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Short Communication

Spectrophotometric determination of furosemide and its palladium(II) complex*

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Introduction

Owing to its extensive use as a powerful diuretic, furosemide has long attracted the attention of many analysts for its assay in dosage forms. Several classical methods have been proposed for the analysis of furosemide: fluorimetry [1, 2], although other fluorescent substances may interfere with the assay; spectrophotometry [3, 4]; absorptiometry [5]; potentiometric titration in non-aqueous media [6]. Other procedures require as a first step the acid hydrolysis of the sample compound to form an anthranilic acid derivative which can be determined either by direct fluorimetry [7] or by colorimetry after diazotization [8]. Gas chromatography of furosemide after basification has also been used [9]. More recently, several HPLC methods have been developed [10–13]. Some of these methods suffer from interference from tablet base, while others are not simple for routine analysis, as they need sophisticated instruments, not yet available in many control laboratories. Therefore, it seemed necessary to develop a simple, sensitive and selective method for the assay of furosemide in tablets and injections.

In this communication, a new spectrophotometric procedure of moderate sensitivity and high operational simplicity is developed with Pd(II) as the reagent. Colorogenic reaction with Pd(II) chloride as the analytical reagent was used to modify the spectrum of furosemide so that it could be detected in the visible region, well separated from other interfering components in the UV spectrum.

Experimental

Reagents

Furosemide bulk drug, Lasix tablets (40 mg) and Lasix ampoules (20 mg) were obtained by courtesy of Hoechst Ag (Frankfurt, FRG). All other chemicals were of analytical grade purity (Merck, Darmstadt, FRG).

Solutions

A standard solution containing 3.3 mg ml^{-1} of furosemide (10^{-2} M) was prepared with distilled water, made alkaline to pH 9 with 2 M sodium hydroxide.

A sample solution containing 0.4 mg ml^{-1} of furosemide was prepared by extracting furosemide from tablet, or a diluted solution from ampoules with distilled water made alkaline to pH 9.0.

Palladium(II) chloride solution, 8.66 mg ml^{-1} (5×10^{-2} M), was prepared by dissolving, with the aid of heat, 43.3 mg of Pd(II) chloride in 2 ml of 2 M HCl and diluting the solution up to 50 ml with water. The ionic strength (μ) of the final solution for spectrophotometric determination was kept constant at 0.2 M by the addition of 2 M potassium chloride solution.

Britton–Robinson buffer solutions covering the pH region 9–12 were made by mixing 0.08 M phosphoric acid, boric acid and acetic

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acid solutions with an appropriate volume of 0.4 M sodium hydroxide and with enough 2 M potassium chloride to adjust the ionic strength to 0.2 M.

Apparatus

The solution absorbance was recorded on a Specrod M 40 Carl Zeiss Jena Spectrophotometer, provided with 10-mm quartz cells.

Measurements of pH were carried out on a "Radiometer 22" pH-meter. The pH values were determined with a saturated calomel–glass electrode system.

Procedure

Furosemide standard solution (2 ml) was placed in a 10-ml volumetric flask, and 2 ml of Pd(II) chloride solution and 1 ml of potassium chloride solution were added. The pH was then adjusted to pH 10 by adding 4 ml of pH 10 Britton–Robinson buffer, and the solution diluted to volume with water. The solution was mixed and the absorbance measured after 15 s at 527 nm against a reagent blank. All measurements were made at room temperature (25 ± 0.5°C). This procedure was applied for measuring the absorption spectrum and for determinations of furosemide in bulk drug, tablets and ampoules.

A series of nine standard solutions containing 0.41–4.96 mg ml^{-1} (1.25×10^{-3}–1.50×10^{-2} M) furosemide was used to check adherence to Beer's law at 527 nm. With each solution three experiments were run following the procedure described.

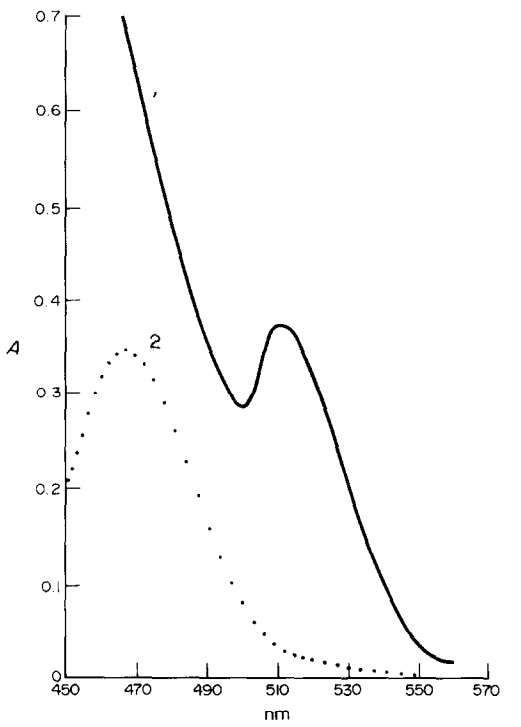

Figure 1
Absorption spectra of furosemide–Pd(II) complex (curve 1) and Pd(II) chloride (curve 2). [Furosemide] = 2×10^{-3} M; [Pd(II)] = 2×10^{-2} M; pH 10; μ = 0.2.

Results and Discussion

Spectrophotometry of furosemide–palladium(II)

Spectral characteristics of the complex. Furosemide reacts with Pd(II) chloride to produce a red complex soluble in Britton–Robinson buffer solution in the pH range 9–13. Absorption spectra were recorded over the wavelength range 400–600 nm. The complex shows a maximum absorbance at 527 nm (Fig. 1 curve 1), which can therefore be used for analytical determinations. Under the same conditions Pd(II) chloride solution has a λ_{max} at 470 nm (Fig. 1 curve 2). Since the reagent has a small absorbance at 527 nm, all measurements were performed against a reagent blank. Furosemide does not absorb at the given wavelength range. Pd(II) chloride solution was added in excess. Investigation showed that the absorbance increased up to molar ratios of 5:1 for Pd(II)–furosemide.

The reaction rate and the amount of the complex produced are considerably influenced by the pH of the reaction mixture and by the effect of time. The complex is only produced between pH 9–13 (Fig. 2). The absorbance gradually increases from pH 9 to 11. Above pH 10 absorbance of the complex decreases. As the shape of the absorbtion curves and position of the absorbtion maxima do not vary with pH, it was assumed that in this pH range only one type of complex is produced. Quite close values for absorbance and the lowest value of the variation coefficient was obtained for pH 10. Thus pH 10 was used as the working pH.

At low ionic strength (0.1 M) the absorbance decreases. At higher ionic strength maximum absorbance is observed after 15 min, and is unchanged up to 60 min. Thus, measurements were made at 15 min using an ionic strength μ = 0.2 M.

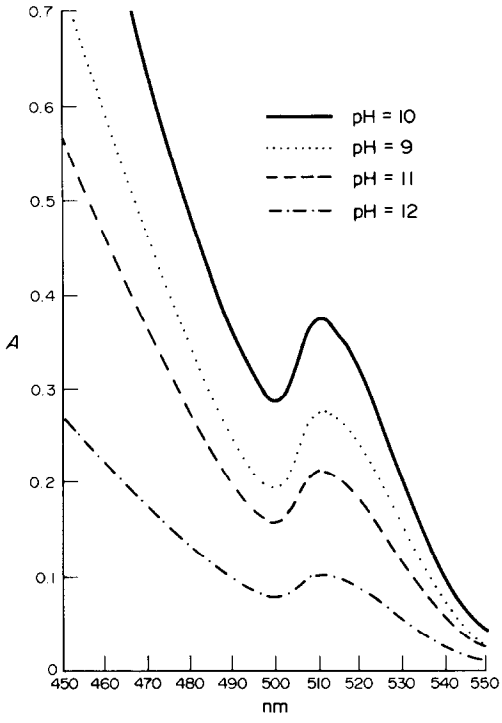

Figure 2
The effect of pH on complex formation. [Furosemide] = 2 × 10^{-3} M; [Pd(II)] = 2 × 10^{-2} M; pH 10; μ = 0.2.

Spectrophotometric determination of furosemide

The composition and the conditional stability constant. The composition of the furosemide–Pd(II) complex was determined by applying Job's method of equimolar solutions [14, 15] and the molar ratio method. By using Job's method of equimolar solution the curves obtained display a maximum at a molar fraction of X_{max} = 0.33, which indicates the formation of 1:2 complex (Fig. 3). The measurements were carried out at the optimum pH 10, at μ = 0.2 and at 527 nm.

In other experiments, the curve obtained with the molar ratio method showed a break point at a furosemide–Pd(II) molar ratio of 1:2, in good agreement with that determined by Job's method.

The conditional stability of the complex was calculated according to the method of Sommer *et al.* [14] by using Job's curve of equimolar solutions. Job's method of non-equimolar solutions [15] was employed with five-fold and 10-fold excess of reagent (Fig. 4). The values for log K'' obtained by these two methods are presented in Tables 1 and 2 and show good agreement.

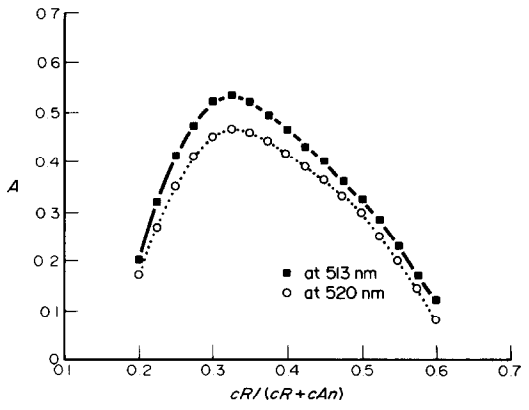

Figure 3
Job's curves of equimolar solutions at 513 and 520 nm. [Furosemide] + [Pd(II)] = 5 × 10^{-3} M; pH 10; μ = 0.2; cK = 2.5 × 10^{-3} M; cAn = 2.5 × 10^{-3} M.

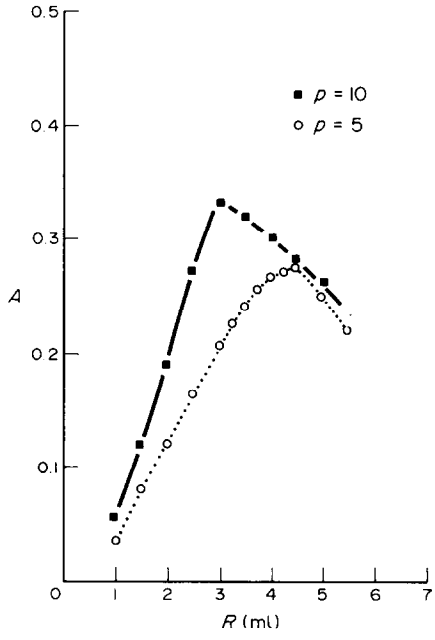

Figure 4
Job's curve of non-equimolar solution at 513 nm. [Furosemide] = 2 × 10^{-3} M; p = 5 and 10; pH 10; μ = 0.2.

Quantification and linearity of the method

Beer's law was verified in the Britton–Robinson buffer solution at pH 10. The absorbance of the complex was found to be directly related to the concentration over the range 0.25–3.5 mmol l^{-1}, calculated in the final solution. The regression equation was $y_x = -0.0038 + 0.1879x$, with a correlation coefficient of 0.9998 (n = 9). The molar absorptivity found for the complex was 1.86 × 10^2 l mol^{-1} cm^{-1}. The lower limit of sensitivity of the method was found to be 8.41 μg ml^{-1}.

Table 1
Conditional stability constant of the furosemide–palladium(II) complex calculated according to Sommer's method

log K'	log K'_{min}	log$'_{max}$	SD	RSD (%)
6.61	6.58	6.74	0.066	0.998

Conditions: pH = 10; μ = 0.2 M; t = 25 ± 0.5°C; n = 6.

Table 2
Conditional stability constant of the furosemide–palladium(II) complex calculated according to Job's method of non-equimolar solutions

[Pd(II)]	p	x_{max}	log K'
10^{-2}	5	0.375	6.45
2×10^{-2}	10	0.250	6.40

Conditions: pH = 10; μ = 0.2 M; t = 25 ± 0.5°C; mean = 6.431.

Table 3
Nominal recovery from bulk drug and tablets

Sample (n = 10)	Concentration of solution (mg ml^{-1})	Found (mg ml^{-1})	SD (mg)	RSD (%)	S_x	Recovery (%)
Furosemide bulk drug	0.33	0.33	0.054	2.43	0.0108	100.0
	0.66	0.66	0.053	2.47	0.0221	100.0
Lasix tablets (40 mg)	0.40	0.389	0.794	2.04	0.2511	97.2
Lasix ampoules (20 mg)	0.40	0.394	0.956	2.43	0.3025	98.2

The validity of the above equation was checked at two different concentrations (Table 3). The relative standard deviation, RSD (n = 10) varied from 2.42 to 2.61% for furosemide concentrations of 1 to 2 mmol l^{-1}.

The reproducibility of the method was examined by analysing Lasix tablets and ampoules. A summary of results is presented in Table 3. The recovery was 97.16% for tablets and 98.50 for ampoules, relative to the labelled strength of these preparations. The RSD of the method varied from 2.04 to 2.43% (n = 10). The results confirm the suitability of the proposed method in routine and control analysis.

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