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Original Research Article

Analytical method development and validation for assay method of Piribedil and Indapamide by High Performance Liquid Chromatography

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Abstract

A reverse phase liquid chromatography method (RP-HPLC) was developed to estimate the amount of Piribedil and Indapamide in bulk and its pharmaceutical formulations. Agilent HPLC system equipped with auto sampler, UV-Visible detector Nucleosil 5 C18, 15 cm X 4.6 mm, 5 µm was used for chromatographic separation by using at a detection wavelength of 233 nm was used. Keeping the flow rate of 1.3 mL/min the composition of mobile phase water: acetonitrile: methanol: trifluro acetic acid (80:18:02:0.2) mL/v: v: v: v in given amount were used for the quantification of the drugs. The objective of this study was to developed and validated for the routine analysis of Piribedil and Indapamide in API and tablet dosage forms. The developed method was validated according to the ICH guidelines. The linearity, precision, range, and robustness were within the limits as specified by the ICH guidelines. Hence, the method was found to be simple, accurate, precise, economic, and reproducible.

Keywords: Indapamide, Piribedil, HPLC, Assay method, ICH guidelin

Introduction

Piribedil (Trivastal, Trivastan) is a relatively selective dopamine (D2/D3) agonist with moderate antidepressant activity. It also has α2-adrenergic (α2A/α2C) antagonist properties. Piribedil is a direct dopamine receptor agonist used for the treatment of Parkinson's disease and of other clinical disorders involving dysfunction of the dopaminergic system [1, 2]. Piribedil has 20 times higher affinity for dopamine D3 than for dopamine D2-like receptors, and very low affinity for the dopamine D1 receptor subtype in rat brain. Piribedil is a potent inhibitor at dopamine D3 receptors with affinity between 30 and 60 nM. Although piribedil is not a potent agent, its affinity at hα2A- and hα2C-ARs was comparable to that at D2 receptors. Piribedil (2.5-4.0 mg/kg s.c.) accelerates hippocampal NE synthesis, elevates dialysis levels of NE in hippocampus and frontal cortex, and blocks hypnotic-sedative properties of the α2-AR agonist xylazine. Although a subchronic treatment with piribedil (0.1-2 mg/kg) is not effective, a dose of 0.3 mg/kg administered for 3 weeks significantly reverses the a kinetic deficits produced by the striatal dopamine depletion and progressively

improves attentional deficits. When co-administered with the dopamine prodrug L-DOPA (3 mg/kg), piribedil (0.3 mg/kg) promotes a rapid and full recovery of preoperative performance [3,4].

Molecular Weight: 298.34

Formula: $C_{16}H_{18}N_4O_2$,

CAS No: 3605-01-4

Solubility: Practically Insoluble in water, partially soluble in Ethanol and soluble in DMSO

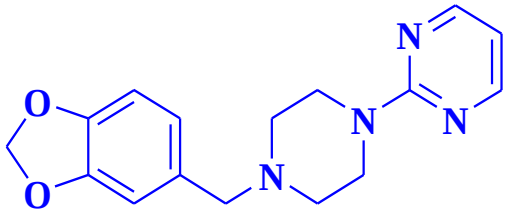

Figure 01: Piribedil: 2-[4-(1, 3-benzodioxol-5-ylmethyl)-1-piperazinyl] pyrimidine

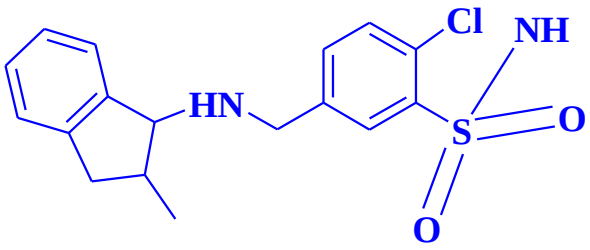

Figure 02 Indapamide: 1-(4-chloro-3sulfamoylbenzamido)-2-methylindoline

Synonyms of this drug are lozol and others like Lorvas, Lozol, Millibar, Natrilix and Noranat are marketed preparation of Single Indapamide. Indapamide is a non-thiazide sulphonamide diuretic compound, generally used in the treatment of hypertension, as well as decompensated cardiac failure. Indapamide is a derivative of benzolsulfonamide and its mechanism of action is analogous to that of thiazide. It is intended for lowering arterial blood pressure and as an adjuvant drug for treating edema caused by cardiac insufficiency [5, 6]

Materials and Methods

Instrument

The analysis of drug was carried out on HPLC of Agilent (Series 1260) Infinity II with Auto injector. HPLC Agilent (Series 1260) with UV detector of chrome software was used. Assembly was equipped with reverse phase (Agilent) C18 Column (Intertsil ODS 2, 25 cm × 4.6 mm, 5 µm) at 60 ºC temperature.

Chemicals and Reagents

Water, Acetonitrile and Buffer solution of HPLC grade were obtained by Merck Limited, India.

Selection of wavelength

Standard solutions of both drugs were scan in UV spectrophotometer between 200 nm and 400 nm on spectrum mode, using methanol as a reference solvent. The drugs were identified by UV detector λmax at 233nm.

Chromatographic Condition [7, 8, 9, 10]

Nucleosil 5 C18, 15 cm X 4.6 mm, 5 µm was used for chromatographic separation at a detection wavelength of 233 nm using flow rate 1.3 ml/min. Mobile Phase used was Water : Acetonitrile : Methanol : Trifluro Acetic Acid, (80:18:02:0.2) mL V:V:V:V . HPLC conditions are given Table 1. Literature survey revealed that some analytical methods were reported for the estimation of piribedil and Indapamide individually or in combination with other drugs by HPLC analytical method. However no HPLC method of new combination of piribedil and Indapamide was available for the simultaneous estimation of this drug HPLC have been developed and validated. [10-16]

Table 01: Chromatographic Condition

HPLC Instrument :	Agilent 1260 Infinity II
Run Time :	10 minutes
Column Temperature :	25 ºC
Column Description :	Nucleosil 5 C18, 15 cm X 4.6 mm, 5 µm
HPLC Instrument No. :	CAL/006/0001&CAL/006/0002
Injection Volume :	20 µL
Wavelength :	233 nm
Flow rate :	1.3 mL per minute
Mobile Phase :	Water : Acetonitrile : Methanol : Trifluro Acetic Acid, (80:18:02:0.2) mL V:V:V:V

Preparation of Control Standard Solution for Piribedil + Indapamide [18, 17]

Weigh accurately 250 mg of Piribedil and 15 mg of Indapamide and diluted to 100 mL of diluent.10 ml Volume was taken and further diluted to 50 mL to get the final concentration of 0.5 mg/mL Piribedil and 0.03 mg/mL of Indapamide respectively.

Preparation of calibration standard solution for Piribedil + Indapamide

Weigh accurately 250 mg of Piribedil and 15 mg of Indapamide and diluted to 100 mL of diluent.10 ml Volume was taken and further diluted to 50 mL to get the final concentration of 0.5 mg/mL Piribedil and 0.03 mg/mL of Indapamide respectively [20, 21]

Preparation of placebo solution

The placebo solution was prepared by adding 710 mg of Placebo diluted to 100ml of Diluents.

Preparation of Piribedil Drug Substance Identification Solution for Piribedil

Weigh accurately 250 mg of Piribedil diluted to 100 mL of diluent.10 ml Volume was taken and further diluted to 50 mL to get the final concentration of 0.5 mg/mL Piribedil.

Preparation of Indapamide drug substance identification solution for Indapamide

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Weigh accurately 15 mg of Indapamide and diluted to 100 mL of diluent.10 ml Volume was taken and further diluted to 50 mL to get the final concentration of 0.03 mg/mL of Indapamide [21, 22]

Preparation of Piribedil + Indapamide drug Substance (Ds) + Placebo Identification Solution

Spiked solution of Piribedil Indapamide drug Substance (Ds) and Placebo Identification Solution were prepared as per the stated amount of and volume was made up to 100 mL to get the required concentration

Preparation of Test Solution for Piribedil + Indapamide Tablets

Tablet triturate 754 mg weight of tablet was dissolved and diluted to the diluent and volume was made up to 100mL.

Result and Discussion

HPLC Method

The data obtained in the calibration experiments when subjected to linear regression analysis showed a linear relationship between peak areas and concentrations in the different ranges. Observation summary for control standard solution and calculation of % recovery against average area of calibration standard solution

Table 02. Observation summary for control standard solution and calculation of % recovery against average area of calibration standard solution

Control Standard	Retention time	Area	Asymmetry	% Recovery
Piribedil	1.35	72022781	1.22	100.0
Indapamide	7.65	2059830	1.15	100.1

Table 03. Calibration standard solution (piribedil)

Calibration Standard	Retention time	Area	Asymmetry
1	1.35	72025915	1.23
2	1.35	71991506	1.24
3	1.35	71994730	1.27
4	1.35	72046701	1.29
5	1.35	71962712	1.23
Average	1.35	72004312.80	1.25
Standard Deviation	0.0000	32595.5721	0.0268
% RSD	0.0	0.0	2.1

Table 04. Calibration standard solution (Indapamide)

Calibration Standard	Retention time	Area	Asymmetry
1	7.65	2061677	1.14
2	7.65	2059297	1.14
3	7.65	2055895	1.13
4	7.65	2056571	1.13
5	7.65	2058748	1.12
Average	7.65	2058438	1.13
Standard Deviation	0.0000	2306.3846	0.0084
% RSD	0.0	0.1	0.7

Table 05. Observation summary for test solution

Particulars	Piribedil		Indapamide	
	Retention time	Area	Retention time	Area
Test solution	1.35	72025915	7.65	2061677

Table 06. Assay for Piribedil and Indapamide Tablet

Sr. No.	Particulars	Piribedil		Indapamide	
		% Assay (Unrounded)	% Assay (Rounded & Truncated)	% Assay (Unrounded)	% Assay (Rounded & Truncated)
1	**Test Solution**	100.030	**100.0**	100.157	**100.2**
2					

Table 07. Summary for % Interference for specificity study

Sr. No.	Particulars		Retention time	Area
1	Blank - diluent	Piribedil + Indapamide	NA	NA
2	Control Standard	Piribedil	1.35	72022781
		Indapamide	7.65	2059830
3	Calibration Standard	Piribedil	1.35	72004313
4	Calibration Standard	Indapamide	7.65	72004313
5	Drug substance identification solution	Piribedil	1.35	72018483
		Indapamide	7.65	2060577
6	Drug substance + placebo solution	Piribedil	1.35	72018483
		Indapamide	7.65	2060577

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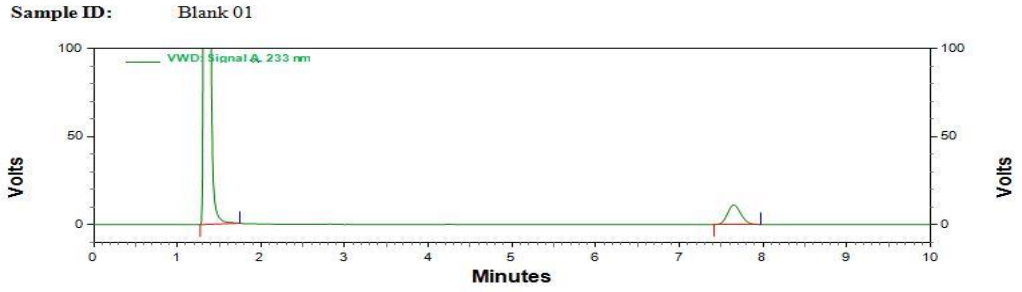
System suitability results for specificity study

The Tailing factor for the peaks due to Piribedil and Indapamide in Standard solution should not be more than 1.5. The Theoretical plates for the Piribedil and Indapamide peaks in Standard solution should not be less than 2000. [10-15] Tailing factor for the peak due Piribedil or Indapamide in calibration standard solution were found to be 1.25 and 1.13 respectively. The system suitability of the method was checked by injecting five different preparations of the Piribedil and Indapamide standard. The parameters of system suitability were checked. % RSD for the area of the peak due to piribedil Fumarate or Indapamide in calibration standard solution for 5 replicate injections was within the Limit. Retention time of Piribedil and Indapamide peak in calibration standard solution were 1.35 and 7.65 minutes respectively. Percentage % recovery for bracketing standard against area of calibration standard solution was 100 to 100.10

Table 08. System suitability results for specificity study

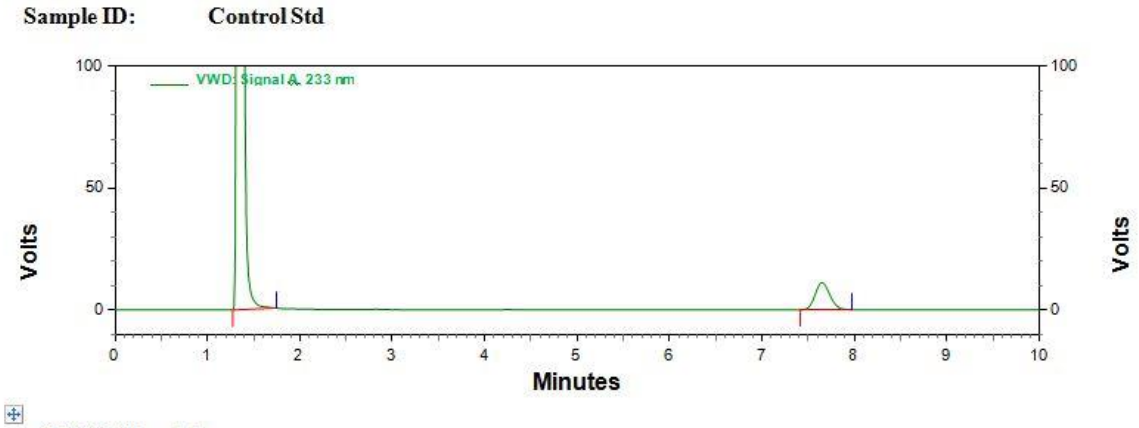
Sr. No.	Evaluation Parameter	Results (PIRIBEDIL)	Results (INDAPAMIDE)	Acceptance Criteria
1	% RSD for the area of the peak due to piribedil Fumarate or Indapamide in calibration standard solution for 5 replicate injections.	0.00	0.10	2%
2	Retention time of Piribedil or Indapamide peak in calibration standard solution.	1.35	7.65	
3	Tailing factor for the peak due Piribedil or Indapamide in calibration standard solution.	1.25	1.13	
4	% Recovery for control standard against area of calibration standard solution.	100.00	100.10	
5	% Recovery for bracketing standard against area of calibration standard solution.	100.00	100.10	



WD: Signal A, 233 nm Results

Peak Number	Name	Retention Time	Area	Asymmetry
1	Piribedil	1.35	72021334	1.21
2	Indapamide	7.65	2060497	1.13

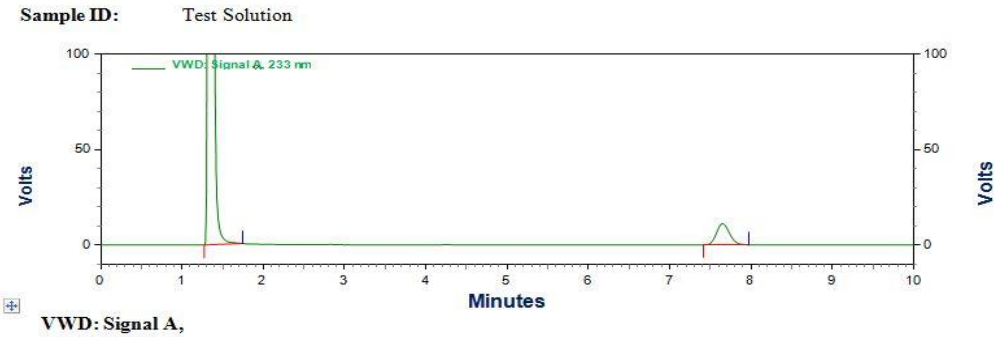
Figure 03: Blank 01 Chromatogram



VWD: Signal A, 233 nm Results

Peak Number	Name	Retention Time	Area	Asymmetry
1	Piribedil	1.35	72022781	1.22
2	Indapamide	7.65	2059830	1.15

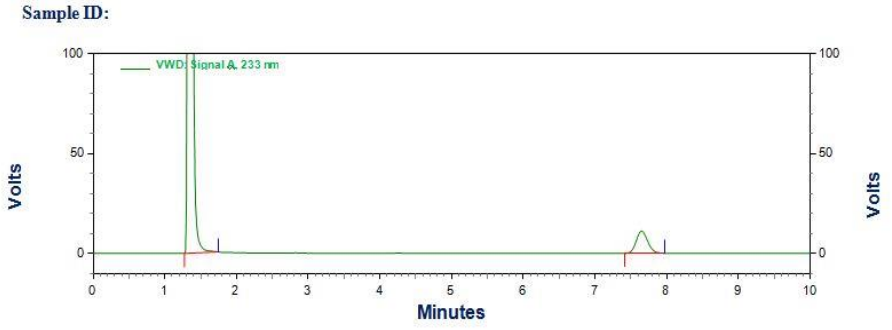
Figure 04: Control 02 Chromatogram



VWD: Signal A, 233 nm Results

Peak Number	Name	Retention Time	Area	Asymmetry
1	Piribedil	1.35	72025915	1.23
2	Indapamide	7.65	2061677	1.14

Figure 05: Test Solution Chromatogram



VWD: Signal A, 233 nm Results

Peak Number	Name	Retention Time	Area	Asymmetry
1	Piribedil	1.35	71975909	1.22
2	Indapamide	7.65	2061078	1.15

Figure 06: Optimizes peaks Chromatogram

Specificity

Specificity is the ability to assess unequivocally the analyte in the presence of components which may be expected to be present. Typically these might include impurities, degradants, matrix, etc. The procedure used to demonstrate specificity will depend on the intented objective of the analytical procedure. This defination has following implications covering Identification to ensure the identify of an analyte, purity test to ensure that all the analytical procedures performed allow an accurate statement of the content of impurities of an analyte, i.e., related substance test, heavy metals, residual solvents content etc.

Specificity for Assay

Assay means to provide an exact result which allows an accurate statement on the content or potency of the analyte in a sample. In case of assay, specificity must be studied for blank/diluent, placebo (in case of finished product such as tablets/ capsule/ cream etc. and impurity and degradation product.

Specificity study results

There was no interference due to blank and placebo at retention time of Piribedil and Indapamide peak. Acceptance criteria there should be no interference of any peak due to blank and placebo at retention time of Piribedil and Indapamide peak. All the parameters were well within acceptance criteria, hence it is concluded that the method was found to be specific.

HPLC Method Validation

Method Validation constitutes the important part of any analytical methods. In recent years, trails have been developed to the harmonization of pharmaceutical regulatory requirements in the United State, Europe and Japan. The FDA method validation draft guidance and USP refer to ICH guidelines. As part of method validation as per ICH guidelines, Linearity, Accuracy, Precision, Robutness and Specificity Studies this parameter were studied.

Linearity

Linearity of an analytical method is its ability to elicit test results that are directly or by a well-defined mathematical transformation, proportional to the concentration of drug in samples within a given range. [20, 21 and 22] Calibration curves were plotted with observed peak areas against concentration to obtain the calibration curve and correlation coefficients. Characteristics parameters for regression equation (y=mx+c) of the method and these parameter were used to confirm the good linearity of the method. The results are shown in Tables 09 and 10 and Figs. 5 and 6.

Table 09: Calibration of Piribedil

Level (%)	Piribedil			
	Concentration (mg/mL)	**Average Concentration (mg/mL)**	**Area**	**Average Area**
25	0.1250	**0.1250**	17981844	**17981212**
	0.1250		17980471	
	0.1250		17981320	
50	0.2500	**0.2500**	35963688	**35963496**
	0.2500		35962910	

	0.2500		35963889	
100	0.5000	**0.5000**	71927376	**71922914**
	0.5000		71918721	
	0.5000		71922645	
150	0.7500	**0.7500**	107891064	**107890358**
	0.7500		107889671	
	0.7500		107890338	
200	1.0000	**1.0000**	142281990	**142282021**
	1.0000		142282201	
	1.0000		142281871	

Table 10: Calibration of Indapamide

Level (%)	**Indapamide**			
	Concentration (mg/mL)	**Average Concentration (mg/mL)**	**Area**	**Average Area**
25	0.0075	**0.0075**	513392	**513586**
	0.0075		512606	
	0.0075		514761	
50	0.0150	**0.0150**	1026784	**1026565**
	0.0150		1025468	
	0.0150		1027442	
100	0.0300	**0.0300**	2053567	**2053173**
	0.0300		2052832	
	0.0300		2053121	
150	0.0450	**0.0450**	3080351	**3080498**
	0.0450		3079781	
	0.0450		3081361	
200	0.0600	**0.0600**	4101481	**4094681**
	0.0600		4081820	
	0.0600		4100743	

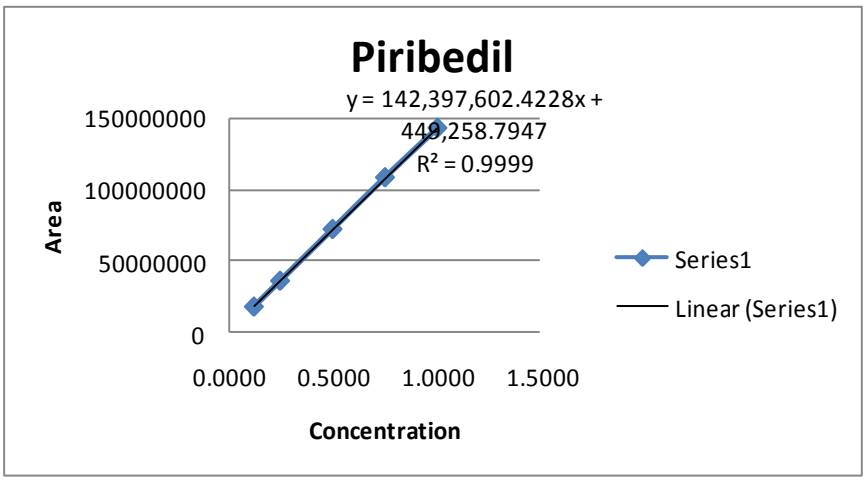


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Figure 05: Calibration of Piribedil

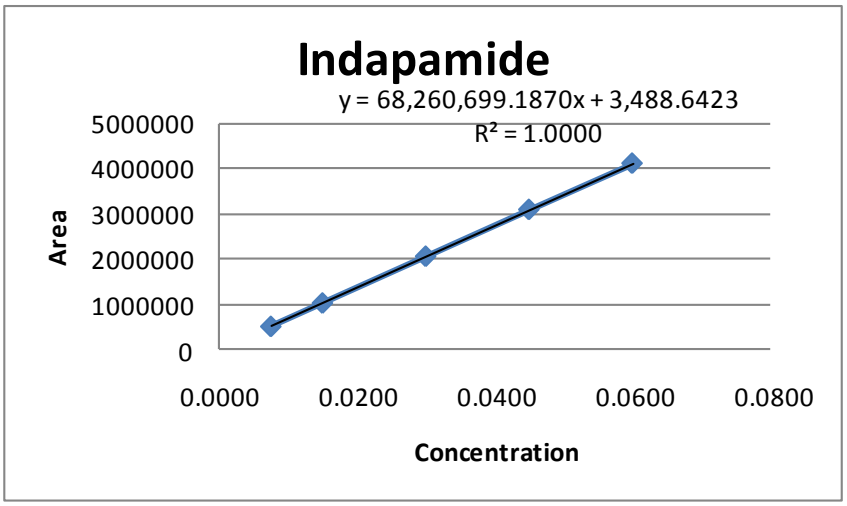

Figure 06: Calibration of Indapamide

Assay method for Piribedil & Indapamide was found to be linear between 25 % to 200 % concentration level of working concentration as all the results are well within the acceptance criteria

Accuracy

The accuracy of an analytical method is the closeness of test results obtained by that method to the true value. Accuracy may often the expressed as present recovery by the assay of known added amounts of analyte.[20, 21 and 22] The accuracy was determined by Piribedil and Indapamide (equivalent to 50 mg of Piribedil and 03 mg of Indapamide) (50%, 100%, and 150% of the label claimed, respectively) to quantity equivalent to average weight of marketed tablets. The resulting mixtures were analyzed in triplicates over 3 days. The % recovery of added drug was taken as a measure of accuracy. The results are shown in Table 11. All the results were well within acceptance criteria, hence the assay method was found to be accurate.

Table 11:

Level	Level (%)	Sr. No.	Placebo (mg)	Concentration (mg/mL) Piribedil	Concentration (mg/mL) Indapamide
1	50	1	710.1	0.2500	0.0150
		2	709.8	0.2500	0.0150
		3	711.2	0.2500	0.0150
2	100	1	710.3	0.5000	0.0300
		2	709.9	0.5000	0.0300
		3	711.3	0.5000	0.0300
3	150	1	710.4	0.7500	0.0450
		2	709.8	0.7500	0.0450
		3	709.5	0.7500	0.0450

Table 12: Observation summary for accuracy study of piribedil

Level	Level (%)	Sr. No.	Area	Added Concentration (mg/mL)	Recovered Concentration (mg/mL)	% Recovery (Rounded)	% Recovery (Rounded & Truncated)
1	50	1	35961469	0.2500	0.2497	99.880	100.0
		2	35956309	0.2500	0.2497	99.880	100.0
		3	35960523	0.2500	0.2497	99.880	100.0
2	100	1	71918734	0.5000	0.4994	99.880	100.0
		2	71922602	0.5000	0.4994	99.880	100.0
		3	71921880	0.5000	0.4994	99.880	100.0
3	150	1	107893101	0.7500	0.7492	99.893	100.0
		2	107689306	0.7500	0.7478	99.707	100.0
		3	108631709	0.7500	0.7543	100.573	101.0
							100
Standard Deviation							0.3333
Relative Standard Deviation							0.3
Minimum % Recovery							100
Maximum % Recovery							101
Sample Size							9
Confidence Coefficient							1.96
Margin of error							0.2178
95% Confidence Interval Upper Limit							100.2
95% Confidence Interval Lower Limit							99.8

Table 13: Observation summary for accuracy study of Indapamide

Level	Level (%)	Sr. No.	Area	Added Concentration (mg/mL)	Recovered Concentration (µg/mL)	% Recovery (Rounded)	% Recovery (Rounded & Truncated)
1	**50**	1	1024916	0.0150	0.0149	99.333	99
		2	1022690	0.0150	0.0149	99.333	99
		3	1023671	0.0150	0.0149	99.333	99
2	**100**	1	2050864	0.0300	0.0299	99.667	100
		2	2055290	0.0300	0.0300	100.000	100
		3	2052779	0.0300	0.0299	99.667	100
3	**150**	1	3081519	0.0450	0.0449	99.778	100
		2	3060819	0.0450	0.0446	99.111	99
		3	3080281	0.0450	0.0449	99.778	100
Average Recovery							100

Standard Deviation	0.5270
Relative Standard Deviation	0.5
Minimum % Recovery	99
Maximum % Recovery	100
Sample Size	9
Confidence Coefficient	1.96
Margin of error	0.3443
95% Confidence Interval Upper Limit	100.3
95% Confidence Interval Lower Limit	99.7
95% Confidence Interval	99.7 to 100.3

Precision and Repeatability [20, 21]

Precision of an analytical method is usually expressed as standard deviation or relative standard deviation. To determine the precision, intra-day and inter-day precision was performed. For intra-day precision, Test solution 1 to 06 containing 50 mg Piribedil of three different concentration and 03 mg of Indapamide. Piribedil and Indapamide were analyzed 3 times on the same day. For inter-day precision above, same concentration was used at different days and %RSD was calculated. The results are shown in Table 14 and 15.

Table 14: Piribedil precision of an analytical method

Sr. No.	Particulars	Injection	Piribedil		
			Retention time	Area	% Assay
1	Test solution 1	1	1.35	71579132	99.7
		2	1.35	71500819	99.5
2	Test solution 2	1	1.35	71460445	99.5
		2	1.35	71581479	99.7
3	Test solution 3	1	1.35	72049309	100.3
		2	1.35	72002502	100.2
4	Test solution 4	1	1.35	71889301	100.1
		2	1.35	71856305	100.0
5	Test solution 5	1	1.35	71278250	99.2
		2	1.35	71242420	99.2
6	Test solution 6	1	1.35	71898307	100.1
		2	1.35	71844783	100.0
				Avg	99.8
				SD	0.3801
				% RSD	0.4

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Table 15: Indapamide precision of an analytical method

Sr. No.	Particulars	Injection	Indapamide		
			Retention time	Area	% Assay
1	Test solution 1	1	7.65	2004633	99.7
		2	7.65	1999946	99.4
2	Test solution 2	1	7.65	1993723	99.1
		2	7.65	1997902	99.3
3	Test solution 3	1	7.65	2018781	100.4
		2	7.65	2017830	100.3
4	Test solution 4	1	7.65	2015549	100.2
		2	7.65	2010692	100.0
5	Test solution 5	1	7.65	2004786	99.7
		2	7.65	2004142	99.7
6	Test solution 6	1	7.65	2010491	100.0
		2	7.65	2012531	100.1
				Avg	99.8
				SD	0.4115
				% RSD	0.4

Conclusion

An attempt has been made to develop the HPLC method for simultaneous estimation of Piribedil and Indapamide in novel combined dosage form. Literature survey revealed that some analytical methods were reported for the estimation of piribedil and Indapamide individually or in combination with other drugs by HPLC analytical method. However no HPLC method of new combination of piribedil and Indapamide was available for the simultaneous estimation of these drugs by HPLC. From the assay studies, it was found that the formulation contains 100 % of Piribedil and 100.10 % of Indapamide. The peaks of Piribedil and Indapamide were found well separated at 1.35 and 7.65 respectively. The system suitability studies showed that all the system suitability parameters were within the acceptance criteria and the drug obeys specificity, linearity, accuracy and robustness. The proposed method was validated as per ICH guideline Q2 (R1); Guidelines for validation of analytical procedures. Being a HPLC method, it does not require any sophisticated

instrumentation and can be used as quality control tool for analysis of piribedil tablets. The developed chromatographic method for the determination of Piribedil and Indapamide in tablet dosage forms was simple, rapid, accurate, precise, specific, robust and economical. Therefore this method may be adopted for the routine analysis of Piribedil and Indapamide in pharmaceutical tablet formulation.

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Authors Contribution

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

Conflict of Interest

The authors have declared no conflict of interest. Nil declared by all authors

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