WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.084
Volume 9, Issue 8, 2099-2113. Research Article ISSN 2277– 7105

SIMULTANEOUS SPECTROPHOTOMETRIC ESTIMATION OF CINNARIZINE IN BINARY MIXTURE WITH PIRACETAM IN BULK AND PHARMACEUTICAL DOSAGE FORMS

Ahmed MS Al-Ghani[1]*, Anes A. M. Thabit[2] and Nabil Albaser[3]

[1]Department of Pharmaceutical Chemistry, Faculty of Medical Sciences, Al-Razi University, Sana'a - Yemen.

[2]Department of Pharmaceutics & Pharmacy Practice, Faculty of Medical Sciences, Al-Razi University, Sana'a - Yemen.

[3]Department of Pharmacology, Faculty of Medical Sciences, Al-Razi University, Sana'a - Yemen.

Article Received on
18 June 2020,

Revised on 08 July 2020,
Accepted on 28 July 2020

DOI: 10.20959/wjpr20208-17418

***Corresponding Author**
Ahmed MS Al-Ghani
Department of Pharmaceutical Chemistry, Faculty of Medical Sciences, Al-Razi University, Sana'a - Yemen.

ABSTRACT

Cinnarizine, an antihistaminic drug, is commonly formulated in combination with piracetam for treat wide range of disease as dizziness, nausea, inner ear syndrome and other diseases of the brain. The aim of this work was to develop simple, precise and accurate spectrophotometric method for the estimation of Cinnarizine (CIN) in binary mixture with piracetam (PRM) in bulk and Formulated dosage form. This method could be used in routine analysis in laboratories of quality control. Two chemometric techniques include principal component regression (PCR) and partial least squares (PLS) were prepared using synthetic mixture containing two drugs, all dissolved in methanol. In PCR and PLS the absorbance of the synthetic mixture in the range 218-230 nm with interval $\Delta\lambda$=0.5 nm in their zero-order spectra were selected. Calibration or regression was then obtained by using the absorbance data matrix and the concentration data matrix for the determination of the unknown concentrations of CIN and PRM in laboratory prepared mixtures and pharmaceutical dosage form. The two proposed technique were positively applied for analysis of the two drugs in laboratory prepared mixture and in dosage form with good recoveries percent in the range of 98-102%. Method validation was conducted according to ICH guidelines. The developed methods are simple

and precise and can be used for routine analysis of the drugs in combined dosage forms in quality control laboratories.

KEYWORDS: Cinnarizine; Chemometric; Partial least squares; Piracetam; Principal component regression; Validation.

INTRODUCTION

Cinnarizine (CIN), [1-(diphenyl methyl)-3-(4-phenylprop-2-enyl)-piperazine] is a derivative of piperazine that has antihistaminic (H1 blocker), sedative and calcium channel blocking activity. It is used for the treatment of vertigo, nausea caused by Meniere's disease and also motion sickness. In addition, it is used in the various peripheral and cerebral vascular disorders management.[1,2] It is commonly used in combination with other drugs for prophylaxis of vertigo.[1,3] Such combination is highly effective as each drug potentiates the other in boosting brain oxygen supply.

Piracetam (PRM) is 2-(2-Oxopyrrolidin-1-yl) acetamide. PRM is a nootropic and psychopharmacological drug.[4] It is a synthetic cyclic derivative of GABA. It is described as a myoclonus and neuroprotective agent. The mechanism of action depends on eliminating of calcium chloride those results in a decrease of the rhythm rate and an increase of the contraction amplitude.[5] Recently, CIN and PRM combination has been established as a dosage form that used to treat wide range of disease as dizziness, nausea, inner ear syndrome and other diseases of the brain, nerve and memory.

Literature review shows that several analytical methods were reported for the spectrophotometric determination of CIN in pharmaceutical preparations and biological fluids. These methods include spectrophotometric,[6-18] spectroflorometric[19-21] and multivariate[7,9-10,22] voltammetry,[23] high performance liquid chromatography (HPLC),[24-39] high performance thin layer chromatography (HPTLC),[38-43] and capillary electrophoresis,[44] Other methods were developed to determination of CIN in combination with PRM which include spectrophotometry,[45] high performance thin layer chromatography and high performance liquid chromatography (HPTLC & HPLC),[31, 45-47]

In this study, the zero order UV absorption spectra of CIN and PRM in methanol at their nominal concentrations ratio in pharmaceutical dosage form shows strong overlap. Thus, direct simultaneous spectrophotometric determination of the two drugs in the binary mixture

is not feasible. Therefore, the main task of this study was to develop and validate simple, accurate, and selective methods based on spectrophotometric measurements and capable of determining the two drugs simultaneously with the help of different chemometric techniques.

In recent years, multivariate calibrations, such as principal component regression (PCR) and partial least square (PLS) started to be applied to the analysis of the analytical data obtained in all the instrumentations. The same methods and their algorithms have been applied to the simultaneous spectrophotometric determination of drugs in the pharmaceutical formulation containing two or more compounds with overlapping spectra. The main advantages of these techniques are the higher speed of processing data concerning the values of concentrations and absorbance of compounds with strongly overlapping spectra. Besides, the errors of calibration model are minimized by measuring the absorbance values at several points in the wavelength range of the zero-order and derivative spectra. Analytical methods using multivariate calibrations and their applications involve the spectrophotometric, chromatographic and electrochemical methods for determinations of analytes in the mixtures[48]

In this part, the chemometric methods applied are PCR and PLS using factor analysis then using a subset of the resulting factors to complete the regression modelling.[49] These multivariate calibrations were useful in spectral analysis because the simultaneous inclusion of many spectral wavelengths instead of single wavelength greatly improved the precision and predictive ability.[49]

MATERIALS AND METHODS

Materials

CIN pharmaceutical standard substance was supplied by quality Control Lab-Ministry of Health- Sana'a, Yemen with certified purity of 99.97% and PRM pharmaceutical standard substance was supplied by the National Organization of Drug Control and Research (NODCAR), Giza, Cairo, Egypt with certified purity 98.40. Cinaretam® capsules were manufactured by Misr Company for Pharmaceuticals. Egypt. Batch No. 116844, each capsule was labelled to contain 25 mg CIN and 400 mg PRM). Methanol used was of analytical grade.

Instrumentation

Shimadzu ultraviolet/visible spectrophotometer 1600 (Japan) connected to an IBM compatible computer and supported with UV probe software version 2.21 was used. The chemometric methods, CFBP-ANN, and data analysis were performed using Matlab™ software, version 7.9.0 with PLS-toolbox 2.0 and neural networks toolbox.

Preparation of solutions

Stock solutions

Accurately weighed 100 mg of CIN and 1600 mg of PRM standards were separately transferred into two 100 ml volumetric flasks, dissolved in and completed to volume with methanol to produce stock solutions of (1 mg/ml) and (16 mg/ml), respectively.

Working solutions

Accurate aliquots (1 ml) were transferred from each stock solution into two separate 100 ml volumetric flasks. The volume was completed with methanol to obtain working solutions of (10 µg/ml) and (160 µg/ml) for CIN and PRM, respectively.

Sample solution's

Ten capsules content of Cinaretam® were weighed and mixed well. An accurate weight of the capsule content powder equivalent to (25 mg) CIN and (400 mg) PRM was transferred into a 100 ml volumetric flask and 50 ml methanol were added. The solution was sonicated for 15 min and completed to volume with methanol, then filtered by filter paper discarding the first few milliliters to produce dosage form stock solution of (200 µg/ml) of CIN and (4000 µg/ml) of PRM.

Ten ml of this stock solution was transferred into a 100 ml volumetric flask and was completed to volume with methanol to obtain the dosage form working solution of (20µg/ml) of CIN and (400 µg/ml) of PRM.

Construction of the training set

Twelve mixtures of CIN and PRM were prepared by transferring different volumes of their working solutions into a series of 10 ml volumetric flasks and completed to volume with methanol. The concentrations of the two drugs, respectively, in the prepared mixtures were 1.8-8.2 µg/ml for CIN and 32-128 µg/ml for PRM. The absorbance of these mixtures were

then scanned between 200 and 400 nm at 0.5 nm intervals with respect to a blank of methanol.

Construction of the PCR and PLS models

Two multivariate calibration models (PCR and PLS) were constructed using the obtained data. In these methods, the absorbance data matrix for the training set concentration matrix was obtained by measuring the absorbance between 218 and 230 nm at 0.5 nm intervals. Calibration or regression was then obtained by using the absorbance data matrix and the concentration data matrix for the determination of the unknown concentrations of CIN and PRM in laboratory prepared mixtures and pharmaceutical dosage form.

For PCR and PLS methods, the training set absorbance and concentration matrices together with PLS-toolbox 2.0 software were used for the calculations.

Selection of the optimum number of factors to build the PCR and PLS models

The cross validation method was used, leaving out one sample at a time, to select the optimum number of factors.[50] PLS and PCR calibration on eleven calibration spectra were performed and, using this calibration, the concentration of the sample left out during the calibration process was predicted. This process was repeated twelve times until each training sample had been left out once. The predicted concentrations of the two drugs in each sample were compared with the actual concentrations in this calibration samples and Root-Mean-Square Error of Cross-Validation (RMSECV), which indicates both the precision and accuracy of predictions, was calculated for each method and then recalculated upon addition of each new factor to the PLS and PCR models as follows:

$$\mathbf{RMSECV=\sqrt{PRESS/n}}$$

where, (PRESS) was the predicted residual error sum of squares and (n) was the number of calibration samples[51]

$$\mathbf{PRESS = \Sigma\ (}\boldsymbol{Ypred - Ytrue}\mathbf{)2}$$

where, (Ypred) and (Ytrue) were the predicted and true concentrations in µg/ml, respectively.

Construction of the validation set

To evaluate the prediction performance of the proposed chemometric models, nine different aliquots of the working solutions equivalent to (18-82 µg of CIN and 320-1280 µg of PRM) were transferred into a series of 10 ml volumetric flasks and completed to volume with

methanol and procedure under construction of the training set was repeated. The suggested models were applied to these mixtures to predict the concentrations of CIN and PRM.

Analysis of CIN and PRM in Cinaretam® capsules

The two chemometric models were applied to simultaneous estimation of CIN and PRM in commercial capsules. Different aliquots of the dosage form working solution equivalent to (25-65 µg) of CIN and (400-1040 µg) of PRM, were transferred into a series of 10 ml volumetric flasks and completed to volume with methanol. The spectra of the prepared solutions were scanned and the procedure was followed up as mentioned previously under construction of the training set. The developed models were applied to calculate the concentrations of CIN and PRM. The experiment was repeated using standard addition technique.

RESULTS AND DISCUSSION

UV scanning of training set

As shown in Fig. 1, the UV absorbance spectra of CIN and PRM mixture showed strong overlap. Nevertheless, the data of absorbance in the wavelength range 218-230 nm were chosen as it provided the higher amount of information of the two drugs in the binary mixture.

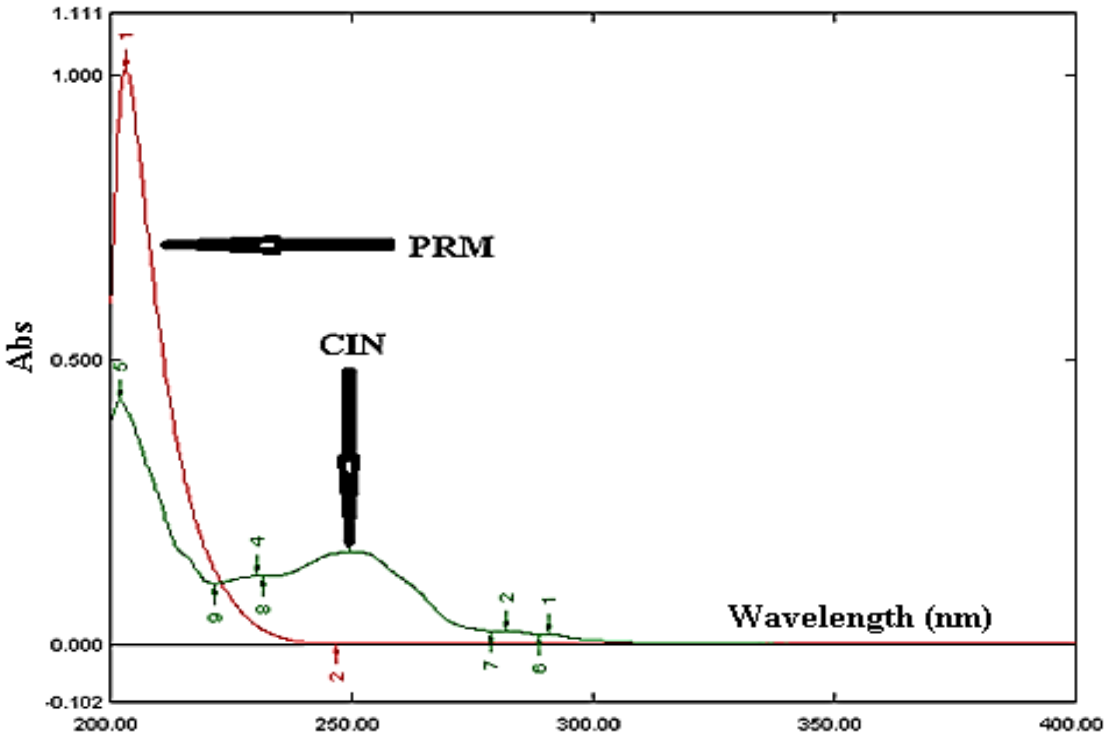

Fig. 1: Zero order absorption spectra of CIN (3µg/ml) and PRM (48 µg/ml) in methanol.

PCR and PLS models Before constructing the two models, the choice of optimum number of factors was very important stage. Hence, when the number taken was less than the required number, meaningful data that would be necessary for the calibration might be ignored. On the other hand, when the number of factors taken was more than the required number, more noise could be added to the data. Selection of the optimum number of factors was performed by visual inspection. Two factors were selected visually and found suitable for both PCR and PLS methods as shown in Fig 2 and 3.

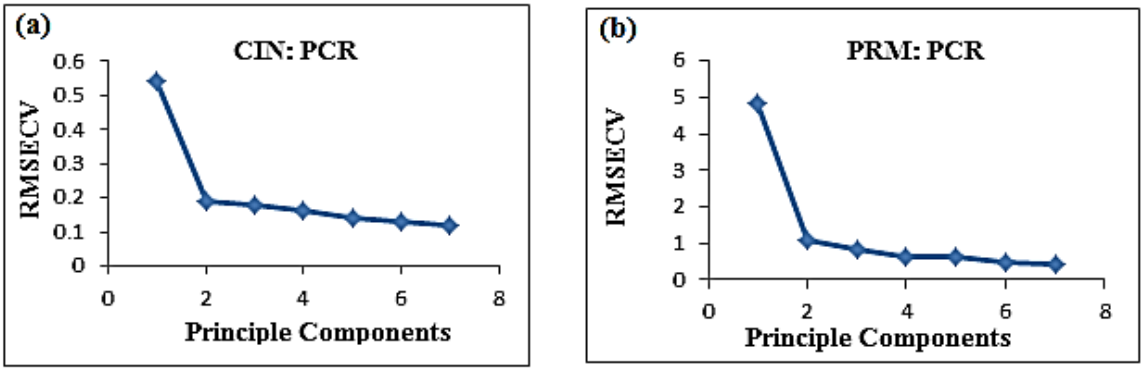

Fig. 2: RMSECV plot as a function of the number of principle components used to construct the PCR model for CIN (a) and PRM (b).

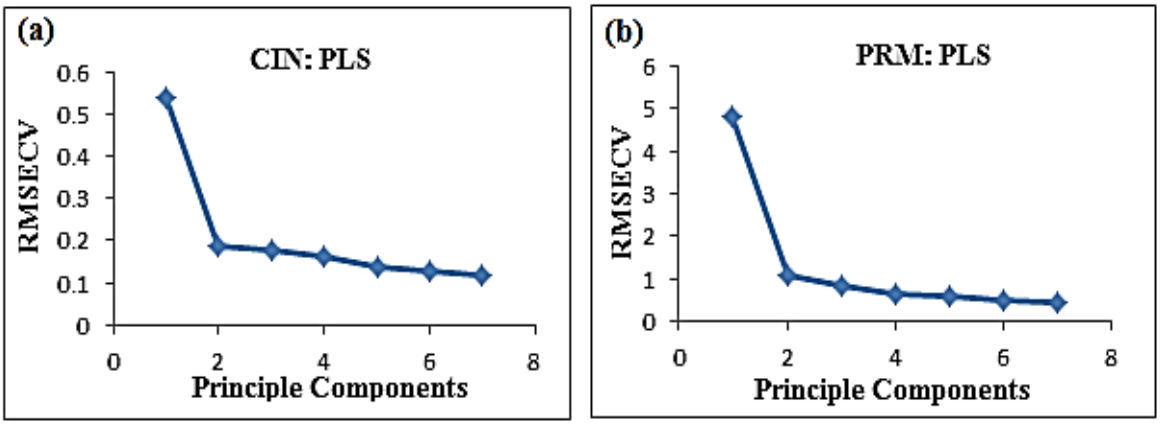

Fig. 3: RMSECV plot as a function of the number of principle components used to construct the PLS model for CIN (a) and PRM (b).

Accuracy

The accuracy was assessed by applying the proposed chemometric methods obtained for the simultaneous determination of CIN and PRM in laboratory prepared mixtures (in a ratio similar to that of the pharmaceutical dosage form) and the mean percentage recoveries were

calculated (Table 1). Accuracy of the method was also confirmed by recovery studies from dosage form (capsule) at different levels of standard additions. Good mean percentage recoveries were obtained, indicating there was no interference from the co-formulated drug or the frequently encountered capsule excipients.

Table 1: Recovery results obtained from the simultaneous UV determination at 218-230 nm, using methanol as solvent, of CIN and PRM in synthetic mixtures (validation set), Cinaretam® capsule and standard addition using PCR and PLS techniques.

Item	Principal Component Regression (PCR)		Partial Least Square (PLS)	
	CIN	PRM	CIN	PRM
Recovery % in the mixture (Validation set)	100.49 ± 1.168	100.45 ± 1.315	100.63 ± 1.209	100.60 ± 1.284
Recovery % in (Cinaretam® capsule)	98.06 ± 0.408	101.23 ± 1.277	97.87 ± 0.400	101.28 ± 1.393
Recovery % of standard added	98.49 ± 0.473	99.52 ± 1.064	98.67 ± 0.497	99.25 ± 1.131

Precision

The intraday and interday precision was determined by calculating the values of relative standard deviation (% RSD) using three different concentrations (2.5, 5 and 7.5 µg/ml) of CIN and (40, 80 and 120 µg/ml) of PRM in triplicates during the same day and on three consecutive days in binary mixtures and results are displayed in table 2.

Table 2: Intra-day and inter-day precision results of the simultaneous determination of CIN and PRM using PCR, and PLS chemometric techniques.

Item		Intra-day*				Inter-day**			
		CIN		PRM		CIN		PRM	
		PCR	PLS	PCR	PLS	PCR	PLS	PCR	PLS
(2.5, 40)µg/ml	Recovery %	101.35	101.34	101.31	101.31	100.95	100.99	101.13	101.15
	SD	0.304	0.304	1.239	1.239	1.258	1.351	1.103	1.125
	RSD %	0.300	0.300	1.223	1.223	1.246	1.338	1.090	1.113
(5, 80)µg/ml	Recovery %	101.79	101.79	101.69	101.67	101.12	100.92	101.35	101.28
	SD	0.209	0.209	0.473	0.472	1.4	1.114	1.204	1.146
	RSD %	0.205	0.205	0.466	0.465	1.384	1.103	1.188	1.132
(7.5, 120)µg/ml	Recovery %	102.42	102.41	101.35	101.35	102.02	102.03	102.03	102.03
	SD	0.373	0.372	0.344	0.344	1.229	1.242	1.128	1.127
	RSD %	0.365	0.364	0.339	0.339	1.204	1.218	1.110	1.107

* The intraday (n = 3), average of three concentrations (2.5, 5 and 7.5 µg/ml) of CIN products and (40, 80 and 120 µg/ml) of PRM repeated three times in the same days; **The interday (n = 3), average of three concentrations (2.5, 5 and 7.5 µg/ml) of CIN products and (40, 80 and

120 µg/ml) of PRM products repeated three times in three successive days; SD: Standard deviation, RSD: Relative standard deviation, CIN: Cinnarizine, PRM: Piracetam, PCR: Principal component regression, PLS: Partial least squares

Selectivity

The two methods selectivity was evident by the good mean percentage recoveries obtained from the laboratory prepared mixtures (validation set) and from the formulated dosage form (Cinaretam® capsules) without any interferences from the used excipients in capsules.

Statistical analysis

All results obtained from the proposed methods were statistically compared with those obtained from reported reference method.[4,45] The student t-test and F ratio test were applied. The obtained values of t and F were less than the values tabulated, confirming that the difference between the developed and reported methods is insignificant in terms of accuracy and precision as shown in table 3.

Table 3: Statistical comparison between the results of the proposed methods and the reference methods for the determination of CIN and PRM in binary mixture.

Statistical Parameters	CIN			PRM		
	Reference Method**	PCR	PLS	Reference Method***	PCR	PLS
Mean	100.48	100.49	100.63	100.77	100.45	100.60
SD	0.536	1.168	1.209	0.662	1.315	1.284
SE	0.240	0.522	0.541	0.296	0.588	0.574
RSD%	0.534	1.162	1.201	0.656	1.309	1.276
n	5	5	5	5	5	5
Variance	0.288	1.363	1.462	0.438	1.729	1.649
t (2.306)*		0.006	0.246		0.484	0.261
F (6.388)*		4.733	5.067		3.947	3.768

SD: Standard deviation, SE: Standard error, RSD: Relative standard deviation; *: Figures in parentheses are the theoretical t and F values at (p=0.05). ** Metwally, F.H., et al. RP-HPLC method,[45] *** BP 2016. RP-HPLC method.[4]

CONCLUSIONS

The proposed methods (PCR and PLS) can be used for simultaneous estimation of CIN and PRM in laboratory prepared mixtures and pharmaceutical dosage form containing them without interference with each other and without the need for previous physical separation of the two drugs. Multivariate calibration models were built from the spectral and concentration data matrices. Verification of the calibrations carried out with the aid of a synthetic set of

mixtures of the two compounds, produced satisfactory results showing simplicity, sensitivity, selectivity and rapidity. Hence, the developed methods can be used for quality control of the cited drugs in ordinary laboratories.

REFERENCES

1. O'Neil, M. J.; Heckelman, P.; Koch, C.; Roman, K.,The Merck Index Whitehouse Station, NJ: Merck, 2006; 14.
2. Sweetman, S. C., Martindale: the complete drug reference. Pharmaceutical press, 2011; 36.
3. Rang, H.; Dale, M.; Ritter, J.; Moore, P., Churchill Livingstone. Pharmacology, 2003.
4. G.B.S., O. a. O. U. K. S., '"British Pharmacopoeia"' Stationery Office. London, 2016.
5. Müller, W.; Eckert, G.; Eckert, A., Piracetam: novelty in a unique mode of action. Pharmacopsychiatry, 1999; 32 (S 1): 2-9.
6. Abdine, H.; Belal, F.; Zoman, N., Simple spectrophotometric determination of cinnarizine in its dosage forms. Il Farmaco, 2002; 57 (4): 267-271.
7. Salem, M. Y.; El-Bardicy, M. G.; El-Tarras, M. F.; El-Zanfally, E. S., Simultaneous determination of domperidone maleate and cinnarizine in a binary mixture using derivative ratio spectrophotometry and classical least squares calibration. Journal of Pharmaceutical and Biomedical Analysis, 2002; 30(1): 21-33.
8. Vinodhini, C.; Vaidhyalingam, V.; Ajithadas, A.; Shantha, A., Simultaneous estimation of cinnarizine and domperidone in solid oral dosage form using spectrophotometric method. Indian drugs, 2002; 39 (9): 491-493.
9. Salem, M. Y.; El-Zanfaly, E. S.; El-Tarras, M. F.; El-Bardicy, M. G., Simultaneous determination of domperidone and cinnarizine in a binary mixture using derivative spectrophotometry, partial least squares and principle component regression calibration. Analytical and bioanalytical chemistry, 2003; 375 (2): 211-216.
10. Zayed, S., Simultaneous determination of cinnarizine and nicergoline in a binary mixture using first derivative spectra, first derivative of ratio spectra and multivariate calibration techniques. Journal of Analytical Chemistry, 2010; 65 (9): 921-928.
11. Ahmed, R.; Supriya, R. S.; Sheetal, D. R., Spectrophotometric Method for Simultaneous Estimation of Paracetamol and Cinnarizine in Tablet Dosage Forms. Research Journal of Pharmacy and Technology, 2012; 5 (5): 667-671.

12. Shah, P. B.; Patel, P. U., Q-absorbance ratio spectrophotometric method for the simultaneous estimation of cinnarizine and dimenhydrinate in their combined dosage form. Journal of Pharmaceutical Science and Bio-Scientific Research, 2012; 2 (2): 83-87.
13. Tarkase, K.; Tarkase, M.; Dokhe, M.; Wagh, V., Development and validation of spectrophotometric method for simultaneous estimation of cinnarizine and domperidone maleate in pure and tablet dosage form. International Journal of Pharmaceutical Sciences and Research, 2012; 3 (8): 2700-2704.
14. Abdelrahman, M. M., Simultaneous determination of Cinnarizine and Domperidone by area under curve and dual wavelength spectrophotometric methods. Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy, 2013; 113: 291-296.
15. Dalwadi, N.; Chhalotiya, U. K.; Shah, D.; Mehta, F.; Bhatt, K., Quantification of cinnarizine and dimenhydrinate in tablet dosage form by simultaneous equation spectrophotometric method. International Journal of Advances in Pharmaceutical Analysis, 2014; 4 (2): 58-61.
16. Kalyankar, T.; Wadher, S.; Kulkarni, P.; Panchakshari, P., Simultaneous Estimation and Development of UV Spectroscopic Method for Determination of Cinnarizine and Domperidone in Bulk and Pharmaceutical Formulation. International Journal of PharmTech Research, 2014; 6 (1): 323-329.
17. Lamie, T., Simultaneous determination of cinnarizine and dimenhydrinate in binary mixture using, first derivative of ratio spectra and bivariate spectrophotometric techniques. Analytical Chemistry Indian, 2014; 14 (3): 93-99.
18. Lamie, N. T., Comparative study of spectrophotometric methods manipulating ratio spectra: An application on pharmaceutical binary mixture of cinnarizine and dimenhydrinate. Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy, 2015; 141: 193-201.
19. Niu, S.-y.; Wang, S.-j.; Shi, C.; Zhang, S.-s., A rapid, simple and highly sensitive second derivative synchronous fluorometric method has been developed for the simultaneous analysis of binary mixture of cinnarizine (CN) and domperidone (DOM). The method is based upon measurement of the native fluorescence of these drugs at Δλ= 80 nm in aqueous methanol (50% V/V). The different experimental parameters affecting the native fluorescence of the. Journal of fluorescence, 2008; 18 (1): 227-235.
20. Walash, M.; Belal, F.; El-Enany, N.; Abdelal, A., Second-derivative synchronous fluorometric method for the simultaneous determination of cinnarizine and domperidone

in pharmaceutical preparations. Application to biological fluids. Journal of fluorescence, 2008; 18 (1): 61-74.

21. Walash, M. I.; Belal, F.; El-Enany, N.; Abdelal, A., Second-derivative synchronous fluorescence spectroscopy for the simultaneous determination of cinnarizine and nicergoline in pharmaceutical preparations. Journal of AOAC International, 2008; 91 (2): 349-359.
22. Tawakkol, S. M.; El-Zeiny, M. B.; Hemdan, A., Full spectrum and selected spectrum based chemometric methods for the simultaneous determination of Cinnarizine and Dimenhydrinate in laboratory prepared mixtures and pharmaceutical dosage form. Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy, 2017; 173 (15): 892-896.
23. El-Sayed, G.; Yasin, S.; El Badawy, A., Voltammetric behavior and determination of cinnarizine in pharmaceutical formulations and serum. Analytical Letters, 2008; 41 (17): 3021-3033.
24. Hundt, H.; Brown, L.; Clark, E., Determination of cinnarizine in plasma by high-performance liquid chromatography. Journal of Chromatography B: Biomedical Sciences and Applications, 1980; 183 (3): 378-382.
25. Nitsche, V.; Mascher, H., Rapid high-performance liquid chromatographic assay of cinnarizine in human plasma. Journal of Chromatography B: Biomedical Sciences and Applications, 1982; 227 (2): 521-525.
26. Rosseel, M.; Lefebvre, R., Sensitive determination of cinnarizine in human plasma by high performance liquid chromatography and fluorescence detection. Journal of Chromatographia, 1993; 36 (1): 356-358.
27. Argekar, A.; Shah, S., Simultaneous determination of cinnarizine and domepiridone maleate from tablet dosage form by reverse phase ion pair high performance liquid chromatography. Journal of pharmaceutical and biomedical analysis, 1999; 19 (6): 813-817.
28. Angelov, T., High-performance liquid chromatographic determination of cinnarizine in workplace air. Journal of Chromatographia, 2003; 58 (7-8): 483-485.
29. Nowacka-Krukowska, H.; Rakowska, M.; Neubart, K.; Kobylińska, M., High-performance liquid chromatographic assay for cinnarizine in human plasma. Acta Poloniae Pharmaceutica -Drug Research, 2007; 64 (5): 407-11.

30. Heda, A.; Sonawane, A.; Naranje, G.; Puranik, P., A rapid determination of cinnarizine in bulk and pharmaceutical dosage form by LC. Journal of Chemistry, 2010; 7 (3); 1080-1084.
31. 31. El-Houssini, O. M.; Zawilla, N. H.; Mohammad, M. A., Development and Validation of Rp-Lc Method for the Determination of cinnarizine/piracetam and cinnarizine/Heptaminol Acefyllinate in presence of cinnarizine Reported Degradation products. Analytical chemistry insights, 2013; 8 (1): 99-106.
32. Kumari, S.; Naga, S., Validated RP-HPLC method for simultaneous estimation of Cinnarizine and Domperidone in bulk and pharmaceutical dosage form. Journal of Pharmacuitical and Scientific Innovation, 2013; 2 (2): 46-50.
33. Prahalad, R.; Rao, R. N.; Konam, K.; Edara, S. R.; Rathna, T., Method development and validation for the simultaneous estimation Of domperidone maleate and cinnarizine in a pharmaceutical formulation by Rp-Hplc method. Indo American Journal of Pharmaceutical Research, 2013; 3 (10): 8111-8120.
34. Chauhan, R. J.; Master, S. M.; Pasha, T.; Thakor, K. A.; Patel, P. U., Development and validation of RP-HPLC method for simultaneous estimation of cinnarizine and paracetamol in their pharmaceutical dosage form. International Bulletin of Drug Research, 2014; 4 (7): 41-52.
35. Kalyankar, T.; Kulkarni, P.; Panchakshari, P.; Narute, A., Simultaneous RP-HPLC estimation of Cinnarizine and Domperidone in Tablet. Research Journal of Pharmacy and Technology, 2014; 7 (6): 650-654.
36. Sunitha, K. S. P., Method development and validation for simultaneous estimation of domperidone maleate and cinnarizine by RP-HPLC. International Journalof Pharmacy and Analytical Research, 2015; 4 (2): 183-192.
37. Lamie, N. T.; Monir, H. H., Simultaneous determination of cinnarizine and dimenhydrinate in binary mixture using chromatographic methods. Journal of chromatographic science, 2016; 54 (1): 36-42.
38. Ahmed, A. B.; Abdelwahab, N. S.; Abdelrahman, M. M.; Salama, F. M., Simultaneous determination of Dimenhydrinate, Cinnarizine and Cinnarizine impurity by TLC and HPLC chromatographic methods. Bulletin of Faculty of Pharmacy, Cairo University, 2017; 55 (1): 163–169.
39. Mahrouse, M. A.; El-Zaher, A. A.; Al-Ghani, A. M., Validated Chromatographic Methods for Simultaneous Estimation of Cinnarizine in Binary Mixture with

Domperidone and Paracetamol in Tablets. Current Pharmaceutical Analysis, 2019; 15 (5): 429-438.

40. Argekar, A.; Powar, S., Simultaneous HPTLC determination of cinnarizine and domperidone maleate in formulations. JPC. Journal of planar chromatography, modern TLC, 1999; 12 (4): 272-274.
41. Bagade, S.; Walode, S.; Charde, M.; Tajne, M.; Kasture, A., Simultaneous HPTLC estimation of cinnarizine and domperidone in their combined dose tablet. Asian Journal of Chemistry, 2005; 17 (2): 1116-1126.
42. El-Kafrawy, D. S.; Belal, T. S., Validated HPTLC method for the simultaneous determination of cinnarizine and dimenhydrinate in their combined dosage form. Journal of the Association of Arab Universities for Basic and Applied Sciences, 2016; 19 (1): 15-22.
43. Shirode, A. R.; Ghuge, A. D.; Kadam, V. J., HPTLC method development and validation of cinnarizine in bulk and marketed formulation. International Journal of Pharmaceutical Sciences and Research, 2016; 7 (6): 2416-2422.
44. Abdelal, A.; Kitagawa, S.; Ohtani, H.; El-Enany, N.; Belal, F.; Walash, M., Method development and validation for the simultaneous determination of cinnarizine and co-formulated drugs in pharmaceutical preparations by capillary electrophoresis. Journal of pharmaceutical and biomedical analysis, 2008; 46 (3): 491-497.
45. Metwally, F. H.; Elzeany, B.; Darwish, H., New methods for determination of cinnarizine in mixture with piracetam by spectrodensitometry, spectrophotometry, and liquid chromatography. Journal of AOAC International, 2005; 88 (6): 1666-1676.
46. Navaneethan, G.; Karunakaran, K.; Elango, K., Stability indicating and simultaneous determination of cinnarizine and piracetam from capsule dosage form by reversed phase high performance liquid chromatography. Indian Journal of Chemical Technology, 2013; 20 (9): 323-326.
47. SM, E.-A.; MH, H., Exploring Novel Isocractic HPLC Method for Quantitative Determination of Cinnarizine and Piracetam in Their Capsule Preparations. Journal of Applied Pharmacy, 2016; 8 (3): 1-5.
48. Dinç, E.; Üstündağ, Ö., Spectophotometric quantitative resolution of hydrochlorothiazide and spironolactone in tablets by chemometric analysis methods. Il Farmaco, 2003; 58 (11): 1151-1161.
49. Ni, Y.; Gong, X., Simultaneous spectrophotometric determination of mixtures of food colorants. Analytica Chimica Acta, 1997; 354 (1): 163-171.

50. Kramer, R., Chemometric techniques for quantitative analysis. CRC Press, 1998.
51. El-Gindy, A., HPLC and chemometric assisted spectrophotometric methods for simultaneous determination of diprophylline, phenobarbitone and papaverine hydrochloride. Il Farmaco, 2005; 60 (9): 745-753.