Neutron Activation Analysis of Halogens in Drugs

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Abstract □ A rapid, efficient, and highly specific method is presented for the determination of total chlorine, bromine, or iodine in various drugs. The halogen content is determined by nondestructive neutron activation and may be used for the presumptive assay of halogen-containing drugs in various dosage forms. The relative freedom from laboratory contamination, the independence from matrix effect, and the rapidity and specificity of analysis make this technique well suited for the determination of major elements in such complex substances as drugs. The method involves subjecting samples to thermal neutron bombardment and correlating the measured activity from the induced radionuclides of samples with that of standards. The radionuclides of interest in this study are ^{38}Cl, ^{80}Br, ^{82}Br, and ^{128}I, which are produced by a neutron reaction (n,γ) in a nuclear research reactor.

Keyphrases □ Neutron activation analysis—halogens in drugs □ Radionuclides, halogen—neutron activation analysis, drugs □ Halogens—neutron activation analysis, drugs

Organic pharmaceutical products containing halogens are frequently assayed by decomposition with an alkali or Schöniger oxygen-flask combustion and subsequent titration of the ionic halide species (1–3). This technique is destructive, tends to be slow and tedious, and is unsuitable for substances combined in intractable oleaginous formulations, particularly when present in microquantities, or for substances containing large amounts and varieties of active and inactive components.

Neutron activation analysis (NAA) is considered most useful for trace analysis because of its unique combination of high sensitivity and specificity and its freedom from contamination by laboratory reagents. To attain high sensitivity, however, radiochemical separation techniques are often required. The chief advantage of NAA for major elemental constituents in pharmaceutical chemicals is its nondestructive nature; *i.e.*, it does not require any physicochemical preparative steps. Consequently, it is rapid, simple, and much less prone to losses; nevertheless, it retains a high degree of specificity, primarily because the technique is normally unaffected by the complex organic matrix of many pharmaceutical products. Thus, NAA is most useful when the preservation of the chemical integrity of the sample is of particular concern, *e.g.*, in forensic or regulatory cases.

Basically, the method involves irradiating a particular product with thermal neutrons and recording and measuring the resulting induced radioactivity with a γ-ray spectrometer. Since the nuclear parameters of each element are highly specific and well known, the reaction with thermal neutrons is predictable (4). The qualitative and quantitative analyses of that element in the product are then derived from the emitted γ-rays obtained as a spectrum.

Table I summarizes the nuclear properties of the halogen elements of interest in this study. The bombardment of these elements with thermal neutrons results in a reaction (n,γ), which is favored by a relatively high cross-section-producing radionuclides (5).

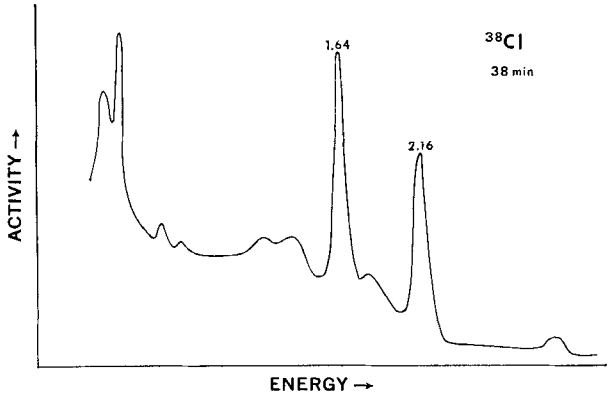

Figure 1—*Typical γ-ray spectrum of ^{38}Cl.*

This study shows that NAA can be used to determine the chlorine, bromine, or iodine content of several pharmaceutical chemicals and that it is useful as a presumptive assay method for various dosage forms.

EXPERIMENTAL

Irradiation Containers—Solid or liquid samples and standards were placed in separate 1-ml. snap-cap polyethylene vials which were then sealed into individual polyethylene bags. The vials had been previously analyzed in this laboratory for their halogen content and were found to contain less than microgram amounts of halogens; these amounts are insignificant compared to the level being determined.

Standards—Standard chlorine, bromine, and iodine solutions were prepared by dissolving accurately weighed samples of reagent grade ammonium chloride, sodium bromide, and potassium iodide in distilled water. Aliquots of each were transferred to the vials. Prior to assay, the concentrations of halide in the samples and standards were ascertained to be at about the same level.

Samples—Milligram quantities of bulk compounds (accurately weighed), 1 ml. of liquid samples or dilutions of them, 1 g. or less of ointments or oils, and tablets or capsules were packaged in the vials and analyzed without further treatment. The bulk chemicals used were readily available from commercial sources (USP grades) and were analyzed as received without drying or any other treatment.

Apparatus—A 1-Mw. nuclear research reactor[1] (swimming pool type) provided the neutrons for sample irradiations. An exposure tube flux of about 10^{13} n/cm.^{2}/sec. was used for samples containing less than about 1 mg. of halogen, and a pneumatic tube (rabbit) flux of about 10^{12} n/cm.^{2}/sec. was used for samples containing more than about 1 mg. of halogen. γ-Ray spectra were obtained with the apparatus previously described (6).

Procedure—Samples were packed individually with a standard into a rabbit and fired to the terminus of the reactor's pneumatic tube facility. When using the exposure tube, three samples and a standard were loaded into an irradiation bucket and lowered into the irradiation position. Irradiation times, ranging from 10 to 120

[1] At the Naval Research Laboratory, Washington, D. C.

Table I—Pertinent Nuclear Properties of Halogens for Activation with Thermal Neutrons

Stable Nuclide	Abundance, %	Cross-Section, barns	Radionuclide Formed	Half-Life, $t_{1/2}$	Major γ-Rays, Mev.
^{35}Cl	75.4	0.005	^{36}Cl	3×10^5 years	—
^{37}Cl	24.6	0.56	^{38}Cl	37.3 min.	1.64, 2.16
^{79}Br	50.5	8.5	^{80}Br	17.6 min.	0.511, 0.618
^{81}Br	49.5	3.1	^{82}Br	35.6 hr.	0.55, 0.78, 1.04, 1.32
^{127}I	100	6.4	^{128}I	25 min.	0.445, 0.525

Table II—Determination of Chlorine in Various Drugs

Sample	Chlorine Found by NAA Method — Percent Actual	Chlorine Found by NAA Method — Percent of Theory	Percent of Drug by Official Method
Chloramphenicol	21.85	99.7	99.3
Chloramphenicol palmitate	13.25	104.9	102.0
Chloramphenicol sodium succinate	15.28	95.9	98.0
Chlortetracycline bisulfate	6.117	99.3	100.5
Demethylchlortetracycline base	7.705	100.9	101.3
Griseofulvin	9.98	99.3	98.4
Sodium cloxacillin monohydrate	6.84	91.9[a]	95.4
Sodium dicloxacillin monohydrate	13.97	100.6	99.1[c]
Chlorobutanol (hydrous)	56.3	93.9[b]	—
Chlorothen citrate	7.23	99.4	—
Carbinoxamine maleate	8.80	101	—
Chlorpheniramine maleate	9.03	99.5	—
Aluminum chlorhydroxyallantoinate	11.4	101	—
Chloranil	56.8	98.2	—

[a] Uncorrected for interference of ^{24}Na (see text). [b] Uncorrected for water content (6% maximum). [c] Based on Schöniger flask combustion method.

sec., were varied to control the total radioactivity produced in the sample.

Samples and accompanying standards were then counted at specific decay times at a suitable distance from the detector to prevent any changes of the pulse height analyzer (PHA) calibration due to activity levels. The photopeak was analyzed by the method of Covell (7). This procedure yielded a practical activity measurement, including the statistical variation associated with radioactive decay.

RESULTS

The γ-ray spectrum of ^{38}Cl shown in Fig. 1 exhibits two major peaks. The peak at 2.16 Mev., generally freer from interferences, was used in this analysis. The chlorine content of several commercial grade pharmaceutical chemicals and the assays of several chlorine-containing drugs in dosage forms, as determined by NAA, are shown in Tables II and III. A large spectral interference from ^{24}Na was observed in sodium cloxacillin monohydrate; this may account for the difference listed in Table II. Other substances containing a lower sodium content relative to chlorine, such as chloramphenicol sodium succinate or sodium dicloxacillin monohydrate, did not exhibit this interference to any noticeable extent.

The neutron activation method was especially useful when applied to veterinary drug formulations used to treat mastitis (6). These products contain varying mixtures of antibiotics, steroids, and sulfonamides in oils and often incorporate a variety of additives such as chlorobutanol as a preservative. However, no convenient analytical method is available for determining the chlorine-containing component in these formulations. In the absence of other chlorine-containing substances, nondestructive NAA was shown to be well suited for control or regulatory purposes. NAA of over two dozen such products from different manufacturers gave results averaging better than 95%, with a coefficient of variation of less than 6%. Although results for chlorine content of these samples could not be confirmed by another method, these results may be considered presumptive substantiation that the method works well with this type of product.

Results shown in Table III for various dosage forms of chloramphenicol, griseofulvin, sodium dicloxacillin, aluminum chlorhydroxide, oxytetracycline hydrochloride, and other oil suspensions generally indicate good correlation between chlorine content as determined by NAA and drug content as found by official methods (8). Because individual capsules or tablets from a given lot were tested by NAA whereas other pooled samples were tested by the official method, some disparity is likely. In some cases, NAA yielded higher values than the official methods. These values are attributable to extraneous sources of chlorine such as colorants or inks used in printing identifying markings.

Two lots of griseofulvin and one of chloramphenicol, which yielded more erratic results, were subjected to closer scrutiny (Table IV). A sampling of each was irradiated repetitively eight

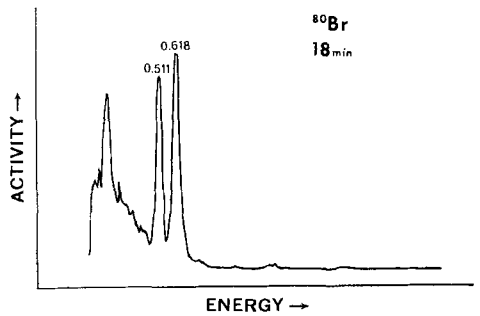

Figure 2—*Typical γ-ray spectrum of ^{80}Br.*

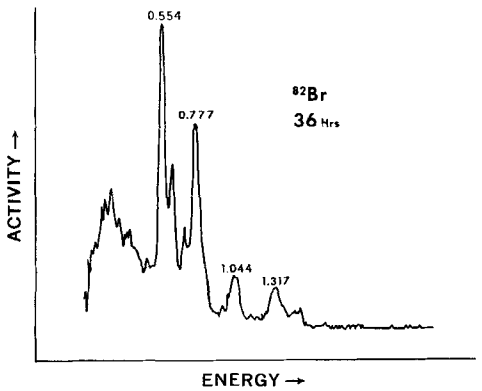

Figure 3—*Typical γ-ray spectrum of ^{82}Br.*

Table III—Determination of Chlorine for Assay in Various Drugs in Dosage Forms

Sample	Type	Chlorine Found by NAA[a] — Milligram Drug	Chlorine Found by NAA[a] — Percent Label Claim	Chlorine Found, Percent Label Claim by Official Method
Chloramphenicol	Soft gelatin capsule	280/capsule	112	98.8[b]
Chloramphenicol	Ointment	10.1/g.	101	97.2[b]
Chloramphenicol	Capsule, Lot 1	257/capsule	102.7	102.8[c]
Chloramphenicol	Capsule, Lot 2	260/capsule	104	105.6[c]
Chloramphenicol	Otic solution, Lot 1	5.79/ml.	116	118[b]
Chloramphenicol	Otic solution, Lot 2	6.28/ml.	126	121[b]
Chloramphenicol palmitate	Suspension	31.4/ml.	100	105.3[b]
Chloramphenicol sodium succinate	Injection	77.0/ml.	106	104.3[c]
Griseofulvin	Capsule, Lot 1	136/capsule	108.8	106.8[c]
Griseofulvin	Capsule, Lot 2	263/capsule	105	100.5[c]
Griseofulvin	Tablet, Lot 1	261/tablet	104	100.6[c]
Griseofulvin	Tablet, Lot 2	500/tablet	99.9	102[c]
Dicloxacillin sodium	Capsule, Lot 1	117/capsule	93.4	100.8[d]
Dicloxacillin sodium	Capsule, Lot 2	125/capsule	99.8	96.0–101.1
Dicloxacillin sodium	Capsule, Lot 3	241/capsule	96.2	98.4[d]
Aluminum chlorhydroxide	Solution, Lot 1	3.52[e]	110	—
Aluminum chlorhydroxide	Solution, Lot 2	3.63[e]	113	—
Aluminum chlorhydroxide	Solution, Lot 3	3.32[e]	109	—
Oxytetracycline hydrochloride	Otic ointment, Lot 1	0.618	107	—
Oxytetracycline hydrochloride	Otic ointment, Lot 2	0.604	104	—
Chlorobutanol	Oil suspension, Lot 1	1.87%	99.5	—
Chlorobutanol	Oil suspension, Lot 2	4.92%	98.4	—
Chlorobutanol	Oil suspension, Lot 3	5.54%	98.8	—

[a] Calculated from theoretical chlorine content of the drug; based on label claim. [b] By microbiological assay. [c] By UV spectrophotometry. [d] By iodometric assay. [e] Calculated as percent chlorine.

times on different days with an accompanying standard. The results of this study show a coefficient of variation of less than 6%.

The γ-ray spectrum of the 17.6-min. ^{80}Br nuclide (Fig. 2) shows the two major photopeaks used for analysis. Results obtained from bromine-containing drugs based on this nuclide are shown in Table V. Figure 3 shows the γ-ray spectrum of the 35.6-hr. ^{82}Br, and results based on this nuclide are listed in Table VI. Analyses based on the two different radionuclides were used mainly for verification. The longer-lived nuclide appeared to yield more precise data, probably due to less background interference from a longer decay time as well as the use of longer counting times to improve statistics.

Although the analyses of these bromine-containing drugs were not confirmed by other methods, the results obtained from NAA are believed to be reliable. The high values obtained for brompheniramine maleate based on both radionuclides and for homatropine methylbromide based on ^{82}Br indicate the probable presence of bromine-containing impurities or degradation products.

The γ-ray spectrum of ^{128}I (Fig. 4) shows the intense γ-ray photopeak at 0.44 Mev. used to analyze iodine-containing samples. Tables VII and VIII show results of analyses made at the milligram and microgram levels of iodine, respectively. The iodine content of several of these samples was also determined by the Schöniger flask combustion technique, but the results appeared to be generally lower than those obtained from NAA. The high results obtained by both methods with one batch of iodochlorhydroxyquin can be

Table IV—Study of Precision of Method for Chlorine[a]

	Chlorine Found, mg. — Griseofulvin Tablets, 500 mg.	Griseofulvin Capsule, 125 mg.	Chloramphenicol Soft Capsule, 250 mg.
	49.92	14.14	59.89
	52.39	13.55	57.99
	48.07	13.46	64.69
	52.50	13.40	56.67
	50.43	14.08	66.09
	48.74	14.57	60.97
	48.13	12.92	62.30
	51.45	13.20	64.75
Average	50.20	13.67	61.67
Calculated chlorine content from label claim, mg.	50.25	12.56	54.86
Percent label claim based on chlorine found	99.9	108.8	112.4
SD	1.80	0.549	3.40
Coefficient of variation, %	3.59	4.02	5.51
95% confidence limit	±3.00%	±3.36%	±4.60%

[a] One sample of each was irradiated eight different times on different days and compared each time with a standard ammonium chloride solution irradiated at the same time.

Table V—Determination of Bromine in Various Drugs Based on ^{80}Br

Sample	Type	Bromine Found, Percent of Label Claim or Theory		
		Percent of Theory	at 0.51 kev.	at 0.63 kev.
Homatropine methylbromide	Bulk	21.58	104.9	111.9
Brompheniramine maleate	Bulk	18.36	119.1	117.9
Hydroxyamphetamine hydrobromide	Bulk	34.42	100.5	97.8
Brompheniramine maleate	Tablet	—	103.6	100.2
Hydroxyamphetamine hydrobromide	Spray	—	101.0	102.4

ascribed to degradation, since the material was noticeably discolored.

Because of the relatively high content of iodine in bulk chemicals and in macrodosage forms, these samples were irradiated in the pneumatic system. Each exposure was comprised of groups of two sets placed on top of each other in the rabbit, each set consisting of one sample and one standard. Since each set was in a different location in the rabbit and thus at a different distance from the neutron source, it was exposed to a different flux, as noted by an activity differential of about 25% (Table IX). However, replications of these irradiations on 12 separate aliquots resulted in a coefficient of variation of less than 3%, due mostly to the short time of irradiation. This reproducibility allows for a reliable correction factor for flux variation, if necessary.

DISCUSSION

Three of the generated radionuclides of halogens have characteristic half-lives of less than 1 hr. Significantly, this situation allows several analyses to be performed within that time interval. In the case of bromine, the existence of another longer-lived radionuclide permits qualitative and quantitative corroboration on the same sample after complete decay of the shorter-lived radionuclide. Although the assay is not as rapid, the usefulness of NAA can thus be extended to include pharmaceuticals containing major amounts of other elements that would normally dominate and, hence, interfere with the accumulated γ-ray spectrum immediately after neutron exposure.

Selection of Test Conditions—The choice of irradiation position, duration, cooling-wait time, and counting geometry was manipulated to maintain a sufficiently low dead-time, generally less than 20%. Securing a low dead-time is necessary for obtaining reliable counts. A lower dead-time allows the gain of the analyzer to remain constant and the γ-ray photopeaks to remain undistorted. The shorter-lived nuclides of ^{38}Cl, ^{80}Br, and ^{128}I were counted for 1 or 2 live min. at a distance of 10–15 cm. from the detector, whereas the ^{82}Br samples were counted for 40 min. in the well detector to gain maximum sensitivity from the detector.

Quantitative analysis based on induced radionuclides of relatively short half-lives requires an adjustment of the activity measurement. A decay factor, calculated according to the standard radioactive decay law, was therefore used to correct all measurements to the same time equivalent, usually the end of neutron exposure.

Table VI—Determination of Bromine in Various Drugs Based on ^{82}Br

Sample	Type	Bromine Content, Theory or Label Claim	Bromine Found, Percent of Theory or Label Claim	
			at 1.04 Mev.	at 0.77 Mev.
Acetyl carbromal	Bulk	28.63%	94.9	95.8
Anisotropine methylbromide	Bulk	22.05%	98.4	98.3
Bromindione	Bulk	26.53%	101.5	104.7
Dexbrompheniramine	Bulk	18.36%	96.1	97.9
Dextromethorphan hydrobromide	Bulk	21.58%	103.7	103.2
Homatropine methylbromide	Bulk	21.58%	113.2	113.6
Merbromine	Bulk	19.86%	97.6	99.8
Pipobroman	Bulk	44.88%	92.1	94.2
Scopolamine hydrobromide	Bulk	20.79%	96.5	97.6
Tetrabromophenolphthalein ethyl ester	Bulk	45.7%	104.7	103.7
5-Bromosalicylamide	Bulk	27.35%	107.5	106.2
4,5-Dibromosalicylamide	Bulk	43.07%	102.1	101.7
Tribromsalan	Bulk	53.28%	91.6	91.9
Tetrabromosalicylamide	Bulk	60.44%	91.7	92.6
Bromisovalum	Bulk	35.82%	97.2	98.1
Brompheniramine maleate	Bulk	18.36%	114.9	110.4
Homatropine methylbromide	Tablet	5.825 mg./5 tablets	95.2	97.9
Homatropine methylbromide	Pediatric solution	0.281 mg./ml.	97.7	94.6
Dextromethorphan hydrobromide	Syrup	0.647 mg./ml.	95.8	91.7
Sulfobromophthalein sodium	Injection	19.1 mg./ml.	104.8	101.0
Homatropine methylbromide	Capsule	0.279 mg./capsule	109.8	105.4
Pipenzolate bromide	Tablet	0.923 mg./tablet	95.5	95.5
Hydroxyamphetamine hydrobromide	Spray	1.721 mg./ml.	102.6	102.7
Hydroxyamphetamine hydrobromide	Solution	3.442 mg./ml.	96.6	101.8

Table VII—Determination of Iodine in Various Drugs

Sample	Type	Iodine Content, Theory or Label Claim	Iodine Found: Percent of Theory or Label Claim	Iodine Found: Percent by Chemical Method
Bismuth oxyiodide	Bulk	36.06%	102.5	—
Erythrosine (FD&C Red No. 3)	Bulk	57.70%	95.5[a]	—
Idoxuridine	Bulk	35.84%	97.5	—
Iodohydroxyquin, Lot 1	Bulk	41.54%	123.8[b]	113[c]
Iodohydroxyquin, Lot 2	Bulk	41.54%	99.9[d]	92[c]
2-Iodobenzoic acid	Bulk	51.17%	102.3	—
Potassium iodide	Bulk	76.45%	99.5	—
Sodium dextrothyroxine	Bulk	63.54%	92.7[e]	—
Sodium diatrizoate	Bulk	59.87%	101.0	—
Sodium iothalamate	Bulk	59.87%	95.5	—
Sodium methiodal	Bulk	52.04%	95.0	—
Meglumine diatrizoate, Lot 1	Injection	15.0%	101.5	98.1[f]
Meglumine diatrizoate, Lot 2	Injection	15.0%	99.7	99.9[f]
Meglumine diatrizoate, Lot 3	Injection	15.0%	99.0	99.9[f]
Meglumine diatrizoate, Lot 4	Injection	15.0%	98.5	97.4[f]
Meglumine diatrizoate, Lot 5	Injection	37.0%	99.9	—
Meglumine diatrizoate, Lot 6	Injection	40.0%	100.1	—
Meglumine iodipamide	Injection	26.0%	100.2	—
Iodochlorhydroxyquin, Lot 1	Ointment	12.5 mg./g.	98.8	101[f]
Iodochlorhydroxyquin, Lot 2	Ointment	12.5 mg./g.	94.5	—
Iodochlorhydroxyquin, Lot 3	Ointment	12.5 mg./g.	96.9	—
Iodochlorhydroxyquin, Lot 1	Lotion	12.5 mg./ml.	104.6	103[f]
Iodochlorhydroxyquin, Lot 2	Lotion	12.5 mg./ml.	103.8	—
Iodochlorhydroxyquin, Lot 3	Lotion	12.5 mg./ml.	103.6	—
Penicillin G diethylaminoethyl hydroiodide, Lot 1	Injection	34.0 mg./ml.	98.9	—
Penicillin G diethylaminoethyl hydroiodide, Lot 2	Injection	34.0 mg./ml.	94.3	—
Sodium iodide	Injection	84.66 mg./ml.	97.5	—

[a] Corrected. These samples normally contain 7% volatiles, 90% tetraiodo, 5% triiodo, and 0–1% diiodo analogs, and about 2% NaCl. [b] Sample was discolored. [c] By Schöniger flask combustion and UV absorption; single assays. [d] Different source, fresh sample. [e] As is, or 98.8% on dried basis. [f] Results submitted by manufacturer.

Factors affecting activity such as variability in the neutron flux are minimized by treating the sample and standard identically so that activity and halogen content are directly related.

Elimination of Interferences—In cases where the half-life of the radionuclide is relatively long, correction due to radioactive decay becomes negligible and may be omitted. Thus, no such correction was used when quantitating bromine based on ^{82}Br. The sample was allowed to decay for about a week to minimize the effect of such radionuclides as ^{24}Na.

Additive interferences from accompanying transmutation reactions with epithermal and fast neutrons, producing ^{38}Cl from Ar, K, or S, or ^{80}Br and/or ^{82}Br from Kr, Rb, U, or Se, or ^{128}I from Xe, are negligible. The quantity of these elements, if present in these products, is very limited. The probability of the reactions is extremely small because of the relative abundance of these elements, the minute cross-section of these reactions, and the short irradiation times.

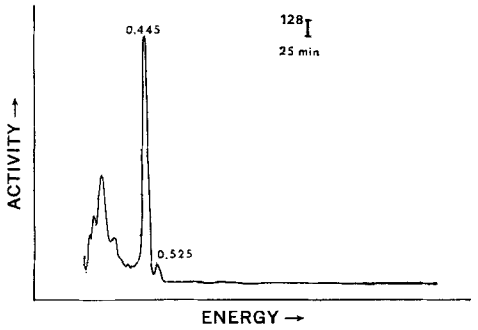

Figure 4—*Typical γ-ray spectrum of ^{128}I.*

Spectral interferences attributed to extraneous radionuclides may be minimized by several techniques. One method employs a lithium-drifted germanium [Ge(Li)] detector; another allows the interfering radionuclides of shorter half-lives to decay first. The use of a Ge(Li) detector is desirable because of its highly discriminate resolution. However, its inherent lower efficiency, roughly 5% relative to sodium iodide, can be a major drawback. Interfering radionuclides having a relatively shorter lifetime than the one of interest are allowed to decay to a negligible level before taking the activity measurements. The use of a differential count, *i.e.*, the difference in the γ-ray spectra for two time intervals, is used to determine the effect of spectral and background interferences. This technique proves particularly useful for lower concentration levels. These techniques of quantitation are performed to ensure the sensitivity and specificity of the NAA method.

Precision—Precision involved in nondestructive NAA is largely determined by weighing the samples and standards and by the net count. Since relatively large sample sizes were used in these studies, the net count had the greatest effect on precision. The irradiation and measurement of activity were controlled to obtain a net average count of better than 50,000 and a standard deviation of better

Table VIII—Determination of Iodine in Thyroid Compounds[a]

Sample	Iodine Content, Theory or Label Claim	Iodine Found	Percent of Theory or Label Claim
T4 (from TLC)	65.34%	67.1%	102.7
T3 standard solution 1	58.48%	73.94%	126.4
T4 standard solution 1	65.35%	69.26%	106.0
T3 (from TLC)	58.48%	57.19%	97.8
T3 standard solution 2	58.48%	61.88%	105.8
T4 standard solution 2	65.34%	67.50%	103.3
Thyroid tablet, 1 gr.	130 mcg./tablet	161.3 mcg./tablet	124
Sodium L-thyroxine, 0.1 mg.	57.1 mcg./tablet	64.2 mcg./tablet	112
Sodium D-thyroxine, 2 mg.	1271 mcg./tablet	1204 mcg./tablet	94.7
Sodium D-thyroxine, 4 mg.	2542 mcg./tablet	2134 mcg./tablet	83.9
Thyroid powder, Lot 1	0.529%	0.597%	113
Thyroid powder, Lot 2	0.0672%	0.0704%	105
Thyroid powder, Lot 3	0.20%	0.225%	113
Thyroid powder, Lot 4	0.225%	0.242%	108
Thyroid powder, Lot 5	0.35%	0.445%	127
Thyroid powder, Lot 6	0.38%	0.418%	110
Thyroid powder, Lot 7	0.49%	0.433%	90.4
Thyroid powder, Lot 8	0.84%	0.785%	93.5
Thyroid powder, Lot 9	0.85%	0.924%	109

[a] Values on thyroid powder all obtained by Schöniger flask combustion and UV absorption.

than 1%. The lowest count obtained was about 2000, which gave a standard deviation of about 5%. Systematic errors associated with other variables are minimized by treating samples and standards together during irradiation and counting them identically with respect to geometry. Uncontrollable variations may arise from nonhomogeneity of samples, particularly solids.

NAA measures the elemental content regardless of the physicochemical state of the sample. It does not necessarily relate the element to the compound nor to the biological activity of the drug, which is of paramount concern. The technique offers the advantages of increased elemental specificity, rapidity, nondestructiveness, and simplicity. Thus, with the ever increasing accessibility of neutron sources and computer interfacing to perform calculations, NAA can readily be employed as a reliable assay method for bulk pharmaceutical chemicals and as a rapid screening method in the presumptive assay of a multitude of drugs.

Table IX—Study of Precision in Iodine Measurement[a]

Standard	Rabbit Top, A_0	Standard	Rabbit Bottom, A_0
1	110,128	2	143,769
3	110,783	4	143,952
5	115,885	6	149,846
7	112,248	8	148,736
9	113,943	10	145,808
11	116,282	12	151,169
13	118,157	14	150,320
15	115,927	16	145,145
17	110,259	18	144,545
19	113,838	20	142,246
21	108,441	22	143,869
23	115,404	24	149,248
Average	113,441		146,554
SD	3,035		3,093
Coefficient of variation, %	2.67		2.11
95% Confidence limit	1.70%		1.34%

[a] Twelve different irradiations of two standard solutions (24 different aliquots) in each rabbit, showing a flux differential of about 25% from the top to the bottom.

REFERENCES

(1) "The United States Pharmacopeia," 18th rev., Mack Publishing Co., Easton, Pa., 1970, pp. 70, 117, 118, 201, 341, 343, 389, 391–393, 558, 559, 622, 637, 639, 642, 643, 645, 667.

(2) "The National Formulary," 13th ed., Mack Publishing Co., Easton, Pa., 1970, pp. 163, 445, 560, 646, 647, 649, 650, 718.

(3) R. A. Egli, *Fresenius' Z. Anal. Chem.*, **247**, 39(1969).

(4) R. C. Koch, "Activation Analysis Handbook," Academic, New York, N. Y., 1960.

(5) C. M. Lederer, J. M. Hollander, and I. Perlman, "Table of Isotopes," Wiley, New York, N. Y., 1968.

(6) J. P. F. Lambert and M. Margosis, *J. Pharm. Sci.*, **59**, 1005 (1970).

(7) D. F. Covell, *Anal. Chem.*, **31**, 1785(1959).

(8) "Code of Federal Regulations," Title 21, 1970, chap. I.

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