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DETERMINATION OF WATER IN PRESSURIZED PHARMACEUTICAL METERED DOSE AEROSOL PRODUCTS

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ABSTRACT

An easy, rapid and reproducible method for the determination of a low level of water content in pressurized metered dose aerosol products is described. A Mitsubishi Moisture Meter Model CA-06 with Karl Fischer reagent was used for this study. The sample can be introduced into the reagent chamber through the septum plug using a syringe needle from the valve of sample canister. One determination takes 2~3 minutes and the results are accurate and reproducible (CV=2~6%) in the

range of 10~30 ppm, H_2O. The linear correlation coefficient was 0.9994 in the range of 50-200 μg of H_2O.

INTRODUCTION

It has been well recognized that the water content in pressurized metered dose suspension aerosol is very critical for the stability and homogeneity of drug suspension, and the reproducibility of drug delivery (1.4). Most drugs are water soluble and trace amount of water in the suspension system usually will function as a cosolvent to increase the solvent power of the liquid propellant phase. This small amount of increasing solubility will induce the particle growth by the Ostwald ripening process (2) in which smaller particles dissolve and larger particles grow. It was also observed that high moisture content may cause particle adherence to each other and on to the container surface which may be polar in nature. This will result in blocking the valve or the actuator, resulting in a lower drug delivery than the target amount. The moisture content in sample canisters in the humid environment varies and increases with the age of such products (3). Therefore, accurate water determination is important in the formulation development and stability study.

A recent article (5) about this subject has been published, however, it was found that the present method

is also a convenient, accurate, and reproducible method as a routine analysis for a large number of samples.

EXPERIMENTAL

Apparatus

A Mitsubishi Moisture Meter, Model CA-06 was used for this study. The experimental set-up and sampling method are illustrated in Figure 1. The titration chamber accommodates detection electrode, anode solution (Aquamicrone A) and cathode solution cell containing cathode solution (Aquamicrone C) and Pt electrodes. A sample canister attached with a long syringe needle using a plastic adaptor (as shown in Figure 2) is inserted through the septum plug of the sample chamber.

Reagents and Materials

1. Karl Fischer anode solution, Aquamicron A, Karl Fischer cathode solution, Aquamicron C. These solutions are from Mitsubishi Kasei Corp.
2. Syringe needle, #18, 10 cm
3. Syringe needle adaptor, it can be conveniently made with the tip of a plastic disc filter (e.g., Millex-HV, Millipore).

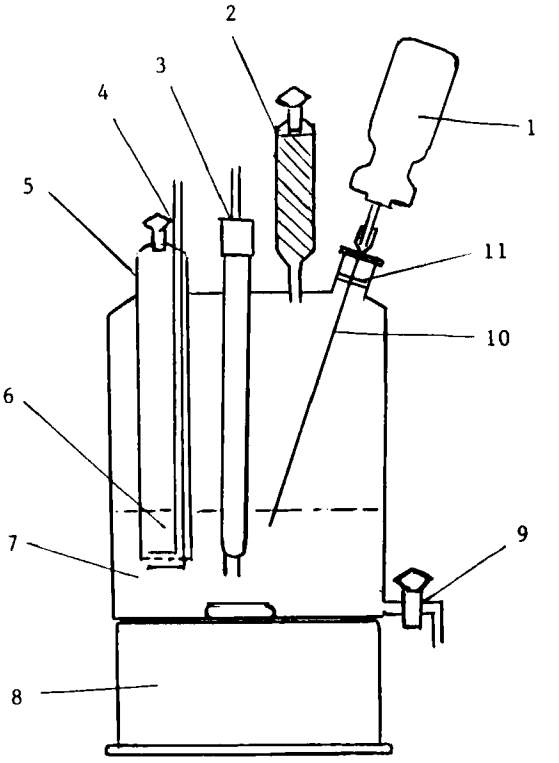

FIGURE 1

Titration Chamber and Sampling Arrangement. 1. Sample, 2. Desiccant, 3. Detector electrode, 4. Cathode electrode, 5. Cathode cell, 6. Cathode solution, 7. Anode solution, 8. Magnetic Stirrer, 9. Drain, 10. Needle, 11. Septum plug

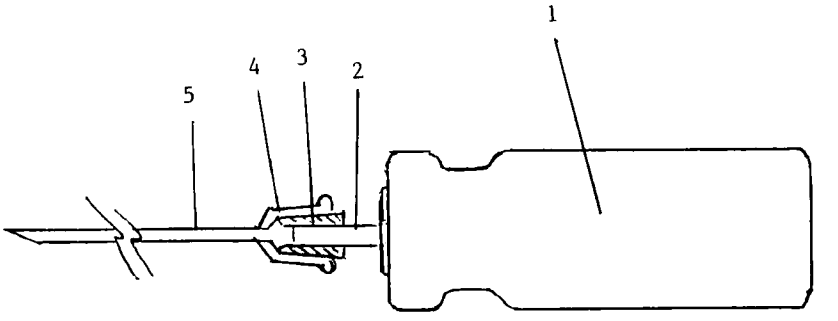

FIGURE 2

Sample Valve Adaptor. 1. Sample canister, 2. Valve stem, 3. Plastic adaptor, 4. Needle hub, 5. Syringe needle.

Procedure

Flush the syringe needle with dry air or N_2 gas and wipe the needle stem with a dry tissue paper. The needle hub is plugged with a plastic plug. Insert the needle through the septum into the sample chamber and maintain the needle tip above the reagent surface. Prime the sample unit about 10 times through an actuator into a hood. Remove the actuator and weigh the unit with the adaptor (for the needle) attached to the valve tip. When the instrument is ready, shake the sample for a few seconds and insert the valve tip with the adaptor into the needle hub after removing the plug. Press the instrument START key and position the needle tip under the reagent surface. Actuate the sample valve 10 times, dispersing the aerosol into the reagent. Remove the sample canister with the adaptor and replace the plug in the needle hub. The needle remains in the sample chamber. Weigh the sample unit with adaptor and enter the weight before and after actuation into the instrument.

RESULTS AND DISCUSSION

Linearity

The moisture content measured by the coulometric method which uses Karl Fischer reagent does not require

TABLE 1

Linearity Between Sample Amount and Water

	5 SPRAY		10 SPRAY		15 SPRAY	
	Sample Wt.(g)	H_2O µg)	Sample Wt.(g)	H_2O µg)	Sample Wt.(g)	H_2O µg)
	0.4221	11.2	0.8309	20.5	1.2500	31.0
	0.4209	10.7	0.8372	21.3	1.1969	31.6
	0.4220	11.0	0.8376	20.7	1.1584	29.9
Avg =	0.4217	10.9	0.8352	20.8	1.2018	30.8
SD =	0.007	0.25	0.0038	0.42	0.046	0.86
RSD =	0.16%	2.3%	0.45%	2.0%	3.8%	2.8%

an external standard for quantitation. The sensitivity of the instrument is 0.1 µg of H_2O. The linearity was tested in the range from 10 µg to 30 µg H_2O which is the expected working range, and a good linearity has been obtained as shown in Table 1, Figure 3.

Precision

The system and method precision was tested with a commercial inhalation aerosol, anhydrous ethanol and with the instrument check solution provided by the manufacturer. The relative standard deviations were 3.7%, 5.4%, and 2.9% at 24 ppm H_2O, 36 µg H_2O, and 0.41% H_2O respectively. (Table 2)

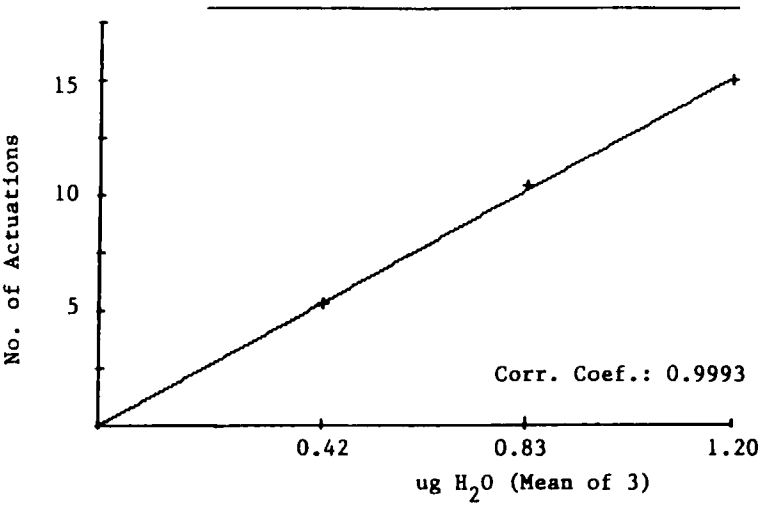

FIGURE 3

Linearity between sample amount and quantity of water measured.

TABLE 2

Precision of the Method for Three Different Type of Samples

Aerosol			Anhydrous Ethanol		Instrument Check Solution	
Sample Wt.	H_2O (µg)	(ppm)	Sample Vol.	H_2O (µg)	Sample Vol.	H_2O (%)
0.8306	20.2	24.3	50 (µL)	39.3	50 (µL)	0.425
0.8404	21.0	24.9	50 (µL)	34.7	50 (µL)	0.401
0.8378	20.7	24.7	50 (µL)	36.5	50 (µL)	0.422
0.8315	18.8	22.7	50 (µL)	36.5	50 (µL)	0.416
0.8367	20.4	24.4	50 (µL)	34.4	50 (µL)	0.399
Avg=0.8354	20.2	24.2		36.3		0.413
SD =0.0042	0.85	0.9		1.95		0.012
RSD=0.5%	4.2%	3.7%		5.4%		2.9%

TABLE 3

Recovery of H_2O From Spiked Anhydrous Ethanol and Linearity*

Volume (µL)	H_2O (µg) (Added)	H_2O (µg) (Found)	% Recovery
50	46.3	50.8	109.7
100	92.6	100.3	108.3
150	138.9	148.2	106.7
200	185.2	204.0	110.1
			Mean=108.7**
			SD = 1.5
			RSD = 1.4%

* Spiked sample was prepared by mixing 4 µL of water in 3.4069g of anhydrous ethanol (d = 0.789). The volume of ethanol is 4.3 mL.
** High recovery may be due to errors in sample preparation, volume measurements, and background water in anhydrous ethanol.

Recovery

Although the method is an absolute method, the accuracy was evaluated with H_2O spiked anhydrous ethanol. The results demonstrate the spiked water was accuratley recovered and a good linear relationship between the quantity of water added and the measured results was obtained as shown in Table 3, Figure 4.

The average recovery and precision by the method of Trotman (5) were 81.5% and >10% which may be due to difficulty of complete sample transfer, eventhough the

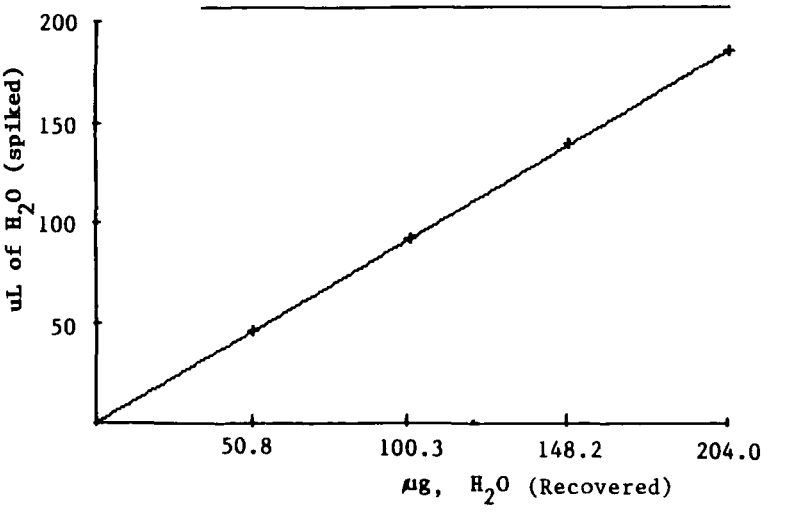

FIGURE 4

Linearity of water from spiked sample and volume of sample.

sample canister was heated by a hair dryer. Also the solid residue could not be transferred completely from the canister and some might be trapped in the long transfer tubing (1/16 inch x 2.5 ft). The present method uses a short and narrow transfer adapter and does not use a whole canister of sample for each determination. This method produced not only good precision (<4%) and good linearity between sample amount and quantity of water, but also significantly reduced the analysis time (2~3 minutes).

Ruggedness

Ruggedness was tested by the determination of water content in three (3) aerosol canisters on two separate

TABLE 4

Ruggedness Test Results.

	ANALYST #1			ANALYST #2		
Sample	1	2	3	1	2	3
ppm, H_2O	27.9	24.2	29.0	28.4	25.9	30.3
	26.3	25.5	27.2	27.9	25.7	29.4
	25.5	25.6	25.3	29.1	25.2	29.4
	26.5	27.8	26.2	29.6	25.6	29.8
	26.9	23.5	28.8	28.9	27.3	29.4
Mean	26.6	25.3	27.3	28.8	25.9	29.7
SD	0.89	1.7	1.6	0.65	0.82	0.38
RSD	3.3%	6.6%	5.9%	2.3%	3.2%	1.3%

days by two different analyst with a given system. Analyst #1 reported means of 26.6 ppm, 25.3 ppm, and 27.3 ppm with relative standard deviation of 3.3%, 6.6%, and 5.9% respectively. Analyst #2 reported means of 28.8 ppm, 25.9 ppm, and 29.7 ppm with relative standard deviations of 2.3%, 3.2%, and 1.3% respectively. Considering the level of water concentrations, the reproducibilities are good. (Table 4)

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