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A new spectrophotometric method for the determination of fluvoxamine maleate in pure form and in pharmaceutical formulation

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ABSTRACT

A simple, accurate and highly sensitive spectrophotometric methods are proposed for the rapid and accurate determination of fluvoxamine maleate (FXA) using bromocressol green (BCG), methyl orange (MO) and bromothymol blue (BTB). The developed methods involve formation of stable yellow colored chloroform extractable ion-associate complexes of the amino derivative (basic nitrogen) of the FXA with three sulphonphthalein acid dyes, namely; BCG, MO and BTB, in potassium hydrogen phthalate buffer pH 3.3, 3.6 and 3.4 respectively. The ion-associates exhibit absorption maxima at 420, 420 and 410 nm for BCG, MO and BTB, respectively. FXA can be determined up to 2.0–16, 2.0–15 and 2.0–20 μgmL^{-1} for BCG, MO and BTB, respectively. The effect of optimum conditions via pH on the ion pair formation, reagent concentration, time and temperature, and solvent was studied. The composition of the ion pairs was found 1:1 by Job's method. The low relative standard deviation values indicate good precision and high recovery values. These methods have been successfully applied for the assay of FXA in pure form and in pharmaceutical formulations and the results are in good agreement with those obtained by the official method.

INTRODUCTION

FXA maleate (Merck Index, 2001) is a selective serotonin (5-HT) reuptake inhibitor (SSRI) belonging to the chemical series, the 2-aminoethyl oxime ethers of aralkyl ketones in the treatment of a variety of depressed states. It is chemically designated as (E)-5-methoxy-1-[4-(trifluoromethyl)phenyl] pentan-1-one-O-2-aminoethyl oxime maleate (Figure 1) and has the empirical formula $C_{15}H_{21}O_2N_2F_3.C_4H_4O_4$, molecular weight is 434.41. FXA is a white to slightly off-white, odourless, crystalline powder, sparingly soluble in water, freely soluble in ethanol and chloroform, practically insoluble in diethyl ether (Claassen, 1983, Wilde *et al.*, 1993).

No official (pharmacopoeia) method has been found for the assay of FXA in its formulations. However, many studies have been reported for the determination of FXA in pharmaceuticals including visible spectroscopy (Kishore *et al.*, 2010, Jat *et al.*, 2010), HPLC (Tadashi OHKUBO *et al.*, 2003, Ulu *et al.*, 2007), fluorimetriy (EI-Enany, 2007), capillary gas chromatography (Berzas Nervado *et al.*, 2000), capillary electrophoresis (Nevado *et al.*, 2000), gas Chromatography-Mass Spectrometry (Maurer *et al.*, 2000), solid-phase microextraction gas chromatography-mass spectrometry (Petinal *et al.*, 2005). No extractive spectrophotometric methods for analysis of FXA in pure form and in pharmaceutical formulation. The present study has shown the development of an accurate, reproducible, fast and adequately sensitive extractive spectrophotometric method based on an ion-pair complex formed between FXA and an anionic dye, BCG, MO and BTB (Nafisur *et al.*, 2000, Nafisur *et al.*, 2004, Gowda *et al.*, 2001, Sevgi et al 2007, Faten *et al.*, 2006). An important advantage of the extractive spectrophotometric method is that it can be applied to the determination of individual compounds in a multi-component mixture. Unlike gas chromatographic (GC) and HPLC procedures, the instrument is relatively simple and affordable. The sensitivity (in terms of molar absorptivity) and precision (in terms of relative standard deviation, RSD) of the methods are suitable for the determination of the drug in pure and mixed dosage forms.

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The reagents utilized in the proposed method are relatively cheap and readily available, and the procedure does not involve any critical reaction condition or tedious sample preparation. These advantages, coupled with reasonable accuracy and precision, render the methods suitable for routine quality control. The proposed method was applied to the determination of FXA in pharmaceutical formulations.

No interference was observed in the assay of FXA from common excipients in levels found in pharmaceutical formulations. The proposed method was validated by statistical data (Barary *et al.,* 1991, Abdelmageed *et al.,* 1993, Botello *et al.,* 1995, Sastry *et al.,* 1995).

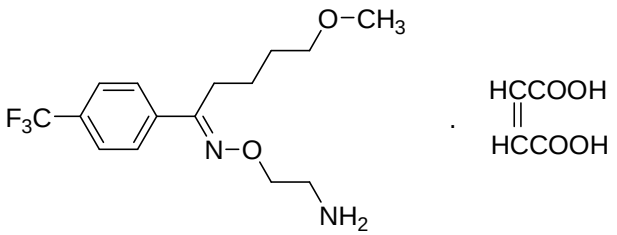

Fig. 1: Structure of FXA maleate.

MATERIAL AND METHODS

Apparatus

A Shimadzu UV-160A UV–Vis spectrophotometer with 1 cm glass cells was used. UV–Vis spectra were automatically obtained by Shimadzu UV-160A system software.

Chemicals

FXA and its tablets were procured from Jazz Pharmaceuticals, Inc. (US). Methyl orange (MO), bromothymol blue (BTB) and bromocresol green (BCG) were purchased from Merck (Darmstadt, Germany). Analytical grade chloroform was used for extraction. Solvents and other chemicals were of analytical grade (Merck, Darmstadt, Germany).

Standard solution

Standard solution 100 µg mL^{-1} of FXA was prepared by dissolving 10 mg of pure drug (pharmaceutical grade) in the least amount of distilled water and made up to 100 mL in measuring flask with distilled water. The solution remained stable for 1 month when kept refrigerated.

Stock solution of bromocresol green (BCG), methyl orange (MO) and bromothymol blue (BTB) (1.0×10^{-3} M), were prepared by dissolving 0.0698, 0.0327 and 0.0624 g, respectively, in 100 mL acetone. The acid dye reagents were stable for several weeks.

Potassium hydrogen Phthalate-HCl buffer (pH = 3.0-3.7) was prepared by dissolving 1.020 g of potassium hydrogen phthalate in water and completed to 50 mL with distilled water and adjusting pH by addition of 0.1M HCl solution. Freshly prepared solutions were always employed.

General analytical procedure for the analysis of bulk drug

Aliquots of (0.2-1.6 mL of BCG; 0.2–1.5 mL of MO; 0.2–2.0 mL of BTB) the working drug solutions (100µg/mL) were transferred to 10 mL measuring flasks and added 3.0 mL potassium hydrogen phthalate buffers of pH 3.3, 3.6 and 3.4 using BCG, MO and BTB, respectively, then add 1.0 mL of BCG, MO and BTB. The mixture was extracted twice with 5.0 mL chloroform by shaking for 2.0 min and then allowed to stand for clear separation of the two phases and the chloroform layer was passed through anhydrous sodium sulphate. The absorbance of the yellow colored complexes was measured at 420, 420 and 410 nm for BCG, MO and BTB, respectively, against corresponding reagent blank similarly prepared. All measurements were made at room temperature (25±2°C). The procedures were repeated for other analyte aliquots and calibration plots were drawn to calculate the amount of drug in unknown analyte samples.

General analytical procedure for the analysis of tablets

The average tablet weight was calculated from the contents of 20 tablets that had been finely powdered and weighed. A portion of this powder, equivalent to 50 mg of FXA, was accurately weighed. The samples were shaken with 25mL of distilled water. The mixtures were then introduced into an ultrasonic bath for 25 min and diluted with distilled water in a 50 mL calibrated flask and filtered. An aliquot of 10 mL of the filtrate was diluted to 100 mL to prepare of working sample solutions (100µg mL^{-1}). An appropriate volume of 100 µg mL^{-1} sample solution (0.2-1.6 mL of BCG; 0.2–1.5 mL of MO; 0.2–2.0 mL of BTB) was added and mixed. This solution was analyzed as in the general analytical procedure for the bulk drug. The amount of FXA per tablet was calculated using the calibration curve method. The proposed method was applied to the determination of FXA in tablets.

RESULTS AND DISCUSSION

Absorption spectra

The nitrogenous drugs are present in positively charged protonated forms and anionic dyes of sulphonpthalein group present mainly in anionic form at pH≥3. So when treated with an acid dye at pH 3.3, 3.6 and 3.4 of potassium hydrogen phthalate buffer using BCP, MO and BTB, respectively, a yellow ion-pair complex which is extracted with chloroform is formed. The absorption spectra of the ion-pair complexes, which were formed between FXA and each of BCG, MO and BTB were measured in the range 400–500 nm against the blank solution and shown in Figure 2. The ion-pair complexes show maximum absorbance at 420, 420 and 410 nm for BCG, MO and BTB, respectively. The optimum reaction conditions for determination of the ion-pair complexes were established. Then linearity, accuracy, precision, sensitivity, and stability of proposed methods were described and these developed methods applied to pharmaceutical preparations as tablets and obtained results evaluated statistically.

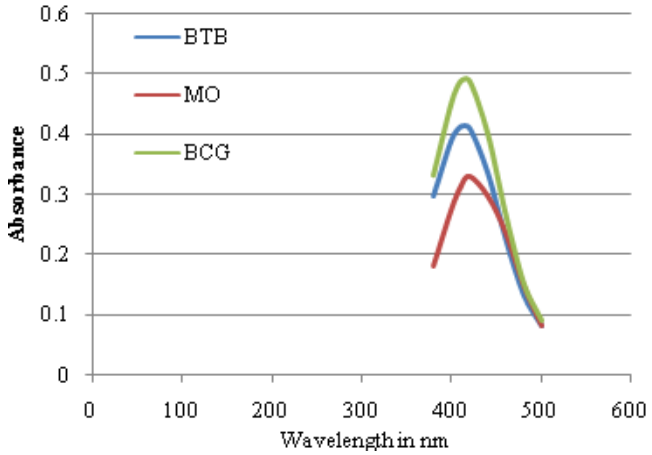

Fig. 2: Absorption spectra of ion-associate complexes of FXA-BTB, FXA-MO and FXA- BCG (10µg/ml) against blank.

Optimum reaction conditions for complex formation

The reaction conditions of the method were carefully studied to achieve complete reaction, highest sensitivity and maximum absorbance. Reaction conditions for the formation of the ion-pair complex were optimized by studying preliminary experiments involving pH of buffer, type of organic solvent, volume of the dye and shaking time for the extraction of ion-pair complexes.

Effect of time and temperature

The optimum reaction time was investigated from 0.5 to 4.0 min by following the color development at ambient temperature (25±2 °C). Complete color intensity was attained after 2.0 min of mixing for all complexes (Figure 3). Raising the temperature up to 30 °C has no effect on the absorbance of the formed complexes, whereas above 30 °C, the absorbance starts to decay. The absorbance remains stable for at least 24 h.

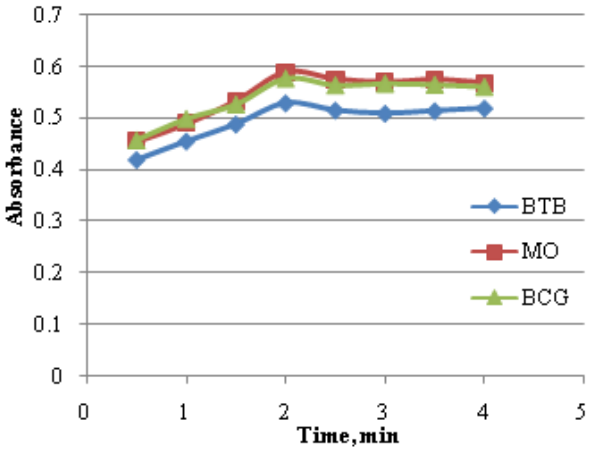

Fig. 3: Effect of shaking time on the ion-pair complexes.

Effects of pH on the ion-pair formation

The effect of pH was studied by extracting the colored complexes in the presence of various buffers such as KCl–HCl (pH = 1.5–5.0), NaOAc–HCl (pH = 1.5–5.0) and potassium hydrogen phthalate–HCl (pH = 1.5–5.0).

It was noticed that the maximum color intensity and highest absorbance value were observed in potassium hydrogen phthalate–HCl buffer of pH 3.3, 3.6 and 3.4 for BCG, MO and BTB in addition to the stability of the color without affecting the absorbance at pH 3.3, 3.6 and 3.4 for BCG, MO and BTB methods, respectively (Figure 4). Further, 3.0 mL potassium hydrogen phthalate buffers gave maximum absorbance and reproducible results.

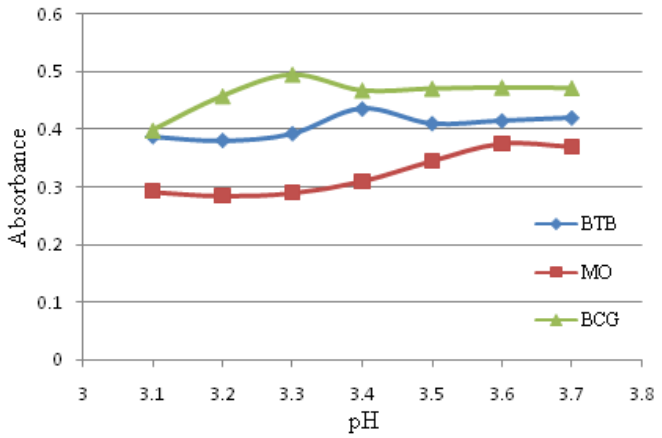

Fig. 4: Effect of pH of potassium hydrogen phthalate buffer solution on the absorbance of FXA (10µg/mL).

Effect of dye Concentration

The effect of the concentration of the dye on the intensity of the color developed at the selected wavelength and constant drug concentration (10µg mL^{-1}) was tested using different volumes of MO, BCG and BTB (0.5 - 2.0 mL). It was observed that 1.0 mL of 0.2% (w/v) dye was necessary for maximum color development of the ion-pair complex. Above this volume, the absorbance remained constant (Figure 5).

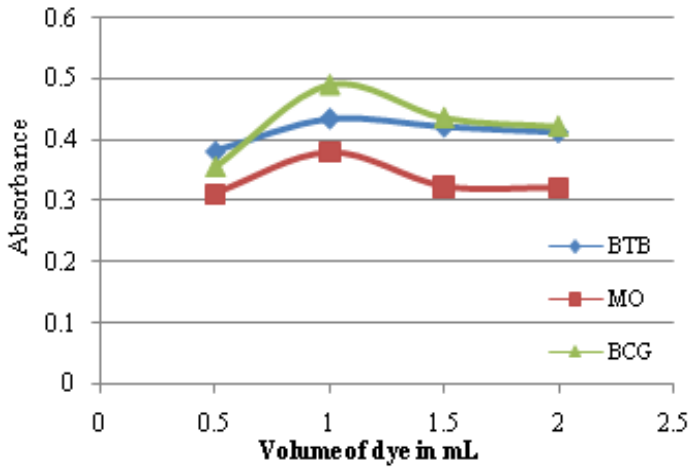

Fig. 5: Effect of reagent concentration on the reaction of (10µgmL^{-1}) FXA with BCG, MO and BTB.

Effect solvents

The effect of several organic solvents viz., chloroform, carbon tetrachloride, ethyl acetate, xylene, diethyl ether, butyl acetate, toluene, dichloromethane and chlorobenzene were tried for effective extraction of the colored species from aqueous phase. Chloroform was found to be the most suitable solvent for extraction of colored complex for all reagents, yielding maximum absorbance intensity and considerably lower extraction ability for the reagent blank and it was also observed that only double extraction was adequate to achieve a quantitative recovery of the complex and the shortest time to reach the equilibrium between both phases.

Stoichiometric Ratio

Job's Method (Inczedy, 1976) of Continuous Variation of equimolar solutions was employed. A 1.0 x 10^{-3} M standard solution of FXA and 1.0 x 10^{-3} solution of BCG, MO and BTB were used. A series of solutions was prepared in which the total volume of drug and reagent was kept at 10 mL. The absorbance was measured at 420, 420 and 410 for BCG, MO and BTB, respectively. The molar ratio of the reagent (drug: dye) in the ion-pair complex was determined by the Method of Continuous Variation (Job's Method) and the results indicated that 1: 1 (drug: dye) was the optimum ratio for the reaction (Figure 6).

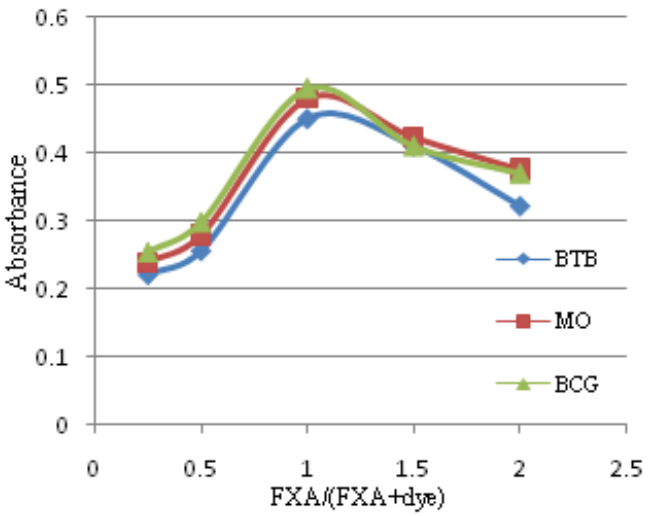

Fig. 6: Job's method of continuous variation graph for the reaction of FXA with acid-dyes BCG, MO and BTB, [drug] = [dye] = 1x10^{-3} M.

Linearity and range

Beer's law range, molar absorptivity, Sandell's sensitivity, regression equation and correlation coefficient determined for each method are given in Table 1. A linear relationship was found between the absorbance at λ_{max} and the concentration of the drug in the range 2.0–16 µg mL^{-1} for BCG, 2.0–15 µg mL^{-1} for MO and 2.0–20 µg mL^{-1} for BTB method in the final measured volume of 10 ml. Regression analysis of the Beer's law plots at λ_{max} reveals a good correlation. The graphs show negligible intercept and are described by the regression equation, A = *mC* + *b* (where *A* is the absorbance of 1 cm layer, *m* is the slope, *b* is the intercept and *C* is the concentration of the measured solution in µg ml^{-1}) obtained by the least-squares method (Miller *et al.*, 1993). The high molar absorptivities of the resulting colored complexes indicate the high sensitivity of the methods. Calibration curve for three proposed methods are shown in Figure 7.

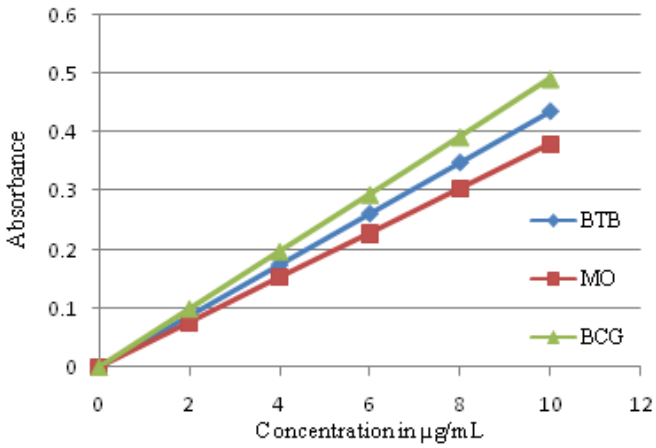

Fig. 7: Calibration curve of ion-associate complexes of FXA-MO, FXA-BCG and FXA-BTB against blank.

Validation of the methods

Samples of pure FXA were prepared and tested at four levels of drug using the proposed procedures. The complete set of validation assays was performed for drug, determined by the proposed methods. The results obtained for pure drugs are given in Table 2. The precision and accuracy of the methods were tested by analyzing six replicates of the drug. The standard deviation, relative standard deviation, recovery and 95% confidence limits of different amounts tested were determined from the calibration curve, as recorded in Table 2. The accuracy of the method is indicated by the excellent recovery (100.00–100.16%), (99.77–100.33%) and (99.83–100.66%) for MO, BCG and BTB methods, respectively (ICH, 1996, Shabir, 2003).

Tablets analysis

The proposed methods were applied to the determination of FXA in commercial tablets. The accuracy of the proposed methods is evaluated by applying standard addition technique, in which variable amounts of the drug were added to the previously analyzed portion of pharmaceutical preparations and the results are tabulated in Table 3. Six replicates determinations were made. Satisfactory results were obtained for drug and were in a good agreement with the label claims (Table 3). The results were reproducible with low R.S.D. values. The average percent recoveries obtained were quantitative (99.50–100.0% for MO, 100.33-101.0% for BCG and 100.50-101.5% for BTB), indicating good accuracy of the methods. The results of analysis of the commercial tablets and the recovery study of drug suggested that there is no interference from any excipients (such as starch, lactose, titanium dioxide, and magnesium stearate), which are present in tablets.

Table 1: Statistical data of the regression equations for determination of BTB, MO, BCG.

Parameters	Spectrophotometric method		
	BTB	MO	BCG
λ_{max}	410	420	420
Linearity range (µg/mL)	2.0 – 20	2.0 - 15	2.0 – 16
Molar absorptivity (L/mol/Xcm)	$1.88X10^4$	$1.65X10^4$	$2.12X10^4$
Sandell's sensitivity (µg cm^{-2} per 0.001 absorbance unit)	0.0229	0.0263	0.0203
Regression equation (y)	0+0.04X	0+0.04X	0+0.05X
Intercept (b)	0	0.0005	0.0009
Slope (a)	0.0435	0.03795	0.04895
Correlation coefficient (r)	1.000	0.9999	0.9999
SD	0.1376	0.1200	0.1548
LOD (µg /mL)	0.346	0.240	0.325
LOQ (µg /mL)	1.030	0.714	0.966

LOD, limit of detection; LOQ, limit of quantification

Table 2: Analysis of FXA in bulk powder by MO, BCG and BTB methods (n=6).

Method	µg/mL		S.D	Recovery (%)	Precision[a] R.S.D (%)	Accuracy ER%	Cofidence limits[b] (95%)
	Taken	Found					
MO	3.00	3.00	0.0578	100.00	1.98	0	2.939-3.061
	6.00	6.01	0.0432	100.16	0.71	0.17	5.965-6.055
	9.00	9.00	0.0581	100.00	0.64	0	8.939-9.061
	12.00	12.01	0.0457	100.08	0.38	0.08	11.962-12.058
BCG	3.00	3.00	0.0742	100.00	2.47	0	2.922-3.078
	6.00	6.02	0.0843	100.33	1.40	0.33	5.932-6.108
	9.00	8.98	0.0571	99.77	0.63	-0.22	8.920-9.040
	12.00	12.02	0.0789	100.08	0.65	0.08	11.937-12.103
BTB	3.00	3.02	0.0546	100.66	1.80	0.67	2.963-3.077
	6.00	5.99	0.0312	99.83	0.52	-0.17	5.957-6.023
	9.00	9.00	0.0727	100.00	0.80	0	8.924-9.076
	12.00	12.00	0.0591	100.00	0.49	0	11.938-12.062

n, number of determination, R.S.D.%, percentage relative standard deviation; Er%, percentage relative error.
[a]Mean of six determination.
[b]Confidence limit at 95% confidence level and five degrees of freedom.

Table 3: Evaluation of accuracy and precision of FXA tablets by standard addition method (n= 6).

Method	µg/mL			S.D	Recovery (%)	Precision[a] R.S.D (%)	Accuracy ER%	Cofidence limits[b] (95%)
	Taken	Added	Found					
MO	5.0	2.0	7.0	0.082	100.0	1.160	0.000	6.914-7.086
		4.0	8.98	0.071	99.50	0.796	-0.222	8.916-9.054
		6.0	10.97	0.077	99.50	0.715	-0.272	10.889-11.051
		8.0	12.99	0.098	99.88	0.750	-0.076	12.887-13.093
BCG	5.0	2.0	7.01	0.095	100.50	1.357	0.142	6.910-7.110
		4.0	9.02	0.097	100.50	1.070	0.222	8.918-9.122
		6.0	11.02	0.082	100.33	0.741	0.182	10.934-11.106
		8.0	13.08	0.104	101.00	0.792	0.615	12.971-13.189
BTB	5.0	2.0	7.03	0.112	101.5	1.586	0.429	6.912-7.148
		4.0	9.03	0.103	100.75	1.141	0.333	8.922-9.138
		6.0	11.09	0.107	101.5	0.967	0.818	10.978-11.202
		8.0	13.04	0.138	100.50	1.061	0.308	12.895-13.185

n, number of determination, R.S.D.%, percentage relative standard deviation; Er %, percentage relative error.
[a]Mean of six determination.
[b]Confidence limit at 95% confidence level and five degrees of freedom.

CONCLUSIONS

The three proposed methods (MO, BCG and BTB) can be used for determination of FXA in tablets. The three methods are rapid, simple and have great sensitivity and accuracy. Proposed methods make use of simple reagents, which an ordinary analytical laboratory can afford. Methods are sufficiently sensitive to permit determination even down to 2.0 µg mL^{-1}. The three proposed methods are suitable for routine determination of FXA in its formulations. The commonly used additives such as starch, lactose, titanium dioxide, and magnesium stearate do not interfere with the assay procedures.

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