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Determination of organically bound iodine by reductive mineralization with aluminium powder

Analytical methods of pharmacopoeias with DBH in respect to environmental and economical concern Part 16[1]

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PH. EUR. 2002, JAP 1996 and USP 2000 mineralize organically bound iodine in x-ray contrast media by boiling under reflux with zinc powder in alkaline solution. The reductive mineralization can be performed at room temperature without filtration, when aluminium powder is used. Resulting iodide is titrated by argentometry and potentiometric indication according to the pharmacopoeia or after oxidation with 1,3-dibromo-5,5-dimethylhydantoin by iodometry.

1. Introduction

The mineralization using zinc in alkaline [2–6] or acetic acidic [7] solution is beside the Schöniger combustion [8–12] the most frequently applied method of pharmacopoeias for the determination of organically bound iodine. The mineralized iodine is titrated as iodide according to PH. EUR. 2002 by argentometry and potentiometric indication. Silver nitrate solutions are not only expensive, but also require costs for disposal [11, 13]. Therefore, argentometric titrations are obsolete in respect to environmental and economical concern.

Furthermore, the reductive method is time-consuming [2, 3] and less suitable for routine analysis. Another reductive mineralization uses sodium tetrahydridoborate and palladium as catalyst [3, 14]. Due to the application of palladium this mineralization is costly and according to my own investigations also susceptible to failure, when using potentiometric indication.

2. Investigations and results

Aluminium powder is substantially more reactive than zinc and reacts already at room temperature. Considerably lower amounts of metal can be employed in comparison to the application of zinc. As aluminium dissolves with formation of aluminate in alkaline media, the time-consuming filtration of the excess of metal is unnecessary. However, it should be pointed out that only finely dispersed aluminium such as the preparation of the Merck company is suitable. Coarse grained aluminium powder reacts poorly and is unsuitable.

Organically bound bromine of 2-bromobenzoic acid is not quantitatively reduced even with boiling, so that the described method can only be used for iodine compounds corresponding to the application of the zinc reduction. The iodide formed after mineralization can be determined according to PH. EUR. 2002 by titration with silver nitrate and potentiometric indication. Due to ecological and economical reasons the application of silver nitrate solutions is not recommendable. As in many other cases [15, 16] for this determination the application of DBH proves advantageous. After oxidation of iodide formed to iodate, the excess of DBH can be removed by 5-sulphosalicylic acid. Iodine, liberated by addition of potassium iodide is titrated with sodium thiosulphate at an optimal pH value of about 3.0 [17]. The aluminium powder applied contains traces of iron, which yield a violet complex with 5-sulphosalicylic acid. Therefore, the solution has to be discoloured for the visual titration by addition 0.1 M $EDTANa_2$. Furthermore, the visual indication is restricted to few samples, because some deiodized x-ray contrast media yield red coloured oxidation products with DBH. A potentiometric indication is necessary, as the decolorization of the iodine starch titration solution is difficult to recognize.

Systematically too low results are obtained using the reductive mineralization with aluminium as well as with zinc if the reaction conditions are not observed exactly. Prescriptions for sample weights in the range of 4 μequiv. to 0.77 mequiv. of iodine are worked out under the conditions, that the required amount of the oxidizing agent is just sufficient and an optimal pH value of about 3.0 exists [11, 17] (see Table 1).

A sample weight corresponding to about 0.7 μequiv. of iodine and a resulting consumption of about 20 ml of 0.02 M $Na_2S_2O_3$ is recommended for the determination of iodine containing drugs (see Table 2).

Alkaline DBH solutions yield no or only extremely small blank values, which can be neglected. This is in contrast to the application of acetic acidic DBH solutions [11], which liberate small amounts of bromine.

3. Discussion

The method described can be performed substantially faster and easier than the method of the pharmacopoeias. Using DBH, a stable and easy to handle crystalline organobromine compound, the initially existing amount of iodine can be sextupled and thus the weights of the analytical sample can be diminished significantly.

In contrast to the oxygen flask combustion according to Schöniger the reductive mineralization with aluminium powder does not require expensive platinum sample carriers and no oxygen from a pressure cylinder. Nevertheless, the iodine determination according to Schöniger using the optimized method [11, 12] is more suitable for routine analysis. In contrast to the aluminium and zinc reduction the Schöniger oxygen flask combustion is more friendly to environment, because deiodized organic compounds do not arise. Furthermore, the reductive mineralization with zinc as well as with aluminium is restricted to drugs soluble in alkaline medium.

Table 1: Determination of organically bound iodide using reductive mineralization with aluminium powder and iodometric titration after oxidation with 1,3-dibromo-5,5-dimethylhydantoin (0.05 M DBH/0.5 M NaOH) with various sample weights and various conditions (2-iodobenzoic acid 51.2% I, see 4.4.3)

Sample weight (mg)	Equivalents of iodine about	Al (a mg)	DBH (b ml)	SSS		HAc (e ml)	$Na_2S_2O_3$ (f M)	n	Mean (% I)	Bias (%)	R.S.D. (%)
				(c ml)	(d ml)						
0.9–1.2	4.0×10^{-6}	50	5	5	0.2	25	0.02	3	50.8	−0.8	0.34
1.5–2.5	8.0×10^{-6}	50	5	5	0.2	25	0.02	3	51.1	−0.2	1.3
3.9–4.0	1.6×10^{-5}	50	5	5	0.2	25	0.02	3	50.9	−0.6	0.34
5.9–6.3	2.5×10^{-5}	50	5	5	0.2	25	0.02	3	50.8	−0.8	0.52
8.0–8.2	3.3×10^{-5}	50	5	5	0.2	25	0.02	3	51.0	−0.3	0.22
10.2–10.6	4.2×10^{-5}	50	5	5	0.2	25	0.02	3	51.0	−0.5	0.30
12.2–12.8	5.0×10^{-5}	50	5	5	0.2	25	0.02	3	51.1	−0.2	0.19
14.3–14.7	5.8×10^{-5}	50	5	5	0.2	25	0.02	3	50.8	−0.9	0.45
15.7–18.9	7.0×10^{-5}	50	5	5	0.2	25	0.02	30	51.0	−0.3	0.36
20.0–20.7	8.2×10^{-5}	50	5	5	0.2	25	0.02	3	50.7	−1.0	0.30
22.1–22.8	9.0×10^{-5}	50	10	10	0.2	25	0.02	6	51.0	−0.5	0.11
24.6–24.9	1.0×10^{-4}	50	10	10	0.2	25	0.02	3	51.0	−0.4	0.00
50.0–54.3	2.0×10^{-4}	50	10	10	0.2	25	0.02	3	50.1	−0.2	0.20
100–101	4.0×10^{-4}	50	10	10	0.2	25	0.02	3	50.6	−1.2	0.19
185–193	7.5×10^{-4}	100	50	10	0.5	50	0.1	5	50.8	−0.8	0.35

4. Experimental

4.1. Instrumentation

Metrohm DMS-Titrino 716, silver-silver chloride electrode Metrohm 6.0404.100 (PA), parameters: meas. pt. density 4; min. incr. 10.0 µl; titr. rate 5 ml/min; signal drift 50 mV/min; equilibr. time 26 s; temperature 25 °C; evaluation: EPC 75; EP recognition: all.

4.2. Chemicals and drugs

Acetic acid [64-19-7], min. 99.8% p.a., Riedel-de Haën art. 33209 = HAc; adipiodone, iodipamide [606-17-7], USP 2000, Schering; aluminium, finely powdered, Merck, Art. 101056 (coarse grained aluminium powder reacts poorly and is unemployable); amidotrizoic acid-dihydrate [50978-11-5] PH. EUR. 2002, USP 2000, Schering; 1,3-dibromo-5,5-dimethylhydantoin = 1,3-dibromo-5,5-dimethyl-2,4-imidazolidinedione [77-48-5], for synthesis Merck art. 803600 = DBH (for analytical purpose qualified); disodium edetate dihydrate, ethylendiaminetetraacetic acid disodium salt dihydrate, EDTA Na_2, [6381-92-6], Titriplex® III, DAB, Ph.Eur., Merck Art. 108421; hydrochloric acid [7647-01-0], fuming, 37%, extra pure Merck, art. 100314; 8-hydroxy-7-iodoquinoline-5-sulfonic acid [547-91-1] Bayer; idoxuridine [54-42-2] PH. EUR. 2002, USP 2000, Winzer; iocetamic acid [16034-77-8] USP 1995, Mundipharma; 2-iodobenzoic acid [88-67-5], Riedel-de Haën, Art. 62705, 1 × vacuum sublimation; ioglicic acid [49755-67-1] Schering; ioglycamic acid [2618-25-9] Schering; iohexol [66108-95-0], PH. EUR. 2002, USP 2000, Schering; iopanoic acid [96-83-3] PH. EUR. 2002, USP 2000, Winthrop; iopodate calcium [1151-11-7] USP 1995, Schering; iopodate sodium [2221-56-3] USP 2000, Schering; iothalamic acid [2276-90-6] PH. EUR. 2002, USP 2000, Mallinckrodt, iotrolan [79770-24-4] Schering; iotroxic acid [51022-74-3] Schering; ioxaglic acid [59017-64-0] Mallinckrodt; potassium iodate [7758-05-6] p.a., volumetric standard, Merck art. 5053; potassium iodide ≥99,5% p.a., Roth Art. 6750; sodium acetate anhydrous [127-09-3] p.a., Merck art. 106268 = NaAc; sodium chloride, [7647-14-5], p.a., volumetric standard, Merck art. 6405; sodium hydroxide, Rotipuran 99% [1310-73-2], Roth, art. 9356; sodium thiosulfate pentahydrate >98.5%, Roth art. 8649; sulphuric acid, 95–97% p.a., Riedel-de Haën art. 30743; starch soluble extra pure Erg. B. 6, Merck, art. 1253; 5-sulphosalicylic acid dihydrate [5965-83-3], extra pure, Merck, art. 689 = SSS; zinc, powder, particle seize <63 µm, Merck, art. 108774

Table 2: Determination of iodine containing drugs by reductive mineralization with aluminium powder

Substance	Sample weight (mg)	n	Mean (% I, %)		Bias (%)	R.S.D. (%)	Deviation of prescription 4.3.3.
			calc.:	found:			
Adipiodone, Iodipamide USP 2000, $C_{20}H_{14}I_6N_2O_6$	13.40–16.37	7	66.81	66.02	−1.18	0.60	10 ml of DBH
Amidotrizoic acid-dihydrate PH. EUR. 2002, USP 2000, $C_{11}H_9I_3N_2O_4 \times 2\ H_2O$	14.99–17.94	9	58.58	58.52	−0.10	0.29	10 ml of DBH
8-Hydroxy-7-iodoquinoline-5-sulfonic acid, $C_9H_6INO_4S$	23.85–25.91	12	36.14	35.94	−0.56	0.39	10 ml of DBH
Idoxuridine PH. EUR. 2002, USP 2000, $C_9H_{11}IN_2O_5$	24.08–25.59	8	35.84	35.74	−0.27	0.15	
Iocetamic acid, USP 1995 $C_{12}H_{13}I_3N_2O_3$	14.10–14.85	11	62.01	61.57	−0.71	0.19	
Ioglicic acid, $C_{13}H_{12}I_3N_3O_5$	15.46–16.73	7	56.74	56.19	−0.97	0.32	10 ml of DBH
Ioglycamic acid, $C_{18}H_{10}I_6N_2O_7$	13.00–13.52	6	67.52	67.32	−0.30	0.12	10 ml of DBH
Iohexol, PH. EUR. 2002, USP 2000, $C_{19}H_{26}I_3N_3O_9$	46.25–46.52	6	46.36	46.39	0.05	0.23	10 ml of DBH
Iopanoic acid, PH. EUR. 2002, USP 2000, $C_{11}H_{12}I_3NO_2$	7.46–9.19	5	66.68	66.47	−0.32	0.23	100 mg of Al, 1 h, 20 ml of 0.5 M NaOH, 0.05 M $Na_2S_2O_3$, no $EDTANa_2$ potentiometric indication
Iopodate calcium, USP 1995, $C_{24}H_{24}CaI_6N_4O_4$	14.13–15.71	8	61.70	61.61	−0.15	0.22	
Iopodate sodium, USP 2000, $C_{12}H_{12}I_3N_2NaO_2$	14.38–15.00	7	61.41	61.16	−0.41	0.16	
Iothalamic acid PH. EUR. 2002, USP 2000, $C_{11}H_9I_3N_2O_4$	13.57–16.54	12	62.01	61.99	−0.01	0.28	
Iotrolan, $C_{37}H_{48}I_6N_6O_{18}$	18.81–19.78	7	46.82	46.71	−0.23	0.20	10 ml of DBH
Iotroxic acid, $C_{22}H_{18}I_6N_2O_9$	14.30–14.90	8	62.63	61.65	−1.57	0.29	
Ioxaglic acid, $C_{24}H_{21}I_6N_5O_8$	14.41–15.41	8	60.01	59.67	−0.57	0.15	

(see 4.4.3; sample weights correspond to 70 µequivalents of iodine; the results obtained refer to the given formula, the water content is determined by Karl-Fischer-titration)

4.3. Solutions

0.05 M DBH/0.5 M NaOH: 1.43 g (5 mmol) of DBH are dissolved with stirring in 0.5 M NaOH to 100.0 ml; 1/60 M KIO_3: 3.567 g of potassium iodate p.a., volumetric standard, are diluted to 1000.0 ml; 0.25 M NaAc/ 10 M HAc, pH-buffer about 3.0: 20.5 g of anhydrous sodium acetate are dissolved in 570 ml acetic acid and water to 1000.0 ml; 0.1 M $Na_2S_2O_3$ is prepared according to PH. EUR. 2002 and standardized with 20.00 ml of 1/60 M KIO_3, 10.0 ml of 0.25 M NaAc/10 M HAc, 5.0 ml of 1 M KI and 0.5 ml of starch solution, iodide-free, PH. EUR. 2002; 0.02 M $Na_2S_2O_3$ is prepared by dilution of 0.1 M and standardized with 20.00 ml of 1/300 M KIO_3, 10.0 ml of 0.25 M NaAc/10 M HAc, 5.0 ml of 0.2 M KI and 0.5 ml of starch solution, iodide-free, PH. EUR. 2002; 0.1 M-$AgNO_3$ was standardized with sodium chloride p.a., volumetric standard; starch solution, iodide-free PH. EUR. 2002, without HgI_2, is stable at a temperature of about 4 °C for about six weeks. It is necessary to avoid a temperature below 0 °C; 0.2 M-SSS: 50.8 g (0.2 mol) of 5-sulphosalicylic acid dihydrate are dissolved with H_2O to 1000.0 ml. 2 M SSS: 5.08 g (0.02 mol) of 5-sulphosalicylic acid are dissolved in water to 100 ml; 0.5 M SSS is prepared analogously.

4.4. Assays

4.4.1. Reductive mineralization using aluminium powder and argentometric titration and potentiometric indication

Weigh 0.7 to 0.8 mequiv. iodine containing organoiodine compound into a 100 ml iodine flask. Dissolve the sample with 20 ml of 1 M NaOH. Wet the grindings of the stopper and the flask in order to avoid a loss of hydrogen iodide and rinse the sample at the walls of the flask into the reaction solution with a part of the sodium hydroxide solution. Then reduce with 100 mg of aluminium powder and magnetic stirring during about 30 min until the metal has completely reacted. Rinse the grindings of the stopper and the flask with 25 ml of H_2O. Acidify with 25 ml of 1 M H_2SO_4. Perform the titration using 0.1 M $AgNO_3$ and potentiometric indication.
2-Iodobenzoic acid, weight: 183–192 mg (0.75 mequiv. I), calc.: 51.2% I, n = 18; found: $\bar{x} = 51.0\%$ I; bias = −0.41%; RSD = 0.38%.
Iotalamiic acid, weight: 148–153 mg (0.75· mequiv. I), calc.: 62.0% I, n = 6; found: $\bar{x} = 62.3\%$ I; bias = 0.51%; RSD = 0.23%.

4.4.2. Reductive mineralization using zinc powder and argentometric titration and potentiometric indication according to PH. EUR. 2002

The prescription of PH. EUR. 2002 is exactly observed. The weight of the sample to be analyzed is chosen in a way that the iodine content corresponds to 0.7 till 0.8 mequiv. Filtrate and wash the remaining zinc precipitate six times with 5 ml of H_2O.
2-Iodobenzoic acid, weight: 183–192 mg (0.75 mequiv. I), calc..: 51.2% I, n = 7; found: $\bar{x} = 51.5\%$ I; bias = 0.50%; RSD = 0.42%.

4.4.3. Reductive mineralization using aluminium powder and iodometric titration after oxidation with 1,3-dibromo-5,5-dimethylhydantoin (DBH) and various sample weights

Weigh the amount of the organoiodine compound, according to Table 1, into a 200 ml iodine flask. Dissolve the sample to be analyzed with 20 ml of 1 M NaOH. Wet the grindings of the stopper and the flask in order to avoid a loss of hydrogen iodide and rinse the sample at the walls of the flask into the reaction solution with a part of the sodium hydroxide solution. Then reduce with **a** mg of aluminium powder and magnetic stirring during about 30 min until the metal has completely reacted. Wash the grindings of the stopper and the flask with 20 ml of H_2O in portions and add **b** ml of 0.05 M DBH/0.5 M NaOH. After 5 min, pipette **c** ml of **d** M SSS. Wait further 5 min with stirring. Acidify with **e** ml of glacial acetic acid to reach a pH value of about 3.0. Add 5 ml of 0.2 M KI and 0.2 ml of 0.1 M $EDTANa_2$ to discolour the 5-sulphosalicylic acid complex with iron, which exists in the aluminium powder. Titrate using **f** M $Na_2S_2O_3$/ starch solution. A blank value can be neglected. The iron contained in the aluminium powder does not disturb.
For the determination of iodine containing drugs the prescription with a sample weight of about 70 μeqivalents iodine is recommended (see Table 2).

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[1] Part 15: [1]

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