METHODS OF ANALYSIS:
1.2.1 MELTING TEMPERATURE AND MELTING RANGE

(July 2013)

DRAFT FOR COMMENT

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**SCHEDULE FOR THE ADOPTION PROCESS OF DOCUMENT QAS/13.532**

### 1.2.1 MELTING TEMPERATURE AND MELTING RANGE

<table>
<thead>
<tr>
<th>Activity</th>
<th>Date</th>
</tr>
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<tbody>
<tr>
<td>Preparation of first draft text by WHO Secretariat</td>
<td>May 2013</td>
</tr>
<tr>
<td>Discussion at informal consultation to discuss new medicines, quality control and laboratory standards</td>
<td>12–14 June 2013</td>
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<tr>
<td>Revision of draft proposal</td>
<td>July 2013</td>
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<tr>
<td>Mailing of draft proposal for comments</td>
<td>July 2013</td>
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<tr>
<td>Collation of comments</td>
<td>September 2013</td>
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<tr>
<td>Presentation to 48th meeting of the WHO Expert Committee on Specifications for Pharmaceutical Preparations for discussion</td>
<td>October 2013</td>
</tr>
<tr>
<td>Further follow-up action as required</td>
<td></td>
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</tbody>
</table>
1.2.1 MELTING TEMPERATURE AND MELTING RANGE

[Note from the Secretariat. It is proposed to list in the general chapter 1.2.1 MELTING TEMPERATURE AND MELTING RANGE the International Chemical Reference Substances issued to calibrate melting-point instruments. Comments are in particular sought on alternatives to the hitherto described mercury-containing thermometers (see line 90 of the document). Changes from the current text are indicated in the text by insert or delete.]

A. Determination of melting temperature and melting range of Pulverizable substances

The melting range of a substance is the range between the corrected temperature at which the substance begins to collapse or form droplets on the wall of a capillary tube and the corrected temperature at which it is completely melted as shown by the disappearance of the solid phase.

The statement in a monograph "melting range a-b °C" means that the melting range determined by the method below must fall within these limits.

The melting temperature of a substance is the corrected temperature at which it is completely melted as shown by the disappearance of the solid phase.

Apparatus

A suitable apparatus for the determination consists of a glass vessel with appropriate liquid, a controlled source of heat, a thermometer, a capillary tube and a magnifying glass.

The glass vessel should have a suitable construction, contain an appropriate liquid and be fitted with a stirring device capable of rapid mixing of the liquid (certain liquid silicones...
are suitable). The controlled source of heat should be capable of raising the temperature
of the liquid heating medium at the required rate.

Standardized thermometers should cover the range -10 to +360 °C, the length of one
degree on the scale being not less than 0.8 mm. These thermometers should preferably be
of the mercury-in-glass, solid-stem type with a cylindrical bulb and made of approved
thermometric glass suitable for the range covered; each thermometer should have a safety
chamber.

Thermometers used for determination of melting temperatures may be calibrated for total
or partial immersion. A total-immersion thermometer should read correctly when it is
immersed at least to the end of the liquid column in the medium, the temperature of
which is to be measured. A partial-immersion thermometer should read correctly when it
is immersed to a prescribed depth and when the emergent liquid column is under
prescribed conditions. When total-immersion thermometers are used partially immersed,
an auxiliary thermometer is required for the determination of the emergent-stem
correction. These two thermometers should be surrounded with a glass tube above the
surface of the heating material.

The capillary tube should be made of borosilicate glass, closed at one end, and have the
following dimensions: thickness of the wall, about 0.10–0.15 mm; length, suitable for the
apparatus used; internal diameter, 0.9–1.1 mm.

A suitable magnifying glass should be used for observation of the capillary tube.

Other apparatus or methods may be used provided they are capable of equal accuracy and
have been calibrated against the method of The International Pharmacopoeia by means
of the WHO Melting Point Reference Substances.\textsuperscript{4,2}
<table>
<thead>
<tr>
<th>Substance</th>
<th>Assigned melting point$^1$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azobenzene M.P.</td>
<td>68.9 °C</td>
</tr>
<tr>
<td>Vanillin M.P.</td>
<td>83.2 °C</td>
</tr>
<tr>
<td>Benzil M.P.</td>
<td>95.9 °C</td>
</tr>
<tr>
<td>Acetanilide M.P.</td>
<td>115.7 °C</td>
</tr>
<tr>
<td>Phenacetin M.P.</td>
<td>136.0 °C</td>
</tr>
<tr>
<td>Benzanilide M.P.</td>
<td>164.7 °C</td>
</tr>
<tr>
<td>Sulfanilamide M.P.</td>
<td>165.9 °C</td>
</tr>
<tr>
<td>Sulfapyridine M.P.</td>
<td>192.7 °C</td>
</tr>
<tr>
<td>Dicyanodiamide M.P.</td>
<td>210.2 °C</td>
</tr>
<tr>
<td>Saccharin M.P.</td>
<td>230.0 °C</td>
</tr>
<tr>
<td>Caffeine M.P.</td>
<td>237.2 °C</td>
</tr>
<tr>
<td>Phenolphthalein M.P.</td>
<td>263.1 °C</td>
</tr>
</tbody>
</table>

$^1$A set of substances with melting points according to The International Pharmacopoeia in the temperature range +69 to +263 °C. These substances are available from the WHO collaborating host organization for International Chemical Reference Substances: European Directorate for the Quality of Medicines & HealthCare, 7 allée Kastner, CS 30026, F-67081 Strasbourg, France; Fax: +33 (0)3 88 41 27 71 – for the attention of EDQM Sales Section; Email: orders@edqm.eu; web site: http://www.edqm.eu/en/WHO-International-Chemical-Reference-Substances-ICRS-1393.html.

$^1$The exact melting points, assigned to the substances, can be found in the leaflets accompanying the standards.
**Recommended procedure**

Spread a small quantity of the finely powdered substance in a thin layer and dry it in a vacuum desiccator over silica gel, desiccant, R, phosphorus pentoxide R or other suitable desiccant for 24 hours, or at a temperature specified in the monograph.

Transfer a quantity of the dried powder to a dry capillary tube and pack the powder, for example, by tapping the tube on a hard surface, so as to form a tightly-packed column about 3 mm in height. Introduce the capillary tube into the heated bath at a temperature 5 °C below the expected lower limit of the melting range, the rise of temperature being regulated beforehand to 1 °C per minute, unless either the temperature of the introduction of the capillary tube into the bath or the rate of temperature rise are otherwise specified in the monograph. The capillary tube should be fitted in the bath in such a way that its closed end is at the level of the middle of the bulb of the standard thermometer.

When a thermometer calibrated for partial immersion is used, care must be taken that it is immersed exactly to its immersion mark when the readings are taken.

Unless otherwise specified in the monograph, readings are taken of the temperature at which the substance is observed to collapse or form droplets on the wall of the tube and of the temperature at which it is completely melted as indicated by the disappearance of the solid phase.

To the temperature readings add the correction for deviation of the standard thermometer. When thermometers calibrated for total immersion are used partially immersed, add to the readings of the standard thermometer also the emergent-stem correction, which is obtained as follows:

Before starting the determination of the melting range, an auxiliary thermometer is attached so that the bulb touches the standard thermometer at a point midway between the
graduation for the expected melting point and the surface of the heating material. When
the substance has melted the temperature is read on the auxiliary thermometer. The
correction to be added to the temperature reading of the standard thermometer is
calculated from the following formula:

$$0.00015 \times N(T-t)$$

where $T$ is the temperature reading of the standard thermometer;
$t$ is the temperature reading of the auxiliary thermometer;
$N$ is the number of degrees of the scale of the standard thermometer between the
surface of the heating material and the level of the mercury.

When needed the emergent-stem correction for thermometers calibrated for partial
immersion may be calculated from the same formula as above, but replacing $T$ by $T_s$,
which is the mean temperature of the emergent-stem of the thermometer at the time of
calibration.

Both the above-mentioned corrections for emergent-stem and any deviation of the
standard thermometer may conveniently be replaced by calibration of the apparatus by
means of the WHO Melting Point Reference Substances.

B. Determination of melting point of fats, waxes, etc.

The melting point of fats, waxes, etc., is the corrected temperature at which the column of
substance in the capillary tube becomes transparent or moves upwards, when tested by
the method described below.

Apparatus

A similar apparatus to that described under A for the determination of melting
temperature and melting range of pulverizable substances should be used with the
following modifications:
– water should be used in the heating vessel;
– an accurately standardized thermometer should cover the range -10 to +100°C;
– a glass capillary tube should have the same dimensions as described under A but be open at both ends; soft glass capillary tubes may be used.

Recommended procedure

Unless otherwise specified in the monograph, melt the substance at as low a temperature as possible and then suck the liquid up to a height of about 10 mm in the capillary tube. Cool the charged tube at 10 °C or lower for 24 hours. If the monograph specifies that the melting temperature is to be determined without previous melting of the substance, charge the capillary tube by pushing it into the unmelted substance so that a column about 10 mm long is forced in. The determination may then be carried out immediately. Attach the tube to the thermometer in the water-bath by means of a rubber band or otherwise so that the lower end of the capillary tube is at the level of the middle of the bulb of the thermometer and the distance between the lower end of the capillary tube and the water level is about 20 mm. Heat the bath with constant stirring, the heating being regulated so that the temperature rise, at a temperature of 5 °C below the expected melting temperature, is about 1 °C per minute.