Determination of Trace Elements in Drugs by Neutron Activation Analysis

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Results of determinations of trace elements in drugs by neutron activation analysis are presented for more than 150 samples including inorganics, salicylates, steroids, vitamins, antibiotics, and chlorinated compounds. Trace elements found include aluminum, antimony, arsenic, bromine, chlorine, copper, gallium, manganese, mercury, scandium, sodium, and thorium.

MONOGRAPHS setting standards for drugs frequently have limit tests for "heavy metals." The tests are more accurately described as "substances colored by sulfide ions under the conditions specified for preparing the sample as compared visually with a lead standard." The sensitivity of the test varies with the metallic ions present and the acidity of the solution. The visual comparison suffers from the differences in color of the various metal sulfides.

Since the test normally sets limits in the parts-per-million range, about 1 Gm. of material must be destroyed. Organic materials obtained from good manufacturing processes almost invariably give no discernible color when tested. The considerations of the cost involved in performing the assay on the more expensive synthetic drugs, and of the possible amounts of impurities that could be introduced by milligram-level doses, have led to a re-examination of the rationale for this test by the Subcommittee on Heavy Metals of the Board of Revision of the United States Pharmacopeia.

A preliminary general investigation of trace elements in drugs was undertaken to collect data for recommendations for tests for trace contaminants. Nondestructive neutron activation analysis was chosen as a rapid method which provided adequate sensitivity for all toxic elements and all common contaminants (except lead) if 100-mg. samples were irradiated in the neutron flux available in the air-cooled portion of the Oak Ridge graphite-moderated reactor (1).

Neutron activation is based on the work of Fermi (2) as further developed by Curie (3), Livingston (4), Hevesy (5), Seaborg (6), and Clark and Overman (7). A comparison of the limits of neutron activation with other methods of analysis has been made in a review by Meinke (8). The physical, chemical, and nuclear limitations of the method have been recognized in a review by Smales (9).

Neutron activation analysis is a method for quantitative and qualitative determinations of the elements in a sample using the technique of nuclear transformation. When a sample is irradiated by neutrons produced in a nuclear reactor or other source, some of the atoms in the sample interact with the neutrons and are converted into radioactive isotopes of the same element (10).

The product produced by irradiation of a stable isotope with neutrons is usually radioactive and produces gamma rays. The energies of the emitted gamma rays and the relative numbers emitted at each energy is the gamma spectrum, a characteristic of each isotope which can be used for qualitative identification (11).

Quantitative measurement is made either by comparison of the sample with a standard (12) or by mathematical calculation based upon a knowledge of the irradiating neutron flux and the geometry and efficiency of the gamma-ray detector (13).

For most samples, the recorded gamma spectrum is complex, consisting of the sum of the spectra from the isotopes present. These can be identified by the process of "spectrum stripping" in which the spectral contribution from an isotope present in the sample is electronically subtracted from the recorded spectrum of the sample (14). This process can be repeated, subject only to the statistical nature of emission of radiation, until all isotopes present have been identified and quantitatively determined. Although results presented in this paper were obtained through the process of spectrum stripping by manual operations, a computer-controlled process has been shown to be feasible (15).

EXPERIMENTAL

Solid samples in Bakelite-capped glass vials were placed in a polyethylene secondary container and were irradiated for appropriate periods of time from a few hours to 1 week in the air-cooled hole of the X-10 graphite-moderated reactor at Oak Ridge National Laboratory. Assays for aluminum were done by irradiation of the sample in polyethylene primary and secondary containers for 1 minute in the pneumatic tube of the Oak Ridge "swimming pool" reactor. After irradiation, samples were weighed and placed in clean containers for counting. Counting was done with a single 3 × 3 in. thallium-activated sodium iodide crystal optically coupled to a 3-in. Dumont photomultiplier tube. This assembly was contained in a graded lead–copper–cadmium shield about 3 ft. in diameter. The geometry of the counter was adjusted and polyethylene absorbers for beta-radiation were used as needed to make proper use of the equipment. The gamma-ray spectrum was obtained by sorting the pulses from the phototube, using a Radiation Instruments Development Laboratory 200-channel analyzer. These spectra were analyzed by manual spectrum stripping using liquid standards of known concentrations irradiated simultaneously with the sample.

RESULTS AND DISCUSSION

The results of the assays are shown in Table I. These results represent a very small sampling compared with the total number of pharmaceutical batches produced. No general conclusions, therefore, should be drawn from the data.

Quite unexpected, however, was the widespread

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TABLE I.—TRACE ELEMENTS FOUND IN DRUG SAMPLES[a]

Substance	No. of Samples	Elements Detected											
		Al	Sb	As	Br	Cl	Cu	Ga	Mn	Hg	K	Sc	Na	Th
Acetophenetidin	5				2		3		2				2	
Acetophenetidin	4												5	
Acetylsalicylic acid	5				3				1				2	
Acetylsalicylic acid	5								3				3	
Aluminum hydroxide	3												8	
Amodiaquine hydrochloride	3				4		4						5	
Ascorbic acid	10			2			2		2	3			4	
Benzoic acid	5								2				4	
Bismuth subcarbonate	3				4		3		3				4	
Bismuth subcarbonate	1												6	
Calcium carbonate	5				4		4						5	
Calcium-*d*-pantothenate	4				5		4	3	5				5	
Calcium gluconate	4				6								4	
Cherry juice	1						3		3		7			
Chloramphenicol	4				4								4	
Chloramphenicol palmitate	4			2	4				3				4	
Chlormezanone	3								4				4	
Chloroquine phosphate	3			3	4		4		3				5	
Cortisone acetate	3				6									
Diphenhydramine hydrochloride	4				6								4	
Diphenylhydantoin	4						4						5	
Ferrous gluconate	3				5		4		5				5	
Hydrocortisone	3				5									
Hydrocortisone acetate	3				4								4	
Magnesium stearate	4		2										6	
Magnesium trisilicate	4											3	8	
Methocel	5					6							6	
Methyl salicylate	5				2	2	1						2	
Niacin	5	4					3		2	3		1	4	2
Methyl salicylate	5				3		2						3	
Niacinamide	5									3			5	
Phenol	3												3	
Phenylephrine hydrochloride	3		3		4								4	
Prednisolone	3				6									
Predisolone acetate	3				5								5	
Prednisone	3				6									
Riboflavin	3			2	3	7			2	3			4	
Talc	2								6			3	7	
Talc	2											3	6	
Tannic acid	4						4		3		6		5	
Contamination from ascorbic acid							6		4				6	

[a] Key: Average of samples in which element was detected. Blank, not detected; 1, less than 0.01 p.p.m.; 2, 0.010 to 0.099 p.p.m.; 3, 0.10 to 0.00 p.p.m.; 4, 1.0 to 9.9 p.p.m.; 5, 10 to 99 p.p.m.; 6, 100 to 990 p.p.m.; 7, 1000 to 9,900 p.p.m.; 8, 10,000 to 49,000 p.p.m.

occurrence of bromine, which may indicate the presence of brominated intermediates, bromine in raw materials, or bromine in the plant atmosphere. Wide differences in sodium content for groups of samples of acetophenetidin, acetylsalicylic acid, methyl salicylate, and talc clearly indicate the origin of samples from different manufacturers. The presence of copper in a grossly discolored portion of a sample of ascorbic acid emphasize the need for care in the manufacture of this substance. The occurrence of arsenic, antimony, and mercury in some samples, albeit in quantities which would not be detected by the U.S.P. heavy metals test, shows the possibility of contamination and the need for retention of the U.S.P. test.

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