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Determination of Water in Aluminum Chlorohydrate and Effervescent Tablets by Karl Fischer Analysis

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Abstract □ A procedure was developed for the quantitative determination of loosely bound water in aluminum chlorohydrate and the water content in denture cleanser effervescent tablets. The basic method involves extracting the water from the sample into dioxane followed by titration of the dioxane in methanol with Karl Fischer reagent. Matrix ingredients did not interfere.

Keyphrases □ Aluminum chlorohydrate—water content analyzed by Karl Fischer titration □ Water content—aluminum chlorohydrate, Karl Fischer titration □ Karl Fischer titration—water content of aluminum chlorohydrate analyzed □ Astringents—aluminum chlorohydrate, water content analyzed by Karl Fischer titration

Aluminum chlorohydrate adsorbs free water depending on the surrounding humidity. In dry powder aerosol formulations containing aluminum chlorohydrate, free water can affect product performance. Similarly, in effervescent tablets in sealed packages, water may cause unwanted reactions that can alter the seal integrity or the product itself.

Thermogravimetric analysis and differential scanning calorimetry were used to show the presence of loosely bound water and hydrated water in aluminum chlorohydrate (1). Although free water can be determined by an electrometric approach (1), the method requires a conductivity apparatus, highly purified water, and a standard curve. Moisture in effervescent tablets may be determined by drying over a desiccant, but this procedure is time consuming and the potential for error is increased due to volatile components.

This paper reports the use of the Karl Fischer technique to determine loosely bound water (free water) in aluminum chlorohydrate and water in denture cleanser effervescent tablets without interference from the matrix ingredients.

EXPERIMENTAL

Analysis of Water in Effervescent Tablets—*Reagents*—Karl Fischer reagent[1], the diluent for Karl Fischer reagent[2], and *p*-dioxane[3] were used as received. Diluted Karl Fischer reagent was prepared by diluting 50 ml of Karl Fischer reagent[1] to 250 ml with the diluent for Karl Fischer reagent[2]. A water standard was prepared by weighing 0.06 g of purified water into a preweighed 50-ml volumetric flask. The flask was diluted to the mark with dioxane[3], which usually contains less than 0.005% water.

Apparatus—Karl Fischer titrations were performed with an automatic titrator[4]. A wrist-action shaker[5] was used at its maximum setting. Commercially available 50-ml glass-stoppered centrifuge tubes were dried in an oven at 105°.

Standardization Procedure—Add 100 ml of methanol to a dry titration vessel and titrate with Karl Fischer reagent to the electrometric end-point. Accurately measure the volume of Karl Fischer reagent required to titrate 100 ml of methanol, remove the reagent from the buret, and substitute with diluted Karl Fischer reagent. Discard the titrated methanol and replace it with a fresh 100 ml of methanol. To the fresh methanol, add from a Mohr pipet approximately 0.5 ml less Karl Fischer reagent than the amount required to reach the end-point. Complete the titration using the diluted reagent to the electrometric end-point.

Pipet 10.0 ml of dioxane into the methanolic solution just titrated. Titrate with the diluted Karl Fischer reagent to the electrometric end-point. Record the volume of diluted Karl Fischer reagent used to titrate this system. This sample represents the dioxane reagent blank.

Pipet accurately 10.0 ml of water standard directly into the same titration vessel and titrate with diluted Karl Fischer reagent to the electrometric end-point. Record the volume of diluted Karl Fischer reagent used.

Sample Preparation—Weigh together, to the nearest 10 mg, five tablets that have been crushed within their individual sealed packets (to avoid moisture adsorption from the environment[6]) and empty them into a dry 50-ml centrifuge tube. Reweigh the empty packets and calculate the sample weight by difference.

Pipet accurately 25.0 ml of dioxane into the centrifuge tube and shake on a wrist-action shaker for 15 min. Centrifuge the tube for 5 min.

Procedure—Pipet carefully (without disturbing the insoluble material) 10.0 ml of the dioxane solution into the Karl Fischer titration vessel containing 100 ml of methanol titrated with diluted Karl Fischer reagent to the electrometric end-point. Titrate this sample solution to the electrometric end-point. Record the volume of titrant used. Additional samples can be analyzed by pipetting 10.0 ml of the dioxane solution from another sample into the sample solution just titrated and titrating with the diluted Karl Fischer reagent to the electrometric end-point. Record the volume of titrant used.

Four samples can be analyzed concurrently in the same titrated system. If there is a few minutes of delay between sample analysis, one should titrate the methanolic solution before the next sample is added because of the possibility of moisture entering the titrated system (this titration value need not be recorded).

Calculations—The following equations were used:

$$T = \frac{W}{(V - D)} \qquad \text{(Eq. 1)}$$

[1] Catalog No. SO-K-3, Fisher Scientific Co., Fair Lawn, N.J.
[2] Catalog No. SO-K-5, Fisher Scientific Co., Fair Lawn, N.J.
[3] J. T. Baker Chemical Co., Phillipsburg, N.J.
[4] Precision Auto-Aquatrator, Precision Scientific Co., Chicago, Ill.
[5] Burrell Corp., Pittsburgh, Pa.
[6] Crushing tablets exposed to the atmosphere produces erroneously high results because of water adsorption from the environment.

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Table I—Recovery of Water from Effervescent Tablets

Sample	A[a]	B	C	D	E	Water Recovered, %
1	9.45	5.67	11.48	17.15	17.62	102.7
2	7.93	4.76	11.48	16.24	16.91	104.1
3	12.30	7.40	11.48	18.88	19.17	101.5

[a] A = milligrams of water left in the original tablets before spiking (determined from a 10-ml aliquot for analysis from a total of 25 ml of dioxane). B = milligrams of water left in the remaining 15 ml of dioxane after a 10-ml aliquot was taken for analysis. C = milligrams of water spiked into B. D = total milligrams of water from B + C. E = milligrams of water found in spiked Sample D.

where T is the titer of diluted Karl Fischer reagent (milligrams of water per milliliter of diluted Karl Fischer reagent), W is the milligrams of water in the 10-ml aliquot used for standardization, V is the milliliters of diluted Karl Fischer reagent used to titrate the standard water, and D is the volume of diluted Karl Fischer reagent used to titrate the dioxane (blank).

The percent water found in the sample (P) was calculated using:

$$P = \frac{(K - D) \times T \times 2.5}{S} \times 100 \qquad \text{(Eq. 2)}$$

where K is the milliliters of diluted Karl Fischer reagent used to titrate the sample, D is the volume of diluted Karl Fischer reagent used to titrate the dioxane blank, T is the titer of diluted Karl Fischer reagent, S is the sample weight (milligrams), and 2.5 is the aliquot factor.

Analysis of Loosely Bound Water in Aluminum Chlorohydrate—*Reagents and Apparatus*—The reagents and apparatus required are the same as those described for the analysis of effervescent tablets except that the Karl Fischer reagent is not diluted and the standardization is simplified.

Standardization Procedure—To 100 ml of methanol titrated with Karl Fischer reagent, add 10.0 ml of dioxane and titrate to the electrometric end-point. Record this volume (blank). Accurately weigh, to the nearest 0.1 mg, about 120 mg of purified water directly into the titration vessel and titrate with Karl Fischer reagent to the electrometric end-point. Record the volume.

Sample Preparation—Weigh accurately and quickly, to the nearest milligram, about 10.0 g of aluminum chlorohydrate into a dry 50-ml centrifuge tube. Pipet accurately 25.0 ml of dioxane into the centrifuge tube; shake on a wrist-action shaker for 0.5 hr. Centrifuge the tube for 5 min.

Procedure—Pipet carefully (without disturbing the aluminum chlorohydrate) 10.0 ml of the dioxane solution into the Karl Fischer titration vessel containing 100 ml of methanol titrated with Karl Fischer reagent to the electrometric end-point. Titrate the resulting sample solution to the electrometric end-point. Record the volume of titrant used for the titration.

Several sample solutions can be titrated concurrently in the same titrated solution.

Calculations—Water content can be calculated using the same basic format employed for the effervescent tablet calculations.

Recovery Study—A recovery study was performed on denture cleanser effervescent tablets to determine if water could be recovered at the desired level (less than 0.1%) and if any ingredient in the matrix interfered in the analysis. Tablets first were analyzed for their water content according to the procedure previously described. To the remaining extracted tablets and 15 ml of dioxane (still in the centrifuge tube), a known amount of water (in dioxane) was added. The tablets were extracted once again, and the water content was determined as before.

Recovery data were calculated after determining the amount of water in the original tablets before spiking, the amount of water left in the remaining dioxane after an aliquot was taken for analysis, and the amount of water added to the sample.

RESULTS AND DISCUSSION

Since only the free water content in aluminum chlorohydrate was of interest, and not its water of hydration, the method had to differentiate between the different types of water. Likewise, the procedure had to determine the water in effervescent denture cleanser tablets without interference from other ingredients in the formulation. Analytical techniques involving GLC, distillation, spectroscopy, oven drying, and other methods were also considered for the analysis of water, but the speed, specificity, simplicity, and adaptability of the Karl Fischer technique to the variety of samples tested made it the first choice.

Dioxane was selected (1–5) as the extractant because aluminum chlorohydrate is insoluble in dioxane and it extracts only the loosely bound water from the insoluble aluminum chlorohydrate and not the water of hydration. Likewise, dioxane extracts only the free water in denture cleanser effervescent tablets, leaving behind the interfering insoluble sodium bicarbonate and other potential interfering ingredients. Under ordinary circumstances, Karl Fischer reagent reacts with sodium bicarbonate (5) and also appears to titrate all of the water in aluminum chlorohydrate, which can amount to 25%. Sodium bicarbonate does not interfere since it is rendered insoluble in dioxane and is removed before titrating the dioxane solution.

Although it was reported that the Karl Fischer method was not successful (1) because of the reactivity of aluminum chlorohydrate to Karl Fischer reagent, the dioxane extraction technique eliminates this problem. However, alcohol is necessary in the titration vessel, because titrating dioxane alone gives a premature end-point.

The recovery data of water in effervescent tablets are shown in Table I. At least 500 analyses were performed on denture cleanser effervescent tablets using this modified Karl Fischer procedure.

Experimental tablets as well as commercially available denture cleanser tablets were found to contain between 0.02 and 0.1% water. Samples of aluminum chlorohydrate also were analyzed for loosely bound water. The results obtained agreed well with samples supplied (1) with known levels of loosely bound water at the 0.5 and 2.0% level.

The foregoing methods, although somewhat different, both contain the same basic dioxane extraction technique followed by the Karl Fischer titration. The concept and simplicity of this approach can be adapted to other similar matrixes. This procedure, with some modification, was applied successfully to aerosol formulations containing sodium bicarbonate or aluminum chlorohydrate. The basic technique is to expel a known amount of sample through a plastic tube leading from the actuator directly into dioxane. The propellant is evaporated above room temperature, and the water analysis is conducted as previously described. This technique determines the total available free water within the aerosol product.

This dioxane extraction–titration technique is simple and rapid and should be applicable to a wide variety of products that formerly could not be analyzed by the basic Karl Fischer titration procedure.

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