Journal of Pharmaceutical & Biomedical Analysis
Vol. 7, No. 12, pp. 1559–1564, 1989
Printed in Great Britain

0731–7085/89 $3.00 + 0.00

Spectrophotometric study of polythiazide–palladium(II) complex*

S. AGATONOVIC-KUSTRIN† and L. J. ZIVANOVIC

Institute of Pharmaceutical Chemistry, Faculty of Pharmacy, Dr. Subotica 8, 11 000 Belgrade, Yugoslavia

Abstract: A quantitative spectrophotometric method using Pd(II) chloride as analytical reagent for the determination of polythiazide in pharmaceutical preparations is described in this study. It has been found that polythiazide reacts with Pd(II) chloride in the pH range 3.6–5.8, forming a red, water-soluble (1:1) complex with maximum absorbance at 527 nm. At the optimum pH of 4.8 and an ionic strength $\mu = 0.1$ M, the conditional stability constant of the complex is found to be $\log K' = 4.77$. The molar absorptivity at 527 nm is 3.2×10^3 l mol^{-1} cm^{-1}. Good agreement with Beer's law was found for polythiazide concentrations up to 2.2 mmol l^{-1}. The nominal percent recovery of polythiazide was 99.5% ($n = 20$). The simplicity, selectivity and sensitivity of the method described is suitable for rapid and accurate determinations of polythiazide in tablets.

Keywords: *Polythiazide; Pd(II) chloride; complexometry; spectrophotometry.*

Introduction

Polythiazide [6-chloro-3,4-dihydro-2-methyl-3-{[(2,2,2-trifluoroethyl)thio]methyl}-2H-1,2,4-benzothiadiazin-7-sulphonamide 1,1-dioxide] is an orally effective non-mercurial diuretic and antihypertensive agent. It is supplied as a tablet, either alone or in combination with reserpine.

Present methods for the determination of polythiazide include TLC, spectrophotometry, column chromatography, polarography and high-pressure liquid chromatography. The NF XIII procedure for the analysis of polythiazide tablets requires a time-consuming TLC separation prior to spectrophotometric measurement of the isolated material [1].

A polarographic method has also been described [2, 3]. Most of the spectrophotometric methods rely on hydrolysis, diazotization of the liberated amines and coupling to form a coloured azo-dye which can be estimated colorimetrically [4–6]. More recently several high-pressure liquid chromatographic methods have been developed [7–10]. Some of these methods suffer from interference from tablet excipients while others are not suitable for routine analysis, as they need sophisticated instruments, not readily available in many control laboratories.

*Presented at the "Third International Symposium on Drug Analysis", May 1989, Antwerp, Belgium.
†To whom correspondence should be addressed.

The aim of the present investigation was to develop a new, sensitive and accurate assay for the determination of polythiazide in dosage forms. Colorogenic reaction with Pd(II) chloride as analytical reagent was used to modify the spectrum of polythiazide so that it could be detected in the visible region, well separated from other interfering components in the UV spectrum. It is known that Pd(II) reacts with halogens, CN and S. Colours from yellow to brown are obtained for aliphatic compounds, which have a sulphur atom in the chain. However, no colour is given when an S-alkyl chain is present, unless the chain is terminated by a halogenated group, as in the case of polythiazide. The method is simple, operationally simple and suitable for routine analysis.

Experimental

Reagents

Polythiazide bulk drug and Renase tablets (2 mg) were obtained by courtesy of Pfizer Inc. (New York, USA). Ethanol, Pd(II) chloride, hydrochloric acid, potassium chloride, acetic acid and sodium hydroxide were obtained from Merck A.G. (Darmstadt, FRG).

Solutions

A freshly prepared (0.4 mg ml^{-1}; 9.1×10^{-4} M) ethanolic solution of polythiazide bulk drug was used as the standard solution for analytical purposes. A sample solution containing 0.4 mg ml^{-1} of polythiazide was prepared by extracting polythiazide from tablets with absolute ethanol.

Pd(II) chloride solution (0.8 mg ml^{-1}; 4.6×10^{-3} M) was prepared by dissolving, with the aid of heat, 40 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 0.1 M by the addition of 1 M potassium chloride solution.

Acetate buffer solutions covering the pH range 3.6–5.8 were made by mixing 1 M acetic acid solution with an appropriate volume of 1 M sodium hydroxide.

Apparatus

The solution absorption was recorded on a Specord M 40 Carl Zeiss Jena Spectrophotometer, provided with matched 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

An aliquot of 2 ml of polythiazide standard solution 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 by adding 2 ml of pH 4.8 acetate buffer solution, and the solution diluted to volume with water. The solution was mixed and the absorbance measured after 15 min at 527 nm against a reagent blank. All measurements were made at room temperature (25 ± 0.5°C). This procedure was employed for measuring the absorption spectrum and for determinations of polythiazide in bulk drug and tablets.

A calibration curve was prepared with twelve standard solutions over the concentration range 0.1–1.2 mg ml^{-1} (1.82×10^{-4} to 2.18×10^{-3} M). For each solution three experiments were carried out following the procedure described.

Results and Discussion

Spectral characteristics of the complex

It was found that polythiazide reacts with Pd(II) chloride producing a red complex soluble in acetate buffer solution in the pH range 3.6–5.8. Absorption spectra were recorded over the wavelength range 400–600 nm. The complex shows maximum absorbance in the visible range at 527.0 nm (Fig. 1, curve 1), which can therefore be used for analytical purposes. Under the same conditions Pd(II) chloride solution itself has a λ_{max} at 470 nm (Fig. 1, curve 2). Since the reagent has a small absorbance at 527.0 nm, all measurements were performed against a reagent blank. Polythiazide does not absorb in the visible spectrum. The maximal production of complex was reached after 5 min and the colour was stable for 5 h. All other measurements were made after 15 min. The relationship between absorbance of the complex and pH is presented in Fig. 2.

The complex is only produced at pH values above 3.6. At higher pH values the absorbance gradually increases, but above pH 5.2 the stability of the complex decreases. As the shape of the absorption curves and position of the absorption maxima do not vary with pH, it was assumed that in this pH range only one type of complex is produced. Since the complex is not stable above pH 5.2 after 15 min, the working pH used was 4.8.

Pd(II) chloride solution was added in excess. Investigation showed that the absorbance increased up to a molar ratio of 5:1 for Pd(II)–polythiazide.

Spectrophotometric determination of polythiazide

The composition and conditional stability constant. The composition of the polythiazide–Pd(II) complex was determined by applying Job's method of equimolar solutions and the molar ratio method. The measurements were carried out at the

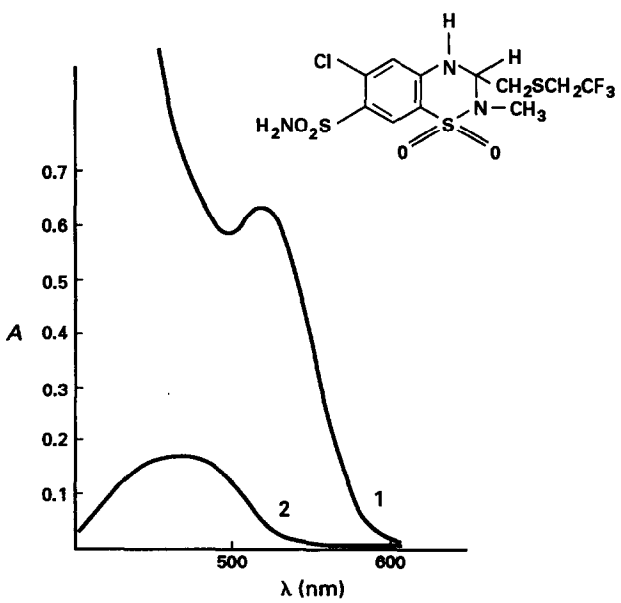

Figure 1
Absorption spectra of polythiazide–Pd(II) complex (curve 1) and Pd(II) chloride (curve 2). [Polythiazide] = 1.83×10^{-5} M; [Pd(II)] = 4.6×10^{-4} M; pH 4.8; μ = 0.23 M.

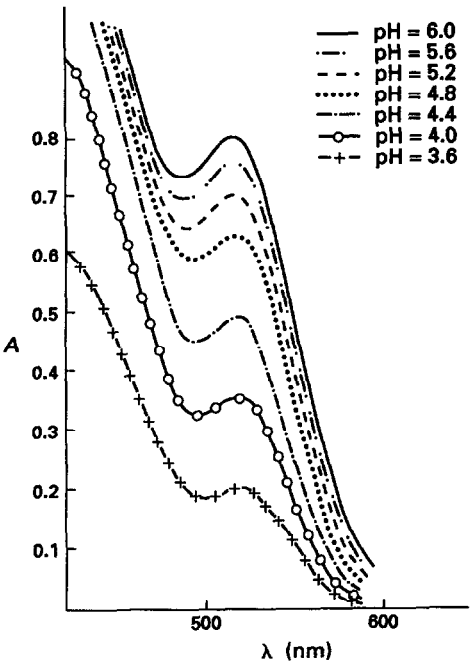

Figure 2
The effect of pH on complex formation. [Polythiazide] = 1.83×10^{-5} M; [Pd(II)] = 4.6×10^{-4} M; pH 4.8; μ = 0.23 M.

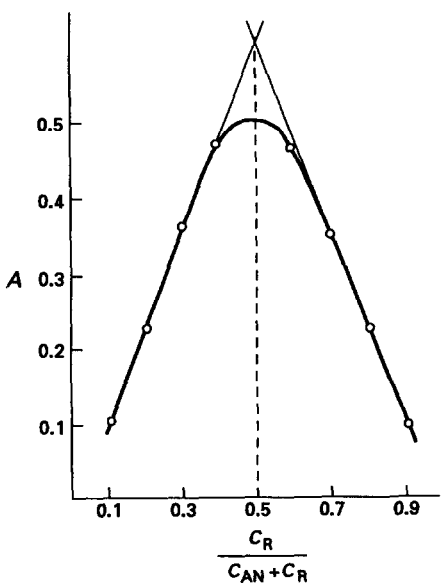

Figure 3
Job's curve of equimolar solution at 527 nm. [Polythiazide] + [Pd(II)] = 4.0×10^{-5} M; pH 4.8; μ = 0.23 M; $C_R = 4.0 \times 10^{-4}$ M; $C_{AN} = 4.0 \times 10^{-4}$ M.

optimum pH 4.8 and at 527 nm. By using Job's method of equimolar solutions, the curve obtained displayed a maximum at a mole fraction of $X_{max} = 0.5$, which indicates the formation of 1:1 complex (Fig. 3).

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

The conditional stability constant of the complex was calculated according to the methods of Sommer and Astmus [11] by using Job's curve of equimolar solutions. Job's method of non-equimolar solutions [12] was employed with five-fold and ten-fold excess of reagent (Fig. 4). The values for log K' obtained by these three methods are presented in Tables 1 and 2 and show in good agreement.

Quantification and linearity of the method

Agreement with Beer's law was verified in acetate buffer solution (pH 4.8) at 527 nm. A linear relationship between absorbance and polythiazide concentration was found up to 2.2 M. The regression equation was: $y_x = 0.321x + 0.013$, with a correlation coefficient of 0.999 ($n = 6$). The molar absorptivity found for the complex was 3.2 ×

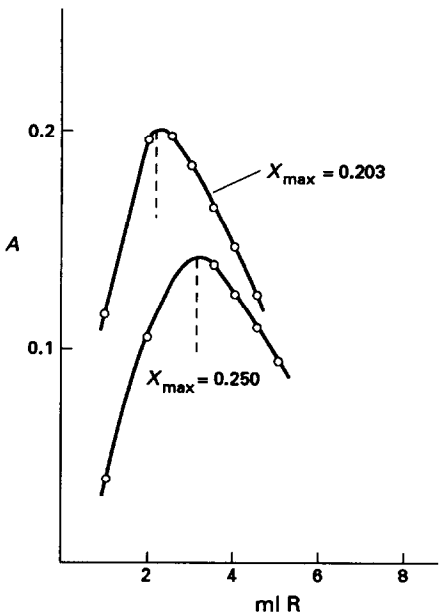

Figure 4
Job's curve of non-equimolar solution at 527 nm. [Polythiazide] = 6×10^{-5} M; $p = 5$ (curve 1); $p = 10$ (curve 2); pH 4.8; $\mu = 0.23$ M; R = $PdCl_2$.

Table 1
Conditional stability constant of the polythiazide–Pd(II) complex Sommer's method*

log K'	logK'_{min}	log K'_{max}	SD	RSD (%)	A_{ext}	A_k	log K'
4.74	4.63	4.75	0.08	1.68	0.61	0.50	4.81

*Conditions: pH 4.8; $\mu = 0.23$ M; $t = 25 \pm 0.5$ min.

Table 2
Conditional stability constant of the complex calculated according to Job's method of non-equimolar solutions*

[Pd(II)]	p	X_{max}	log K'
3×10^{-4}	5	0.250	4.76
6×10^{-4}	10	0.203	4.77
			Mean: 4.765

*Conditions: pH 4.8; $\mu = 0.23$ M; $t = 25 \pm 0.5$ min.

Table 3
Nominal recovery from bulk drug and tablets

Sample (n = 20)	Concentration of solutions	Found (mg ml^{-1})	SD (mg)	RSD (%)	S_x	Recovery (%)
Polythiazide bulk drug	0.4 mg ml^{-1}	0.400	0.117	0.29	0.026	100.0
"Renese" tablets (2 mg)	0.4 mg ml^{-1}	0.398	0.156	0.39	0.035	99.5

10^3 l mol^{-1} cm^{-1}. The lower limit for reliable quantification of polythiazide was 2 μg ml^{-1}.

The accuracy and precision of the method were assessed by analysing 20 solutions containing known quantities of polythiazide. Reproducibility studies were performed by analysing Renese 2-mg tablets. A summary of results is presented in Table 3. Further work would be required to confirm the lack of interference by degradation products of polythiazide.

The nominal percent recovery of polythiazide was 99.5% (n = 20), relative to the label strength of Renese tablets. The high recovery and the low relative standard deviation confirm the suitability of the proposed method for the routine analysis of polythiazide in pharmaceutical preparations.

References

[1] *The National Formulary*, 13th edn, p. 565. Marck Publishing Co., Easton, PA (1970).
[2] P. Gantes and J. Barat, *Ann. Pharm. Fr.* **25**, 447–452 (1967).
[3] E. Kholos and J. Walker, *Analytica Chim. Acta* **80**, 17–30 (1975).
[4] H. Kala, *Pharmazie* **20**, 82–91 (1965).
[5] H. Shepard, T. F. Mowles and A. J. Plummer, *Pharm. Assoc.* **49**, 722–723 (1960).
[6] J. B. Perez, A. C. Danhier and J. A. Brieva, *Anal. Abstr.* **21**, 2723 (1971).
[7] C. K. Wong, D. Y. J. Tsau, D. M. Cohen and K. P. Munnelly, *J. Pharm. Sci.* **66**, 736–738 (1977).
[8] R. E. Moskalyk, R. A. Lococ, L. G. Chatten, A. M. Veltman and M. F. Bielech, *J. Pharm. Sci.* **64**, 1406–1408 (1975).
[9] W. J. Bachman, *J. Liq. Chromatogr.* **9**, 1463–1478 (1986).
[10] W. J. Bachman, *J. Liq. Chromatogr.* **9**, 1033–1049 (1986).
[11] L. Sommer, V. Kuban and J. Havel, *Spectrophotometric Stud. Complexation Solution*, Tomus XI, Chemia 7, opus 1, 25–27 (1970).
[12] W. C. Vosburg and G. R. Cooper, *J. Am. Chem. Soc.* **63**, 437–442 (1941).

[*Received for review 16 May 1989; revised manuscript received 24 May 1989*]