Rapid Determination of Aluminum in Pharmaceutical Dosage Forms by Neutron Activation

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Abstract □ A rapid, efficient, and highly accurate assay by neutron-activation analysis is presented for aluminum content as a function of the aluminum compounds contained in complex antibiotic formulations. The assay requires no chemical isolation or cleanup. The relatively short half-life of ^{28}Al allows rapid analysis, and the technique favors the detection of aluminum over possible interferences by longer lived radionuclides.

Keyphrases □ Aluminum in dosage forms—determination □ Oleaginous products—aluminum determination □ Neutron-activation analysis—aluminum

Aluminum monostearate (AMS) is incorporated as a thixotropic gelling agent in oleaginous pharmaceutical formulations. Many of these products are intended for use as intramammary infusions for the treatment of mastitis in dairy animals. These often comprise assorted mixtures of antibiotics (procaine penicillin G, neomycin sulfate, dihydrostreptomycin sulfate, polymyxin B sulfate, and sodium novobiocin), sulfonamides, corticosteroids, and various preservatives. Milk-out studies indicate that prolonged antibiotic residues in milk may be associated with certain formulations containing AMS, with greater prolongation being correlated with higher soap content.

The product known as sterile procaine penicillin G with aluminum stearate suspension is used in human medicine as a depot preparation to obtain prolonged duration of penicillin in the blood following a single intramuscular injection. Aluminum chlorohydroxide is a drug possessing astringent properties commonly used in antiperspirant formulations.

The analysis of aluminum salts in pharmaceutical dosage forms is usually performed titrimetrically with EDTA or gravimetrically as Al_2O_3 after combustion (USP, NF). These methods are often cumbersome, inefficient, tedious, occasionally erroneous, and generally lacking in specificity.

Well over 100 applications of neutron activation for the analysis of aluminum have been reported (1) but none in the field of pharmaceutical dosage forms. The technique reported here should be most valuable to drug chemists because of its specificity, accuracy, and practical application at the common dosage concentration. The reaction of thermal neutrons with aluminum, $^{27}Al(n,\gamma)^{28}Al$, is favorable, and the resulting radioactive nuclide has a half-life of 2.3 min. and a γ-ray energy of 1.78 Mev. A rapid recording of the γ-ray spectrum at the reactor site is dictated by the relatively short half-life of ^{28}Al. The short irradiation enhances the discrimination against longer lived radionuclides and enables the rapid analysis for aluminum of a large volume of samples.

Interferences from fast neutrons reacting with silicon or phosphorus and from thermal neutrons reacting with magnesium (2) are minimized, since the analysis involves relatively large quantities of aluminum as compared with the amounts of the interfering elements, if at all present. Gamma-ray spectral interferences are also minimal, since the matrix is essentially organic, time of irradiation is short, and the γ-ray energy for aluminum is relatively high. Neutron-activation analysis is rendered even more efficient in this case, because there is no necessity to separate and isolate the aluminum in any fashion from these intractable formulations. This study covers mainly a variety of oleaginous commercial products containing antibiotics, but the method is readily applicable to any aluminum-containing drug.

EXPERIMENTAL

Irradiation Containers—The 0.40-dr. (1 ml.), capped polyethylene vials[1] were cleaned with 1:1 HNO_3, rinsed with distilled water, and dried with acetone or methanol.

Standards—A stock solution of aluminum standard was prepared by dissolving 12.3534 g. of reagent grade $Al_2(SO_4)_3 \cdot 18H_2O$ in distilled water and diluting to 1 l. in a volumetric flask. A secondary standard was prepared by dissolving 0.0458 g. of aluminum wire (grade 1100) in dilute H_2SO_4 and diluting to 100 ml. in a volumetric flask. Aliquots of 1.00 ml. were transferred to the polyethylene vials.

Samples—About 1 g. of the oily product was accurately weighed into a polyethylene vial. Antiperspirants were prepared by diluting an accurately weighed sample of about 1 g. to 25 ml. with distilled water and transferring a 1.00-ml. aliquot to a polyethylene vial.

Apparatus—All samples were irradiated in either an exposure tube (thermal neutron flux of approximately $10^{13} n/cm.^2$ sec.) or a pneumatic tube facility (thermal neutron flux of approximately $10^{12} n/cm.^2$ sec.) at the 1-Mw. nuclear reactor of the Naval Research Laboratory, Washington, D. C. The γ-ray spectra were obtained with a 1024-channel pulse height analyzer,[2] using a 7.62 × 7.62-cm.(3 × 3-in.) NaI(Tl) detector.[3] The readout equipment consisted of a teletype printer and an X-Y recorder.[4] The samples were mounted approximately 10 cm. from the detector, which is housed in a large steel shield. This detector, which was covered with a 1-cm. thick plastic β-absorber, has a resolution of 8.0% at 662 kev. The pulse height analyzer was divided into four 256 channels, so four independent counts could be recorded. The gain control of the analyzer was set at 10 kev./channel over the 256 channels.

Procedure—Three samples and one standard were packaged into an irradiation bucket and lowered into the exposure tube for a 60-sec. irradiation, or one sample and one standard were packaged into

[1] Chemical Rubber Co., Cleveland, Ohio.
[2] Northern Scientific, Madison, Wis.
[3] The Harshaw Chemical Co., Cleveland, OH 44106
[4] Mosley model 7590.

Table I—Neutron-Activation Analysis of Aluminum in AMS

Sample	Al Found, %	AMS (w/w), % Tech.[a]	AMS (w/w), % USP[b]	Expected AMS[c] (w/v), %
1	0.01	—	—	None
2	0.01	—	—	None
3	0.003	—	—	None
4	0.003	—	—	None
5	0.001	—	—	None
6	0.001	—	—	None
7	0.01	—	—	None
8	0.01	—	—	None
9	0.02	—	—	None
10	0.104	2.34	1.31	2
10A[d]	0.0916	2.06	1.15	2
11	0.119	2.68	1.50	2
12	0.0955	2.15	1.20	2
12A	0.102	2.30	1.28	2
13	0.0950	2.14	1.20	2
14	0.0734	1.65	0.92	1.78[e]
15	0.107	2.11	1.35	1.49[e,f]
15A	0.101	2.27	1.27	1.49[e,f]
16	0.0911	2.05	1.15	—
17	0.0872	1.96	1.10	—
18	0.0985	2.22	1.24	1.47[e,f]
18A	0.105	2.36	1.32	1.47[e,f]
19	0.136	3.06	1.71	2.00[e]
19A	0.143	3.22	1.80	2.00[e]
20	0.123	2.77	1.55	2.00[e]
20A	0.122	2.75	1.53	2.00[e]
21	0.126	2.84	1.59	2.00[e]
21A	0.135	3.04	1.70	2.00[e]
22	0.173	3.89	2.18	3.60
22A	0.150	3.38	1.89	3.60
23	0.138	3.11	1.74	3.60
23A	0.135	3.04	1.70	3.60
24	0.131	2.95	1.65	3.60
24A	0.148	3.33	1.86	3.60
25	0.147	3.31	1.85	3.60
25A	0.153	3.44	1.92	3.60
26	0.127	2.86	1.60	2
27	0.148	3.33	1.86	2
28	0.133	2.99	1.67	2
28A	0.137	3.08	1.72	2
29	0.137	3.08	1.72	2
30	0.161	3.62	2.03	2.12
31	0.146	3.29	1.84	2.12
32	0.170	3.83	2.14	1.94
33	0.187	4.21	2.35	3
34	0.208	4.68	2.62	—
34A	0.186	4.19	2.34	—
35	0.232	5.22	2.92	6.00
36	0.189	4.25	2.38	3
37	0.220	4.95	2.77	6.00
37A	0.206	4.64	2.59	6.00
38	0.249	5.60	3.13	—
38A	0.239	5.38	3.01	—
39	0.298	6.71	3.75	6.60
39A	0.280	6.30	3.52	6.60

[a] Based on technical grade containing 4.45% Al by neutron-activation analysis. [b] Based on USP grade containing 7.95% Al. [c] Actual or labeled amount on weight/volume basis. [d] Samples labeled A are duplicates. [e] Weight/weight basis. [f] Official drug.

a pneumatic tube shuttle and irradiated for 60 sec. in the pneumatic tube facility.

After a group irradiation, the standard was counted for 1 min. at a decay time of 10 min., whereas the three samples were counted individually for 1 min. at suitable decay times based on the indicated dead time of the pulse height analyzer.

The direct method of quantitation involves taking one count for each irradiated specimen at a given time, whereas the differential method requires a count of two different times for each specimen. The data were analyzed by the Covell method (3) for the photopeak area at 1.78 Mev., and the activity (net count summation) was adjusted to the time equivalent to the end of irradiation, using a calculated decay factor, according to equation

$$A_0 = A_1/e^{-\lambda t} \qquad \text{(Eq. 1)}$$

where A_0 is the activity of specimen at time equivalent to the end of irradiation; A_1 is the activity of specimen at time count was made; λ is specific decay constant for nuclide; and t is equivalent time of count. When a sample and a standard are treated identically in every respect, the activity to aluminum content ratio is directly comparable.

Table II—Neutron-Activation Analysis of Aluminum in Products Containing Different Aluminum Salts

Salt	Al Found, %	Expected, %	% of Expected
Tristearate	0.0630	0.07078	89.0
Tristearate	0.0644	0.07078	91.0
Chlorohydroxide	4.50	4.79	93.9
Chlorohydroxide	4.95	5.03	98.4
Chlorohydroxide	4.86	5.03	96.6
Chlorohydroxide	5.00	5.03	99.4
Chlorohydroxide	5.00	5.03	99.4

The differential method subtracts the sample activity at two given times, t_1, t_2, and A_0 is determined as follows:

$$A_1 - A_2 = A_0(e^{-\lambda t_1} - e^{-\lambda t_2}) \qquad \text{(Eq. 2)}$$

$$\therefore A_0 = \Delta A/(e^{-\lambda t_1} - e^{-\lambda t_2}) \qquad \text{(Eq. 3)}$$

The relationship between activity and aluminum content of the sample is again compared to that of the standard.

The data obtained for all samples are based on total aluminum content, regardless of source, and physicochemical state of the specimen.

RESULTS

Table I lists results obtained for 39 different samples of oleaginous drug formulations from various manufacturers. Column 2 lists the actual amount of aluminum found; the values in Column 3 are calculated to the monostearate salt based on the technical grade (Table IV); and Column 4 lists the values calculated on the basis of the USP grade for comparison to the actual or labeled amounts as listed in Column 5. Table II likewise lists results for aluminum salts found in one otic and several antiperspirant formulations. The results obtained from various standard samples, using the pneumatic tube facility, are listed in Table III. Table IV shows results from several determinations of a sample of aluminum monostearate. Table V lists the results from four identical irradiations of the secondary standard, using the pneumatic tube facility.

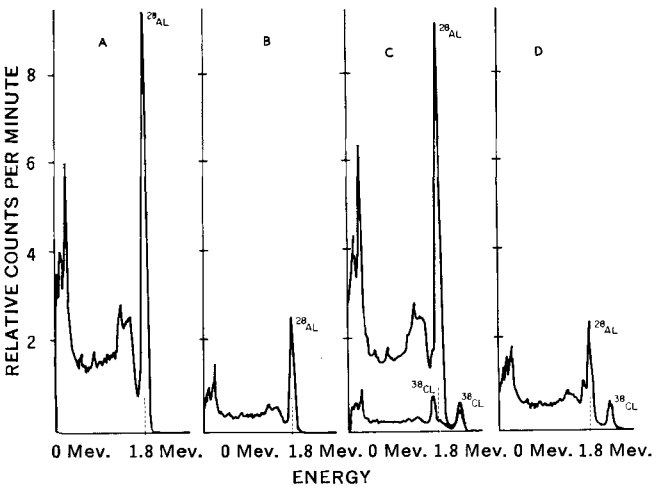

Figure 1—*Typical γ-ray spectra for an aluminum standard and a mastitis drug sample after a 1-min. irradiation in a flux of* 10^{12} *n/cm.*^{2} *sec. Key: A, aluminum standard counted after 3-min. decay period; B, aluminum standard counted after 8-min. decay period; C, drug counted after 5-min. (upper) and 20-min. (lower) decay period; and D, drug counted after 10-min. decay period.*

Table III—Recovery of Aluminum from Materials Used as Standards

Sample	Weight, mg.	Al Found, mg.	Al Expected, mg.	Recovery, %[a]
1100 wire, solution	0.4576, mg./ml.	0.458, mg./ml.	0.4576, mg./ml.	100
1100 wire, solid	5.00	5.04	5.00	101
99.9% Al + 0.1% Au wire	1.11	1.08	1.11	97.3
SRM-87a Al–Si alloy[b]	1.77	1.79	1.61	111
Al monostearate, in oil	27.7	1.22	2.20[c]	55.5
Al monostearate, powder	13.7	0.6	1.09[c]	59
Al_2O_3 reagent grade	24.9	8.53	13.2[d]	64.7

[a] Ratio of Al determined by neutron activation to that calculated from sample weight. [b] SRM-87a Al–Si alloy is an NBS reference standard containing 91.0% Al. [c] Calculated on basis of USP value of 7.95% Al. [d] Sample assumed to be anhydrous, but was in fact the trihydrate; actually 99.2% recovery as $Al_2O_3 \cdot 3H_2O$.

Figure 1 shows examples of typical γ-ray spectra for an aluminum standard and a drug.

DISCUSSION

Sterile procaine penicillin G with aluminum stearate suspension is an official USP drug containing 2% of aluminum monostearate. The soap, however, usually contains mixtures of stearates, palmitates, oleates, and free or loosely combined fatty acids, as well as hydrates and basic soaps (4). The aluminum content of AMS (USP) is equivalent to 14.5–16.0% of Al_2O_3 obtained by combustion, whereas the technical grade salt may yield around 10% Al_2O_3.

The results in Table I may then be used as a presumptive test, if necessary, to determine the grade of soap used in the formulation for control and regulatory purposes. In the first grouping, there was no ^{28}Al photopeak detected, and an upper limit value was computed from the counts. Considering an approximate 10% variation in density of the samples in comparing percent weight/weight against percent weight/volume, it is noted that most samples fall into one or the other grade. The standard deviation for samples listed in Table I approached 10%. When samples were handled individually, the standard deviation was lower than 3%; however, the rate of sample handling decreased about threefold.

The precision is also affected by the background, which may occasionally show other isotopes to be present in substantial amounts. For instance, peaks due to sodium, chlorine, and cobalt have been detected in many of these samples. The presence of chlorine (Fig. 1) and/or sodium contributes to the ^{28}Al γ-ray spectrum peak area. The Covell method or the differential technique of data analysis is used to correct for these spectral interferences. These corrections somewhat limit the overall precision of neutron-activation analysis for aluminum.

To verify the results in Table III, the AMS bulk and the aluminum oxide standard were subjected to combustion. The residue on ignition values of 9.4 and 67%, respectively, confirmed the results from neutron-activation analysis and verified the accuracy of the method. The sample of AMS was indeed of a technical grade; the aluminum oxide was indeed a trihydrate. The only outlying result in Table III is 111% recovery for the standard reference material.

Table IV—Determination of Aluminum in a Batch of AMS

Sample[a]	Weight, mg.	Al Found, mg.	Al, %
1A	23.90	1.07	4.48
1B	23.90	1.05	4.39
1C	23.90	1.077	4.51
2	13.71	0.635	4.63
3	20.25	0.885	4.37
4A	27.7	1.25	4.51
4B	27.7	1.24	4.48
4C	27.7	1.194	4.31
5	37.2	1.630	4.38

Av. = 4.45%
SD = 0.031 (0.7%)

[a] Samples 1 and 4 were irradiated and counted three times each.

Table V—Precision in Relative Counts in Irradiations

Identification[a]	Relative Net Counts
Aliquot 1	9409
	9295
	9473
Aliquot 2	9597
	9615
Av.	9478
SD	119 (1.26%)

[a] The same sample was irradiated more than once over a period of 2 days. Both aliquots are from the same stock solution. A blank stock solution contained less than 0.002 mg. of Al.

However, this was not unexpected since the geometry of the sample was different from that of the primary standard, and the sample was small.

The secondary standard was handled individually; the results listed in Table V indicate that the relative counts from different irradiations are reproducible, showing a precision of better than 3%. Comparisons of values also indicate excellent accuracy.

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