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Spectrophotometric determination of cimetidine in the presence of its acid-induced degradation products

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Abstract: Cimetidine has been determined in the presence of its acid-induced degradation products using a second derivative (D_2-) spectrophotometric method (method I) or a colorimetric method (method II). The former is based on D_2-value measurement at 216 nm, whilst the latter depends on charge-transfer complexation with dichlorophenol–indophenol. The two methods are proved to be stability indicating, since plots of log *C*% versus time were linear. The application to cimetidine determination in tablets and ampoules gave good results.

Keywords: *Derivative spectrophotometry; colorimetry; determination of cimetidine; dichlorophenol–indophenol; pharmaceutical preparations; stability studies.*

Introduction

Various methods have been reported for the determination of cimetidine in pure and pharmaceutical preparations. These include spectrophotometry by measuring the absorbance difference (ΔA) in 0.1 N H_2SO_4, and titrimetry using perchloric acid [1] and $KBrO_3$–KBr solution [2] titrants.

The colorimetric methods using different diazotized reagents were used to determine cimetidine in tablets and ampoules [3]. Likewise complexometric methods involving the use of different cations [4], have been used for cimetidine assay. HPLC can be also applied for cimetidine analysis in raw materials, tablets [5,6], ampoules [7] and biological fluids [8,9].

Recently, derivative UV-spectrophotometry [10] has been successfully applied for the determination of some drugs in the presence of their degradation products. These include the determination of procaine in presence of *p*-aminobenzoic acid [11], some 1,4-benzodiazepines in presence of acid-induced degradation products [12], and some cephalosporins in presence of their degradation products [13–15].

In this work, cimetidine is determined in the presence of its acid-induced degradation products using second-derivative (D_2-) UV-spectrophotometry (method I). Following the successful application of dichlorophenol–indophenol (DCPIP) in the assay of certain imidazoline derivatives [16] and some alkaloids [17], it is here used for colorimetric estimation of cimetidine in the presence of its acid-induced degradation products (method II).

Experimental

Materials

Authentic cimetidine, cimetidine (Tagamet®) tablets (200 or 400 mg tablet^{-1}), and cimetidine (Tagamet®) ampoules (200 mg/2 ml) were obtained from Smith, Kline and French Labs (UK).

Reagents: 2,6-dichlorophenol-indophenol (0.1%) solution [13]

About 108.61 mg of DCPIP sodium salt equivalent to 100.0 mg of DCPIP, was accurately weighed and transferred to a separatory funnel using about 30 ml water. It was acidified (to litmus) with about 5 ml 2 N hydrochloric acid, then extracted with four successive portions of chloroform. The combined extract was washed with about 10 ml water and then passed through anhydrous sodium sulphate into a 100-ml volumetric flask. The solution was made up to volume using chloroform and mixed well. The solution was kept in the refrigerator until use. The reagent is stable for about 1 month.

Spectrophotometer

Perkin–Elmer Model 550S UV–vis spectro-

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photometer with fixed slit width 2 nm and Hitachi Model 561 recorder was used. Suitable settings were: scan speed, 120 nm min^{-1}; chart speed, 60 nm min^{-1}; mode, $D_2 = (d^2A/d\lambda^2)$; scan range, 200–280 nm; response time, 4 s; and the ordinate maximum settings were selected to record the A_{max} values at approximately 80% of full-scale deflection.

Standard solutions

(1) *Cimetidine, 200 μg ml^{-1} (standard A).* An accurate weight of 20 mg of cimetidine was transferred to a 100-ml volumetric flask with 20 ml 0.1 N hydrochloric acid, dissolved and completed to volume with the same solvent.

(2) *Cimetidine, 1000 μg ml^{-1} (standard B).* An accurate weight of 100 mg of cimetidine was transferred to a 100-ml volumetric flask with 20 ml methanol, dissolved and completed to volume with the same solvent.

(3) *Acid-induced degradation products [1], corresponding to 200 μg ml^{-1} cimetidine (standard C).* An accurate weight of 40 mg of cimetidine was dissolved in a 100-ml volumetric flask containing 20 ml of 10 N, hydrochloric acid, heated in a boiling water-bath for 2 h, cooled, and completed to volume with water. Fifty ml of this solution were transferred into a beaker and neutralized using a pH-meter, with 30% sodium hydroxide solution. The neutralized solution was transferred quantitatively to another 100-ml volumetric flask, 1 ml 10 N hydrochloric acid was added and completed to volume with water.

(4) *Acid-induced degradation products [1], corresponding to 1000 μg ml^{-1} cimetidine (standard D).* An accurate weight of 100 mg of cimetidine was dissolved in a 100-ml volumetric flask containing 20 ml of 10 N hydrochloric acid and heated in a boiling water-bath for 2 h. Twenty ml of methanol were added (to lower the boiling point of the solution), evaporated to dryness on a boiling water-bath and then cooled to room temperature (≃25°C). The residue was dissolved in 20 ml methanol and transferred quantitatively to 100-ml volumetric flask and completed to volume with methanol.

Sample solutions

(1) *Ampoules.* An accurate volume of the mixed contents of 10 ampoules equivalent to 20 mg (for method I) or 100 mg (for method II) of cimetidine was transferred to a 100-ml volumetric flask and completed to volume with 0.1 N hydrochloric acid (method I) or methanol (method II).

(2) *Tablets.* Twenty tablets were weighed and powdered. An accurately weighed quantity of the powder equivalent to 20 mg (for method I) or 100 mg (for method II) of cimetidine was shaken with 50 ml 0.1 N hydrochloric acid (method I) or 50 ml methanol (method II) for 10 min, filtered into a 100-ml volumetric flask and completed to volume with the corresponding solvent.

General procedure

(a) *Second derivative method (Method I).* Aliquots, 0.5–4 ml were transferred accurately (in 0.5-ml steps) from standard A, or 2 ml from the previously prepared sample solutions for method I, into a series of 25-ml volumetric flasks and made up to volume with 0.1 N hydrochloric acid. The second derivative spectra were recorded against 0.1 N hydrochloric acid and the peak amplitude was measured at 216 nm.

(b) *Colorimetric method (Method II).* Aliquots 0.3–1 ml were transferred (in 0.1-ml steps) from standard B, or 0.6 ml from previously prepared sample solutions for method II, into a series of 5-ml volumetric flasks. One ml of DCPIP solution was added and completed to volume with methanol. The absorbance was measured at 640 nm against a reagent blank simultaneously prepared.

Treatment of results (quantitation)

The cimetidine content in tablets and ampoules was determined with reference to the corresponding standard calibration graphs prepared simultaneously.

Stability investigation of cimetidine by the proposed methods

An accurate weight of 20 or 100 mg (method I or II, respectively) of cimetidine was dissolved in a 100-ml volumetric flask containing 20 ml 1 N hydrochloric acid, completed to volume with the same solvent and placed in a constant-temperature water-bath maintained at 45°C. It was allowed to equilibrate thermally for 5 min.

(a) *Using the second derivative method (method I).* Aliquots (2.5 ml) equivalent to 20 μg ml^{-1} cimetidine were transferred into a series of 25-ml volumetric flasks, each containing 2.5 ml 1 N sodium hydroxide solution, at zero time and 30-min intervals for 3 h and completed to volume with 0.1 N-hydrochloric acid. The D_2-value of each solution was measured at 216 nm using 0.1 N hydrochloric acid as blank. The cimetidine concentration was calculated after each time interval, from the calibration graph.

(b) *Using the colorimetric method (method II).* Aliquots (1 ml) equivalent to 200 μg ml^{-1} of cimetidine were transferred into a series of 5-ml volumetric flasks, each containing 1 ml 1 N sodium hydroxide solution, at zero time and 30-min intervals for 3 h. 1 ml of methanol was added, allowed to evaporate to dryness in a boiling water-bath, then cooled to room temperature (≈25°C). The residue was dissolved in 2 ml methanol, 1 ml DCPIP was added and completed to volume with methanol. The blue colour was measured at 640 nm against reagent blank. The cimetidine concentration was calculated after each time interval from the calibration graph.

Results and Discussion

Spectral characteristics

Figure 1(a) shows the zero-order UV-spectra of cimetidine and its acid-induced hydrolytic products in 0.1 N hydrochloric acid, while Figs 1(b) and 1(c) present their corresponding first and second derivative curves, respectively. From the last figure it is apparent that the intact cimetidine exhibits optimum D_2-peak at 216 nm, while its acid-induced degradation products show almost nil contribution. Accordingly, zero-crossing measurement validates the intact cimetidine estimation without interference from its degradation products.

DCPIP gives with cimetidine in methanol–chloroform (4:1) medium a blue-coloured

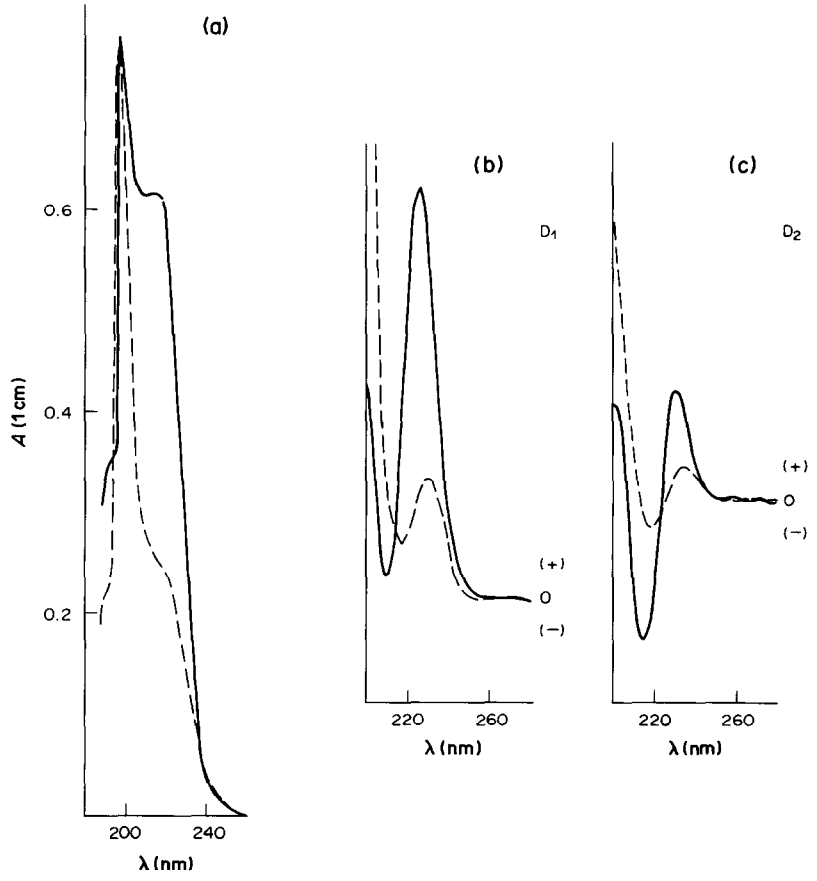

Figure 1
(a) Zero-order, (b) first derivative and (c) second-order spectra of 8 μg ml^{-1} cimetidine before (——) and after (----) acid-induced degradation.

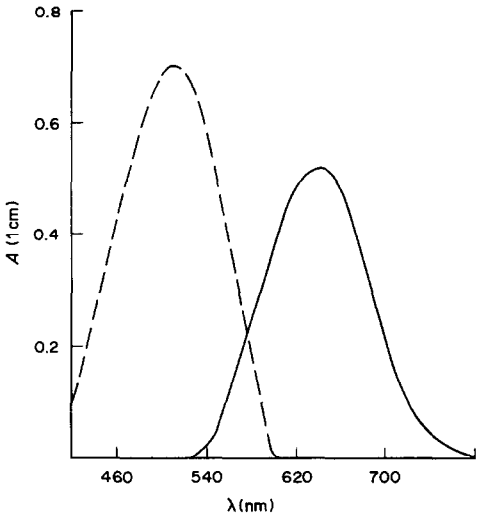

Figure 2
Absorption spectra of 140 μg ml^{-1} cimetidine with DCPIP (——) against reagent blank and 65 μg ml^{-1} DCPIP reagent (----) against chloroform.

chromogen with absorption maximum at 640 nm (Fig. 2) and apparent A (1%, 1 cm) of 38.5. Meanwhile, DCPIP in chloroform shows a maximum at 510 nm. Such phenomena could be due to the charge transfer complex (DA) formation through the electron transfer from the drug (the basic centre or electron donor, D) to the DCPIP (the acceptor, A):

$$D + A \rightarrow DA \xrightarrow{h\nu} D^+ - A^-.$$

The formed complex absorbs light in a manner different from that of either the donor or acceptor alone.

The reaction stoichiometry using Job's method [18] and molar-ratio method [19] between DCPIP and cimetidine has been determined to be a 1:1 ratio. A volume of 1 ml of 0.1% (w/v) DCPIP in chloroform was found to be optimum to give instant blue colour at room temperature (≈25°C) with cimetidine. The colour stability lasted for at least 90 min.

Calibration curves and reproducibility

The correlation between D_2 at 216 nm or absorbance of blue chromogen at 640 nm and the drug concentration was found to be linear with negligible intercept. Regression analysis using the method of least-squares [20] was made for the slope (b), intercept (a) and correlation coefficient (r) for the two proposed methods.

The two linear equations are:

$$D_2(1\text{ cm})_{216\text{nm}} = 1.28571 + 4.35268C,$$
for method I
$$A\ (1\text{ cm})_{640\text{nm}} = 0.01082 + 0.00371C,$$
for method II

where C is the concentration over the range 8–32 μg ml^{-1} (method I) and 60–200 μg ml^{-1} (method II). The correlation coefficients (r) were 0.99994 and 0.99981 for methods I and II, respectively.

Separate determinations at different drug concentration levels were carried out using the two proposed methods to assess their reproducibility. The relative standard deviations (RSD) were found to be <2%, indicating good reproducibility.

To prove the validity and applicability of the two proposed methods, seven synthetic mixtures of cimetidine and its acid-induced degradation products were prepared with different proportions and assayed for cimetidine content. The results of both methods (Table 1) were of equal accuracy (t-test) and equal precision (F-test).

Kinetic investigations

Using 10 N hydrochloric acid, the degradation of cimetidine is reported [1]. The final guanidine derivative thereby-formed failed to give a complex with DCPIP, though still containing the imidazole nucleus. This is because of the lower molecular weight of the degradation products compared with the intact drug [21, 22]. Aiming at the assessment of the specificity of the two proposed methods, the degradation kinetics of cimetidine was investigated. Cimetidine in 1 N hydrochloric acid at 45°C was found to follow the first-order reaction-kinetics, since log C% versus time was linear. The determined parameters like slopes, half-life periods ($t_{½}$) and the first-order rate constants (K) are presented in Table 2.

Assay results

The applicability of the two proposed methods was appraised through the assay of different dosage forms. The results have been compared with the traditional UV-spectrophotometric method (A_{max}-method at 219 nm) and the official HPLC method [5] using the t-test for accuracy and the F-test for precision assessment. The calculated values did not exceed the corresponding theoretical values,

Table 1
Spectrophotometric determination of cimetidine in presence of its acid-induced degradation products using the proposed methods

Second derivative method		Colorimetric method	
Added (μg ml^{-1})*	Recovery (%)	Added (μg ml^{-1})†	Recovery (%)
4	101.7	60	99.4
8	101.1	80	101.2
12	100.0	100	99.6
16	100.1	120	101.0
20	99.6	140	100.0
24	99.8	160	99.7
28	100.3	180	100.6
Mean ± SD	100.4 ± 0.76		100.2 ± 0.72
RSD (%)	0.75		0.72

F = 1.11 (4.28), t = 0.50 (2.18). Values in parentheses are the theoretical values at P = 0.95.
*Each contains degradation products corresponding to 4 μg ml^{-1} of cimetidine.
†Each contains degradation products corresponding to 60 μg ml^{-1} of cimetidine.

Table 2
Slopes, half-life periods ($t_{½}$) and first-order rate constants (K) for the acid hydrolysis of cimetidine by the proposed methods

	Second derivative method (method I)	Colorimetric method (method II)
Slope (min^{-1})	-4.310×10^{-3}	-4.286×10^{-3}
K (min^{-1})	9.93×10^{-3}	9.87×10^{-3}
$t_{½}$ (min)	69.79	70.21

Table 3
Assay results for the determination of cimetidine by the two proposed methods

Pharmaceutical preparations		D_2-method*	Found (as % of declared amount) Official method†	Colorimetric method‡
Tablets	Mean ± SD	100.5 ± 0.68	99.9 ± 1.31	100.1 ± 0.92
		(1.14)	(0.35)	
		3.71	2.03	
Ampoules	Mean ± SD	99.5 ± 0.77	100.4 ± 1.07	100.1 ± 0.79
		(1.84)	(0.61)	
		1.93	1.83	

Number of replicates are 7,8,7 in *, † and ‡, respectively.
Figures in parentheses are the calculated t-values, for which the corresponding theoretical value (P = 0.95) is 1.77.
The underlined figures are the calculated F-values, for which the corresponding theoretical value (P = 0.95) is 4.21.
Since cimetidine ampoules are non-official, conventional A_{max} method results are used for comparison.

indicating the insignificant difference between the results of the compared methods (Table 3).

A_{max} and D_1-measurement cannot be applied to cimetidine assay without prior separation of its degradation products since the spectra of the latter exhibits extensive interferences [Fig. 1(a,b)]. The merits of the proposed methods, however, are in the application of cimetidine assay even in the presence of its acid-induced degradation products. Accordingly, these methods may find a wide application for cimetidine quality control in many analytical laboratories.

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