

## 〈741〉 MELTING RANGE OR TEMPERATURE

The terms melting range, melting point, or melting temperature are all used in pharmacopeial contexts. Most substances exhibit a melting transition, spanning the temperatures at which the first detectable change of phase or liquid phase is detected to the temperature at which no solid phase is apparent. The transition may appear instantaneous for a highly pure material, but usually a range is observed from the beginning to the end of the process. Factors influencing this transition include the sample size, the particle size, the efficiency of heat diffusion within the sample, and the heating rate, among other variables, that are controlled by procedure instructions.

For pharmacopeial purposes, the temperatures of the beginning (onset temperature) and end of transition (clear temperature) represent the melting range, except as defined otherwise for *Procedure for Class II* and *Procedure for Class III* below. The terms melting point and melting temperature are considered to be equivalent.

Substances which melt with no decomposition or chemical change are known to melt congruently. In these cases, the melting point is taken to be the end of the melting range, i.e., the temperature at which no solid phase is apparent. In some articles, the melting process is accompanied by simultaneous decomposition, which is visually evidenced as a side event like darkening of the material, charring, bubbling, or other incident. These transitions are known to be non-congruent. The visual impact of this side reaction frequently obscures the end of the melting process, which may be impossible to accurately determine. In those circumstances, only the beginning of the melting can be accurately established, and it is to be reported as the melting point.

Since there may be a thermal lag between the heating medium and the sample within the capillary tube, in order to achieve consistency and repeatability, it is important to perform the melting determination at a heating rate, also referred to as ramp rate, of 1°/min.

The accuracy of the apparatus to be used as described below should be checked at suitable intervals by the use of one or more of the available USP Melting Point Standards, preferably those that melt nearest the melting temperatures of the compounds being tested (see *USP Reference Standards* 〈11〉). The USP Melting Point Standards are intended to check the accuracy of the device and may be suitable to calibrate.

Eight procedures for the determination of melting range or temperature are given herein, varying in accordance with the nature of the substance. When no class is designated in the monograph, use the *Procedure for Class Ia* for crystalline or amorphous substances and the *Procedure for Class II* for waxy substances.

The procedure known as the mixed-melting point determination, whereby the melting range or temperature of a solid under test is compared with that of an intimate mixture of equal parts of the solid and an authentic specimen of it, e.g., the corresponding USP Reference Standard, if available, may be used as a confirmatory identification test. Agreement of the observations on the original and the mixture constitutes reliable evidence of chemical identity.

### APPARATUS

Apparatus with cameras or other computerized equipment to improve accuracy, sensitivity, or precision may be used provided that the apparatus is properly qualified.

#### Apparatus I

An example of a suitable melting range *Apparatus I* consists of a glass container for a bath of transparent fluid, a suitable stirring device, an accurate thermometer, and a controlled source of heat. The bath fluid is selected with a view to the temperature required, but light paraffin is used generally and certain liquid silicones are well adapted to the higher temperature ranges. The fluid is deep enough to permit immersion of the thermometer to its specified immersion depth so that the bulb is still about 2 cm above the bottom of the bath. The heat may be supplied by an open flame or electrically. The capillary tube is about 10 cm long and 0.8–1.2 mm in internal diameter with walls 0.2–0.3 mm in thickness.

#### Apparatus II

An instrument may be used in the *Procedure for Class I*, *Procedure for Class Ia*, and *Procedure for Class Ib*. An example of a suitable melting range *Apparatus II* consists of a block of metal that may be heated at a controlled rate, with its temperature being monitored by a sensor. The block accommodates the capillary tube containing the test substance and permits monitoring of the melting process, typically by means of a beam of light and a detector. The detector signal may be processed by a microcomputer to determine and display the melting point or range, or the detector signal may be plotted to allow visual estimation of the melting point or range. Some approaches broadly used by automated systems employ optical methods such as light absorption or bulk reflection.

### PROCEDURES

#### Procedure for Class I, Apparatus I

Reduce the substance under test to a very fine powder, and, unless otherwise directed, render it anhydrous when it contains water of hydration by drying it at the temperature specified in the monograph, or, when the substance contains no water of hydration, dry it over a suitable desiccant for NLT 16 h (or at the conditions stated in *Loss on Drying* 〈731〉, if appropriate).

Charge a capillary glass tube, one end of which is sealed, with a sufficient amount of the dry powder to form a column in the bottom of the tube to a nominal height of 3 mm high when packed down as closely as possible by moderate tapping on a solid surface. Due to the instrument design, alternative sample sizes may be used as instructed by the instrument manufacturer.

Heat the bath until the temperature is about 10° below the expected melting point. Remove the thermometer, and quickly attach the capillary tube to the thermometer by wetting both with a drop of the liquid of the bath or otherwise, and adjust its height so that the material in the capillary is level with the thermometer bulb. Replace the thermometer, and continue the heating, with constant stirring, sufficiently to achieve the ramp rate of about 3°/min. When the temperature is about 3° below the lower limit of the expected melting range, reduce the heating so that the ramp rate of about 1°/min is achieved. Continue heating until melting is complete.

The temperature at which the column of the substance under test is observed to collapse definitely against the side of the tube at any point indicates the beginning of melting, and the temperature at which the test substance becomes liquid throughout corresponds to the end of melting or the melting point. The two temperatures fall within the limits of the melting range. If melting occurs with decomposition, the melting temperature corresponding to the beginning of the melting (melting point) is within the range specified.

### Procedure for Class Ia, Apparatus I

Prepare the test substance and charge the capillary as directed in *Procedure for Class I, Apparatus I*. Heat the bath until the temperature is about 10° below the expected melting point and is rising at a rate of about 1°/min. Insert the capillary as directed in *Procedure for Class I, Apparatus I* when the temperature is about 5° below the lower limit of the expected melting range, and continue heating until melting is complete. Record the melting range as directed in *Procedure for Class I, Apparatus I*.

### Procedure for Class Ib, Apparatus I

Place the test substance in a closed container and cool to 10°, or lower, for at least 2 h. Without powdering, charge the cooled material into the capillary tube as directed in *Procedure for Class I, Apparatus I*, then immediately place the charged tube in a vacuum desiccator and dry at a pressure not exceeding 20 mm of mercury for 3 h. Immediately upon removal from the desiccator, fire-seal the open end of the tube, and as soon as practicable proceed with the determination of the melting range as follows. Heat the bath until the temperature is about 10° below the expected melting range, then introduce the charged tube, and heat at a rate of rise of about 1°/min until melting is complete. Record the melting range as directed in *Procedure for Class I, Apparatus I*.

If the particle size of the material is too large for the capillary, precool the test substance as directed above, then with as little pressure as possible gently crush the particles to fit the capillary, and immediately charge the tube.

### Procedure for Class I, Apparatus II

Prepare the substance under test and charge the capillary tube as directed in *Procedure for Class I, Apparatus I*. Operate the apparatus according to the manufacturer's instructions. Heat the block until the temperature is about 10° below the expected melting point. Insert the capillary tube into the heating block, and continue heating at a rate of temperature increase of about 1°/min until melting is complete.

The temperature at which the detector signal first leaves its initial value indicates the beginning of melting, and the temperature at which the detector signal reaches its final value corresponds to the end of melting, or the melting point. The two temperatures fall within the limits of the melting range. If melting occurs with decomposition, the melting temperature corresponding to the beginning of the melting (melting point) is within the range specified.

### Procedure for Class Ia, Apparatus II

Prepare the test substance and charge the capillary as directed in *Procedure for Class I, Apparatus I*. Operate the apparatus according to the manufacturer's instructions. Heat the block until the temperature is about 5° below the expected melting point and is rising at a rate of about 1°/min. Insert the capillary as directed in *Procedure for Class I, Apparatus I*, and continue heating until melting is complete. Record the melting range as directed in *Procedure for Class I, Apparatus I*. If melting occurs with decomposition, the melting temperature corresponding to the beginning of the melting (melting point) is within the range specified.

### Procedure for Class Ib, Apparatus II

Place the test substance in a closed container and cool to 10°, or lower, for at least 2 h. Without previous powdering, charge the cooled material into the capillary tube as directed in *Procedure for Class I, Apparatus I*, then immediately place the charged tube in a vacuum desiccator, and dry at a pressure not exceeding 20 mm of mercury for 3 h. Immediately upon removal from the desiccator, fire-seal the open end of the tube, and as soon as practicable proceed with the determination of the melting range as follows. Operate the apparatus according to the manufacturer's instructions. Heat the block until the temperature is about 10° below the expected melting range, then introduce the charged tube, and heat at a rate of rise of about 1°/min until melting is complete. Record the melting range as directed in *Procedure for Class I, Apparatus I*.

If the particle size of the material is too large for the capillary, precool the test substance as directed above, then with as little pressure as possible gently crush the particles to fit the capillary, and immediately charge the tube.

## Procedure for Class II

Carefully melt the material to be tested at as low a temperature as possible, and draw it into a capillary tube, which is left open at both ends, to a depth of about 10 mm. Cool the charged tube at 10°, or lower, for 24 h, or in contact with ice for at least 2 h. Then attach the tube to the thermometer by suitable means, adjust it in a water bath so that the upper edge of the material is 10 mm below the water level, and heat as directed in *Procedure for Class I, Apparatus I* except, within 5° of the expected melting temperature, to regulate the rate of rise of temperature of about 1.0°/min. The temperature at which the material is observed to rise in the capillary tube is the melting temperature.

## Procedure for Class III

While stirring, melt a quantity of the test substance slowly until it reaches a temperature of 90°–92°. Remove the source of the heat, and allow the molten substance to cool to a temperature of 8°–10° above the expected melting point. Chill the bulb of a suitable thermometer to 5°, wipe it dry, and while it is still cold dip it into the molten substance so that approximately the lower half of the bulb is submerged. Withdraw it immediately, and hold it vertically away from the heat until the wax surface dries, then dip it for 5 min into a water bath having a temperature NMT 16°.

Fix the thermometer securely in a test tube so that the lower point is 15 mm above the bottom of the test tube. Suspend the test tube in a water bath adjusted to about 16°, and raise the temperature of the bath at the rate of about 2°/min to 30°, then change to a rate of about 1°/min, and note the temperature at which the first drop of melted substance leaves the thermometer. Repeat the determination twice on a freshly melted portion of the test substance. If the variation of three determinations is less than 1°, take the average of the three as the melting point. If the variation of three determinations is 1° or greater than 1°, make two additional determinations and take the average of the five.