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Research Article

SMART SPECTROPHOTOMETRIC METHODS FOR THE DETERMINATION OF CHLORZOXAZONE AND PARACETAMOL FORM TABLETS

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ABSTRACT

Two simple, accurate and precise spectrophotometric methods have been introduced for the simultaneous measurement of chlorzoxazone and paracetamol in a combined tablet form. The first method is a graphical spectrophotometric method utilizes the data taken at multiple wavelengths to generate linear plots, from which the concentration of analytes can be determined, the second method is dual wavelength spectrophotometric method which is based on selecting two wavelengths for each drug to ensure that the absorbance difference is zero for the other drug. In the graphical method the absorbance was measured at 240, 260, 280 and 300nm, while in the dual wavelength method; 224.5nm and 264nm were chosen for chlorzoxazone determination since paracetamol shows equal absorbance at these wavelengths. Conversely, for paracetamol determination, wavelengths 234.5nm and 273.5nm were selected, with chlorzoxazone having zero absorbance difference at these wavelengths. Both drugs adhere to Beer-Lambert's law within a concentration range of 4–20µg/ml. The methods accuracy and precision were assessed following the International Conference on Harmonization (ICH) guidelines. Recovery studies further validated the method's accuracy. The precision of the method was demonstrated by low relative standard deviations (% RSD) less than 2%, indicating good repeatability and intermediate precision. Method accuracy was confirmed by the agreement between the determined and actual contents, also with % RSD less than 2%. The two methods enable direct analysis of chlorzoxazone and paracetamol in commercially available tablet formulations without the need for prior separation.

INTRODUCTION

Absorption spectroscopy stands out as a highly effective and commonly employed method for quantitatively analyzing various analytes. The relationship between the analyte's concentration and the light absorbed serves as the foundation for most molecular spectroscopy-based analytical techniques. Spectrophotometric methods offer numerous advantages: they are straightforward, quick, precise, highly accurate, consume less time, and can be used in virtually any laboratory setting, given that many active compounds absorb light in the UV region. However, a common challenge arises when these compounds are present in mixtures. In such cases, their spectra often overlap significantly, making it difficult to determine their concentrations simultaneously. Depending on the degree of overlap, different strategies can be employed to address this issue. These methods can handle spectra with varying degrees of overlap, as long as the spectra are not identical[1].

Various techniques have been developed to manipulate absorption data, including using different order derivatives, ratios of spectra derivatives, ratio subtraction, dual-wavelength methods, and chemometric-assisted approaches. These methods

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offer solutions to the overlapping spectra challenge, allowing for more accurate and reliable quantitative analysis[2].

Chlorzoxazone (CHL) chemically is 5-Chlorobenzoxazol-2(3H)-one, it is a centrally acting skeletal muscle relaxant with sedative properties. It is claimed to inhibit muscle spasm by exerting an effect primarily at the level of the spinal cord and subcortical areas of the brain[3]. Paracetamol (PAR) chemically is N-(4-Hydroxyphenyl) acetamide, has analgesic and antipyretic properties and weak anti-inflammatory activity. Paracetamol is often the analgesic or antipyretic of choice, especially in the elderly and in patients in whom salicylates or other nonsteriodal anti-inflammatory drugs (NSAIDs) are contra-indicated[3]. Chlorzoxazone and paracetamol combination is indicated as an adjunct to other measures, such as rest and physical therapy, for relief of pain and muscle spasm associated with acute, painful musculoskeletal conditions[4].

The combination of the two drugs is not officially appearing in any compendia; hence no official method is available for their simultaneous estimation in their combined synthetic mixture or dosage forms. Literature survey revealed that different methods have been described for the simultaneous determination of paracetamol and chlorzoxazone in dosage forms and in combination with other drugs. To our knowledge so far no graphical spectrophotometric method has been reported for the simultaneous determination of CHL and PAR, however other spectrophotometric methods employing: chemometrics-assisted UV spectrophotometric methods[5], Q-absorbance ratio [6] orthogonal functions-ratio spectrophotometry[7], H-point standard additions[8], multi-wavelength spectrophotometry[9] and simultaneous equation [10] were reported. Chromatographic methods such as reversed phase liquid chromatography[10-14] and thin layer chromatography[15,16] were also reported.

The widespread use of the two drugs in combination necessitates development of simple analytical methods for their simultaneous estimation. The aim of the work is to develop two novel spectrophotometric methods based on the graphical and dual wavelength spectrophotometric methods for the simultaneous determination of paracetamol and chlorzoxazone in combination. The methods were validated and found to be sensitive, accurate, precise; beside its cost effectiveness.

Theoretical Background

Graphical Spectrophotometric Method

The method permits data taken at multiple wavelengths to generate linear plots, from which the concentration of analytes can be determined[17]:

For a two component mixture of A and B, we can write

$$A_t = a_A C_A + a_B C_B \quad (1.1)$$

where A_t, is the absorbance of the mixture, and a_i and C_i are the absorptivity and concentration of species i, the absorbance and absorptivities referring to a common wavelength. To analyze the mixture spectrophotometrically, a_A and a_B must be different functions of wavelength. Then, from Equation 1.1

$$\frac{A_t}{a_A} = C_A + \frac{a_B}{a_A} C_B \quad (1.2)$$

Thus a plot of A_t/a_A vs. a_B/a_A, all quantities evaluated at the same wavelength, is made with data points taken at as many wavelengths as desired. The concentration C_B is obtained from the slope, and C_A can be evaluated by extrapolation to $a_B/a_A = 0$; alternatively, the sum C_A+C_B is determined by interpolation at the point where $a_B/a_A = 1$.

Another way to is to replot the data as A_t/a_B vs. a_A/a_B; then C_A is found from the slope. Yet another means is to extrapolate the line (for Equation 1.2) to $A_t/a_A = 0$.

Dual Wavelength Spectrophotometric Method

The dual-wavelength method operates on the principle that the difference in absorbance at two specific points in the spectra correlates directly with the concentration of the component of interest. This relationship holds true independent of the interference from the other component in the mixture. This method offers a straightforward approach to determining the concentration of the target component in a mixture with minimal complexity[18].

Consider a sample composed of two components, x and y. The absorbance values measured at wavelengths λ_1 and λ_2 can be represented by the following equations:

$$A_{\lambda 1} = a_x C_x + a_y C_y \quad (2.1)$$

$$A_{\lambda 2} = a'_x C_x + a'_y C_y \quad (2.2)$$

Here, a_x and a_y are the absorptivities of components x and y at λ_1, respectively. Similarly, a'_x and a'_y are the absorptivities of the two components at λ_2. C_x and C_y represent the concentrations of components x and y, respectively.

The absorbance difference in the dual-wavelength measurement can be expressed as:

$$A_{\lambda 2} - A_{\lambda 1} = A = (a'_x C_x + a'_y C_y) - (a_x C_x + a_y C_y) \quad (2.3)$$

If component y exhibits the same absorbance at both λ_1 and λ_2, i.e., $A_{\lambda 2} - A_{\lambda 1} = 0$, equation (2.3) simplifies to

$$\Delta A = (a'_x C_x + a_x C_x) \quad (2.4)$$

In this simplified form, the difference in absorbance, ΔA, becomes independent of the concentration of component y. Similarly, the contribution of component x can be eliminated by selecting two wavelengths where x exhibits equal absorbance. A comparable equation to equation (2.4) can then be formulated for component y:

$$\Delta A = \left(a'_y C_y + a_y C_y\right) \quad (2.5)$$

The concentration of either component x or y in the mixture can be determined by plotting the absorbance difference at the two selected wavelengths, where the other component exhibits equal absorbance, against its corresponding concentration. This plot can be used to derive a regression equation for calculating the concentration of the target component in the mixture.

MATERIALS AND METHODS

Instrument

A double beam UV/V is spectrophotometer, Shimadzu UV-1800, was employed with a pair of 1 cm quartz cells for all analytical work.

Chemicals and Reagents

Paracetamol and Chloroxazone working standards were provided as a gift by Blue Nile Pharmaceutical Company, Sudan. Nilogesic caplets manufactured by Blue Nile Pharmaceutical Company, labelled to contain paracetamol 300mg and chloroxazone 250mg per caplet was procured from the local market.

Methanol of analytical grade and double distilled water were used throughout the analysis. Methanol 50%v/v in water was used as a diluent.

Preparation of stock standard solutions

Separate stock solutions of PAR and CHL containing 200µg/mL each were prepared by accurately weighing about 10mg of each analyte into a separate 50ml volumetric flask, the mass was then dissolved using methanol and completed to mark with the diluent.

Preparation of the Synthetic Mixtures

Nine laboratory mixtures with varying concentrations of paracetamol and chlorzoxazone were prepared according to the multilevel multifactor approach[19]. Different volumes from stock solutions were combined in nine individual 50 mL volumetric flasks, the flasks were then made filled to mark using the diluent.

Sample Preparation

Twenty tablets were accurately weighed and crushed to a fine powder; weight of powder equivalent to one tablet was transferred into a 100ml volumetric flask and dissolved in methanol with the aid sonication for 15 minutes, cooled and completed to the mark with the methanol. The solution was allowed to stand for 30 minutes and filtered using 0.45µm nylon filter, 5ml of the filtrate were transferred into 100ml volumetric flask and completed with diluents then 5 mL from the diluted solution transferred into 50mL volumetric flask, volume was then completed to mark with the diluent.

General Procedure

For the application of the graphical method the absorbance of the mixtures was measured at 240, 260 280 and 300nm, the ratio of the mixture absorbance value to the slope at each wavelength for CHL or PAR was calculated and plotted versus the analytes slopes ratio (slope values obtained in the linearity study). The resulting straight line's slope and intercept were utilized to determine the analytes concentration.

According to the dual wavelength method, the absorbance of each mixture was measured at the pre-defined wavelength pair for the determination of analyte, the analytes concentrations were then determined from the regression equation of the absorbance differences versus concentration obtained in the linearity study.

Method Validation

The method validation parameters like linearity, precision and accuracy were checked as per ICH guidelines[20].

Linearity

Graphical Method

The response linearity with the concentration of each analyte was evaluated at five concentration levels ranging from 4-20µg/mL at 20nm interval over the range of 240-300nm. Calibration curves were generated by plotting the absorbance values at each wavelength against their corresponding concentrations.

Dual Wavelength

The absorbance difference linearity with the concentration of each analyte was evaluated at five concentration levels ranging from 4-20µg/mL at the wavelength pair selected for its determination. The calibration curves were obtained by linear regression of the absorbance differences against their corresponding concentrations.

Accuracy

The accuracy of the method was evaluated by analyzing nine synthetic mixtures containing different concentrations of the two analytes, the average percentage content of each nine mixtures and relative standard deviations (% RSD) were then calculated.

Precision

The precision of the method was evaluated by inter day and intraday variation studies. In intraday studies, six samples from the commercial product at the 100% nominal concentration were analysed, percentage content of each analyte and relative standard deviations (% RSD) of the six determinations were calculated. The same procedure was repeated on a different day using fresh reagents and chemicals, to determine the intraday variation.

RESULTS AND DISCUSSION

Optimum Wavelengths Selection

For the dual wavelength method to work effectively, the wavelength pairs should be chosen such that the interfering component has equal absorbance, whereas the component of interest varies significantly in absorbance with concentration[21].

The overlaid spectra indicated that paracetamol has equal absorbance at 224.5nm and 264nm. Consequently, these wavelengths were chosen for determining chloroxazone. On the other hand, chloroxazone displayed equal absorbance at 234.5nm and 273.5nm, leading to the selection of these wavelengths for paracetamol determination.

Using the calibration line data (shown in Tables 1 and 2), the appropriateness of the chosen wavelength pairs was confirmed by the absence of absorbance differences measured at the two wavelengths at each concentration level in the calibration curve and equality of the regression lines' slopes.

Table 1: Linearity data for paracetamol at 224.5 and 264nm (Chlorzoxazone determination)

Concentration (µg/mL)	Wavelength (nm)		ΔA
	264.0	224.5	
4	0.093	0.093	0.000
8	0.160	0.161	-0.001
12	0.245	0.244	0.001
16	0.321	0.321	0.000
20	0.389	0.389	0.000
Slope	0.0376	0.0376	
Slopes ratio	1.0		
Intercept	0.016	-0.0004	
Correlation coefficient (r^2)	0.9994	1.000	

Table 2: Linearity data for chloroxazone at 234.5 and 273.5 nm (Paracetamol determination)

Concentration (µg/mL)	Wavelength (nm)		ΔA
	273.5	234.5	
4	0.051	0.051	0.000
8	0.096	0.095	0.001
12	0.142	0.142	0.000
16	0.189	0.187	0.002
20	0.235	0.232	0.003
Slope	0.0231	0.0227	
Slopes ratio	1.01		
Intercept	0.0052	-0.00097	
Correlation coefficient (r^2)	1.000	1.000	

Linearity

Linear regression of the absorbance values measured at 20nm interval over the range of 240-300nm for each analyte against the corresponding concentrations produced a straight line with correlation coefficients greater than 0.990, the residuals were spread uniformly and at random around the regression lines, passing the normality distribution test ($p<0.05$)[20]. The calibration data is shown in Table 3 and 4.

Table 3: Linearity data for graphical method (chlorzoxazone)

	240 nm	260 nm	280 nm	300 nm
Slope	0.0537	0.0139	0.0307	0.0166
Intercept	0.0152	0.0023	0.0048	0.0087
r^2	0.9998	0.9993	0.9997	0.9996

Table 4: Linearity data graphical method (paracetamol)

Chlorzoxazone	240 nm	260 nm	280 nm	300 nm
Slope	0.0537	0.0139	0.0307	0.0166
Intercept	0.0152	0.0023	0.0048	0.0087
r^2	0.9998	0.9993	0.9997	0.9996

Linear regression of the absorbance differences at the selected wavelength pair for each analyte against the corresponding concentrations produced a straight line with correlation coefficients greater than 0.990, the residuals were spread uniformly and at random around the regression lines, passing the normality distribution test ($p<0.05$) (20). The calibration data is shown in Table 5.

Table 5: Linearity data (dual wavelength method)

Parameter	PAR	CHL
Slope (b)	0.0354	0.0298
Intercept (a)	0.0054	- 0.0061
Correlation coefficient (r^2)	0.9993	0.9990
Standard deviation of the slope (S_b)	0.0005	0.0005
Standard deviation of the intercept (S_a)	0.003	0.003
LOD (µg/ml)	0.28	0.33
LOQ (µg/ml)	0.85	0.99

Accuracy

The results obtained by both methods are in good agreement with the label and have low relative standard deviation < 2% (20). The accuracy study data is summarized in Tables 6 and 7.

Table 6: Accuracy data of the graphic method

	Paracetamol			Chlorzoxazone		
	Actual	Theoretical	% LC	Actual	Theoretical	% LC
1	15.00	15.35	102.33	15.00	14.68	97.86
2	3.00	3.08	102.53	15.00	14.96	99.75
3	9.00	9.40	104.44	15.00	14.72	98.14
4	15.00	15.55	103.64	3.00	2.93	97.60
5	3.00	3.18	105.85	3.00	3.08	102.52
6	9.00	9.43	104.75	3.00	2.95	98.20
7	9.00	9.42	104.62	9.00	8.97	99.70
8	9.00	15.51	103.37	9.00	8.72	96.88

9	3.00	3.12	103.96	9.00	8.96	99.59
Average			103.94			98.91
Standard deviation			1.05			1.59
Relative standard deviation (%)			1.01			1.61
Confidence interval (p = 0.05)			± 0.81			± 1.23

Table 7: Accuracy data of dual wavelength method

	Paracetamol			Chlorzoxazone		
	Actual	**Theoretical**	**% LC**	**Actual**	**Theoretical**	**% LC**
1	20.28	20.00	101.42	19.94	20.00	97.93
2	16.00	16.00	100.00	19.80	20.00	98.96
3	12.18	12.00	101.42	20.14	20.00	100.68
4	20.28	20.00	101.42	15.92	16.00	98.27
5	16.12	16.00	101.71	15.94	16.00	99.56
6	12.22	12.00	101.90	16.20	16.00	101.29
7	20.34	20.00	101.71	11.86	12.00	98.85
8	16.22	16.00	101.42	11.94	12.00	99.42
9	12.22	12.00	100.95	12.00	12.00	100.00
Average			101.33			99.44
Standard deviation			0.57			1.10
Relative standard deviation (%)			0.56			1.09
Confidence interval (p =0.05)			± 0.43			± 0.84

Precision

The proposed methods precision was verified in its repeatability and intermediate precision parameters according to the ICH guideline. Six replicate determinations of the samples containing 100% of the two analytes expected concentrations in the pharmaceutical product were analyzed. The concentrations of the two drugs were calculated each from the corresponding calibration curve equation. Satisfactory % RSD values <2% were obtained. The intermediate precision was verified by repeating the process was on a different day with fresh reagents and samples, satisfactory %RSD levels below 2% were achieved from the combined results of the two analysis days. Statistical comparison of the two days' precision results using the Student's t-test confirmed that the results were consistent regardless of the day of the assay or reagent preparation. The t-statistics were found to be less than the t-critical value at p=0.05, as presented in Table 8 and 9.

Table 8: Precision data of graphical method

	Repeatability		Intermediate precision	
Sample No.	**PAR**	**CHL**	**PAR**	**CHL**
1	105.89	100.03	103.37	98.80
2	103.56	98.91	104.62	98.58
3	103.18	99.00	104.75	100.66
4	102.42	100.05	103.64	99.56
5	104.37	102.05	104.44	99.02
6	103.95	100.99	102.33	99.05
Average	103.90	100.17	103.86	99.28
Standard deviation	1.19	1.20	0.85	0.69
Relative standard deviation%	1.14	1.20	0.82	0.69

Table 9: Precision data of dual wavelength method

	Repeatability		**Intermediate precision**	
Sample No.	**PAR**	**CHL**	**PAR**	**CHL**
1	103.62	99.31	104.00	99.86
2	104.4	99.31	105.52	100.41
3	105.9	98.76	103.62	99.86
4	105.52	99.86	103.23	99.31
5	104.38	99.31	104.76	99.31
6	104.76	100.41	105.14	99.86
Average	104.76	99.49	104.38	99.4
Standard deviation (n =6)	0.86	0.57	0.9	0.64
Relative standard deviation%	0.83	0.57	0.86	0.65

CONCLUSION

The proposed methods provide straightforward and fast approach for the direct determination of chlorzoxazone and paracetamol in commercially available tablet formulations without the need for prior separation. The analysis results for both drugs from the tablet formulation were very close to the actual concentrations. The standard deviations were satisfactorily low, indicating the method's accuracy and precision, as well as its freedom from interference by excipients. This method is suitable for routine analysis, in-process control and as alternative to the expensive chromatographic separation techniques.

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