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Tracer and Radioactivation Studies on Tartar Emetic Impurities

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The problem of contamination of tartar emetic with arsenic and lead was examined using the radioactive isotopes, ^{76}As and ^{209}Pb . Neutron activation and radiochemical separation methods have been applied for the determination of arsenic and lead concentrations throughout the different stages of tartar emetic synthesis. It has been shown that, while most of arsenic is eliminated during the synthesis process, the major portion of lead remains in the final product. It was also found that the two impurities can be eliminated by successive washing of the starting materials with 0.2 M nitric acid and water. Tartar emetic synthesized from purified starting materials conforms to the requirements in pharmacopias.

ONE OF THE most important problems of the pharmaceutical industry is the production of synthetic drugs in a suitably pure condition. The classical methods of tracing impurities are either misleading, tedious, or inaccurate. Antimony potassium tartrate (tartar emetic) is the most commonly employed drug in the treatment of bilharziasis, schistosomiasis, leishmaniasis, filariasis, ascariasis, and other tropical diseases (1). It is one of the early drugs found to be active against trypanosomes (2). The drug is widely used in Africa, Asia, and Latin America because of the simplicity and easiness of its synthesis and acceptance among patients and physicians. It is still the drug of choice in the treatment of bilharziasis in Egypt as well as other countries where infections occur (3). Cases of toxicity and inconvenience of intravenous injection of this drug are reported, however, and have been attributed, at least partly to the presence of toxic impurities such as arsenic and lead (3, 4).

Most pharmacopias in which tartar emetic is mentioned require certain specifications for arsenic and lead limits for the sake of its medical safety. These limits vary in the case of arsenic to not more than 200 p.p.m. in the U.S.P. (5), 10 p.p.m. in the E. P. (6), 8 p.p.m. in the B.P. (7), and in case of lead to not more than 10 p.p.m. in the E.P. and 5 p.p.m. in the B.P.

The quantitative determination of the two metals, particularly arsenic, at such low concentrations in the presence of antimony cannot be performed with accuracy by the conventional analytical methods (8-11). The utilization of radioactive isotopes in working some production problems and in working

up technical operations in the pharmaceutical industry has found its way only recently (12). Some studies have been published on the manufacture of pure tartar emetic (3, 13), but none of the authors have made use of radioactive isotope techniques.

The purpose of the present paper was to find an economical method to eliminate arsenic and lead and to produce tartar emetic in pure form. For tracing these two metals, the radioactive isotopes, ^{76}As and ^{209}Pb , have been used, while their concentrations in the starting materials and in the final products have been determined by a neutron radioactivation procedure.

EXPERIMENTAL

Materials.—Unless otherwise stated, all chemicals employed were analytical grade reagents. The radioactive isotopes ^{76}As and ^{209}Pb were prepared by irradiating spectrographically pure arsenic trioxide and lead. Arsenic trioxide was then dissolved in dilute hydrochloric acid, while lead was dissolved in dilute nitric acid. Standard and carrier solutions of arsenic and lead were prepared by dissolving inactive arsenic trioxide and lead in a similar manner.

Apparatus.—The instruments used were an EKCO scintillation assembly for counting the γ radiation of ^{76}As and a Philips counting instrument with an end window G.M. tube for measuring ^{209}Pb β -radiations.

Irradiations.—Samples to be irradiated were wrapped in thin aluminum sheets and were enclosed in aluminum cans which were then irradiated at a flux of about 1.3×10^{18} neutrons/cm.²/sec. in the U.A.-RR-1, 2 MW reactor. For the radioactivation analysis of arsenic and lead, every sample was placed together with the standards in one can and exposures were of about 5 hr. duration.

Procedure.—All experiments on the study of arsenic and lead uptake were performed in 100-ml. conical flasks. For evaluating arsenic uptake on

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TABLE I.—ARSENIC UPTAKE OF TARTAR EMETIC^a

Expt.	Synthesis Conditions	Original Arsenic, p.p.m.	Arsenic Content in Tartar Emetic, p.p.m.
1 ^b	Reaction mixture (paste) was left for 24 hr., then boiled for 15 min.	1000	8.2
2		1000	6.6
3		1100	9.6
4		1250	12.0
5		1500	13.0
6 ^c	Reaction mixture was refluxed for 1 hr.	1500	39.0
7 ^d		1500	18.0
8		1000	7.0
9		1500	13.0

^a The values given are the average of two or three experiments. ^b Solution of tartar emetic was cooled in refrigerator. ^c EDTA was added to the reaction mixture. ^d 8-Hydroxyquinoline was added to the reaction mixture.

TABLE II.—LEAD UPTAKE OF TARTAR EMETIC^a

Original Lead Added, p.p.m.	Lead Content in Tartar Emetic, p.p.m.
~200	~130
~200	~110

^a The values given are the average of two or three experiments.

TABLE III.—VARIATION OF ARSENIC UPTAKE WITH ITS AMOUNT BEFORE RECRYSTALLIZATION^a

Expt.	Amt. of Arsenic Added to Tartar Emetic, p.p.m.	Arsenic Content of Synthesized Tartar Emetic Crystals, p.p.m.
1	6.7	0.12
2	16.7	0.20
3	33.3	0.27
4	53	0.75
5	127	1.9
6	163	3.6
7 ^b	163	4.9
8	203	6.0
9 ^b	203	7.5
10	1000	19.2

^a The values given are the average of four experiments. ^b Cooled in refrigerator.

tartar emetic, in the course of its synthesis, the following procedure was followed: 1.5 Gm. of antimony trioxide, 1.8 Gm. of acid potassium tartrate, both in a finely powdered form, were thoroughly mixed with a few drops of distilled water and a known amount of arsenic containing its radioactive isotope. The paste was left for 24 hr., boiled with 12 ml. of distilled water for 15 min., filtered while hot, and the clear filtrate was left to crystallize at room temperature or in a refrigerator. The crystals of tartar emetic thus obtained, after being filtered off and washed with ice cold water, were dried. The arsenic content of the filtrate and crystals were determined by measuring the radioactivity of ⁷⁶As. In some other series of experiments a mixture of antimony trioxide, acid potassium tartrate, and arsenic was refluxed with 12 ml. of distilled water for 1 hr., filtered while hot, and the procedure was completed as mentioned before. The study of tartar emetic purification from arsenic by recrystallization was carried out as follows: 3 Gm. of tartar emetic was dissolved in 10 ml. of hot dis-

tilled water to which was added a known amount of arsenic. The mixture was then cooled, and tartar emetic was examined for its arsenic content as in the above two series.

The lead contamination of tartar emetic was investigated by refluxing the reaction mixture to which is added a known amount of lead, and in the same manner as in the case of arsenic. The purification of tartar emetic from lead was studied also as in the case of arsenic. Lead which is added in the above two cases, however, was prepared by mixing a known volume of lead solution in nitric acid with 0.5 ml. of concentrated hydrochloric acid. Lead chloride thus precipitated was washed once with ice cold water before being used in the experiment.

The purification of antimony trioxide (Sb₂O₃) was studied by stirring 5 Gm. of crude Sb₂O₃ with different washing solutions. The Sb₂O₃ was then filtered off and examined for the arsenic and lead content.

Radioactivation analysis of arsenic and lead was done by methods similar to those published in the literature (14, 15) except for some modifications to fit with the given samples. For arsenic, a double distillation process was necessary to separate it from antimony, while the preliminary separation of lead from antimony was done by extraction (16).

Radiochemical Purity.—This was checked by measuring the spectra (arsenic) or from the decay curves (lead) of the corresponding radioactive species.

RESULTS AND DISCUSSION

Arsenic and Lead Uptake on Tartar Emetic During Its Synthesis.—The experimental results of arsenic uptake on tartar emetic throughout the process of its synthesis (Table I) show that this uptake increases with the increase of its amount

TABLE IV.—VARIATION OF LEAD UPTAKE ON TARTAR EMETIC WITH THE CONDITION OF EXPERIMENT^a

Condition of Expt.	Original Lead Added, p.p.m.	Lead Uptake on Tartar Emetic Crystals, p.p.m.
Cooled at room temp.	~200	~132
Cooled in refrigerator	~200	~138

^a The values given are the average of two experiments.

TABLE V.—PURIFICATION OF ANTIMONY TRIOXIDE^a

Washing Soln.	Before Washing		After Washing	
	As, p.p.m.	Pb, p.p.m.	As, p.p.m.	Pb, p.p.m.
Water	450	60	75	58
Water	75	58	1	58
10% ammonium acetate	450	60	380	55
5% sodium carbonate	450	60	425	60
0.1 M nitric acid	450	60	...	5
0.1 M nitric acid	...	5	...	1
0.2 M nitric acid	450	60	...	1

^a The values given are the average of two or three experiments.

originally present in the reaction mixture. The uptake, however, is always less than 1%. It is clear, also, that when tartar emetic is left to crystallize gradually at room temperature, the arsenic uptake on the crystals is less than in case of enhancing crystallization by cooling the solution. The addition of some complexing agents such as ethylenediaminetetraacetic acid (EDTA) and 8-hydroxyquinoline to the reaction mixture increases the arsenic contamination of tartar emetic. The contamination, however, is the same for the synthesis of the drug by the two methods, *i.e.*, with or without refluxing the reaction mixture.

The uptake of lead, on the other hand, was found to be about 60% of its amount originally added to the reaction mixture (Table II).

Purification of Tartar Emetic by Crystallization.—Table III presents the experimental results of the recrystallization of tartar emetic in the presence of different amounts of arsenic. It is evident that the uptake of arsenic is about 2–3% of its original amount. Cooling the solution increases the arsenic contamination. The percentage uptake, however, is higher than in the case of tartar emetic synthesis. This is most probably due to the uptake of some arsenic onto the unreacted residue.

In some separate experiments, it has been found that the addition of a little amount of hydrochloric acid decreases the arsenic uptake onto the crystals.

The uptake of lead is given in Table IV. It is clear that, while most arsenic can be removed from tartar emetic by recrystallization, the major part of lead remains in the crystals.

The preliminary investigation has shown that the two impurities are mainly present in antimony trioxide, hence, the authors' efforts were directed toward the study of its purification. Water and other washing solutions have been tried for eliminating arsenic and lead from antimony trioxide. The results are presented in Table V.

Washing antimony trioxide with water and 0.2 M nitric acid is evidently sufficient to eradicate the arsenic and lead impurities, while losses are negligible. Moreover, this is simpler than eliminating arsenic as arsine using reducing amalgam or complexing lead by a chelating agent (13). Acid potassium tartrate containing arsenic and lead can be sufficiently purified by washing in a similar manner.

RECOMMENDED PROCEDURE AND CONCLUSION

The foregoing data show the different possibilities of eliminating arsenic and lead impurities from tartar emetic. In light of the above discussion, the recommended procedure for the synthesis of highly pure tartar emetic is summarized as follows.

Antimony trioxide is washed once with 0.2 M nitric acid and then twice with water. The volume in liters of nitric acid and of water must be fivefold the weight in kilograms of antimony trioxide. Every washing should be followed by filtering the slurry produced. Antimony trioxide is then thoroughly mixed with the calculated amount of similarly washed acid potassium tartrate to obtain a homogeneous paste, and left for 24 hr. The paste is then boiled for 15 min. with distilled water, filtered while hot, and the filtrate is left to cool. The crystals of tartar emetic thus obtained are washed with cold water and then dried. This procedure, while retaining a better yield, is more economic. The product obtained is almost free from arsenic and lead.

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