

SPECIFIC GRAVITY

The specific gravity of a fat or oil is determined at 25°, except when the substance is a solid at that temperature, in which case the specific gravity is determined at the temperature specified in the monograph, and is referred to water at 25°.

Clean a suitable pycnometer by filling it with a saturated solution of chromic acid (CrO₃) in sulfuric acid and allowing it to stand for at least 4 h. Empty the pycnometer, rinse it thoroughly, then fill it with recently boiled water, previously cooled to about 20°, and place in a constant-temperature bath at 25°. After 30 min, adjust the level of water to the proper

point on the pycnometer, and stopper. Remove the pycnometer from the bath, wipe dry with a clean cloth free from lint, and weigh. Empty the pycnometer, rinse several times with alcohol and then with ether, allow to dry completely, remove any ether vapor, and weigh. Determine the weight of the contained water at 25° by subtracting the weight of the pycnometer from its weight when full.

Filter the oil or melted sample through filter paper to remove any impurities and the last traces of moisture, and cool to a few degrees below the temperature at which the determination is to be made. Fill the clean, dry pycnometer with the sample, and place it in the constant-temperature bath at the specified temperature. After 30 min, adjust the level of the oil to the mark on the pycnometer, insert the stopper, wipe dry, and weigh. Subtract the weight of the empty pycnometer from its weight when filled with the sample, and divide the difference by the weight of the water contained at 25°. The quotient is the specific gravity at the temperature of observation, referred to water at 25°.

SPECIFIC GRAVITY

Specific gravity is defined as the ratio of the mass of the sample to the mass of an equal volume of the standard material. The specific gravity (d_t) means the ratio of the weight of the sample at t'' to that of an equal volume of water at t' . Unless otherwise specified, specific gravity means d_{20}^{20} . Specific gravity is determined by one of the following methods, unless otherwise specified.

Measurement by Pycnometer

A pycnometer is a vessel made of glass with a capacity of usually 10 to 100 ml. It has a ground, glass stopper fitted with a thermometer, and has a side tube with a mark and a ground glass cap. Weigh a pycnometer previously cleaned and dried, and note the weight W . Remove the stopper and the cap, fill the pycnometer with a sample, keep at the temperature of about 1° to 3° lower than that specified, and stopper, taking care not to leave bubbles. Raise the temperature gradually until the thermometer shows the specified temperature. Remove the sample above the mark from the side tube, replace the cap, and wipe the outside thoroughly. Weigh, and note the weight W_1 . Using the same pycnometer, perform the similar determination with water. Weigh the pycnometer containing water at the specified temperature, and note the weight W_2 . Calculate the specific gravity of the sample by the following formula.

$$d = \frac{W_1 - W}{W_2 - W}$$

Measurement by Mohr-Westphal Balance

Keep the balance horizontal, attach the glass tube in which a thermometer is enclosed by a wire onto the end of the arm. Immerse the glass tube in water in a cylinder, place the largest rider on the arm at the mark 10, and adjust the balance by moving the nut at the specified temperature.

After that, immerse the glass tube in the sample, adjust the balance by hanging riders on the arm, and read the specific gravity at the marks at which riders are placed. It is necessary to make the length of the part of wire which is immersed in a sample equal to that immersed in water by changing the height of the sample in the cylinder.

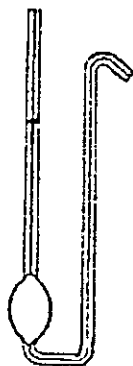
Measurement by Hydrometer

Use a hydrometer with a necessary precision intended for use at the specified temperature.

Clean the hydrometer with alcohol. Shake the sample well, and place in the hydrometer after bubbles have disappeared. At the specified temperature, when the hydrometer has settled, read the specific gravity at the upper brim of the meniscus. In case of any hydrometer, however, for which special directions are given, follow the directions.

Measurement by Sprengel-Ostwald Pycnometer

A Sprengel-Ostwald pycnometer (see figure) is a vessel made of glass with a capacity of usually 1 to 10 ml. As shown in the figure, both the ends are thick-walled fine tubes one of which has a mark on it. A platinum or an aluminium wire is attached to hang on the arm of a chemical balance.



Sprengel-Ostwald Pycnometer

Weigh the pycnometer, previously cleaned and dried (W). Immerse the curved tube in the sample kept at a temperature 3° to 5° lower than the specified temperature, attach a rubber tube at the end of the straight tube, and suck the sample gently until it comes up above the mark, taking care to prevent formation of bubbles. Immerse the pycnometer in a water bath kept at the specified temperature for about 15 min, and by attaching a piece of filter paper at the end of the curved tube, adjust the end of the sample to the mark. Remove the pycnometer from the water bath, and wipe the outside well. Weigh and note the weight W_1 . By using the same pycnometer, perform the same determination with water. Weigh the pycnometer containing water at the specified temperature, and note the weight W_2 . Calculate the specific gravity by the following formula:

$$d = \frac{W_1 - W}{W_2 - W}$$

第7版 食品添加物公定書

屈折率測定法

屈折率測定法は、試料の空気に対する屈折率を測定する方法である。等方性の物質の場合、光の波長、温度及び圧力が一定のとき、屈折率は、物質に固有の定数であり、純度試験に用いる。

屈折率 n_D^t とは、光線としてナトリウムスペクトル中のD線を用い、温度 $t^\circ\text{C}$ で測定したときの空気に対する屈折率を意味する。屈折率の測定は、別に規定するもののほか、アッペ屈折計を用い、規定温度の $\pm 0.2^\circ\text{C}$ の範囲内で行う。

17. 屈折率測定法

屈折率測定法は、試料の空気に対する屈折率を測定する方法である。一般に、光が一つの媒質から他の媒質に進むとき、その境界面で進行方向を変える。この現象を屈折という。光が等方性の第 1 の媒質から第 2 の媒質に入るとき、入射角 i の正弦と屈折角 r の正弦との比は、入射角によらずに、この二つの媒質間では一定で、これを第 2 の媒質の第 1 の媒質に対する屈折率又は相対屈折率といい、 n で表す。

$$n = \frac{\sin i}{\sin r}$$

第 1 の媒質が特に真空である場合の屈折率を第 2 の媒質の絶対屈折率といい、 N で表す。

等方性の物質において、波長、温度及び圧力が一定のとき、その屈折率は物質に固有の定数である。したがって、物質の純度の試験又は均質な 2 物質の混合物の組成の決定などに用いられる。

通例、温度は、 20°C 、光線はナトリウムスペクトルの D 線を用い、 n_D^{20} で表す。

操作法

屈折率の測定には、通例、アッペ屈折計を用い、医薬品各条に規定する温度の $\pm 0.2^{\circ}\text{C}$ の範囲内で行う。アッペ屈折計では、白色光を用いて n_D を直接読むことができ、測定のできる n_D の範囲は 1.3 ~ 1.7、精密度は 0.0002 である。

(831) REFRACTIVE INDEX

The refractive index (n) of a substance is the ratio of the velocity of light in air to the velocity of light in the substance. It is valuable in the identification of substances and the detection of impurities.

Although the standard temperature for Pharmacopoeial measurements is 25°, many of the refractive index specifications in the individual monographs call for determining this value at 20°. The temperature should be carefully adjusted and maintained, since the refractive index varies significantly with temperature.

The values for refractive index given in this Pharmacopoeia are for the D line of sodium (doublet at 589.0 nm and 589.6 nm). Most instruments available are designed for use with white light but are calibrated to give the refractive index in terms of the D line of sodium light.

The Abbé refractometer measures the range of refractive index for those Pharmacopoeial materials for which such values are given. Other refractometers of equal or greater accuracy may be employed.

To achieve the theoretical accuracy of ± 0.0001 , it is necessary to calibrate the instrument against a standard provided by the manufacturer and to check frequently the temperature control and cleanliness of the instrument by determining the refractive index of distilled water, which is 1.3330 at 20° and 1.3325 at 25°.

2.2.6. REFRACTIVE INDEX

The refractive index of a medium with reference to air is equal to the ratio of the sine of the angle of incidence of a beam of light in air to the sine of the angle of refraction of the refracted beam in the given medium.

Unless otherwise prescribed, the refractive index is measured at 20 ± 0.5 °C, with reference to the wavelength of the D line of sodium ($\lambda = 589.3$ nm); the symbol is then n_D^{20} .

Refractometers normally determine the critical angle. In such apparatus the essential part is a prism of known refractive index in contact with the liquid to be examined.

Calibrate the apparatus using certified reference materials.

When white light is used, the refractometer is provided with a compensating system. The apparatus gives readings accurate to at least the third decimal place and is provided with a means of operation at the temperature prescribed.

The thermometer is graduated at intervals of 0.5 °C or less.

BP

E. Determination of Refractive Index

(Ph. Eur. method 2.2.6)

The *refractive index* (n) of a substance with reference to air is the ratio of the sine of the angle of incidence to the sine of the angle of refraction of a beam of light passing from air into the substance. It varies with the wavelength of the light used in its measurement.

Refractive indices, n_D^{20} , are stated in terms of the wavelength of the sodium D-line (589.3 nm) at a temperature of 19.5° to 20.5° unless otherwise specified.

Apparatus

Commercial refractometers normally determine the critical angle. In such apparatus the essential part is a prism of known refractive index in contact with the liquid being examined. Such instruments are normally constructed for use with white light but are calibrated to give the refractive index in terms of the wavelength of the sodium D-line. When white light is used, the refractometer is provided with a compensation system. The apparatus gives readings accurate to at least the third decimal place and is provided with a method by which the temperature may be varied, if required. The thermometer is graduated in increments of 0.5° or less.

The manufacturer's instructions relating to a suitable light source should be followed subject to the directions given in the monograph. Calibrate the apparatus using certified reference materials.

F C C

REFRACTIVE INDEX

The refractive index of a transparent substance is the ratio of the velocity of light in air to its velocity in that material under like conditions. It is equal to the ratio of the sine of the angle of incidence made by a ray in air to the sine of the angle of refraction made by the ray in the material being tested. The refractive index values specified in this Codex are for the D line of sodium (589 nm) unless otherwise specified. The determination should be made at the temperature specified in the individual monograph, or at 25° if no temperature is specified. This physical constant is used as a means for identification of, and detection of impurities in, volatile oils and other liquid sub-

REFRACTIVE INDEX

The refractive index of a transparent substance is the ratio of the velocity of light in air to its velocity in that material under like conditions. It is equal to the ratio of the sine of the angle of incidence made by a ray in air to the sine of the angle of refraction made by the ray in the material being tested. The refractive index values specified are for the D line of sodium (589 nm) unless otherwise specified. The determination should be made at the temperature specified in the individual monograph, or at 25° if no temperature is specified. This physical constant is used as a means for identification of, and detection of impurities in, volatile oils and other liquid substances. The Abbé refractometer, or other refractometers of equal or greater accuracy, may be employed at the discretion of the operator.

第7版 食品添加物公定書

融点測定法

融点とは、次の方法により測定するとき、固体がその温度又は温度の範囲内で完全に融解する温度をいう。測定の便宜上、固体物質を次の2種類に分ける。

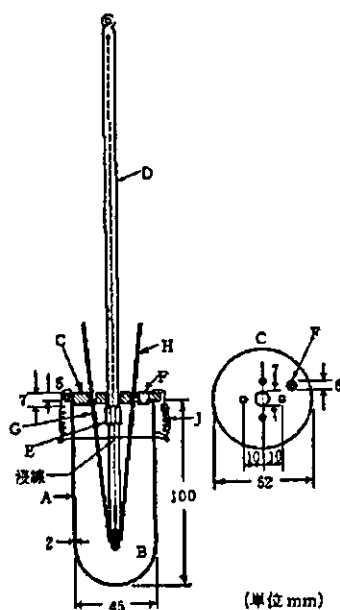
第1種物質 粉末にしやすいもの

第2種物質 脂肪、脂肪酸、パラフィン、ろう等のような粉末にしにくいもの

(1) 第1種物質の場合

装置

概略は、次の図による。



- A：加熱容器（硬質ガラス製）
- B：浴液（常温における動粘度 $50\sim 100\text{mm}^2/\text{s}$ の透明なシリコン油を用いる。）
- C：テフロン製ふた
- D：浸線付温度計（棒状、融点が 50°C 未満のときは1号、 50°C 以上 100°C 未満のときは2号、 100°C 以上 150°C 未満のときは3号、 150°C 以上 200°C 未満のときは4号、 200°C 以上 250°C 未満のときは5号、 250°C 以上 320°C 未満のときは6号を用いる。）
- E：温度計固定ばね
- F：浴液量加減用小孔
- G：コイルスプリング
- H：毛细管（内径 $0.8\sim 1.2\text{mm}$ 、長さ 120mm 、壁の厚さ $0.2\sim 0.3\text{mm}$ で一端を閉じた硬質ガラス製のものを用いる。）
- J：テフロン製ふた固定ばね

出典：食品衛生関係法規集

操作法

試料を微細な粉末とし、別に規定するもののほか、デシケーターで約 24 時間乾燥する。また、成分規格・保存基準各条において乾燥物とある場合は、それぞれの成分規格・保存基準各条において規定する乾燥減量の条件で乾燥する。次に、この試料を毛細管 H に厚さ 2.5~3.5mm の層となるようにできるだけ堅く詰める。成分規格・保存基準各条などに（封管中）とある場合は、開いている方の一端を閉じる。また（減圧封管中）とある場合は、開いている方の一端から、減圧（0.67kPa 以下）にしながらい開いている方の一端を弱く加熱して閉じる。

浴液 B を加熱して予想される融点の約 10℃以下の温度まで徐々に上げ、浸線付温度計 D の浸線を浴液メニスカスに合わせ、試料を入れた H をコイルスプリング G に差し込み、試料を詰めた部分が D の水銀球の中央にくるようにする。次に 1 分間に約 3℃上昇するように加熱して温度を上げ、予想される融点より約 5℃低い温度から 1 分間に 1℃上昇するように加熱を続ける。

H の内壁と試料との接触部にわずかに浸潤又は崩壊を認めたときの温度を融解し始めの温度とし、試料が完全に融解して透明となったときの温度を融解し終わりの温度とし、融解し終わりの温度を融点とする。

(2) 第 2 種物質の場合

操作法

試料をできるだけ低温で融解し、これを両端の開いた毛細管（第 1 種物質の場合の装置で両端を開いたもの）中に吸い上げて約 10mm の高さとする。この毛細管を約 10℃で約 24 時間放置するか、少なくとも 2 時間氷冷した後、試料の位置が水銀球の中央外側になるようにゴム輪で温度計に取り付け、これを水を入れたビーカーに入れ、試料の上端を水面下約 10mm の位置に保つ。水を絶えずかき混ぜながら加温し、予想される融点より約 5℃低い温度に達した後は、2 分間に 1℃ずつ上昇するように加熱する。H 中で試料が浮上するときの温度を融点とする。

第 14 改正 日本薬局方

63. 融点測定法

融点は、次のいずれかの方法で測定する。ある物質の融点が範囲で示されているときには、その物質の融点はその範囲内にあればよいことを示す。

その測定法は医薬品の性状によって次の 3 方法に分ける。別に規定するもののほか、第 1 法を用いる。

第 1 法 粉末にしやすすいものは、この方法による。

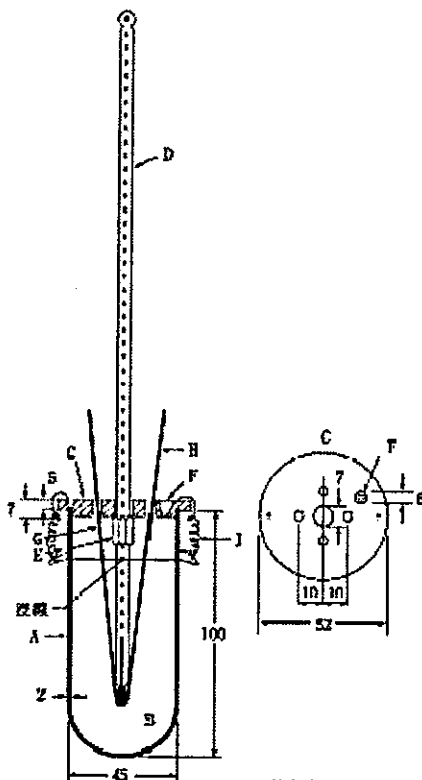
(1) 装置

図 63-1 に示すものを用いる。

浴液：常温における動粘度 50 ~ 100 mm²/s の澄明なシリコン油を用いる。

浸線付温度計：融点が 50°C 未満のときは 1 号、50°C 以上 100°C 未満のときは 2 号、100°C 以上 150°C 未満のときは 3 号、150°C 以上 200°C 未満のときは 4 号、200°C 以上 250°C 未満のときは 5 号、250°C 以上 320°C 未満のときは 6 号を用いる。

毛细管：内径 0.8 ~ 1.2 mm、長さ 120 mm、壁の厚さ 0.2 ~ 0.3 mm で一端を閉じた硬質ガラス製のものを用いる。



- A: 加熱容器 (厚質ガラス製)
- B: 試料
- C: テフロン製加熱コイル
- D: 浸線付温度計
- E: 温度計固定ばね
- F: 溶解量加減用小孔
- G: コイルスプリング
- H: 毛细管
- J: テフロン製上蓋固定ばね

図 63-1 融点測定装置

(2) 操作法

試料を微細の粉末とし、別に規定するもののほか、デシケーター (シリカゲル) で 24 時間乾燥する。また、乾燥後とあるときは、乾燥減量の項の条件で乾燥したものを用いる。

この試料を乾燥した毛细管 H に入れ、閉じた一端を下にしてガラス板又は石板上に立てた長さ約 70 cm のガラス管の内部に落とし、はずませて固く詰め、厚が 3 mm 又はこれに近い厚さとなるようにする。

浴液 B を加熱して予想した融点の約 10°C 下の温度まで徐々に上げ、浸線付温度計 D の浸線を浴液のメニスカスに合わせ、試料を入れた毛细管 H をコイルスプリング G に挿入し、試料を詰めた部分が D の水銀球の中央にくるようにする。次に 1 分間に約 3°C 上昇するように加熱して温度を上げ、予想した融点より約 5°C 低い温度から 1 分間に 1°C 上昇するように加熱を続ける。

試料が H 内で液化して、固体を全く認めなくなったときの D の示度を読みとり、融点とする。

第 2 法 脂肪、脂肪酸、パラフィン又はろうのようなもので、水に不溶性で粉末にしにくいものは、この方法による。

操作法

試料を注意しながらできるだけ低温で融解し、これを、泡が入らないようにして毛细管 (第 1 法のもので両端を開いたもの) 中に吸い上げ、約 10 mm の高さとする。毛细管から試料が流出しないように保ち、10°C 以下で 24 時間放置するか、又は少なくとも 1 時間水上に放置した後、試料の位置が水銀球の中央外側にくるようにゴム輪で温度計 (浸線付又は全液式) を取り付け、水を入れたビーカーに入れ、試料の下端を水面下 30 mm の位置に保ち、水を絶えずかき混ぜながら加熱して、予想した融点より 5°C 低い温度に達したとき、1 分間に 1°C 上昇するように加熱を続ける。毛细管中で試料が浮上するときの温度を融点とする。

第 3 法 ワセリン類は、この方法による。

操作法

試料をよくかき混ぜながら徐々に 90 ~ 92°C まで加熱して融解し、加熱をやめ、試料を融点より 8 ~ 10°C 高い温度まで冷却する。温度計 (浸線付又は全液式) を 5°C に冷却し、ぬぐって乾燥し、直ちに水銀球の半分を試料中にさし込み、直ちに抜き取り、垂直に保ち、冷却し、付着した試料が混濁してきたとき、16°C 以下の水中に 5 分間浸す。次に試験管に温度計を挿入し、温度計の下端と試験管の底との間が 15 mm になるようにコルク栓を用いて温度計を固定する。この試験管を約 16°C の水を入れたビーカー中につるし、浴の温度が 30°C になるまでは 1 分間に 2°C 上昇するように、その後は 1 分間に 1°C 上昇するように加熱を続ける。温度計から最初の 1 滴が覆れたときの温度を測定する。この操作を 3 回行い、測定値の差が 1°C 未満のときはその平均値をとり、1°C 以上のときは更にこの操作を 5 回行い、その 5 回の平均値をとり、融点とする。

A. Determination of melting point

For monographs from the European Pharmacopoeia, use the method indicated in the monograph. For other monographs, use Method II unless otherwise directed.

Method I

(Ph. Eur. method 2.2.14)

The melting point determined by the capillary method is the temperature at which the last solid particle of a compact column of a substance in a tube passes into the liquid phase. When prescribed in the monograph, the same apparatus and method are used for the determination of other factors, such as meniscus formation or melting range, that characterise the melting behaviour of a substance.

Apparatus

- (a) A suitable glass vessel containing a suitable liquid, for example water, liquid paraffin or silicone oil, and fitted with an appropriate means of heating.
- (b) A suitable stirring device capable of maintaining the uniformity of temperature of the liquid.
- (c) A thermometer suitable for the substance under examination, graduated at not more than 0.5° intervals and provided with an immersion mark. The range of the thermometer is not more than 100° .
- (d) Capillary tubes of alkali-free hard glass, closed at one end, with a wall thickness of 0.10 to 0.15 mm and of internal diameter 0.9 to 1.1 mm.

The apparatus may be calibrated using certified reference substances of declared melting point, such as those of the World Health Organization or other suitable substances¹.

Method

Unless otherwise specified, dry a small quantity of the finely powdered substance at a pressure of 1.5 to 2.5 kPa over *anhydrous silica gel* for 24 hours. Transfer a sufficient portion to a dry capillary tube to form a compact column 4 to 6 mm in height. Raise the temperature of the bath to about 10° below the presumed melting point and then adjust the rate of heating to about 1° per minute. When the temperature is 5° below the presumed melting point, adjust the height of the thermometer so that the immersion mark is level with the surface of the liquid and insert the capillary tube so that its lower end is near the middle of the thermometer bulb. The temperature at which the last solid particle passes into the liquid phase is the melting point of the substance.

Method II

(No Ph. Eur. equivalent method)

Apparatus

- (a) A glass heating vessel of suitable construction and capacity containing one of the following, or another suitable liquid, to a height of not less than 14 cm.
- (i) A liquid paraffin of sufficiently high boiling point.
 - (ii) A silicone fluid of sufficiently high boiling point.
 - (iii) Water.
- (b) A suitable stirring device capable of rapidly mixing the liquid.
- (c) An accurately standardised thermometer suitable for the substance being examined complying with the requirements of British Standard 1365:1990 (Specification for short-range short-stem thermometers) for thermometers designated by one of the following Schedule Marks.

Schedule mark at each (max)	Range °C	Graduated	Diameter of stem mm	Overall length mm
SA 55C/80	-10 to 55	0.5°	5.5 to 8	200
SA 105C/80	45 to 105	0.5°	5.5 to 8	200
SA 155C/80	95 to 155	0.5°	5.5 to 8	200
SA 205C/80	145 to 205	0.5°	5.5 to 8	200
SA 225C/80	195 to 255	0.5°	5.5 to 8	200
SA 305C/80	245 to 305	0.5°	5.5 to 8	200
SA 360C/80	295 to 360	0.5°	5.5 to 8	200

- (d) Thin-walled capillary glass tubes of hard glass, closed at one end, with a wall thickness of 0.10 to 0.15 mm, at least 12 cm in length and of internal diameter 0.9 to 1.1 mm. The tubes should preferably be kept sealed at both ends and cut as required.

Method

Dry a small quantity of the finely powdered substance at a temperature considerably below its melting point or at a pressure of 2 kPa over a suitable desiccant, unless otherwise directed. Transfer a portion to a dry capillary tube and pack the powder by tapping on a hard surface so as to form a tightly packed column 4 to 6 mm in height. Heat a suitable liquid in the heating vessel and regulate the rate of rise of temperature, prior to the introduction of the capillary tube, to 3° per minute, unless otherwise directed, stirring constantly. When the temperature reaches 10° below the lowest figure of the range for the substance being tested,

adjust the height of the thermometer so that the immersion mark is at the level of the surface of the liquid and insert the capillary tube so that the closed end is near the middle of the bulb of the thermometer. Note the temperature at which the liquefaction of the substance occurs, which is indicated by the formation of a definite meniscus or, for substances that decompose, the temperature at which frothing begins. Correct the observed temperature for any error in the calibration of the thermometer and for the difference, if any, between the temperature of the emergent stem of the thermometer and the temperature of the emergent stem under the conditions of standardisation of the thermometer. The temperature of the emergent stem is determined by placing the bulb of a second thermometer in contact with the emergent stem at a point approximately midway along the mercury thread in the emergent stem.

The correction to be applied is given by the following equation:

$$t_c = 0.00016n(t_s - t_d)$$

where t_c = correction to be added to the observed temperature of the melting point,

t_s = mean temperature of the emergent column when standardised,

t_d = mean temperature of the emergent column at the observed melting point,

n = number of °C over which the exposed column extends.

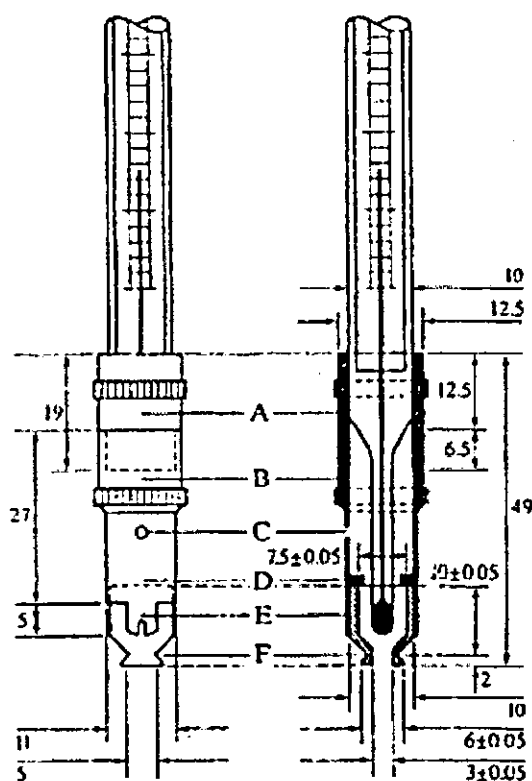


Fig. 5A-1 Apparatus for the determination of melting point (Method III)

Dimensions in mm

The corrected temperature is regarded as the melting point of the substance. When the melting point in the monograph is expressed as a range, the melting point of the substance being tested must fall within that range.

Method III

(Ph. Eur. method 2.2.17)

The drop point is the temperature at which the first drop of the melting substance falls from a cup under defined conditions.

Apparatus

The apparatus (Fig. 5A-1) consists of the following parts.

A metal sheath (A) fixed to a mercury thermometer and screwed to another metal sheath (B). A metal cup (F) is loosely fixed to the lower part of sheath (B) by two tightening bands (E). The exact position of the cup is determined by two fixed supports (D), 2 mm long, which are also used to centre the thermometer. A hole (C) pierced in the wall of sheath (B) is used to balance the pressure.

The draining surface of the cup must be flat and the edges of the outflow orifice at right angles to it. The mercury thermometer is of the form shown in Fig. 5A-1 with a mercury reservoir 3.3 to 3.7 mm in diameter and 5.7 to 6.3 mm long; it is calibrated from 0° to 110° and on its scale a distance of 1 mm represents a difference of 1°. The apparatus is placed in the axis of a tube (about 20 cm × 4 cm) and fixed by means of a stopper through which the thermometer passes and which is provided with a side groove. The opening of the cup should be about 15 mm from the bottom of the tube. The tube is immersed in a 1-litre beaker filled with water so that the bottom of the tube is about 25 mm above the bottom of the beaker and the water level reaches the upper part of sheath (A). A stirrer is used to ensure that the temperature of the water remains uniform.

2.2.14. MELTING POINT - CAPILLARY METHOD

The melting point determined by the capillary method is the temperature at which the last solid particle of a compact column of a substance in a tube passes into the liquid phase.

When prescribed in the monograph, the same apparatus and method are used for the determination of other factors, such as meniscus formation or melting range, that characterise the melting behaviour of a substance.

Apparatus. The apparatus consists of:

- a suitable glass vessel containing a liquid bath (for example, water, liquid paraffin or silicone oil) and fitted with a suitable means of heating,
- a suitable means of stirring, ensuring uniformity of temperature within the bath,

(741) MELTING RANGE OR TEMPERATURE

For Pharmacopeial purposes, the melting range or temperature of a solid is defined as those points of temperature within which, or the point at which, the solid coalesces and is completely melted, except as defined otherwise for *Classes II* and *III* below. Any apparatus or method capable of equal accuracy may be used. The accuracy should be checked at suitable intervals by the use of one or more of the six USP Melting Point Reference Standards, preferably those that melt nearest the melting temperatures of the compounds being tested (see *USP Reference Standards (11)*).

Five 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*.

The procedure known as the mixed-melting point determination, whereby the melting range 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 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 (see *Thermometers (21)*), 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 to 1.2 mm in internal diameter with walls 0.2 to 0.3 mm in thickness.

Apparatus II—An instrument may be used in the procedures for *Classes I, Ia, and Ib*. An example of a suitable melting range *Apparatus II* consists of a block of metal that may be heated at a controlled rate, 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.

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 not less than 16 hours.

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 2.5 to 3.5 mm high when packed down as closely as possible by moderate tapping on a solid surface.

Heat the bath until the temperature is about 30° 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 cause the temperature to rise at a rate of about 3° per minute. When the temperature is about 3° below the lower limit of the

expected melting range, reduce the heating so that the temperature rises at a rate of about 1° to 2° per minute. 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 is defined as the beginning of melting, and the temperature at which the test substance becomes liquid throughout is defined as the end of melting or the "melting point." The two temperatures fall within the limits of the melting range.

Procedure for Class Ia, Apparatus I—Prepare the test substance and charge the capillary as directed 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 $1 \pm 0.5^{\circ}$ per minute. Insert the capillary as directed under *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 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 hours. Without previous powdering, charge the cooled material into the capillary tube as directed 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 hours. 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 a temperature $10 \pm 1^{\circ}$ below the expected melting range is reached, then introduce the charged tube, and heat at a rate of rise of $3 \pm 0.5^{\circ}$ per minute until melting is complete. Record the melting range as directed for *Class I, Apparatus I*.

If the particle size of the material is too large for the capillary, pre-cool the test substance as above directed, 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 for *Class I, Apparatus I*. Operate the apparatus according to the manufacturer's instructions. Heat the block until the temperature is about 30° 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° to 2° per minute until melting is complete.

The temperature at which the detector signal first leaves its initial value is defined as the beginning of melting, and the temperature at which the detector signal reaches its final value is defined as the end of melting, or the *melting point*. The two temperatures fall within the limits of the melting range.

In the event of dispute, only the melting range or temperature obtained as directed for *Class I, Apparatus I*, is definitive.

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 hours, or in contact with ice for at least 2 hours. 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 for *Class I, Apparatus 1* except, within 5° of the expected melting temperature, to regulate the rate of rise of temperature to 0.5° to 1.0° per minute. The temperature at which the material is observed to rise in the capillary tube is the melting temperature.

Procedure for Class III—Melt a quantity of the test substance slowly, while stirring, until it reaches a temperature of 90° to 92°. Remove the source of the heat and allow the molten substance to cool to a temperature of 8° to 10° above the expected melting point. Chill the bulb of a suitable thermometer (see *Thermometers (21)*) 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 dulls, then dip it for 5 minutes into a water bath having a temperature not higher than 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 2° per minute to 30°, then change to a rate of 1° per minute, 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.

- a suitable thermometer with graduation at not more than 0.5 °C intervals and provided with an immersion mark. The range of the thermometer is not more than 100 °C,
- alkali-free hard-glass capillary tubes of internal diameter 0.9 mm to 1.1 mm with a wall 0.10 mm to 0.15 mm thick and sealed at one end.

Method. Unless otherwise prescribed, dry the finely powdered substance *in vacuo* and over *anhydrous silica gel R* for 24 h. Introduce a sufficient quantity into a capillary tube to give a compact column 4 mm to 6 mm in height. Raise the temperature of the bath to about 10 °C below the presumed melting point and then adjust the rate of heating to about 1 °C/min. When the temperature is 5 °C below the presumed melting point, correctly introduce the capillary tube into the instrument. For the apparatus described above, immerse the capillary tube so that the closed end is near the centre of the bulb of the thermometer, the immersion mark of which is at the level of the surface of the liquid. Record the temperature at which the last particle passes into the liquid phase.

Calibration of the apparatus. The apparatus may be calibrated using melting point reference substances such as those of the World Health Organisation or other appropriate substances.

EP

2.2.15. MELTING POINT - OPEN CAPILLARY METHOD

For certain substances, the following method is used to determine the melting point (also referred to as slip point and rising melting point when determined by this method).

Use glass capillary tubes open at both ends, about 80 mm long, having an external diameter of 1.4 mm to 1.5 mm and an internal diameter of 1.0 mm to 1.2 mm.

Introduce into each of 5 capillary tubes a sufficient amount of the substance, previously treated as described, to form in each tube a column about 10 mm high and allow the tubes to stand for the appropriate time and at the prescribed temperature.

Unless otherwise prescribed, substances with a waxy consistency are carefully and completely melted on a water-bath before introduction into the capillary tubes. Allow the tubes to stand at 2-8 °C for 2 h.

Attach one of the tubes to a thermometer graduated in 0.5 °C so that the substance is close to the bulb of the thermometer. Introduce the thermometer with the attached tube into a beaker so that the distance between the bottom of the beaker and the lower part of the bulb of the thermometer is 1 cm. Fill the beaker with water to a depth of 5 cm. Increase the temperature of the water gradually at a rate of 1 °C/min.

The temperature at which the substance begins to rise in the capillary tube is regarded as the melting point.

Repeat the operation with the other 4 capillary tubes and calculate the result as the mean of the 5 readings.

2.2.16. MELTING POINT - INSTANTANEOUS METHOD

The instantaneous melting point is calculated using the expression:

$$\frac{t_1 + t_2}{2}$$

in which t_1 is the first temperature and t_2 the second temperature read under the conditions stated below.

Apparatus. The apparatus consists of a metal block resistant to the substance to be examined, of good heat-conducting capacity, such as brass, with a carefully polished plane upper surface. The block is uniformly heated throughout its mass by means of a micro-adjustable gas heater or an electric heating device with fine adjustment. The block has a cylindrical cavity, wide enough to accommodate a thermometer, which should be maintained with the mercury column in the same position during the calibration of the apparatus and the determination of the melting point of the substance to be examined. The cylindrical cavity is parallel to the upper polished surface of the block and about 3 mm from it. The apparatus is calibrated using appropriate substances of known melting point.

Method. Heat the block at a suitably rapid rate to a temperature about 10 °C below the presumed melting temperature, then adjust the heating rate to about 1 °C/min.

At regular intervals drop a few particles of powdered and, where appropriate, dried substance, prepared as for the capillary tube method, onto the block in the vicinity of the thermometer bulb, cleaning the surface after each test. Record the temperature t_1 at which the substance melts instantaneously for the first time in contact with the metal. Stop the heating. During cooling drop a few particles of the substance at regular intervals on the block, cleaning the surface after each test. Record the temperature t_2 at which the substance ceases to melt instantaneously when it comes in contact with the metal.