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Value of thermal analysis in the critical evaluation of classical methods of melting point determination

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Summary

In some cases the use of classical methods of melting point determination may lead to erroneous interpretation of the data obtained. The main sources of errors are the presence of polymorphic or pseudo-polymorphic modifications, and the thermal instability of the solid, which may decompose without melting. The present work was aimed at demonstrating the utility of using Differential Scanning Calorimetry (DSC) and Thermogravimetry (TG) in the critical evaluation of melting point data obtained from the more classical methods recommended by the European Pharmacopoeia.

Introduction

The melting point value is one of the physical data routinely used for characterizing a substance in the solid state, especially in the case of pharmaceuticals, for which the melting point range is often also taken as an estimate of the purity.

Two methods are classically used for melting point determination: the capillary tube method, which is accepted by all the Pharmacopoeiae, and the Maquenne block determination method, which is recommended by the Romanian as well as the French Pharmacopoeia.

More than 20 years have now elapsed since the first arguments have been raised concerning these methods. It is in 1966 indeed that Rabiant (1966), while examining results obtained with calorimetric techniques, first questioned the methods described in the French Pharmacopoeia. Two years later Youssefnejadian (1968) discussed the discrepancies sometimes observed between the results of the two methods and strongly emphasized the need of chemical and thermal stability of both the solid and the liquid phases as a prerequisite for using the melting point methods to characterize a substance. Later Vergnon and Drevon (1974) proposed an empirical classification mainly for substances exhibiting poor chemical or thermal stability.

More recently Azibi et al. (1981, 1982) clearly demonstrated the advantages of an accurate knowledge of the polymorphic and thermal behaviour of a pure substance gained with calorimetric techniques, infrared spectroscopy and X-ray powder diffraction measurements.

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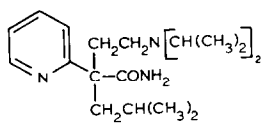
With the help of a few typical examples the present work is aimed at demonstrating the utility of Differential Scanning Calorimetry (DSC) and Thermogravimetry (TG) techniques in the critical evaluation of melting point data obtained from the more classical methods.

Materials and Methods

Chemicals

CM 7857, or penticainide (I), and its phosphate



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salt are Sanofi Recherche compounds exhibiting interesting antiarrythmic properties useful in cardioprotection. The purity of the samples used in this study was determined by HPLC (high-performance liquid chromatography) and was found to be better than 99.5% (CM 7857) and 99.3% (CM 7857 phosphate salt monohydrate).

Commercial Carbamazepine (Sanofi Pharma, Geneva, Switzerland) and citric acid monohydrate (Hoffman La Roche et Cie, Neuilly sur Seine, France) were used without further purification.

Differential Scanning Calorimetry (DSC)

DSC was carried out in a DSC-2 Perkin-Elmer module. Heating rates of $5\,^{\circ}C \cdot min^{-1}$ or $10\,^{\circ}C \cdot min^{-1}$ were used in the temperature range 22–400 °C. Non-hermetic aluminium pans were used. The DSC apparatus was calibrated by performing melting curves with metallic indium (melting point 156.6 °C). Samples ranging from 2.000 to 5.000 mg with an accuracy of within ± 0.001 mg were weighted.

Thermogravimetry (TG)

TG was carried out in a TGS-2 Perkin-Elmer thermogravimetric system coupled with a DSC-2 Perkin-Elmer module. The heating rates were either $5\,^{\circ}C \cdot min^{-1}$ or $10\,^{\circ}C \cdot min^{-1}$ and the experiments were performed in a closed thermobalance using special gas flow (nitrogen 99.9995% purity). The samples used ranged between 2.000 and 5.000 mg with an accuracy of within ± 0.001 mg.

Results and Discussion

Each of the 4 compounds examined in this work exhibits a typical behaviour during a continuous temperature rise aimed at melting the substance, i.e. at transforming the solid structure into a stable liquid without altering the chemical entity of the substance.

CM 7857 base

The TG and DSC curves of CM 7857 base are shown in Fig: 1. The DSC curve presents a single endothermic peak, which corresponds to the melting of the substance. There is no mass change, neither in the solid nor in the liquid phase, as evidenced by the TG curve. This example is illustrative of an ideal melting behaviour. The (corrected) melting point obtained by the classical method of the European Pharmacopoeia (2nd edn., V.6.11.1), $112.6 \pm 0.1\,^{\circ}C$, is in excellent agreement with the value obtained from the DSC experiment, $112.7 \pm 0.1\,^{\circ}C$.

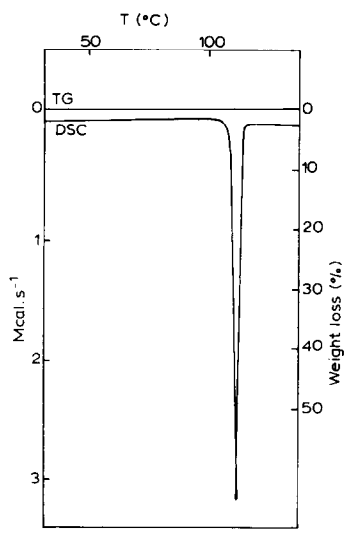

Fig. 1. DSC and TG curves of CM 7857.

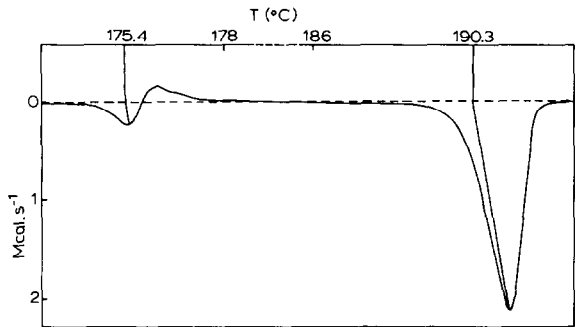

Fig. 2. DSC curve of carbamazepine.

Carbamazepine

The DSC curve of carbamazepine is shown in Fig. 2. The features of the DSC curve demonstrate the existence of polymorphic modifications: one form melts at 175.4 °C and recrystallizes instantly (the heating rate being 5 °C · min^{-1}) into a second form melting at 190.3 °C, i.e. nearly 15 °C higher than the first one.

In this case the existence of polymorphic modifications would have remained undetected by the classical methods, which request observing the melting of a substance at a heating rate of 1 °C · min^{-1}, starting 10 °C below the expected melting point.

It is interesting to note here that, being aware of such difficulties, the U.S. Pharmacopoeia recommends routinal X-ray powder diffraction measurements for characterization of carbamazepine samples.

CM 7857 phosphate salt

The TG and DSC curves of CM 7857 phosphate salt are shown in Fig. 3. Examination of the two curves reveals the occurrence, at about 120 °C, of a phase transition accompanied by a weight loss, easily attributable to the departure of one molecule of water, whereas the small endothermic shoulder at 90–100 °C is due to the vaporization of absorbed water. The major endothermic peak at 177 °C corresponds thus to the melting of a substance, which is not simply another modification of the original substance but is also chemically different. Besides, the stability of the liquid phase obtained at 177 °C is poor as it decomposes shortly after its formation.

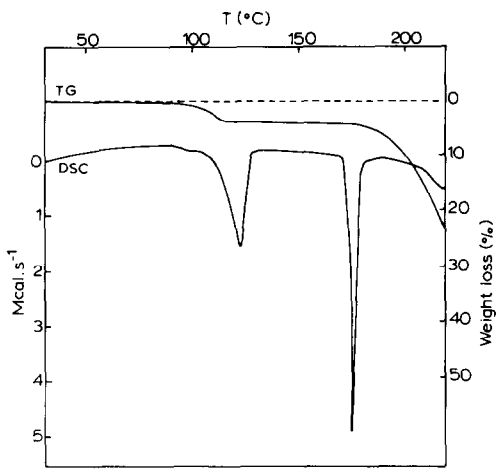

Fig. 3. DSC and TG curves of CM 7857 phosphate salt.

Considering the events taking place around 120 °C it is possible to distinguish 3 different phenomena: firstly, the melting of the substance, the subsequent loss of water occurs then in the liquid phase but is followed by immediate recrystallization of the sample.

The X-ray powder diffraction spectra obtained at room temperature before and after heating the sample at 145 °C are shown in Fig. 4 and are clearly different.

Visually the melting of the substance can be detected only with a microscope (100 ×) using a heating rate of 20 °C · min^{-1}. This is a typical example of pseudo-polymorphism.

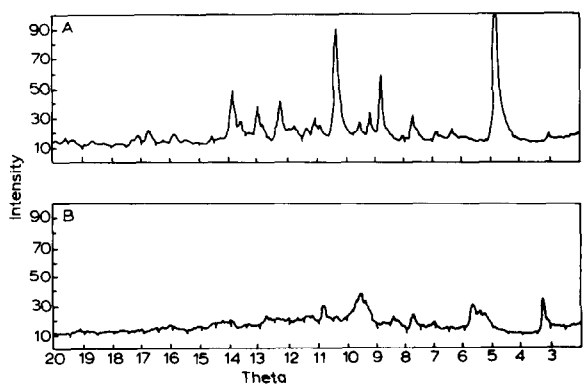

Fig. 4. X-Ray powder diffraction spectra of CM 7857 phosphate salt obtained at room temperature before (A) and after (B) heating the product for 10 min at 145 °C.

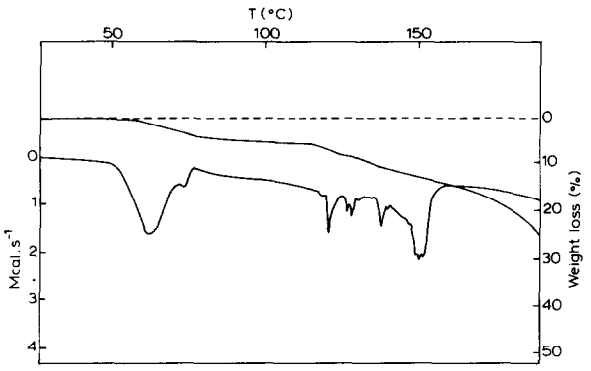

Fig. 5. DSC and TG curves of citric acid monohydrate.

Citric acid monohydrate

The TG and DSC curves of citric acid monohydrate are shown in Fig. 5 and are also typical of pseudo-polymorphism. Between 50 and 80 °C the substance loses one molecule of water and the anhydrous compound thus formed decomposes without melting between 120 and 160 °C, i.e. decomposition takes place at a temperature lower than the melting temperature usually given for anhydrous citric acid (153 °C in Handbook of Chemistry and Physics, 62nd edn., 1981–1982).

In this case, however, even with heating rates as high as 20–40 °C · min^{-1} it is not possible to observe the liquid phase under the microscope. The departure of water can be evidenced by observing the gas bubbles formed between 50 and 80 °C when the compound is in suspension in silicon oil.

In such a situation only the decomposition of a compound which is no longer citric acid monohydrate would have been detected by the classical means of melting point determination.

Conclusion

The purpose of pharmacopoeial methods is to provide basic data without having recourse to sophisticated equipment; however, the examples described here suggest a few comments about the melting points obtained by classical methods.

(a) It is only in the cases exemplified by the first compound studied, CM 7857 base, that the classical melting point determinations lead to meaningful results. The value obtained is then very similar to that measured by calorimetry. The characteristics of this class of compounds are:

- no polymorphism;
- no pseudo-polymorphism;
- stability of both the solid and the liquid phases.

However, as already underlined 10 years ago by Bouche and Draguet-Brughmans (1977) in a review article, the occurrence of either polymorphism or pseudo-polymorphism is quite high among organic substances, the various classes of drugs being no exception. These authors thus report the existence of two or more polymorphic or pseudo-polymorphic forms for numerous barbiturates, sulfamides, steroids or antibiotics. More recently polymorphism and pseudo-polymorphism have been studied in phenylbutazone, a non-steroidal anti-inflammatory drug by Mueller (1978), in barbiturates such as pentobarbital and butobarbital by Draguet-Brughmans et al. (1979, 1981), in benperidol, a tranquilizer, by Gassim et al. (1986), in the antibiotic cephradine and the antibacterial cephalexin by Jacobson (1986), and medetomidine hydrochloride, a drug with sedative and analgesic properties, by Laine et al. (1986), to cite but a few examples in this area.

(b) A good knowledge of the thermal behaviour of a substance seems to be a prerequisite for determining with certainty the melting point of a particular chemical and crystalline species.

In addition, this knowledge is becoming of utmost importance as the link between the nature of the crystalline states and the bioavailability of a substance is increasingly recognized.

(c) For new compounds it would seem sensible to use thermal analysis to check the validity of the methods of melting point determination recommended by the European Pharmacopoeia, or for critically evaluating the data obtained using these classical methods.

Acknowledgements

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