Stannous-Ion Quantitation in Pyrophosphate and Polyphosphate Radiopharmaceutical Kits Using Differential Pulse Polarography

MARTIN H. D. McBRIDE, ROBERT E. GEORGE, WAYNE V. KESSLER, and STANLEY M. SHAW ˣ

Abstract □ Stannous salts are used as reducing agents in many radiopharmaceutical kits. Differential pulse polarography, with 1 *M* sulfuric acid as the supporting electrolyte, is a relatively simple and effective technique for stannous quantitation and can be used in the quality assurance testing of pyrophosphate and polyphosphate radiopharmaceutical kits.

Keyphrases □ Stannous ion—differential pulse polarographic analysis in pyrophosphate and polyphosphate radiopharmaceutical kits □ Polarography, differential pulse—analysis, stannous ion in pyrophosphate and polyphosphate radiopharmaceutical kits □ Radiopharmaceutical kits—pyrophosphate and polyphosphate types, differential pulse polarographic analysis of stannous content □ Tin—stannous ion, differential pulse polarographic analysis in pyrophosphate and polyphosphate radiopharmaceutical kits

Stannous ion, Sn(II), is the most effective and widely used reducing agent in radiopharmaceutical kits. However, Sn(II) is unstable in the presence of oxygen. Even in the crystalline state, stannous chloride can react with oxygen to form insoluble oxychlorides (1) and stannic, Sn(IV), "material" (2). In aqueous solution, Sn(II) can be precipitated as an insoluble basic chloride (3) or oxidized to Sn(IV) (4) by dissolved oxygen.

A quantitative test for Sn(II) content during the manufacture and storage of various radiopharmaceutical kits would be a very desirable quality assurance procedure. This Sn(II) test must be highly sensitive, because many kits contain much less than 1 mg of stannous salt. Furthermore, the test must be accurate in the presence of Sn(IV) contamination.

Differential pulse polarography was studied as a method for measuring the Sn(II) content of pyrophosphate and polyphosphate kits. Measured Sn(II) levels, 10^{-3}–10^{-4} *M*, were in the range of those found in many reconstituted commercial kits.

EXPERIMENTAL

The relationship between polarographic peak height and Sn(II) content of pyrophosphate and polyphosphate kits was studied by assaying a series of each kit type. The total tin concentration of each pyrophosphate kit was 8.3×10^{-4} *M* (equivalent to the tin supplied by 0.49 mg of stannous chloride dihydrate in a kit). The total tin concentration in each polyphosphate kit was 2.8×10^{-3} *M* (equivalent to 1.3 mg of stannous chloride dihydrate). The fraction of total tin as Sn(II) was varied among the kits from 0 to 1.0 in steps of 0.1 to illustrate the sensitivity range of differential pulse polarographic Sn(II) analysis and to demonstrate any polarographic interference produced by the presence of Sn(IV).

Tin Solutions—Sn(II) stock solutions were prepared by dissolving stannous chloride dihydrate[1] in concentrated reagent grade hydrochloric acid and diluting to volume with distilled water. The Sn(IV) stock solutions were prepared in a similar manner with anhydrous stannic chloride[2]. Tin concentrations in these stock solutions were 1.4×10^{-3} *M* for use with pyrophosphate kits and 5.5×10^{-3} *M* for use with the polyphosphate kits. The hydrochloric acid concentration in all tin stock solutions was 2 *M*. To reduce the chance of Sn(II) deterioration, Sn(II) stock solutions were placed in 20-ml multiple-dose vials, purged with nitrogen, and stored under 2.4 atm of nitrogen.

Radiopharmaceutical Kits—Pyrophosphate kits were prepared in 10-ml vials by combining 1.1 ml of an aqueous solution containing 17 mg of tetrasodium pyrophosphate[3] with an appropriate aliquot of Sn(IV) stock solution. Polyphosphate kits were prepared in 10-ml vials by combining 1.0 ml of an aqueous solution containing 67 mg of polyphosphate, prepared by the method of Subramanian *et al.* (5), with an appropriate aliquot of Sn(IV) stock solution. All vials were sealed, nitrogen purged, and stored under a positive nitrogen pressure for a maximum of 8 hr.

An appropriate amount of Sn(II) stock solution was added to the kits just prior to the polarographic analysis (*i.e.*, during the sulfuric acid outgassing in the cell). The combined volume of Sn(II) and Sn(IV) stock solutions added to each pyrophosphate kit was 1.5 ml. The combined volume of tin stock solutions added to each polyphosphate kit was 1.0 ml.

Instrumentation and Analyses—An unmodified, commercially available polarographic analyzer[4] was used for the differential pulse polarographic analysis as follows. Nine milliliters of 1 *M* H_2SO_4 was placed in the polarographic cell, and the cell was outgassed with nitrogen (prepurified grade, scrubbed with vanadous chloride) for 1 min. A 1-ml portion of the kit was then added through the cell top with a 1-ml disposable syringe, and the cell solution was outgassed for 1 additional min. The nitrogen was then diverted over the solution, and a differential pulse polarographic scan was made from −0.30 to −1.00 v with a saturated calomel electrode (SCE) as reference. The following parameters were used: drop time, 0.5 sec; modulation amplitude, 25 mv/pulse; and scan rate, 5 mv/sec.

The peak heights and peak potentials of the scans were calculated and recorded. Peak heights were measured from the baseline of the peak. Each kit analysis required approximately 3.5 min.

RESULTS

Differential pulse polarographic peaks corresponding to Sn(II) reduction were found at peak potentials of −0.44 v for pyrophosphate kits (Fig. 1) and −0.48 v for polyphosphate kits. Standard curves of peak height *versus* Sn(II) concentration were prepared and were linear. The slope of the curves was 0.14 μamp/10^{-4} *M* for polyphosphate kits (correlation coefficient of 0.9962) and 0.17 μamp/10^{-4} *M* for pyrophosphate kits (correlation coefficient of 0.9994). Peak heights for individual kits, especially those with low Sn(II) concentrations, varied with maximum standard deviations of 7% for pyrophosphate and 17% for polyphosphate over four calibration runs.

The polyphosphate Sn(II) peaks were somewhat asymmetric, suggesting the presence of maxima. Ordinary pulse polarography scans confirmed the maxima. The larger standard deviation for the polyphosphate kits as well as the shift in peak potential may be attributed

[1] Analytical reagent grade, Fisher Scientific Co.

[2] Baker analyzed reagent.

[3] Sigma Chemical Co.

[4] Princeton Applied Research polarographic analyzer model 174 with cell and drop timer.

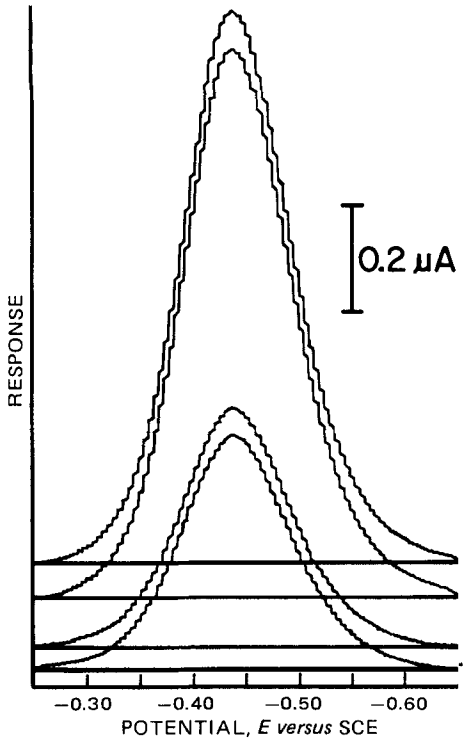

Figure 1—*Differential pulse polarographic scans of two pyrophosphate kits (8.3 × 10⁻⁴ M total tin). The top two scans are of a kit containing 70% of the tin as Sn(II) and 30% as Sn(IV). The lower two scans are of a kit containing 30% Sn(II) and 70% Sn(IV). The peaks occurred at −0.44 v. The vertical positioning of the scans is unimportant, since peak height was measured from the baseline of each peak.*

to the maxima. However, the potential shift could also be an indication of the differences between the Sn(II)–pyrophosphate and Sn(II)–polyphosphate complexes. Nothing was done to suppress the maxima because the polyphosphate variability was not so great to warrant an added step, namely the addition of a surfactant to the supporting electrolyte prior to each analysis.

Several supporting electrolytes were used, but only 1 *M* H_2SO_4 was satisfactory. Since Sn(IV) is not soluble in this electrolyte (6), it does not produce a reduction peak that could interfere with the Sn(II) peak.

Sn(II) solutions in 0.12 *M* HCl were tested by the differential pulse polarographic technique. The method was effective in quantitating Sn(II) at concentrations as low as 8×10^{-6} *M* (2 μg of stannous chloride dihydrate in 1 ml). Sn(IV) interference was not examined at these low Sn(II) concentrations.

DISCUSSION

Classical dc polarography, electrolysis on a microscale in which the magnitude of current flow is proportional to the sample concentration, is useful in tin analysis (6). Differential pulse polarography is a relatively new, highly sensitive version of this technique (7) and is a convenient and effective method for the quantitation of Sn(II) in pyrophosphate and polyphosphate radiopharmaceutical kits. One should not assume that simple Sn(II)–hydrochloric acid solutions can be used as standards, since different peak potentials and slopes can be expected for different kit types as the result of different matrixes. This Sn(II) analytical technique is currently being studied for its value in the qualitative control testing of other radiopharmaceutical products.

REFERENCES

(1) "The Merck Index," 8th ed., Merck & Co., Rahway, N.J., 1968, p. 978.

(2) J. D. Donaldson and W. Moser, *J. Chem. Soc.*, **1960**, 4000.

(3) "Mellor's Modern Inorganic Chemistry," G. D. Parkes, Ed., Wiley, New York, N.Y., 1967, pp. 790, 791.

(4) F. A. Cotton and G. Wilkinson, "Advanced Inorganic Chemistry," 3rd ed., Interscience, New York, N.Y., 1972, p. 331.

(5) G. Subramanian, J. G. McAfee, E. G. Bell, R. J. Blair, R. E. O'Mara, and P. H. Ralston, *Radiology*, **102**, 701 (1972).

(6) J. J. Lingane, *Anal. Chem.*, **18**, 429 (1946).

(7) J. B. Flato, *ibid.*, **44**, 75A (1972).

ACKNOWLEDGMENTS AND ADDRESSES

Received March 17, 1976, from the *Bionucleonics Department, School of Pharmacy and Pharmacal Sciences, Purdue University, West Lafayette, IN 47907.*

Accepted for publication July 21, 1976.

Supported in part by U.S. Public Health Service Training Grant 5-T01-ES00076 from the National Institute for Environmental Health Sciences.

The authors thank Dr. A. M. Knevel for making available the polarographic equipment.

[x] To whom inquiries should be directed.

GI Absorption of Niacin in Humans

HELLE BECHGAARD [x] and S. JESPERSEN

Abstract □ By using the GI tube technique, niacin was shown to be equally well absorbed from the stomach and the upper small intestine. The maximum plasma niacin concentrations occurred 10–20 and 5–10 min, respectively, after instillation. Thus, the physiological prerequisites for a physically retarded niacin preparation were established.

Keyphrases □ Absorption, GI—niacin, stomach and small intestine compared, humans □ Niacin—absorption from stomach and small intestine compared, humans □ Vitamins—niacin, absorption from stomach and small intestine compared, humans

It is generally accepted that weak organic acids or bases are absorbed primarily by penetration of the unionized form of the drug through a lipoidal barrier (1). Niacin (nicotinic acid) (pKa 4.8) should theoretically be better absorbed from the stomach than from the small intestine. However, salicylic acid (pKa 3.0) is reportedly well absorbed even at pH values where it is predominantly ionized (2).

Limited data are available concerning the GI absorption of niacin in humans. In a steady-state situation, about 85% of an orally administered dose (3 g/day) of niacin was recovered from the urine, and it was concluded that absorption was nearly complete (3).

In a comparative study of plain and enteric-coated niacin tablets (4), niacin was absorbed from the small intestine to only a small extent. Based on this finding, in-