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## 2 **1.2.1. MELTING TEMPERATURE AND MELTING RANGE**

### 3 **Draft proposal for inclusion in *The International Pharmacopoeia***

4 (July 2023)

### 5 **DRAFT FOR COMMENTS**

A large, faint grey 'X' mark is positioned in the upper right corner of the page.

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For any technical queries, please contact **Dr Herbert Schmidt**, Technical Officer, Norms and Standards for Pharmaceuticals, Technical Standards and Specifications ([schmidth@who.int](mailto:schmidth@who.int)), with a copy to Ms Sinéad Jones ([jonessi@who.int](mailto:jonessi@who.int), [nsp@who.int](mailto:nsp@who.int)).

Comments should be submitted through the online platform on or by **28 September 2023**. Please note that only comments received by this deadline will be considered for the preparation of this document.

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35            SCHEDULE FOR THE ADOPTION PROCESS OF DOCUMENT QAS/22.916

36            **1.2.1. MELTING TEMPERATURE AND MELTING RANGE**

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Description	Date
First draft prepared by the Secretariat of <i>The International Pharmacopoeia</i> .	June 2022
Discussion at the Consultation on Quality Control and Pharmacopoeial Specifications for Medicines	April 2023
Public consultation of the draft revision.	July – September 2023
Further follow-up action as required.	

38

39    *[Note from the Secretariat. The World Health Organization (WHO) provides Melting*  
40    *Point Reference Substances for the calibration of instruments to determine melting*  
41    *points. The appropriate use of such reference substances is considered essential for*  
42    *achieving true and comparable results and is thus required as per Good Laboratory*  
43    *Practices and Good Manufacturing Practices.*

44    *WHO is seeking comments on the draft proposal for revision of chapter 1.2.1 Melting*  
45    *temperature and melting range in The International Pharmacopoeia. Comments on the*  
46    *proposed changes to the text are welcome – also proposes for information/aspects so*  
47    *far not included but deemed necessary. Changes to the current chapter are indicated*  
48    *by insert or delete.*

49    *In addition, WHO is inviting laboratories to participate in an inter-laboratory study to*  
50    *establish new batches of melting point ICRS. Participants will be provided with three*  
51    *reference substances to calibrate their instruments plus one reference substance to*  
52    *verify the calibration and will be asked to determine the melting points of four*

53 *candidate reference substances. Participation in the study is for free. The results are  
54 statistically evaluated and a report of the findings will be circulated.*

55 *Participation in inter-laboratory studies is advantageous for laboratories: such  
56 studies increase confidence in a laboratory's results and among all the laboratories  
57 involved in comparison testing.*

58 *The invitation to participate is addressed to the following laboratories:*

- 59 • *laboratories associated with other pharmacopoeias or organizations providing  
60 reference substances for the calibration of melting point instruments;*
- 61 • *manufacturers of melting point instruments;*
- 62 • *WHO Collaborating Centres;*
- 63 • *quality control laboratories included on the WHO List of Prequalified  
64 Medicines Quality Control Laboratories;*
- 65 • *laboratories of manufacturers of WHO prequalified medicines; and*
- 66 • *accredited national quality control laboratories.*

67 *If you wish to participate in the study, kindly contact Dr Herbert Schmidt (at  
68 [schmidth@who.int](mailto:schmidth@who.int).)]*

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71 **1.2.1. Melting temperature and melting range**

72 **A. Determination of melting temperature and melting range of pulverizable  
73 substances**

74 The *melting range* of a solid substance is the range between the corrected  
75 temperature at which the substance begins to collapse or forms droplets on the  
76 wall of a transparent glass capillary tube and the corrected temperature at  
77 which it is completely melted, as shown by the disappearance of the solid  
78 phase.

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

81 The *melting temperature* of a substance is the corrected temperature at which  
82 the solid substance is completely melted to a liquid or a decomposed state.

83 **Apparatus**

84 A suitable apparatus for the determination consists of a controlled source of  
85 heat, either a metal heating block with one or more compartments for capillary  
86 tubes or a glass vessel with an appropriate liquid and fitted with a suitable  
87 means of heating and stirring. The apparatus is equipped with a temperature  
88 sensor or a suitable certified thermometer allowing readings at least to the  
89 nearest 0.1 °C. A suitable apparatus for the determination consists of a glass  
90 vessel with appropriate liquid, a controlled source of heat, a thermometer, a  
91 capillary tube and a magnifying glass. The glass vessel should have a suitable  
92 construction, contain an appropriate liquid and be fitted with a stirring device  
93 capable of rapid mixing of the liquid (certain liquid silicones are suitable).

94 The controlled source of heat should be capable of raising the temperature of  
95 the sample liquid heating medium at the required rate at a rate of 1 °C/min or  
96 less.

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

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

112 Samples are introduced into the equipment in glass ~~The capillary tubes should~~  
113 ~~be made of borosilicate glass, closed at one end, and have the following~~  
114 ~~dimensions: thickness of the wall, about 0.10–0.15 mm; length, suitable for the~~  
115 ~~apparatus used; internal diameter, 0.9–1.1 mm. The dimensions are chosen~~  
116 ~~according to the manufacturer's requirements, typically with an external~~  
117 ~~diameter of 1.3–1.5 mm and a wall thickness of 0.1–0.3 mm. In some,~~  
118 ~~apparatus glass slides are used instead of capillary tubes.~~

119 In case of visual detection, a suitable magnifying glass should be used for  
120 observation of the capillary tube.

121 Other apparatus or methods may be used provided they are capable of equal  
122 accuracy and have been calibrated against the method of *The International*  
123 *Pharmacopoeia* by means of the WHO Melting Point Reference Substances.

124        **Recommended procedure**

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

129        Transfer a quantity of the dried powder to a dry capillary tube and pack the  
130        powder carefully by tapping the tube on a hard surface (ensure the capillary  
131        tube bottom is not damaged or cracked). Pack the sample column tightly to a  
132        height of about 4-6 3 mm. Coarse crystals are to be avoided as they might lead  
133        to false results. If necessary, crush the sample into a fine powder. Introduce the  
134        capillary tube into the controlled source of heat heated bath at a temperature of  
135        5 °C below the expected lower limit of the melting range, the rise of  
136        temperature being regulated beforehand to 1 °C per minute, unless either the  
137        temperature of the introduction of the capillary tube into the bath or the rate of  
138        temperature rise are otherwise specified in the monograph. If a bath with a  
139        suitable liquid is used, the The capillary tube should be fitted in the bath in  
140        such a way that its closed end is at the level of the middle of the bulb of the  
141        standard thermometer.

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

145        Unless otherwise specified in the monograph, readings are taken of the  
146        temperature at which the substance is observed to collapse or form droplets on  
147        the wall of the tube and of the temperature at which it is completely melted as  
148        indicated by the disappearance of the solid phase. In case of instrumental  
149        detection, follow the instrument manufacturer's requirements for the  
150        determination of the melting point.

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

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

162  $0.00015 N(T-t)$

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.

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

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

170

171

172      **System suitability**

173      Carry out a system suitability test before the measurements, for example, by  
174      choosing a suitable reference material with a melting point close to that  
175      expected for the test substance.

176      **B. Determination of melting point of low melting solids**

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

180      **Apparatus**

181      A similar apparatus to the glass vessel with an appropriate liquid, as that  
182      described under A for the determination of melting temperature and melting  
183      range of pulverizable substances, should be used with the following  
184      modifications:

185      – water should be used in the heating vessel;  
186      – an accurately standardized thermometer should cover the range -10 to  
187      +100 °C; and  
188      – a glass capillary tube should ~~have the same dimensions as described under A~~  
189      ~~but be open at both ends; soft glass capillary tubes may be used, open at both~~  
190      ~~ends, about 80 mm long, having an external diameter of 1.4 mm to 1.5 mm and~~  
191      ~~an internal diameter of 1.0 mm to 1.2 mm.~~

192      **Recommended procedure**

193      Unless otherwise specified in the monograph, melt the substance at as low a  
194      temperature as possible and then suck the liquid up to a height of about 10 mm  
195      in the capillary tube. Cool the charged tube at 10 °C or lower for 24 hours. If

196 the monograph specifies that the melting temperature is to be determined  
197 without previous melting of the substance, charge the capillary tube by pushing  
198 it into the unmelted substance so that a column about 10 mm long is forced in.  
199 The determination may then be immediately carried out.

200 Attach the tube to the thermometer in the water bath by means of a rubber band  
201 or otherwise so that the lower end of the capillary tube is at the level of the  
202 middle of the bulb of the thermometer and the distance between the lower end  
203 of the capillary tube and the water level is about 20 mm. Heat the bath with  
204 constant stirring, the heating being regulated so that the temperature rises, at a  
205 temperature of 5 °C below the expected melting temperature, which is about  
206 1 °C per minute.

207 **C. Qualification of the equipment**

208 The qualification is carried out periodically according to the instrument  
209 manufacturer's requirements, using WHO Melting Point Reference Substances.  
210 These are selected to cover the temperature range that is used on the  
211 equipment. Use capillary tubes with the same dimensions as those used for  
212 sample measurement.

213 WHO Melting Point Reference Substances.

Substance	Assigned melting point <sup>1</sup>
Azobenzene	<u>Biphenyl M.P.</u> 68.9/[to be assigned] °C
Vanillin M.P.	83.2 °C
Benzil M.P.	95.9 °C
Acetanilide M.P.	115.7 °C
Phenacetin M.P.	136.0 °C
Benzanilide M.P.	164.7 °C
Sulfanilamide M.P.	165.9 °C

Sulfapyridine M.P.	192.7 °C
Dicyanodiamide M.P.	210.2 °C
Saccharin M.P.	230.0 °C
Caffeine M.P.	237.2 °C
Phenolphthalein M.P.	263.1 °C

214       <sup>1</sup> The exact melting points assigned to the substances can be found in the  
215 leaflets accompanying the standards.

216       These substances are available from the WHO collaborating host organization  
217 for International Chemical Reference Substances: European Directorate for the  
218 Quality of Medicines & HealthCare, 7 allée Kastner, CS 30026, F-67081  
219 Strasbourg, France; fax: +33 (0)3 88 41 27 71 – for the attention of EDQM  
220 Sales Section; email: [orders@edqm.eu](mailto:orders@edqm.eu); website: <http://www.edqm.eu> .

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