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Quantitative determination of some pharmaceutical piperazine derivatives through complexation with iron(III) chloride

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Abstract

A simple, accurate and sensitive spectrophotometric method has been developed for the determination of three pharmaceutical piperazine derivatives, namely ketoconazole (KC), trimetazidine hydrochloride (TMH) and piribedil (PD). This method is based on the formation of yellow orange complexes between iron(III) chloride and the investigated drugs. The optimum reaction conditions, spectral characteristics, conditional stability constants and composition of the water soluble complexes have been established. The method permits the determination of KC, TMH and PD over a concentration range 1–15, 1–12 and 1–12 μg ml^{-1}, respectively. Sandell sensitivity is found to be 0.016, 0.013 and 0.013 μg cm^{-2} for KC, TMH and PD, respectively. The method was sensitive, simple, reproducible and accurate within ±1.5%. The method is applicable to the assay of the three drugs under investigation in different dosage forms and the results are in good agreement with those obtained by the official methods (USP and JP).

Keywords: Ketoconazole; Trimetazidine hydrochloride; Piribedil; Iron(III) chloride; Spectrophotometry; Tablets and creams

1. Introduction

Ketoconazole (KC), *cis*-1-acetyl-4-[4-[[2-(2,4-dichlorophenyl)-2-(1*H*-imidazole-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl] piperazine is a highly effective broad spectrum antifungal agent [1]. It is used to treat a wide variety of superficial and systemic mycoses [2] and has the advantage over other imidazole derivatives of producing adequate sustained blood levels following oral administration [3]. Some methods have been reported for its determination including potentiometry [4,5], spectrophotometry [6–13], polarography [14] and chromatography [15–23].

Trimetazidine hydrochloride (TMH), 1-[(2,3,4-trimethoxyphenyl) methyl] piperazine dihydrochloride regulates ionic and extracellular exchanges, correcting the abnormal flow of ions across the cell membrane caused by ischaemia and preventing cellular oedema caused by anoxia [24]. Few methods for the estimation of trimetazidine in biological fluids have been reported e.g. TLC [25], HPLC with fluorescence [26] or electrochemical detection [27] and GC-MC [28]. Trimetazidine is also determined in tablets using HPTLC [29]. These methods are often time-consuming, expensive and cumbersome.

Piribedil (PD), is an alkoxybenzyl-4-(2-pyrimidinyl) piperazine derivative with vasodilatory activity [30]. PD has proved active in patients with Parkinson's disease, particularly in the control of tremors [31]. Methods for the analysis of PD or its basic metabolites in biological specimens have used gas chromatography with a nitrogen-sensitive detector [32] or combined with mass spectrometry [33], spectrophotometry [13,34], HPLC [35] and ion-selective electrodes [36].

The use of iron(III) chloride as a complexing agent for the quantitation of drugs is fairly wide [37–42]. The chelate complex of iron(III) ions bears the advantage of being water-soluble, and hence does not necessitate any extraction procedure. Iron(III) chloride has been used in this work to determine KC, TMH and PD in pharmaceutical preparations. The compositions and the stability constants of their chelates with iron(III) were

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calculated using spectrophotometric and potentiometric methods.

2. Experimental

2.1. Apparatus

A Shimadzu UV-1601 spectrophotometer with quartz cells of 1-cm optical path length and HI 9321 Hanna Microprocessor pH-meter with a combined glass-saturated calomel electrode were used.

2.2. Materials

KC, TMH and PD were of pharmaceutical grade, KC (Janssen, Beerse, Belgium), TMH (Serveir, France) and PD (Eutherapia, France). Pharmaceutical preparations of the studied drugs were obtained from commercial sources.

2.3. Reagents

The reagents used were of analytical grade and all water was doubly distilled.

Standard iron(III) solution, 0.1 M, was prepared by dissolving 1.622 g of anhydrous iron(III) chloride (Merck) in distilled water, acidified with a few milliliters of concentrated HCl to prevent hydrolysis and then diluted to 100 ml with water to give a pH 2 solution. The concentration of the resulting solution was determined complexometrically [43]. Solutions of lower concentrations were obtained by accurate dilution of this solution with water.

Standard KC or PD, 500 μg ml^{-1}, was prepared by dissolving 50 mg of pure drug in 20 ml of 0.1 M HCl and completed to 100 ml with water.

Standard TMH, 500 μg ml^{-1}, was prepared by dissolving 50 mg of pure drug in 100 ml of water. Whenever required dilute solutions were obtained by appropriate dilution with water. Such drug solutions are stable for a period of 3 days when refrigerated (4 °C).

Acetate buffer solutions covering the pH range from 2.5 to 5.5 was prepared by mixing appropriate quantities of 0.2 M sodium acetate with 0.2 M acetic acid to get the desired pH.

2.4. General procedure

A solution containing 10–150 μg of pure drug or sample solution was transferred into a 20 ml stoppered tube, 2 ml 0.05 M iron(III) chloride solution, 5 ml 0.2 M acetate buffer solutions of pH 4.5 with thorough mixing. The mixture solutions were heated on a water bath at 50±2 °C for 30 min and after cooling the contents were diluted to volume in a 10-ml standard flask with water. The absorbance of the complex was measured at 420 nm for the studied drugs, against a reagent blank similarly prepared without drug solution.

2.5. Analysis of Nizoral tablets or cream (KC) and Trivastal tablets (PD)

An accurately weighed amount of cream or the powdered tablets equivalent to 50 mg of drug was transferred to a 100 ml conical flask and extracted with 20 ml 0.1 M HCl for 10 min and diluted with water. The mixture was filtered through a filter paper (No. 41) and washed with water. The filtrate and washing were collected in a 100-ml standard flask and diluted to volume with water. A volume of the later solution was diluted with water to obtain a solution equivalent to 100 μg ml^{-1} of KC or PD and then subjected to analysis by the recommended procedure.

2.6. Analysis of Vastarel tablets (TMH)

An accurately weighed amount of the finely powdered tablets equivalent to 50 mg of the drug salt was transferred to a 100 ml conical flask and extracted with water. The mixture was filtered through a filter paper and washed with water and then continued as directed in the analysis of KC and PD tablets.

3. Results and discussion

Pharmaceutical piperazine derivatives as KC, TMH and PD react with iron(III) chloride to form stable complexes which depend largely on the reaction conditions.

3.1. Effect of pH

The most suitable pH for formation of iron(III)–drug complexes was determined by mixing 0.5 ml 10^{-3} M drug and 1 ml 0.05 M iron(III) chloride, 5 ml 0.2 M acetate buffer solutions of pH 2.5–5.5. The mixture solutions were heated on a water bath at 50±2 °C for 30 min in stoppered tubes and after cooling, the contents were diluted to volume in a 10-ml standard flask with water. The spectra of the formed yellow–orange coloured complexes were scanned over the range of 300–500 nm against a reagent blank. The results are represented in Fig. 1 (TMH, as example). It is clear from this figure that the colour intensity of iron(III) complexes is largely dependent upon the pH of the medium and the absorbance maximum is slightly shifted to a higher wavelength. Starting from pH 2.5 a yellow–

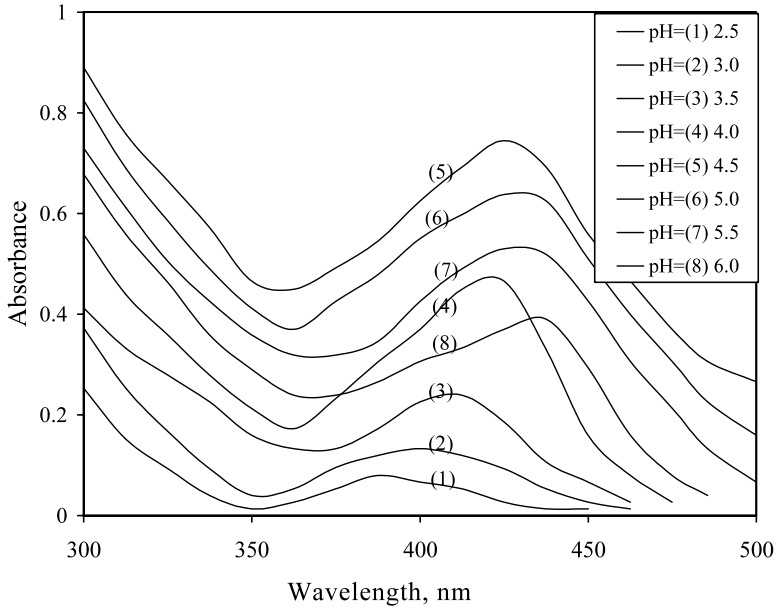

Fig. 1. Absorption spectra of TMH–iron(III) complex at different pH values. $[TMH] = 5 \times 10^{-5}$ M; $[Fe(III)] = 5 \times 10^{-3}$ M.

orange colour appears and the intensity of this colour increases with increase of pH of the solution up to pH 4.5. On further increase of the pH the absorbance decreases, probably due to the dissociation of the complex followed by the formation of iron(III) hydroxide. The results show that pH 4.5 gives a relatively high absorbance for all studied drugs, then acetate buffer of pH 4.5 was chosen to carry out the other studies.

Effect of acetate buffer concentration (0.05–0.5 M) was found to have a little influence on the course of the reaction. The best spectrum was obtained in 0.1 M acetate buffer.

Effect of ionic strength was checked using potassium chloride, sodium chloride, potassium nitrate and sodium sulphate (0.01–0.10 M), The absorbance of iron(III) complex decreased with increase ionic strength in the reaction solution from 0.01 to 0.10 M. The composition and the conditional stability constant of the complex were studied at constant ionic strength using 0.05 M KCl for example.

3.2. Selection of the suitable wavelength

The absorption spectra of drug and its iron complex at pH 4.5 were scanned against the same buffer as a blank (Fig. 2). Curves a, b and c show that the drugs absorb maximally at 227, 280 (KC); 235, 270 (TMH); 239 and 287 nm (PD). While the curve 1, 2 or 3 shows that iron(III) drug complex absorbs at 420 nm which is the recommended wavelength for studying the other factors influencing the formation of iron(III)–drug complexes. Iron(III) chloride (curve 4) has a low absorbance at 420 nm under the same conditions.

3.3. Effect of iron(III) concentration

An investigation of the effect of iron(III) chloride concentration on the complex formation showed that the drug (5×10^{-5} M) was converted quantitatively into the complex in the presence of a relatively large excess of iron(III) chloride, i.e. an increasing concentration of iron(III) chloride produced an increase in the absorbance of the complex up to a concentration of 0.01 M, at which point the absorbance of the complex reached a maximum. On further increasing the iron(III) concentration the absorbance remained constant. The maximum absorbance was shifted to longer wavelength (380–420 nm) with increasing iron(III) chloride concentration (Fig. 3), this confirmed that more than one type of complex is formed.

3.4. Effect of temperature and heating time

The reaction rate and the amount of the complex produced are considerably influenced by the temperature of the reaction mixture and by the effect of heating time. Heating the solutions up to 50 ± 2 °C for 30 min was found to contribute significantly to the complete development of the drug complexes. The colour of the formed complexes is stable for more than 24 h.

3.5. Sequence of addition

Under the optimum conditions stated before, it was found that the most favourable sequence of addition suitable for developing the colour of iron(III)–drug complex with the highest absorbance is; drug, iron(III) chloride, acetate buffer.

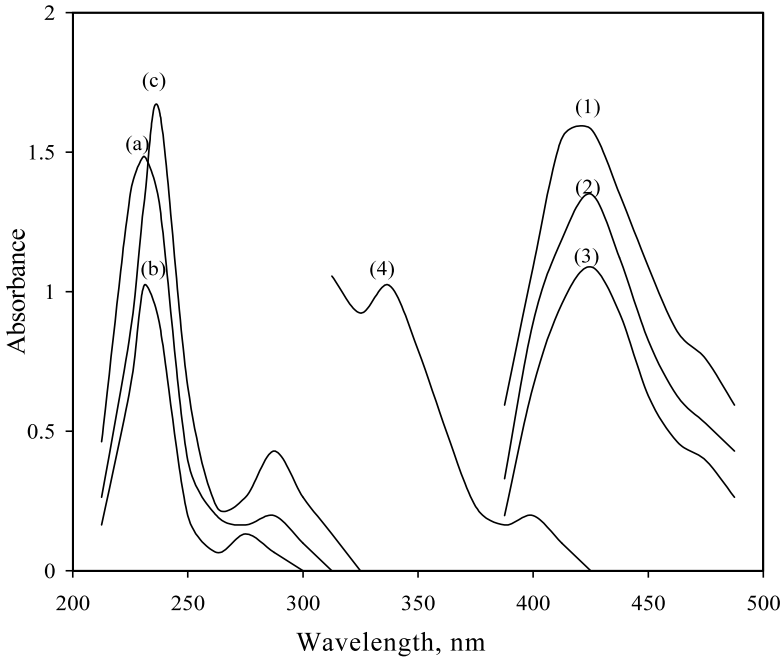

Fig. 2. Absorption spectra of drugs and iron(III) complexes of: (1) KC; (2) TMH; and (3) PD; (4) [Fe(III)] = 0.01 M; [Drug]: (a) KC; (b) TMH; or (c) PD = 5×10^{-5} M, pH 4.5.

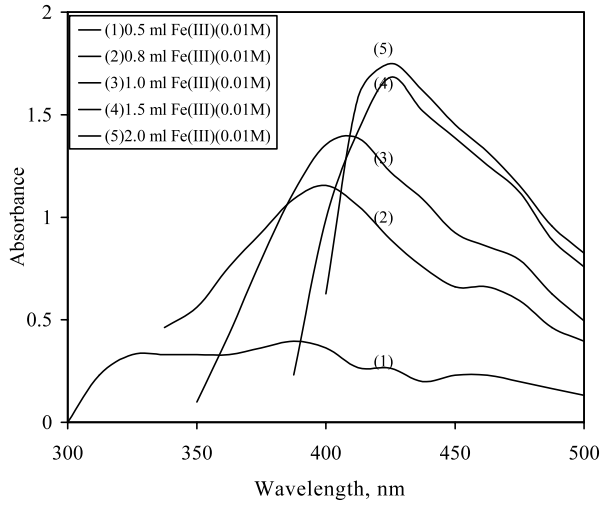

Fig. 3. Effect of iron(III) chloride concentrations on absorption spectra of iron(III)–TMH complex. [TMH] = 1×10^{-4} M; pH 4.5.

Table 1
Formation constants of iron(III) complexes (log β_n) of KC, TMH and PD at 0.05 M KCl and 25 °C

Drug	Spectrophotometric method	Potentiometric method	
	log β_1	log β_1	log β_2
KC	5.45	5.52	9.27
Trimetazidine	5.26	5.40	9.02
PD	4.93	5.12	8.62

3.6. Specificity and interference studies

The influence of commonly used excipients and additives (lactose, microcrystalline cellulose, talc, magnesium stearate and starch) was investigated before the determination of these drugs in their dosage forms. No interference could be observed (Table 3). The three investigated drugs were dispensed and used as single components (tablets or creams), so the assay in presence of other drugs is of little important.

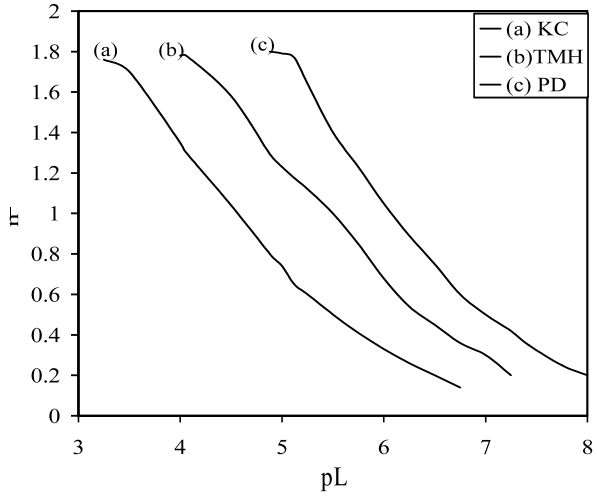

Fig. 4. Formation curves of iron(III) complexes of KC, TMH and PD.

Table 2
Analytical parameters for the iron(III) complexes of piperazine drugs

Parameters	Drug		
	KC	TMH·2HCl	PD
λ_{max} (nm)	420	420	420
Beer's law limits (μg ml^{-1})	1–15	1–12	1–12
Detection limit (μg ml^{-1})	0.11	0.16	0.12
Molar absorptivity (l mol^{-1} cm^{-1})	3.30×10^4	2.61×10^4	2.36×10^4
Sandell sensitivity (ng cm^{-2})	16.12	12.98	12.66
Slope (m)	0.0617	0.0776	0.0796
Intercept (b)	0.0039	0.0040	0.0045
Correlation coefficient (r)	0.9999	0.9997	0.9998
Relative standard deviation (%, $n = 6$)	0.35	0.61	0.50
Ringbom optimum concentration range (μg ml^{-1})	2.2–15.0	1.9–12.0	1.8–12.0

3.7. Composition and stability of the complex

The composition of the complex was determined at the optimum pH value, by applying the continuous variation [44] and molar ratio [45] methods. The results indicated that the components of the complex are largely dependent upon the drug or the iron(III) concentration. The curve of continuous variation exhibits the maximum at $X_{max} = 0.5$, with means that the components of the complex react in 1:1 stoichiometric ratio. In case of molar ratio method, the curve obtained shows two break points at the iron(III)–drug molar ratio of 1:1 and 1:2, after which the absorbance remained unchanged. These results are confirmed with those obtained by the potentiometric titration method.

The formation stability constants ($\log \beta_1$) of the iron(III) complexes (1:1) of the investigated drugs under the experimental conditions described above and at 0.05 M KCl ionic strength were calculated from the continuous variation data. The results in Table 1, indicated that $\log \beta_1$ increases in the order KC > TMH > PD, these results reflect the degree of formation of the complex. The higher $\log \beta_1$, for KC is probably due to its highest basicity with compared to TMH or PD, The $\log \beta_1^H$ values of the investigated drugs which were determined by potentiometric titration method [46] were 9.85, 9.65 and 9.25 for KC, TMH and PD, respectively.

The formation constant of iron(III) chelates was also determined potentiometrically using the method of Sarin and Munshi [46]. The formation curves of the investigated complexes were obtained by plotting a graph between average number of ligand attached per metal ion (n^-) and free ligand exponent (pL) as indicated in Fig. 4, The n^- values ($0.2 < n^- < 1.8$) obtained for the metal–ligand systems indicate the formation of 1:1 and 1:2 complexes. The $\log \beta_1$, and $\log \beta_2$ values have been calculated both by the half integral method as well as the point-wise method [47]. Table 1 summarizes the values of formation constants of iron(III) complexes of KC, TMH and PD in aqueous medium and room temperature (25 °C). The results of $\log \beta_1$ by this method are comparable with those obtained from spectrophotometric method.

Table 3
Tests of precision of the method on samples of pure drugs

Sample ($n = 6$)	Taken (μg ml^{-1})	Found (μg ml^{-1})	SD (μg)	Recovery (%)	RSD (%)
KC	4	3.98	0.05	99.5	1.26
	8	8.04	0.07	100.5	0.87
	10	10.06	0.11	100.6	1.09
	14	13.96	0.09	99.7	0.64
TMH	2	2.02	0.03	101.0	1.48
	4	4.03	0.04	100.7	0.99
	8	7.99	0,08	99.9	1.00
	10	10.04	0.12	100.4	1.20
PD	2	1.98	0.02	99.0	1.01
	4	3.99	0.05	99.7	1.25
	8	8.04	0.09	100.5	1.12
	10	10.05	0.06	100.5	0.57

Table 4
Determination of piperazine drugs in pharmaceutical preparations

Drug	Name of preparation	Recovery ± SD% [a]	
		Proposed method	Official methods [4,50]
KC	Nizoral tablets [b] (200 mg per tablet)	99.76 ± 0.66 $t = 0.42$ $F = 1.29$	99.93 ± 0.75 [4] (2.23) [d] (5.05) [d]
	Nizoral cream [b] (20 mg g^{-1})	100.81 ± 0.50 $t = 0.94$ $F = 1.59$	101.12 ± 0.63 [4]
TMH	Vastarel tablets [c] (20 mg per tablet)	100.12 ± 0.42 $t = 1.32$ $F = 1.97$	100.51 ± 0.59 [50]
PD	Trivastal tablets [c] (20 mg per tablet)	99.95 ± 0.56	

[a] Mean ± standard deviation of six determinations.
[b] Nizoral tablets or cream (Janssen, Beerse, Belgium).
[c] Vastarel or Trivastal tablets (Servier-Egypt Industries Limited under Licence of les Laboratories, Servier-France).
[d] Values in parentheses are the theoretical values at $P = 0.05$.

The formation constants ($\log \beta_1$ and $\log \beta_2$)of iron(III) complexes are in the order: KC > TMH > PD.

3.8. Analytical parameters

Under the experimental conditions described, standard calibration curves for KC, PD and TMH with iron(III) chloride were constructed by plotting absorbance versus concentration. Conformity with Beer's law was evident in the concentration range of the final dilution cited in Table 2. The molar absorptivity, Sandell sensitivity and the linear regression equation for each drug are listed in Table 2. The correlation coefficients were 0.9997–0.9999, indicating good linearity. For more accurate results, Ringbon plots [48] for optimum concentration ranges were obtained (Table 2).

According to ICH recommendation [49] the approached based on the SD of the response and the slope (m) of the calibration curve, was used for determining the detection limits (Table 2), applying the following equation: D.L. $= K \times \mathrm{SD}/m$, where $K = 2$.

Six replicate determinations at different concentration levels were carried out to test the precision of the method (Table 3). The relative standard deviations were found to be less than 1.5%, indicating reasonable repeatability of the proposed method.

3.9. Application to commercial dosage forms

The proposed method for the determination of the three drugs was applied to their pharmaceutical formulations (tablets or creams). It was carried out on the same batch of samples together with the official methods [4,50] in which the non-aqueous titrations were used. The results were compared statistically by the Student's t-test and variance ratio F-test (Table 4). The experimental values did not exceed the theoretical ones, indicating the absence of any significant difference between the methods compared.

4. Conclusion

The iron complex formed under the above mentioned conditions with the drugs under investigation (KC, TMH and PD) and measured spectrophotometrically can offer a sensitive, simple, reproducible and accurate procedure for the determination of KC, TMH and PD in bulk, tablets and creams dosage forms. The formed complexes were found to be soluble in acetate buffer solutions of pH 2.5–5.5, without the need for organic solvent to extract the reaction products. From the calculation of stability constants of the complex, the later was found to be stable. The method had been validate for the determination of these drugs. The statistical analysis of the results confirmed that the developed method was accurate and precise and could be recommended for use in quality control labs.

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