diluent. Dilute 5 mL of the solution to 100 mL with diluent and filter through a 0.45µm PVDF syringe filter, discarding the first 5 ml of filtrate.

Sample Preparation (Thermal and Humidity Degradation)

Tablet powder containing 20 mg of Flunarizine was weighed and transferred to a 200 mL volumetric flask. The flask was placed in in oven at 60°C for 24 hours. After 24 hours, cool to room temperature. 150 mL of diluent was added and sonicated to achieve proper solubility of drug. The solution was made to the mark using diluent. Dilute 5 mL of the solution to 100 mL with diluent and filter through a 0.45µm PVDF syringe filter, discarding the first 5 ml of filtrate.

Sample Preparation (Photolytic Degradation)

For photolytic degradation, samples kept under UV light for 4 days at not less than 1.2 million lux hours and no less than 200 watt hours per square meter. After 4 days, samples withdraw from chamber and prepare as per the proposed method.

RESULTS

Table 5: Results of repeatability

S. No.	Sample Set No.	Assay of FLN (%)	Assay of PRH (%)
1	Set-1	99.1	100.4
2	Set-2	101.3	100.6
3	Set-3	100.7	100.6
4	Set-4	101.5	101.2
5	Set-5	100.9	100.2
6	Set-6	101.2	100.8
Average		100.8	100.6
% RSD		0.9	0.3

Table 6: Results of Intermediate precision

S. No.	Sample Set No.	Assay of FLN (%)	Assay of PRH (%)
1	Set-1	100.2	99.6
2	Set-2	99.1	100.1
3	Set-3	99.5	100.0
4	Set-4	99.6	100.3
5	Set-5	98.3	101.9
6	Set-6	99.5	99.6
Average		99.4	100.3
% RSD		0.6	0.9

System Suitability

The system suitability study was performed to ensure the efficacy of the instrument used for the experiment. This parameter is very critical, as it shows the consistent accuracy of instrument and analytical method. Various parameters were check like tailing factor, percentage RSD and retention time of the analyte. The results tabulated in Table 1.

Specificity

No interference of any degradation product and excipient peak with analyte peak shows the proposed method is specific.

Linearity and Range

The validation technique for linearity findings show that the above analytical approach was linear over the concentration range investigated, with regression coefficient R^2= 0.9999 for FLN and R^2= 0.9997 for PRH. The formula for FLN and PRH are Y= 20928x + 486.96 and Y= 16660x + 6224.8 respectively. The suggested method's linearity test resulted in R^2 value greater than 0.99, indicating that it is liner.

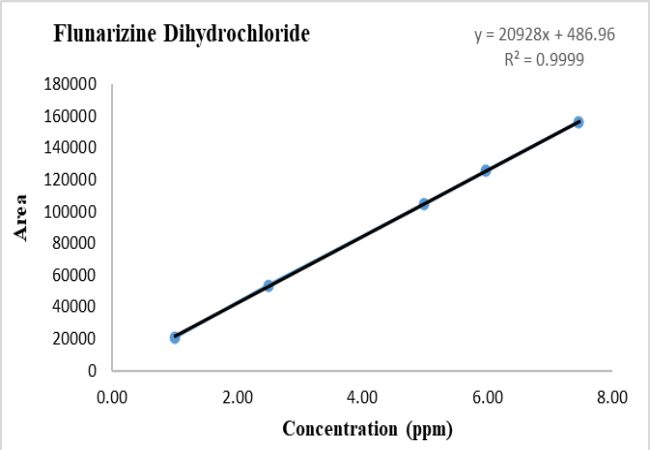

Figure 3: Calibration curve for flunarizine dihydrochloride

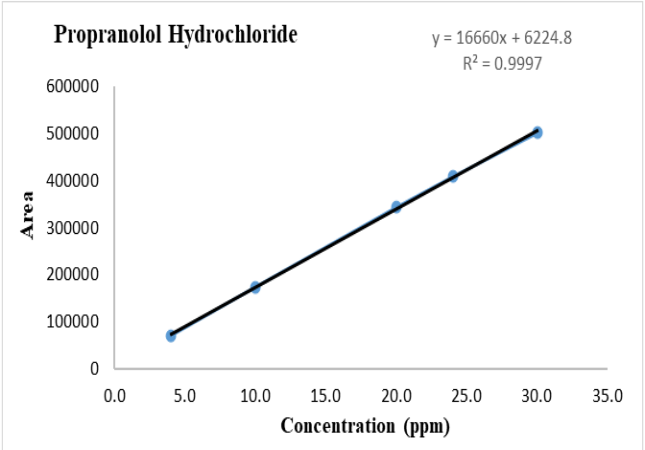

Figure 4: Calibration curve for propranolol HCl

Table 7: Result of Robustness Study

Parameter	Level	Area		% RSD	
		FLN	PRH	FLN	PRH
Flow Rate	Lower	120121	345622	0.9	0.2
	Upper	95809	283703	0.5	0.3
Organic	Lower	105582	344450	0.3	0.2
	Upper	106298	345644	0.2	0.3
pH	Lower	102661	313713	1.0	0.2
	Upper	102861	313671	1.4	0.2
Temperature	Lower	106070	348814	0.1	0.2
	Upper	105785	348270	0.2	0.1
Wavelength	Lower	97809	607515	0.1	0.1
	Upper	116585	162990	0.2	0.1

Filter Compatibility Study

To check filter compatibility for the proposed method, sample solution was prepared as mentioned above and filtered with 0.45µm PVDF syringe filter as well as 0.45µm nylon syringe filter. Results compared with centrifuge solution. Both filters found suitable for the analysis. Results of the study shown in table 2.

Accuracy

This technique involves the addition of pure drug to placebo powder at 25%, 50%, 100%, and 150% of the targeted concentration. The percentage recoveries were 99.3-100.8% (FLN), 100.2-101.2% (PRH) (Table 3 and 4).

Precision

To demonstrate the precision of the suggested procedure, six separate samples were produced using it. Repeatability study was performed on first day. On another day, for intermediate precision, another six samples were prepared and results evaluated against percentage RSD. Table 5 and 6 show the results of repeatability and intermediate precision, respectively.

Robustness

Small, intentional changes were made to the optimal technique parameters in the developed RP-HPLC process. Changes in flow rate, buffer pH, wavelength, column temperature, and organic ratio were examined for their impact on retention time and assay percentage. The findings indicated that the pH shift had a minor impact on FLN retention time. Further, change in organic ratio also affect the drastic change in retention time of FLN. Results are described in table-7.

Stability of Analyte in Solution

Both the standard solution and the sample solution were made as described above in order to show the analyte's stability in solution. At each 4-hour interval, same solutions of standard and sample injected into the chromatography. For standard solution, percentage RSD evaluated with initial injected replicate injections of standard solution. For sample solution, percentage assay was calculated and evaluated against initial assay of the drug product. At room temperature (25 ± 2°C), the standard solution remained stable for 42 hours, while the sample solution remained stable for 40 hours.

Limit of Detection and Limit of Quantification

Limits of detection and quantification using s/n method were used to gauge the method's sensitivity. The limit of quantification should be above 10 and the limit of detection should be above 3. The LOQ solution's area percentage RSD should not exceed 10%. Table 8 shows the results of the limit of quantification and limit of detection.

Table 8: Results of limit of detection and limit of quantification

Name of Solution	No. of injection	Area of FLN	s/n (FLN)	Area of PRH	s/n (PRH)
LOQ solution (0.2 ppm)	1	4280	71	4002	102
	2	4278	62	3948	99
	3	4328	61	3962	104
	4	4286	62	3975	105
	5	4327	64	4014	100
	6	4293	75	3913	104
	Avg.	4299	66	3969	102
	% RSD	0.5	N.A.	0.9	N.A.
LOD solution (0.1 ppm)	1	2041	33	2147	49
	2	1949	27	2308	59
	3	1945	29	3076	73
	Avg.	1978	30	2510	60

Table 9: Forced degradation study of Flunarizine and Propranolol

Name	Condition	% Recovery	% Degradation
FLN	Normal	100.8	--
	Acid hydrolysis	98.1	2.7
	Alkaline hydrolysis	99.1	1.7
	Oxidation	98.4	2.4
	Photolysis	99.3	1.5
	Thermal Hot air oven	101.4	--
	Humidity	100.6	0.2
PRH	Normal	100.3	--
	Acid hydrolysis	97.5	2.8
	Alkaline hydrolysis	91.3	9.0
	Oxidation	93.5	6.8
	Photolysis	98.1	2.2
	Thermal Hot air oven	98.7	1.6
	Humidity	98.6	1.7

Force Degradation Study

To demonstrate that the suggested approach is stability suggesting, force degradation research was conducted. To optimize the force degradation condition, different trails taken such as different concentration of acid, alkali and peroxide at different time interval. 0.1N hydrochloric acid (5 mL, 35 hours at R.T.), 0.1N sodium hydroxide (5 mL, 35 hours at R.T.) and 3% hydrogen peroxide (5 mL at R.T.) conditions selected to achieve optimum degradation. Thermal, humidity and photolytic degradation also carried out as per ICH guideline. Results of force degradation study tabulated in Table 9.

DISCUSSION

After deep literature survey, it was observe that there are several analytical methods available with TLC[5], UV,[14,26-28] GC[17] and HPLC[29-35]. Reported methods can measure propranolol in single or combined formulations. In 2013, Prashanth KN *et. al* described spectrophotometric method for propranolol using cerium (IV) sulphate.[17] For flunarizine hydrochloride, the european and british pharmacopoeias suggest potentiometric titration with

sodium hydroxide. Single method was also reported by UPLC.[36] These methods evaluate FLN hydrochloride's efficacy alone or with other drugs. For combine estimation of flunarizine and propranolol hydrochloride, HPTLC[37] method is available. There is only single method available, which is by HPLC[38] for the simultaneous measurement of flunarizine and propranolol hydrochloride. The reported method having higher run time then proposed method. The suggested approach was developed and validated in accordance with ICH guidelines due to the lacking in previously reported data. Proposed method is superior over reported method with short run time of 4 minutes. Force degradation study was also carried out for the proposed method. For FLN, slight degradation observed in acidic, alkali and peroxide condition, while for PRH, major degradation observed in alkali and peroxide condition. For another condition, slight degradation observed for PRH.

CONCLUSION

For combined evaluation of flunarizine and propranolol hydrochloride, for in process samples and (SR) tablet dosage formulation, an accurate, rapid, economic, sensitive, stability indicating and specific method developed and fully validated. In accordance with ICH guidelines, the procedure was developed on RP-HPLC and thoroughly verified. Validation of analytical method was done for system suitability, specificity, method precision, ruggedness, accuracy, linearity of detector response, robustness, detection limit/quantification limit and stability of solution parameters. The proposed method is able to quantify the both drug at 0.2-ppm level. Hence, the suggested approach can be applied to both initial and stability sample analysis in pharmaceutical industries.

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Conflict of Interest

There are no conflicts of interest disclosed by the authors for article publication.

Contribution of Authors

Mr. Chetan Mashru performed laboratory experiments (i.e. development and validation) and prepared the manuscript. Dr. Chintan Somaiya and Dr. Kaushik Joshi have evaluated chromatograms and results. Dr. Jayesh Dhalani has conceptualized and reviewed manuscript.

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