September 2009 Volume 8 Issue 3

Trade Science Inc.

Analytical CHEMISTRY

An Indian Journal

Full Paper

ACAIJ, 8(3) 2009 [325-333]

Spectrofluorimetric determination of flupentixol dihydrochloride and quetiapine in pharmaceutical preparations and spiked human plasma *via* oxidation with cerium (IV)

N.El-Enany*, F.Belal, A.El-Brashy, N.El-Bahy

Departments of Analytical Chemistry Chemistry, Faculty of Pharmacy, Mansoura University, Mansoura, 35516, (EGYPT)

E-mail : nelenany1@yahoo.com

Received: 26th June, 2009 ; Accepted: 6th July, 2009

ABSTRACT

A simple and sensitive kinetic spectrofluorometric method was developed for the determination of flupentixol (FPX) and Quetiapine (QTP). The method was based upon oxidation of the studied drugs with cerium (IV) ammonium sulphate in acidic medium. The fluorescence of the produced Ce (III) was measured at 362 nm after excitation at 255 nm. The fluorescence –concentration plots were rectilinear over the concentration ranges of 0.04 to 0.2 $\mu g/ml^{-1}$ and 0.025 to 0.6 $\mu g/ml^{-1}$ with LOD of 1.7×10^{-3} and 7.7×10^{-4} $\mu g/ml^{-1}$ and LOQ of 5.2×10^{-3} and 2.3×10^{-3} $\mu g/ml^{-1}$ for FPX and QTP respectively. The method was successfully applied to the analysis of commercial tablets and ampoules. The results obtained were in good agreement with those obtained with reference methods. The mean % recoveries of FPX in tablets and ampoules (n=5) were 100.22 ± 0.75 and 99.70 ± 0.58 for tablets and ampoules respectively. The mean % recoveries of QTP in tablets (n=5) were 101.09 ± 0.74. The high sensitivity attained by the proposed method allowed the determination of QTP in spiked human plasma. The mean % recoveries of QTP in spiked human plasma (n=3) were 97.43 ± 0.81.

KEYWORDS

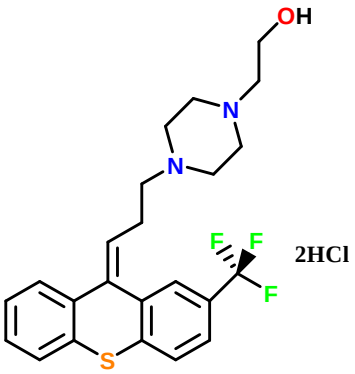
Flupentixol (FPX);
Quetiapine (QTP);
Cerium (IV);
Biological fluids.

INTRODUCTION

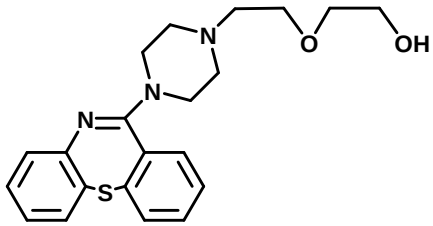
Flupentixol dihydrochloride [FPX], 2-[4-[3-[2-(trifluoromethyl) thiothanthen-9-ylidene] propyl] piperazin-1-yl] ethanol (Figure 1) acts on a subset of dopamine receptors. It specifically antagonizes D1 and D2 dopamine receptors (as well as serotonin). Flupentixol decanoate ester is used as an intramuscular depot injection as a long-acting antipsychotic (1).

Quetiapine [QTP], 2-(2-(4-dibenzo [b,f][1,4] thiazepine- 11-yl-1-piperaminyl) ethoxy) ethanol (Figure 1) belongs to a series of neuroleptics known as "atypical antipsychotic", which have, over the last four decades, become increasingly popular alternatives to '' typical antipsychotics'', such as haloperidol. It is used for the treatment of schizophrenia, acute maniain Bipolar disorder.Recently, it is used to treat other disorders, such as post-traumatic stress disorder, alcoholism, anxiety disarders, hallucinations in Parkinson's disease patients using ropinirole, and as a sedative for those with sleep disorders[1].

Full Paper



Flupentixole. 2HCl (FPX)



Quetiapine (QTP)

Figure 1 : Structural formulae of FPX 2HCl and QTP

Various methods have been published for the determination of FPX either *per se* or in pharmaceutical preparations and biological fluids. These methods include: spectrophotometry,[2,3] spectrofluorometry,[4,5] HPLC[6-9] and capillary electrophoresisand spectrophotometry.[10]

Similarly, various methods have been reported for the estimation of QTP either *per se* or in pharmaceutical preparations and biological fluids *viz* spectrophotometry,[11] voltammetry,[12,13] HPLC,[14-20] and capillary electrophoresis.[21-23]

In the present study, cerium (IV) ammonium sulphate has been utilized for the oxidation of the studied drugs in acidic medium yielding an equivalent amount of fluorescent Ce (III) which exhibits maximum fluorescence at 362 nm after excitation at 255 nm.

To the best of our knowledge, up to the present time, nothing has been reported concerning the fluorimetric determination of QTP either *per se* or in pharmaceutical preparations or in biological fluids, this initiated the present study.

EXPERIMENTAL

Materials and reagents: All chemicals were of Analytical Reagent Grade. Flupentixol (FPX 2HCl) pure drug was kindly provided by Lundbeck Company, England . Fluvixal tablets (labeled to contain 2 mg FPX 2HCl per tablet, batch # 06768) were obtained from Egypt Delta Pharma Company, Cairo, Egypt. Fluanxol® depot ampoules (labeled to contain 40 mg FPX decanoate per 2 mL ampoule, batch # 2050869) were manufactured in Denmark by H. Lundbeck A/S Copenhagen, imported and distributed by Multipharma Company, Cairo, Egypt. Quetiapine (QTP) pure drug was kindly provided by Multipharma Company, Cairo, Egypt. Seroquel tablets (labeled to contain 300 mg QTP per tablet, batch # 10081) were obtained from UK Zeneca Company. Cerium (IV) ammonium sulphate (BDH, Pool, UK), 5×10^{-4} M aqueous solution was freshly prepared in 0.4, 1.4 M sulphuric acid for QTP and FPX 2HCl respectively. Sulphuric acid, (Prolabo, France), 0.4, 1.4, 1 and 2 M aqueous solutions were used. Plasma samples were obtained from Mansoura University Hospital, Mansoura, Egypt and were kept frozen until use after gentle thawing.

Apparatus: The fluorescence spectra and measurements were performed on a Perkin-Elmer UK model LS 45 luminescence spectrometer, equipped with a 150 W Xenon arc lamp, grating excitation and emission monochromators for all measurements and a Perkin-Elmer recorder. Slit widths for both monochromators were set at 10 nm. A 1 cm quartz cell was used.

Sample preparation and procedure: Stock solution of FPX 2HCl was prepared by dissolving 10.0 mg of the drug in 100 mL of distilled water in a measuring flask and further diluting with the same solvent to get working solutions as appropriate. Stock solution of QTP was prepared by dissolving 10.0 mg of the drug in 10 ml of 2 M H_2SO_4, then completing to 100 ml with distilled water in a measuring flask and was further diluted with the same solvent to get working solutions as appropriate. The standard solutions were stable for one week when kept in the refrigerator.

Construction of calibration graph: Aliquot volumes of FPX 2HCl or QTP standard solutions covering the

working concentration range cited in TABLE 1 were transferred into a series of 10 mL volumetric flasks; followed by 1.4 ml or 1 ml of 5×10^{-4} M Ce (IV) solution for FPX or QTP respectively. The flasks were heated in a thermostatically controlled water-bath at 100ºC for 20 min for FPX 2HCl. or at 80ºC for 30 min. for QTP respectively. The solutions were cooled and diluted to the mark with distilled water. A blank experiment was performed simultaneously. The relative fluorescence intensity (FI) of the solutions was measured at 362 nm after excitation at 255 nm. The corrected FI was plotted *vs* final concentration of the drug (µg/ml) to get the calibration graphs. Alternatively, the corresponding regression equations were derived.

Assay procedure for FPX 2 HCl and QTP in tablets

Ten tablets containing FPX 2HCl or QTP were weighed and pulverized. An accurately weighed amount of the powder equivalent to 10.0 mg of FPX 2HCl or QTP were transferred into a small conical flask and extracted with 3× 30 ml of distilled water or with 10 ml of 2 M H_2SO_4 solution for FPX 2HCl or QTP, respectively. The extract was filtered into a 100 ml volumetric flask. The conical flask was washed with few mLs of distilled water for QTP. The washings were passed into the same volumetric flask and completed to the mark with distilled water. Aliquots covering the working concentration range cited in TABLE 2 were transferred into a series of 10 ml volumetric flasks and continued as described under *"*Construction of calibration graph*"*. The nominal content of tablets was determined either from the previously plotted calibration curve or using the corresponding regression equation.

Assay procedure for FPX oily ampoules

The contents of 5 ampoules were mixed well, then an aliquot volume of the mixed solution equivalent to 10.0 mg of FPX decanoate was transferred into a separating funnel and 5 ml of 2 M NaOH was added to liberate the base. 30 ml of 2 M H_2SO_4 was added to dissolve the precipitated base. The extract was transferred into a 100 ml volumetric flask. The separating funnel was washed with few mls of distilled water. The washings were passed into the same volumetric flask and completed to the mark with distilled water. Aliquots covering the working concentration range cited in TABLE 2 were transferred into 10 ml volumetric flasks and completed as described under *"*Construction of calibration graph*"*. The nominal content of the ampoule was determined either from the previously plotted calibration curve or using the corresponding regression equation.

Assay procedures for spiked human plasma

One ml aliquot of human plasma spiked with increasing quantities of QTP were transferred into a series of centrifugation tubes. The contents of the tubes were mixed well with 1 ml of 0.1 M NaOH. The reaction mixture was extracted with 3 × 5 ml of diethylether and centrifuged at 2500 rpm for 15 min. The supernatant was collected and dried under a stream of nitrogen. The residue was dissolved in 1 ml of 2 M H_2SO_4, then, the procedure was performed as described under "General Procedure". A blank experiment was carried out simultaneously. The nominal content of the drug was determined using the corresponding regression equation.

RESULTS AND DISCUSSION

Fluorescence spectra of Ce (III)

Recently, cerium (IV) has been frequently utilized as a useful reagent for the determination of several pharmaceutical compounds, such as antivirals,[24] psychoactive drugs,[25] and aztreonam[26].

The proposed method is based on oxidation of the

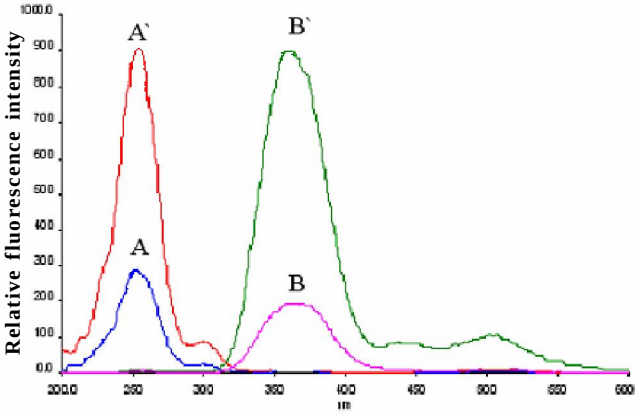


Figure 2 : Excitation and emission spectra of the reaction products induced by oxidation with Ce (IV) in 1.4 M H_2SO_4.
(A, B) Blank Ce (IV).
(A', B') After addition of 1 µg mL^{-1} flupentixol.

Full Paper

studied drugs with excess cerium (IV) ammonium sulphate in acidic medium and measuring the equivalent amount of Ce (III) produced fluorimetrically. The later exhibits maximum fluorescence at 362 nm after excitation at 255 nm (Figures 2 and 3).

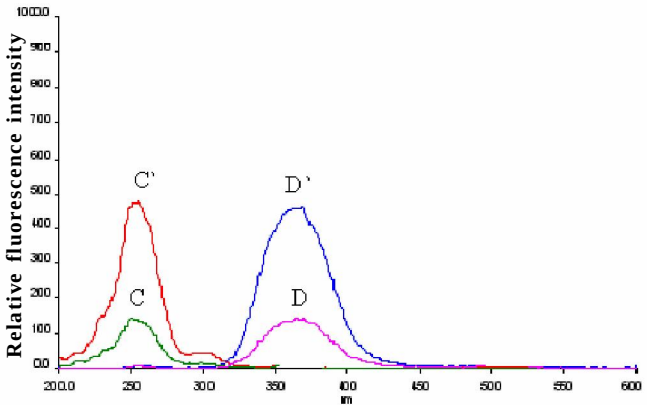


Figure 3 : Excitation and emission spectra of the reaction products induced by oxidation with Ce (IV) in 0.4 M H_2SO_4.
(A, B) Blank Ce (IV).
(A', B') After addition of 0.6 µg /ml quetiapine.

Although the oxidation product of FPX is fluorescent yet, it doesn't interfere with the proposed method since it exhibits fluorescence at 440 nm after excitation at 370 nm[5].

Optimization of Experimental Conditions

The spectrofluorometric properties of Ce (III) as well as the different experimental parameters affecting its formation and its stability were carefully studied and optimized. Such factors were changed individually while the others were kept constant. These factors included Ce (IV) concentration, type of acid and its concentration, heating time, temperature and diluting solvents.

The influence of Ce (IV) concentration on the fluorescence intensity of the resulting Ce (III) was studied using increasing concentrations of Ce (IV) solution. It was found that, maximum and constant fluorescence intensity was attained upon using $7 \pm 1\times10^{-5}$ M and $6 \pm 1\times10^{-5}$ M (final concentration) for each of FPX 2HCl and QTP, respectively as shown in (Figure 4). Higher concentrations of Ce (IV) caused a slight decrease in the fluorescence intensity of QTP, probably subsequent reactions might occur leading to quenching of Ce (III).

The oxidation reaction with Ce (IV) has to be performed in acid medium to prevent precipitation of

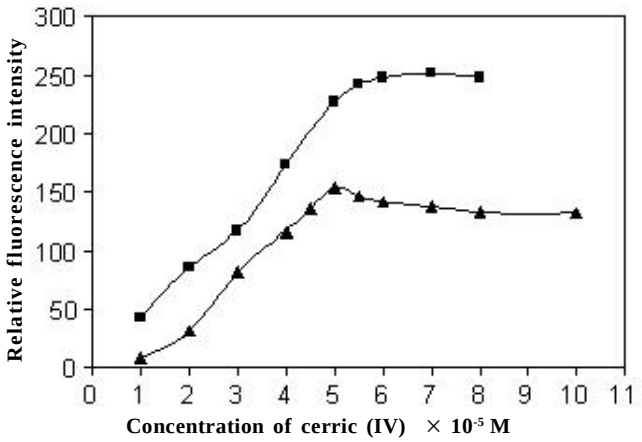


Figure 4 : Effect of Ce (IV) on the relative fluorescence intensity of Ce (III) produced by:
■ Flupentixol 0.2 µg /ml ▲ Quetiapine 0.2 µg /ml

$Ce(OH)_3$. Different acids such as, sulphuric acid, hydrochloric acid, nitric acid and perchloric acid were tested to determine the most suitable one for the reaction. Nitric acid is not preferred owing to the inhibitory effect of nitrate ions on the fluorescence of Ce (III)[24]. In the prescence of hydrochloric acid, perchloric acid and sulphuric acid, the reaction rate and the fluorescence of Ce (III) were found to be high. However, hydrochloric acid and perchloric acid gave high blank readings,so, sulphuric acid was selected for this study.

The effect of sulphuric acid concentration on the fluorescence intensity of Ce (III) was studied using concentrations ranging from 0.1 up to 2.5 M or 1.5 M for FPX or QTP respectively (Figure 5). It was found that, the relative fluorescence intensity increased with increasing sulphuric acid concentration up to 1.4 M and 0.4 M

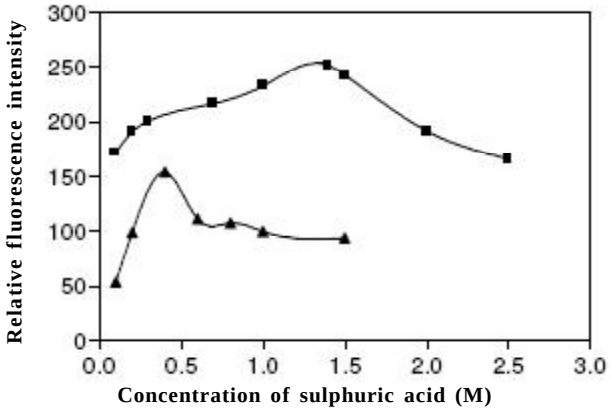


Figure 5 : Effect of sulphuric acid on the relative fluorescence intensity of Ce (III) produced by:
■ Flupentixol 0.2 µg /ml ▲ Quetiapine 0.2 µg /ml

for FPX and QTP respectively. Therefore, these values were used as the optimum concentrations of suphuric acid through out the study.

Effect of temperature and heating time

Oxidation of the studied drugs with Ce (IV) was carried out at different temperature settings, using a thermostatically controlled water bath, ranging from ambient temperature, 40ºC, 60ºC, 80ºC and boiling water for periods of times ranging from 5 to 40 min. Preliminary experimental results revealed that, the reaction is strongly dependent on the temperature and time of heating. At ambient temperature (25 ºC), the reaction proceeds slowly. However, heating the reaction mixture was found to increase both the reaction rate and the fluorescence intensity of the formed Ce (III). The results revealed that the optimum temperature was 100 ºC and 80 ºC for FPX and QTP respectively (Figure 6). Complete reaction was attained upon heating for 20 min. for FPX and 30 min. for QTP, after which the relative fluorescence intensity started to decrease gradually as shown in (Figure 7).

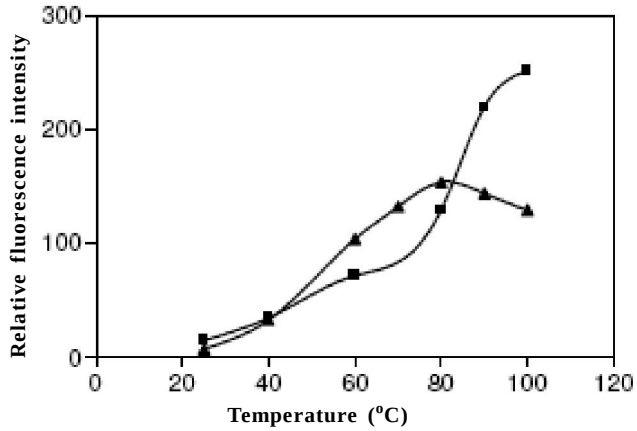


Figure 6 : Effect of temperature on the relative fluorescence intensity of Ce (III) produced by:
■ Flupentixol 0.2 µg /ml ▲ Quetiapine 0.2 µg /ml

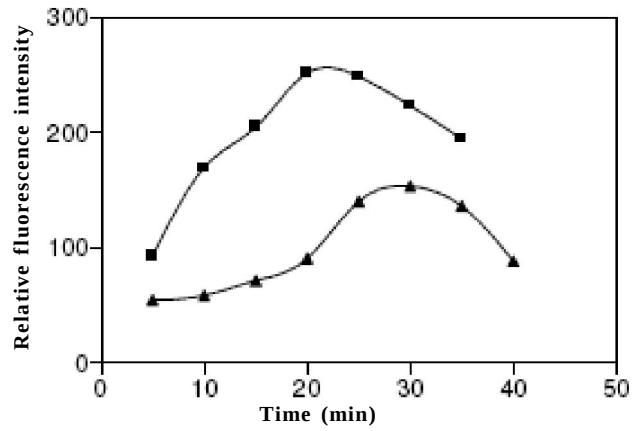


Figure 7 : Effect of heating time on the relative fluorescence intensity of Ce (III) produced by:
■ Flupentixol 0.2 µg /ml ▲ Quetiapine 0.2 µg /ml

Effect of diluting solvents

Dilution with different solvents such as water, methanol, acetonitrile, dimethyl sulfoxide and dimethyl formamide was attemped. It was found that, water was the best solvent for dilution as it gave the highest fluorescence intensities and the lowest blank readings.

Analytical Performance

Validation of the proposed methods

The validity of the method was tested regarding; linearity, specificity, accuracy,

Linearity

The fluorescence-concentration plots for the studied drugs were rectilinear over the range 0.04 – 0.20 µg mL^{-1} and 0.025 – 0.60 µg mL^{-1} for FPX 2HCl and QTP, respectively. The results are shown in TABLE 1

Linear regression analysis of the data gave the following equations:

for FPX 2HCl F = 3.90 + 1237 C (r = 0.9998)

and for QTP F = 0.42 + 770 C (r = 0.9999)

Where F is fluorescence intensity, C is the concentration of the drug (µg mL^{-1}) and r is correlation coefficient.

The limits of quantitation (LOQ) and the limits of detection (LOD) were calculated according to ICH Q2B Recommendations.[27]

LOQ = 10 S_a / b and LOD = 3.3 S_a /b

Where S_a = standard deviation of the intercept of the calibration curve and

b = slope of the calibration curve.

LOQ were found to be 5.2×10^{-3} and 2.3×10^{-3} µg/ml for FPX 2HCl and QTP, respectively and LOD were found to be 1.7×10^{-3} and 7.7×10^{-4} µg/ml for FPX 2HCl and QTP, respectively

The proposed method was evaluated by studying the accuracy as percent relative error and precision as percent relative standard deviation. The results are abridged in TABLE 1.

Full Paper

TABLE 1 : Performance data of the proposed method.

Parameter	FPX 2HCl	QTP
Concentration range (µg/ml)	0.04 - 0.20	0.025 - 0.60
Limit of detection (LOD) (µg/ml)	1.7×10^{-3}	7.7×10^{-4}
Limit of Quantitation (LOQ) (µg/ml)	5.2×10^{-3}	2.3×10^{-3}
Correlation coefficient (r)	0.9998	0.9999
Slope	1237	770
Intercept	3.90	0.42
Standard deviation of the residuals ($S_{y/x}$)	0.71	0.30
Standard deviation of the intercept (S_a)	0.64	0.18
Standard deviation of the slope (S_b)	5.67	0.53
Relative standard deviation (RSD, %)	1.13	0.63
% RSD/ √n (% Error)	0.51	0.22

Precision of the method was also evaluated by statistical analysis of the regression data regarding standard deviation of the residuals ($S_{y/x}$), the standard deviation of the intercept (S_a), and the standard deviation of the slope (S_b). The small values abridged in TABLE 1 point out to the low scattering of the points around the calibration curve, thus indicating high precision of the method.

Statistical analysis,[28] of the results, obtained by both the proposed and the comparison methods,[5,10] using Student's t-test and variance ratio F-test, shows no significant difference between the two methods regarding the accuracy and precision, respectively.

The comparison method of FPX 2HCl (5) depends on oxidation with sodium nitrite in glacial acetic acid, then measuring the fluorescence intensity of the sulphoxide derivative at 440 nm after excitation at 370 nm.

The comparison method of QTP,[10] depends on direct spectrophotometric measurement of the absorbance of the methanolic solution at 246 nm.

Pharmaceutical Applications

The proposed method was applied to the determination of the studied drugs in their dosage forms.

The selectivity of the method was investigated by observing any interference encountered from the common tablet excepients, such as talc, lactose, starch, avisil, gelatine, and magnesium stearate. These excepients didn't interfere with the proposed method in case of FPX.2HCl and QTP tablets (TABLE 2). On the other hand, FPX ampoules exhibit some problems due to its oily nature and had to be firstly treated with NaOH to liberate the base then with H_2SO_4 to dissolve it.

Accuracy

The results of the proposed method were compared with those obtained using the comparison methods.[5,10] Statistical analysis,[28] of the results obtained using Student's t-test and variance ratio F-test revealed no significant difference between the performance of the two methods regarding the accuracy and precision, respectively (TABLE 2).

TABLE 2 : Application of the proposed and comparison methods to the determination of flupentixol and quetiapine in raw material and dosage forms.

Sample	Amount Taken (µg/ ml)	Amount found (µg/ ml)	Found %	Reference method[5,10] % Recovery
1- FPX. 2HCl raw	0.04	0.0396	99.23	100.70
material	0.08	0.0817	101.25	99.07
	012	0.1180	98.33	100.35
	0.16	0.1600	100.00	
	0.20	0.2010	100.50	
Mean±SD			99.86±1.13	100.04±0.86
Student t-test			0.29 (2.45)	
F-value			1.73 (6.94)	
2-Fluvixal tablets®	0.04	0.0404	101.00	100.44
(FPX 2HCl, 2 mg/	0.08	0.0792	99.05	100.63
tablet)[a]	012	0.1208	100.67	99.28
	0.16	0.1600	100.00	
	0.20	0.2008	100.40	
Mean±SD			100.22±0.75	100.12±1.07
Student t-test			0.19 (2.45)	
F-value			1.06 (6.94)	
3- Fluanxol depot®	0.04	0.0400	100.00	99.12
(FPX decanoate,	0.08	0.0793	99.06	100.00
40mg/2mL ampoule)[b]	0.12	0.1192	99.32	100.48
	0.16	0.1608	100.52	
	0.20	0.1992	99.60	
Mean±SD			99.70±0.58	99.87±0.95
Student t-test			0.38 (2.45)	
F-value			1.41 (6.94)	
4-QTP raw	0.025	0.0254	101.60	99.12
Material	0.05	0.501	1100.20	101.20
	0.10	0.0995	99.50	99.56
	0.20	0.1996	99.80	
	0.30	0.2997	99.90	
	0.40	0.4010	100.25	
	0.50	0.4998	99.96	
	0.60	0.5999	99.98	
Mean±SD			100.15±0.63	99.96±1.09
Student t-test			0.26 (2.26)	
F-value			3.03(4.74)	

(Continued)

Sample	Amount Taken (µg/ ml)	Amount found (µg/ ml)	Found %	Reference method[5,10] % Recovery
5-Seroquel tablets	0.20	0.203	101.30	101.25
(QTP, 300 mg/	0.30	0.305	101.75	99.60
tablet)[c]	0.40	0.401	100.30	100.85
	0.50	0.509	101.78	
	0.60	0.608	100.30	
Mean±SD			101.30±1.4	101.25±1.5
Student t-test			0.05 (2.45)	
F-value			1.07 (6.94)	

N.B.:

- Figures between parenthesis are the tabulated t and F values respectively at p = 0.05.[28]

[a]Fluvixal tablets (labeled to contain 2 mg FPX 2HCl per tablet, batch # 06768) were obtained from Egypt Delta Pharma Company.

[b] Fluanxol® depot ampoules (labeled to contain 40 mg FPX decanoate per 2 mL ampoule, batch # 2050869) were manufactured in Denmark by H. Lundbeck A/S – Copenhagen then imported and distributed by Multipharma Company.

[c]Seroquel tablets (labeled to contain 300 mg QTP per tablet, batch # 10081) were obtained from UK Zeneca Company.

Robustness of the method

The robustness of the proposed method is demonstrated by the constancy of the fluorescence intensity with the deliberated minor changes in the experimental parameters such as, volume of 5×10^{-4} M Ce (IV), 1.4 ± 0.1 ml, 1 ± 0.1 ml for FPX 2HCl and QTP, respectively and change in the concentration of sulphuric acid, 1.4 ± 0.1 M, 0.4 ± 0.1 M for FPX and QTP, respectively. These minor changes that may take place during the experimental operation didn't affect the fluorescence intensity.

Co-administered drugs

Co-administered drugs such as imipramine showed a slight positive interference. On the other hand, clozapine, sertraline and triprolidine introduced negative interference and decrease the fluorescence intensities of the produced Ce (III). The tolerance limits were calculated as the concentration causing 3% relative error for a sample of QTP 0.3 µg/ml (TABLE 3).

TABLE 3 : Tolerance limits of Co-administered drugs causing 3% relative error for a sample of quetiapine 0.3 µg/ml.

Drug	%Fluorescence intensity	%Change in fluorescence	Tolerance limit (µg/ml)
Quetiapine	100.00	–	–
Clozapine	57.91	- 42.09	0.051
Imipramine	224.18	+124.18	0.013
Sertraline	21.19	- 78.81	0.142
Triprolidine	35.82	- 64.18	0.084

Biological applications

The high sensitivity of the proposed method allowed the *in-vitro* determination of QTP in spiked human plasma.

QTP is readily absorbed from the gastrointestinal tract. The mean plasma therapeutic level is about 0.4 µg/ml,[29]. This value lies within the working concentration range of the proposed method. The extraction procedure described by Zhou *et al.*,[30] was adopted here.

Accuracy and precision

The intra-day precision was evaluated through replicate analysis of plasma samples spiked with different concentrations of QTP ranging from 0.05 – 0.2 µg/ml. The mean % recovery of QTP in spiked human plasma samples was 97.43 ± 0.81. The results are abridged in TABLE 4.

The inter-day precision was evaluated through replicate analysis of plasma spiked with 0.1 µg ml^{-1} of QTP on three successive days. The mean percentage recoveries was 99.23 ± 1.63. This indicates the high accuracy of the proposed method. The results are abridged in TABLE 4.

The proposed method is specific for QTP in presence of its degradation product (quetiapine sulfoxide).[31]

TABLE 4 : Spectrofluorimetric determination of quetiapine in spiked human plasma.

Precision test	Day number	Amount added (µg/ml)	Amount found (µg/ml)	% Recovery
1- Intra–day		0.05	0.0490	98.00
		0.10	0.0978	97.80
		0.20	0.1930	96.50
Mean±S.D.				97.43±0.81
2- Inter–day	1st	0.10	0.0989	98.90
	2nd	0.10	0.1012	101.00
	3rd	0.10	0.0978	97.80
Mean±S.D.				99.23±1.63

Stoichiometry of the reaction

The stoichiometry of the reaction between the studied drugs and cerric (IV) was studied adopting the lim-

Full Paper

iting logarithmic method.[32] The fluorescence intensities of the Ce (III) were alternatively measured in the presence of excess Ce (IV) and the studied drugs. Plots of log [drugs] *vs* log F and log [Ce (IV)] *vs* log F gave straight lines, the values of the slopes were 0.975 : 0.915 for FPX 2HCl : Ce (IV) and 0.982 : 1.262 for QTP: Ce (IV) (Figure 8). Hence, it is concluded that, the molar reactivity of the reaction is 1 : 1 in both cases.

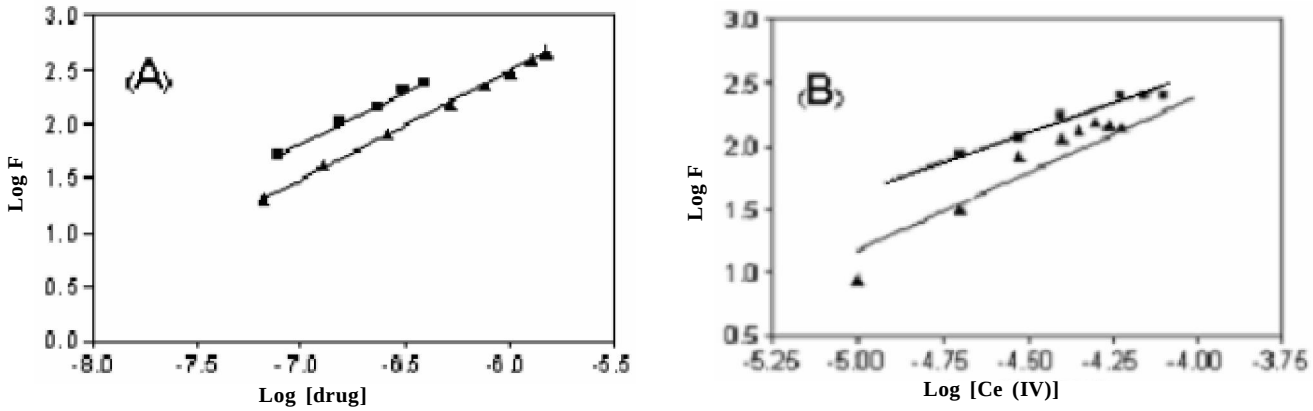
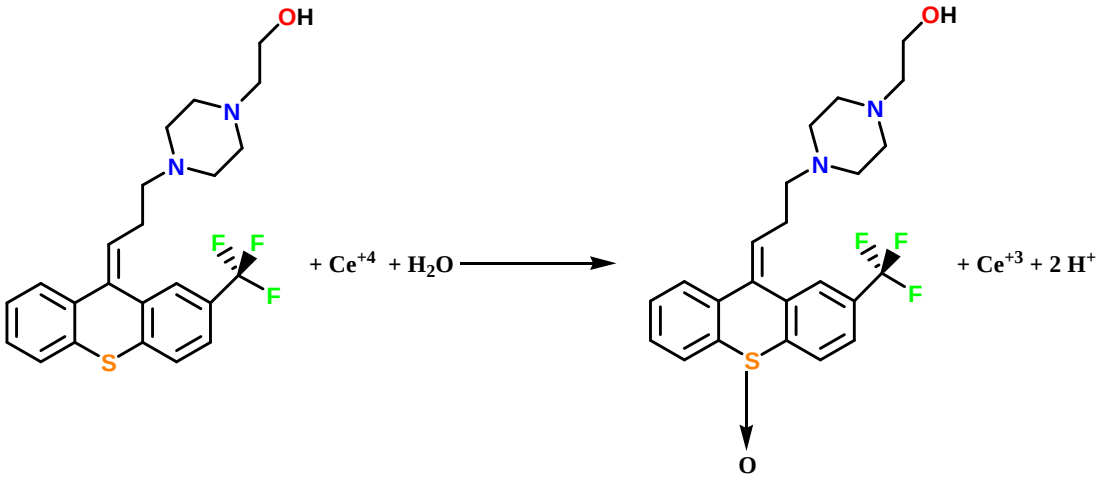
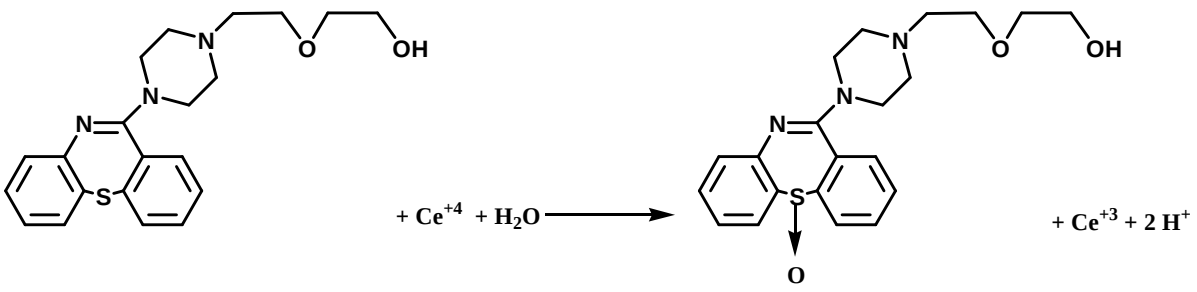


Figure 8 : Stoichiometry of the reaction between each of flupentixol and quetiapine with Ce (IV) adopting limiting logarithmic method.
(A) Log [drug] *vs* log F. (B) Log [Ce (IV)] *vs* log F.
■ Flupentixol ▲ Quetiapine

Based on the observed molar reactivity of the reaction of both drugs with Ce^{+4} and by analogy to previous reports,[25] it is assumed that the thioether group -S- in both compounds is oxidized to the corresponding sulphoxides.[5] Proposals for the reaction pathways are shown in the following schemes:



Scheme 1: The proposal for the reaction pathway between flupentixol and Ce (IV).



Scheme 2: The proposal for the reaction pathway between quetiapine and Ce (IV).

CONCLUSION

The present study describes a sensitive spectrofluorometric method for the determination of FPX 2HCl and QTP in tablets without interference from common tablet excepients. Hence, it can be applied for the routine quality control of the studied drugs either in bulk or in their corresponding dosage forms. The proposed method could be successfully adopted to the determination of quetiapine in spiked human plasma samples. The methodology appears to be straight forward and the results are relevant. From the economic point of view, the proposed method is simple, rapid and inexpensive. Besides, the use of water as diluting solvent is a further advantage. So, it is considered as a good alternative to the other reported methods and to the high cost HPLC methods.

REFERENCES

[1] Through Internet http://enwikipedia.org/wiki/chemical_compounds.
[2] N.Bergemann, A.Frick, P.Parzer, Kopitz; J.Pharmacopsychiatry., **37**, 63 **(2004)**.
[3] S.Walter, S.Bauer, I.Roots, J.Brockmoller; J.Chromatogr., **720**, 231 **(1998)**.
[4] N.Maki, P.Hafkemeyer, S.Dey; J.Biol.Chem., **278**, 18132 **(2003)**.
[5] I.A.Shehata, S.M.El-Ashry, M.A.El-Sherbeny, D.T.El-Sherbeny, F.Belal; J.Pharm Biomed Anal., **22**, 729 **(2000)**.
[6] H.Kirchherr, W.N.Kuhn-Velten; J.Chromatogr.B., **843**, 100 **(2006)**.
[7] T.Sokoliess, U.Menyes, U.Roth, T.Jira; J.Chromatogr.A., **948**, 309 **(2002)**.
[8] M.Kollroser, G.Henning, R.Gatternig, C.Schober; Forensic Sci.Int., **123**, 243 **(2001)**.
[9] M.T.Purnell, C.J.Mitchell, D.J.Taylor, I.C.Kokay, A.R.Mercer; Brain Res., **855**, 206 **(2000)**.
[10] T.Sokoliess, M.Gronau, U.Menyes, U.Roth, T.Jira; Electrophoresis., **24**, 1648 **(2003)**.
[11] M.A.Raggi; Curr.Med Chem., **9**, 1397 **(2002)**.
[12] P.Hertel, M.W.Massing, R.D.Madis; Synapse., **60**, 543 **(2006)**.
[13] M.M.Marcus, G.G.Nomikos, T.H.Svensson; Eur Neuropsychopharmacol., **10**, 245 **(2000)**.
[14] C.E.Marx, L.J.Shampine, G.E.Duncan, M.J.VanDoren, A.C.Grobin, D.W.Bradford, M.I.Butterfield, J.A.Lieberman, A.L.Morrow; Pharmacol Biochem Behav., **84**, 598 **(2006)**.
[15] H.Kirchherr, W.N.Kuhn-Velten; J.Chromatogr., **843**, 100 **(2006)**.
[16] M.A.Saracino, L.Mercolini, G.Flotta, L.J.Albers, R.Merli, M.A.Raggi; J.Chromatogr B., **843**, 227 **(2006)**.
[17] J.Sachse, J.Koller, S.Hartter, C.Hiemke; J.Chromatogr., **830**, 342 **(2006)**.
[18] Z.Li, J.Ichikawa, M.Huang, A.J.Prus, J.Dai, H.Y.Meltzer; Psychopharmacology., **183**, 144 **(2005)**.
[19] D.R.Parker, I.M.McIntyre; J.Anal.Toxicol., **29**, 407 **(2005)**.
[20] S.Kropp, V.Kern, K.Lange, D.Degner, G.Hajak, J.Kornhuber, E.Ruther, H.M.Emrich, U.Schneider, S.Bleich; J.Neuropsychiatry Clin Neurosci, **17**, 227 **(2005)**.
[21] G.Garrido, C.Rafols, E.Bosch; Eur J Pharm Sci., **28**, 118 **(2006)**.
[22] S.Hillaert, L.Snoeck, W.Van den Bossche; J Chromatogr A., **1033**, 357 **(2004)**.
[23] V.Pucci, R.Mandrioli, A.Ferranti, S.Furlanetto, M.Augusta Raggi; J.Pharm.Biomed Anal., **32**, 1037 **(2003)**.
[24] I.A.Darwish, A.S.Khedr, H.F.Askal, R.M.Mahmoud; Farmaco, **60**, 555-562 **(2005)**.
[25] F.A.Mohamed, H.A.Mohamed, S.A.Hussein, S.A.Ahmed; J.Pharm.Biomed.Anal., **39**, 139-146 **(2005)**.
[26] H.Mahgoub; J.Pharm.Biomed.Anal., **31**, 767-774 **(2003)**.
[27] Guidance for Industry; Q2B of Analytical Procedures: Methodology; International Conference on Hormonization (ICH), November 1996. http://www.fda.gov/eder/guidance/1320fnl.pdf (accessed September 1), **(2004)**.
[28] J.C.Miller, J.N.Miller; Pearson Prentice Hall. Statistics and Chemometrics For Analytical Chemistry. Fifth edition. p. 256 **(2005)**.
[29] A.C.Moffat, M.D.Osselton, B.Widdop, in L.Y.Galichet; Clark's Analysis of Drugs and Poisons. Third Edition. Pharmaceutical Press London. 1514 **(2004)**.
[30] Z.Zhou, X.Li, K.Li, Z.Xie, Z.Cheng, W.Peng, F.Wang, R.Zhu, H.Li; J.Chromatogr., **802**, 257 **(2004)**.
[31] J.Hasselstrom, K.Linnet; J.Chromatogr. B., **798**, 9 **(2003)**.
[32] J.Rose; Advanced Physicochemical Experiments, Pitman, London, p. 67 **(1964)**.