

Compliance with amended General Chapter USP<741>Melting Range or Temperature

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Abstract

Laboratories measuring melting temperature according to USP<741> Melting Range or Temperature, must comply with the amended calibration and adjustment requirements described in this regulation. Compliance is ensured by adjusting the instrument with secondary reference standards, traceable to USP, followed by verification of accuracy using USP primary reference standards.

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I. INTRODUCTION

For the purposes of United States Pharmacopeia (USP), melting range, melting temperature, or melting point is defined as those points of temperature within which, or the point at which, the first detectable liquid phase is detected to the temperature at which no solid phase is apparent [1]. Even for highly pure materials, during melting transition, a temperature range is observed from the beginning to the end of the phase change. Modern production processes frequently require knowledge of the thermal behavior of substances under different conditions. Whether developing new products with optimized properties or routinely determine deviations from a quality control perspective, melting temperatures are key indicator.

II. REFERENCE STANDARDS

In order to correctly measure thermal values, the accuracy of an instrument should be checked at regular intervals by one or more reference standards, preferably those which closest match the melting temperatures of the samples being tested. In order to perform such checks, various reference materials are available.

A. Primary reference standards

A series of USP standards are recommended and released under the authority of the USP Reference Standard Committee, in collaboration with the US Food and Drug Administration (FDA). For metrology and certification purposes, these are known as primary reference standards [2].

B. Secondary reference standards

Following the same terminology, secondary reference standards are those which are released by third parties other than USP, but are fully-traceable to USP standards. Amongst others,

LGC and Fluka produce such substances. The FDA and USP both recognize the use of secondary standards [3].

III. CHANGES TO USP<741>

Factors influencing a melting process include the sample amount, the particle size, the efficiency of heat transfer, and the heating rate, among other variables. In order to achieve consistency and repeatability during melting point determinations, controlled procedural instructions shall be followed.

As highlighted in a recent Pharmacopeial Forum Stimuli to the Revision Process article [4], previous versions of General Chapter USP<741> Melting Range or Temperature allowed certain flexibility in the analytical conditions for melting point determination. These versions allowed the instrument to be both adjusted and then checked for accuracy using USP primary reference substances.

The study evaluated the effects of ramp rate, pulverization, and amount of sample (column height in the capillary) on the melting range and melting point measurements.

Further to this study, a revision was made to Chapter <741>, in order to provide more consistency and repeatability of the melting point values [1]. The revised Chapter now specifies the use of gently pulverized dried material filled to a height of 3 mm in the capillary tube, to be heated at a rate of 1 °C/min.

Importantly, the revised Chapter <741>states that USP primary reference standards are intended only to check the accuracy of the device (i.e. compare the measured value against the certified value of the standard) and are not suitable for adjusting the instrument.

In order to comply with these changes, we have established a new procedure, using secondary reference standards to adjust the instrument and then primary reference standards to check the accuracy of the instrument.

We will now demonstrate how this procedure can be successfully performed on the METTLER TOLEDO Melting Point Excellence range of instruments.

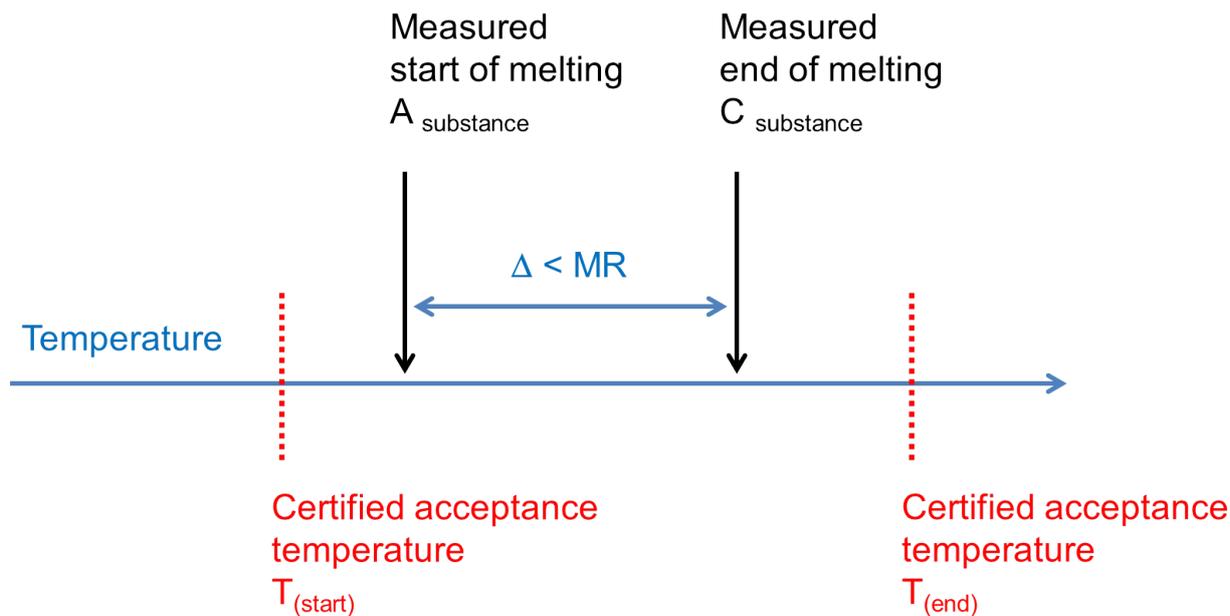


Figure 1: Diagram of USP melting point test procedure according to USP<741>. $C_{substance} - A_{substance}$ (indicated as Δ) must be lower than the MR specified in the relevant certificate.

IV. INSTRUMENT ADJUSTMENT

Melting range analyses were performed on eight METTLER TOLEDO Melting Point Excellence instruments. Depending on the instrument, simultaneous measurements of up to 6 samples are possible. The instruments were adjusted using secondary reference standards following conventional two-point adjustment procedure, as described in the instrument Operating Instructions and Equipment Qualification Package (EQPac). This procedure measures two different substances with different melting ranges.

V. PERFORMANCE CHECK

To check the accuracy of the instrument, USP primary standards must be used. The type of standard, lot number, specific acceptance temperature ($T_{(start)}$ and $T_{(end)}$) and maximum range (MR) are provided on the respective USP certificates. Lot-specific expiry dates can be found in the USP catalog.

Figure 1 illustrates the performance check used. The test is passed if i) the measured

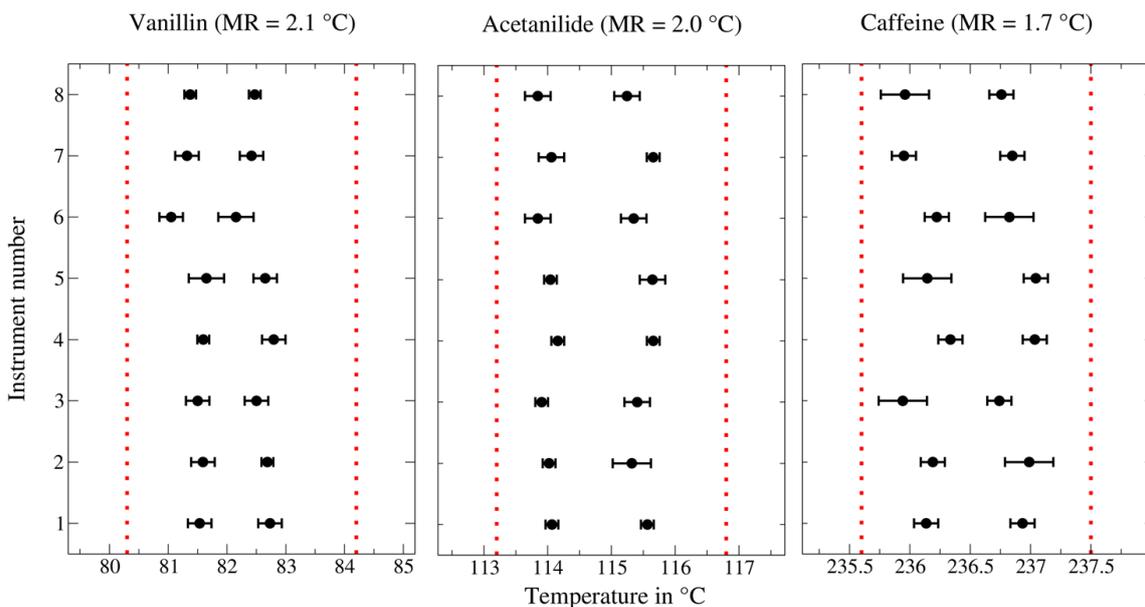


Figure 2: Mean measured start– and end of melt temperatures (dots) and standard deviation compared to the acceptance temperatures (dashed red lines) for three USP primary reference standards. Simultaneous measurements were performed.

melting temperature falls within the certified acceptance temperatures and ii) the difference between the end of melting and the start of melting (i.e. the melting range $C_{substance} - A_{substance}$), is lower than MR. These conditions are summarized as follows:

i) $T_{(start)} < A_{substance}$; and $C_{substance} < T_{(end)}$

ii) $C_{substance} - A_{substance} < MR$

In our analyses, three USP primary reference substances were used. Multiple, simultaneous measurements per instrument were carried out. Figure 2 shows, for each instrument, the mean value of the start– and end of the melt for each USP substance. Mean values are represented by black dots with standard deviation bars. The certified start– and end of melt temperatures are shown as dashed red lines which represent the acceptance temperatures of the substance.

Figure 3 shows the mean values of measured range ($C_{substance} - A_{substance}$) with the associated standard deviation. The certified maximum range (MR) is represented for each substance as a dashed red line.

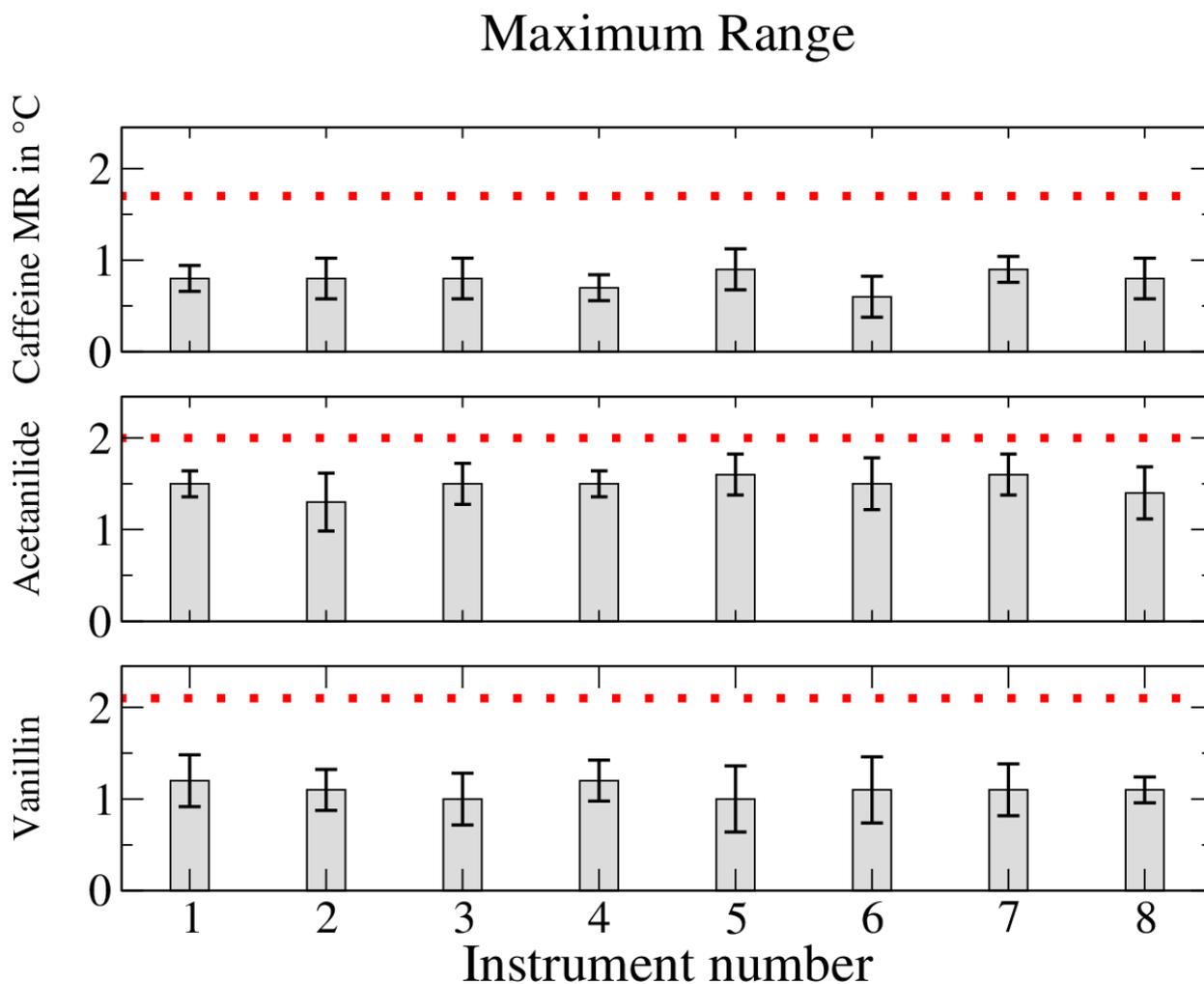


Figure 3: Mean measured range ($C_{substance} - A_{substance}$), and standard deviation compared to the certified MR (dashed red lines), for three USP primary reference standards. Simultaneous measurements were performed. Each range was calculated from multiple, simultaneous measurements

In order to pass the performance check, the measured start- and end of the melt values must lie within the dashed red lines of Figure 2 (condition i) and the range also be below the maximum range (MR), shown in Figure 3, as specified on the certificate (condition ii).

All eight instruments fulfilled conditions i) and ii) for all three substances, showing accurate performance of the instruments following adjustment using secondary reference materials.

VI. CONCLUSIONS

According to the revised General Chapter USP<741>, primary reference standards can no longer be used to adjust melting point instruments. A new procedure is proposed by METTLER TOLEDO using secondary reference substances to perform the adjustment. Primary reference standards are used to check the accuracy of the instrument.

This procedure is compliant with General Chapter USP<741> and guarantees highly accurate analytical results when performed on Melting Point Excellence instruments.

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