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Simultaneous determination of chlorpheniramine maleate, dextromethorphan hydrobromide and pseudoephedrine HCl in syrup pharmaceutical form using RP-HPLC

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Abstract

A new simple and precise HPLC method has been developed for the estimation of chlorpheniramine maleate, dextromethorphan hydrobromide and pseudoephedrine hydrochloride in syrup pharmaceutical form. The separation of the mixture has been achieved in a short time. Chromatographic separation has been done on Chromegabond WR C18 column 5 µm 120 A 30 cm * 3.9 mm as stationary phase. The mobile phase was contained a 2 gm of sodium perchlorate in mixture of (200 mL acetonitrile + 500 mL methanol + 300 mL Water+ 2 ml triethylamine with a flow rate 1.5 ml/min. The PDA detection is 262 nm and the injection volume was 20 µl. The method has been validated for linearity with great correlation coefficients, accuracy recovery was 98.0-102., and precision with RSD less than 2.0%. This method was successfully used to separate and estimate these drugs purchased from Iraq. The analysed syrup contains three active ingredients (chlorpheniramine maleate, dextromethorphan hydrobromide, pseudoephedrine hydrochloride) within 100 ±2 % of stated amount of the active ingredients. Validation of this method has been done and this method can be used for determination of these drugs in syrup pharmaceutical form.

Introduction

Different forms of medications used to treat common cough (tablet, capsule, syrup) these medications contain mixture of nitrogenous compounds. These medications have been found in various proportions, have various properties essential to the formulation, desired action, and dominate, similar chemical and physical properties making their separation difficult to separate [1].

Some syrups contain many active ingredients and different kinds of excipients for example flavoring agents, dyes sweeteners, acidulants, colorings, aspartame, preservatives, and

saccharose [2]. These excipients are existed in the syrup form in different concentrations which present different natures of chemical form [3].

Chlorpheneramine maleate is 2-[p-Chloro - a - [2-(dimethylamino ethyl] benzyl] pyridine maleate, is used to avoid symptoms of allergic conditions for instance rhinitis and urticarial[4-5]. Dextromethorphan hydrobromide, (3-methoxy-17-methylmorphinan hydro bromide monohydrate) [5] Dextromethorphan hydro bromide is used to treat cough. After oral administration, the period of action for dextromethorphan hydrobromide is about 3-8 h [6].

Pseudoephedrine hydrochloride, is (1S, 2S)-2-(methylamino)-1-phenylpropan-1-ol hydrochloride. It is used to relieve of nasal congestion. It can be mixed with some ingredients to prepare a drug to relieve cough and cold symptoms [7]. A combination of Pseudoephedrine, dextromethorphan and chlorpheniramine maleate is used to relieve allergic effects, cough and cold symptoms [8].

There are many chromatographic methods to separate and determine the concentration of drugs using ion-pair HPLC (IPC) [9]. However, IPC methods are time-consuming because of the long equilibration time. This method usually is not robust [10-11]. On the other hand, revers phase -HPLC is widely used in pharmaceutical analysis [12-16].

Consequently, we presented a new simple and precise method for estimation of dextromethorphan hydrobromide, chlorpheniramine maleate and pseudoephedrine hydrochloride in syrup pharmaceutical form. This method is simple, precise, and can be used without ion-pair reagents.

Materials and methods

Chemicals and reagents

The working standards are obtained from Wadi al- Rafidain for pharmaceutical products – Iraq- Baghdad. Chlorpheniramine maleate purity is (99.91%), Pseudoephedrine hydrochloride purity is (99.61%). And dextromethorphan hydrobromide Purity is (99.24%). sodium perchlorate was purchased from Sigma Aldrich. Acetonitrile, methanol, and triethylamine were purchased from ISOLAB GmbH, Germany. All chemicals were HPLC grade.

Instrumentation

The HPLC instrument is used SHIMADZU, Japan with a diode array detector. The spectrophotometer was UV-Vis Spectrophotometer Shimadzu 1800 with UV probe software. Analytical balance was Shimadzu. pH meter was WTW Germany. A pipette was from ISOLAB.

Standard solution

Each standard solution has been prepared using (20, 150, and 300 mg) of, Chlorpheniramine, Dextromethorphan HBr and Pseudoephedrine HCl respectively and dissolving in (50 mL) of ultra-pure water. Then (5 mL) of this solution was diluted to (20mL) of ultra-pure water to give a final concentration of (0.1, 0.75, and 1.5mg/mL) for, Chlorpheniramine, Dextromethorphan, and Pseudoephedrine respectively.

Wavelength selection

Dextromethorphan HBr, Chlorpheniramine, and pseudoephedrine show a good absorbance at 262 ± 2 nm, so the selected wavelength was 262 nm for this method.

Results and Discussion

HPLC method of analysis

Many trials have been done to obtain the best results in developing method for the separation of chlorpheniramine maleate dextromethorphan HBr and pseudoephedrine HCl. This method was developed to achieve peak separation with short retention times. Chromatographic separation has been done on Chromegabond WR C18 column 5 µm 120 A 30 cm * 3.9 mm as stationary phase. The mobile phase was 2 g of sodium perchlorate in a mixture (200 ml acetonitrile +500 ml methanol + 300 ml Water+ 2 mL triethylamine, flow rate of 1.5 mL/min, and PDA detection at 262 nm and the injection volume 20 µL. The tailing factor was, 1.06 for Chlorpheniramine and 1.12 for Dextromethorphan, 1.02 for Pseudoephedrine hydrochloride with great resolution. The peaks have no interferences as shown in Fig1.

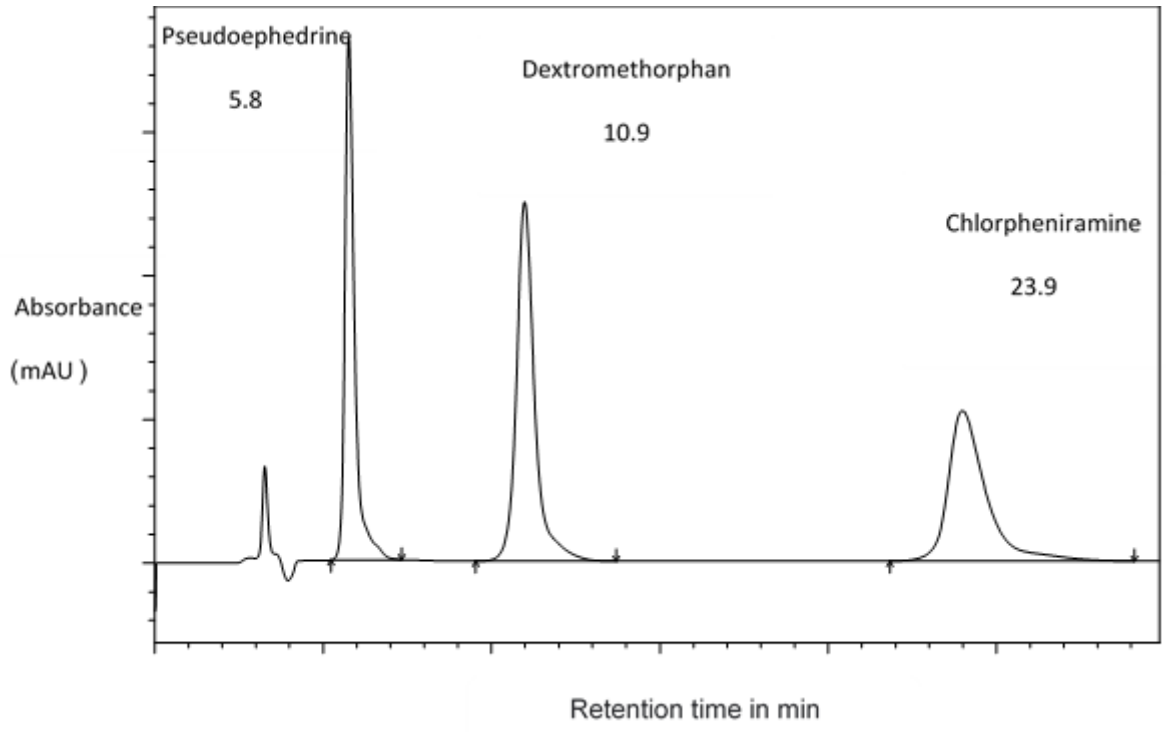

Fig. 1: Standard of Chlorpheniramine, Dextromethorphan, and Pseudoephedrine

Method validation

This method was validated according to ICH guidelines [17] and the United States Pharmacopeia 42[18].

Linearity

Ranges between 75 - 125 %, five different standard solutions have been prepared and injected five times using HPLC. The solutions of concentrations (0.075-0.125 mg/mL) of Chlorpheniramine maleate, (0.5625-0.9375 mg/mL), Dextromethorphan hydrobromide, and (1.125-1.875 mg/mL) for Pseudoephedrine hydrochloride.

As shown in Fig2, Fig3, and Fig4, the estimation coefficients for Chlorpheniramine maleate, Dextromethorphan hydrobromide, and Pseudoephedrine hydrochloride are (0.9993,

0.9993, 0.9996) respectively. The values of R2 are greater than 0.998 which indicates the linearity.

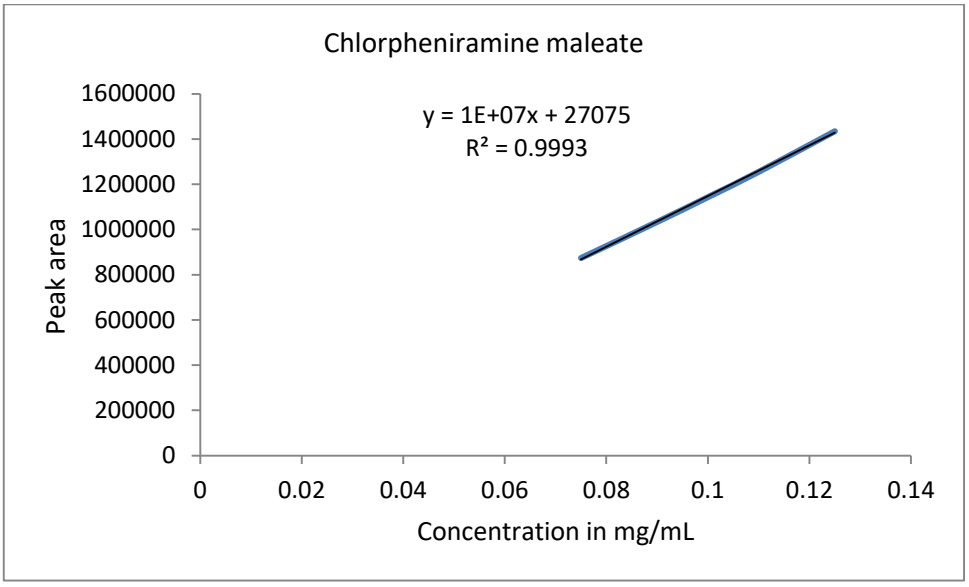

Fig2: Calibration curve of Chlorpheniramine maleate

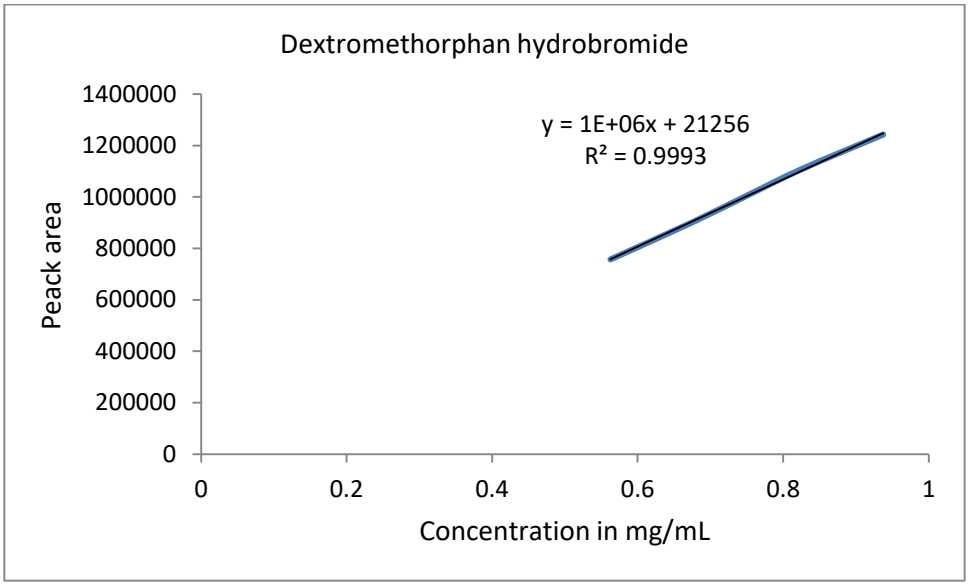

Fig 3: Calibration curve of Dextromethorphan hydrobromide

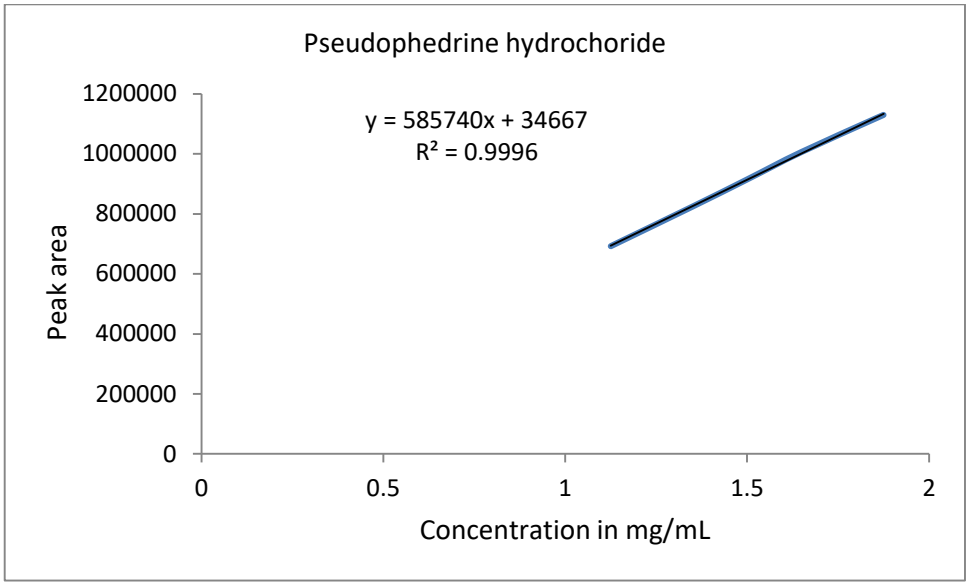

Fig4: Calibration curve of Pseudoephedrine hydrochloride

Accuracy

Solutions of concentrations (75, 90, 100, 110, 125 %) have been prepared and injected in order to study the accuracy for each ingredient. As shown in, (Table 1, Table 2, and Table 3) the accuracy has been confirmed and the data in (Table1, Table2, and Table3) show the mean recovery for Chlorpheniramine, Dextromethorphan and Pseudoephedrine HCl using this method is between 98 – 102%.

Table 1: Accuracy for chlorpheneramine

Concentration mg/mL	Calculated Area	Calculated Conc in mg/mL	Recovery	AVR
0.075	873842	0.07441	99.218	99.496
0.075	873209	0.07486	99.821	
0.075	872863	0.07471	99.626	
0.075	873925	0.07443	99.247	
0.075	873258	0.07467	99.568	
0.09	1036445	0.09011	100.128	99.9954
0.09	1034772	0.09025	100.282	
0.09	1028529	0.09005	100.058	
0.09	1029662	0.08983	99.820	
0.09	1037442	0.08972	99.689	
0.1	1141994	0.10002	100.026	99.886
0.1	1139975	0.09944	99.448	
0.1	1138739	0.10004	100.408	
0.1	1147935	0.09964	99.640	
0.1	1146903	0.09990	99.908	
0.11	1256873	0.11013	100.120	100.1832
0.11	1252396	0.10964	99.680	
0.11	1261108	0.11020	100.188	
0.11	1248852	0.11072	100.660	
0.11	1256604	0.11029	100.268	

0.125	1433492	0.12483	99.866	100.0432
0.125	1435573	0.12493	99.944	
0.125	1442860	0.12585	100.680	
0.125	1429905	0.12498	99.986	
0.125	1432290	0.12467	99.740	

Table2: Accuracy for dextromethorphan

Concentration mg/mL	**Calculated Area**	**Calculated Conc in mg/mL**	**Recovery**	**AVR**
0.5625	756550	0.55755	99.12	99.824
0.5625	755990	0.5605	99.660	
0.5625	756884	0.56317	100.120	
0.5625	756996	0.56452	100.360	
0.5625	755893	0.56171	99.860	
0.675	900437	0.67486	99.980	100.0732
0.675	902118	0.67722	100.330	
0.675	900236	0.67815	100.468	
0.675	900863	0.67425	99.890	
0.675	901823	0.67296	99.698	
0.75	990956	0.74985	99.980	99.8748
0.75	1009552	0.74721	99.628	
0.75	1014890	0.75105	100.140	
0.75	1009845	0.7473	99.640	
0.75	998840	0.74989	99.986	
0.825	1101474	0.82721	100.268	100.0912
0.825	1104479	0.82836	100.408	
0.825	1110380	0.82686	100.226	
0.825	1102946	0.82409	99.890	
0.825	1120297	0.82222	99.664	
0.9375	1243723	0.93776	100.028	100.0828
0.9375	1241193	0.9093	100.366	
0.9375	1239201	0.93675	99.920	
0.9375	1240291	0.936	99.840	
0.9375	1250293	0.93993	100.260	

Table3: Accuracy for pseudoephedrine

Concentration mg/mL	Calculated Area	Calculated Conc in mg/mL	Recovery	AVR
1.125	692679	1.1277	100.240	100.3156
1.125	691993	1.1259	100.086	
1.125	691892	1.1365	101.026	
1.125	692448	1.1248	99.986	
1.125	692769	1.1277	100.240	
1.35	823977	1.3457	99.686	100.0888
1.35	824119	1.3522	100.168	
1.35	824083	1.3565	100.482	
1.35	823882	1.3538	100.284	
1.35	825099	1.3476	99.824	
1.5	914428	1.5027	100.180	100.0972
1.5	914229	1.4979	99.860	
1.5	913992	1.5101	100.674	
1.5	914772	1.4968	99.790	
1.5	915028	1.4997	99.982	
1.65	1001828	1.6485	99.912	100.1872
1.65	1003318	1.6520	100.126	
1.65	1012284	1.6689	101.148	
1.65	1010038	1.647	99.820	
1.65	1003062	1.6488	99.930	
1.875	1124363	1.8558	98.980	99.6742
1.875	1123384	1.8724	99.864	
1.875	1139926	1.8803	100.286	
1.875	1128048	1.8684	99.648	
1.875	1130277	1.8673	99.593	

Precision

Standard solutions with concentration of 0.1 mg/mL for Chlorpheniramine maleate, 0.75 mg/ml for Dextromethorphan hydrobromide, and 1.5 mg/mL for Pseudoephedrine hydrochloride were prepared and injected in HPLC six times. As shown in Table.4, the RSD % for chlorpheniramine 0.319 %, dextromethorphan 0.379 %, and pseudoephedrine hydrochloride 0.749 is not more than 1 % which means the method is precise.

Table4: method precision.

Repeatability						
Injection number	Chlorpheniramine		Dextromethorphan		Pseudoephedrine hydrochloride	
	Concentration mg/ml	area	Concentration mg/ml	Area	Concentration mg/ml	area
1	0.1	1141994	0.75	990956	1.5	914428
2	0.1	1139975	0.75	1009552	1.5	914229
3	0.1	1138739	0.75	1014890	1.5	913992
4	0.1	1147935	0.75	1009845	1.5	914772
5	0.1	1146903	0.75	998840	1.5	915028
6	0.1	1139828	0.75	1002286	1.5	914226
AVR		1142562		1004395		914445.8
SD		3578.144		7982.844		352.8288
RSD%		0.529		0.468		0.270

Robustness

In order to check the ruggedness of this method, Changes in mobile phase composition (±2 %), and wavelength (±2 nm) have been changed. did not affect this method. These changes have shown no difference. This method shows a high level of robustness.

Specificity

The ingredients were analyzed and separated nicely and have great resolution. There are no interferences, shown between the different peaks, which indicate the reported method is specific. No interfaces were shown between the ingredients and the excipients used when applying this method to commercial syrup.

System Suitability

The flow rate and the wavelength can't be changed. It is very important to control them before applying this method.

LOD and LOQ

This method has been used to quantitative three active ingredients. The calculated LOD and LOQ for the active ingredients are presented in Table 5.

Table5: LOD and LOQ for the active ingredients.

Ingredient	**LOD**	**LOQ**
Chlorpheniramine maleate	1 µg/mL	3 µg/mL
Dextromethorphan hydrobromide	1 µg/mL	4 µg/mL
Pseudoephedrine hydrochloride	2.5 µg/mL	8 µg/mL

Concentration of active ingredients in syrup (Congestadain)

Congestadain is syrup produced by WADI AL- RAFIDAIN COMPANY that contains Chlorpheniramine 1 mg/5mL, Dextromethorphan 7.5 mg/5mL, and Pseudoephedrine 15mg/5mL. This syrup was used to check this validated method. The analysis using this method is specific and accurate as shown in table 6.

Table 6: Results of congestadain obtained using this method

Active component	Chlorpheniramine	Dextromethorphan	Pseudoephedrine hydrochloride
Stated amount	1 mg/5ml	7.5 mg/5ml	15 mg/5ml
Result found	0.992	7.57	15.16
Result found % ± (SD)	99.2 (± 0.76)	100.933(± 0.65)	101.066 (± 0.54)

Conclusions

A reversed - phase HPLC method was developed and validated. This method is new, simple and precise for simultaneous assay of chlorpheniramine maleate, dextromethorphan and pseudoephedrine hydrochloride. This method is simple and precise and can be used without ion-pair reagents. It can be used to calculate the concentration of the three active ingredients in a routine work of the drug in quality control lab.

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طريقة لتقدير ماليات كلورفينيرامين، ديكستروميثورفان هيدروبروميد، هيدروكلوريد السودوإيفيدرين في شراب صيدلاني بواسطة كوزموغرافيا السائل عالي الاداء

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الكلمات المفتاحية:

كروموتغرافيا السائل عالي الاداء، تقييم الطرق التحليلية، ماليات كلورفينيرامين، ديكستروميثورفان هيدروبروميد، هيدروكلوريد السودوايفيدرين

معلومات المؤلف

الخلاصة:

طورت طريقة جديدة بسيطة ودقيقة لتقدير ماليات كلورفينيرامين، هيدروبروميد ديكستروميثورفان وهيدروكلوريد السودوإيفيدرين في شراب صيدلاني باستخدام جهاز كروموتغرافيا السائل عالي الاداء. فصل المزيج في وقت قصير. وإجري الفصل الكروماتوغرافي باستخدام Chromegabond WR C18 5ميكرون 30 سم * 3.9 ملم كطور ثابت. الطور المتحرك يتكون من 2 غم من بيركلورات الصوديوم في خليط من (200 مل أسيتونيتريل + 500 مل ميثانول + 300 مل ماء + 2 مل ثلاثي إيثيل أمين بسرعة جريان 1.5 مل / دقيقة.تم استخدام الطول الموجي 262 نانومتر وحجم الحقن 20 ميكرولتر. تم التحقق من صحة الاستقامة الخطية للطريقة وكانت معاملات الارتباط جيدة، والاستردادية بين 98.0-102.، والدقة مع الانحرافات المعيارية أقل من 2.0٪. استخدمت هذه الطريقة بنجاح لتقدير هذه الأدوية المصنوعة في العراق. يحتوي الشراب الذي حلل على ثلاثة مواد فعالة (ماليات كلورفينيرامين، ديكستروميتورفان هيدروبروميد ، سودوإيفيدرين هيدروكلوريد) في حدود 100 ± 2٪ من كمية المواد الفعالة المذكورة على القنينة .تم التحقق من هذه الطريقة ويمكن استخدام هذه الطريقة لتقدير تركيز هذه المواد الفعالة في شراب صيدلاني.