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Utility of Extracted Colored Ion – Associate Complexes Formation Reaction for the Determination of Fexofenadine Hydrochloride in Pure Forms and in Dosage Forms

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Abstract

A spectrophotometric reliable, rapid and sensitive methods have been developed and validated for the determination of fexofenadine hydrochloride. A method was described for the determination of fexofenadine hydrochloride in pure form or pharmaceutical formulations using bromophenol blue (BPB) bromothymol blue (BTB), bromocresol green (BCG) and bromocresol purple (BCP). This method involved the formation of colored chloroform ($CHCl_3$) extractable ion-associate complexes with BPB, BTB, BCG and BCP in acidic medium. All variables affecting the reaction have been investigated and the conditions were optimized. The extracted complexes showed absorbance maximum at λ_{max} 411, 414, 409, and 411 nm, respectively. The reagents form a chloroform – soluble colored ion association complex with fexofenadine hydrochloride at pH 2.4, 2.4, 2.2 and 2.4 using BPB, BCG, BTB and BCP respectively. Regression analysis of Beer – Lambert plots showed good correlation in the concentration ranges 1.0 – 6.0, 0.5 – 9.0, 1.0 – 8.0 and 0.5 – 6.0 µg mL^{-1}, respectively. The apparent molar absorptivity. Sandell sensitivity, detection and Quantitation limits were calculated. Applications of the proposed methods to representative pharmaceutical formulations are successfully presented.

Keywords: Spectrophotometric; Fexofenadine hydrochloride; Ion-associate complex formation; Dosage forms

Introduction

Fexofenadine hydrochloride [1,2], α,α-Dimethyl-4-[4-(hydroxydiphenyl methyl-1-piperidinyl] benzene acetic acid (Figure 1), is the active compound of the pharmaceutical formulations, and active metabolite of terfenadine, is a non –sedating antihistamine H^1-receptor antagonist. It does not possess significant sedative or antimuscarinic actions. Fexofenadine is used as hydrochloride in the symptomatic relief of allergic conditions including seasonal allergic rhinitis and urticaria.

However, analytical methods reporting the determination of fexofenadine hydrochloride alone are relatively uncommon. In pharmaceutical dosage forms, it was quantified by ion – complex reactions [3], capillary electrophoresis [4-6], anodic voltammetry [7], new polymeric membrane [8,9] and HPLC with ultraviolet detection [10-12]. In biological fluids, fexofenadine hydrochloride has been determined employing anodic voltammetry[7] as well as HPLC with different detections, including ultraviolet [13], mass spectrometry [14-16] fluorescence [17] and spectrophotometric method [18-20].

However spectrophotometric methods suffer from disadvantages such as low sensitivity, and take long reaction time for color development. BPB, BTB, BCG and BCP have been used as active reagents for the determination of different drugs [21-30]. These methods involve colored ion – associate formed between drugs and reagents and extracted with pure chloroform.

Material and Methods

Instrumentation

All the absorption spectral measurements were made using JASCO V – 530 (UV-VIS) Spectrophotometer (Japan) with scanning speed 400 nm min^{-1} and band width 2.0 nm equipped with 10 mm matched quartz cells. Values of pH were measured with an Orion research model 601 A/digital ionalyzer. The pH meter was calibrated regularly before use with standard buffer solutions [31].

Materials and reagents

Pure fexofenadine hydrochloride was obtained from the Egyptian International pharmaceutical Industries Company (EIPICO). Fexofenadine hydrochloride stock solution (100 µg mL^{-1}) was prepared by dissolving 0.01 g in warm water and completed to mark in 100 ml calibrated flask with water. The Working standard solutions were obtained by further dilution of stock solution with water.

All chemicals were of analytical grade and double distilled water was used throughout. Bromophenol blue (BPB), bromothymol blue (BTB), bromocresol green (BCG) and bromocresol purple (BCP) are analytical grade quality of the highest purity from Merck products. A solution (10^{-4} M) of BPB, BTB, BCG and BCP were prepared by dissolving an accurate weight of dye in least amount of ethyl alcohol and completed to the mark in a 250 mL calibrated flask.

General procedure

For pure form: To each 10 mL calibrated flask containing 2.0 mL of 10^{-4} BPB, BCG, BTB and BCP 2.0 mL of universal puffer solution (at pH = 2.4, 2.4, 2.2 and 2.4 respectively) and (5.0 – 30, 2.5 – 45, 5.0 – 40 and 2.5 – 30 µg mL^{-1} respectively) of fexofenadine hydrochloride were added and the solutions were diluted to 10 mL. After 2 min shaking time, the solution was transferred to a 25 mL separating funnel containing 5.0 ml chloroform. The solution was shaken for three min, then the organic layer contained ion – pair was separated.

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The absorbance was measured at 411, 414, 409 and 411 nm, respectively against blank solution prepared with the same manner without drug concentration. The amount of drug in any sample was calculated from its calibration curve.

For dosage forms: Tablets: At least ten tablets of the drug were weighed into a small dish, powdered and mixed well. A portion equivalent to 100 mg was weighed and dissolved in 100 mL distilled water, shaken well and filtered. A 1.0 mL aliquot of test solution (1.0 mg mL^{-1} of fexofenadine hydrochloride) was diluted to 100 mL in calibrated flask. Aliquot of the test solution was then treated as described above.

Results and Discussion

Method development

The proposed method was used to establish simple colorimetric methods for the determination of fexofenadine hydrochloride containing amino group which contain loin pair of electrons forming colored extractable ion – associate complex using chloroform. After that the absorbance was measured at suitable λ_{max}. The effect of essential parameters was described.

Effect of pH: To examined the optimum pH value for each ion - associates formed between fexofenadine hydrochloride and BPB, BCG, BTB and BCP different types of buffer [31] were used. The ion associate formed in acidic medium and the best buffer was universal and acetate buffer solution. Moreover the universal buffer is chosen for fasting the reaction, in addition to higher stability. The highest absorbance values were obtained at pH 2.4, 2.4, 2.2 and 2.4, respectively, since the results were highly concordance.

Effect of time and temperature: The time required for complete color development of the ion-associate formation was investigated.

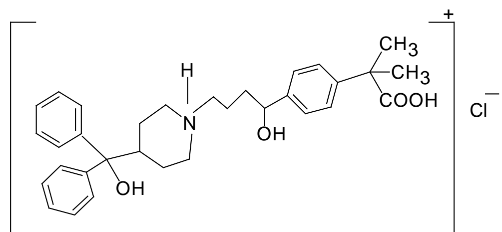

Figure 1: Chemical structure of fexofenadine hydrochloride.

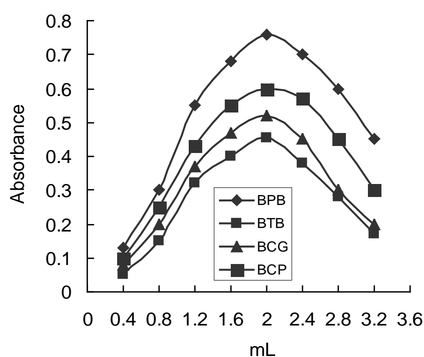

Figure 2: Effect of 10^{-4} M reagent concentration on the absorbance of 4.0 µg mL^{-1} of drug.

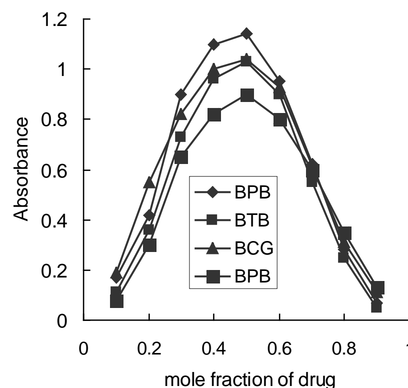

Figure 3: The continuous variation method for the studied ion associate complexes.

Allowing the reactants to stand for different time intervals, it was observed that the time has no effect on the maximum color intensity. Consequently 2.0 min was enough for standing. The formed ion - associates were found to be stable for more than 24 hours. Raising the temperature does not accelerate the reaction process and dose not give reproducible results, so the optimum temperature is the ambient (25 ± 1°C). The effect of time for completely extractable ion pair was also studied indicating that 3.0 min is sufficient to give reliable results.

Effect of reagent concentration: When various concentrations of reagent were added to fixed concentrations of fexofenadine hydrochloride, 2.0 mL of BPB, BCG, BTB and BCP (10^{-4} M) solution were found to be sufficient for the production of the maximum and reproducible color intensity. Higher concentration of the reagent decreased the absorbance and color intensity of the formed ion – associate (Figure 2).

Effect of the extracting solvent: A number of organic solvents were examined for extraction of the ion – associate complexes in order to provide an applicable extraction procedure. Chloroform was preferred for its selective extraction of ion – associate complexes from the aqueous solution, in addition to reagents unextracted in that solvent. Reproducible absorbance readings were obtained after a single extraction with 3.0 mL of chloroform. The over-all extraction efficiency was 99.8, 83.4, 74.8, 66.8, and 57.2 % using chloroform, dichloromethane, carbon tetrachloride, benzene and toluene, respectively. Repeated extraction did not show any increase in the recovery percent results.

Stoichiometric ratio

In order to investigate the molecular ratio of the complexes formed between the fexofenadine hydrochloride and the studied reagents at the selected conditions, the molar ratio and continuous variation methods were carried out. The results indicated that the molar ratio of the drugs to reagent was found to be (1: 1) in all ion – associate formed. In continuous variation method, 5.0×10^{-4} mol L^{-1} solutions of drug and dyestuff were mixed in varying volume ratio in such a way that the total volume of each mixture was the same. The absorbance of each solution was measured and plotted against the mole fraction of the drug. The shape of the curves indicated that the complexes were labile, as shown in Figure 3. Hence, a large excess of reagent must always be used to enhance the formation of the complex.

Quantification

Beer – Lambert law limits, molar absorptivity, Sandell sensitivity, regression equations and correlation coefficients obtained by linear squares treatment of the results are given in Table 1. The detection and Quantitation limits were calculated from the standard deviation of the absorbance measurements obtained from a series of 10 blank solutions for each procedure. The limits of detection (K= 3) and of Quantitation (K=10) were established according to IUPAC definitions [32] In order to determine the accuracy and precision of the methods, solutions containing three different concentrations of fexofenadine hydrochloride were prepared and analyzed in six replicates. The analytical results obtained from this investigation are summarized in Table 2. The percentage range of error at 95% confidence level (≤ ± 1.44) can be considered to be very satisfactory.

Interferences

Experiments showed that there was no interference from additives and expedients, e.g. lactose, glucose, fructose, calcium hydrogen phosphate, magnesium stearate and starch for the examined methods.

Analytical applications

The proposed methods were successfully applied to determine fexofenadine hydrochloride in its dosage forms. The results obtained were compared statistically by student's t-test (for accuracy) and variance ratio F-test [33] (for precision) with the official method[1]

Parameters	Reagents			
	BPB	BTB	BCG	BCP
Beer's law limits (µg mL^{-1})	1.0 - 6.0	0.5 - 9.0	1.0 – 8.0	0.5 - 6.0
Ringbom limits (µg mL^{-1})	1.2 – 5.4	0.6 – 8.5	1.1 – 7.4	0.8 – 5.7
Molar absorptivity (L mol^{-1} cm^{-1}) x 10^4	10.22	6.14	6.98	8.07
Sandell sensitivity((µg cm^{-1})	0.0053	0.0088	0.0077	0.0067
Detection limit (µg mL^{-1})	0.312	0.186	0.25	0.156
Quantitation limit (µg mL^{-1})	1.04	0.62	0.85	0.52
Regression equation* Slope (b)	0.1900	0.114	0.13	0.15
Intercept (a)	0.0015	- 0.0077	- 0.0095	0.0060
Standard deviation (SD)	0.0052	0.0062	0.0085	0.0052
Correlation coefficient (r)	0.9997	0.9995	0.9998	0.9988

*with respect to A=a + bC where A is the absorbance in µg mL^{-1}, a is the intercept, b is the slope

Table 1: Spectral and regression characteristics of the formed ion - associates.

Dyes	Taken (µg mL^{-1})	Found (µg mL^{-1})	Recovery (%)	RSD[a] (%)	RE (%)	Confidence[b] Limits
BPB	3.00	3.01	100.33	1.621	1.169	3.01 ± 0.035
	5.00	5.02	100.04	0.694	0.940	5.02 ± 0.047
	7.00	6.97	99.57	0.319	0.425	6.97 ± 0.030
BCG	2.00	2.017	100.85	1.134	1.081	2.02 ± 0.022
	3.50	3.51	100.29	1.288	1.228	3.51 ± 0.043
	5.00	5.02	100.40	0.748	0.713	5.02 ± 0.036
BTB	2.00	2.02	100.10	1.460	1.391	2.02 ± 0.028
	4.00	4.01	100.25	1.494	0.426	4.01± 0.057
	6.00	5.97	99.50	0.671	0.639	5.97± 0.038
BCP	2.00	2.03	101.50	0.507	0.483	2.03 ± 0.010
	4.00	4.07	101.75	0.902	0.859	4.07 ± 0.035
	6.00	6.05	100.83	0.732	0.698	6.05 ± 0.042

[a]Relative standard deviation for six determinations
[b]95% confidence limits and five degrees of freedom

Table 2: Evaluation of the accuracy and precision of the proposed procedures.

Dodage forms	Supplier	Nominal value	Recovery (%)[a]				
			BPB	BTB	BCG	BCP	Official
Allerfen tablet	Amoun pharmaceutical Co. S.A.E.	60 mg per tab	99.98	100.10	100.05	100.08	99.97
			t- 0.19	t-0.97	t- 0.97	t- 0.97	
			F- 1.33	F- 2.96	F- 2.47	F- 1.57	
Fexon tablet	Alkan Pharma. S.A.E.	180 mg per tab.	100.01	100.04	99.98	100.02	99.89
			t- 0.25	t- 0.89	t- 0.89	t- 0.69	
			F- 1.73	F- 1.92	F- 2.83	F- 1.92	
Fastofen tablet	EIPICO	120 mg per tab.	100.33	100.01	100.01	100.05	100.2
			t- 0.17	t- 1.28	t- 0.73	t- 0.92	
			F- 2.18	F- 1.96	F-1.97	F- 2.73	

[a]The average of six determinations
The t- and F- values refer to comparison of the proposed methods with the official method. Tabulated t- and F- values for p= 0.05 and five degrees of freedom are 2.33 and 5.05

Table 3: Determination of fexofenadine hydrochloride in pharmaceutical formulation using proposed method.

(based on HPLC) at 95% confidence level with five degrees of freedom as recorded in Table 3. The results showed that the t- and f- values were less than the critical value indicating there was no significant difference between the proposed and official methods. The proposed methods were more accurate with high recoveries than the official methods so the proposed methods can be recommended for routine analysis in the majority of drug quality control laboratories.

Conclusion

All the proposed methods were advantageous over the reported visible spectrophotometric methods with respect to their higher sensitivity which permits the determination of up to 0.5 µg mL^{-1}, simplicity, reproducibility, precision, accuracy, and stability of colored species. The proposed methods can be applied for routine analysis and in quality control laboratories for the quantitative determination of the studied drug in raw materials and in pharmaceutical formulations.

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