A "Go, No-Go" Assay Procedure for Residual Amounts of Acetone in Film-Coated Tablets

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The iodoform reaction has been adapted as a quantitative method for the determination of residual amounts of acetone in film-coated tablets. The procedure makes use of a "Go, No-Go" principle in order to provide a rapid means of determining whether the acetone is within established limits.

TABLETS THAT are enteric coated with an acetone solution of cellulose acetate phthalate, even after considerable drying, retain residual amounts of the solvent. This residual acetone, if present in high enough concentration, results in an objectionable odor in the packaged product.

It was necessary to develop a method for the rapid determination of residual acetone and to set a limit at which no odor would be detectable. At first a colorimetric method involving formation of the 2,4-dinitrophenylhydrazone was used, and a limit of 300 mcg. per tablet established. The method, however, was time consuming (it took several hours) as it required extraction of the color from the reaction mixture before measurement (1).

For in-process control and feed-back information, a procedure that could be performed in the production area by a person with little or no technical training was desired. Instead of determining the exact quantity of residual acetone, this procedure would determine compliance with the specification limit and hence be called a "Go, No-Go" method.

The volumetric procedure that best fitted these requirements was patterned after the methods of Messinger (2) and Romijn (3). The method makes use of the familiar haloform reaction

$$CH_3-\overset{\overset{O}{\|}}{C}-CH_3 + 3I_2 + 4OH^- \rightarrow CHI_3 + CH_3COO^- + 3I^- + 3H_2O$$

Since 1 mole of acetone reacts with six equivalents of iodine, the method is suitable for measuring small amounts of acetone accurately. The determination is carried out as a back titration of excess iodine. The accuracy of this procedure has been previously reported by Goltz and Glew (4).

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TABLE I.—TESTS ON STANDARD ACETONE SOLUTIONS

Solution	Acetone Equivalent, mcg./tablet	"Go, No-Go" Result
A	297	Go
B	298	Go
C	299	Go
D	300	Go
E	301	No-Go
F	302	No-Go

EXPERIMENTAL

Reagents.—Approximately 0.1 *N* sodium hydroxide solution; concentrated hydrochloric acid; starch indicator suspension U.S.P.; standardized 0.051 *N* iodine solution; standardized 0.040 *N* sodium thiosulfate solution were the reagents utilized.

The procedure and the normalities of the iodine and thiosulfate solutions are specific for a "Go, No-Go" limit of 300 mcg. of acetone per tablet, or 0.310 meq. in the sample taken (ten tablets). The exact normalities are not critical; however, the difference (0.310 meq.) must be maintained. For other "Go, No-Go" limit concentrations of acetone, the number of meq. must be calculated and this difference maintained between the normalities of the iodine and thiosulfate solutions.

Equipment.—Automatic Palo pipets[1] of 50 ml., 10 ml., and 5 ml. delivery and standard laboratory glassware were employed.

Procedure.—Place a sample of 10 tablets in a glass-stoppered 125-ml. flask. Using Palo pipets, add 50 ml. of approximately 0.1 *N* sodium hydroxide solution and 10 ml. of the standardized 0.051 *N* iodine solution. Shake this mixture occasionally for 10 minutes or until the tablets are completely disintegrated. Add 1 ml. of concentrated hydrochloric acid. Immediately add, by means of a Palo pipet, 5 ml. of the standardized 0.040 *N* sodium thiosulfate solution.

A dark brown mixture indicates the presence of unreacted iodine and that the residual acetone in the sample is well below the limit—the sample passes (Go). If the mixture is white or pale yellow (CHI_3), the sample is above or close to the limit. In this case, add 1 ml. of starch indicator suspension. If the mixture is now blue, unreacted iodine is present and the sample passes (Go). However, if the mixture remains white or pale yellow, there is no unreacted iodine present; the acetone concentration is above the limit and the sample fails (No-Go).

[1] Marketed by Palo Laboratory Supplies, Inc., 75 Ninth Ave., New York 11, N. Y.

TABLE II.—TESTS ON TABLETS

Sample	Colorimetric Result, mcg./tablet	"Go, No-Go" Result
20	80	Go
7	269	Go
12	270	Go
19	273	Go
1	274	Go
3	274	Go
5	276	Go
2	277	Go
18	279	Go
11	283	Go
10	295	Go
4	308	No-Go
6	321	No-Go
16	324	No-Go
17	327	No-Go
14	332	No-Go
15	332	No-Go
9	443	No-Go
13	443	No-Go
8	775	No-Go

RESULTS AND DISCUSSION

The results in Table I obtained by the "Go, No-Go" test on several standard acetone-water solutions show the accuracy of the procedure to be better than ±0.5%.

Table II lists a number of tests on actual tablets and shows the correlation between the quantitative 2,4-dinitrophenylhydrazine assay and the "Go, No-Go" procedure.

These results show the test to be reliable and free from bias caused by the reaction of iodine with the tablet ingredients.

The method fulfills the original requirements which were: (*a*) it can be performed quickly (less than 15 minutes); (*b*) it can be performed by nontechnical personnel; (*c*) it can be done in the immediate production area.

This results in considerable time saving since samples do not have to be submitted to a control laboratory, and there is no waiting period for results. Also tests can be performed during drying operations and the tablets removed from the dryer as soon as they are below the limit. This frees the dryers for other work since it minimizes oven-drying time per lot.

This "Go, No-Go" concept, commonly used in other industries, appears to have many applications in pharmaceutical quality control when applied to the chemical checking for tolerance limits only.

SUMMARY

A general chemical procedure has been presented for rapidly determining whether a product is within a specified tolerance, *i.e.*, a "Go, No-Go" procedure. As an example the procedure is applied to the control of residual acetone in film-coated tablets. This principle could easily be extended to other product ingredients and a "Go, No-Go" test performed at both the maximum and the minimum tolerances.

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Book Notices

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