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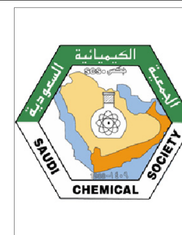

ORIGINAL ARTICLE

Simultaneous determination of hyoscine N-butyl bromide and paracetamol in their binary mixture by RP-HPLC method

Nouruddin W. Ali [a], Mohammed Gamal [a,c,*], Mohammed Abdelkawy [b]

[a] *Pharmaceutical Analytical Chemistry Department, Faculty of Pharmacy, Beni-Suef University, Alshaheed Shehata Ahmed Hegazy St., 62574 Beni-Suef, Egypt*
[b] *Pharmaceutical Analytical Chemistry Department, Faculty of Pharmacy, Cairo University, Kasr El-Aini St., 11562 Cairo, Egypt*
[c] *Pharmacy Program, Ibn Sina National College of Medical Science, Mahgar Street 31906, Jeddah 21418, Saudi Arabia*

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Abstract RP-HPLC chromatographic method was developed for the determination of hyoscine N-butyl bromide (HBB) and Paracetamol (PAR). In this chromatographic method, HBB and PAR were separated using C18 (25 cm × 4.6 mm i.d. 5 μm particle size) column as a stationary phase and water: methanol (50:50, V/V pH adjusted to 3.9 with CF_3COOH acid) as a mobile phase, maintaining the flow rate at 1.0 mL min^{-1} with UV detection at 210 nm. The proposed method was successfully applied for the determination of HBB and PAR in pure form over a concentration range of 2.0–50.0 μg mL^{-1} for HBB with mean percentage recovery of 100.10 ± 0.475 and over a concentration range of 5.0–200.0 μg mL^{-1} for PAR with mean percentage recovery of 99.87 ± 0.942 and in their pharmaceutical formulations (Buscopan plus® tablets, Buscamol® tablets and Buscopan plus® suppositories).

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1. Introduction

Hyoscine N-butyl bromide is a quaternary ammonium anticholinergic agent. It has antispasmodic action on the smooth muscles of the gastrointestinal, biliary and urinary tracts (Martindale, 2007).

Paracetamol (PAR), 4-acetamidophenol, is an effective analgesic and antipyretic for the treatment of minor, non-inflammatory conditions in patients who are prone to gastric symptoms (Martindale, 2007). The structural formulas of HBB and PAR are shown in Fig. 1.

There are many reports for the determination of HBB and PAR either separately or in combination with other drugs including spectrophotometric methods (Mohamed et al., 1997; Mahrous et al., 1992; Issopoulos and Pavlou-Zervou, 1994; Thomos et al., 1994; Gouda, 2010; Issa et al., 2011; Mujahid et al., 2014; Gouda et al., 2013), chromatographic

* Corresponding author. Tel.: +20 1141618950.
E-mail address: mgamalm3000@yahoo.com (M. Gamal).
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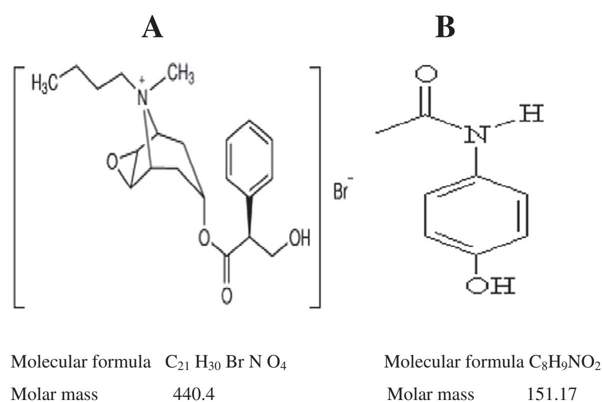

Figure 1 Chemical structure of HBB (A) and PAR (B).

methods (Papadoyannis et al., 1994; Lau and Mok, 1997; Dewani et al., 2014; Favreto et al., 2012), electrochemical methods (El-Saharty et al., 2007; Farhadi and Karimpour, 2007; Ganjali et al., 2010; Wassel and Abu-Talib, 2010), Capillary electrophoresis methods (Cherkaoui et al., 1999; Chang et al., 2000) and titrimetric methods (British Pharmacopoeia, 2009; Kumar and Letha, 1997; Vyas and Kharat, 1988).

Few methods have been mentioned for the analysis of HBB and PAR in the binary mixture. In The first method, Erk (1996) analyzed HBB and Paracetamol in their binary mixture by precipitating HBB with ammonium reineckate at pH 6.0 selectively and reading the absorbance of the solution of the precipitate in acetone at 525.0 nm for HBB and by measuring the dA/dλ values at 254.5 nm in the first derivative spectra of the remaining solution for paracetamol.

In the second method (Parissi-Poulou and Panderi, 1999), solid phase extraction procedure using strong cation exchange cartridges followed by a reversed-phase HPLC assay was applied to the analysis of HBB, PAR and lidocaine hydrochloride in injection forms. The chromatographic separation was performed on a C-18 column. The mobile phase consisted of a mixture of acetonitrile: ammonium acetate 0.2 M (30:70, V/V) pumped at a flow rate 1.2 mL min^{-1}.This method suffers a lot of drawbacks among which is the use of complicated procedures such as solid phase extraction procedure. This technique is expensive, time consuming and not suitable for the routine analysis of the binary mixture of HBB and PAR in quality control analysis so there is a great need for developing a simple HPLC method for routine analysis of the cited drugs.

Therefore, the objective of this work is to develop sensitive, selective and reproducible RP-HPLC method for simultaneous determination of HBB and PAR for routine quality control analysis of these drugs either in bulk powder or in pharmaceutical formulations. Chromatographic methods are well known for providing high selectivity and sensitivity when used for the determination of pharmaceutical drugs.

2. Experimental

2.1. Apparatus

Shimadzu Class – LC 10 AD Liquid Chromatography supplied with Shimadzu SPD – 10 A UV–vis Detector (Shimadzu Corporation, Japan). Phenomenex C18 (25 cm × 4.6 mm i.d, 5 μm particle size) column was used as a stationary phase for HPLC determinations (USA).

Sonix TV ss-series ultrasonicator (USA).

2.2. Materials

2.2.1. Pure samples

Paracetamol (PAR) and hyoscine N-butyl bromide (HBB) were kindly supplied by CID Co. Chemical Industries Development, Giza, Egypt. Their purity was found to be 99.94 ± 1.537 and 99.21 ± 1.012, respectively, according to the company analysis certificate (HPLC).

2.2.2. Market samples

1-. Buscopan plus® tablets (Batch No 116738T) labeled to contain 500 mg of (PAR) and 10 mg of (HBB), CID Co. Chemical Industries Development, Giza, Egypt.
2-. Buscamol. F.C® tablets (Batch No 12001025) labeled to contain 500 mg of (PAR) and 10 mg of (HBB), DELTA PHARMA, Egypt.
3-. Buscopan plus® Suppositories (Batch No 105) labeled to contain 800 mg of (PAR) and 10 mg of (HBB), CID Co. Chemical Industries Development, Giza, Egypt.

2.2.3. Reagents

All reagents and chemicals used were of analytical grade and were used without further purification

1-. Methanol HPLC grade (Sigma Aldrich, Germany).
2-. Deionized water (SEDICO pharmaceutical Co., 6th October City, Egypt).
3-. Orthophosphoric acid and glacial acetic acid (EL - NASR Pharmaceutical Chemicals Co., Abu - Zabaal, Cairo, Egypt).
4-. Trifluoroacetic acid (Spectrochem, India).

2.3. Preparation of standard solutions

2.3.1. Paracetamol (PAR) and hyoscine N-butyl bromide (HBB) stock standard solutions (1 mg mL^{-1})

Weigh accurately 0.1 g of each drug into two separate 100-mL volumetric flask, 50 mL methanol was added, shaken to dissolve then complete the volume to the mark with methanol.

2.3.2. Paracetamol (PAR) and Hyoscine N butyl bromide (HBB) working standard solutions (100 μg mL^{-1})

Transfer accurately 10 mL of the stock solution of each drug into two separate 100-mL volumetric flasks and complete to the volume with methanol to get 100 μg mL^{-1} working solution for each drug.

2.4. Procedures

2.4.1. Linearity and construction of calibration curves

Transfer accurate aliquots equivalent to (20–500) μg of HBB and (50–2000) μg of PAR from their corresponding working solutions (100 μg mL^{-1}) or stock solutions (1000 μg mL^{-1}) into two separate sets of series of 10-mL volumetric flasks.

Complete the volume with methanol. Make triplicate 20 μL injections for each concentration. The separation was done on a C_{18} column using water: methanol 50: 50 V/V, pH adjusted to 3.9 with triflouroacetic acid as a mobile phase. All solvents were filtered through a 0.45 μm membrane filters before use and degassed in an ultrasonic bath for 20 min. Record the chromatograms at ambient temperature maintaining the flow rate at 1.0 mL min^{-1} and detect the effluent at 210 nm. Construct the calibration curves for each compound by plotting the peak area/10^4 versus the corresponding concentration and then compute the regression equations.

2.4.2. Analysis of laboratory prepared mixtures

Prepare mixtures containing HBB and PAR in different ratios. Proceed as mentioned under linearity and construction of calibration curves. Calculate the concentrations of the two compounds from their corresponding regression equations.

2.4.3. Application of the proposed methods to pharmaceutical formulations

2.4.3.1. For tablet dosage form. The contents of ten tablets of Buscopan plus® (also for Buscamol®) were thoroughly powdered and mixed then an amount of the powder equivalent to 500 mg of PAR and 10 mg of HBB was weighed accurately in a 250-mL beaker, 70 mL of methanol was added, stirred for about 30 min then filtered through filter paper into a 100-mL volumetric flask, the beaker and the funnel were washed and the volume was completed with methanol to get a concentration of 5.0 and 0.10 mg mL^{-1} for PAR and HBB, respectively. Appropriate dilutions were made to bring up a concentration of 100.0 and 2.0 μg mL^{-1} for PAR and HBB, respectively. The proposed HPLC method was applied for the analysis and calculation of HBB and PAR concentrations.

2.4.3.2. For suppositories dosage form. The contents of five suppositories of Buscopan plus® were thoroughly cut into small fragments then an amount of the fragments equivalent to 800 mg of PAR and 10 mg of HBB was weighed accurately in a 250-mL beaker, 70 mL of methanol was added, stirred for about 30 min, left to cool then filtered through filter paper into a 100-mL volumetric flask, the beaker and the funnel were washed and the volume was completed with methanol to get a concentration of 8.0 and 0.10 mg mL^{-1} for PAR and HBB, respectively. Appropriate dilutions were made to bring up a concentration of 160.0 and 2.0 μg mL^{-1} for PAR and HBB, respectively. The proposed HPLC method was applied for the analysis and calculation of HBB and PAR concentrations.

3. Results and discussion

3.1. Method development and optimization

The aim of this work is to develop a method that can be applied successfully for separation and quantification of the studied drugs without prior separation.

A simple, selective, sensitive and accurate isocratic RP – HPLC method was adopted for the simultaneous determination of HBB and PAR, either in bulk powder or in pharmaceutical formulations.

To optimize the RP-HPLC method, it was necessary to test the effect of different variables:

3.1.1. The choice of the stationary phase

The reversed-phase separation was preferred to the normal phase due to the drawbacks of the normal-phase mode, for example, hydration of the silica with water, which causes peak

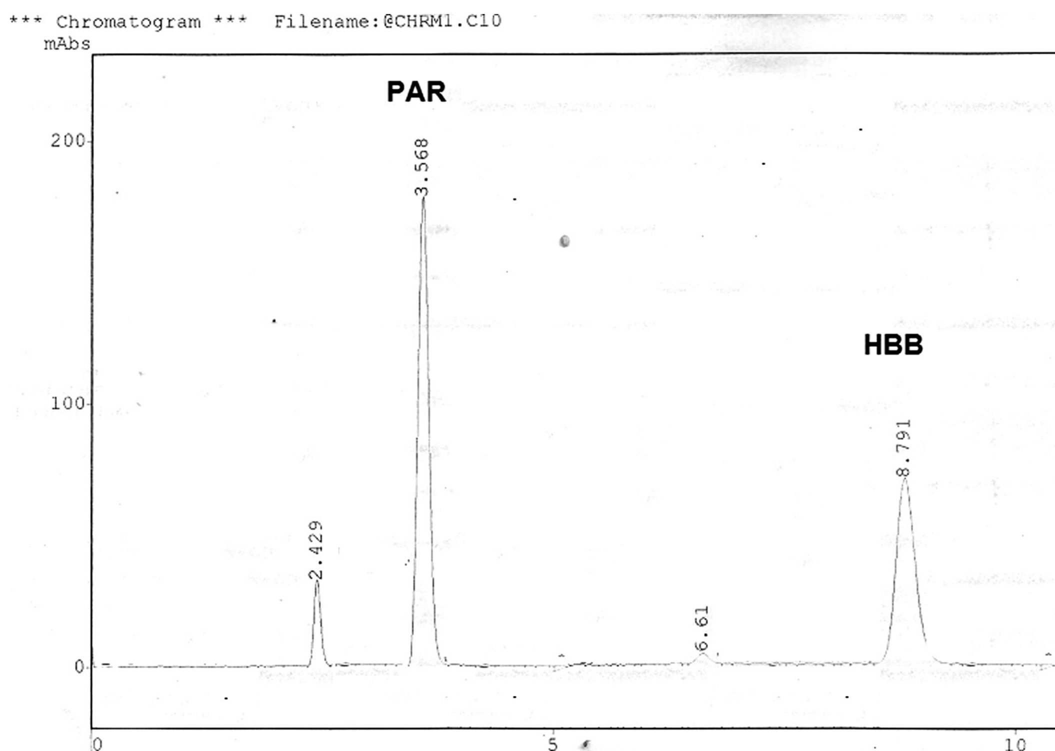

Figure 2 HPLC chromatogram showing separation of mixture of HBB and PAR 50 μg mL^{-1} of each.

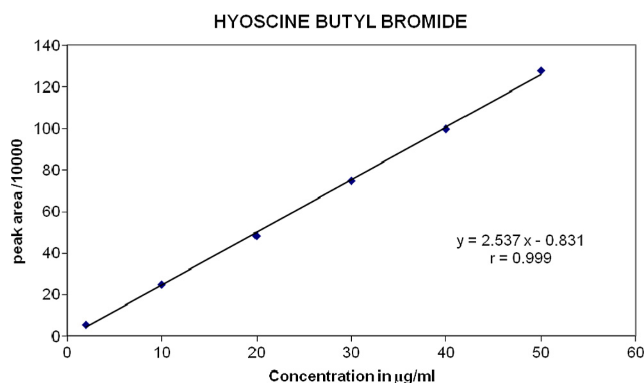

Figure 3 Linearity of the peak area at 210 nm to the corresponding concentration of HBB (2–50 µg mL^{-1}) using HPLC method.

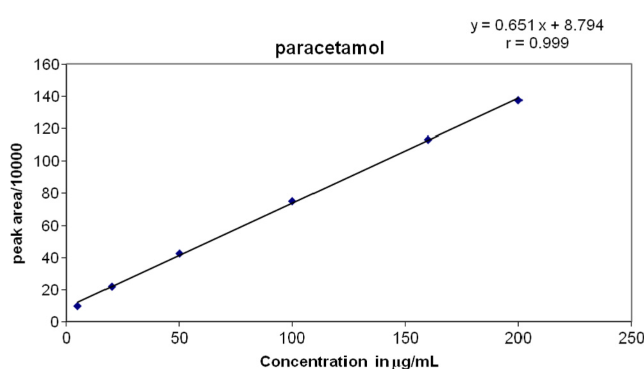

Figure 4 Linearity of the peak area to the corresponding concentration of PAR (5–200 µg mL^{-1}) using HPLC method.

tailing .C_{18} column was found to be more efficient than C_8 column.

3.1.2. The choice of the mobile phase

Mobile phase systems of different compositions and ratios were tried e.g. (water: methanol) using different acids (H_3PO_4, CH_3COOH and CF_3COOH) at different pH values. A complete separation of HBB and PAR without interference within a suitable time was achieved using water: methanol (50:50, V/V pH adjusted to 3.9 with CF_3COOH acid). This mobile phase allows the determination of HBB and PAR in combination without interference and within a suitable time.

3.1.3. The effect of pH

Forked peak of HBB at basic medium was a problem. Adjustment of pH was done to inhibit this. It was tried using glacial acetic acid, triflouroacetic acid and orthophosphoric acid. Forked peak could be overcome by adjusting the pH at 3.9. In addition, the effect of pH was studied by using acids of different pk_a values (H_3PO_4, CF_3COOH and CH_3COOH). It was found that pH = 3.9 with CF_3COOH acid was suitable for optimum resolution and peak shape.

3.1.4. Flow rate and the scanning wavelength

Different flow rates were tried of which 1.0 mL min^{-1} proved to be of choice providing good separation within 9 min.

The two drugs under investigation were dissolved in methanol separately and examined by the spectrophotometer. It was found that detection at 210 nm gave good sensitivity for both compounds.

Finally, a satisfactory separation was obtained using C_{18} (25 cm × 4.6 mm i.d. 5 µm particle size) column as a stationary phase and water: methanol (50:50, V/V pH adjusted to 3.9 with CF_3COOH acid) as a mobile phase, maintaining the flow rate at 1.0 mL min^{-1} with UV detection at 210 nm. The retention times for HBB and PAR were 3.5 and 8.7 min respectively, Fig. 2.

3.2. Method validation

Method validation was performed according to ICH guidelines (ICH, 2005).

Linearity of the proposed method was evaluated and it was evident in the concentration range of 2–50 µg mL^{-1} for HBB and 5–200 µg mL^{-1} for PAR. Good linearity was evident by the high value of the correlation coefficient and the low intercept value, (Figs. 3 and 4) and (Table 4).

The regression equations were calculated and found to be:

$$Y1 = 2.537C1 - 0s.831\ r1 = 0.9995$$

$$Y2 = 0.651C2 - 8.794\ r2 = 0.9998$$

where Y_1 and Y_2 are the peak area/10^4, C_1 and C_2 are HBB and PAR concentrations in µg mL^{-1} respectively and r_1 and r_2 are the correlation coefficients.

Precision of the proposed RP-HPLC method was evident as shown in Table 4.

Accuracy of the proposed method was checked by applying the proposed method for the determination of different blind

Table 1 Results of accuracy for determination of pure authenticity of HBB and PAR by the proposed HPLC method.

HBB			PAR		
Taken (µg mL^{-1})	Found* (µg mL^{-1})	Recovery %	Taken (µg mL^{-1})	Found* (µg mL^{-1})	Recovery %
2.00	2.02	101.00	5.00	4.91	98.20
10.00	10.02	100.20	10.00	10.07	100.70
20.00	19.95	99.75	50.00	49.92	99.84
30.00	29.92	99.73	100.00	100.15	100.15
40.00	40.00	100.00	150.00	151.12	100.75
50.00	49.95	99.90	200.00	199.10	99.55
Mean ± SD	100.10 ± 0.475			99.87 ± 0.942	

* Average of three determinations.

Table 2 Determination of HBB and PAR in laboratory prepared mixtures by the proposed HPLC method.

Mix. No.	Ratio HBB:PAR	HBB			PAR		
		Taken (μg band^{-1})	Found* (μg band^{-1})	Recovery %	Taken (μg band^{-1})	Found* (μg band^{-1})	Recovery %
1	1:1	10.00	9.98	99.80	10.00	10.02	100.20
2	1: 2	10.00	10.10	101.00	20.00	19.95	99.75
3	1: 5	10.00	10.04	100.40	50.00	50.06	100.12
4	1 :10	2.00	2.00	100.00	20.00	20.04	100.20
5	1: 50**	2.00	2.02	101.00	100.00	99.55	99.55
6	1:80***	2.00	1.99	99.50	160.00	159.00	99.38
Mean ± SD				100.28 ± 0.627			99.87 ± 0.357

* Average of three determinations.
** The ratio present in Buscopan plus® tablets and Buscamol ® tablets.
*** The ratio present in Buscopan plus® suppositories.

Table 3 Application of standard addition technique to analysis of HBB and PAR in dosage forms by the HPLC method.

Dosage form	Drug	Taken (μg mL−1)	Found* (μg mL^{-1})	Found%	Pure added (μg mL^{-1})	Pure found** (μg mL^{-1})	Recovery%	Mean ± SD
Buscopan plus® tablets					2.00	2.00	100.00	100.15 ± 0.132
Batch No 116738T	HBB	2	1.97	98.50	10.00	10.02	100.20	
					20.00	20.05	100.25	
	PAR	100	100.2	100.2	10.00	10.01	100.10	100.26 ± 0.214
					20.00	20.10	100.50	
					30.00	30.05	100.17	
Buscamol.F.C® tablets					2.00	1.96	98.00	99.80 ± 1.637
Batch No 12001025	HBB	2.00	1.97	98.5	10.00	10.12	101.20	
					20.00	20.04	100.20	
	PAR	100.00	100.45	100.45	10.00	9.91	99.10	100.07 ± 0.95
					20.00	20.20	101.00	
					30.00	30.03	100.10	
Buscopan plus® suppositories					2.00	1.97	98.50	99.70 ± 1.058
Batch No 105	HBB	2.00	2.01	100.5	10.00	10.05	100.50	
					20.00	20.02	100.10	
	PAR	160.00	161.5	100.94	10.00	9.99	99.90	100.46 ± 0.764
					20.00	20.03	100.15	
					30.00	30.40	101.33	

* Average of six determinations.
** Average of three determinations.

samples of HBB and PAR. The concentrations were calculated from the corresponding regression equations. The results were obtained as shown in Tables 1 and 2.

Accuracy of the method was assured by applying the standard addition technique on different pharmaceutical dosage forms where good recoveries were obtained as shown in Table 3 revealing no interference from excipients and good accuracy of the proposed method.

Specificity of the proposed method is evident from the RP-HPLC chromatogram in Fig. 2.

Robustness of the proposed method was evaluated in the development phase by making small changes in the composition of the mobile phase and detection wavelength. The low value of % RSD shows that the method is robust and that deliberate small changes in the studied factors did not lead to a significant change in retention values, area or symmetry of the peaks.

System suitability tests are based on the concept that the equipment, electronics, analytical operations and samples constitute an integral system that can be evaluated as whole. System suitability is used to ensure system performance before or during the analysis of the drugs. System suitability was checked by calculating the capacity factor (K'), tailing factor (T), column efficiency (N), the selectivity factor (γ) and resolution (Rs), where the system was found to be suitable as shown in Table 5.

Table 4 Results of assay validation parameters of HPLC for the determination of HBB and PAR in binary mixture.

Parameters	HBB	PAR
Range (μg mL^{-1})	2–50 (μg mL$^{-1)}$	5–200 (μg mL$^{-1)}$
Slope	2.537	0.651
Intercept	−0.831	8.794
Correlation coefficient (r)	0.9995	0.9998
Accuracy (mean ± SD)	100.10 ± 0.475	99.87 ± 0.942
(RSD%)^{a*}	0.863	1.021
(RSD%)^{b*}	0.916	1.151

(RSD%)a*, (RSD%)b* the intra-day and inter-day relative standard deviations of the average of concentrations (20, 40 and 50 μg mL^{-1} for each).

Table 5 Statistical analysis of parameters required for system suitability testing of HPLC method.

Parameters	For RP-HPLC method		
	Obtained value		Reference value
	HBB	PAR	
Resolution (R_s)	10.46		> 1.5
Capacity factor(K')	2.66	0.48	1–10 acceptable
Tailing factor (T)	1.16	1.00	< 1.5–2
Selectivity factor(γ)	5.54		> 1
Number of Theoretical plate (N)	34339600	1267360	Increases with increases efficiency
HETP (cm plate^{-1}) Height equivalent to theoretical plate	0.0728	0.1973	The smaller the value, the higher the efficiency

Table 6 Statistical analysis of the results obtained by proposed method and reference method for the determination of HBB and PAR.

Parameter	RP-HPLC method		Reference method[a]	
	HBB	PAR	HBB	PAR
Mean%	100.10	99.87	99.21	99.94
SD	0.475	0.942	1.012	1.537
n	6	6	6	6
Student's t-test (2.23)[b]	0.092	0.927		
F-value (5.05)[b]	4.539	2.662		

[a] Manufactured method personal communications.
[b] The values between parenthesis are the theoretical values for t and F at $P = 0.05$.

4. Conclusion

The proposed method is efficient for providing sensitive and accurate quantitative analysis for simultaneous determination of HBB and PAR in bulk powder and pharmaceutical formulations, without any interference from excipients. The RP-HPLC method has the advantages of short analysis time and the availability of the device in every quality control unit so it is suitable for routine analysis.

The statistical analysis was performed by comparing the results of the proposed method with those of the manufacturer's method. No significant difference was observed regarding accuracy and precision, as shown in Table 6.

The suggested method provides selective, accurate and sensitive analytical procedure for the determination of HBB and PAR. It is suitable for routine analysis and quality control of HBB and PAR in their pharmaceutical formulations.

References

British Pharmacopoeia, 2009, British Pharmacopoeia Commision, London.

Chang, Y.S., Ku, Y.R., Wen, K.C., Ho, L.K., 2000. Analysis of synthetic gastrointestinal drugs in adulterated traditional chinese medicines by HPCE. Journal of Liquid Chromatography & Related Technologies 23 (13), 2009–2019.

Cherkaoui, S., Mateus, L., Christen, P., Veuthey, J.-L., 1999. Nonaqueous versus aqueous capillary electrophoresis for the dosage of N-butylscopolamine in various pharmaceutical formulations. Journal of Pharmaceutical and Biomedical Analysis 21 (1), 165–174.

Dewani, A.P., Barik, B.B., Chipade, V.D., Bakal, R.L., Chandewar, A.V., Kanungo, S.K., 2014. RP-HPLC-DAD method for the determination of phenylepherine, paracetamol, caffeine and chlorpheniramine in bulk and marketed formulation. Arabian Journal of Chemistry 7 (5), 811–816.

El-Saharty, Y., Metwaly, F., Refaat, M., El-Khateeb, S., 2007. Development of membrane electrodes for the selective determination of hyoscine butylbromide. Talanta 72 (2), 675–681.

Erk, N., 1996. Spectrophotometric determination of paracetamol and hyoscine N-butyl bromide in film-coated tablets. Scientia Pharmaceutica 64 (2), 173–183.

Farhadi, K., Karimpour, A., 2007. Electrochemical behavior and determination of hyoscine-N-butylbromide from pharmaceutical preparations. Journal-Chinese Chemical Society Taipei 54 (1), 165.

Favreto, W.A.J., Pugens Pinto, A.M., Manfio, J.L., Fiametti, K.G., Percio, M.F., Santos, M.B.d., 2012. Development and validation of a UPLC-ESI-MS/MS method for the determination of N-butylscopolamine in human plasma: Application to a bioequivalence study. Drug Testing and Analysis 4 (3-4), 215–221.

Ganjali, M.R., Memari, Z., Larijani, B., Faridbod, F., Riahi, S., Norouzi, P., 2010. Symmetric and asymmetric hyoscine membrane sensor for determination of hyoscine butyl bromide in pharmaceutical formulation and biological fluids; a computational study. Sensor Letters 8 (4), 545–553.

Gouda, A.A., 2010. Kinetic spectrophotometric determination of hyoscine butylbromide in pure form and in pharmaceutical formulations. Arabian Journal of Chemistry 3 (1), 33–38.

Gouda, A.A., Kotb El-Sayed, M.I., Amin, A.S., El Sheikh, R., 2013. Spectrophotometric and spectrofluorometric methods for the determination of non-steroidal anti-inflammatory drugs: a review. Arabian Journal of Chemistry 6 (2), 145–163.

ICH Harmonized Tripartite Guideline, 2005. Validation of Analytical Procedures: Text and Methodology, Q2(R1)Geneva.

Issa, Y.M., Zayed, S.I.M., Habib, I.H.I., 2011. Simultaneous determination of ibuprofen and paracetamol using derivatives of the ratio spectra method. Arabian Journal of Chemistry 4 (3), 259–263.

Issopoulos, P., Pavlou-Zervou, E., 1994. Application of ion pair complexes of some acid-base indicators in pharmaceutical analysis. I: Spectrophotometric microdetermination of L-hyoscine butyl bromide by its ion pair complex with methyl organge. Il Farmaco 49 (3), 205–210.

Kumar, K.G., Letha, R., 1997. Determination of paracetamol in pure form and in dosage forms using N, N-dibromo dimethylhydantoin. Journal of Pharmaceutical and Biomedical Analysis 15, 1725–1728.

Lau, O.W., Mok, C.S., 1997. High-performance liquid chromatographic determination of atropine and atropine-like alkaloids in pharmaceutical preparations with indirect conductometric detection. Journal of Chromatography A 766 (1), 270–276.

Mahrous, M., Daabees, H., Beltagy, Y., 1992. New sensitive method for the analysis of some non uv absorbing quaternised compounds. Spectroscopy Letters 25 (3), 389–400.

Martindale "The Extra Pharmacopoeia", 2007, 31st ed. Pharmaceutical press, London.

Mohamed, F.A., AbdAllah, M.A., Shammat, S.M., 1997. Selective spectrophotometric determination of p-aminophenol and acetaminophen. Talanta 44, 61–68.

Mujahid, A., Ali, Y., Afzal, A., Hussain, T., Tufail Shah, A., Shehzad, K., Umar Farooq, M., 2014. Rapid assay of the comparative degradation of acetaminophen in binary and ternary combinations. Arabian Journal of Chemistry 7 (4), 522–524.

Papadoyannis, I., Zotou, A., Samanidou, V., Georgarakis, M., 1994. Solid-phase extraction and RP-HPLC analysis of atropine sulphate and scopolamine-N-butylbromide in pharmaceutical preparations and biological fluids. Instrumentation Science & Technology 22 (1), 83–103.

Parissi-Poulou, M., Panderi, I., 1999. Determination of hyoscine n-butyl-bromide, lidocaine hydrochloride, and paracetamol in injection forms using solid-phase extraction, high-performance liquid chromatography, and UV–VIS spectrophotometry. Journal of Liquid Chromatography & Related Technologies 22 (7), 1055–1068.

Thomos, K.M., Dabholkar, D.A., Jain, C.L., 1994. Spectrophotometric determination of hyoscine butyl bromide in pharmaceutical formulations. Indian Drugs 31 (8), 391–392.

Vyas, P., Kharat, R., 1988. Potentiometric titration of paracetamol in non aqueous medium. Indian Journal of Pharmaceutical Sciences 50, 279.

Wassel, A.A., Abu-Talib, N., 2010. Sensors membrane electrodes for sensitive determination of hyoscine butylbromide in pharmaceutical formulation and in human plasma. In: Vytřas, K. Kalcher, I. Švancara (Eds.), Journal of Sensing in electroanalysis, Volume 5.