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Mylan	GENERAL TEST PROCEDURE	Mylan, Nashik
Title: Loss on Drying		
GTP No: GTP005-09	**Reference/s:** USP/ BP/ Ph.Eur./JP/IP	
Supersedes: GTP005-08	**Effective Date:** 30 OCT 2020	

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1.0 OBJECTIVE: To determine "Loss on Drying" of the test sample.

2.0 PRINCIPLE: This test determines the amount of volatile matter of any kind that is driven off under the conditions specified.

UNITED STATES PHARMACOPEIA

Note: Follow the instructions before proceeding with the analysis.

Procedure:

1. Weigh an empty glass-stoppered, shallow weighing glass bottle that has been previously dried for 30 minutes under the same conditions to be employed in the determination. Cool to room temperature in a desiccator over silica gel and weigh. Note down the weight, in g, as W_1.
2. Mix and accurately weigh about 1 to 2 g (or the quantity specified in the individual standard test procedure) of the substance, into the above dried and cooled empty glass bottle and replace the cover. Accurately weigh the bottle and the contents. Note down the weight, in g, as W_2.
3. By gentle, sidewise shaking, distribute the test specimen as evenly as practicable to a depth of about 5 mm generally and not more than 10 mm in the case of low bulky materials.
4. Place the loaded bottle in the drying chamber, remove the stopper and leave it also in the chamber. Dry the test specimen at the specified temperature and for the time conditions.

   [**Note:**

   - The loss on drying is a function of both the temperature and time. Therefore, these values must be identified and reported.
   - The temperature specified in the standard test procedure is to be regarded as being within the range of ± 2° of the stated value.]
5. When "Dry to constant weight" is specified in a monograph, drying shall be continued until two consecutive weighings do not differ by more than 0.50 mg of specimen taken, where the second weighing follows an additional hour of drying.
6. Upon opening the chamber, reapply the same stopper to the bottle, and allow it to come to room temperature in a desiccator before weighing accurately. Weigh the bottle and its contents. Note down the weight, in g, as W_3.

$$\text{Loss on drying (\% w/w)} = \frac{(W_2 - W_3)}{(W_2 - W_1)} \times 100$$

Note: Continue testing through point No.6 if the individual standard test procedure mentions performing the test to constant weight.

7. Place the loaded bottle (from point No. 5) in the drying chamber, removing the stopper and leaving it also in the chamber. Dry the bottle with contents at the temperature mentioned in the individual standard test procedure and for a period of 1 hour.

8. Upon opening the chamber, close the bottle promptly, and allow it to come to room temperature in a desiccator. Weigh the bottle and its contents. Note down the weight, in g, as W_4.

9. Continue the drying-cooling-weighing procedure (as given under points No. 6 & 7) till constant weight is achieved, i.e. consecutive weighings do not differ by more than 0.50 mg / g of the substance taken.

10. Note down the final weight of the bottle with the contents, in g, as W_f.

$$\text{Loss on drying (\% w/w)} = \frac{(W_2 - W_f)}{(W_2 - W_t)} \times 100$$

Instructions:

1. If the test specimen is in the form of large crystals, reduce the particle size to about 2 mm by quickly crushing.
2. If the substance melts at a lower temperature than that specified for the determination of Loss on drying, maintain the bottle with its contents for 1 to 2 hours at a temperature 5°C to 10°C below the melting temperature, then dry at the specified temperature.
3. Where capsules are to be tested, use a representative sample mixture, excluding the capsule shell, from not fewer than 4 capsules.
4. Where tablets are to be tested, use a representative sample mixture from NLT 4 crushed tablets.
5. When the standard test procedure directs that loss on drying be determined by thermogravimetric analysis, sensitive electrobalance should be used.
6. Where drying in vacuum over a desiccant is directed in the individual standard test procedure, a vacuum desiccator or a vacuum drying pistol, or other suitable vacuum drying apparatus, is to be used. The term "in vacuum" denotes exposure to pressure of less than 20 mm of mercury, unless otherwise specified in the individual standard test procedure.
7. Where drying in a desiccator is specified, exercise particular care to ensure that the desiccant is fully effective.
8. Where drying in a capillary-stoppered bottle in vacuum is directed in the individual standard test procedure, use a bottle or tube fitted with a stopper having a 225 ± 25 µm diameter capillary, and maintain the heating chamber at a pressure of 5 mm or less of mercury.

9. At the end of the heating period, admit dry air to the heating chamber, remove the bottle, and with the capillary stopper still in place allow it to cool to a room temperature in a desiccator before weighing.

EUROPEAN/ BRITISH PHARMACOPOEIA

Principle:

Loss on drying is the loss of mass after drying under specified conditions, calculated as per percentage (m/m)

Drying to constant mass means that 2 consecutive weighings do not differ by more than 0.5mg, the 2nd weighing following an additional period of at least 30 min of drying under the conditions prescribed for the substance to be examined.

Equipment:

The equipment typically consists of:

- Weighing bottle that are made up of suitable inert material and can easily be dried to constant mass; their diameter is large enough so that the layer of substance to be examined does not exceed about 5mm;
- An analytical method by which it is possible to determine a change in mass of 0.1 mg;
- Depending on the procedure to be applied, a desiccator , a vacuum cabinet, a vacuum oven or ordinary laboratory oven ; in any case, the temperature of oven is adjustable to specified temperature ± 2°C; vacuum oven in which the pressure can at least be reduced to about 2 kPa are suitable; ovens are qualified according to established quality system procedure, for example by using a suitable certified reference material (Sodium aminosalicylate dihydrate for equipment qualification CRS may be used)

Equipment using other means of drying such as microwaves, halogen lamps, infrared lamps or mixed technologies may be used provided they are demonstrated to be fit for purpose.

Note: Follow the instructions given before proceeding with the analysis.

Procedure:

Note: It is recommended to perform the test in an environment that has minimal impact on sample measurement (e.g. humidity)

1. Weigh an empty glass-stoppered, shallow weighing glass bottle that has been previously dried for 30 minutes under the same conditions to be employed in the determination. Cool to room temperature in a desiccator and weigh. Note down the weight, in g, as W_1.

2. Transfer an accurately weighed amount of the substance as given in the individual standard test procedure, into the above dried and cooled empty glass bottle and replace the cover. Accurately weigh the bottle and the contents. Note down the weight, in g, as W_2.

3. By gentle, sidewise shaking, distribute the test specimen as evenly as practicable.

4. Place the loaded bottle in the drying chamber, removing the stopper and leaving it also in the chamber. Dry the test specimen at the temperature and for the time specified in the individual standard test procedure. [Note—where the drying temperature in the standard test procedure is indicated by a single value rather than a range, drying should be carried out at the prescribed temperature ± 2°C].

Use one of the following procedures, unless otherwise prescribed in monograph.

- **In a desiccator:** the drying is carried out over about 100 g of molecular sieve R at a atmospheric pressure and at room temperature.

- **In vacuo:** the drying is carried over about 100 g of molecular sieve R at a pressure not exceeding 2.5 kPa, at room temperature or at temperature prescribed in the monograph.

- **In an oven at a specified temperature:** the drying is carried out at atmospheric pressure in an oven at the temperature prescribed in the monograph.

5. Upon opening the chamber, close the bottle promptly, and allow it to come to room temperature in a desiccator. Weigh the bottle and its contents. Note down the weight, in g, as W_3.

$$\text{Loss on drying (\% w/w or \% m/m)} = \frac{(W_2 - W_3)}{(W_2 - W_1)} \times 100$$

Note: Continue testing through point No.6 if the individual standard test procedure mentions performing the test to constant weight.

6. Place the loaded bottle (from point No. 5) in the drying chamber, removing the stopper and leaving it also in the chamber.

7. Dry the bottle with contents at the temperature mentioned in the individual standard test procedure and for a period of 1 hour or as mentioned in the individual standard test procedure.

8. Upon opening the chamber, close the bottle promptly, and allow it to come to room temperature in a desiccator. Weigh the bottle and its contents. Note down the weight, in g, as W_4.

9. Continue the drying-cooling-weighing (as given under points 6 and 7) procedure till constant weight is achieved, i.e. consecutive weighings do not differ by more than 0.5 mg.

10. Note down the final weight of the bottle with the contents, in g, as W_f.

$$\text{Loss on drying (\% w/w or \% m/m)} = \frac{(W_2 - W_f)}{(W_2 - W_1)} \times 100$$

JAPANESE PHARMACOPOEIA

Objective:

To measure the loss in mass of the sample, when dried under the conditions specified in each monograph.

Note: This method is applied to determine the amount of water, all or a part of water of crystallization, or volatile matter in the sample, which is removed during the drying.

The description, for example, "not more than 1.0% (1 g, 105°C, 4 hours)" in a monograph, indicates that the loss in mass is not more than 10 mg per 1 g of the substance in the test in which about 1 g of the substance is accurately weighed and dried at 105°C for 4 hours, and "not more than 0.5% (1 g, in vacuum, phosphorus (V) oxide, 4 hours)," indicates that the loss in mass is not more than 5 mg per 1 g of the substance in the test in which about 1 g of the substance is accurately weighed, transferred into a desiccator (phosphorus (V) oxide), and dried in vacuum for 4 hours.

Procedure

1. Weigh accurately a weighing bottle (W_1) that has been dried for 30 minutes according to the method specified in the monograph.
2. Take the sample within the range of ± 10% of the amount directed in the monograph, transfer into the weighing bottle, and, unless otherwise specified, spread the sample so that the layer is not thicker than 5 mm, then weigh it accurately (W_2).
3. Place the loaded bottle in a drying chamber, and dry under the conditions specified in the monograph.
4. When the size of the sample is large, convert it to small particles having a size not larger than 2 mm in diameter by quick crushing, and use the crushed sample for the test.

5. After drying, remove from the drying chamber, and reweigh accurately (W_3).
6. When the sample is dried by heating, the temperature is within the range of ± 2°C of that directed in the monograph, and, after drying the bottle, the sample is allowed to cool in a desiccator (silica gel) before weighing.

$$\text{Loss on drying (\% w/w)} = \frac{(W_2 - W_3)}{(W_2 - W_1)} \times 100$$

Note: If the sample melts at a temperature lower than that specified in the monograph, expose the sample for 1 to 2 hours to a temperature between 5°C and 10°C below the melting temperature, dry under the conditions specified in the monograph. Use a desiccant specified in the monograph, and renew frequently.

INDIAN PHARMACOPOEIA

Definition: Loss on drying is the loss of weight expressed as percentage w/w resulting from water and volatile matter of any kind that can be driven off under specified conditions.

The test is carried out on a well-mixed sample of the substance. If the substance is in the form of large crystals, reduce the size by rapid crushing to a powder.

Where the drying temperature is indicated by a single value other than a range, drying is carried out at the prescribed temperature ± 2°.

Unless otherwise specified in the individual monograph, use Method A.

Method A:

Weigh a glass-stoppered, shallow weighing bottle that has been dried under the same conditions to be employed in the determination. Transfer to the bottle the quantity of the sample specified in the individual monograph, cover it and accurately weigh the bottle and the contents. Distribute the sample as evenly as practicable by gentle sidewise shaking to a depth not exceeding 10 mm.

Dry the substance by placing the loaded bottle in the drying chamber as directed in the monograph, remove the stopper and leave it also in the chamber. Dry the sample to constant weight or for the specified time and at the temperature indicated in the monograph. Dry by one of the following procedures. After drying is completed, open the drying chamber, close the bottle promptly and allow it to cool to room temperature (where applicable) in a desiccator before weighing. Weigh the bottle and the contents.

a) "in a desiccator": dry over phosphorus pentoxide at atmospheric pressure and at room temperature;
Note: Care must be taken to keep the desiccant fully effective by frequent replacement.

b) "in vacuo": dry over phosphorus pentoxide, at a pressure of 1.5 kPa to 2.5 kPa at room temperature;

c) "in vacuo within a specified temperature range": dry over phosphorus pentoxide, at a pressure of 1.5 kPa to 2.5 kPa within the temperature range given in the monograph;

d) "in an oven within a specified temperature range": dry in an oven within the range given in the monograph;

Note: Where the drying temperature is indicated by a single value, dry at the prescribed temperature ± 2°.

e) "under high vacuum": dry over phosphorus pentoxide, at a pressure not exceeding 0.1 kPa, at the temperature given in the monograph.

Method B:

Thermogravimetry: Thermogravimetry is a technique in which the weight of a sample is recorded as a function of temperature according to a controlled temperature programme.

Apparatus:

A thermobalance consisting of a device for heating or cooling the substance being examined according to a given temperature programme, a sample holder in a controlled atmosphere, an electrobalance and a recorder. The instrument may be coupled to a device permitting the analysis of volatile products.

Temperature verification: Check the temperature scale using nickel or other suitable material according to the manufacturer's instruction.

Calibration of the electrobalance:

Place a suitable quantity of calcium oxalate monohydrate RS in the sample holder and record the weight. Set the heating rate according to the manufacturer's instructions and start the temperature programme. Record the thermogravimetric curve as a graph with temperature on the abscissa, increasing from left to right, and weight on the ordinate, increasing upwards. Stop the rise in temperature at 230°. Measure the distance on the graph between the initial and final weight temperature plateaux that corresponds to the loss of weight. The declared loss of weight for calcium oxalate monohydrate RS is stated on the label.

Note: If the apparatus is in frequent use, carry out temperature verification and calibration regularly. Otherwise, carry out such checks before each measurement.

Procedure:

Apply the same procedure to the substance under examination, using the conditions prescribed in the monograph. Calculate the loss of weight of the substance under examination from the distance measured on the graph obtained and express as a percentage w/w of the substance taken.

The actual procedure and the calculations to be employed are dependent on the particular instrument used. Consult the manufacture's literature and or the thermal analysis literature for the most appropriate technique for a given instrument. In any event, it is imperative to keep in mind the limitations of solid solution formation, insolubility in the melt, polymorphism and decomposition during the analysis.

References:

United States Pharmacopeia	: <731> Loss on Drying.
European Pharmacopoeia	: <2.2.32> Loss on Drying.
British Pharmacopoeia	: <Ph. Eur. 2.2.32> Appendix IX, D. Determination of Loss on Drying.
Japanese Pharmacopoeia	: <2.41> Loss on Drying Test.
Indian Pharmacopoeia	: <2.4.19> Loss on Drying.

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Change History:

Effective Date	GTP No.	Supersedes	Change Details
18 AUG 2014	GTP005-06	GTP005-05	Following changes have been made as per Document Change Request No.: DCR/SP/14/07/004. 1. Format has been revised as per revised SOP. 2. Under the test procedure for 'United states Pharmacopoeia' in 'Instructions', point no. 9 has been modified. 3. Test has been updated for European/ British Pharmacopoeia following changes have been made; 3.1. Weight expression for "Loss on Drying" in British Pharmacopoeia has been changed to "m/m" from "w/w". 3.2. Under "In an oven within a specified temperature range" statement "Instrument performance verification may be carried out using a suitable certified reference material (for example amoxicillin trihydrate for performance verification CRS)" has been newly incorporated. 4. Pharmacopoeia Chapter reference(s) have been newly incorporated. 5. Periodic Revision.
31 MAR 2018	GTP005-07	GTP005-06	As per CMS-Change Control PR# 1463085; 1. Format has been revised as per SOP 2. Under the 'Europcan Pharmacopeia' Point No. 'd' in the 'Instructions' has been revised.
29 JUN 2019	GTP005-08	GTP005-07	As per CMS-Change Control PR# 1883611; Under the heading 'European/British Pharmacopoeia' following changes have been made; 1. "**Note:** Loss on drying is the loss of mass expressed as % m/m." has been removed 2. 'Method' and 'Instruction' has been removed. 3. 'Principle', 'Equipment' has been newly incorporated. 4. Under the 'Procedure' note "It is recommended to perform the test in an environment that has minimal impact on

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			sample measurement (e.g. humidity)" has been newly incorporated. 5. Under the 'Procedure' After point 4, drying procedures/method 'In a desiccator', 'In vacuo' and 'In an oven at a specified temperature' has been newly incorporated.
30 OCT 2020	GTP005-09	GTP005-08	As per Change Control No. 2303414 1. Format has been revised as per SOP. 2. Under 'United States Pharmacopoeia' following changes have been made, 2.1 Under the procedure point no.03, word 'bulky materials' has been revised to 'low bulky materials'. 2.2 Under the procedure point no.04, word 'removing' and 'leaving' has been change to 'remove' and 'leave'. Word 'specified' has been included Sentence 'specified in the individual standard test procedure' has been removed. 2.3 Under the procedure, 'Note: The loss on drying is a function of both the temperature and time. Therefore, these values must be identified and reported.' has been newly included. 2.4 Under the procedure, in the note word 'figure' has been replaced with 'value'. 2.5 Under the procedure in point 5, sentence 'per g of substance taken, the second weighing following' has been replaced with 'specimen taken, where the second weighing follows' has been included'. 2.6 Under the procedure in point 6, sentence 'close the bottle promptly' has been replaced with 'reapply the same stopper to the bottle'. Sentence 'before weighing accurately' newly included. 2.7 Under the 'Instructions', sentence 'Take a portion of the mixed contents of not fewer than 4 capsules to test Loss on drying for capsules.' replaced with 'Where capsules are to be tested, use a representative sample mixture, excluding the capsule shell, from not fewer than 4 capsules'.

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			2.8 Under the 'Instructions', sentence 'Take powder from not fewer than 4 tablets to test Loss on drying for tablets.' replaced with 'Where tablets are to be tested, use a representative sample mixture from NLT 4 crushed tablets.' 2.9 Under the 'Instructions', form point no.7 word 'kept' and 'by frequent replacement' has been removed.

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