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Development and Validation of Green Spectrophotometric Methods for Simultaneous Determination of Paracetamol, Pamabrom and Pyrilamine Maleate in Bulk and Pharmaceutical Dosage Form

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Authors' contributions

This work was carried out in collaboration between all authors. Authors MMF, FIH and NSR designed the study and wrote the protocol. Authors ESM and NSR managed the analyses of the study and wrote the first draft of the manuscript. Authors ESM and MMF managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Four simple and accurate spectrophotometric methods were developed for the simultaneous determination of paracetamol, pamabrom and pyrilamine maleate. The first is a zero order spectrophotometric method used for the determination of pyrilamine maleate in presence of paracetamol and pamabrom in the range of 0.5-60 µg/mL by measuring the absorbance at 306.8 nm where paracetamol and pamabrom exhibits zero reading. The other three methods;

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bivariate, dual wavelength and area under the curve methods were developed for the simultaneous determination of paracetamol, pamabrom in presence of pyrilamine maleate. Bivariate calibration algorithm involves the use of two selected wavelengths; 260 nm and 280 nm for the determination of the two studied drugs. For the dual wavelength, paracetamol shows equal absorbance at 212.87 and 220.0 nm, where the differences in absorbance were measured for the determination of PBM. Similarly, differences in absorbance at 264.23 nm and 292.28 nm were measured for determination of paracetamol. In the area under curve method; the area between 237.14 to 247.14 nm was used for determination of paracetamol and 273.6 to 283.6 nm for pamabrom. Beer's law was obeyed in the concentration ranges of 1-30 µg mL^{-1} for paracetamol and pamabrom in all methods. LOD was calculated and ranges from 0.149-0.766 µg/mL, while LOQ was found to be in the range of 0.556-1.145 µg/mL. The proposed methods were successfully applied for the simultaneous determination of PCM, PBM and PAM in their pharmaceutical preparation without interference from additives present with mean recovery ranging from 98.99 to 101.44%. Statistical analysis of the results obtained by the proposed spectrophotometric methods compared with a reported method revealed no significant difference between the proposed and reported methods confirming accuracy and precision at 95% confidence limit.

Keywords: Paracetamol; pamabrom; pyrilamine maleate; zero order; bivariate; dual wavelength; area under the curve.

1. INTRODUCTION

Paracetamol (PCM) is a pain reliever and a fever reducer. It is chemically known as N-(4-hydroxyphenyl) acetanilide. It is used to treat many conditions such as headache, muscle aches, arthritis, backache, toothaches, colds and fevers [1]. Pamabrom (PBM) is a mixture containing 2-amino-2-methyl-1-propanol and 8-bromotheophylline (a methylxanthine) in a 1:1 ratio, with mild diuretic activity. It is used for the treatment of premenstrual symptoms, swelling, feeling full and weight gain [2]. Pyrilamine maleate (PAM); 1, 2- ethanediamine, N-[(4-methoxy phenyl) methyl -N', N'-dimethyl-N-2-pyridinyl-(Z)-2-butenedioate (1:1) is classified as antihistaminic drug and used for treatment of common cold, flu, allergies, breathing illnesses and other conditions [3]. The combination of PCM, PBM, and PAM is used to treat symptoms of premenstrual syndrome, such as tension, bloating, water weight gain, headache, back pain, cramps, aches and irritability [4]. Chemical structures of the three studied drugs are presented in Fig. 1.

Literature review revealed only one HPLC method [5] for the simultaneous determination of PCM, PBM and PAM. Several spectrophotometric [6-11], HPLC [12-18] and GC [19-21] methods have been reported for PCM determination either individually or in combination with other active ingredients. PCM and PBM have been determined simultaneously by different spectrophotometric [22-25], HPLC [26-31] and TLC [31-33] methods. Whereas, only few analytical methods [34-36] have been found for the determination of PAM. The aim of the present work is to develop validated, simple, accurate, and reproducible spectrophotometric methods for the simultaneous determination of the three cited drugs.

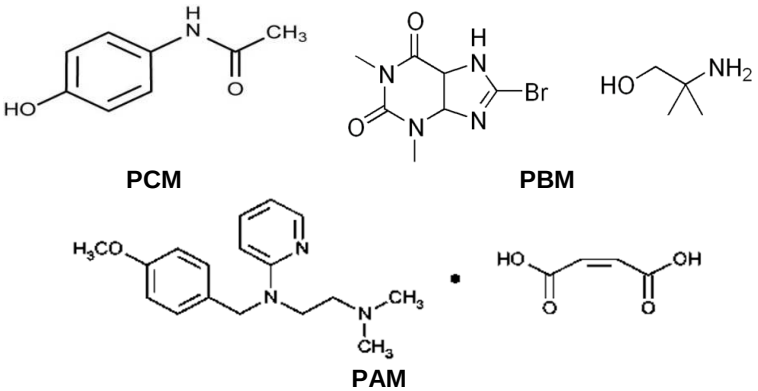

Fig. 1. Chemical structures of PCM, PBM and PAM

2. EXPERIMENTAL

2.1 Instrumentation

Shimadzu, UV-Vis 1601PC Spectrophotometer (Tokyo, Japan), with two matched 1 cm path length quartz cell. Data was processed using UV probe software.

2.2 Samples

2.2.1 Pure samples

- PCM; batch no. NA106116002 and PBM; NA106116001 were kindly supplied by Haya Pharm. (Port Said, Egypt). PAM; batch no. P 01100211 was obtained from (Sigma – Aldrich, Germany). Their purity was found to be 99.16%, 100.47% and 99.85% for PCM, PBM and PAM; respectively as stated by the supplier.

2.2.2 Market sample

Pamprine multi- symptoms® tablets; lot no 08F33, labeled to contain 500 mg PCM, 25 mg PBM and 15 mg PAM; Chattem, Inc, China.

2.3 Standard Solutions

Standard solutions of the drugs (0.1 mg mL^{-1}) were prepared by dissolving 10 mg of PCM, PBM or PAM in 100 mL distilled water.

2.4 Procedures

2.4.1 Calibration curve

Aliquots of PCM, PBM or PAM standard solution equivalent to 0.01-0.3 mg of PCM or PBM and 0.005-0.6 mg of PAM were transferred separately into three sets of 10- mL volumetric flasks, and then diluted to volume with distilled water. Zero order absorption spectra of PCM, PBM and PAM were recorded over the range of 200 – 400 nm and stored in the computer.

2.4.1.1 Zero order method

The zero order spectra of the prepared solutions were measured at 306.8 nm against distilled water as a blank. The calibration curve relating the absorbance at 306.8 nm to corresponding concentrations in µg mL^{-1} of PAM was constructed**.**

2.4.1.2 Bivariate method

From the zero order spectra of PCM and PBM, calibration curves at different wavelengths from 260 to 280 nm with 2 nm interval were constructed and the regression equation at each wavelength was calculated. From both sets of regression equations; the sensitivity matrices K were calculated.

2.4.1.3 Dual wavelength method

Absorbance difference of PCM or PBM solutions was measured at 264.23 and 292.28 nm or at 212.87 and 220 nm; respectively. Calibration curves were constructed by plotting the absorbance difference versus concentration in µg mL^{-1} and the regression equations were computed.

2.4.1.4 Area under the curve method

Using zero order spectra of PCM and PBM, calibration curves at 237.14- 247.14 nm (λ_1-λ_2) and 273.6 -283.6 nm (λ_3-λ_4) were constructed by plotting area integrated between these selected wavelength ranges for both drugs and their corresponding concentrations.

2.4.2 Assay of laboratory prepared mixtures

Different aliquots volumes of PCM, PBM and PAM (0.1 mg mL^{-1}) with different ratios were transferred into a series of 10 - mL volumetric flasks and diluted to the volume with distilled water. After applying the corresponding manipulation steps, the obtained solutions were analyzed by the four proposed spectrophotometric methods and the concentration of each drug was calculated by substitution in the corresponding equation.

2.5 Application to Pharmaceutical Preparation

Five Pamprine multi- symptom ®tablets each labeled to contain 500 mg PCM, 25 mg of PBM and 15 mg of PAM were weighed, powdered and mixed well. An accurately weighed quantity of the powder equivalent to one tablet was introduced into a 100 - mL volumetric flask and volume was adjusted up to the mark with distilled water. The flask was sonicated for 15 minutes then filtered. The clear filtrate claimed to contain 5 mg mL^{-1} of PCM, 0.25 mg mL^{-1} of PBM and 0.15 mg mL^{-1} of PAM. The solutions were further diluted to the desired concentration and analyzed by the proposed methods. The drug concentrations were calculated from the appropriate regression parameters.

3. RESULTS AND DISCUSSION

Nowadays, in the development of new analytical procedures, care about toxicity and danger of the reagents used and the wastes produced are as important as other analytical feature. Hence, there is an urgent necessity to develop methods which are less harmful to human and to the environment according to 12 principles of Green Chemistry [37].

Accordingly, four different green analytical procedures were developed; using only water as a solvent through out the whole procedures aiming for the simultaneous determination of PAM, PCM and PBM.

3.1 Zero Order Method

Zero order absorption spectra of PCM, PBM and PAM showed that intact PAM exhibit strong band at 306.8 nm showing no interference from PCM and PBM, thus PAM can be determined at this wavelength; Fig. 2.

3.2 Bivariate Method

Bivariate calibration spectrophotometric method is a direct method which has been proposed for the resolution of mixtures. The principle of bivariate calibration is the measurement of two components (A and B) at two selected wavelengths ($\lambda_1$and λ_2) to obtain two equations [38]:

$A_{AB1} = m_{A1}C_AC_B + e_{AB1}$ $A_{AB2} = m_{A2}C_AC_B + e_{AB2}$

The resolution of each equation set allows the evaluation of CA and CB values:

$C_A = (A_{AB1} - e_{AB1} - m_{B1}C_B)/m_{A1}$ $C_B = [m_{A2}(A_{AB1} - e_{AB1}) + m_{A1}(e_{AB2} - A_{AB2})/m_{A2}m_{B1} - m_{A1}m_{B2}]$

Where C_A, C_B is the concentration of component A (PCM), component B (PBM); m_{A1}, m_{A2} are the slope values of PCM at λ_1, λ_2; m_{B1}, m_{B2} are the slope values of PBM at λ_1, λ_2; A_{AB1}, A_{AB2} are the absorbance of the binary mixture at λ_1, λ_2; e_{AB1}, e_{AB2} are the sum of the intercepts of PCM and PBM at λ_1 and λ_2, respectively.

In order to apply the bivariate method in the resolution of binary mixture of PCM and PBM, the absorbance of the two components at selected wavelengths was recorded in the region of overlapping; from 260 to 280 nm at 2 nm interval. The calibration curve equations and their respective linear regression coefficients were obtained to ensure a linear relationship between the absorbance and the corresponding concentration.

The slope values of the linear regression equations for both PCM and PBM at the selected wavelengths were used according to Kaiser method [39] to calculate the sensitivity matrices K to find out the optimum pair of wavelength at which the binary mixtures were recorded.

$$K = \begin{bmatrix} m_{A_1} & m_{B_1} \\ m_{A_2} & m_{B_2} \end{bmatrix}$$

3.3 Dual Wavelength Method

The principle for dual wavelength method is “the absorbance difference between two points on the mixture spectra is directly proportional to the concentration of the component of interest”. This method offer an efficient method for analysis of binary mixtures where dual analytical wavelengths were selected in a way to make the

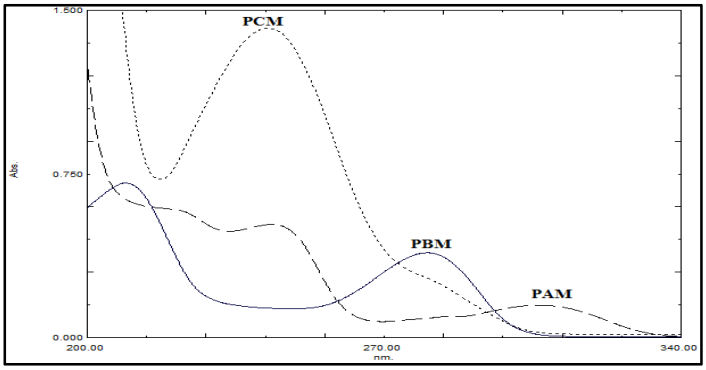

Fig. 2. Zero order Absorption spectra of 30 µg mL^{-1} PCM (……), 10 µg mL^{-1} of PBM ( ) and 20 µg mL^{-1}of PAM (-----) in distilled water

Table 1. Values of sensitivity matrix values calculated according to Kaiser's method (K× 10^{-6}) for the determination of PCM and PBM

λ/ λ	260	262	264	266	268	270	272	274	276	278	280
260	0	180	390	580	750	920	1060	1180	1260	1310	**1330**
262		0	460	610	740	880	990	1090	1160	1200	1210
264			0	180	340	500	610	720	790	840	850
266				0	160	310	420	520	590	640	660
268					0	150	260	350	420	460	490
270						0	110	200	270	310	340
272							0	90	160	200	230
274								0	65.9	110	140
276									0	460	490
278										0	32.4
280											0

Maximum value of K was obtained at 260 and 280nm, thus can be used for the determination of PCM and PBM

absorbance difference zero for one drug in order to analyze the other drug [40,41].

The difference in absorbance at 212.87 and 220.0 nm was zero for PCM so they were selected or determination of PBM, whereas the difference in absorbance at 264.23 and 292.28 nm was zero for PBM and hence they were used to analyze PCM.

3.4 Area under the Curve Method

Area under the curve spectrophotometric method was developed for determination of PCM and PBM without interference with PAM in pure and pharmaceutical dosage form. The principle of this method is "the area under two points on the mixture spectra is directly proportional to the concentration of the component of interest" [42]. Calibration curve was plotted at the wavelength ranges selected for estimation of PCM (237.14-247.14 nm (λ_1-λ_2)) and PBM (273.6 -283.6 nm (λ_3-λ_4)) and area were integrated between these selected wavelength ranges for both drugs.

Concentration of two the drugs in mixed solution were calculated according to the following equations [43]:

$C_{PCM} = A_2ay_1 - A_1ay_2 / ax_2ay_1 - ax_1ay_2 C_{PBM} = A_1ax_2 - A_2ax_1 / ax_2ay_1 - ax_1ay_2$

Where

A_1 = Area at 237.14 - 247.14 nm (λ_1-λ_2);
A_2 = Area at 273.6 -283.6 nm (λ_3-λ_4);
ax_1 = Absorptivity value of PCM at 237.1- 247.1 nm;
ax_2= Absorptivity value of PCM at 273.6 -283.6 nm;
ay_1 = Absorptivity value of PBM at 237.1 - 247.1 nm;
ay_2 = Absorptivity value of PBM at 273.6 – 283.6 nm.

3.5 Methods Validation

The proposed methods were validated according to ICH guidelines [44].

3.5.1 Linearity

The linearity of the proposed methods was evaluated through the analysis of serial concentrations of each drug. The produced response was plotted as a function of the corresponding concentration in which the linearity range is 1-30 µg mL^{-1} for PCM and PBM while PAM showed good linearity from 0.5 to 60 µg mL^{-1}; Table 2.

3.5.2 LOD and LOQ

LOD and LOQ were determined using the standard deviation of multiple blank samples and the slope of the calibration curve; Table 2.

3.5.3 Accuracy and precision

The accuracy and precision of the proposed methods were assessed using three different concentrations of pure samples of the drug covering the linearity range, each in triplicate, within one day for intraday analysis and three different days for interday analysis. RSD% for the three methods were found to be less than 2% indicating good precision of the developed methods; Table 2.

Table 2. Spectral data for the determination of PCM, PBM and PAM by the proposed methods

Parameter	Zero order method	Bivariate method				Dual wavelength method		Area under the curve method	
	PAM	PCM		PBM		PCM	PBM	PCM	PBM
λ_{max} (nm)	308	260	280	260	280	220.5-277.5	217.28-262.5	237.14-247.14	273.6-283.6
Linearity range (µg mL^{-1})	0.5-60	1-30	1-30	1-30	1-30	1-30	1-30	1-30	1-30
Regression parameters									
Slope± SD(S_Y)	0.015±0.0001	0.039±0.0005	0.012±0.0002	0.016±0.0002	0.037±0.0002	0.023±0.0002	0.003±0.0002	0.017±6.96×10^{-5}	0.021±0.002
Intercept± SD(S_x)	0.009±0.007	0.017±0.008	0.002± 0.003	0.008±0.003	0. 019 ±0.003	-0.004±0.003	0.009 ± 0.003	0.081±0.001	0 .068±0.003
SD of Residual(S_{YX})	0.009	0.012	0.004	0.004	0.004	0.004	0.005	0.002	0.004
Correlation coefficient (r^2)	0.9997	0.9996	0.9996	0.9998	0.9995	0.9995	0.9996	0.9994	0.9996
Accuracy(R)									
Interday	99.88 ±0.223	100.23±0.650	100.44±1.248	100.42±00.75	100.55±0.798	100.34±0.676	100.06±1.132	100.19±0.624	100.30±1.53
Intraday	100.21±0.287	99.45±0.811	100.41±1.217	100.23±0.499	100.77±0.460	100.64±0.960	100.61±1.116	99.91±1.126	100.32±0.676
Precession									
Interday	0.939	0.944	1.101	0.935	0.931	0.847	1.082	1.214	0.810
Intraday	1.061	0.634	0.916	1.110	0.996	1.055	0.983	0.991	0.964
LOD(µg mL^{-1})	0.284	0.691	0.776	0.492	0.242	0.149	0.172	0.234	0.483
LOQ(µg mL^{-1})	0.556	1.094	1.105	1.088	0.735	0.816	0.937	0.708	1.145

Table 3. Determination of PCM, PBM and PAM in laboratory prepared mixtures by the proposed methods

PCM : PMB : PAM Ratio	Zero Order method	Bivariate method		Dual wavelength method		Area under the curve method	
	Recovery %						
	PAM	PCM	PBM	PCM	PBM	PCM	PBM
1 : 1 : 1	100.67	97.61	100.03	101.01	101.28	101.02	101.3
2 : 2 : 1	99.54	99.76	98.7	99.05	98.81	101.86	98.95
1 : 1 : 2	101.75	98.32	98.07	99.19	101.85	99.88	101.14
20 : 1 :0.6	98.33	99.02	101.99	99.65	100.59	101.25	99.03
Mean% ± S.D.	100.07±1.471	98.67 ±0.923	99.69 ±1.733	99.72 ±0.894	100.63 ±1.319	101.00 ±0.828	100.10 ±1.289

Table 4. Results obtained by the proposed methods compared with reported method [5] for determination of PCM, PBM and PAM in pharmaceutical dosage form

Parameter	Zero Order method	Bivariate method		Dual wavelength method		Area under the curve method		Reported method [5]		
	PAM	PCM	PBM	PCM	PBM	PCM	PBM	PCM	PBM	PAM
Linearity range (µg mL^{-1})	0.5-60	1-30	1-30	1-30	1-30	1-30	1-30	50-150	2.5-7.5	1.5-4.5
N	3	3	3	3	3	3	3	3	3	3
Mean %	98.99	101.04	99.88	99.75	101.44	100.35	100.62	100.14	100.07	99.87
SD	1.474	1.503	0.601	1.588	0.501	1.600	1.112	0.510	1.776	0.945
Variance	2.173	2.261	0.36	2.524	0.251	2.561	1.237	0.260	3.154	0.894
t	0.870 (2.776)	0.978 (2.776)	0.169 (2776)	0.404 (2.776)	1.288 (2.776)	0.220 (2.776)	0.457 (2.776)	-	-	-
F	2.430 (19)	8.682 (19)	8.761 (19)	9.693 (19)	12.557 (19)	9.833 (19)	2.549 (19)	-	-	-

-The values in parenthesis are the theoretical t- and F- at P = 0.05.

-Reported method [5] for determination of PCM, PBM and PAM is stability indicating HPLC assay method using C_{18} column with mobile phase of methanol and acidified water (pH 1.8) in the ratio of (27: 73 v/v respectively). Flow rate of the mobile phase was 1.5 mL/min with detection at 300 nm

3.5.4 Selectivity

Methods selectivity was assured by analyzing laboratory prepared mixtures of the studied drugs with different ratios within the linearity range. Good recoveries of the three drugs, ranging from 98.67-101.00% indicate high selectivity of the proposed methods; Table 3.

3.5.5 Robustness

The robustness of the proposed methods was examined by evaluating the influence of using other spectrophotometers (Perkin Elmer and Jasco spectrophotometric instrument). The RSD % in all cases did not exceed 1.82% indicating the reliability of the proposed methods.

3.4.6 Stability of standard solutions

The stability of PCM, PBM and PAM solutions was evaluated by analyzing of two different solutions; one of them was kept at room temperature while the other in refrigerator against freshly prepared standards. The results showed that the three drugs were stable for one week either kept at room temperature or in refrigerator.

3.6 Application to Pharmaceutical Preparation

The proposed methods were successfully applied for the simultaneous determination of PCM, PBM and PAM in pharmaceutical preparation without interference from the additives present. Satisfactory results were obtained for each drug with mean recovery ranging from 98.99 to 101.44%. Statistical analysis of the results obtained by the proposed methods compared with a reported method [5] revealed no significant difference between the proposed and reported methods confirming accuracy and precision at 95% confidence limit; Table 4.

4. CONCLUSION

The proposed study describes four different spectrophotometric methods for the simultaneous estimation of PCM, PBM and PAM in bulk or in their combination; zero order method, bivariate, area under the curve and dual wavelength methods. From economic point of view, the proposed methods are simple, rapid and inexpensive as it is less time-consuming and does not require various elaborate treatment or tedious extraction procedures. From environmental point of view, the proposed method is environmentally safe since water is the reaction solvent which is the most important green solvent and volatile solvents are omitted in the present work.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

DISCLAIMER

This manuscript was presented in the conference Conference name: “8th international scientific conference of faculty of pharmacy, Cairo University”.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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