

continuously record the weight loss as the sample is heated at a rate of 20° per minute from room temperature to about 200 ° C. The weight loss plateau, or inflection, at about 150 ° C is taken as the total volatile weight loss. Calculate the percent weight loss on drying.

[39 FR 18944, May 30, 1974, as amended at 50 FR 48397, Nov. 25, 1985; 51 FR 11572, Apr. 4, 1986]

§ 436.201 Moisture determination.

(a) *Equipment*—(1) *Apparatus*. Use a closed system consisting of all glass automatic burettes, platinum electrodes, and a magnetic stirrer connected to a suitable electrometric apparatus. This apparatus embodies a simple electrical circuit which serves to pass 5 to 10 microamperes of direct current between a pair of platinum electrodes immersed in the solution to be titrated. At the endpoint of the titration a slight excess of the reagent increases the flow of current to between 50 and 150 microamperes for 30 seconds or longer, depending upon the solution being titrated.

(2) *Titration vessel*. Use a suitable titrating vessel which has been previously dried at 105° C. and cooled in a desiccator.

(b) *Reagents*—(1) *Karl Fischer reagent*. Dissolve 125 grams of iodine in 170 milliliters of pyridine, add 670 milliliters of methanol and cool. To 100 milliliters of pyridine kept in an ice bath, add sulfur dioxide until the volume reaches 200 milliliters. Slowly add this solution to the cooled iodine-methanol-pyridine mixture and shake well. (A commercially prepared Karl Fischer reagent, pyridine containing or pyridine-free, may be used.) Preserve the reagent in glass-stoppered bottles protected from light and from moisture in the air.

(2) *Methanol solution*. Add sufficient water (usually 2 milligrams per milliliter) to methanol so that each milliliter of the resulting methanol solution is equivalent to about 0.5 milliliter of Karl Fischer reagent.

(3) *Solvents*—(i) *Solvent A*. Methanol:chloroform:carbon tetrachloride (1:2:2 by volume).

(ii) *Solvent B*. Chloroform:carbon tetrachloride (1:1 by volume).

(iii) *Solvent C*. Anhydrous methanol.

(c) *Standardization of reagents*—(1) *Water equivalence of Karl Fischer reagent*. Standardize the Karl Fischer reagent no longer than 1 hour before use by one of the following methods.

(i) Accurately weigh 25–35 milligrams of water into a dry titration vessel and add 20 milliliters of solvent A. Start the stirrer and titrate to the endpoint by adding measured quantities of Karl Fischer reagent. Calculate the water equivalence of the Karl Fischer reagent as follows:

$$e = \frac{W}{V_T - V_A}$$

where:

e=Water equivalence of the Karl Fischer reagent in terms of milligrams of water per milliliter;

W=Milligrams of water;

V_T=Milliliters of Karl Fischer reagent used;

V_A=Milliliters of Karl Fischer reagent equivalent to the 20 milliliters of solvent A, determined as directed in paragraph (c)(3) of this section.

(ii) Accurately weigh about 25–35 milligrams of water into a dry titration vessel, add an excess of Karl Fischer reagent, start the stirrer, and titrate to the endpoint with methanol solution. Calculate the water equivalence of the Karl Fischer reagent as follows:

$$e = \frac{W}{V_T - V_A}$$

where:

e=Water equivalence of the Karl Fischer reagent in terms of milligrams of water per milliliter;

W=Milligrams of water;

V_T=Milliliters of Karl Fischer reagent used;

V_m=Milliliters of methanol solution used;

f=Milliliters of Karl Fischer reagent equivalent to each milliliter of methanol solution determined as directed in paragraph (c)(2) of this section.

(2) *Karl Fischer reagent equivalence of methanol solution*. Titrate a known volume of Karl Fischer reagent with methanol solution until the endpoint is reached. Calculate the milliliters of Karl Fischer reagent equivalent to each milliliter of methanol solution as follows:

$$e = \frac{W}{(V_T - V_m) \times f}$$

where:

f =Milliliters of Karl Fischer reagent equivalent to each milliliter of methanol solution;

V_T =Milliliters of Karl Fischer reagent used;

V_m =Milliliters of methanol solution used.

(3) *Karl Fischer reagent equivalence of solvents.* (i) Solvent A: Use 20 milliliters of solvent A as the sample. Start the stirrer and titrate to the endpoint by adding measured quantities of Karl Fischer reagent.

(ii) Solvent B: Use 10 milliliters of solvent B as the sample. Add an excess of Karl Fischer reagent to the sample and start the stirrer. Titrate to the endpoint with methanol solution.

(iii) *Solvent C.* Use 20 milliliters of solvent C as the sample. Start the stirrer and titrate to the endpoint by adding measured quantities of Karl Fischer reagent.

(iv) Calculate the Karl Fischer reagent equivalence of the solvents as follows:

$$V_A = V_C = V_T,$$

$$V_B = (V_T - V_m) \times f$$

where:

$V_A, V_B,$ and V_C =Milliliters of Karl Fischer reagent equivalent to the aliquots used of solvents A, B, and C, respectively;

V_T =Milliliters of Karl Fischer reagent used;

V_m =Milliliters of methanol solution used;

f =Milliliters of Karl Fischer reagent equivalent to each milliliter of methanol solution determined as directed in paragraph (c)(2) of this section.

(d) *Sample preparation*—(1) *Powders.* In the case of tablets, grind 4 tablets to a fine powder. In the case of capsules containing enteric-coated pellets, grind the pellets to a fine powder. If the maximum moisture limit is greater than 1 percent, accurately weigh about 300 milligrams of the sample into a dry titrating vessel. If the maximum moisture limit is less than 1 percent, accurately weigh 1 to 2 grams of the sample. Proceed as directed in paragraph (e)(1) or (2) of this section.

(2) *Ointments and oils.* (i) Transfer about 1 to 2 grams, accurately weighed, into a dry titrating vessel. Proceed as directed in paragraph (e)(1) of this section; or

(ii) Transfer about 1 to 2 grams, accurately weighed, into a dry titrating vessel. Add 10 milliliters of solvent B and proceed as directed in paragraph (e)(2) of this section.

(3) *Aerosols with propellant.* Place the immediate container to be tested in a suitable freezing unit having a temperature of not higher than 0° C. for at least 2 hours. Remove the container from the freezing unit, puncture it, mix the entire contents by swirling. Proceed as directed in paragraph (e)(3) of this section, using an accurately measured 10-milliliter aliquot from the container as the sample and allowing the solution to warm to at least 10° C. before determining the endpoint.

(4) *Hygroscopic powders.* Weigh the immediate container. Using a suitable dry hypodermic needle and syringe, inject 3 milliliters of anhydrous methanol into the container and shake to dissolve the contents. Using the same syringe, remove the withdrawable contents and transfer into the titration vessel. Rinse the syringe and needle by drawing in an additional 3 milliliters of anhydrous methanol. Add the rinsings to the titration vessel. Titrate the solution immediately, proceeding as directed in paragraph (e)(3) of this section. Determine the Karl Fischer equivalent (in milliliters), if any, of the anhydrous methanol by titrating a blank of the same total volume used in preparing the sample and rinsing the syringe and needle. Dry the immediate container and its closure for three hours at 100° C., cool to room temperature in a desiccator, and weigh. Determine the weight of sample tested by subtracting the weight obtained from the original weight of the immediate container.

(5) *Solutions.* Proceed as directed in paragraph (e)(3) of this section, using about 1 to 2 grams of the sample, accurately weighted.

(e) *Titration procedures and calculations*—(1) *Procedure 1.* Add 20 milliliters of solvent A to the sample. Start the stirrer and titrate to the endpoint by adding measured quantities of Karl Fischer reagent. Determine the percent moisture in the sample as follows:

$$\text{Percent moisture} = \frac{(V_T - V_A) \times e \times 100}{W_s}$$

where:

e =Water equivalence of the Karl Fischer reagent determined as directed in paragraph (c)(1) of this section;

V_T =Milliliters of Karl Fischer reagent used;

V_A =Milliliters of Karl Fischer reagent equivalent to the 20 milliliters of solvent A, determined as directed in paragraph (c)(3) of this section;

W_s =Weight of the sample in milligrams.

(2) *Procedure 2.* Add an excess of Karl Fischer reagent to the sample, start the stirrer, and titrate to the endpoint with methanol solution. Calculate the percent moisture in the sample as follows:

(i) For powders:

$$\text{Percent moisture} = \frac{(V_T - V_m f) \times e \times 100}{W_s}$$

(ii) For oils and ointments:

$$\text{Percent moisture} = \frac{(V_T - V_m f - V_B) \times e \times 100}{W_s}$$

where:

V_T =Milliliters of Karl Fischer reagent used;

V_m =Milliliters of methanol solution used;

f =Milliliters of Karl Fischer reagent equivalent to each milliliter of methanol solution determined as directed in paragraph (c)(2) of this section.

V_B =Milliliters of Karl Fischer reagent equivalent to the 10 milliliters of solvent B determined as directed in paragraph (c)(3) of this section;

e =Water equivalence of the Karl Fischer reagent determined as directed in paragraph (c)(1) of this section;

W_s =Weight of the sample in milligrams.

(3) *Procedure 3.* Add about 20 milliliters of solvent A to a dry titrating vessel and proceed as directed in titration procedure 1 or 2. Disregard the volume of reagents used to determine the endpoint. Promptly introduce an accurately weighed or measured quantity of sample into the titrating vessel and titrate to the endpoint using either titration procedure 1 or 2 without additional solvents. Calculate the percent moisture in the sample as follows:

(i) If titration procedure 1 is used:

$$\text{Percent moisture in weighed samples} = \frac{V_T \times e \times 100}{W_s}$$

$$\text{Percent moisture in aerosols} = \frac{V_T \times e}{\text{Milliliters of sample} \times 10}$$

Percent moisture in hygroscopic powders=

$$\text{Percent moisture in hygroscopic powders} = \frac{(V_T - V_b) \times e \times 100}{W_s}$$

(ii) If titration procedure 2 is used:

$$\text{Percent moisture in weighed samples} = \frac{(V_T - V_m f) \times e \times 100}{W_s}$$

$$\text{Percent moisture in aerosols} = \frac{(V_T - V_m f) \times e}{\text{Milliliters of sample} \times 10}$$

$$\text{Percent moisture in hygroscopic powders} = \frac{(V_T - V_m f - V_b) \times e \times 100}{W_s}$$

where:

V_T =Milliliters of Karl Fischer reagent used;

V_m =Milliliters of methanol solution used;

f =Milliliters of Karl Fischer reagent equivalent to each milliliter of methanol solution determined as directed in paragraph (c)(2) of this section;

V_b =Karl Fischer equivalent (in milliliters) of the methanol used as a sample solvent;

e =Water equivalence of the Karl Fischer reagent determined as directed in paragraph (c)(1) of this section.

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§ 436.202 pH.

(a) *Apparatus.* A suitable potentiometer fitted with two electrodes, one being constructed of glass and sensitive to hydrogen ion activity and the other being a calomel or a silver/silver chloride reference electrode. A combination electrode with glass electrode and reference electrode contained in the same system may be used.

(b) *Standardization.* Select two standard buffer solutions such that the expected pH value of the sample is within their pH range and is also within 2 pH