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SIMULTANEOUS DETERMINATION OF CHLORPHENIRAMINE MALEATE AND PHENYLEPHRINE HYDROCHLORIDE IN LIQUIDDOSAGE FORMS BY UV SPECTROSCOPIC METHODS

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Abstract:

Simple, rapid, accurate, precise and economical UV Spectroscopic methods like simultaneous equation method and first derivative zero crossing method were developed and validated for simultaneous determination of chlorpheniramine maleate (CPM) and phenylephrine hydrochloride (PHCL) in pharmaceutical liquid dosage forms (syrup, oral drops). These drugs are employed in the treatment of Nasal problems in pediatrics. Simultaneous equation method of CPM & PHCL was determined at 261 & 272 nm. First derivative zero crossing method of CPM & PHCL was determined at 245 & 257 nm. Both methods exhibited good linearity (R2 =0.999). and the calibration curve of CPM & PHCL was plotted in the range of 10-60 µg/ml & 10-110 µg/ml by using distilled water as solvent. The values of %RSD for intraday and inter-day precision was found to be within limits (< 2%) thus the values confirm that the methods are precise. The values of % recovery and assay of formulation was within 90-110% w/w, which shows both the methods were accurate and free from the interference of excipients used in formulation and these methods also applicable for analysis of marketed formulation. The method was validated according to the ICH guidelines and the results were simple, accurate, sensitive and precise.

Key words: Simultaneous equation method, First derivative zero crossing method, Chlorpheniramine maleate (CPM), Phenylephrine hydrochloride (PHCL), validation, linearity, ICH guidelines.

INTRODUCTION:

Combinations of drugs are single preparations that contain two or more APIs (active pharmaceutical ingredients) to be administered as a fixed dose mixing combination medicine concurrently. The majority of multi-component medication formulations typically have two or more active components that work together to provide the drug's combined therapeutic effect. Due to improved efficacy, microorganisms increased resistance to single component formulations, dependency, and/or tolerance, there is a rise in the production of multicomponent drug formulations. Chemically, PhenylephrineHCl (R) – 3[1-m-hydroxy-2-(methyl amino) methyl] benzyl alcohol hydrochloride is a direct selective alpha adrenergic receptor agonist and used as a decongestant. Chlorpheniramine maleate is chemically, (RS)-3-(4-chlorophenyl)-3-(pyrid-2- yl) propyl dimethyl amine hydrogen maleate and is an antihistamine drug which is employed in the treatment of common cold and allergic diseases.

In the literature, it was revealed that very few methods have been reported for estimation of these drugs alone and numerous methods were reported for the combination with other drugs in pharmaceutical dosage forms [1-7].The aim of the present work was to develop and validate simple and economical UV Spectrophotometric methods for quantitative estimation of Chlorpheniramine Maleate and Phenylephrine Hydrochloride in Oral Drops and Syrup dosage form. The UV Spectrophotometric methods developed were Simultaneous equation method and First derivative zero crossing method[8-20].

MATERIALS AND METHODS

Instruments and chemicals

Shimadzu UV-1800 spectrophotometer with matched pair of 10mm quartz cells is used for all the experiments. Data acquisition was performed by UV Probe software. Chlorpheniramine maleate (CPM) and Phenylephrine hydrochloride (PHCL) pure drug samples was purchased from TCI Chemicals Ltd. Maxtra oral drops (Zuventus Healthcare Limited) and Ascoril Syrup (Glenmark pharmaceutical Ltd.) were purchased from local pharmacy.

Spectrophotometric method development and validation

Different Solvents like Water 0.1N HCl, and 0.1N NaOH were employed for the optimization of the method. Distilled Water gave a single distinct peak with good absorbance for all the two drugs. So, it was employed as the solvent. From trial-and-error method λmax of Chlorpheniramine maleate bulk drug was determined by preparing the solution in Distilled Water in UV spectrophotometer and the λmax was found to be 261nm.λmax of Phenylephrine hydrochloride bulk drug was determined by preparing the solution in Distilled water in UV spectrophotometer and the λmax was found to be 272nm.

Preparation of Standard solutions

100mg of each drug was weighed and transferred separately in to two 10 ml volumetric flasks and dissolved in distilled water to make up the volume. Further dilutions were made to get a concentration of 100µg/ml. The final concentrations of Chlorpheniramine maleate was prepared in the range of 10-60 µg/ml and Phenylephrine hydrochloride in the range of 10-110 µg/ml. Linearity and calibration curves were recorded at their respective absorption maxima.

Preparation of assay solutions

1ml of Oral drop was added into 10ml of Distilled water to get concentrations of 200µg/ml and 500µg/ml of Chlorpheniramine maleate and Phenylephrine hydrochloride. The sample solution was kept in sonicator for 10 min and filtered it by using Filter paper. 1ml of the solution was taken and diluted to 10 ml to get concentrations of 20µg/ml and 50µg/ml of Chlorpheniramine maleate and Phenylephrine hydrochloride respectively.

5ml of Syrup was added into 10ml of Distilled water to get concentrations of 200µg/ml and 500µg/ml of Chlorpheniramine maleate and Phenylephrine hydrochloride. The sample solution was kept in sonicator for 10 min and filtered it by using Filter paper. 1ml of the solution was taken and diluted to 10 ml to get concentrations of 20µg/ml and 50µg/ml of Chlorpheniramine maleate and Phenylephrine hydrochloride respectively.

Simultaneous equation method

Both the drugs showed good solubility in Distilled water and hence this solvent is used for their simultaneous estimation. Simple, specific, accurate and precise spectrometric method using simultaneous equation was developed for simultaneous determination of Chlorpheniramine maleate and Phenylephrine hydrochloride from their binary mixture. In this Spectrophotometric method, the spectra of binary mixture containing Chlorpheniramine maleate and UV were measured at 261nm and 272nm which are λmax of individual drugs. Laboratory prepared mixtures and pharmaceutical formulation was successfully analyzed using this developed method.

For Chlorpheniramine maleate

CX = (A2ay1-A1ay2) / (ax2ay1-ax1ay2)

For Phenylephrine hydrochloride

CY= (A1ax2-A2ax1) / (ax2ay1-ax1ay2)

Where, CX= Concentration of Chlorpheniramine maleate

- Cy = Concentration of Phenylephrine hydrochloride
- A1=Test sample absorbance at 261nm

- A2=Test sample absorbance at 272nm
- ax1= Absorptivity of Chlorpheniramine maleate at λ1 (261nm)
- ax2=Absorptivity of Chlorpheniramine maleate at λ2 (272nm)
- ay1=Absorptivity of Phenylephrine hydrochloride at λ1 (261nm)
- ay2= Absorptivity of Phenylephrine hydrochloride at λ2 (272nm)

The above equation was used to calculate the test concentrations of Chlorpheniramine maleate and Phenylephrine hydrochloride in the formulation.

First Derivative Zero Crossing Method

Simple, specific, accurate and precise 1st derivative zero-crossing Spectrophotometric method was developed for simultaneous determination of CPM and PHCL from their binary mixture. In this 1st derivative zero-crossing Spectrophotometric method the amplitudes of the 1st derivative of the spectra of the binary mixture containing CPM were measured at 245.0 nm (zero crossing of CPM) and for determination of PHCL at 257.0 nm (zero crossing of PHCL). Pharmaceutical formulations were successfully analyzed using the developed methods.

The absorption spectra of working standard solutions of CPM and PHCL were recorded in the range of 200-400 nm and stored in the memory of the instrument. The 1st derivative of the working standard solutions were tresses with smoothing at smoothing factor (Δλ) = 16 and multiplying the entire spectra with a constant factor 10 for determining zero cross points for both the drugs. It was found that the 1st derivative spectrum of CPM crosses at 245 nm and that of PHCL crosses at 257 nm. The absorption spectra of the binary mixture solutions of CPM and PHCL were recorded in the range of 200 nm to 400 nm and were stored in the memory of the instrument after smoothing it at Δλ = 16 interval. The entire 1st derivative spectra of the binary mixtures were then multiplying with a constant factor 10. The amplitudes at 245.0 nm were plotted against the respective concentrations of CPM. The method shows good linearity in the range of 10-60 µg/ml for CPM. Similarly, the amplitudes at 257.0 nm were plotted against the respective concentration of CPM. The method shows good linearity in the range of 10-110 µg/ml for PHCL.

RESULTS AND DISCUSSION

Simultaneous Equation Method (SEM)

The spectrophotometric method using simultaneous equation was successfully developed for simultaneous determination of chlorpheniramine maleate and phenylephrine hydrochloride from binary mixture. The results obtained are discussed below.

Optimization and selection of method parameters

All the optimized parameters are summarized in the table. Based on the solubility profile of selected drugs methanol is used as common solvent for both the drugs. The wavelength selected

for the determination of Chlorpheniramine maleate and Phenylephrine hydrochloride were 261nm & 272 nm respectively.

Validation Parameters

Linearity & Range

The calibration curve constructed was evaluated by using correlation coefficient. The absorbance was linear over the range of 10-60 µg/ml for Chlorpheniramine maleate and 10-110 µg/ml for Phenylephrine hydrochloride. The average absorbance of each concentration obtained was plotted against the concentration of the analyte. The correlation coefficient for Chlorpheniramine maleate and Phenylephrine hydrochloride was found to be 0.9991 and 0.9993 respectively.

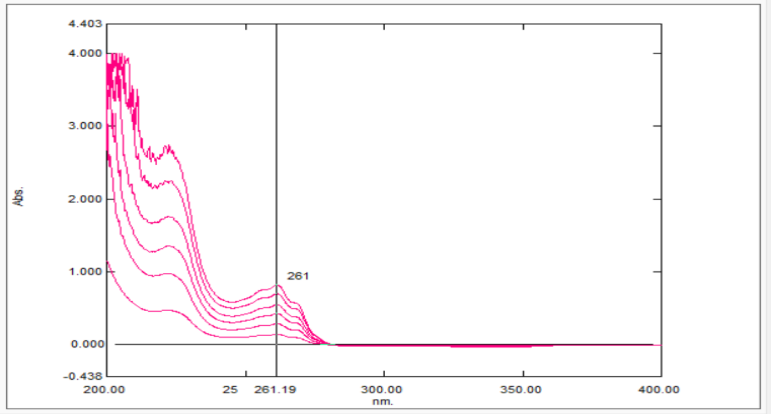

Figure 1. Linearity spectra of Chlorpheniramine maleate at 261 nm

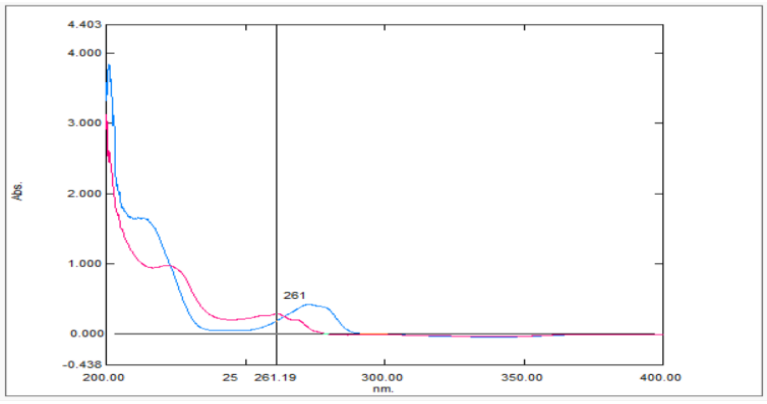

Figure 2. Linearity spectra of Phenylephrine hydrochloride at 272 nm

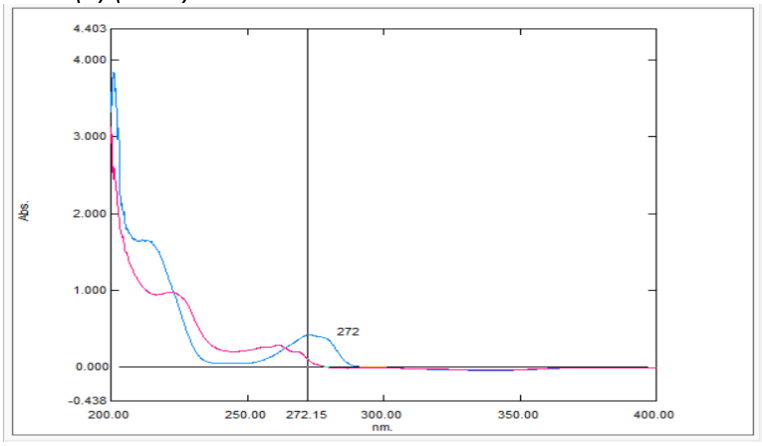

Figure 3: Overlay spectra of Chlorpheniramine maleate and Phenylephrine hydrochloride at 261 nm

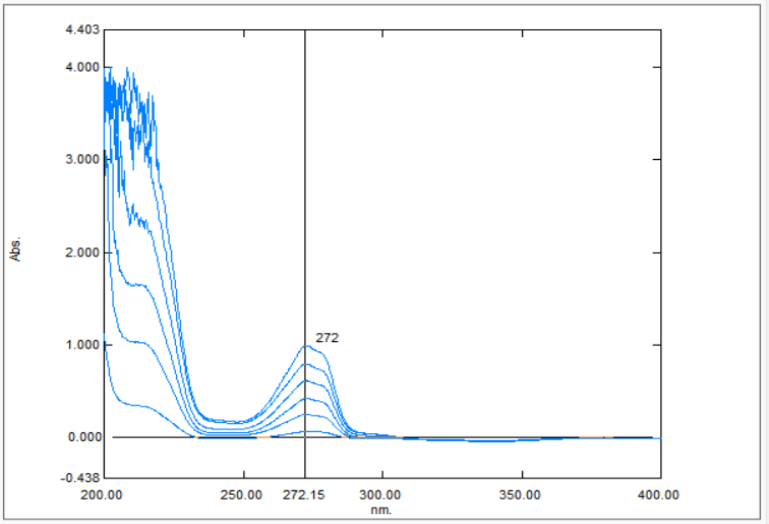

Figure 4: Overlay spectra of Chlorpheniramine maleate and Phenylephrine hydrochloride at 272 nm

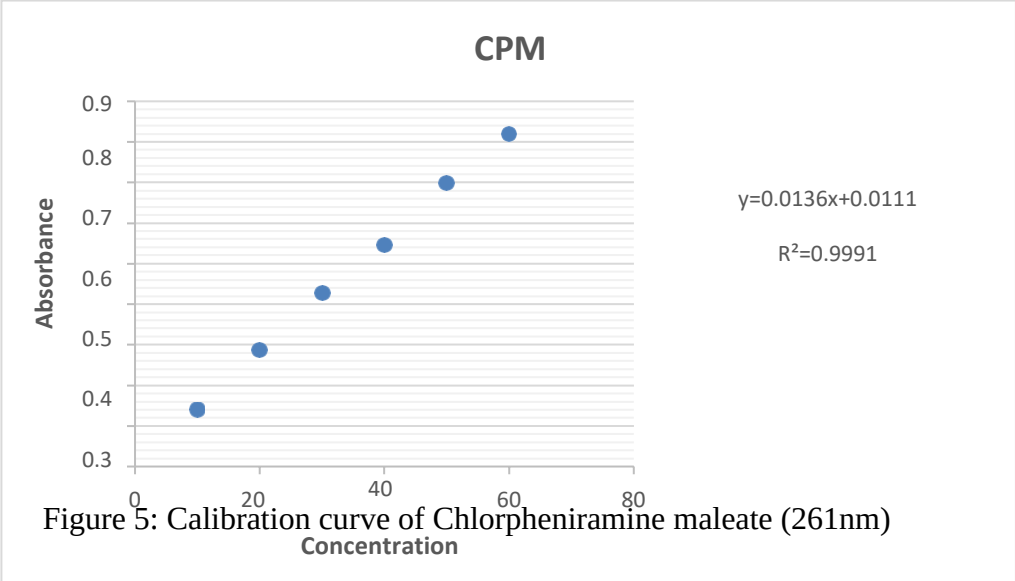

Figure 5: Calibration curve of Chlorpheniramine maleate (261nm)

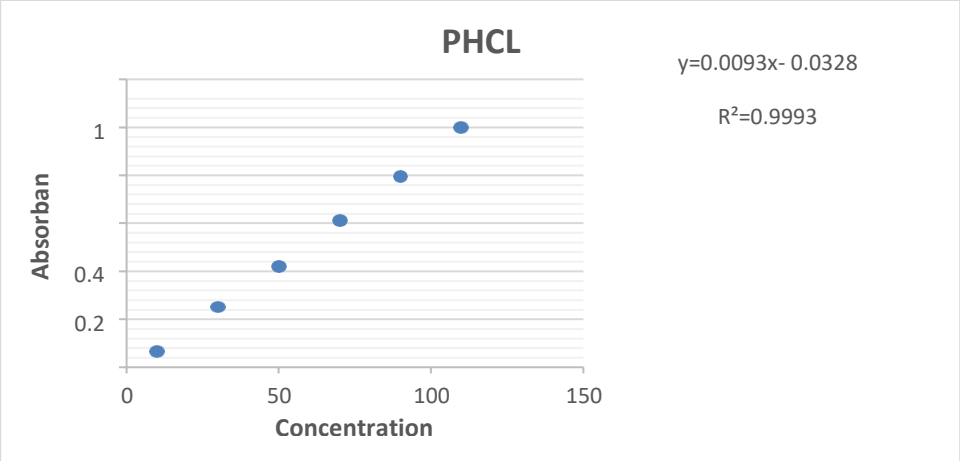

Figure 6: Calibration curve of Phenylephrine Hydrochloride (272nm)

Table 1: Linearity of Chlorpheniramine Maleate (261nm)

Concentration (µg/ml)	Absorbance (261nm)
10	0.140
20	0.287
30	0.427
40	0.547
50	0.699
60	0.820

Table 2: Linearity of Phenylephrine Hydrochloride(272nm)

Concentration (µg/ml)	Absorbance (272nm)
10	0.066
30	0.250
50	0.419
70	0.610
90	0.793
110	0.998

Precision

The precision of an analytical procedure expresses the closeness of agreement between a series of measurements from multiple sampling of the same homogeneous sample under prescribed conditions. Variation of results within the same day (intra- day), variation of results between

days (inter-day) was analyzed. Intra-day precision was determined by analyzing the two drugs for three times in the same day at their respective absorption maxima. Inter-day precision was determined by analyzing next day three times and %RSD was calculated.

Table 3 : Inter Day Precision for Chlorpheniramine maleate

S.NO	CONC(mcg/ml)	DAY	Abs-I	Abs-II	Abs-III	MEAN	STD DEV	%RSD
1	20	1	0.287	0.294	0.288	0.289667	0.003786	1.306998
2	20	2	0.289	0.296	0.293	0.292667	0.003512	1.199961
3	20	3	0.29	0.292	0.296	0.292667	0.003055	1.04867
								1.183609

Table 4 : Inter Day Precision for Phenylephrine Hydrochloride

S.NO	CONC(mcg/ml)	DAY	Abs-I	Abs-II	Abs-III	MEAN	STD DEV	%RSD
1	50	1	0.419	0.423	0.422	0.421333	0.002082	0.494066
2	50	2	0.432	0.425	0.423	0.426667	0.004726	0.107613
3	50	3	0.426	0.427	0.425	0.426	0.001	0.234742
								0.61214

Accuracy

Accuracy is the closeness of test results obtained by the method to the true value. To determine the accuracy was performed in three levels of concentrations i.e., 80%, 100%, 120% of label claim by standard addition technique. Test formulation was prepared in the concentration 20 µg/ml (Chlorpheniramine maleate) and 50 µg/ml (Phenylephrine hydrochloride). To this solution, standard solution was spiked and solution was recorded in UV-Spectrophotometer at 261nm and 272 nm. The percentage recovery of the added sample drug was calculated.

Table 5 : Accuracy table of Chlorpheniramine maleate drops

S.NO	Formulation	%addition of std	Conc.ofstd added	Total amount of Drug	Absorbance	Amount obtained	%Recovery of oral drops
1.	10	80%	8	18	0.412	17.90	99.4%

2.	10	100%	10	20	0.503	21.7	108%
3.	10	120%	12	22	0.514	22.86	103.9%

Table 6: Accuracy table of Phenylephrine Hydrochloride drops

S.NO	Formulation	%addition of std	Conc.of std added	Total amount of Drug	Absorbance	Amount obtained	%Recovery of oral drops
1.	25	80%	20	45	0.46	42.82	107.05%
2.	25	100%	25	50	0.564	52.62	105.02%
3.	25	120%	30	55	0.559	51.27	93%

Table 7: Accuracy table of Chlorpheniramine maleate

S.NO	Formulation	%addition of std	Conc.of std added	Total amount of Drug	Absorbance	Amount obtained	%Recovery of syrup
1.	10	80%	8	18	0.417	18.42	102%
2.	10	100%	10	20	0.467	21.7	104.4%
3.	10	120%	12	22	0.487	21.26	96.6%

Table 8: Accuracy table of Phenylephrine Hydrochloride

S.NO	Formulation	%addition of std	Conc.of std added	Total amount of Drug	Absorbance	Amount obtained	%Recovery of syrup
1.	25	80%	20	45	0.457	42.1	93%
2.	25	100%	25	50	0.505	46.19	92.39 %
3.	25	120%	30	55	0.541	50.23	91.3%

First derivative zero crossing method

A 1st derivative zero crossing Spectrophotometric method was successfully developed for simultaneous determination of CPM and PHCL from their binary mixture. The results obtained are discussed below.

Optimization and selection of method parameters

All the optimized method parameters are summarized in table 17. Based on the solubility profile of selected drugs, Distilled water was used as common solvent for both drugs i.e., CPM and PHCL. The wavelengths selected for the determination of CPM & PHCL were 245.0nm as the 1st derivative spectra of PHCL shows zero amplitude and 257.0 nm for PHCL (zero cross of CPM) respectively.

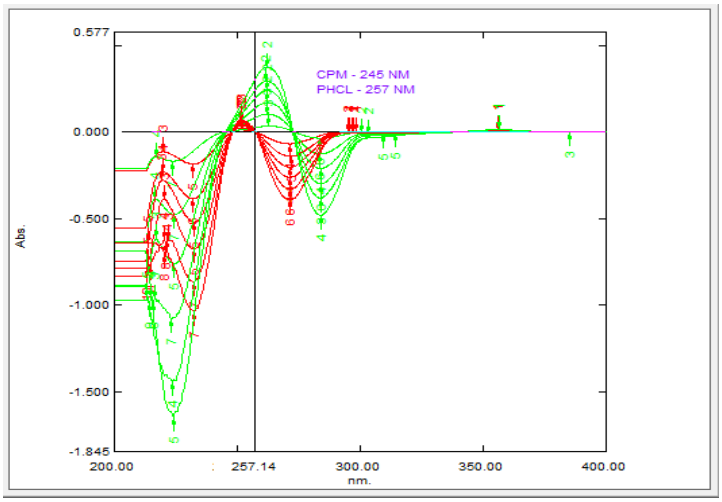

Figure 7: First derivative overlay spectra of CPM and PHCL

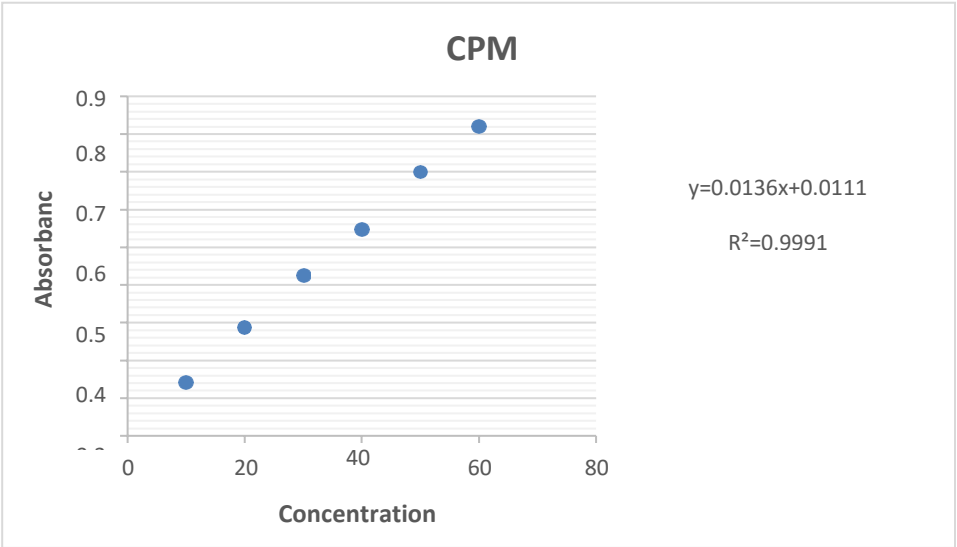

Figure 8: Calibration curve of Chlorpheniramine maleate (261nm)

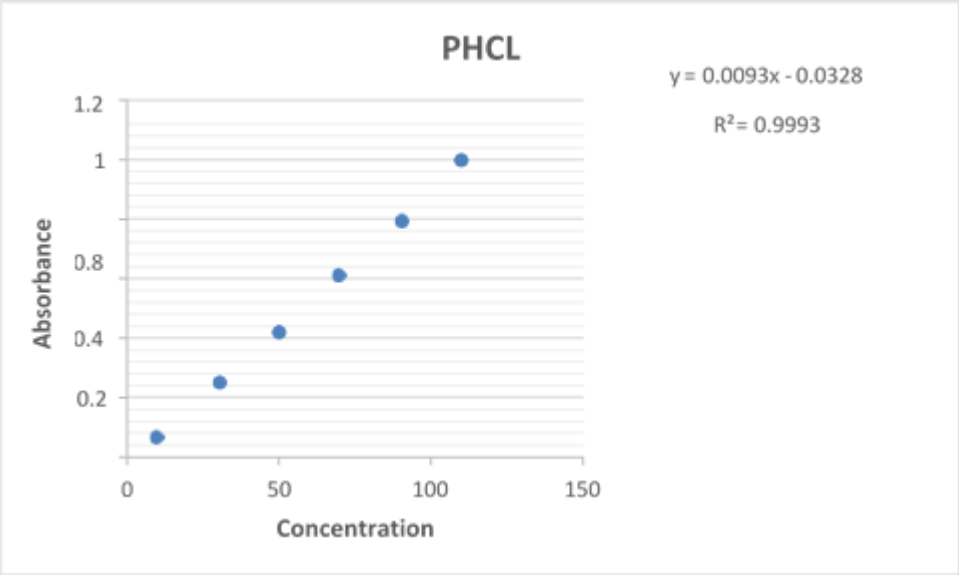

Figure 9: Calibration curve of Phenylephrine Hydrochloride (272nm)

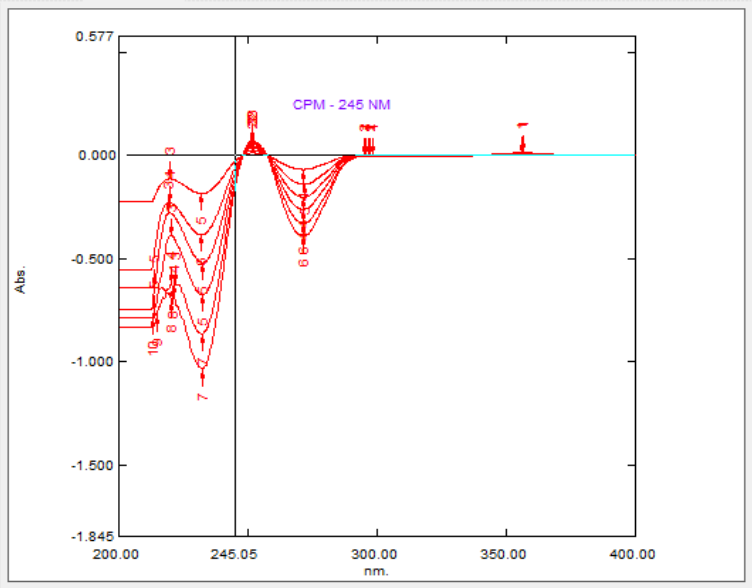

Figure 10: Linearity spectra of CPM at 245 nm

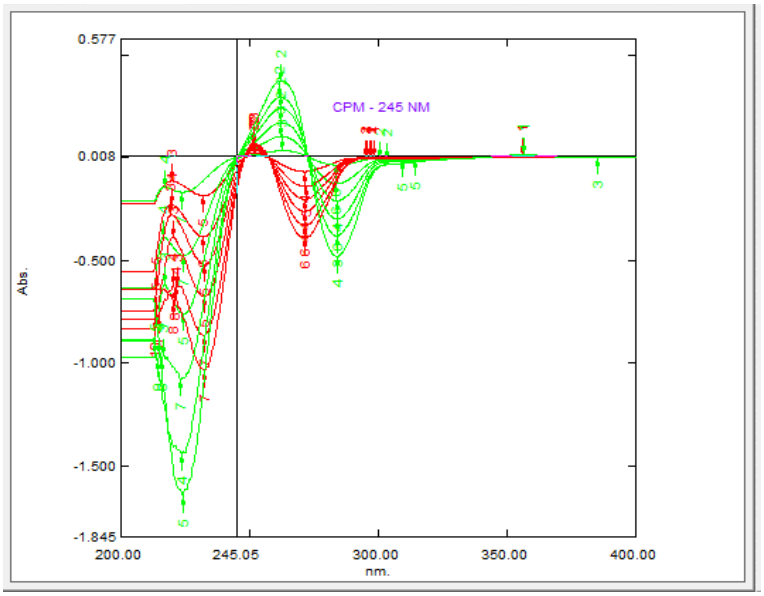

Figure 11: Linearity spectra of PHCL at 257 nm

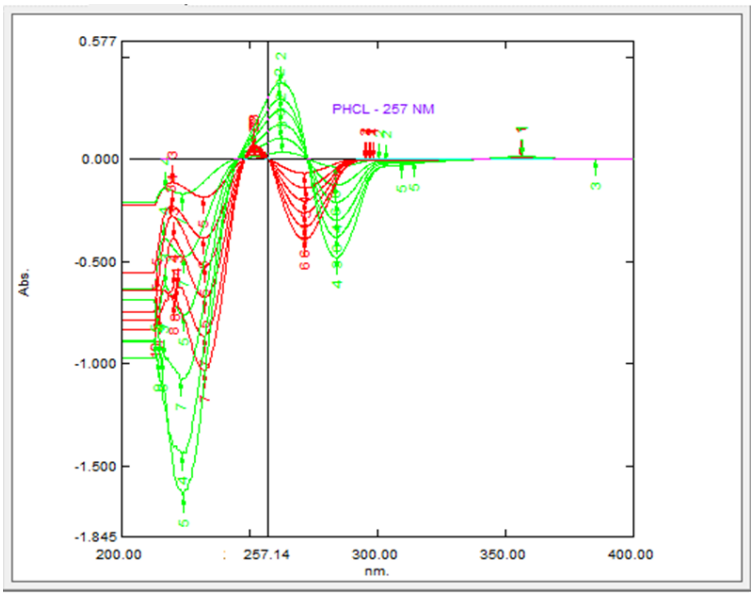

Figure 12: Overlay spectra of CPM and PHCL at 245 nm

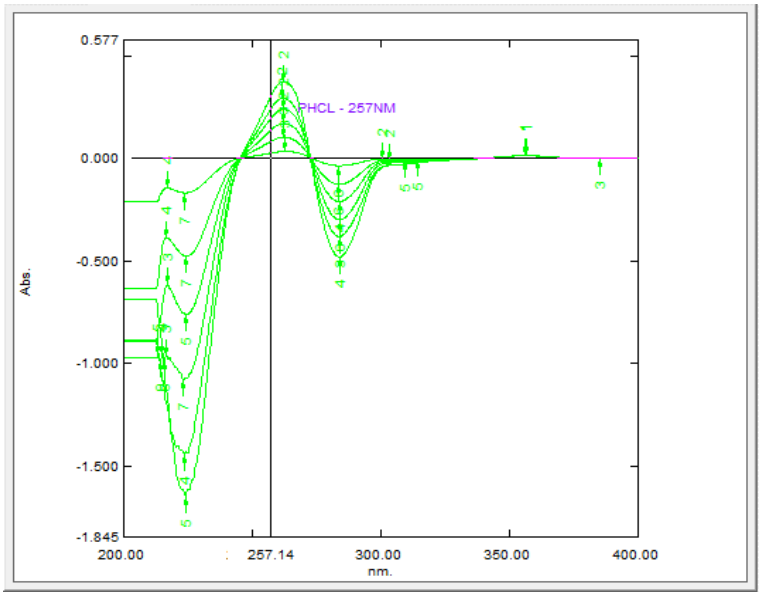

Figure 13: Overlay spectra of CPM and PHCL at 257 nm

Linearity and Range

The proposed method showed good linearity in the concentration range of 10-60 µg/ml for CPM and 10-110 µg/ml for PHCL with correlation co-efficient of 0.9991 for CPM and 0.9994 for PHCL respectively.

Table 9: Linearity of Chlorpheniramine maleate(245nm)

Concentration (µg/ml)	**Amplitude (245nm)**
10	-0.03
20	-0.059
30	-0.083
40	-0.107
50	-0.134
60	-0.157

Table 10: Linearity of Phenylephrine hydrochloride(257nm)

Concentration(µg/ml)	**Amplitude(257nm)**
10	0.025
30	0.081
50	0.135
70	0.191
90	0.238
110	0.298

Precision and accuracy was performed in the same way as followed under simultaneous equation method. The results were shown in Table.

Table 11: Inter Day Precision for Chlorpheniramine maleate

S.NO	CONC(mcg/ml)	DAY	Abs-I	Abs-II	Abs-III	MEAN	STD DEV	%RSD
1	20	1	0.059	0.06	0.061	0.06	0.001	1.666667
2	20	2	0.062	0.063	0.064	0.063	0.001	1.587302
3	20	3	0.062	0.063	0.064	0.063	0.001	1.587302
								1.613757

Table 12: Inter Day Precision for Phenylephrine Hydrochloride

S.NO	CONC(mcg/ml)	DAY	Abs-I	Abs-II	Abs-III	MEAN	STD DEV	%RSD
1	50	1	0.135	0.136	0.138	0.136333	0.001528	1.120434
2	50	2	0.138	0.142	0.138	0.136333	0.002309	1.657465
3	50	3	0.136	0.138	0.139	0.137667	0.001528	1.109582
								1.295827

Table 13: Accuracy of Chlorpheniramine maleate

S.NO	Formulation	%addition of std	Conc.of std added	Total amount of Drug	Absorbance	Amount obtained	%Recovery
1.	10	80%	8	18	0.415	18.03	100.1%
2.	10	100%	10	20	0.505	21.79	108.9%
3.	10	120%	12	22	0.517	23.26	105.7%

Table 14: Accuracy of Phenylephrine Hydrochloride

S.NO	Formulation	%addition of std	Conc.of std added	Total amount of Drug	Absorbance	Amount obtained	%Recovery
1.	25	80%	20	45	0.463	43.08	95.08%
2.	25	100%	25	50	0.568	53.08	106.17%
3.	25	120%	30	55	0.555	50.56	91.9%

The assay of both the formulations were calculated as mentioned in the respective methods and the results were mentioned below.

Table 15: Summary of results

S.NO	VALIDATION PARAMETERS	RESULTS			
		Simultaneous equation method		First derivative zero order method	
		CPM (261 nm)	PHCL (272 nm)	CPM (245 nm)	PHCL (257 nm)
1	Linearity	10-60 µg/ml	10-110 µg/ml	10-60 µg/ml	10-110 µg/ml
2	Correlation coefficient	0.9991	0.9993	0.9991	0.9994
3	Slope	0.0136	0.0093	- 0.0025	0.0027
4	Intercept	0.0111	- 0.0328	- 0.0066	- 0.0008
5	Precision	Limit <2%			

	Intra-day precision	1.894806%		1.438005%		1.492537%		0.419383%	
	Inter-day precision	1.183609%		0.61214		1.613757%		1.295827%	
6	Assay	Limit 90-110 %							
	Conc. (µg/ml)	Oral drops	syrup	Oral drops	syrup	Oral drops	syrup	Oral drops	syrup
		21.07 µg/ml	19.29 µg/ml	48.21 µg/ml	49.75 µg/ml	20.56 µg/ml	21.46 µg/ml	45.48 µg/ml	45.32 µg/ml
	% Found	105.35%	96.45%	96.42%	99.5%	102.5%	107.32%	90.96%	90.64%

7	Recovery	Oral drops				syrup				Oral drops				syrup			
		CPM		PHCL		CPM		PHCL		CPM		PHCL		CPM		PHCL	
		CONC	%	CONC	%	CONC	%	CONC	%	CONC	%	CONC	%	CONC	%	CONC	%
		18	99	45	107	18	102	45	93	18	100	45	95	18	102	45	92
		20	108	50	105	20	104	50	92	20	106	50	106	20	104	50	93
		22	103	55	93	22	96	55	91	22	91	55	91	22	104	55	92

CONCLUSION

An attempt was made to develop Simple, Accurate, Precise, Rapid, Green, Sensitive two UV Spectrophotometric methods for simultaneous estimation of chlorpheniramine maleate and phenylephrine in liquid dosage forms (i.e., syrup & oral drops).

Two UV spectrophotometric methods (i.e., simultaneous equation method & First derivative zero crossing method was exhibited good linearity, precision and assay, recovery of syrup & oral drops was found within the limits, by optimizing the methods the validation had performed as per ICH guidelines.

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