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Simultaneous Spectrophotometric Analysis of Phenylpropanolamine Hydrochloride, Chloropheniramine Maleate and Dextromethorphan Hydrobromide in Syrups

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Present communication deals with two simple and economical methods requiring no prior separation for simultaneous analysis of phenylpropanolamine hydrochloride, chloropheniramine maleate and dextromethorphan hydrobromide in combination in pharmaceutical formulations. The methods employ multicomponent analysis procedure and simultaneous equations after spectral manipulation for quantification. In 0.1N hydrochloric acid, phenylpropanolamine hydrochloride has an absorbance maxima at 257 nm, chloropheniramine maleate at 265 nm and dextromethorphan hydrobromide at 278 nm. All three drugs obey Beer's law in the concentration range employed for these methods. The linearity was validated by Least Squares method. The results of analysis have been validated statistically and by recovery studies. Both methods are simple, accurate, reproducible and rapid.

Cough syrups containing phenylpropanolamine hydrochloride (PPM), chloropheniramine maleate (CPM) and dextromethorphan hydrobromide (DXB) are significant marketed formulations, indicated for symptomatic relief of nonproductive dry and irritating coughs and upper respiratory symptoms such as irritation of throat, running nose, nasal congestion and watery eyes associated with allergy or common cold. Fixed combination of PPM (25 mg), CPM (4 mg) and DXB (20 mg) per each 10 ml of syrups are marketed by various manufacturers.

Official assay methods are available for analysing individual drugs and their formulations and one listed in IP[1,2], BP[3,4] and USP[5,6]. UV spectrophotometric[7-9], GLC[10,11] and HPLC[12-16] methods are reported for the quantification of CPM along with PPM or DXB in multicomponent formulations. The combined dosage form of PPM, CPM and DXB is not official and none of the official compendia specify simultaneous analysis of said analytes in multicomponent formulations. The traditional methods of separation of individual components followed for estimation by various official/reported methods are tedious and moreover time consuming. Although few HPLC methods[17-20] are available for the simultaneous estimation of the said components, these methods are comparatively expensive and time-consuming. The paper presents two simple, accurate, reproducible and economical spectrophotometric methods for the determination of PPM, CPM and DXB in multicomponent formulations.

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EXPERIMENTAL

A Shimadzu UV/Vis recording spectrophotometer (Model 160A) with spectral band width of 3 nm and a wavelength accuracy of ±0.5 nm (with automatic wavelength correction) was employed for all spectroscopic measurements using a pair of 10 mm matched quartz cells. PPM (BP), CPM (IP), DXB (IP), hydrochloric acid (Ranbaxy A.R. Grade) chloroform (Ranbaxy, A.R. Grade), Sodium hydroxide (Qualigens ExcelaR), anhydrous sodium sulfate and double distilled water were used in the present investigation.

Stock solutions of PPM (1000 µg/ml), CPM (200 µg/ml) and DXB (500 µg/ml) were prepared separately in 0.1N HCl. Each stock solution was suitably diluted to different concentrations and the linearity was studied.

TABLE 1 : RESULTS OF LINEARITY TEST AND MEAN ABSORPTIVITY VALUES

Analytes	Wavelength nm	Slope	Intercept	Coeff. of Correlation	Mean absorptivity
PPM	257.0	1054.603	-0.8631	0.9999	0.9528
CPM	257.0	56.9953	-0.0653	0.9993	17.6279
	265.0	45.411	-0.0892	0.9999	22.2342
	276.6	84.5565	-0.0593	0.9988	11.8787
	284.0	182.7216	-0.0154	0.9960	5.4831
DXB	257.0	962.649	-3.2168	0.9987	1.0868
	276.6	195.647	0.6869	0.9999	5.1615
	278.0	191.67	-0.5266	0.9999	5.2885
	284.0	208.1776	-0.5243	0.9999	4.8398

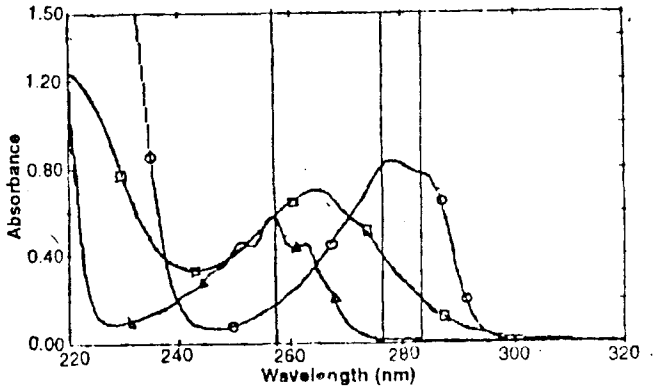
*N=7

Linear relationships were observed in the range 0-800 µg\ml for PPM, 0-50 µg/ml for CPM and 0-200 µg/ml for DXB. The correlation coefficients, slopes and intercepts were evaluated by Least Squares Method. The results obtained after replicate determinations are given in Table - 1.

Method - 1:

The absorbance maxima of PPM (257 nm), CPM (265 nm) and DXB (278 nm) were utilized for multicomponent analysis (Fig. 1). Eight mixed standards were prepared as per Table-2 by using appropriate volumes of stock solutions. The sampling wavelengths selected and concentration of three analytes in mixed standards were fed to the instrument in multicomponent mode. Each mixed standard was scanned consequitively between 320 and 220 nm at slow scan speed (≅480 nm/min) (Fig. 2). The inbuilt microprocessor complied the signals to form a matrix equation suitable for quantification of analytes. This equation was stored in the memory of instrument and was used for further analysis of samples by retrieval of equation.

Before switching to analysis of commercial formulations, the method was validated by analysing authentic samples containing all the analytes in ratio as per the formulation requirement and random samples prepared in laboratory. The results of replicated determinations (n=5) were validated statistically and are shown in Table-3 (A).



* Markers showing selected wavelengths in method II

Fig. 1 : Overlain Spectra of PPM, CPM and DXB

Absorbance spectra obtained at different wavelengths in the rage of 220-320nm of PPM (Δ) (600 µg/ml), CPM (□) (32 µg/ml) and DXB (O) (160 µg/ml) overlain over each other.

Three batches of syrup formulations, procured from local markct were used for analysis by proposed method. A selective extraction procedure was adopted to avoid interferences due to adjuvants in formulations. Ten millilitres of each syrup was taken and made alkaline with 10 ml of 1N NaOH. The resulting alkaline syrup solution was extracted successively 5 times with each 10ml of chloroform and the extracts were collected. The solvent was driven off completely under reduced pressure at 45±2°. The residue was dissolved in 0.1N HCl and the volume

TABLE 2 : CONCENTRATION OF ANALYTES IN MIXED STANDARDS (μg/ml)

Analytes	I	II	III	IV	V	VI	VII	VIII
PPM	50	100	150	200	250	250	00	00
CPM	08	16	24	32	40	00	40	00
DXB	40	80	120	160	200	00	00	200

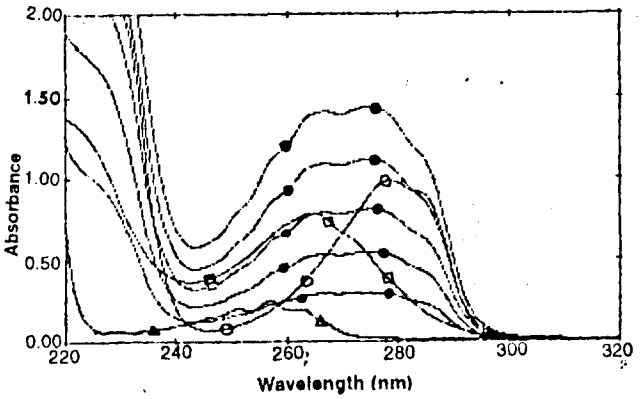


Fig. 2 : Overlain spectra of mixed standards (●) of PPM (Δ), CPM (□) and DXB (O). (Refer Table - 2)

was made upto 100 ml. The resulting solution was treated as stock sample solution labeled to contain 250 μg/ml, 40 μg/ml and 200 μg/ml of PPM, CPM and DXB respectively. Different dilutions were prepared from the above solutions and analysed using the instrument through retrieval of previously stored equation. However, one of the commercial formulations containing menthol as adjuvant was found to interfere seriously in analysis, showing spectral interference in the wavelength region selected. Hence, a slight modification for this formulation was made to exclude menthol. The residue after complete withdrawal of chloroform from the extract was further dried under reduced pressure at 45±2° for another 2 h and subsequent process was followed as in other formulations. The statistical data of results obtained after replicate determinations (n=4) are shown in Table-4. The solvent extraction process adopted was quantitatively assured through analysis of a simulated syrup prepared in laboratory by proposed method.

Method-II:

The absorbance maxima 257, 265 and 278 nm were initially used for generation of simultaneous equations. However, complexities arose in solution of equations containing each three variables and the unsatisfactory results obtained after solving equations through matrix, lead to rejection of wavelengths selected for estimations. Framing simplified equations containing two variables leads to selection of wavelengths 257, 276.6 and 284 nm (Fig. 1). At wavelengths 276.6 and 284 nm, only CPM and DXB showed significant absorbance. The contribution of PPM to total absorbance in this region may be ignored because PPM shows absorbance value below 0.008 and was independent of concentration. Hence errors of maximum 0.5% in quantification of CPM and DXB may be involved by ignoring corresponding contribution from PPM theoritically, which is within the permissible limit. This factor was also established through a series of experimentation. The wavelength 284 nm (shoulder peak of DXB) was selected again to keep both selected wavelengths quite separate ($\delta\gamma$ =7.4 mm), so that lower spectral interference with maximum sensitivity attained. At these selected wavelengths two simultaneous equations were generated using corresponding absorptivity coefficient values.

$$A_2 = 11.872\ C_y + 5.1615C_z \quad \text{——— (1)}$$

$$A_3 = 5.4831C_y + 4.8398C_z \quad \text{—— (2)}$$

where, C_y are conc. of CPM and DXB respectively. A_2 and A_3 are absorbances of samples solution measured at 276.6 and 284 nm respectively. The numericals shown are the corresponding absorptivity coefficients obtained from seven independent determinations in the whole range of analysis (Table - 1).

By solving the equations for C_y and C_z conc. of CPM and DXB could be readily found out. For quantifications of PPM the peak 257 nm was selected, which results generation of an equation containing three variables. However an initial finding of conc. of CPM and DXB i.e. C_y and C_z from equations (1) and (2) made it possible to work out conc. of PPM from eqn (3) without any complexity.

$$A_1 = 0.9528\ C_x + 17.62798\ C_y + 1.08688\ C_z \text{ — (3)}$$

TABLE 3 : ANALYSIS OF AUTHENTIC SAMPLES PREPARED IN LABORATORY (A) AND RECOVERY STUDY DATA (B)

	Method I				Method II			
Analyte	C.I.	SD	%SE	't'	C.I.	SD	%SE	't'
PPM	99.236±1.422	1.146	0.512	1.49	99.233±1.217	1.16	0.474	1.619
A CPM	99.667±1.522	1.226	0.548	0.607	99.477±1.234	1.175	0.48	1.09
DXB	100.088±0.727	0.586	0.262	0.335	100.82±1.211	1.271	0.519	1.58
PPM	100.012±1.592	1.001	0.501	0.024	99.994±1.532	0.963	0.481	0.012
B CPM	99.59±1.268	0.797	0.398	1.028	100.532±1.804	1.134	0.567	0.938
DXB	100.328±0.853	0.536	0.268	1.223	99.23±1.742	1.095	0.548	1.406

SD: Standard deviation % SE: Per cent standard error. C.I. (Confidence Interval within which true value may be found at 95% confidence level) = R±ts/√n R = Mean per cent result of analysis of authentic samples (n=5) in method I n= 6 in method-II) or Recovery (n=4) Theoritical 't' values at 95% confidence level for n-1 degrees of freedom are t (0.5,3) = 3.182, t(0.05,4) = 2.776, t(0.05,5) = 2.571

where, Cx is conc. of PPM, A_1 is absorbance of sample solution measured at 257 nm. Numericals shown are absorptivity values of corresponding analytes at 257 nm (Table - 1).

Before analysing commercial formulations using this method, the analytical procedure was validated through analysing authentic laboratory samples as in method - 1. However considering the wide variance observed in estimation of PPM and considering its lower absorptivity values as compared to CPM and DXB, standard addition of PPM was effected in this method. Reproducible results with good accuracy was observed with standard addition of 200 per cent with considerable lower standard deviation values (Table - 3(A), n = 6). This amount of standard addition was quantitatively established after a series of preliminary trials.

The commercial syrup samples were processed similarly as in method - 1 with addition of pure PPM to 200 per cent. Absorbances at selected wavelengths were recorded and the concentration of each analyte was determined using the equations generated. Sample solutions containing PPM, CPM and DXB in concentration ranges 200-600 µg/ml, 10-32 µg/ml and 50-160 µg/ml respectively were found to yield more accurate and precise results. The result of analysis of syrup formulations within this analytical range are stated in Table - 4.

To study the recovery of PPM, CPM and DXB, preanalysed samples were taken to which different quantity of pure drugs (reference standard) were added within the analytical concentration range limitations by both methods. The added quantity as estimated by both methods are recorded in Table-3 (B) (n=4).

RESULTS AND DISCUSSION

The proposed methods were found to be accurate, simple and convenient for simultaneous determination of PPM, CPM and DXB in pharmaceutical formulations. The modalities adopted in experimentation were successfully validated as per analytical procedures laid down in routine. Both methods were validated by preliminary analysis of authentic laboratory samples and by recovery studies. The solvent extraction process adopted for exclusion of interfering adjuvants was also quantitatively assured through analysis of simulated syrup prepared in laboratory. The results of analysis of authentic samples and the average recoveries obtained in each instance were compared with the theoritical value of 100 per cent by means of Student's 't' test. As the calculated 't' values are less than theoritical 't' values (Table-3), it is concluded that the results of analysis and recoveries obtained were in agreement with 100 per cent for each analyte.

The mean percentage of recoveries at 95 per cent confidence limit were calculated for three degrees of freedom (n=4) and were found to be 100.01±1.59, 99.59±1.27, 100.33±0.85 in method-I and 99.99±1.53, 100.53±1.80, 99.23±1.71 in method-II for PPM, CPM and DXB respectively. This show the recoveries obtained do not

TABLE 4 : ANALYSIS OF COMMERCIAL FORMULATIONS

Method		PPM		CPM		DXB	
Formulations		C.I.	SD	C.I.	SD	C.I.	SD
M-I	A	98.733±0.762	0.479	97.342±1.077	0.677	102.3±1.205	0.758
	B	102.153±2.026	1.274	98.324±0.859	0.54	102.929±0.631	0.397
	C	102.44±0.727	0.457	98.948±2.466	1.55	99.986±1.557	0.979
M-II	A	100.264±1.687	1.06	99.439±1.35	0.85	99.432±1.462	0.919
	B	100.124±1.463	0.92	101.889±1.466	0.921	99.656±0.885	0.556
	C	102.016±1.462	0.919	98.861±1.486	0.934	99.228±0.692	0.435

*N=4, T(0.053) = 3.182

differ significantly from 0 to 100 per cent and there was no interference from common adjuvants used in the formulations, indicating the accuracy and reliability of both methods.

Method-I is extremely suitable for analysis of PPM, CPM and DXB in higher concentrations through a conventional recording spectrophotometer with multicomponent mode. The method is recommended for routine analysis in quality control laboratories. Method-II is based on rational development of simultaneous equations at selected wavelengths after spectral manipulation. Hence simplification of complexities in conventional used was achieved within permissible limits of analytical procedure. This method is quite simple and only require measurement of absorbances at selected wavelengths, once the equations have been generated. This method is particularly useful to the analyst equipped with nonrecording spectrophotometer and is recommended for routine in-process quality control and for quantification of said drugs in combinations. The values of SD 0.435 to 1.55 percent are also indicative of accuracy and reproducibility of both proposed methods and these merits in addition to simple reagents support their routine use.

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