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Short Communication

Determination of cimetidine in pharmaceutical preparations by capillary zone electrophoresis

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ABSTRACT

A method was developed for the determination of cimetidine (the active ingredient in the ulcer medication Tagamet) in the comm cial preparations in which it is sold. Samples were dissolved, diluted and extracted with petroleum ether before capillary zone electr phoresis in 20 m*M* phosphate buffere at pH 7. Analysis of over 60 samples from commercially available formulations gave relati standard deviations of 1.9 to 6.4%.

INTRODUCTION

Cimetidine is a first-generation anti-ulcer drug manufactured by Smith Kline and French (Beecham), and sold under the trade name Tagamet. Many analytical procedures for cimetidine are available, and these methods have been applied commonly to body fluids. The most widely used is high-performance liquid chromatography (HPLC), typically employing UV absorbance detection at 228–229 nm [1–5]. Differences in the cited procedures are in extraction, sample type, internal standard, or interfering compounds. Less-commonly employed procedures use colorimetry [6,7], titration [8], polarography [9], and even ion-selective electrodes [10].

Most pharmaceutical work with capillary zone electrophoresis (CZE), and its relative, micellar electrokinetic capillary chromatography (MECC), has been of a qualitative nature [11–13]. CZE was investigated as the basis of a method, in the present application, in order to take advantage of the speed, separating capability, and small sample requir ment of the technique. The underutilized quantit tive potential of this technique is also thus illustra ed.

EXPERIMENTAL

Chemicals and reagents

Phosphoric acid, potassium hydroxide, hydr chloric acid, light petroleum (b.p. 30–75°C) a phenol were ACS grade and purchased from VW Scientific (Irving, TX, USA). Cimetidine was o tained from ICN Biomedicals (Costa Mesa, C USA) and kept in refrigerated storage. Commerc cimetidine pharmaceuticals were obtained at a loc pharmacy.

Electrophoretic system

The electrophoretic system employed a Hip tronics 840A 0-30KVDC (Hipotronics, Brewst NY, USA) power supply. The 80-cm, 50 μm I. capillary (No. TSP050375, Polymicro Techno

gies, Phoenix, AZ, USA) was fitted with an on-column detector (model CV^4, ISCO, Lincoln, NE, USA) 24 cm from the negative (grounded) terminus. The positive electrode was enclosed in a plexiglass box to prevent electrical shock. Signals were detected concurrently by a 0–1 mV recorder (BD40, Kipp en Zonen, Delft, Netherlands) and an integrator (Model 4290, Varian Associates, Walnut Creek, CA, USA). Sample degassing was accomplished using a Branson 2200 (Branson Ultrasonics, Danbury, CT, USA) ultrasonic cleaner.

Instrumental and chemical parameters for electrophoresis

Resolution and peak symmetry were found to be optimized in a buffer of 20 m*M* phosphate at pH 7, prepared by titrating a 20 m*M* solution of H_3PO_4 to neutrality with 20% potassium hydroxide. Initially, the capillary was forcibly syringe-purged, and the reservoirs at the capillary termini were filled with buffer, following degassing of the phosphate solution for 15 min using sonication and aspirator vacuum. Subsequently, degassing the reservoirs only was usually sufficient.

The UV spectrum of cimetidine showed a single peak at the wavelength employed, 220 nm. An electropherogram of a mixture of cimetidine ($5.6 \cdot 10^{-5}$ g/ml) and the chosen internal standard, phenol ($8 \cdot 10^{-5}$ g/ml) in buffer is shown in Fig. 1. Separations, performed at 25 kV, gave currents of 25–40 μA.

Samples were introduced by 10-s immersions of the entrance end of the capillary into sample solution elevated 25 cm above the exit reservoir level. Estimates of sample size, using a method previously reported [14] indicated that *ca.* 5 nl was injected in the 10-s period.

Pharmaceuticals assay

Preparation of the calibration curve for use in assaying the pharmaceutical preparations was accomplished by first preparing stock solutions of cimetidine (*ca.* 0.07 g/100 ml) and phenol (*ca.* 0.08 g/100 ml) in pH 7 phosphate buffer. Five standards, each containing 5 ml of the phenol solution, and 2, 4, 6, 8, and 10 ml, respectively, of the cimetidine solution were placed in 50-ml volumetric flasks, then made to volume with phosphate buffer. Duplicate 10-s injections of each were made after degassing. The average peak area ratios, when graphed *vs.* concentration, showed the expected linearity.

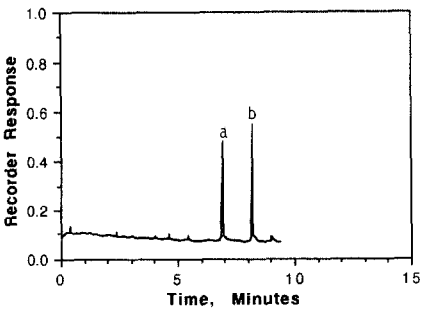

Fig. 1. Electropherogram of CZE separation of (a) cimetidine and (b) phenol in 20 mM phosphate buffer, pH 7.

The amount of cimetidine in tablets was determined by placing one tablet in a 250-ml volumetric flask, adding phosphate buffer to the mark, and stirring overnight on a magnetic stirrer. A 10-ml aliquot was transferred to a 100-ml volumetric flask, 10 ml of phenol solution added, and the flask made to volume with phosphate buffer. A 50-ml aliquot of this final solution was extracted twice with 25 ml light petroleum, and the extracts were discarded. Duplicate 10-s injections were made after degassing. The only variation to be noted is that 5-ml aliquots of the 250-ml initial solutions were used on the 800-mg tablet samples, in order to keep the peak area ratios within the limits of the calibration curve.

Tagamet liquid preparations (label claim 300 mg/5 ml) were assayed by pipetting 5 ml of the liquid into 250-ml volumetric flasks, then diluting to volume with phosphate buffer. Aliquots of 10 ml of this solution were then treated the same as the 10-ml aliquots of the tablet solutions above.

Injectable preparations followed a similar protocol to the liquids described above. The entire 2 ml contents of each vial were emptied into 250-ml volumetric flasks which were made to volume with phosphate buffer; 10 ml aliquots were used for determination as before. The results of over 60 assays of commercial preparations are summarized in Table I. Tabular values were calculated from the average of duplicate peak area ratios, using the slope and intercept of the best-fit line for the cimetidine standard solutions.

RESULTS AND DISCUSSION

Assay parameters

The linear range of instrument response, as shown by increases in peak area ratios with increasing cimetidine concentration, is demonstrated in Fig. 2. Above approximately $1.8 \cdot 10^{-4}$ g/ml, direct proportionality is lost. At this concentration, the detector response is maximized, and further increases are not able to be measured.

Initial quantitation attempts utilized measurement of relative peak heights as an estimate of cimetidine level. Much more consistent values were obtained if relative peak areas are used. Twenty duplicate injections of the same sample (heights hand-measured from the recorder trace, areas taken from the electronic integrator) gave a relative standard deviation of 3.3% for peak height ratios, 1.8% for peak area ratios.

Since the internal standard, phenol, was neutral at the chosen pH, it migrates with the electroosmotic flow; however, no problems associated with this coincidence were noted. All pharmaceutical preparation types were analyzed, and no problems with interferences were encountered.

Capillary performance deterioration

When pharmaceuticals were diluted and the solutions introduced into the capillary without pretreatment, successive electropherograms showed poorer resolution, smaller peaks, and a more erratic baseline. The light petroleum extraction in the procedure eliminated this problem; after extraction, capillary performance remained constant over hundreds of samples. Repeated light petroleum extractions of pure solutions of cimetidine and internal standard showed the peak area ratio is unaffected by this step.

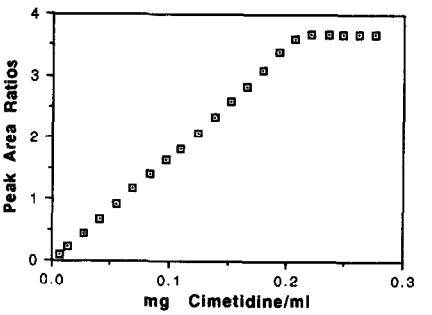

Fig. 2. CZE linearity response test: cimetidine peak area/phenol peak area as a function of cimetidine concentration.

Sample dissolution time

Tablet samples which stood in buffer solution showed cimetidine peaks which increased in size for several hours. After standing overnight, the peaks stabilized at a maximum, therefore tablet samples were stirred overnight before dilution, extraction and assay. Similar observations were not noted in the liquid and injectable preparations; they could be determined immediately.

Comparison with existing methods

One HPLC method for cimetidine and its degradation products in preparations which included

TABLE I

SUMMARY OF ANALYSES OF PHARMACEUTICAL PREPARATIONS

Preparation	Number of samples	Amount (mg)[a]	CZE method results (mg)			R.S.D.[b] (%)
			Avg.	High	Low	
Tablet	14	200	212	232	196	6.4
Tablet	14	300	314	335	290	3.9
Tablet	14	400	402	411	380	2.3
Tablet	15	800	830	870	790	3.5
Liquid	10	300/5 ml	327	339	314	2.7
Injectable	10	300/2 ml	324	332	314	1.9

[a] Manufacturer's stated amount.
[b] R.S.D. = Relative standard deviation.

tablets [15] had relative standard deviations which ranged up to 7.1%, while another in biological fluids had coefficients of variation of as much as 20% [16]. Therefore, CZE is at least comparable in precision, while requiring fewer manipulations, a much smaller sample, and less time than the more common methods. Extraction and pretreatment, usual in HPLC, is simple here, and the CZE method requires less operator skill.

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