gave a chromatogram that showed many extraneous peaks for the 200-ppm sample, but the chromatogram of the 6000-ppm sample was relatively clean. The difference on the baseline between I and the nearest extraneous peak on the 6000-ppm chromatogram was >1 min (Fig. 3). Procedure a gave very few additional peaks for the 200-ppm sample (Fig. 2). In the liquid chromatogram of the 6000-ppm sample, only two small peaks were observed.

Essentially complete recoveries were obtained when known amounts of I were analyzed in the absence of feed using both cleanup procedures. When a solution of I in acetone was added to a placebo feed, however, the overall percent recoveries ($\pm SD$) obtained by Procedure a were 90.0 ± 2.0 (n = 5) and 95.9 ± 1.6% (n = 5) for the 200- and 6000-ppm samples, respectively (Table II). Similarly, Procedure b gave overall percent recoveries ($\pm SD$) of 92.9 ± 1.6 (n = 5) and 97.4 ± 1.8% (n = 5) for the 200- and 6000-ppm samples, respectively (Table II). To provide better representation of the analytical potency, a concomitant standard may be used; *i.e.*, the standard can be subjected to the same analytical steps in the cleanup procedures.

The cleanup procedures were evaluated by spiking acetone extracts of a placebo feed with a solution of I in acetone. The recoveries, again <100%, were in close agreement with those obtained when the drug was added directly to the dry feed followed by manual extraction (Table I). Attempts to improve the recoveries by doubling the analytical sample size were not successful. Apparently, an interaction occurs between the drug and one or more of the extractable feed components, which affects the analytical recovery.

This hypothesis was supported by subsequent recovery studies using cleanup Procedure a and placebo feed samples spiked with I at the 6000-ppm level. Duplicate results of 90.9 and 92.1% were obtained when the synthetic samples were mixed using a mortar and pestle. When two similar samples were assayed 7 days after mixing, recoveries of only 82.8 and 82.5% were achieved. No peaks that could be attributed to decomposition products of I were seen in the chromatograms.

The HPLC method is stability indicating; various degradation studies showed that the I peak decreased upon decomposition with or without the appearance of new peaks.

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Potentiometric Determination of Iodine in Pharmaceutical Preparations

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Abstract □ Methods for the determination of organically bound iodine were compared. A preliminary destruction of the sample was preferable. The sample was mineralized using the Schöniger combustion. Since direct potentiometry of the iodide ion was used, further reduction of the sample was necessary. Several reductors were compared, and the best results were obtained with Devarda alloy. The proposed method was employed for the determination of iodine in X-ray contrast products. Pure compounds and pharmaceutical preparations were investigated. The coefficient of variation of the method was 0.9%.

Keyphrases □ Iodine—analysis, potentiometric, various pharmaceuticals, ion-selective electrodes □ Potentiometry—analysis, iodine in various pharmaceuticals

The increased number of commercially available ion-selective electrodes has stimulated their use in pharmaceutical analysis. The potentiometric determination of halide salts of pharmaceutical compounds such as alkaloids and phenothiazines was described (1–3). Halogen-containing organic compounds also can be determined by ion-selective electrodes. Since halide ion-specific electrodes measure only the inorganic ionic halogen in solution, preliminary liberation of the covalently bound halogen from the organic product is necessary and usually is achieved by destruction of organic matter (3–11). Methods for halogen liberation from organic compounds (hydrolysis, decomposition by acids or oxidizing acids, melting of solids, combustion in a gas stream, and oxygen flask combustion) were discussed previously (12).

Some investigators reported the liberation of organically bound iodine by a metallic reductor. Catalytic dehalogenation with sodium borohydride in the presence of palladium was described for the analysis of X-ray contrasting media (13). The use of an aluminum foil in alkaline solution was proposed for the iodine determination in liothyronine (triiodo-L-thyronine, T_3) and thyroxine (tetraiodo-L-thyronine, T_4) (14).

If a combustion method such as the Schöniger combustion (15, 16) is used to mineralize the organic matter, the halogen content can be determined by measuring the iodate or iodide content. After combustion, the iodine is present as iodine and iodate. The iodine and iodate can be reduced to iodide ions, which can be measured potentiometrically with an iodide-ion-selective electrode. In this case, a reduction step is necessary. Reduction of iodate has already been described.

Stannous chloride was used for iodate determination in iodized cooking salt with an iodide-selective electrode (17), and use of an aluminum foil in alkaline solution was reported for the iodate reduction (18). The purpose of this

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Table I—Performance of Metallic Reductors for the Reduction of a Sodium Iodate Solution Equivalent to 1.000 ppm of I^-

Metallic Reductor	Yield, %	Mean Yield, %	s
Raney nickel	90.2, 97.5, 102.0, 103.0 93.6, 95.5	97.0	4.9
Devarda alloy	95.5, 96.4, 101.1, 95.5, 99.2, 100.2	98.0	2.5
Aluminum wire	62.7, 45.3, 85.2, 84.0, 85.0	72.4	14.8

work was to develop a suitable method for potentiometric determination of iodine in organic compounds. Two methods for the liberation of organically bound iodine were compared: dehalogenation without complete destruction and mineralization. Furthermore, several metallic reductors for iodine and iodate reduction were tested. Finally, the preferred method was employed for iodine determination in pharmaceutical preparations.

EXPERIMENTAL

Apparatus—Potential readings were taken on a high-input-impedance digital pH/mv meter[1]. Potentiometric measurements were carried out using an iodide-specific electrode[2] in conjunction with a single-junction reference electrode[3] in a thermostated (25.0 ± 0.1°) polyethylene vessel.

Reagents—All reagents were analytical grade. Reductors were Devarda alloy[4], nickel–aluminum alloy (50:50)[5], and aluminum wire[6]. Raney nickel was prepared from the nickel–aluminum alloy according to a literature procedure (19).

A stock solution of 1000 ppm of I^- was prepared with dried sodium iodide. The solution was standardized by potentiometric titration using a silver nitrate solution. A stock potassium iodate solution (equivalent to 1000 ppm of I^-) was prepared by dissolving 1.6864 g of potassium iodate in 1 liter of water.

Iodine Determination in Pharmaceutical Compounds without Preliminary Destruction—The method proposed by Paletta and Pazenbeck (14) was followed except that an aluminum spiral, 30 cm in length, was used instead of aluminum foil. The wire was activated before use by boiling for 20 min in 1 *N* NaOH. The iodide determination was performed with and without neutralization of the solution with 1 *N* HCl.

Reductor Testing—The following reductors were tested: Devarda alloy powder at room temperature, Raney nickel at 55°, and aluminum wire at 60°. A 5-ml volume of iodate solution was mixed with 20 ml of 5 *M* NaOH. After shaking for 30 min at the respective temperatures, the solution was cooled, filtered, and made up to 100 ml with water. This solution was diluted 1:1 with 2 *M* KNO_3, and the iodide content was determined by direct potentiometry. Appropriate standards prepared from the iodide stock solution were treated in the same manner.

Potentiometric Determination of Iodine in Pharmaceutical Compounds after Schöniger Combustion[7] (Preferred Method)—An amount of sample[8] containing ~5 mg of iodine was weighed accurately on ashless paper[9]. A 20-ml volume of 5 *M* NaOH was used as the absorption liquid. The combustion was carried out in a Schöniger flask filled with oxygen.

After combustion, the content of the combustion flask was transferred quantitatively to a conical flask. After 1 g of Devarda alloy powder was added, the mixture was shaken for 30 min at room temperature, filtered into a 100-ml volumetric flask, and made up to volume with water.

This solution was diluted 1:1 with 2 *M* KNO_3. The iodide content was determined by direct potentiometry, using a calibration curve obtained by standards treated in the same manner.

[1] Model 801, Orion Research, Cambridge, Mass.
[2] Model 94-53, Orion Research, Cambridge, Mass.
[3] Model 90-01, Orion Research, Cambridge, Msss.
[4] U.C.B., Brussels, Belgium.
[5] Catalytic quality, B.D.H. Chemicals, Poole, England.
[6] Carlo Erba, Milan, Italy.
[7] Model mikro K, Heraeus, Hanau, Germany.
[8] Tablets are ground first; solutions are spotted directly or after dilution on ashless paper.
[9] Whatman.

Table II—Iodine Determination in Pharmaceutical Compounds

Compound Analyzed	Iodine Calculated, %	Iodine Measured, %	Mean Yield, %
		Preferred Method	
Ipodate sodium	61.4	61.6, 61.6, 60.9, 61.2, 61.1, 61.5, 60.5, 61.8, 62.5, 61.5	100.0 ± 0.9
Ipodate calcium	61.7	61.5, 61.1, 62.2	99.8
Ioglycamic acid	67.5	63.4, 63.3, 64.1, 64.9	94.7
Iodomethamate sodium	51.5	47.5, 47.5	92.3
Iothalamic acid	62.0	63.1, 64.1, 64.1, 62.1	102.2
Amidotrizoic acid	62.0	59.3, 59.4, 59.1	95.6
Iopydol	60.3	57.7, 57.8, 58.0	95.9
Iodipamide	66.8	68.4, 66.3, 67.3, 67.0	100.7
Iobenzamic acid	57.5	57.0, 58.2, 57.0	99.8
Liothyronine sodium	56.6	53.5, 54.0, 54.6	95.5
		BP Method	
Ipodate sodium	61.4	60.3, 60.5, 60.6, 60.5, 264.3, 61.3	99.7 ± 2.5

RESULTS AND DISCUSSION

The quantitative liberation of organically bound iodine by reductive dehalogenation (14) was used for the determination of iodomethamate sodium, an X-ray contrast product: iodine calculated (%), 51.4; iodine found after neutralization (%), 10.6, 17.1, 19.9, 18.1, 20.2, and 13.8; yield (% of given content), 32.3; iodine found without neutralization (%), 38.2, 35.7, and 38.2; and yield (% of given content), 72.6. The recovery was very poor with neutralization. The aluminum hydroxide precipitate, which is formed at a neutral pH, might have adsorbed iodide ions so that the latter could not be detected by the electrode. To avoid precipitation, the determination was also performed without neutralizing the solution with hydrochloric acid after reduction; the recovery was better but not satisfactory.

These findings suggest that this procedure was not able to liberate quantitatively the organically bound iodine and that a mineralization of the organic product is required. The Schöniger combustion was chosen over other mineralization methods because it is the least time consuming. However, with this method, the liberated halogen will be present as iodate and iodine, which cannot be detected potentiometrically by the iodide electrode. Hence, a reduction step is necessary to convert the iodate and iodine to iodide. Metallic reductors that can be removed from the solution after the reduction step are indicated for this purpose; otherwise, reductors can damage the electrode surface (20).

The performance of several iodate reductors was tested (Table I). Comparable yields were obtained with Raney nickel and Devarda alloy, but the latter was preferred because the dispersion on the results was smaller. The recovery with the aluminum wire was much lower.

The quantitative liberation of organically bound iodine with Devarda alloy, but without combustion, was tested on ipodate sodium. Since the mean recovery was only 43.6%, preliminary destruction was necessary.

The iodine contents of the pharmaceutical compounds were determined after Schöniger combustion (Table II). The iodine recovery was at least 95% except for one compound. The lower yield obtained for the iodomethamate sodium sample can be explained by its possible obsolescence. Unfortunately, a new sample could not be obtained from the manufacturer.

The precision of the method was 0.9%. These results were compared with those obtained with the method proposed by the British Pharmacopoeia (21) for the determination of organically bound iodine in ipodate sodium. The method involves volumetric titration with sodium thiosulfate after quantitative oxidation of iodine to iodate (Table II). A comparison of these values with those obtained with the developed method for ipodate sodium shows that the recovery was nearly the same. The potentiometric method precision was slightly better. The latter method is preferable for routine analysis because it is less cumbersome.

Table III—Iodine Determination in Pharmaceutical Preparations

Active Compound	Iodine Calculated, %	Iodine Measured, %	Mean Yield, %
		Tablets	
Iodochlorhydroxyquin, 200 mg	41.5	31.0[a], 40.8[b], 27.4[a], 39.9[b]	70.3[a], 97.2[b]
Iobenzamic acid, 750 mg	57.5	53.2[a], 57.6[b], 54.0[a], 58.7[b]	93.2[a], 101.2[b]
		Suspensions/Solutions	
Ipodate calcium, 3 g/8 g	61.7	61.5, 61.6	99.8
Iodomethylhexamethylenetetramine, 250 mg/ml	45.0	44.9, 44.9	99.7
		Ampuls	
Iodazine, 5 mg/ml	63 8	61.1, 59.9	94.8
Meglumine amidotrizoate, 650 mg/ml	47.1	46.4, 48.6	100.0
Meglumine iodipamide, 300 mg/ml	49.8	50.7, 50.3	101.5
Ioglycamic acid, 260 mg/ml	67.5	66.4, 66.4	98.3
Meglumine iothalamate, 600 mg/ml	47.0	47.4, 48.5, 47.4	101.5
Meglumine iocarmate, 604 mg/ml	46.4	45.2, 46.6, 47.0	99.8

[a] The active compound was extracted with a suitable solvent from the ground sample. [b] Direct determination on the ground sample without the extraction step.

The developed method also was applied to check the active compound content of pharmaceutical preparations. Tablets, suspensions, and solutions were analyzed. For tablets, the determination was performed on the ground tablet and for two preparations after extraction with a suitable solvent. Pyridine was used for iodochlorhydroxyquin, and dioxane was used for iobenzamic acid. A known volume of the obtained solution was then spotted on ashless paper.

All recovery values obtained for the pharmaceutical preparations were between 94.8 and 101.5% (Table III). For the tablets, however, the yield was better when the determination was performed directly on the ground tablet instead of on the extract, which shows that the extraction of the active compound was incomplete.

The proposed method yields accurate and reproducible results for the determination of organically bound iodine in pharmaceutical compounds. It is useful for routine analysis and is sensitive enough to determine the active compound in unit doses.

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