Academic Sciences International Journal of Pharmacy and Pharmaceutical Sciences

ISSN- 0975-1491 Vol 5, Suppl 4, 2013

Research Article

NEW RAPID RP-HPLC METHOD FOR SIMULTANEOUS DETERMINATION OF SOME DECONGESTANTS AND COUGH-SEDATIVES

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Received: 21 Aug 2013, Revised and Accepted: 06 Oct 2013

ABSTRACT

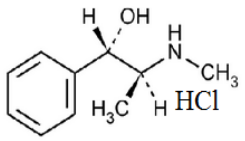
A rapid, simple, precise, and accurate method for determination of pharmaceutical preparations containing decongestants, cough-sedatives and antihistamine drugs as paracetamol (PAR), pseudoephedrine hydrochloride (PSH), chlorpheniramine maleate (CPM) and dextromethorphan hydrobromide (DEX) using chlordiazepoxide (CDZ) as internal standard (IS) through 5.4min using a photo-diode array detector at 203nm was developed. Separation was achieved on a BDS Hypersil column C_{18} (250×4.6mm i.d, 5µm) using a mobile phase consisting of acetonitrile/water (60/40, *v/v*), water is containing sodium dodecyl sulfate and triethylamine hydrochloride, pH=2.5 with 0.01M orthophosphoric acid and 0.01M potassium dihydrogenphosphate with flow rate 1.0 mL/min. This new method is validated according USP. Linearity range of concentration was 20-2000, 6-2400, 2-160 and 15-1200µg/mL with (R^2 >0.9991) for PAR, PSH, CPM, and DEX, respectively, and recovery was of 97.0–102.4%, (*n=5*). Limits of detection (LODs) of 0.33, 0.09, 0.12 and 0.03µg/mL, and limits of quantification (LOQs) of 1.10, 0.30, 0.40 and 0.10µg/mL for PAR, PSH, CPM and DEX, respectively. The proposed RP-HPLC method was successfully applied for the determination of these compounds in different pharmaceutical preparations with no interference from the excipients.

Keywords: Paracetamol; Pseudoephedrine hydrochloride; Chlorpheniramine maleate; Dextromethorphan hydrobromide; Decongestants; Cough-sedatives; RP-HPLC.

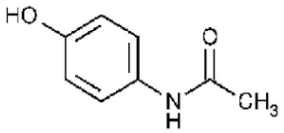
INTRODUCTION

Pseudoephedrine hydrochloride (PSH), dextromethorphan hydrobromide (DEX), chlorphenamine maleate (CPM) and paracetamol (PAR) are effective components in cold curing medicines and a combination of them is used in pharmaceutical preparations for reducing symptoms which are usually associated with the common cold. PAR is one of the major metabolic products of phenacetin and acetanilide, and is widely used to cure the fever, the headache and neuralgia, etc. PSH has the function of constringing the blood vessel, eliminating mucous membrane congesting and tumefying of nasopharynx, alleviating symptom of the nasal congestion. DEX can ease pain of centrum, being applicable for cold, acute and chronic bronchitis, bronchus asthma, tuberculosis, etc. CPM is anantihistamine, used for the allergic disease [1-2-3]. In this respect, an analytical method is needed for the determination of this combination. The structure of these compounds with chlordiazepoxide are shown scheme 1.

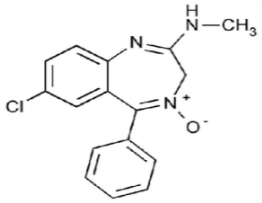
Several methods have been employed to determination of these compounds in pure form and pharmaceutical formulations such as normal-phase HPLC [3] and ion-pair HPLC [4]. High performance liquid chromatography (HPLC) is one of the most useful techniques for the quantification of some of the four compounds and others are also employed to separation a combination of three or two from these compounds with another drugs, but the using of HPLC in these methods is restricted by long analysis times, peak asymmetry and poor efficiency [4-7]. Many chromatographic methods are also employed to separation a combination of three or two from these compounds with another drugs [8-11].



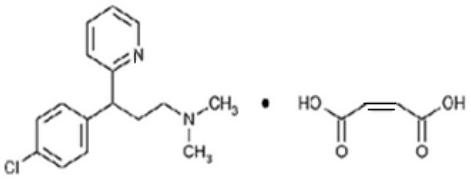
(PSH)



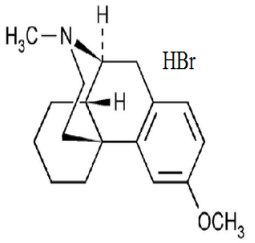
(PAR)



(CDZ)



(CPM)



(DEX)

Scheme 1: The chemical structures of Pseudoephedrine hydrochloride (PSH), Paracetamol (PAR), Chlordiazepoxide (CDZ), Chlorpheniramine maleate (CPM) and Dextromethorphan hydrobromide (DEX)

Separation and determination of the four compounds completed by flow injection-capillary electrophoresis [12]. PSH, DEX and CPM have been separated and determined by nonaqueous capillary electrophoresis (NACE) [13]. PSH, DEX and PAR have been analysed by CZE (capillary zone electrophoresis) [14-15]. Second-derivative photodiode method was suggested for simultaneous determination of PSH, DEX and CPM in tablet preparations [16]. Finally, many spectrophotometric and derivative spectrophotometry methods were employed to separation and determination a combination from these compounds [17-19]. Gas liquid chromatography have also

been reported for the determination some of these analytes [20, 21]. These methods usually require complicated pretreatment procedures prior to analysis.

Aim of this study was to develop a new, rapid, accurate and selective isocratic HPLC method for the simultaneous determination of four of the most commonly used active ingredients found in cough and cold medicines (PSH, DEX, CPM and PAR) as well as the preservatives and excipients in the presence of other recipients during a short time and high sensitivity.

MATERIALS AND METHODS

Reagents and chemicals

Chlorpheniramine maleate from Supriya Lifescience Ltd (Maharashtra, India); dextromethorphan hydrobromide from Divi's Laboratories Limited (India); pseudoephedrine hydrochloride from Cheng Fong Chemical Co., Ltd (Dayuan Township, Taiwan) and paracetamol from Hebei Jiheng (Group) Pharmaceutical Co., Ltd (Hengshui City, China). The internal standard, chlordiazepoxide, was obtained from Centaur Pharmaceuticals PVT. HPLC grade acetonitrile (ACN) was obtained from Scharlau Scharlab S.L (Spain).Analytical grade potassium dihydrogenphosphate, orthophosphoric acid (85%, *w/w*) and potassium hydroxide were obtained from Merck (Darmstadt, Germany). Analytical reagent grade triethylamine hydrochloride (TEA), triethylamine solution (TEAs) and sodium dodecyl sulfate (SDS) from Surechem Products Ltd. Water used was deionized and passed through Milli Q system, Milli pore, USA.

HPLC System and Chromatographic conditions

Chromatographic System consisted of Hitachi (Japan) model L-2000 equipped with a binary pump (model L-2130, flow rate range of 0.000-9.999mL/min), degasser and a column oven (model L-2350, temperature range of 1-85°C). All samples were injected (10µL) using a Hitachi L-2200 autosampler (injection volume range of 0.1-100µL). Elutions of all analytes were monitored at 203nm by using a Hitachi L-2455 photo-diode array detector (190-900nm) containing a quartz flow cell (10mm path and 13µL volume). Each chromatogram was analyzed and integrated automatically using the Ezchrom Elite Hitachi Software. Separation was achieved on BDS Hypersil column C_{18} (250mm length, 4.6mm inner diameter, 5µm particle size) from Thermo Scientific Company. Mobile phase was a mixture of a acetonitrile and aqueous phosphate buffer solution (0.01M, pH=2.5) 60/40 *v/v*, respectively. Mobile phase was filtered and degassed by ultrasonic agitation before use. Flow rate was 1.0mL/min. The system was operated at 25°C.

Standard solutions

Phosphate buffer was prepared by dissolving 1.36g of potassium dihydrogen phosphate and 0.8mL of orthophosphoric acid (85%, *w/w*, d=1.71kg/L) in 1000mL of distilled water contains a 1.00g of sodium dodecyl sulfate (SDS) and 0.6g of triethylamine hydrochloride (TEA). A filtered and degassed mixture of acetonitrile and buffer (60/40, *v/v*) was employed as a mobile phase at a flow rate of 1.0mL/min and a detection wavelength of 203nm. Stock standard solution was prepared by dissolving 200mg of PAR, 200mg of DEX, 160mg of PSH, and 160mg of CPM in 100mL of mobile phase. Nominal standard solution was prepared by diluting 10mL of stock standard solution to 100mL with mobile phase to obtain a solution having a known concentration of 0.20mg/mL of PAR and DEX and 0.16mg/mL of PSH and CPM. Internal standard solution was prepared by dissolving 50mg of CDZ in 100mL of mobile phase then 10mL internal standard solution was diluted to 100mL with mobile phase to obtain a solution having a known concentration of 0.05mg/mL of CDZ.

Assay Procedure for Dosage Forms

Pharmaceuticals of decongestants and cough-sedatives are commercialized under different presentations, such as tablets, soft gelatin capsules, suspension and syrups. 20 tablets were weighed, ground in a mortar and finally, an adequate amount of the solid equivalent the weight of one or half tablet according to the studied sample was taken and dissolved in mobile phase, using an ultrasonic bath (10min). In the case of the pharmaceutical presentations, after grinding the tablets, the powder obtained was dissolved in mobile phase. After that, the volume was diluted with mobile phase to 50mL in volumetric flask. The resulting solution was centrifuged at 5000 rpm for 5min. 10 soft gelatin capsules were completely dissolved in 50mL fifty-fifty acetonitrile and water using a magnetic stirrer with gentle heating, then an adequate volume of the solution equivalent the one or half soft gelatin capsule according to the studies was taken and diluted with mobile phase to 50mL in volumetric flask. At this stage, a precipitate could be obtained when the mobile phase is added. In this case, the solution was centrifuged and filtered before injecting into the chromatograph. Finally, in syrups and suspension, a 5mL portion of every sample was transferred into a 50mL volumetric flask and volume was completed with mobile phase.

In all cases, after the appropriated dilution with mobile phase to 50mL, a suitable concentration was prepared by diluting 5mL with mobile phase to 10mL in volumetric flask containing 2mL of the internal standard (CDZ; 50µg/mL). Test solution was mixed well, cooled to room temperature, filtered through 0.45µm nylon membrane filter and 10µL was injected into the chromatographic system. Peak area ratios of PAR, PSH, CPM and DEX to that of CDZ were then measured for the determination. PAR, PSH, DEX and CPM concentrations in the samples were then calculated using peak data and standard curve. Finally, for each pharmaceutical presentation, three independent sample solutions were prepared and for each sample solution, four injections into the chromatograph were carried out (twelve injections per pharmaceutical).

RESULTS AND DISCUSSION

Optimization of the chromatographic conditions

RP-HPLC is generally more applicable for analytical pharmaceutical analysis than other types of HPLC. The columns are efficient, reproducible and stable and UV detection is easier with the solvents used. During optimization of the assay, different stationary and mobile phase compositions were evaluated for their performance in separating PAR, PSH, DEX and CPM. Different columns phenyl and C_{18} columns and several mobile phase compositions for the effective separation of the four compounds were tried. BDS Hypersil column C_{18} (250mm length, 4.6mm inner diameter, 5µm particle size) gave the minimal elution time with good resolution. It was observed that separation could not be affected by column temperature obviously, so the column temperature was set at 25°C during analysis. The effect composition of the mobile phase on the retention time of PAR, PSH, DEX and CPM was investigated. Results of acetonitrile percentage in the mobile phase are presented in figure 1. An increase in the percentage of acetonitrile decrease retention of all compounds. Increasing acetonitrile percentage to more 70% the peaks of PAR and PSH, and CPM and DEX will be overlapp, while at acetonitrile percentage lower than 50% the retention became along and the peaks are tailed. In this study, we show five peaks were result from the four studied compounds. CPM gave tow peaks, the first was shown at 2.333min, representing to group of maleate (MAL), and second at 4.533min representing to chlorpheniramine [9]. The peak of MAL did not effect on the separation of remained peaks. The five peaks are shown in figure 6.

Impact of the flow on the chromatographic elution to a combination of these materials were also change the flow values between 0.5 and 2.0mL/min. The increase in flow associated with a decrease in retention time, but also coincided with a decrease in sensitivity, and if at all remained good resolution between all peak. Results of the effect of the flow values are presented in figure 2.

Effects of pH in the chromatographic elution of the compounds was also investigated by change pH values of the aqueous component of the aqueous phosphate buffer solution, that consists of 0.01M orthophosphoric acid and potassium dihydrogenphosphate by using orthophosphoric acid solution (10%, w/w) and potassium hydroxide (10%, w/v), from 1.5 to 7.0, consequently, pH values of the mobile phase were changed from 2.7 to 8.0, respectively. A constant range of a short retention times for all compounds is defined when the pH values of mobile phase changed from 3.0 for 6.2. Result of the effect of pH values of the mobile phase are presented in figure 3.

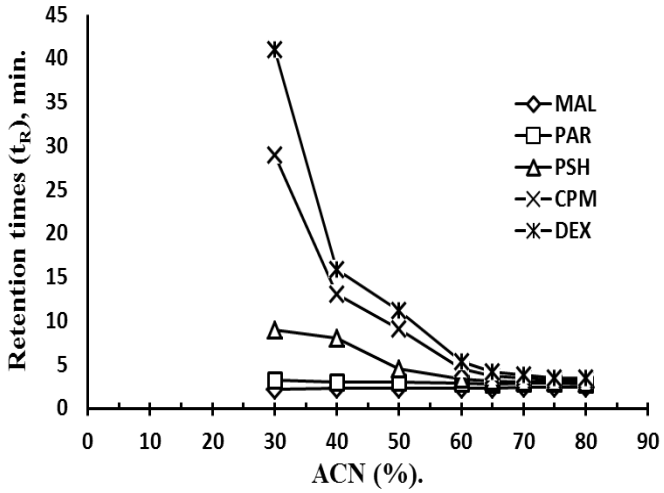


Fig. 1: Plots of retention time *vs.* acetonitrile percentage in the mobile phase of MAL, PAR, PSH, CPM and DEX.

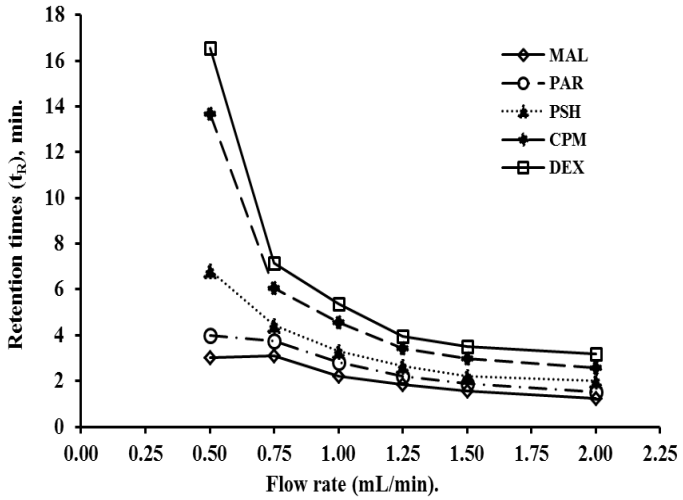


Fig. 2: Variation of the retention time of MAL, PAR, PSH, CPM and DEX with the flow rate of the mobile phase.

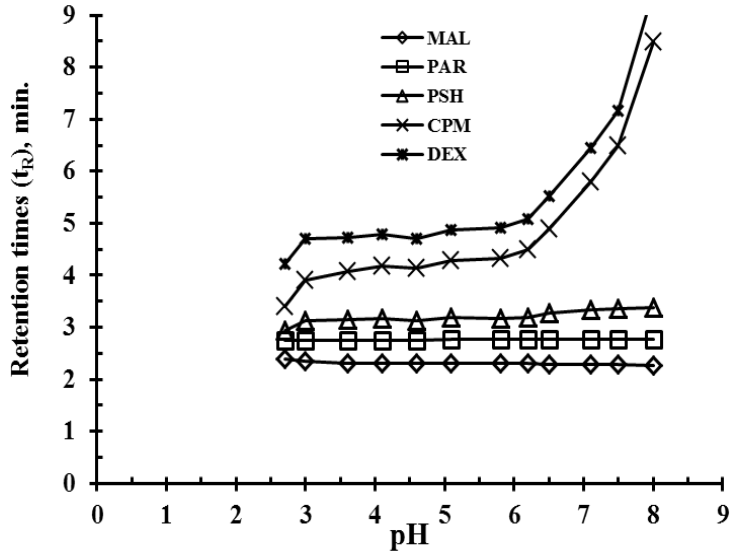


Fig. 3: Variation of the retention time of MAL, PAR, PSH, CPM and DEX with the pH of the mobile phase.

Effects of ion-pair in the chromatographic elution of the compounds; we used two ions-pair that were sodium dodecyl sulfate (SDS) and triethylamine hydrochloride (TEA). The influence of SDS completed by change the concentration of it in aqueous buffer solution, from 0.0 to 2000.00mg/L without TEA, and from 31.25 to 1800.00mg/L in presence 600mg/L of TEA. Results of an influence SDS are shown in figure 4.

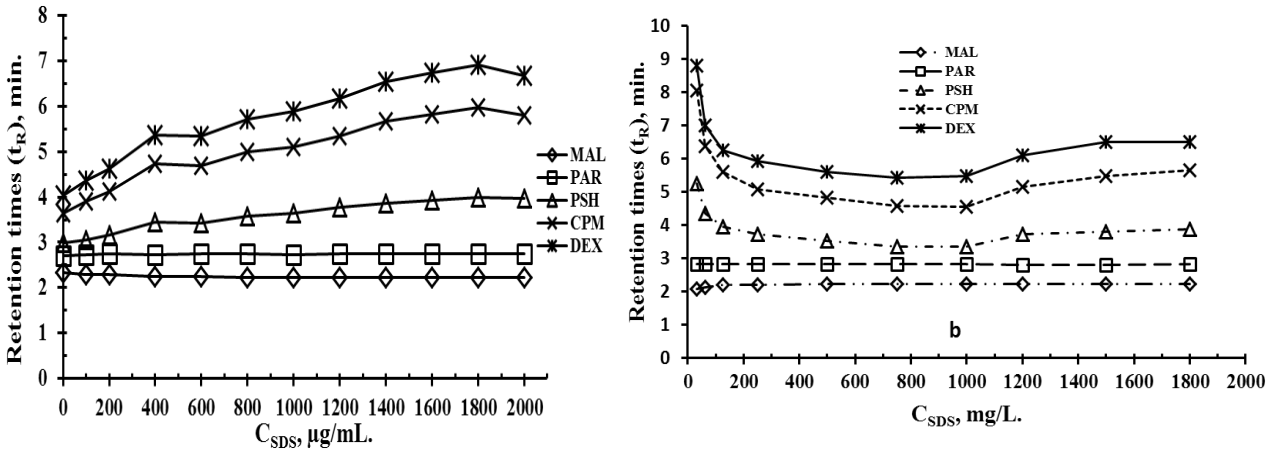


Fig. 4: Effect of SDS concentration on the separation of MAL, PAR, PSH, CPM and DEX, (a) without TEA and (b) with 600mgTEA/L.

The influence of TEA completed by change the concentration of it in aqueous buffer solution from 0.0 to 1400 mg/L without using SDS. The results of the influence TEA are shown in figure 5.

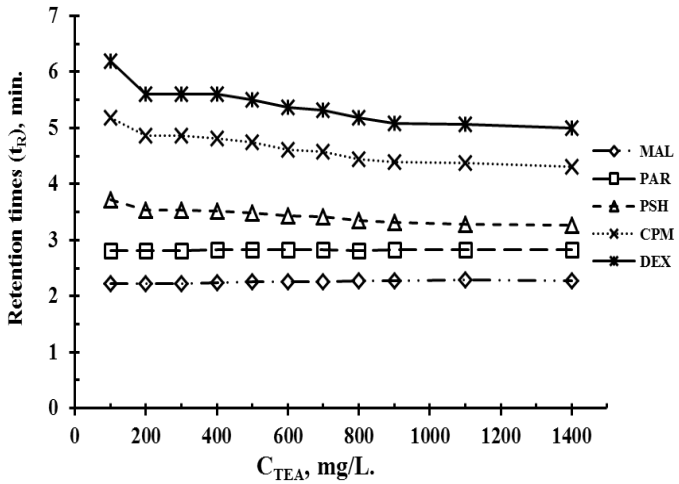


Fig. 5: Effect of TEA concentration on the separation of MAL, PAR, PSH, CPM and DEX without using SDS.

After study all preceding effects we test some other compounds to be as internal standard such as diphenhydramine hydrochloride, dipotassium clorazepate, bromocriptine mesylate, clidinium bromide, fluphenazine and chlordiazepoxide. Chlordiazepoxide has been separated at a short retention time with good resolution and shapely chromatogram that shown of figure 6 for the compounds without IS and in figure 7 for the compounds with IS.

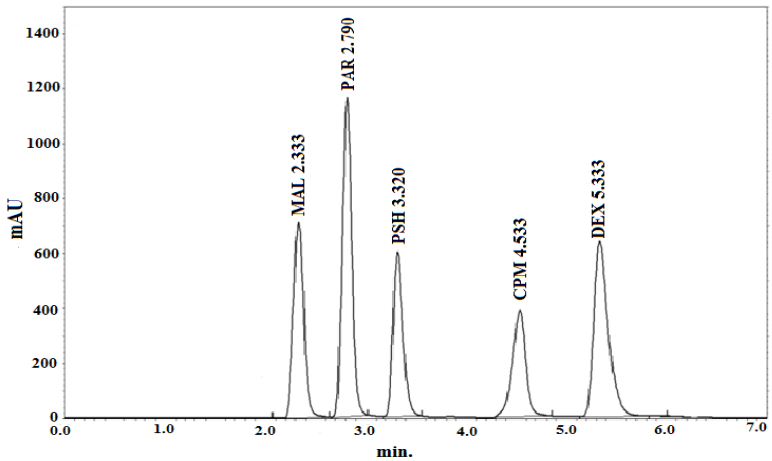


Fig. 6: A typical chromatogram of a mixture of PAR (200µg/mL), PSH, CPM (160µg/mL for every one) and DEX (200µg/mL) without using IS. Mobile phase: 60/40 (*v/v*) acetonitrile/phosphate buffer (0.01M, pH=2.5); column Hypirsel C_{18}; detector = 203nm and flow rate: 1mL/min.

A satisfactory and peak symmetry for the drug was obtained with mobile phase acetonitrile/water (containing 1.0g of sodium dodecyl sulfate and 0.6g of triethylamine hydrochloride per liter, pH=2.5 with phosphate buffer consisting of 0.01M orthophosphoric acid and potassium dihydrogenphosphate), (60/40, *v/v*) respectively, pumped at a flow rate 1.0mL/min at 25°C and a detection wavelength of 203nm afforded the best separation of these analytes. Quantitation was achieved with UV detection at 203nm for CPM and DEX, at 214nm for PSH and at 273nm for PAR based on peak area. A representative chromatogram is shown in figure 7. The retention time of 2.767, 3.333, 4.020, 4.537 and 5.341min for PAR, PSH, CDZ, CPM and DEX, respectively.

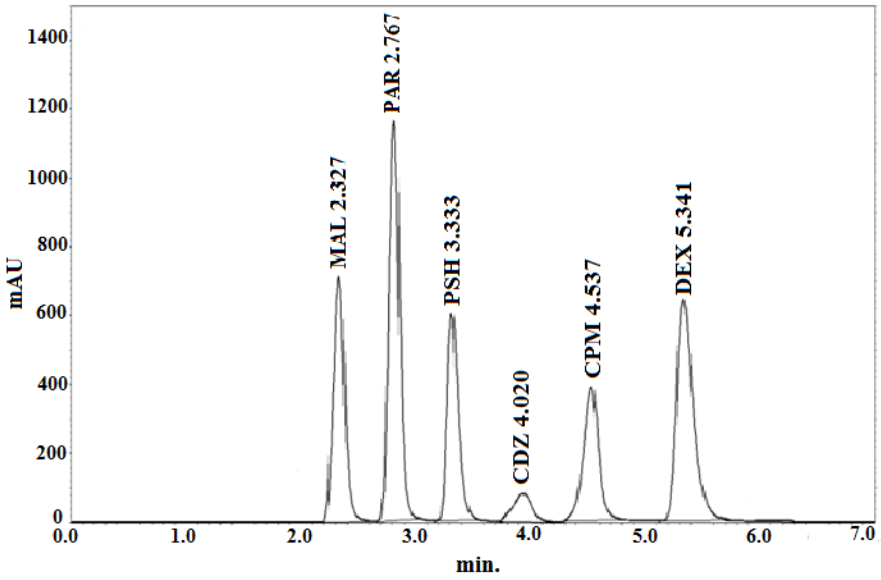


Fig. 7: A typical chromatogram of a mixture of PAR (200µg/mL), PSH, CPM (160µg/mL for every one) and DEX (200µg/mL) with using IS (CDZ, 50µg/mL). Mobile phase: (60/40 *v/v*) acetonitrile/phosphate buffer (0.01M, pH=2.5); column Hypirsel C_{18}; detector = 203nm and flow rate: 1.0mL/min.

System suitability

The system suitability requirements for PAR (200µg/mL), PSH, CPM (160µg/mL for every one) and DEX (200µg/mL) without using IS and for PAR (200µg/mL), PSH, CPM (160µg/mL for every one) and DEX (200µg/mL) in the presence IS (CDZ, 50µg/mL) has been given a RSD% for peak area less than 1.8% for all. These parameters include theoretical plates, resolution factor, tailing factor, capacity factor and RSD% are shown in table 1 for the compounds without IS and in table 2 for the compounds with IS.

Table 1: System suitability parameters for PAR (200µg/mL), PSH, CPM (160µg/mL for every one) and DEX (200µg/mL) without using IS

Parameters	Compounds without IS			
	PAR	PSH	CPM	DEX
Retention times (t_r), min.	2.790	3.320	4.533	.333
Theoretical plates (N)	4259	5497	5726	6490
Capacity factor (k')	1.790	2.320	3.533	4.333
Resolution factor (R)	2.684	2.882	5.795	3.172
Tailing factor (T)	1.059	1.224	0.949	1.364
RSD% (*n=5*)	1.3	1.0	1.6	1.8

Table 2: System suitability parameters for PAR (200µg/mL), PSH, CPM (160µg/mL for every one) and DEX (200µg/mL) in the presence IS (CDZ, 50µg/mL).

Parameters	Compounds with IS			
	PAR	PSH	CPM	DEX
Retention times (t_r), min.	2.767	3.333	4.537	5.341
Theoretical plates (N)	4212	5509	5789	6444
Capacity factor (k')	1.767	2.333	3.537	4.341
Resolution factor (R)	1.974	2.624	1.866	1.869
Tailing factor (T)	1.108	1.154	1.177	1.135
RSD% (*n=5*)	0.3	0.7	0.9	0.4

Validation

After method development, the validation of the current method has been performed in accordance with USP requirements for assay determination which include accuracy, precision, selectivity, linearity and range, robustness and ruggedness.

Linearity and limits of quantitation and detection

Calibration graph was drown in the range of 20-2000, 6-2400, 2-160 and 15-1200µg/mL of PAR at 273nm, PSH at 214nm, CPM and DEX at 203nm, respectively, solutions prepared freshly for 30 days. Curves were linear with R^2>0.9991 and characteristic parameters for regression equations and correlation coefficients were given in table 3. The minimum level at which the investigated compounds can be reliably detected (limit of detection, LOD) and quantified (limit of quantitation, LOQ) were determined experimentally. The LOD was expressed as the concentration of drug that generated a response to three times of the signal to-noise (S/N) ratio, and the LOQ was 10 times of the S/N ratio [22]. The LOD was found to be 0.33, 0.09, 0.12 and 0.03µg/mL, respectively. The LOQ was found to be 1.10, 0.30, 0.40 and 0.10µg/mL, respectively.

Accuracy and precision

The accuracy of the method was determined by analyzing standard solutions of PAR, PSH, CPM and DEX in the range 20-2000, 6-2400, 2-160 and 15-1200µg/mL, respectively. The proposed method was successfully applied for the analysis of the drugs by intra-day (analysis of standard solutions of PAR, PSH, CPM and DEX in replicates of five in the same day). The percent recoveries obtained were from 97.0 to 102.4%. The standard deviation, relative standard deviation and relative error % of different amount tested were determined from the calibration curve, as recorded in table 4.

Application of the Assay

The validity of the proposed method for the determination of PAR, PSH, CPM and DEX was assessed by measuring drugs concentration of pharmaceutical dosage forms. The results obtained with the proposed method were compared with the official method [3] and are shown in table 5. Mean values were obtained with a Student's *t*- and *F*-tests at 95% confidence limits three degrees of freedom. The results showed comparable accuracy (*t*-test) and precision (*F*-test), since the calculated values of *t*- and *F*-tests were less than the theoretical data. The values of *t*- and *F*-tests obtained at 95% confidence level did not exceed the theoretical tabulated value indicating no significant difference between the methods compared. The proposed method is simply, rapid, accurate, highly sensitive and suitable for the routine quality control without interference from excipient such as glucose, sugar, magnesium stearate, sodium benzoate, methylparaben, and starch or from common degradation products.

Table 3: Calibration data for the estimation of PAR, PSH, CPM and DEX by using CDZ as IS by HPLC

Ingredient	Concentration range (µg/mL)	Regression equation	R^2	LOD (µg/mL)	LOQ (µg/mL)
PAR	20-2000	y = 0.0134x + 0.3860	0.9993	0.33	1.10
PSH	6-2400	y = 0.0162x + 0.3853	0.9993	0.09	0.30
CPM	2-160	y = 0.0470x - 0.0418	0.9992	0.12	0.40
DEX	15-1200	y = 0.0486x + 0.3433	0.9992	0.03	0.10

Table 4: Accuracy and precision for determination of PAR, PSH, CPM and DEX by using IS by HPLC.

Ingredient	Nominal concentration (µg/mL)	Mean concentration [a] (µg/mL)	RSD%	Recovery% [b]	Relative error%
PAR	20.00	19.74	1.8	98.7	-1.3
	100.00	102.44	1.5	102.4	2.4
	400.00	409.51	1.1	102.3	2.3
	1600.00	1636.91	0.9	102.3	2.3
	2000.00	1974.42	0.6	98.7	-1.3
PSH	6.00	6.04	1.5	100.6	0.6
	30.00	29.11	1.1	97.0	-3.0
	120.00	121.38	0.8	101.1	1.1
	1200.00	1198.13	0.6	99.8	-0.2
	2400.00	2408.8	0.5	100.4	0.4
CPM	2.00	2.05	2.1	102.4	2.4
	8.00	7.77	1.8	97.1	-2.9
	40.00	39.39	1.2	98.5	-1.5
	80.00	81.58	1.0	102.0	2.0
	160.00	160.16	0.9	100.1	0.1
DEX	15.00	14.76	2.0	98.4	-1.6
	60.00	58.24	1.4	97.1	-2.9
	300.00	305.25	1.0	101.8	1.8
	600.00	602.97	1.1	100.5	0. 5
	1200.00	1188.25	0.7	99.0	1.0

[a, b] (*n=5*).

Table 5: Determination of PAR, PSH, CPM and DEX by using IS (CDZ) by HPLC in pharmaceutical dosage forms. Mobile phase: (60/40, v/v) acetonitrile/ aqueous (containing phosphate buffer (0.01M, pH=2.5), 1.0g SDS, 0.6g TEA per 1000mL); column Hypirsel C18; detector = 273nm for PAR, 214nm for PSH, 203nm for CPM and DEX, and flow rate: 1.0mL/min.

Sample	Ingredient	Labled	Mean ± SD [a]	Recovery%, (*n=5*)	t-value [b]	F-value [b]
	PAR	160mg per 5 mL	158.816 ± 1.88	99.3	0.12	3.54
Tullin-D,Oral Suspension.	PSH	15mg per 5 mL	15.016 ± 0.21	100.1	0.66	3.87
Asia (Syria)	CPM	1mg per 5 mL	0.985 ± 0.02	98.5	1.29	3.54
	DEX	7.5mg per 5 mL	7.443 ± 0.07	99.2	1.60	1.25

	PAR	160mg per 5 mL	160.889 ± 2.60	100.5	1.87	6.16
Grippe-Stop, Suspension.	PSH	15mg per 5 mL	14.973 ± 0.24	99.8	0.17	5.21
Pharmasyr (Syria)	CPM	1mg per 5 mL	1.001 ± 0.03	100.1	1.38	1.41
	DEX	7.5mg per 5 mL	7.523 ± 0.15	100.3	1.87	6.19
	PAR	325mg per gel. cap	322.669 ± 1.62	99.2	0.37	1.58
Tullin-D, Soft Gelatin Capsules.	PSH	30mg per gel. cap	29.919 ± 0.47	99.7	0.04	4.98
Asia (Syria)	CPM	2mg per gel. cap	2.034 ± 0.05	101.7	3.00	1.26
	DEX	10mg per gel. cap	9.928 ± 0.09	99.2	1.74	1.18
	PAR	325mg per tablet	322.542 ± 3.62	99.2	0.09	3.18
Balmedrine, Tablets.	PSH	30mg per tablet	29.499 ± 0.44	98.3	-2.09	4.32
Balsam Pharma (Syria)	CPM	2mg per tablet	1.952 ± 0.01	97.6	-1.87	2.12
	DEX[c]	—	—	—	—	—
	PAR	325mg per tablet	326.173 ± 3.45	100.3	2.44	2.88
Tussi Grip, Tablets.	PSH	30mg per tablet	30.170 ± 0.28	100.5	2.11	1.70
Sandy Pharma (Syria)	CPM[c]	—	—	—	—	—
	DEX	15mg per tablet	14.989 ± 0.24	99.9	1.82	4.17
	PAR[c]	—	—	—	—	—
Eskonad New, Capsules.	PSH	120mg per cap	119.150 ± 0.61	99.2	-1.79	1.90
Alpha-Aleppo Pharma (Syria)	CPM	8mg per cap	7.814 ± 0.05	97.6	-1.53	2.46
	DEX[c]	—	—	—	—	—

[a] four independent analyses.

[b] Theoretical values for *t*- and *F*-values at three degree of freedom and 95% confidence limit are t=4.30 and F=9.28. [c]Sample do not contain this ingredient.

CONCLUSION

The proposed method for the simultaneous determination of combination from PAR, PSH, CPM, and DEX was simple, rapid, accurate and precise and hence can be used for the routine analysis of combination or single in bulk and pharmaceutical formulations. The method provided excellent specificity and linearity with a limits of detection of 0.33, 0.09, 0.12 and 0.03µg/mL, and limits of quantification of 1.10, 0.30, 0.40 and 0.10µg/mL for PAR, PSH, CPM and DEX, respectively. The sample recoveries were in good agreement with their respective label claims, which suggested non-interference of formulations excipients in the estimation.

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