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A validated spectrofluorimetric method for determination of some psychoactive drugs

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Abstract

Five psychoactive drugs namely, chlorpromazine HCl, thioridazine HCl, clomipramine HCl, imipramine HCl and desipramine HCl were analyzed by a simple spectrofluorimetric method. The method is based on oxidation of the studied drugs using cerium(IV) in presence of sulphuric acid and monitoring the fluorescence of the formed cerium(III) at $\lambda_{ex.} = 254$ nm and $\lambda_{em.} = 355$ nm. All variables affecting the reaction conditions such as; cerium(IV) concentration, sulphuric acid concentration, heating time, temperature and dilution solvents were carefully studied. The effect of potential interference due to common ingredients as glucose, sucrose, lactose, citric acid and propylene glycol were investigated. A validation study of the proposed method was carried out according to USP 2002. Beer's law was obeyed for all the studied drugs in the concentration range of 0.05–1.3 μg/ml. Limits of detection range was 0.035–0.038 μg/ml and limits of quantitation of 0.116–0.125 μg/ml were obtained. The method was successfully applied for the assay of the studied drugs in pure form and in pharmaceutical dosage forms. Results were compared with official methods. The *t*- and *F*-values were calculated and compared with the theoretical values, which indicate high accuracy and good precision of the proposed method.

Keywords: Pharmaceutical analysis; Spectrofluorimetry; Cerium(IV); Oxidation; Phenothiazines; Dibenzazepines

1. Introduction

The use of drugs with well-demonstrated efficacy in psychiatric disorders has become wide spread since 1950s. Nowadays about 20% of prescriptions written in the United States are for medications intended for mental processes [1].

Several analytical methods have been reported for determination of psychoactive drugs either in pure form or in their pharmaceutical preparations. These methods include; spectrophotometry [2–18], spectrofluorimetry[19–24], titrimetry[25–30], chromatography[31–42], flow injection analysis [43–47], radio-immunoassay [48–49], electrochemical methods [50–51] and chemiluminescence methods [52–54].

Ce(IV) has been used as an oxidizing agent for spectrofluorimetric determination of trimeprazine and trifluoperazine [55], reserpine [56] and macrolides [57]. Measuring the fluorescence of Ce(III) was found to be more than four times fluorescent as their oxidation products, and therefore, the measurement of its fluorescence can be used as a very sensitive method for determination of such drugs [55].

Since the official and reported methods for determination of the studied psychoactive drugs were found to be laborious, expensive and time consuming so the aim of this work was to develop a new spectrofluorimetric method for determination of the studied psychoactive drugs, that is, more sensitive, simple, rapid and less expensive than the reported and official methods. The suggested spectrofluorimetric method depends simply on oxidation of all the studied psychoactive drugs using Ce(IV) in sulphuric acid medium and the relative fluorescence intensity of the formed Ce(III) was monitored at $\lambda_{ex.} = 254$ nm and $\lambda_{em.} = 355$ nm.

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2. Experimental

2.1. Instrumentation

- Spectrofluorimeter RF 5301 PC (Shimadzu, Japan).
  The spectrofluorimeter was set with excitation and emission slits at 1.5 nm.
- UV-1601 PC, UV–vis Spectrophotometer (Shimadzu, Japan).
- MLW type thermostatically controlled water bath (Germany).

2.2. Reagents and solutions

2.2.1. Materials

Ceric ammonium sulphate (Sigma chemie GmbH, Germany), imipramine HCl (%purity 100.26 ± 0.36), clomipramine HCl (%purity 99.92 ± 0.25) and desipramine HCl (%purity 99.28 ± 0.57) (Novartis Pharma AG, Basle, Switzerland), chlorpromazine HCl (%purity 98.91 ± 0.45) (May and Baker, England) and thioridazine HCl (%purity 98.35 ± 0.60) (Swiss Pharma, Cairo).

Pharmaceutical preparations containing studied drugs were obtained from the local market. Neurazine® tablets (B.N. 143021,Misr, Cairo, Egypt), promacid® tablets (B.N.15895,CID, Giza, Egypt), supranil® capsules (25 mg B.N.01109127, 50 mg B.N. 91100194, ACAPI, Cairo, Egypt), melleril retard® tablets (200 mg B.N. 183, 30 mg B.N. 118) tofranil® tablets(B.N. 172) desipramine (laboratory prepared synthetic mixtures), and anafranil® tablets(25 mg B.N.082, 75 mg B.N. 145) (Novartis Pharma AG, Basle, Switzerland).

All other chemicals and solvents used in work were of analytical grade.

2.2.2. Ceric ammonium sulphate solution

Solutions of ceric ammonium sulphate in concentration range (0.0002–0.0040 M) were prepared fresh daily by dissolving in sulphuric acid 0.25 M for phenothiazines and 0.40 M for dibenzazepines.

2.2.3. Solvents

Analytical grade, methanol, ethanol, propanol, acetonitrile, sulphuric acid, hydrochloric acid, acetic acid, nitric acid and perchloric acid, were used throughout the investigation. Freshly boiled and cooled distilled water was used throughout the work.

All studied drugs and cerium(IV) solutions were stored in amber-colored bottles. The drug solutions were kept at $\pm 4\,^{\circ}C$ to ensure stability. Working solutions were freshly prepared from stock solutions by suitable dilution.

2.3. Standard drug solution

Standard drug solutions were prepared by dissolving 50 mg of the studied drug (as a salt) in 100 ml of distilled water. The working standard solutions were prepared by further dilution to obtain concentration ranges from 0.005 to 1.500 μg/ml. The stock and working standard solutions were kept $\pm 4\,^{\circ}C$ in light protected flasks.

2.4. Preparation of sample

2.4.1. Tablets and capsules

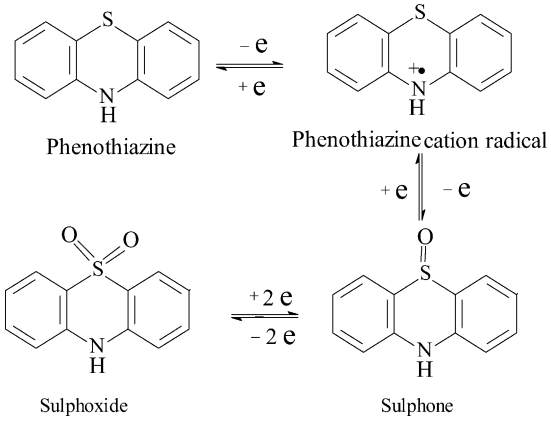
An accurately weighed amount of powder obtained from 20 tablets or capsules equivalent to 25 mg of the drug was transferred into 100 ml volumetric flask. About 50 ml distilled water was added and the flasks were shaked for 10 min, then was completed to 100 ml with distilled water then the solution was filtered and the first portion of filtrate was rejected. The prepared solution was diluted quantitatively to obtain the required concentration for assay.

2.5. General assay procedure

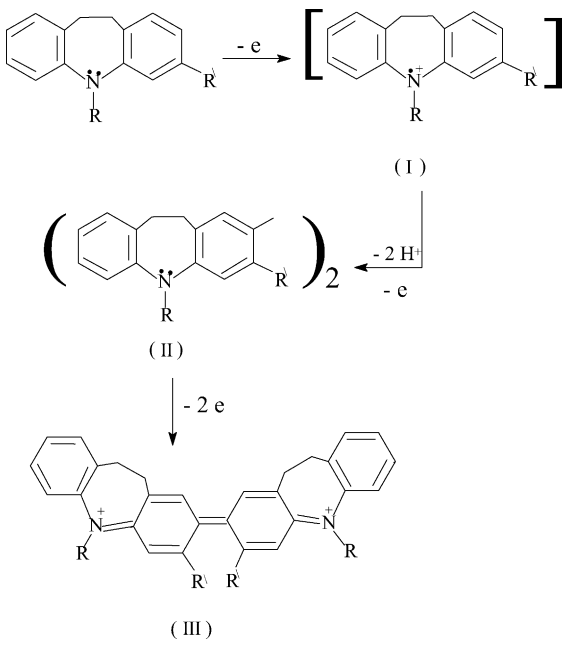
One milliliter of standard or sample solution was transferred into a 10 ml volumetric flask. This was followed by addition of 1 ml of ceric ammonium sulphate 0.001 M for phenothiazines or 0.002 M for dibenzazepines. The solutions were mixed well and heated in a thermostatically controlled water bath at $100\,^{\circ}C$ for 10 min in case of phenothiazines and for 20 min in case of dibenzazepines. The flasks were then cooled and diluted to the final volume with distilled water. The relative fluorescence intensity was measured spectrofluorimetrically at $\lambda_{ex.} = 254$ nm and $\lambda_{em.} = 355$ nm against blank treated similarly.

3. Results and discussion

Phenothiazines and dibenzazepines have various oxidation steps. Phenothiazines may be oxidized to sulphone or sulphoxide (Scheme 1) [58]. On the other hand dibenzazepines may oxidized to form radical cation I, fast coupling of I at the 2-position to form a dimeric compound II



Scheme 1. Some oxidation steps of phenothiazine ring.



Scheme 2. Oxidation of dibenzazepines.

then oxidation of compound II to give dimeric species III (Scheme 2) [59].

Different oxidants were tried such as; ceric sulphate, potassium periodate, potassium iodate, potassium chlorate, hydrogen peroxide and potassium persulphate. It was found that Ce(IV) produced the highest fluorescence intensity relative to other oxidants (more than 100 times). Additional advantage of Ce(IV) is its purity and stability even at boiling temperature.

Chlorpromazine HCl, thioridazine HCl, desipramine HCl, imipramine HCl and clomipramine HCl were oxidized by Ce(IV) in sulphuric acid medium and the relative fluorescence intensity of the formed Ce(III) was monitored at $\lambda_{ex.} = 254$ nm and $\lambda_{em.} = 355$ nm against a reagent blank treated similarly. Fig. 1 shows excitation and emission spectra

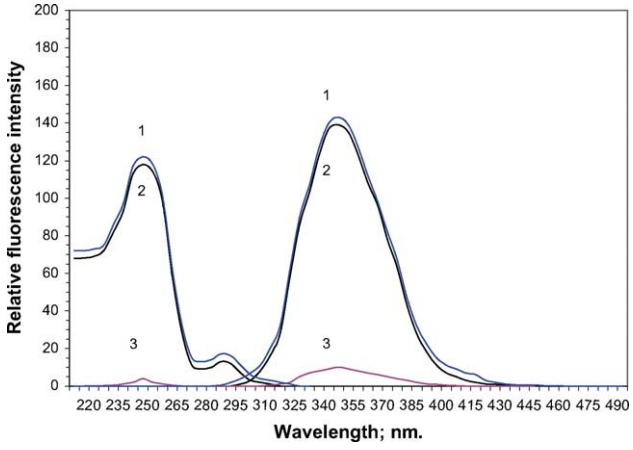


Fig. 1. Excitation and emission spectra of 1 μg/ml chlorpromazine HCl (1) and thioridazine (2) induced by oxidation with 0.001 M Ce(IV) and spectra of reagent blank (3).

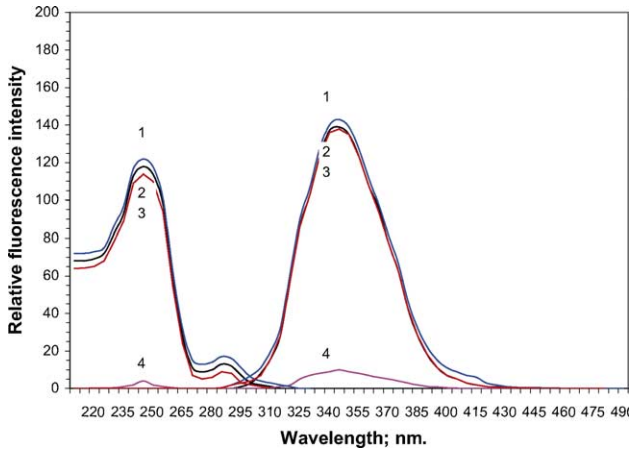


Fig. 2. Excitation and emission spectra of 1 μg/ml desipramine HCl (1), clomipramine HCl (2) and imipramine HCl (3) induced by oxidation with 0.002 M Ce(IV) and spectra of reagent blank (4).

of 1 μg/ml chlorpromazine HCl and thioridazine HCl induced by oxidation with 0.001 M Ce(IV) and those of a reagent blank. In addition, Fig. 2 shows excitation and emission spectra of 1 μg/ml clomipramine HCl, imipramine HCl and desipramine HCl induced by oxidation with 0.002 M Ce(IV) and those of a reagent blank.

3.1. Optimization of variables

3.1.1. Effect of Ce(IV) concentration

The effect of variation of Ce(IV) concentration was studied. chlorpromazine HCl or clomipramine HCl were used as representative examples for phenothiazines and dibenzazepines, respectively (Fig. 3). In case of chlorpromazine HCl, it was found that the relative fluorescence intensity increased by increasing concentration of Ce(IV) till optimum concentration ranged from 0.0008 to 0.0012 M and therefore, 0.001 M of Ce(IV) solution was selected for determination of

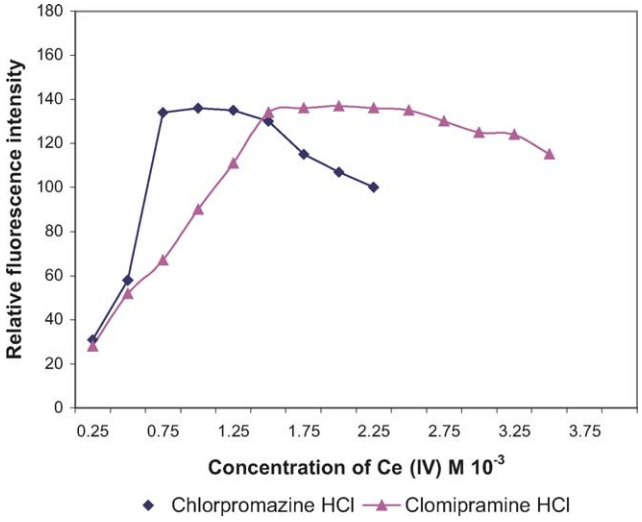


Fig. 3. Effect of Ce(IV) concentration on the fluorescence intensity induced due oxidation of chlorpromazine HCl and clomipramine HCl; 1 μg/ml.

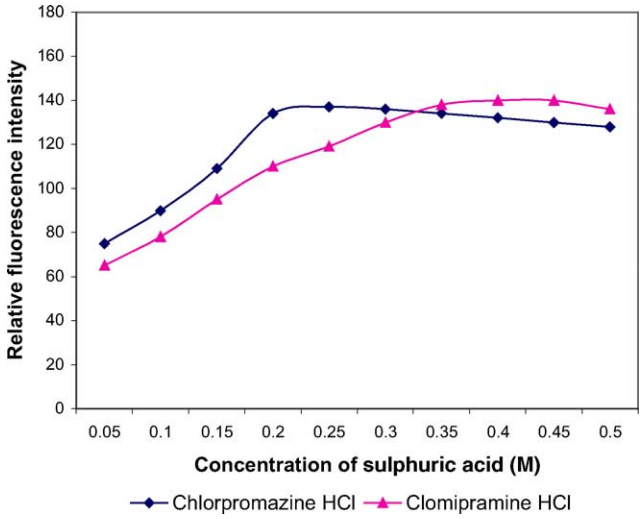


Fig. 4. Effect of sulfuric acid concentration on the fluorescence intensity induced due oxidation of chlorpromazine HCl and clomipramine HCl; 1 μg/ml using Ce(IV).

phenothiazines. On the other hand, the optimum concentration for clomipramine HCl was found to range from 0.0015 to 0.0025 M. Therefore, concentration 0.002 M of Ce(IV) was chosen as optimum concentration for determination of dibenzazepines.

3.1.2. Effect of acid type and concentration

The oxidation reactions of Ce(IV) have to be performed in acid medium to prevent precipitation of $Ce(OH)_3$. Different acids such as, sulphuric acid, hydrochloric acid, nitric acid, perchloric acid and acetic acid were tested to determine the most suitable acid for the reaction. Nitric acid is not preferred to be used owing to the inhibitory effect of nitrate ions on the fluorescence of Ce(III) [57]. In the presence 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 in this study. The effect of sulphuric acid concentration on the fluorescence intensity was studied using concentration ranged from 0.05 to 0.5 M (Fig. 4). It was found that the relative fluorescence intensity increased by increasing sulphuric acid concentration till 0.25 M (in case of chlorpromazine HCl) and 0.4 M (in case of clomipramine HCl). So these concentrations of sulphuric acid were used for subsequent work.

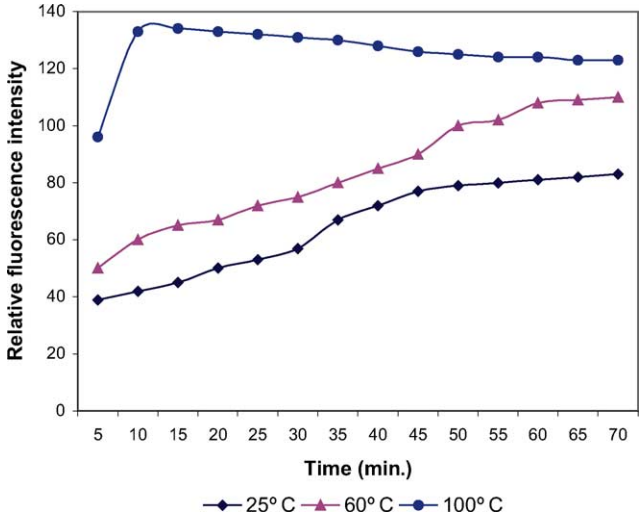


Fig. 5. Effect of heating time on fluorescence intensity induced by Ce(IV) after oxidation of chlorpromazine hydrochloride; 1 μg/ml.

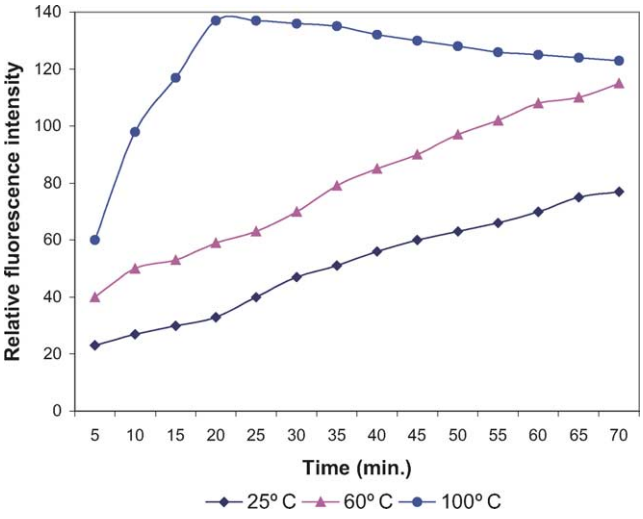


Fig. 6. Effect of heating time on fluorescence intensity induced Ce(IV) after oxidation of clomipramine hydrochloride; 1 μg/ml.

3.1.3. Effect of heating time and temperature

The influence of different heating temperatures and heating times were studied using a thermostatically controlled water bath. Figs. 5 and 6 show effect of heating time at three different temperatures 25, 60 and 100 °C for chlorpromazine

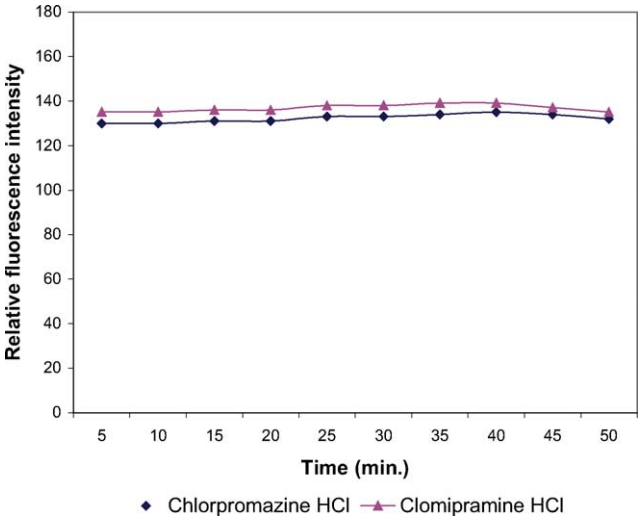


Fig. 7. Effect of stability time on fluorescence intensity induced due to oxidation of chlorpromazine HCl and clomipramine HCl;1 μg/ml by Ce(IV).

Table 1
Quantitative parameters and statistical data for spectrofluorimetric determination of the studied drugs by oxidation using Ce(IV)

Drug	Linearity range (μg/ml)	LOD	LOQ	Slope (S.D.)	Intercept (S.D.)	Correlation coefficient
(1) Chlorpromazine HCl	0.05–1.30	0.036	0.119	117.4 (1.9)	1.2750 (1.402)	0.9983
(2) Thioridazine HCl	0.05–1.30	0.035	0.116	114.8 (1.7)	2.5832 (1.332)	0.9986
(3) Clomipramine HCl	0.05–1.10	0.038	0.125	106.9 (2.1)	3.6431 (1.336)	0.9990
(4) Imipramine HCl	0.05–1.20	0.035	0.117	118.4 (2.0)	2.7882 (1.381)	0.9982
(5) Desipramine HCl	0.05–1.20	0.036	0.119	116.3 (1.9)	3.4541 (1.383)	0.9984

LOD: Limits of detection (μg/ml); LOQ: limits of quantitation (μg/ml).

HCl and clomipramine HCl, respectively. It was found that the relative fluorescence intensity increases by increasing time at room temperature (25 °C) and when heating to 60 °C. On the other hand, when heating at 100 °C maximum relative fluorescence intensity was obtained after 10 min for phenothiazines and after 20 min for dibenzazepines. These optimum heating conditions were used for subsequent work.

3.1.4. Effect of stability time

The stability of the formed fluorescent products was studied. The results are shown in Fig. 7. It was found that the induced fluorescence remained stable for more than 30 min.

3.1.5. Effect of diluting solvents

Solvents such as; water, methanol, ethanol, propanol and acetonitrile were tried for dilution of reaction mixture. It was found that maximum fluorescence intensity was obtained when using water as dilution solvent.

3.2. Validation of the proposed method

3.2.1. Linearity, detection and quantitation limit

Under the proposed experimental conditions, the relationship between the relative fluorescence intensity and concentration for each studied drug was quite linear in the concentration range 0.05–1.3 μg/ml. The intercepts (a), slopes (b), correlation coefficients, limits of detections and limits of quantitations for all the studied drugs are summarized in Table 1. Limits of detection (LOD) and limits of quantitation (LOQ) for all the analytes were calculated as follow [60]; LOD or LOQ = KS.D.$_a$/b

Where; K = 3 for LOD, K = 10 for LOQ, S.D.$_a$ is the standard deviation of intercept and b is the slope. Results in Table 1 indicate that thioridazine HCl showed the best detection and quantitation limits. The slopes of the calibration curves reflect the sensitivity of the proposed procedures. Results listed in Table 1 indicate high sensitivity and low background effect of the method.

3.2.2. Precision

The precision of the proposed method was checked by replicate analysis of ten separate solutions of working standards at three different concentration levels for the studied phenothiazines and dibenzazepines (Table 2).The relative standard deviations were found to be less than 1.5% indicating reasonable repeatability of the proposed method [60]. Intermediate precision was studied using within-laboratory variations as the use of analytical procedures on different days (%R.S.D. = 1.121) and with different analysts (%R.S.D. = 1.290) indicating reasonable results.

3.2.3. Selectivity

In order to access the possible analytical applications of the proposed method the effect of some common excipients

Table 2
Results of analysis of the studied phenothiazines and dibenzazepines at three different concentration levels

Drug	Concentration (μg/ml)	Mean[a] ± S.D.	R.S.D.
Chlorpromazine HCl	0.1	99.22 ± 1.474	1.486
	0.5	99.45 ± 1.386	1.394
	1.0	99.77 ± 1.103	1.106
Thioridazine HCl	0.1	99.59 ± 1.474	1.480
	0.5	99.08 ± 1.278	1.290
	1.0	100.16 ± 1.059	1.056
Clomipramine HCl	0.1	99.47 ± 1.470	1.478
	0.5	99.91 ± 1.433	1.434
	1.0	99.69 ± 1.153	1.157
Imipramine HCl	0.1	99.86 ± 1.349	1.351
	0.5	99.14 ± 1.288	1.299
	1.0	98.71 ± 1.014	1.027
Desipramine HCl	0.1	100.06 ± 1.463	1.462
	0.5	100.22 ± 1.286	1.283
	1.0	99.49 ± 1.152	1.158

[a] Average of 10 determinations.

Table 3
Tolerance of the proposed method to interference

Additives	Chlorpromazine HCl[a]		Clomipramine HCl[a]	
	Tolerance molar ratio (M/M)	%Recovery[b]	Tolerance molar ratio (M/M)	%Recovery[b]
(1) Sucrose	100	102.51	100	103.02
(2) Lactose	90	102.61	80	103.18
(3) Glucose	80	103.10	60	103.29
(4) Citric acid	6	103.27	4	102.67
(5) Propylene glycol	2	103.40	1	103.83
(6) Gum acacia	60	103.50	60	103.12
(7) Gum tragacanth	60	102.91	50	103.54

[a] Concentration used 3×10^{-3} M.
[b] Average of four determinations.

used in pharmaceutical preparations were studied by analyzing sample solutions containing a fixed amount of clomipramine HCl or chlorpromazine HCl (3×10^{-3} M) with various amounts of each excipient. The studied tablet excipients were sucrose, glucose, lactose, gum acacia, citric acid and propylene glycol. Results are listed in Table 3. The recovery results show that no serious interferences occurred from the classical additives tested. The tolerance ratio of each foreign compound was taken as the largest amount yielding an error of not less than ±4% [57]. The proposed method is able to access the analyte in the presence of common excipients and hence, it can be considered selective.

3.2.4. Robustness

It was examined by evaluating the influence of small variation of method variables including; concentration of Ce(IV), sulphuric acid concentration, heating time and temperature on the method suitability and sensitivity. Results are shown in Table 4. It was found that non of these variables

Table 4
Robustness of the proposed spectrofluorimetric method

Variation	%Recovery ± S.D.				
	Chlorpromazine HCl[a]	Thioridazine HCl[a]	Clomipramine HCl[a]	Imipramine HCl[a]	Desipramine HCl[a]
No variation[b]	99.7 ± 0.92	99.4 ± 0.89	100.3 ± 0.82	99.6 ± 0.88	99.1 ± 0.76
(1) Ce(IV) concentration					
For phenothiazines					
8×10^{-4} M	99.3 ± 0.66	99.6 ± 0.61			
12×10^{-4} M	99.5 ± 0.92	99.9 ± 0.88			
For dibenzazepines					
18×10^{-4} M			99.7 ± 0.62	99.3 ± 0.91	98.7 ± 0.60
22×10^{-4} M			100.5 ± 0.77	98.9 ± 0.77	99.2 ± 0.78
(2) H_2SO_4					
For phenothiazines					
0.20 M	99.2 ± 0.98	99.3 ± 0.88			
0.30 M	99.7 ± 0.90	98.7 ± 0.64			
For dibenzazepines					
0.35 M			99.4 ± 0.99	100.2 ± 0.97	99.7 ± 0.75
0.45 M			98.9 ± 0.92	98.7 ± 0.76	99.1 ± 0.60
(3) Heating temperature					
100 °C	99.8 ± 0.59	99.4 ± 0.90	100.2 ± 0.91	99.4 ± 0.80	99.3 ± 0.90
95 °C	99.1 ± 0.99	99.5 ± 0.82	100.6 ± 0.83	98.9 ± 0.77	98.6 ± 0.95
(4) Reaction time (min)					
For phenothiazines					
8 min	99.5 ± 0.69	99.1 ± 0.98			
12 min	100.2 ± 0.79	99.7 ± 0.71			
For dibenzazepines					
18 min			100.1 ± 0.91	99.8 ± 0.74	98.9 ± 0.90
22 min			100.5 ± 0.80	99.6 ± 0.77	98.5 ± 0.90

[a] Drug concentration used 1 μg/ml.
[b] Results using general assay procedure conditions.

Table 5
Determination of studied drugs in some pharmaceutical preparations using proposed and official methods

Product	Ingredient (content, mg)	% Recovery[a] ± S.D.		*F*-value	*t*-Value
		Proposed method	Official method		
(1) Promacid (tablets)[b]	Chlorpromazine HCl (100 mg)	99.17 ± 0.794	100.23 ± 0.978	1.516	1.871
(2) Neurazine (tablets)[b]	Chlorpromazine HCl (100 mg)	98.90 ± 0.87	100.07 ± 0.765	1.305	2.245
(3) Melleril retard (tablets)[c]	Thioridazine HCl (30 mg)	99.37 ± 0.67	100.36 ± 1.058	2.499	1.770
(4) Melleril retard (tablets)[c]	Thioridazine HCl (200 mg)	99.44 ± 0.64	100.12 ± 1.043	2.655	1.238
(5) Desipramine (mixture)[a,d]	Desipramine HCl (25 mg)	99.71 ± 0.90	100.39 ± 1.047	1.360	1.099
(6) Tofranil (tablets)[b]	Imipramine HCl (25 mg)	99.46 ± 0.87	99.03 ± 1.035	1.430	0.904
(7) Supranil (capsules)[c]	Clomipramine HCl (50 mg)	99.23 ± 0.62	98.97 ± 1.072	2.950	0.475
(8) Supranil (capsules)[c]	Clomipramine HCl (25 mg)	99.68 ± 0.85	99.31 ± 1.33	2.417	0.521
(9) Anafranil SR (tablets)[c]	Clomipramine HCl (75 mg)	99.47 ± 0.71	98.70 ± 1.24	3.070	1.209
(10) Anafranil (tablets)[c]	Clomipramine HCl (25 mg)	98.63 ± 1.04	99.21 ± 1.28	1.520	0.777

Theoritical values at 95% confidence limit; $t = 2.306$, $F = 6.388$.
[a] Average of five determination ± S.D.
[b] USP 2002 [60].
[c] BP 98 [61].
[d] Laboratory prepared mixture.

Table 6
Percent recovery of standard drugs added to their commercial dosage forms

Drug	Dosage form	Declared amount (mg)	Amount added (mg)	%Recovery[a] ± S.D.
(1) Chlorpromazine HCl	Promacid (tablets)	100	100	98.65 ± 1.09
			150	99.61 ± 0.91
(2) Thioridazine HCl	Melleril retard (tablets)	30	30	99.41 ± 1.25
			45	98.72 ± 0.83
(3) Desipramine HCl	Lab. prepared mix.	25	25	99.50 ± 0.75
			50	99.71 ± 0.85
(4) Imipramine HCl	Tofranil (tablets)	25	25	98.82 ± 0.91
			50	99.56 ± 1.08
(5) Clomipramine HCl	Anafranil (tablets)	25	25	100.22 ± 0.95
			50	99.16 ± 0.87
	Supranil (capsules)	25	25	99.25 ± 0.66
			50	99.01 ± 0.72

[a] Average of five determinations.

significantly affect the method. This provides an indication of the reliability of the proposed method during normal usage and so the proposed spectrofluorimetric method considered robust.

3.3. Application on pharmaceutical preparations

Some commercial dosage forms of the studied drugs were successfully analyzed by the proposed and official methods. Recovery experiments were performed for each drug in its dosage forms or laboratory prepared mixtures. The results are listed in Table 5, which indicate that common excipients and additives did not interfere with the determination. It is clear from the table that there is no significant difference between results obtained by the proposed or official methods, as indicated by *t*- and *F*-tests.

In addition recovery experiments were carried out for the studied drugs in their respective pharmaceutical formulations by standard addition method. The results in Table 6 indicate that there is no interference from frequently encountered excipients or additives. The proposed method is sensitive, accurate and precise. It is suitable for analysis of the studied drugs in their dosage forms and application in quality control laboratories.

3.4. Conclusion

The present work describes a validated spectrofluorimetric method for the assay of some psychoactive drugs without interference from common excipients. Hence, it can be recommended for the routine quality control of the studied psychoactive drugs either in bulk or in their corresponding dosage forms. The methodology appears to be straightforward and results are relevant. Another advantage is that, compared to the existing spectrofluorimetric methods for determination of the studied psychoactive drugs it is several times more sensitive. From economic point of view, the proposed method is simple, rapid and inexpensive besides the use of water as dilution solvent. So it is a good alternative to the reported methods and to high cost HPLC methods. A part from that, the possibility of oxidation of readily oxidizable drugs by Ce(IV) does not exist since the studied drugs are not prescribed in combinations.

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