

Pharmacopeia vs. Thermodynamic Melting Point Determinations

Application Note #3

Pharmacopoeia Melting Point

The procedural rules for melting point determinations are defined in the pharmacopeias. The medical handbooks include minimum requirements for the design of the melting point apparatus and for performing the measurements. Automated melting point determination procedures are generally included. Very often, the pharmacopeias also list special methods for difficult or unusual cases of melting point determination.

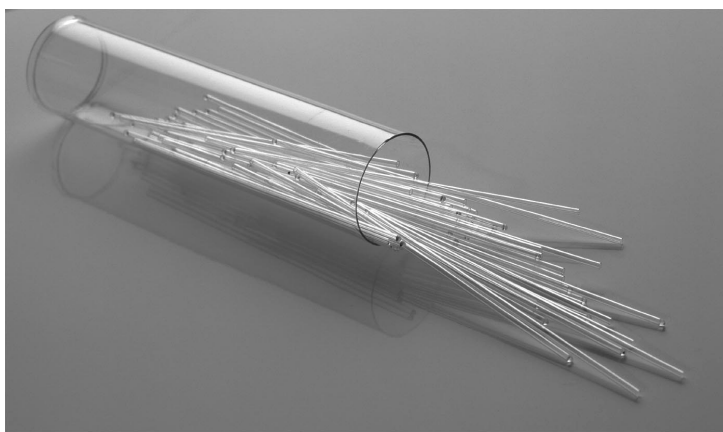


Figure 1. Standard capillary tubes used in melting point determinations.

The pharmacopeias regard the **capillary technique** as the standard method for melting point determination. In this method, thin glass capillary tubes containing packed samples of the substance are introduced into a heating stand that is continuously being heated up.

The capillary technique is the standard method used for melting point determinations in most organic and pharmaceutical chemistry laboratories.

The procedures for melting point determinations in the pharmacopeias call for a fixed rate of temperature rise in the “heating stand” (i.e. liquid bath and/or metal block), typically between 0.2 °C/min and 2 °C/min, within a temperature range that brackets the expected melting temperature of the compound. The oven continues to heat at a constant rate until the sample is completely melted (i.e. clear point). In determining the melting point, the temperature on the

thermometer at the clear point (and/or sometimes at the meniscus point) is recorded. *This is not the temperature of the sample itself but rather that of the heating stand where the thermometer is located (i.e. the temperature is determined by the heating medium).*

When different heating rates are used for determining the melting point of a sample, the values obtained for the clear point are dependent on the temperature ramping rate. Because the heat transfer from the heating stand to the sample cannot be increased proportionally to the temperature ramping rate, the temperature in the heating stand rises to a higher level with faster rates of heat increase than it does with lower rates. As a result, the faster the temperature is ramped, the higher the clear points are found to be. Due to this dependence on heating rate, *measurements taken for melting points are comparable with one another only if they were taken using the same ramping rates.* Any variance from the temperature ramping rates specified by pharmacopoeia procedures must be properly recorded for Good Laboratory Practice documentation.

Table 1 is an example of the dependence of the clear point determination on ramping rate for phenacetin samples (MP: 133 °C) analyzed with an OptiMelt system. As expected, the clear point increases with increasing ramping rates. The need to specify ramping rates along with the results of the melt is demonstrated by this data.

Table 1. Clear point of phenacetin at various ramp rates.

Ramp Rate, r [°C/min]	Clear Point [°C]
0.1	134.2
0.2	134.4
0.5	134.9
1	135.4
2	136.2
5	137.9

The capillary techniques described in early pharmacopeias were mostly concerned with visual detection of the melting point. Recent reviews of the published procedures have been supplemented to account for automated detection of the melting point, such as the digital image processing technology used by the OptiMelt system.

The heating stands used by commercial melting point apparatuses are divided into two categories:

- Liquid Bath—The capillaries are immersed in a liquid bath (typ. silicone oil) that is continuously being heated up.

- Metal Block—A small, dry thermal block (metal oven) has proven to be a good alternative to a liquid bath.

The melting point procedures described in early pharmacopeias were designed for “liquid bath” heating stands. However, in recent years most monographs have been updated and supplemented to include the more prevalent metal block setups.

Tip

A slight drift in MP results is expected when the MP numbers obtained with a liquid bath oven are compared to those obtained with a metal block stand. This difference is well known and generally ignored since it typically falls within the intrinsic uncertainty of the measurement.

Thermodynamic Melting Point

The transition from solid to liquid does not take place instantaneously—it requires a finite amount of time. The melting process begins at the point where the first particles of the bulk substance turn into the liquid state—the **onset point**. The end of the melt is reached when the last solid particles have gone over into the liquid phase—the **clear point**. During the entire melting process of a pure compound, the temperature of the pure substance remains constant (thermodynamic melting point) while heat is transferred from the heating stand to the sample. The heating stand itself experiences a range of temperatures that depends on the selected heating rate.

When determining the melting point according to pharmacopoeia, the temperature of the heating stand at the end of the melt (i.e. clear point) is read. That single temperature record depends on the temperature ramping rate. It ignores the range between the start and the end of the melt, and it is not the “true” thermodynamic melting point of the pure compound.

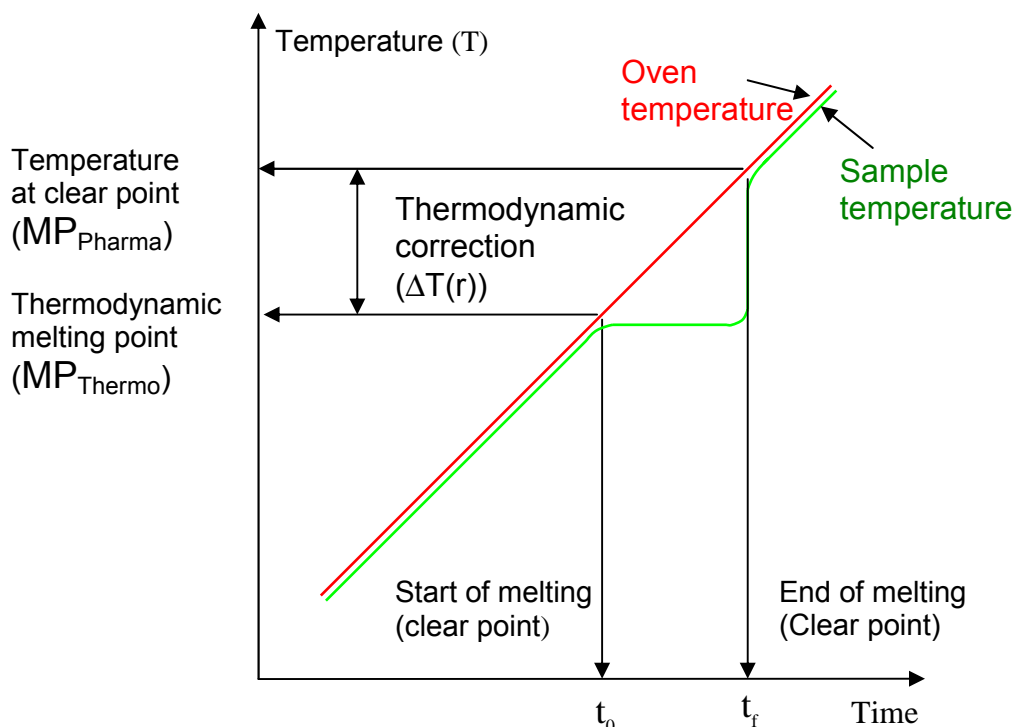


Figure 2. Graphical representation of the thermodynamic correction

Figure 2 is a simple representation of the sequence of events that take place during the melting of a pure substance. At the start of the melting (time = t_0), the block and the sample are at approximately the same temperature. As soon as the melt starts the sample temperature stabilizes while the block continues heating up. As the melt progresses, the sample remains at constant temperature (thermodynamic melting point, MP_{therm}) while the block continues to heat up. Heat is constantly transferred from the block to the sample at a rate that is proportional to the temperature gradient between the sample and the block. The temperature of the block at the end of the melt (time = t_f) is recorded as the clear point (pharmacopoeia melting point, MP_{pharma}). The thermodynamic correction is defined as:

$$\Delta T(r) = MP_{\text{pharma}} - MP_{\text{therm}} \quad (\text{eqn. 1})$$

and is represented as a function of the ramping rate, r .

In order to obtain the thermodynamic melting temperature of a pure substance, it is necessary to calculate and subtract the thermodynamic correction from the

detected clear point. This calculates back to the temperature at the beginning of the melt so that the value obtained includes practically no dependence on the temperature ramping rate used for the determination.

Instruments with automated melting point determination facilities often pack enough data analysis infrastructure to automate the thermodynamic correction procedure: (1) the clear point is accurately identified and recorded, (2) the ramping rate is known and carefully controlled, and (3) the thermodynamic correction algorithm can be programmed and stored in memory. Knowledge of the functional dependence of the thermodynamic correction, $\Delta T(r)$, on r is the only requirement to automate the thermodynamic correction process. A parametric derivation of that functional dependence is presented in the following section.

Thermodynamic Correction

At any given time, t , during the melt, the amount of heat, $dQ(t)$, transferred from the heating stand to the sample during a time dt is:

$$dQ(t) = \alpha \cdot (T - MP_{\text{thermo}}) \cdot dt \quad (\text{eqn. 2})$$

where,

T : temperature of the heating stand, [$^{\circ}\text{C}$]

t : is the time variable, [min]

$r = dT/dt$: temperature ramping rate of the instrument [$^{\circ}\text{C}/\text{min}$]

α : heat transfer constant for the melting point apparatus [calories/ $(^{\circ}\text{C} \cdot \text{min})$]

Substituting dt with dT in eqn. 2, leads to:

$$dQ(t) = \alpha \cdot (T - MP_{\text{thermo}}) \cdot dT/r \quad (\text{eqn. 3})$$

Integration of the heat transferred from the block to the sample, over the entire melting process, provides the “heat of fusion” of the sample, ΔH_f [calories], which is dependent on its mass but independent of the ramping rate, r .

$$\Delta H_f = (MP_{\text{thermo}}, MP_{\text{pharma}}) \cdot \alpha \cdot (T - MP_{\text{thermo}}) \cdot dT/r \quad (\text{eqn. 4})$$

Calculation of the integral term leads to the analytical expression:

$$\Delta H_f = [0.5 \cdot \alpha/r] \cdot (MP_{\text{pharma}} - MP_{\text{thermo}})^2 \quad (\text{eqn. 5})$$

which can be rearranged to provide an equation for the thermodynamic correction:

$$\Delta T (r) = MP_{\text{pharma}} - MP_{\text{therm}} = [2 \cdot \Delta H_f / \alpha]^{1/2} \cdot r^{1/2} = (\text{Thermo CF}) \cdot r^{1/2} \quad (\text{eqn. 6})$$

According to eqn. 6, *the thermodynamic correction is directly proportional to the square root of the ramping rate*, and in order to calculate the thermodynamic melting temperature, it is necessary to know the value of the Thermodynamic Correction Factor (Thermo CF) for the melting point apparatus:

$$MP_{\text{therm}} = MP_{\text{pharma}} (\text{clear point}) - (\text{Thermo CF}) \cdot r^{1/2} \quad (\text{eqn. 7})$$

The above theory indicates that the value of the thermodynamic correction factor (Thermo CF), depends, among other things, on the (1) heat of fusion of the sample, (2) the thermal conductivity of the sample, (3) the thermal conductivity of the glass capillary, (4) the sample preparation/packing method, and (5) the geometry/construction of the oven. In practice, the value of Thermo CF is both compound and instrument dependent and must be calculated through empirical determination.

Thermodynamic Correction with OptiMelt

A user-programmable Thermodynamic Correction Factor (Thermo CF) can be programmed into OptiMelt and used by the instrument to automatically calculate Thermodynamic Corrections, $\Delta T (r) = (\text{Thermo CF}) \cdot r^{1/2}$, at the end of a melt-point determination.

Tip

- Thermodynamic corrections are appended to melt-point reports if Thermo MP is set to “Calculate” in the Options menu of the Melt Screen.
- Use the ThermoCF menu button to program the value of Thermo CF for the compound being measured.
- Compound specific thermodynamic correction factors can be stored within the analysis methods saved to memory.
- Use the thermodynamic corrections calculated by your OptiMelt to correct “ramp-dependent” clear points (manual or automatic) and to obtain a true thermodynamic melting point for your samples—independent of the rate of heat rise used.
- Empirical measurements have shown that in most cases a good approximation to the Thermodynamic Correction Factor (Thermo CF) for OptiMelt is a value of ≈ 1.0 , when r is expressed in standard units of [$^{\circ}\text{C}/\text{min}$].

- Calculation of your sample's Thermodynamic Correction Factor (Thermo CF) is recommended when accuracy is required. See next section for details.

Calculation of Thermodynamic Correction Factor

The Thermodynamic Correction Factor (Thermo CF) is compound specific and depends on several factors:

- Specific heat of fusion of the sample
- Mass of the sample
- Thermal conductivity of the sample
- Thermal conductivity of the glass capillary
- Sample preparation method
- Geometry of the oven

Experimental measurements have shown that in most cases a good approximation to the Thermodynamic Correction Factor (Thermo CF) for OptiMelt is a value of ≈ 1.0 , when r is expressed in standard units of [$^{\circ}\text{C}/\text{min}$]. However, empirical calculation of the Thermodynamic Correction Factor is recommended when more accurate results are required for a specific compound.

A Step-by-step calculation procedure is described below.

Step 1. Perform complete pharmacopoeia melting point determinations on your sample at six different temperature ramping rates: 0.1, 0.2, 0.5, 1, 2 and $5^{\circ}\text{C}/\text{min}$.

- Three samples are analyzed simultaneously for each ramping rate. Load three capillaries with a 2 to 3 mm column of sample and insert the tubes into the three adjacent sample slots of the OptiMelt oven.
- To increase the accuracy of results, load the capillaries using the same grinding, loading and packing techniques used for routine MP determinations.
- For each ramping rate, average the detected "clear points" (according to pharmacopoeia) for the three samples to obtain the final value.
- To increase the accuracy of results, use manual (automatic) clear point readings if manual (automatic) determinations are routinely performed in the lab.

Step 2. Plot the resulting Clear Point records versus the square root of their corresponding temperature ramping rate ($\text{MP}_{\text{pharma}}$ vs $r^{1/2}$). A linear dependence between the two sets of numbers should be observed. Calculate the slope of the

straight line, and program the result into the Thermodynamic Correction Factor (Thermo CF) of your OptiMelt.

Step 3. Use the Thermodynamic Correction Factor to calculate the thermodynamic melting point of the sample from the measured clear points (eqn. 7). An agreement within the accuracy of measurement should be observed for all calculated thermodynamic melting points.

An example of this calculation procedure is included below.

Thermo CF Calculation Example

In order to demonstrate the simplicity of the calculation procedure described in the previous section, a series of melts were performed on a phenacetin sample with ramping rates 0.1, 0.2, 0.5, 1.0, 2.0 and 5.0 °C/min.

Figure 3 summarizes the results and shows the expected linear relationship between the clear point determinations and the square root of the ramping rate. The slope of the straight line corresponds to a thermodynamic correction factor, Thermo CF= 1.9 for phenacetin samples.

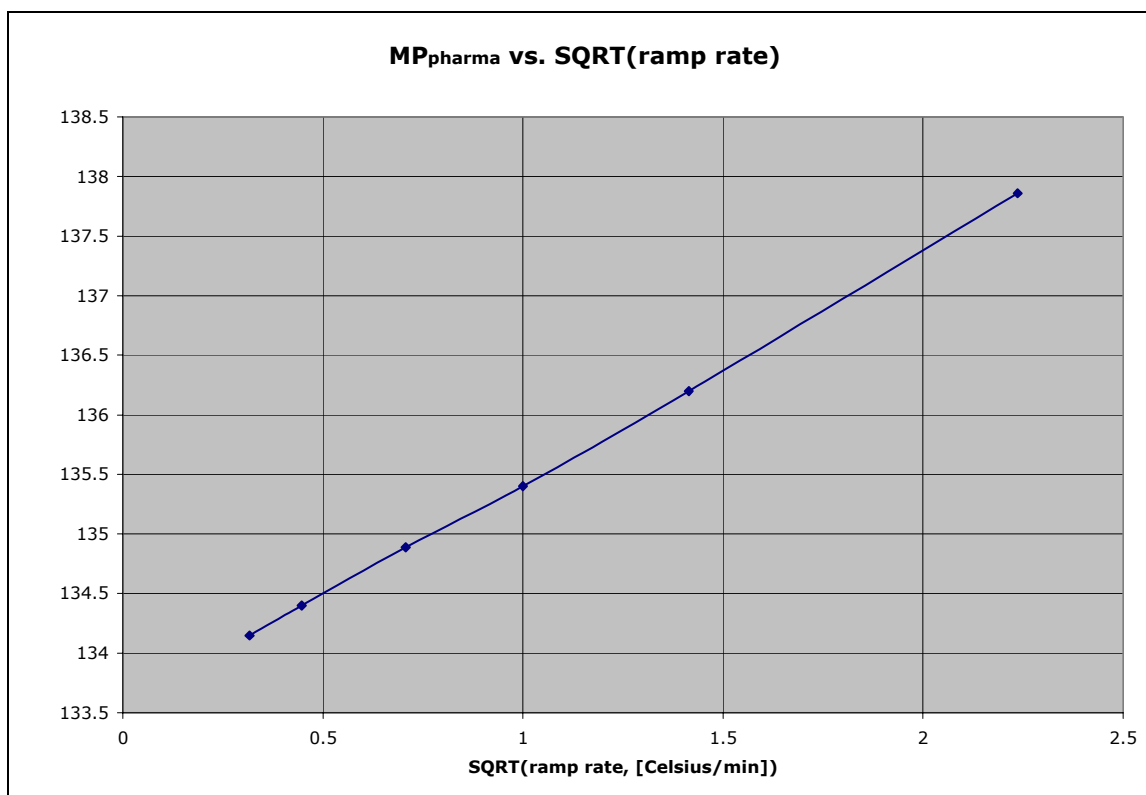


Figure 3. “Clear point temperature vs. square root of ramping rate” for a phenacetin sample melted at 0.1, 0.2, 0.5, 1.0, 2.0 and 5.0 °C/min. The slope of the straight line, Thermo CF=1.9, is programmed into OptiMelt as the thermodynamic correction factor (Thermo CF) for this compound.

Table 2 demonstrates the use of the thermodynamic correction factor to calculate the thermodynamic melting point of a phenacetin sample. In contrast to the clear point results, and within the accuracy of the measurement (± 0.3 °C), the thermodynamic MP results are independent of the ramp rate as expected from a thermodynamic constant.

Table 2. Clear and Thermodynamic Melting Point of Phenacetin at various ramp rates (Thermo CF= 1.9).

Ramp Rate, r [°C/min]	Clear Point [°C]	MP _{therm} = MP _{pharma} – Thermo CF · r ^{1/2} [°C]
0.1	134.2	133.6
0.2	134.4	133.4
0.5	134.9	133.6
1	135.4	133.5
2	136.2	133.5

5	137.9	133.6
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Tip

Thermodynamic corrections, $\Delta T(r)$, are automatically appended to melt-point reports if Thermo MP is set to Calculate in the Options menu of the Melt Screen.