DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 17(5), 665-679 (1991)

RAPID DETERMINATION OF LOW LEVELS OF WATER IN PRESSURIZED PHARMACEUTICAL INHALATION AEROSOL PRODUCTS

Jo Anne Trotman,* Donna M. Caster, Phyllis E. Zuk and Gregory Rullo

ICI Pharmaceuticals Group
A Business Unit of ICI Americas Inc.
Concord Pike and New Murphy Rd.
Wilmington, DE 19897

ABSTRACT

A simple, fast and rugged method for the determination of low levels of water in pressurized pharmaceutical inhalation aerosol products is described. The pressurized canister is pierced and the contents are directly transferred into a Karl Fischer unit. The water content is measured by coulometric titration. This method has been applied to two commercial products and two development formulations.

INTRODUCTION

Pressurized inhalation aerosol products have been used in the pharmaceutical industry for more than three decades [1]. This drug delivery approach provides for direct administration of active ingredient to the targeted respiratory region. The type of pressurized inhalation aerosol product under study consists of these basic components: propellant, concentrate containing active ingredient, container, valve, and actuator [2]. As such, the analysis of pressurized aerosol products provides a special challenge to pharmaceutical chemists.

One of the analytical methods that can provide meaningful information about the quality of a suspension inhalation aerosol product is the determination of water. Although the water content of such formulations is generally low, even small amounts can hinder the development of a successful aerosol product [2]. For example, the presence of water can alter the physical stability of the active ingredient. Particles can agglomerate, causing a shift of the particle size distribution, and resulting in improper dosing of the targeted respiratory area. Valve sticking and poor dose uniformity are other possible results of agglomeration. If the aerosol product is

stored in a metal canister, dissolved solids and gases in the water can cause corrosion [3]. For active ingredients which tend toward degradation by hydrolysis, the water content of the aerosol product might be significant. Steps can be taken to minimize the water content of the aerosol product during manufacturing by drying valve components and raw materials. A water analysis can be used to determine to what extent this procedure has been successful and as a development tool to monitor water content during storage.

Despite the importance of monitoring water in inhalation aerosol products, a search of primary literature revealed no details of a simple, fast, and rugged method suitable for the routine analysis of water content in a large number of aerosol product samples. In particular, a method adapting a commercially available, automatic Karl Fischer titrator to this application has yet to be published. Literature published in the 1950s addressed non-pharmaceutical applications. In 1954, Reed published his work with refrigerant-oil mixtures in which samples were collected in a small cylinder and then drawn slowly into the titration flask using a positive pressure of dry air [4]. The endpoint was

determined by a manual Karl Fischer titration, and the total analysis time was about one hour per sample. The method provided questionable results below 15 ppm. For use with aerosol insecticide formulations, Downing and Reed published a method in which the sample canister was pierced with a threaded brass piece and the contents titrated into a pressure bottle containing methanol and a known excess of Karl Fischer reagent. Deflection of an attached pH meter was used to determine the endpoint [5]. The analysis time was 20 to 30 minutes with an estimated accuracy error of 20% or less. For the determination of water in propellants (as a raw material analysis), numerous methods are available [6-12]. The ones that utilize Karl Fischer analysis are not specific for use with a modern, commercially available, automatic Karl Fischer titrator.

We report here a simple and rugged method, ideal for routine analysis of a large number of samples, for the determination of low levels of water in pharmaceutical inhalation aerosol products. The pressurized metal canister is pierced and its contents transferred directly into a Karl Fischer titrator for coulometric determination of water. Total analysis time is less than 10 minutes per sample.

Problem areas which were overcome in the development of this method included the following: 1) identification of a suitable automatic titrator with time delay and stable background in the presence of propellants, 2) identification of a rugged, reproducible piercing device, 3) quantitative transfer of the sample canister contents into the titration vessel in a controlled manner, and 4) prevention of atmospheric water contamination during sampling and titration.

EXPERIMENTAL

Apparatus

A Photovolt Aquatest 8 Coulometric Karl Fischer unit with a dual platinum sensing electrode was used. Success was not obtained with a single loop platinum electrode. The transfer apparatus with canister holder as illustrated in Figure 1 required the following for installation. The canister holder (B) was constructed to fit the canister diameter. The holder illustrated is a brass cylinder, 7/8 inch i.d. x 1 1/2 inch o.d. x 1 inch height. A hole was drilled into the cylinder to accept a 1/4 inch NPT threaded fitting. The piercing device (C) is manufactured by Robinair (Robinair Division, Sealed Power Corporation, Robinair Way,

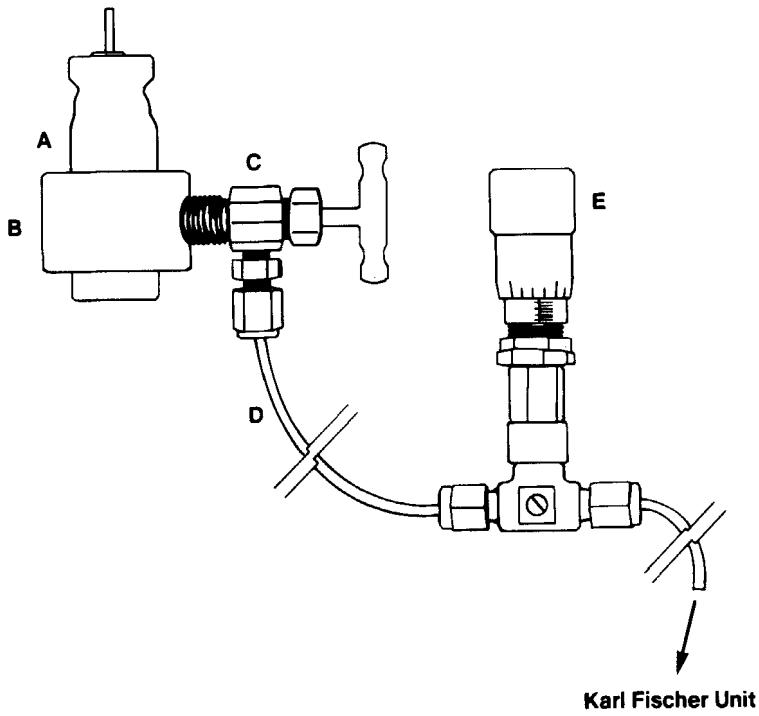

FIGURE 1

Transfer Apparatus. (A) Canister (B) Canister Holder (C) Piercing Device (D) Teflon Tubing (E) Flow Metering Valve

Montpelier, OH, can tap valve #11007) and was obtained from a refrigeration supply store. Figure 2 is a close-up of this device. The fitting on the sidearm of the piercing valve was replaced with a double male-ended adapter. One end of the adapter was made to accept a 1/8 inch female compression fitting and the other end was made to fit the manufacturer's threads on the piercing valve. The Teflon® tubing (D) is 1/8 inch

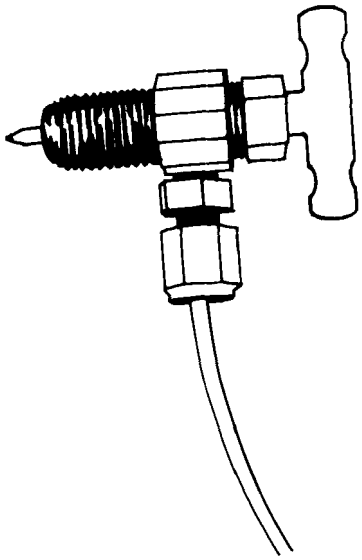

FIGURE 2

Close-up of Piercing Device

o.d. x 1/16 inch i.d. The length from the piercing valve to the flow control valve is 10-12 inches and the length from the flow control valve to the Karl Fischer unit is 14-18 inches. The flow metering valve (E) is a 1/8 inch Nupro straight M-series with Nylon Vernier.

Reagents and Materials

A. Coulometric reagents: HYDRANAL®, Coulomat A and Coulomat C (Riedel-de Haën)

B. Oleic acid, trichloromonofluoromethane, dichlorodifluoromethane, dichlorotetrafluoroethane: National Formulary grade (NF-grade)

C. Canister: Presspart (C128S), aluminum, non-anodized

D. Valve: Bespak (BK356641s)

Procedure

Karl Fischer Unit Setup

Enclose the titration vessel in a plastic bag and purge with dry nitrogen to lower the humidity which inevitably enters the Karl Fischer cell. Set the delay time for 6 min. This time is dependent on the evacuation time observed for the formulation being assayed and should be modified accordingly. Run pure blanks (i.e., introduce no sample) at the beginning, middle, and end of the run. A reading of less than 50 μg should be obtained.

Installation/Setup of Transfer Apparatus

Assemble components of the transfer apparatus as shown in Figure 1. Direction of flow should be from piercing valve to Karl Fischer unit. Place the end of the Teflon tubing (coming from the flow control valve)

through the septum to the bottom of the Karl Fischer vessel.

At the beginning of the assays and after each transfer assay, blow dry nitrogen through the system. The transfer apparatus must be thoroughly rinsed upon completion of the entire day's set of assays with methanol, acetonitrile, or any solvent appropriate for dissolving the formulation being assayed.

Transfer of Aerosol from Canister into Karl Fischer Unit

Shake the sample thoroughly. Ensure that the sample canister fits snugly into the canister holder. Close the flow control valve. Back the stem out of the piercing valve by turning the handle counterclockwise until the piercing needle does not extend past the rubber seal. This is to avoid premature piercing of the canister. Screw the piercing device into the side of the sample canister through the opening in the canister holder. Screw until there is a snug fit. Turn the valve handle clockwise to pierce the canister. As soon as a resistance drop is felt, turn the valve handle counterclockwise to release the contents of the canister.

Press the start button on the Karl Fischer unit. Open the flow control valve slowly, trying to obtain a controlled bubbling (steady stream with slight

agitation of vessel solution) of the aerosol into the vessel. Because the canister will become cool upon release of the propellants, use a hair dryer to keep both the sample canister and flow control valve at a warm to ambient temperature. Shake the canister frequently during the transfer process. Adjust the flow control valve as necessary to obtain a constant bubbling. When the formation of bubbles has slowed down considerably, open the flow valve completely. The transfer is complete when no more bubbles are observed coming from the tubing. For the formulations observed, the transfer of aerosols into the Karl Fischer unit was complete in 3-5 min., hence the 6 min. delay. The amount of water in the canister is the reading on the Karl Fischer unit corrected for the blank. If the average blank is less than 5% of the sample reading, it is not necessary to use this correction.

RESULTS AND DISCUSSION

Accuracy

Recovery studies were performed by spiking uncapped canisters containing a drug substance with 0 μL (control), 1 μL, 2 μL, and 3 μL of water. Oleic acid

TABLE 1

Recovery Study Performed by Spiking Canisters Containing an Aerosol Formulation with 0 μL (Control), 1 μL, 2 μL, and 3 μL of Water.

SAMPLE	μg WATER	% RECOVERY	MEAN RECOVERY
0 μL spiked	268	--	
	349	--	
	263	--	--
1 μL spiked	1190	89.7	
	1086	79.3	84.5
2 μL spiked	2089	89.8	
	1828	76.8	83.3
3 μL spiked	2573	76.0	
	2621	77.6	76.8

and trichloromonofluoromethane were added, the valves were crimped on the canisters, and the canisters were pressure filled with dichlorodifluoromethane and dichlorotetrafluoroethane. Care was taken to minimize the time elapsed from the spiking procedure to the crimping of the valves onto the canisters (less than 3 minutes). The assays were performed approximately 2-4 hours after manufacture. The results obtained for the samples containing the various amounts of water are shown in Table 1. The mean recovery for the three levels was 81.5% with a range of 76.0 to 89.8%.

TABLE 2

Precision Results of Two Inhalation Aerosol Development Lots of an In-house Formulation and Two Commercial Inhalation Aerosol Products.

IN-HOUSE A [μg Water / Canister]	IN-HOUSE B [μg Water / Canister]	COMMERCIAL C [μg Water / Canister]	COMMERCIAL D [μg Water / Canister]
1462	923	795	1084
1700	846	875	784
1780	848	967	891
1416	862	1027	841
1338	785	980	904
1297	821	1061	779
± = 1499	848	951	881
%RSD = 13.1	5.4	10.4	12.8

Although this is lower than theory, recovery is sufficient for monitoring aerosol products.

Precision

Precision experiments were performed on 2 lots (In-house A and B) of pharmaceutical inhalation aerosol products of the same formulation as referred to in the accuracy section. The relative standard deviations (n=6) were 13.1 and 5.4%. Precision was also performed on 2 commercially available inhalation aerosol

products. The relative standard deviations (n=6) were 10.4 and 12.8%. The results, which are given in Table 2, represent typical water determinations on canisters we have analyzed. Although the percent relative standard deviation is relatively high, it is not only a measure of the precision of the method but also of the variation of moisture content from canister to canister.

Detection Limit

The detection limit is estimated to be 10–50 μg water per canister, which represents 0.5 to 2.5 ppm for a 20 g fill weight. The actual detection limit is dependent upon the degree of protection of the coulometric cell from laboratory humidity and, as such, may vary among testing sites.

Ruggedness

The three factors studied to evaluate their effect on the method were evacuation time, application of heat, and necessity of shaking. Lot In-house A was used for these studies. The evacuation time varied from 1–6 min. The canisters were evacuated both with and without heat and shaking. The results were not significantly different for any of the three factors.

The values ranged from 1467 to 1655 μg per canister which is consistent with the precision data.

If solubility problems occur from the aerosol formulation coming into direct contact with the Karl Fischer reagents, an indirect delivery method can be utilized. Using the piercing device, the contents of the aerosol product are transferred into a closed, vented test tube containing methanol into which the water is extracted. A Karl Fischer coulometric titration is then performed on the methanolic solution. Similar accuracy and precision are obtained as with direct delivery. However, this method is more time consuming and labor intensive.

ACKNOWLEDGEMENT

The authors thank Alan Kirschner and Daniel Steible for their assistance.

REFERENCES

1. Mintzer, H., Pharm. Technol., 7(3), 40 (1983).
2. Lachman, L., Lieberman, H. A., Kanig, J. L., "The Theory and Practice of Industrial Pharmacy," Lea and Febiger, Philadelphia, 1986.
3. Sanders, P. A. "Handbook of Aerosol Technology," van Nostrand Reinhold, New York, 1979.
4. Reed, F. T., Refrig. Eng., 62, 65 (1954).

5. Reed, F. T., Downing, R. C., 38th Ann. Meet. Chem. Spec. Manuf. Assoc., 1951, 41.
6. Du Pont Freon Technical Bulletin B-23, E. I. du Pont de Nemours & Company, 1956.
7. Technical Paper No. 8, E. I du Pont de Nemours & Company, 1950.
8. Griest, W. P., Refrig. Eng., 42, 316 (1941).
9. Benning, A. F., Ebert, A. A., Irwin, C. F., Refrig. Eng., 55, 166 (1948).
10. Elsey, H. M., Refrig. Eng., 57, 665 (1949).
11. Pennington, W. A., Anal. Chem., 21, 766 (1949).
12. ASTM Designation: E700-79, General Products, Chemical Specialties, and End Use Products, 1987, 15.05, 614.