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Design and testing of a small-scale sublimation apparatus

Lars-Erik Briggner · Rene Céolin · Julien Giovannini · Nathalie Payraudeau · Ingemar Wadsö

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Abstract In many areas of scientific research and development, for example in the pharmaceutical industry, it is important to prepare and to characterize crystals of pure organic compounds which are thermodynamically stable. The formation of crystals from the gas phase is technically less straightforward than crystallisation from solution, but sublimation techniques can have several important features. In the present paper we report the design and testing of a novel apparatus for small scale sublimation and fractional deposition of crystals. The instrument has been developed with special reference to the needs in the pharmaceutical industry. A few mg of the samples are enclosed, under reduced pressure, in thin-walled glass tubes, along which a well defined temperature gradient can be formed. During an experiment the substance will sublime from the hot end of the glass tube and crystals will be deposited along the temperature gradient. The applicability of the instrument has been verified by experiments with several test compounds. Results from experiments with carbamazepine, are reported in some detail. Carbamazepine single crystals of high quality were obtained and the transition temperature between the triclinic (Form I) and the monoclinic (Form III) crystal modifications agreed with literature values.

Keywords Drug development · Pharmaceutical industry · Polymorph · Single crystal · Sublimation

L.-E. Briggner
Pharmaceutical and Analytical R&D, AstraZeneca, Lund, Sweden

R. Céolin
Laboratoire de Chimie Physique, EA4066, Faculté des Sciences Pharmaceutiques et Biologiques, Université Paris-Descartes, 75270 Paris Cedex 06, France

J. Giovannini
Pharmaceutical and Analytical R&D, AstraZeneca, Charnwood, UK

N. Payraudeau
University of Sciences of Rennes 1, Rennes, France

I. Wadsö (✉)
Chemical Center, Physical Chemistry 1, Lund University, 221 00 Lund, Sweden
e-mail: ingemar.wadso@fkem1.lu.se

Introduction

In the early phase of a drug development project in the pharmaceutical industry several key properties of the drug candidates have to be evaluated, for example the stability, solubility and several other properties important in pharmaceutical processing. Some of the most important of these properties are directly linked to the physical state of the compounds. Hence, it should be controlled if the material available is amorphous or crystalline and if the crystalline state includes solvates and/or polymorphs. Further, transitions between polymorphs may occur during various pharmaceutical processes and even during storage, which normally will lead to significant changes in their physical properties [1]. In order to proceed with the development work with some confidence, it is therefore important to identify the most stable polymorphs of the compound over a relevant temperature range. Normally, for such investigations performed in the early stage of development only mg amounts of material are available.

Crystals formed from solution are always affected by specific solvent interactions, solvent entrapment or solvate formation. Impurities, the concentration at which nucleation

occurs and kinetic factors can also influence the nature of the obtained material. Further, the crystalline material obtained may consist of a mixture of polymorphs and/or solvates.

Problems caused by interactions with solvents are avoided if the crystals are formed from the gas phase. A sublimation/deposition process can serve as an efficient purification step and in the absence of impurities and solvent interactions the possibility to obtain a crystalline material will increase. Under suitable conditions regarding vapour pressure and thermal stability of the compound, sublimation can lead to a fractional deposition of pure polymorphs as single crystals. Normally, the crystals formed are thermodynamically stable at the experimental temperature at which they condense [1], and it is therefore possible to obtain estimates of transition temperatures of the polymorphs.

In this paper we report on the design and testing of an apparatus for small scale sublimation and fractional deposition, by which single crystals can be obtained. The sublimation/deposition process is conducted at reduced pressure in glass tubes, along which suitable temperature gradients can be created and monitored. Crystals deposited in the glass tubes can be identified in situ by visible inspection or Raman analysis. Crystals can also be extracted and either prepared for X-ray powder diffraction (XRPD) or single crystals can be used for structure determination by single crystal X-ray diffraction (SXRD). Further, in order to obtain a large amount of a certain polymorph the extracted crystals can serve as seeds in subsequent crystallization from solution.

A simple apparatus used to explore the utility of this kind of instrument has earlier been reported by Céolin et al. [2].

Experimental

Instrument design

The design of the instrument is shown schematically in Fig. 1. Samples are enclosed in glass tubes, which are in thermal contact with a metal rod along which a temperature gradient can be formed. During an experiment the substance will sublime from the hot end of the glass tube and will condense along the temperature gradient applied, in a temperature range which is characteristic for the substance.

A brass rod e, length 286 mm, diameter 18 mm, is enclosed by a brass tube g. Experiments can be conducted simultaneously with three samples contained in thin-walled glass tubes positioned in the grooves f, o and p, which are milled out from the rod. The groves have square cross-sections of 2.5 mm (o, p) or 5.5 mm (f), resulting in a close thermal contact between the rod and the sample tubes, exterior diameters 2.2 and 5.2 mm, respectively. The glass tubes (not indicated in the figure) are closed in one end. The length of the tubes is about 400 mm and their wall thickness is 0.1 mm. Thermal contacts between the glass tubes and the rod are further secured by the brass tube g, which has a tight fit to the rod. One end of the rod e is connected to a furnace (a, b), which is used to heat the sample to the desired sublimation temperature. In the other end of the rod a cooling unit (j, k) is positioned. By activating the furnace and the cooling unit a temperature gradient is created along the rod and the sample tubes.

The furnace is made up by a heating coil b (Thermocoax SAS, France), which is wound on a bobbin made from brass, a. The bobbin is soldered to the end of tube g. The furnace is enclosed by a two-piece heat resistant polymer (PEEK), n, which is fastened to the end of rod e. The temperature of the furnace is regulated by a PID regulator (CAL3300, CAL Controls Ltd., UK), using a platinum resistance thermometer as sensor. A thermal fuse c, melting temperature 242 °C, is inserted into a horizontal hole of a brass ring d, which is in thermal contact with tube g.

The cooling unit is designed in analogy with the furnace. Cooling liquid, consisting of a mixture of ethylene glycol and water (normally 50% by volume) is continuously pumped through the circular cavity k, which is formed by a two-piece brass ring j. The two parts are sealed by use of O-rings, while the inner part is soldered to rod e. A thermal fuse, i, will break the heating current if the temperature of the cooling unit would exceed 100 °C. The cover l of the cooling unit is made from PEEK. The temperature gradient along the brass rod e can be measured by use of six Pt thermometers (Pt-100), which are positioned at regular intervals in groove m; two of them are placed at the furnace and the cooling unit, respectively. The Pt-thermometers are not indicated in Fig. 1. Most parts of the apparatus are thermally insulated by a 20 mm layer of rock wool, h.

Materials and supporting techniques used in the test experiments

A number of test substances were used in investigations during the development of the experimental procedures. A few experiences from that work will be briefly reported for some of these substances (androstanolone, androsterone, cinchonidine, 5,7-dibromo-8-hydroxyquinoline, phenothiazine, phenylbutazone and santonin).

DSC and TGA measurements were conducted on all substances, providing information about the thermal behaviour, indications of decomposition processes as well as identification of possible solid–solid transitions and vaporization processes. With both techniques measurements were made in N_2 atmosphere and at a heating rate of 5 °C min^{-1}.

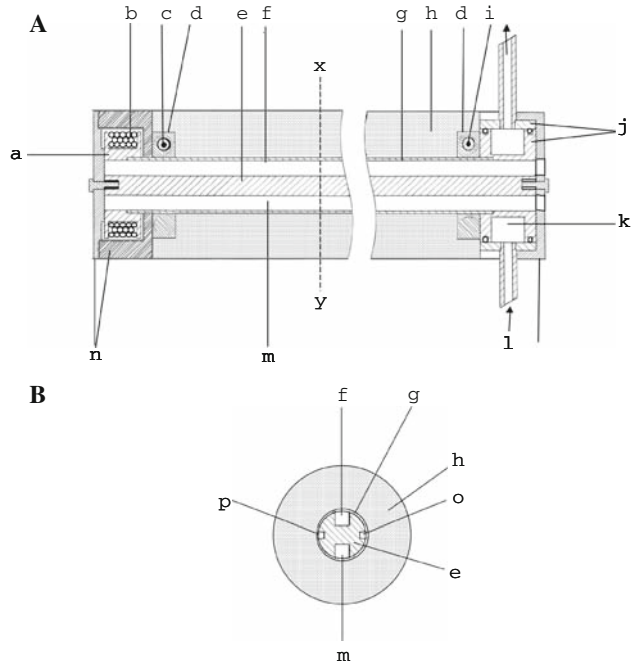

Fig. 1 Schematic picture of the sublimation apparatus. **A** Longitudinal section, **B** cross section *x*–*y*. *a*, Brass bobbin; *b*, heating coil; *c*, thermal fuse; *d*, brass ring; *e*, brass rod; *f*, groove; *g*, brass tube; *h*, rock wool insulation; *i*, thermal fuse; *j*, cooling unit; *k*, circular cavity; *l*, cover of the cooling unit; *m*, groove; *n*, furnace enclosure; *o*, *p*, grooves

Following the preliminary experiments measurements were performed on carbamazepine (Aldrich, purity stated to be 99% w/w), a well-known anticonvulsant drug, for which different polymorphs have been reported [3, 4].

Experimental procedure

When samples were introduced into the sample tubes special care was taken to avoid spilling any substance along the wall of the tube, which could act as crystallisation seeds. When the 2.2 mm tubes were used the samples were first inserted into the end of a thin-walled steel tube that was introduced into the glass tube. The substance was then pushed out from the steel tube at the closed end of the sample tube by use of a metal piston. In experiments with the 5.2 mm tubes the samples were contained in glass vials, length 30 mm and diameter 5 mm, making a close fit with the inner walls of the sample tubes. The samples were positioned at the closed end of the sample tubes. The open ends of the tubes extend through the holes in the end plate of the polymer enclosure 1 of the cooling unit and were connected to a low vacuum system, about 3,000 Pa, or to a mechanical vacuum pump, pressure about 2×10^{-7} Pa.

After the sublimation-condensation experiments the sample tubes were sealed by a flame and were then examined visually for deposits of large crystals. Fractions of small crystals were inspected by use of a light microscope, equipped with crossed polarizers. The different crystal fractions were also analysed in situ by Raman spectroscopy (Labram HR, Jobin-Yvon, France). In some cases the sample tubes were broken and crystals were collected for XPRD analysis (PanAlytical, The Netherlands).

Results and discussion

Figure 2 shows plots of the temperatures in groove m as a function of the distance from the hot end of the furnace. Measurements were made at different temperature settings for the furnace. Temperature and flow rate of the cooling liquid were kept at 5 °C and 8.5 L/min, respectively. It is seen that for each setting the temperature gradient in the rod e is almost linear between its hot end and the sensor positioned about 50 mm from the cold end.

It is important to optimize the experimental conditions for each compound, in particular with respect to possible decomposition processes. Lowering the furnace temperature will lead to a decrease of the decomposition rate. However, the duration of stay for the sample in the hot zone will then increase and the amount of material decomposed may still be significant. It is therefore important to find the optimal compromise between time and temperature. We have found that a sublimation temperature of 10–20 °C below the melting point of the compound often is feasible. Values for melting points (mp) and indications about sublimation and/or degradation processes for the compounds were obtained from results of DSC and TGA measurements.

The time required for the sublimation of a 5 mg sample varied between a few hours and 2 days and in a manner

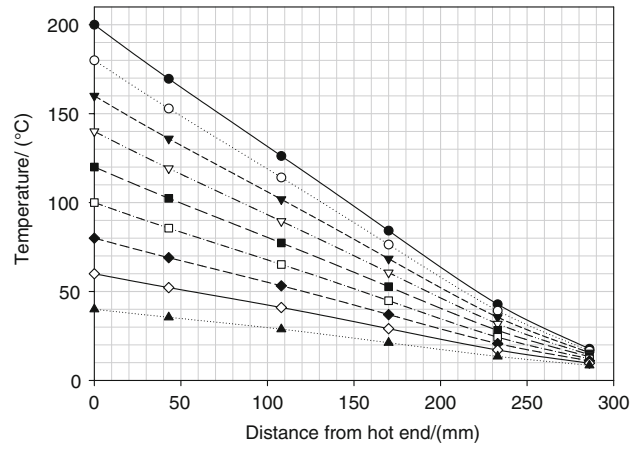

Fig. 2 Temperature gradients in the brass rod (*e*, Fig. 1) at different temperature settings (hot end temperature). Rod temperatures are shown at different distances from the hot end of the rod

which could not easily be predicted, especially in the absence of vapour pressure data; for examples about 3 h for 5,7-dibromo-8-hydroxyquinoline (mp 198 °C), 7 h for phenothiazine (mp 183 °C) and 2 days for phenylbutazone (mp 103 °C). For a few compounds, for example cinchonidine (mp 206 °C), experiments could not be conducted without the formation of large amount of degradation products. In other cases it was shown that a relatively small change in sublimation temperature dramatically altered the results. For example, sublimation of androstanolone and androsterone close to 180 °C (mp 179 and 181 °C, respectively) was accompanied by formation of large amounts of degradation products, whereas at the sublimation temperature 150 °C no degradation was observed. In most of the preliminary experiments a low vacuum was used (3,000 Pa). However, as expected, it was found that a higher vacuum (7×10^{-2} Pa) significantly increased the rate of the sublimation at a given temperature.

The crystals were often large and directly suitable for structure determination by SXRD. In several of the experiments small deposits were identified as impurities or degradation products, but they were normally well separated from the crystals of the pure compounds.

The crystal deposits were investigated by Raman spectroscopy conducted in situ. In most cases the results indicated that the crystals were made of the same phase as the starting sample, implying that the starting material is a polymorph which is stable over the temperature range within which the crystals condense from the vapour phase. In some cases, for example for carbamazepine (cf. below), Raman spectroscopy showed that different polymorphs were formed, which subsequently was confirmed by XRPD analysis.

Carbamazepine

In a series of preliminary experiments with carbamazepine three different types of crystals were obtained, A, B and C. Crystals in fraction A were shaped as needle bundles whereas fraction B and C consisted of tabular crystals. Crystals in fraction A and B were colourless, but those in fraction C were orange. Three experiments were conducted under final conditions with the furnace temperature set at 150 °C. In the first experiment, using 2.2 mm sample tubes and a pressure of 3,000 Pa, the obtained crystal fractions were the same as in the preliminary experiments.

Raman spectra of fraction A, deposited at the hot end of the tube, agreed with those reported by Auer et al. [4], indicating that this fraction is the triclinic modification, which is stable at high temperature. Fraction B, deposited thereafter, was identified as the monoclinic modification, which is stable at lower temperatures and is identical with the starting material. Crystals were large enough to be extracted from the glass tubes and were used for XRPD analysis. Results for fractions A and B were in good agreement with literature reports [3] and were also verified by a peak indexation followed by Pawley Refinement [5]. From the deposition temperatures of fractions A and B, the transition temperature between the two polymorphs was estimated to be 132 °C, in close agreement with the value reported previously [2]. From visual inspection of the size and shape of the crystals in the whole of fraction A, it was quite clear that all of the starting material had transformed to the triclinic modification exhibiting an initial range of needles from the hot end of the tube. Fraction C most likely consisted of iminostilbene, a degradation product known to be formed from carbamazepine when stored at or above 150 °C [2].

Two experiments with 5.5 mm tubes were performed at a pressure of 7×10^{-2} Pa leading to a much increased sublimation rate. In the experiments mentioned above, using the more narrow tube, the experimental time was a few days while the experiments using the larger tube and a more efficient vacuum lasted for about 12 h. Under these conditions only fractions A and B were obtained; the non-appearance of fraction C apparently was due to the shorter stay of the starting material in the furnace zone. A photograph of part of a sample tube showing the needle shaped crystals of fraction A (length about 1 mm) and the tabular crystals of fraction B (size about 0.5 mm) is shown in Fig. 3.

The transition temperature between the polymorphs A and B was in these experiments estimated to be 133 and 134 °C respectively; in close agreement with the result found in the experiment reported above and also with the value in [2]. From our collected experiences it appears as if estimates of the transition temperatures between polymorphs, which are based on the separation line between deposition temperatures, are reproducible to within a span of a few degrees using the present set-up.

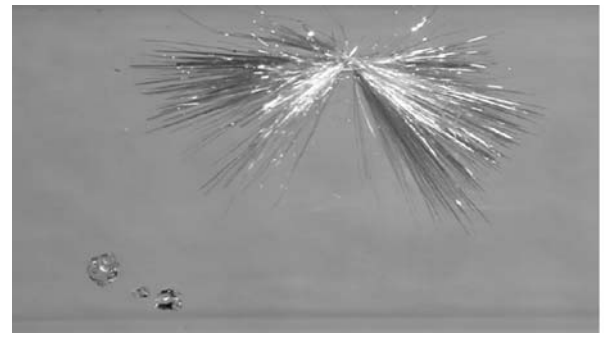

Fig. 3 Photograph of the monoclinic and triclinic modifications of carbamazepine as obtained within the sublimation tube. The diameter of the tube corresponds to the *vertical black bar* (5 mm in length)

Conclusions

Sublimation of molecular organic compounds, followed by fractional deposition along a temperature gradient, has proved to be an excellent method for preparation of crystals of high purity, without influence from impurities or solvent molecules. Polymorphs can be separated and single crystals obtained are suitable for structure determination using SXRD. The instrument described in this report is designed for work on mg quantities of substances, of particular importance during the early phases of drug developments in the pharmaceutical industry, where normally only small amounts of compounds are available. Although the properties of the present prototype instrument are satisfactory it is felt that further method work on the technique would be useful.

It could be valuable to explore the use of even higher vacuum in order to further increase the sublimation rate and thus to decrease the risk of sample decomposition. The effects of different temperature gradients should be investigated: a weaker gradient may lead to an improved fractionation of the crystal species and, possibly, to more accurate estimates of transition temperatures. It is expected that the surface properties of the sublimation tubes will influence the crystallisation processes, which ought to be explored. The liquid cooling system is simple and works well, but could be replaced by an air-cooled Peltier effect heat pump, which can be more convenient to use.

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