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SIMULTANEOUS DETERMINATION OF CHLORPHENIRAMINE MALEATE, PHENYLEPHRINE HYDROCHLORIDE, PARACETAMOL AND CAFFEINE IN PHARMACEUTICAL PREPARATION BY RP-HPLC

A reversed-phase High-Performance Liquid-Chromatography (RP-HPLC) method was successfully developed for the simultaneous determination of quaternary mixture consisting of chlorpheniramine maleate (CPM), phenylephrine hydrochloride (PE), paracetamol (PCM) and caffeine in pharmaceutical preparation. The method was found to be simple, sensitive and rapid. The separation of the drugs was carried out using an Inertsil ODS C_{18} column using 0.05M dibasic phosphate buffer: acetonitrile (93: 07; v/v) as the mobile phase. The flow rate of the mobile phase was adjusted to 1.5 ml/min and the column oven temperature was kept at 30 °C. All the drugs were resolved successfully with retention times 2.74 (CPM), 3.48 (PE), 9.5 (PCM) and 26.32 (caffeine) min when detection was carried out at 215 nm. The correlation coefficient was found to be 0.999, 0.998, 0.999 and 0.999, respectively for CPM, PE, PCM and caffeine. The relative standard deviation in the tablets was found to be less than 2% for six replicates. The method was validated for precision and accuracy. Thus, the proposed method can be successfully applicable to the pharmaceutical preparation containing the above mentioned drugs without any interference of excipients.

Keywords: chlorpheniramine maleate, phenylephrine hydrochloride, paracetamol, caffeine, RP-HPLC.

Chlorpheniramine maleate (CPM), 3-(*p*-chlorophenyl)-3-(2-pyridyl)-*N*,*N*-dimethyl propylamine ($C_{16}H_{19}ClN_2$, $C_4H_4O_4$), is a powerful first-generation alkyl amine antihistamine, H_1-receptor antagonist, widely used for symptomatic relief of common cold and allergic rhinitis, with weak sedative properties [1]. Phenylephrine hydrochloride (PE), (*R*)-1-(3-hydroxyphenyl)-2-methylaminoethanol hydrochloride ($C_9H_{13}NO_2$, HCl) is useful as a nasal and sinus decongestant [2]. Paracetamol (PCM), acetaminophen, 4--hydroxyacetanilide ($C_8H_9NO_2$), is a popular over-the-counter non-opiate, non-salicylate, analgesic and antipyretic drug. Addition of PCM to NSAID is well tolerated and effective in the treatment of osteoarthritis flare pain because of synergistic analgesic effect [3]. Caffeine, 3,7-dihydro-1,3,7-trimethyl-1*H*-purine-2,6-dione ($C_8H_{10}N_4O_2$), is ranked as the number one drug worldwide and is usually employed as central nervous system stimulant. Along with PCM, its effectiveness as an analgesic and antipyretic in pharmaceutical formulation is well established [4].

High Performance Liquid Chromatography (HPLC) has been highly used in the quality control of drugs because of its sensitivity, reproducibility and specificity. Even though HPLC is the method of choice for analysis of multi-component pharmaceutical preparation, it requires a separation treatment and several injections during analysis. In chromatographic analysis, the main problem of this method involves the optimization of experimental conditions such as se-

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lection of column type, temperature of the column, variety and composition of the mobile phase, selection of specific wavelength and cheap instrumenttation. In spite of the fact that this method undoubtedly provides more sensitive determination than the spectrophotometric methods, Reversed Phase Chromatography (RPC) is effective, reproducible and rugged and often easier for UV detectors. It has now become the method of choice for most of drug and combinations of drugs [5,6].

Literature survey shows that several HPLC methods have been reported for PCM and its combinations in pharmaceuticals or in biological fluids. Most of them are used for the determination of binary combinations like PCM-CPM [7,8] or ternary combinations like PCM-caffeine-codeine [9], PCM-caffeine-propylphenazone [10], PCM-caffeine-CPM [11] and PCM-aspirin-caffeine [12]. Various methods have been reported for estimation of CPM and PE combinations in pharmaceuticals by HPLC [13-21]. Few HPLC methods have been reported for the estimation of caffeine in combination like PCM, caffeine and dipyrone [22].

Several spectrophotometric methods have also been reported for the estimation of CPM and PE combinations [2,13,23]. Capillary electrophoresis methods have been reported for the estimation of PCM, CPM and PE combination [21], methods for determination of PCM, caffeine, pseudoephedrine, CPM and cloperastine in human plasma by LC-MS [24] and H-point standard addition method for the estimation of PCM and caffeine [25] have been reported.

Motivated by the aforementioned findings, it was thought to estimate quaternary mixture of PCM, CPM, PE and caffeine by RP-HPLC as no RP-HPLC method is reported for combination of all these four drugs. Since these drugs in combination are accepted widely in respiratory tract infections, there is need to develop and validate analytical methods for their determination in dosage form. Thus, an attempt has made to develop and validate HPLC method for the estimation of PCM, CPM, PE and caffeine from the tablet formulation.

EXPERIMENTAL

Materials and reagents

CPM, PE, PCM and caffeine were kindly supplied by Plethico Pharmaceuticals Ltd. (India). Acetonitrile (HPLC grade) was obtained from Rankem, India. Methanol (HPLC grade) and potassium dihydrogen phosphate (A. R. grade) were obtained from Merck Mumbai, India, and used as obtained. Water was deionised and double distilled. Pharmaceutical dosage form containing CPM, PE, PCM and caffeine was obtained commercially. Each tablet was labelled to contain 4 mg CPM, 5 mg PE, 500 mg PCM and 30 mg caffeine.

Equipment and chromatographic conditions

The HPLC consisted of a degasser DGU-20 A5, pump LC-20 AT, oven CTO-10 ASVP, SPD M-20A photo diode array detector and a SIL-M 20AC prominence auto sampler with data processor LC solution (Shimadzu, Japan). All pH measurements were performed on a µ pH System 362 (Systronics, India). Chromatographic separation was carried isocratically at room temperature with an Inertsil ODS C_{18} (250 mm×4mm i.d., 5 µm) column from G. L. Sciences Inc., Japan. Mobile phase was prepared by dissolving 6.8 g of potassium dihydrogen phosphate in 1000 ml of double-distilled water. The buffer solution was sonicated for 10 min and finally the volume was fulfilled up to 1000 ml with the same solvent. The pH of the dibasic phosphate buffer was adjusted to 4.0 with ortho-phosphoric acid. A mixture of 0.05 M dibasic phosphate buffer and acetonitrile in the ratio of 93:07 was prepared. Finally, the mobile phase was filtered through a 0.45 µm membrane filter and degassed for 10 minutes. The injection volumes for samples and standards were 20 µl and eluted at a flow rate of 1.5 ml/min at 30 °C. The eluents were monitored at 215 nm.

Preparation of standard solutions

A working standard solution containing CPM 4 µg/ml, PE 5 µg/ml, PCM 500 µg/ml and caffeine 30 µg/ml was prepared by dissolving CPM, PE, PCM and caffeine reference standard in diluents (acetonitrile:buffer, 50:50v/v). The mixture was sonicated for 15 min or until the reference standard dissolved completely.

Preparation of sample solutions

Twenty tablets, each containing 4 mg CPM, 5 mg PE, 500 mg PCM and 30 mg caffeine are weighed accurately and powdered finely. A quantity of powder which is equivalent to 4 mg of CPM, 5 mg of PE, 500 mg of PCM and 30 mg of caffeine was weighed accurately and transferred into a 200 ml calibrated volumetric flask. About 50 ml of diluent was added and ultrasonicated for 15 min; finally the volume was adjusted to the mark. The resulting solution obtained was then filtered, through 0.45 µm filter for complete removal of particulate matter. 5 ml of the filtrate was diluted to 25 ml in the volumetric flask with the diluent for analysis.

Method validation

The proposed method was subjected to validation for various parameters like system suitability, specificity, range and linearity, accuracy, precision and robustness in accordance with International Conference on Harmonization guidelines [26]. The replicates of drugs (50 µg/ml) were carried out to assess the system suitability. It was further evaluated by analyzing the repeatability, peaks symmetry (symmetry factor), theoretical plates of the column, resolution between the peaks, tailing factor and relative retention time. The specificity of the chromatographic method was determined to ensure separation of CPM, PE, PCM and caffeine. Specificity was also determined in the presence of excipients used in formulation, CPM, PE, PCM and caffeine was spiked (at a concentration of 4 µg/ml CPM, 5 µg/ml PE, 500 µg/ml PCM and 30 µg/ml caffeine) in placebo and chromatogram was observed and compared with that of reference standard. A PDA detector was used to check the peak purity.

The linearity is important to demonstrate that the response of the measurement of detector system is linear over the range of interest of the method. This was determined by means of calibration graph using increasing amounts of a standard solution (80, 90, 100, 110 and 120%) of all four drugs. Six replicates of the standard were tested according to ICH guidelines. A calibration curve was constructed and the proposed method was evaluated by its correlation coefficient and intercept value (ANOVA, $p < 0.05$). The correlation co-efficient was found within limit.

The method was validated for accuracy and precision. The accuracy of the method was studied as mean % recovery. Accuracy was determined by means of recovery experiments, by spiked addition of active drug to placebo formulations. It was shown that the recoveries were independent of the concentration of the active drug over a reasonable concentration range normally 80 to 120% of the nominal concentration. The accuracy of the assay was measured by analyzing samples of CPM, PE, PCM and caffeine, by spiking known amounts of said drugs in the placebo, at different concentration levels (*viz.* 80, 100 and 120%).

ICH guidelines recommend that precision must be considered at two levels, *i.e.*, repeatability and intermediate precision. The repeatability of the method was tested by injecting 100% concentration of four analytes of the regular analytical working value consecutively for six times and examining the effects on the results. The intermediate precision was tested with respect to laboratory variations, *i.e.*, by using different equipments, different analysts and days. The relative standard deviation (%RSD) was determined to assess the precision of the assay and it was not more than 2.0%.

Robustness studies were done by making slight variations in flow rate, amount of acetonitrile, and detection wavelength changes once at a time.

The sensitivity of the proposed method was estimated in terms of limit of detection (LOD) and limit of quantitation (LOQ); $LOD = 3.3SD/S$ and $LOQ = 10SD/S$, where SD is the residual standard deviation and S is the slope of the line. For the LOD and LOQ study, concentrations between first and second were selected. The concentrations between 3.2-3.6, 4 -4.4, 400-450, 24-27 µg/ml were prepared of CPM, PE, PCM and caffeine respectively.

RESULTS AND DISCUSSION

Quality control of drugs or drug products is of prime importance. HPLC methods are used routinely for the quantitation of drug substances. The goal of this study was to develop a rapid, sensitive, accurate, precise and reliable HPLC method for the analysis of CPM, PE, PCM and caffeine from tablets formulations using the most commonly employed C_{18} column with PDA detector.

Methods development and optimization

This isocratic-mode method with PDA detection was developed for the determination of the active ingredients, CPM, PE, PCM and caffeine at 100% level. Firstly, the reversed-phase column was tested. The column gives very efficient and reproducible separation of the components while minimizing solvent usage. Consequently, it was selected for the method development. The system suitability studies were carried out as specified in ICH guidelines.

The mobile phase consisted of dibasic phosphate buffer solution and acetonitrile at various ratios (80:20, 85:15, 90:10 and 93:07, v/v) was tested as starting solvent. The variation in the mobile phase leads to considerable changes in the chromategraphic parameters. However, the proportion buffer: acetonitrile at a ratio of 93:07 (v/v) yielded the best results.

For studying the effect of excipients on quantification of CPM, PE, PCM and caffeine, a placebo was analysed. The result obtained indicates that excipients have no interference. Based on the highest UV absorbance for CPM, PE, PCM and caffeine, 215 nm was chosen for detection of this new HPLC method at which the best detector responses for all substances were obtained. The overlaid UV spectrum is shown in Figure 1.

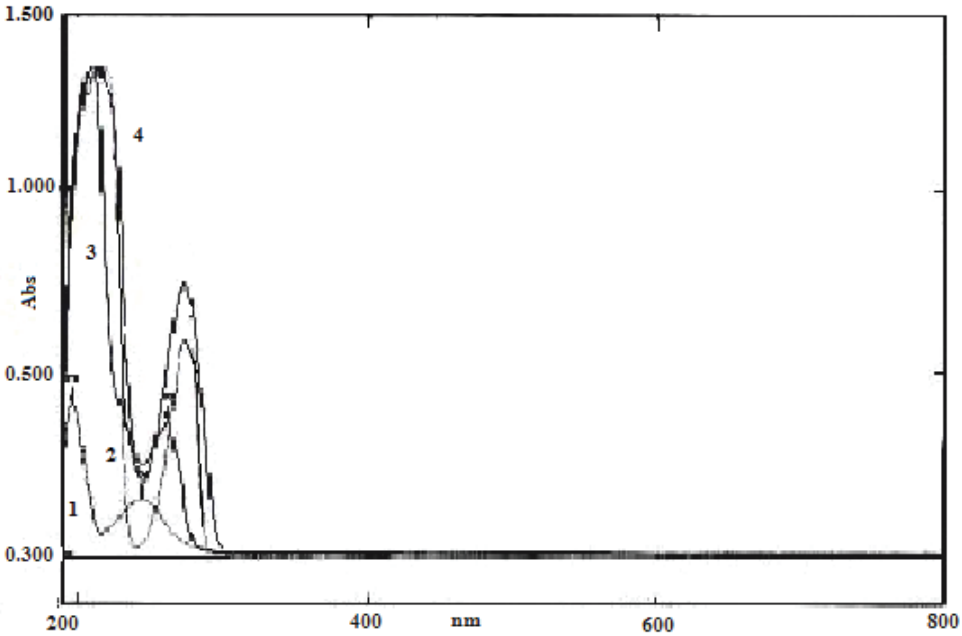

Figure 1. Overlaid UV spectra of CPM (1), PE (2), PCM (3) and caffeine (4).

Method validation

System suitability testing

The results obtained for system suitability are summarized in Table 1 and the values are found within the limits. System suitability test are an integral part of chromatographic methods and are used to verify that the resolution and reproducibility of the system are adequate for the analysis to be performed.

Range and linearity

The range of an analytical method is the interval between analytical concentration for upper and lower limit of a sample where the method has shown to demonstrate acceptable accuracy, precision and linearity. The linearity of the method was observed in the expected concentration range demonstrating its suitability for analysis. The calibration curves were constructed with five concentrations (Figure 2). The regression statistics are shown in Table 2. The goodness-of-fit (r^2) was found to be > 0.999 and value of intercept was less than 2% of the response of 100% concentration in all the cases indicating functional linear relationship between the concentration of analyte and area under the peak.

Accuracy

The accuracy was evaluated by the recovery of CPM, PE, PCM and caffeine at three different levels (80, 100 and 120%). The results of accuracy studies are shown in Table 3. Recoveries of CPM, PE, PCM and caffeine were 99.38-101.48%, 100.29-101.68%, 100.65-101.29% and 98.74-100.25%, respectively, with coefficients of variation ranging from 0.10%-0.29%, 0.34%-0.85%, 0.21%-0.24% and 0.09%-0.13%, respectively. Therefore, it is evident that the method is accurate within the desired range.

Precision

The precision of this method was determined by intra-day and inter-day precision. It was expressed as %RSD of a series of measurement. The experimental values obtained for the repeatability of CPM, PE, PCM and caffeine in samples are presented in Table 4. The obtained results show %RSD < 2, indicating good intra-day precision. Inter-day variability was also calculated by performing the assay on two days, and the mean %RSD was < 2 (Table 5). All the data obtained were within the acceptance criteria.

Table 1. System suitability parameters

Parameter	Chlorpheniramine	Phenylephrine	Paracetamol	Caffeine
Theoretical plates (*N*)	2474	6351	11966	15141
Resolution (*Rs*)	7.9	5.6	23.2	28.0
Tailing factor (*T*)	1.31	1.23	1.12	1.03
Retention time (*Rt* / min)	2.74	3.48	9.5	26.32

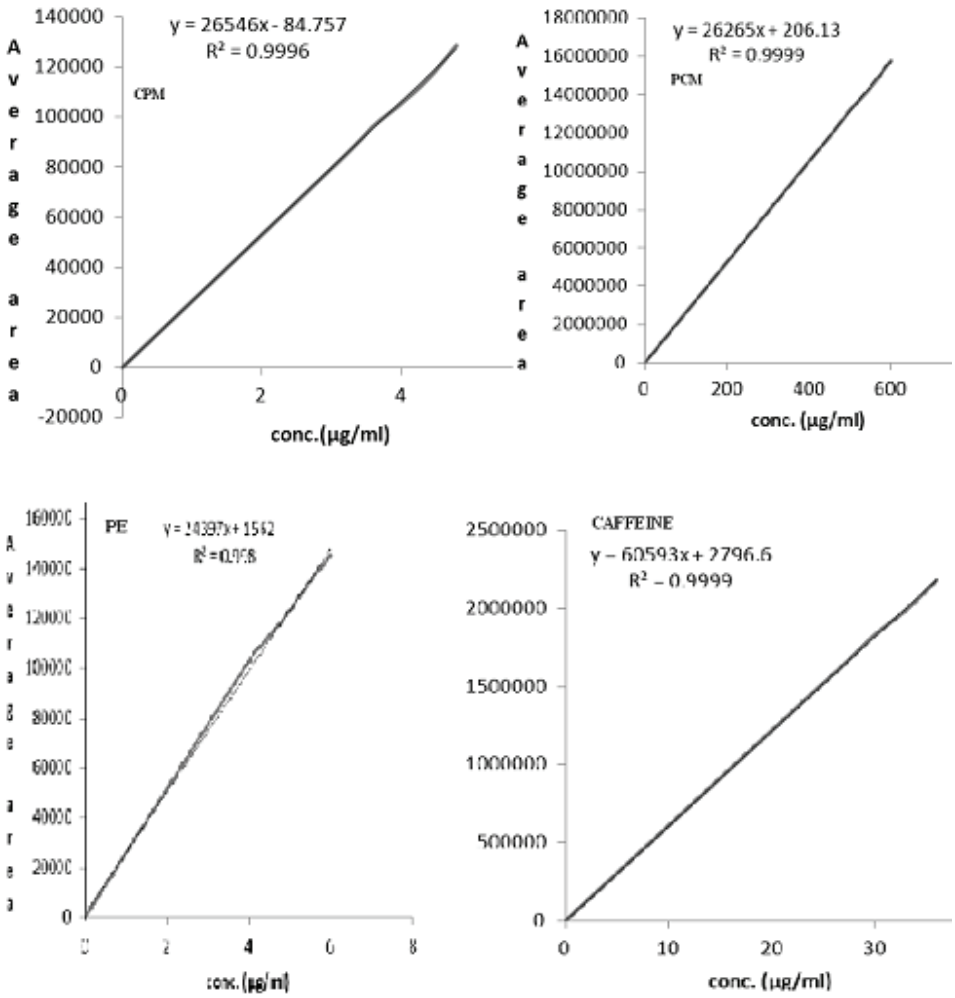

Figure 2. Calibration curves for CPM, PE, PCM and caffeine showing linearity.

Table 2. Linearity study data

Parameter	CPM	PE	PCM	Caffeine
Linearity range, µg/ml	3.2-4.8	4-6	400-600	24-36
Regression equation	$y = 1061.8x - 84.76$	$y = 1219.9x + 1562.3$	$y = 131327x + 206.1$	$y = 18178x + 2796.6$
Correlation coefficient (r^2)	0.999	0.998	0.999	0.999

Table 3. Recovery study data; SD - standard deviation; RSD - the relative standard deviation

Drugs	Amount added, %	Amount added, mg	Amount recovery, mg	Amount recovery±SD, %	Mean recovery, %	%RSD
CPM	80	3.3	3.35	101.48±0.30	100.43	0.29
	100	4.2	4.17	99.38±0.20		0.20
	120	4.7	4.72	100.45±0.10		0.10
PE	80	3.8	3.86	101.68±0.86	101.29	0.85
	100	5.3	5.40	101.91±0.89		0.87
	120	5.9	5.92	100.29±0.34		0.34
PCM	80	403.5	405.17	100.66±0.24	100.87	0.24
	100	509.1	512.4	100.65±0.21		0.21
	120	610.1	618.09	101.29±0.21		0.21
Caffeine	80	23.5	23.08	98.74±0.13	99.48	0.13
	100	30.1	30.17	100.25±0.22		0.22
	120	36.4	36.20	99.45±0.09		0.09

Table 4. Repeatability; SD - standard deviation; RSD - the relative standard deviation

Drug	Mean area[a]±SD	%RSD
Chlorpheniramine	102845±246	0.24
Phenylephrine	120491±163	0.14
Paracetamol	12607302±9251	0.07
Caffeine	1812047±813	0.04

[a]Average of six determinations

Table 5. Intermediate precision

Inter-day				
Sample	Day 1		Day 2	
Drugs	Mean Area±SD	% RSD	Mean Area±SD	% RSD
CPM	103071±166	0.16	102834±249	0.24
PE	120501±314	0.26	119532±508	0.43
PCM	12579873±30798	0.24	12621530±49616	0.39
Caffeine	1813174±2037	0.11	1809529±2138	0.12
Different Instruments				
Sample	Instrument 1		Instrument 2	
Drugs	Mean Area±SD	% RSD	Mean Area±SD	% RSD
CPM	103071±166	0.16	103034±437	0.42
PE	120501±314	0.26	120518±555	0.46
PCM	12579873±30798	0.24	12622959±25363	0.20
Caffeine	1813174±2037	0.11	1813367±1953	0.11
Different Analysts				
Sample	Analyst 1		Analyst 2	
Drugs	Mean Area±SD	% RSD	Mean Area±SD	% RSD
CPM	103071±166	0.16	102895±112	0.11
PE	120501±314	0.26	120386±504	0.42
PCM	12579873±30798	0.24	12590144±20324	0.16
Caffeine	1813174±2037	0.11	1810949±4450	0.25

Specificity

For determining the specificity of the method for drug formulation, the drug was spiked, wherein the excipients used in different formulation products did not interfere with the drug peak and thus the method was found to be specific for CPM, PE, PCM and caffeine (Figure 3). The present method demonstrates good resolution between the peaks and was found to be free of interference.

Robustness of method

To evaluate robustness, various parameters were deliberately varied. The parameters Include variation of flow rate, percentage of ACN, detection wavelength, column etc. using 4, 5, 500 and 30 mg of CPM, PE, PCM and caffeine, respectively. Results are shown in Table 6.

Sensitivity

The sensitivity of method is described in terms of *LOD* and *LOQ*. The *LOD* were 0.29, 0.41, 38, 2.4 and *LOQ* were 0.4, 0.51, 49, and 3.3 for CPM, PE, PCM and caffeine, respectively.

Label claim recoveries from tablets

The proposed method was evaluated in the assay of commercially available tablets containing CPM (4 mg), PE (5 mg), PCM (500 mg) and caffeine (30 mg). Six replicate determinations (n = 6) were carried out on an accurately weighted amount of the pulverized tablets equivalent to 4 mg of CPM, 5 mg of PE, 500 mg of PCM and 30 mg of caffeine. The label claim found is shown in Table 7. The chromatogram of the sample is shown in Figure 4.

CONCLUSION

A reversed-phase HPLC method was developed and validated for the simultaneous determination of CPM, PE, PCM and caffeine and proved to be more convenient and effective for the quality control of these drugs in pharmaceutical dosage forms. The me-

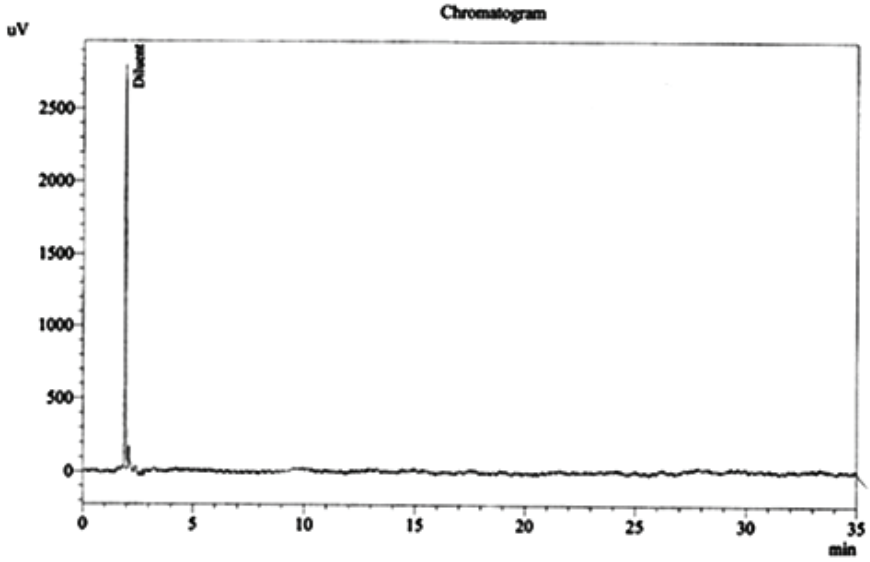

Figure 3. Chromatogram of placebo solution showing no interference.

Table 6. Robustness of method

Parameter	Variation	CPM (RT)	PE (RT)	PCM (RT)	Caffeine (RT)
Flow rate	1.4	2.94	3.70	10.17	28.08
	1.6	5.56	3.21	8.77	23.90
Mobile Phase	92:8	2.67	3.16	8.15	19.85
Composition	94:6	2.82	3.28	11.07	34.53
Wavelength	210	2.74	3.46	9.5	26.35
	220	2.74	3.46	9.5	26.35

Table 7. Assay of tablet formulation; SD - standard deviation

Component	Labeled amount, mg	Amount found, mean[a]±SD, mg	Amount found, mean±SD, %
Chlorpheniramine	4	4.02±0.01	100.51±0.24
Phenylephrine	5	4.99±0.01	99.87±0.14
Paracetamol	500	508.37±0.37	101.67±0.075
Caffeine	30	29.82±0.02	99.39±0.05

[a]Average of six determinations

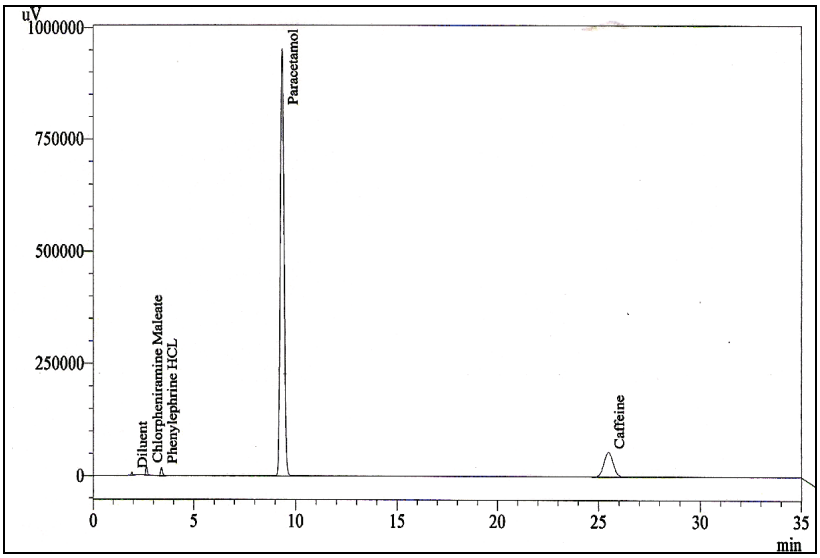

Figure 4. Typical chromatogram of sample.

thod is found to be simple, precise, accurate, specific, selective and linear over the concentration range tested (80-120%) with a correlation coefficient better than 0.9991. The good percentage recovery in tablet dosage forms suggests that the excipients present in the dosage forms have no interference in the determination. The percent RSD was also less than 2% showing high degree of precision of the proposed method. So, the method is suitable for the determination of the drugs in tablets without interference from commonly used excipients, and could be used in a quality control laboratory for routine sample analysis.

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REFERENCES

[1] D.M. Paton, D.R. Webster, Clin. Pharmacokin. **10** (1983) 477

[2] I. Savic, G. Nikolic, V. Bankovic, Maced. J. Chem. Chem. Eng. **27**(2) (2008) 149-156

[3] V.G. Dongre, S.B. Shah, G.S. Bayes, M. Phadke, V.K. Jadhav, Chromatographica. **69** (2009) 1019-1023

[4] D. Erdal, J. Pharm. Biomed. Anal. **21**(4) (1999) 723-730

[5] D. Erdal, O. Abdil, A. Halil, U. Ozgür. B. Dumitru, Chem. Pharm. Bull. **54**(4) (2006) 415-421

[6] L.R. Snyder, J.J. Kirkland, J.L. Glajch, Practical HPLC Method Development, 2nd ed., Wiley-Interscience, Hoboken, 1997, p. 234

[7] C.Celma, J.A. Allue, J. Prunaonosa, C. Peraire, R. Obach, J. Chromatogr., A **870**(1-2) (2000) 77-86

[8] L. Gasco, H.R. Izquierdo, A. Jiminez, J. Chromatogr., A **775**(1-2) (1997) 179-185

[9] K. Murat, J. Pharm. Biomed. Anal. **26**(5-6) (2001) 857-864

[10] J. Avramova, J. Pharm. Biomed. Anal. **7**(10) (1989) 1221--1224

[11] M.L. Qil, P. Wang, Y.X. Leng, J.L. Gu, R.N. Fu, Chromatographia **56**(5-6) (2002) 295

[12] H. Hashem, A. Abdel, Chromatographia **71**(1-2) (2010) 31--35

[13] N. Erka, M. Kartal, Farmaco **53** (1998) 617-622

[14] R. Heydari. Anal. Lett. **41**(6) (2008) 965-976

[15] A. Marin, E. Garcia, A. Garcia, C. Barbas, J. Pharm. Biomed. Anal. **29**(4) 701-714

[16] U.R. Cieri, J. AOAC Int. **89**(1) (2006) 53-57

[17] S.M. Amer, S.S. Abbas, M.A. Shehata, N.M. Ali, J. AOAC Int. **91**(2) (2008) 276-284

[18] C. Hamide, O. Tuncel, J. Chromatogr. Sci. **40**(2) (2002) 97--100

[19] M. Palabiyik, F. Onur, Chromatographia **66**(1) (2007) 93-96

[20] M.L. Altun, Turk. J. Chem. **26** (2002) 521-528

[21] A. Marin, C. Barbas, J. Pharm. Biomed. Anal. **35**(4) (2004) 769-777

[22] S. Dalibor, N. Isabel, S. Petr, S. Hana, M. Conceicao, BSM. Montenegro, N.A Alberto, J. Sep. Sci. **27**(7-8) (2004) 529--536

[23] M. Kazemipour, M. Ansari, Iran. J. Pharm. Res. **3** (2005) 147-153

[24] L. Hao, Z. Chao, W Jiang, J. Yao, F. Paul, G. Jingkai, J. Pharm. Biomed. Anal. **51**(3) (2010) 716-722

[25] H. Tavallali, M. Sheikhaei, afri. J. Pure Appl. Chem. **3**(1) (2009) 11-19

[26] ICH, Q2(R1), Validation of analytical procedures: Text and Methodology International Conference on Harmonization, Geneva, Switzerland, 2005.

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NAUČNI RAD

SIMULTANO ODREĐIVANJE HLORFENIRAMIN MALEATA, FENILEFRIN HIDROHLORIDA, PARACETAMOLA I KAFEINA U FARMACEUTSKIM PREPARATIMA RP-HPLC METODOM

RP-HPLC metoda je uspešno primenjena za određivanje hlorfeniramin maleata (CPM), fenilefrin hidrohlorida (PE), paracetamola (PCM) i kafeina u kvaternernoj smeši u farmaceutskim preparatima. Nađena metoda je brza, jednostavna i osetljiva. Razdvajanje ispitivanih jedinjenja je izvedeno na koloni Inertsil ODS C_{18} uz upotrebu mobilne faze fosfatni puffer:acetonitril (93:7; v/v). Protok mobilne faze je podešen na 1,5 ml/min, a temperatura kolone je održavana na 30 °C. Sva ispitivana jedinjenja su uspešno razdvojena, komponente su detektovane na 215 nm, a njihova retenciona vremena su sledeća: 2.74 (CPM), 3.48 (PE), 9.5 (PCM) i 26.32 (kafein) min. Korelacioni koeficijenti određivanja su 0,999 za CPM, 0,998 za PE, 0,999 za PCM i 0,999 za koefin. Relativna standardna devijacija za oderđivanja u tabletama je manja od 2 % za šest ponavljanja. Metoda je validirana za preciznost i tačnost. Predložena metoda se uspešno može primeniti za određivanje ispitivanih lekova u farmaceutskim preparatima bez interferencije pomoćnih supstanci.

Ključne reči: hlorfeniramin maleat, fenilefrin hidrohlorid, paracetamol, kafein, RP-HPLC.