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THERMAL ANALYSIS IN THE QUALITY CONTROL AND STANDARDIZATION OF SOME DRUGS

M. Sh. Lvova, E. I. Kozlov and I. A. Wishnevezkaya

ALL-RUSSIAN SCIENTIFIC INSTITUTE FOR VITAMIN RESEARCH, NAUCHNY PROEZD, 14 A, GSP-7, 117820 MOSCOW, RUSSIA

DSC was used together with other methods of pharmaceutical analysis (spectrophotometry, thin-layer chromatography) to estimate the quality and standardization of two drugs - lipoic acid (polymerization upon melting, purity) and progesterone (melting temperature, polymorphism).

Keywords: drugs, melting temperature, polymorphism

Introduction

Lately method of thermal analysis, differential scanning calorimetry (DSC) has been used for the control of quality of drugs as much as possible. Combining with traditional methods of pharmaceutical analysis the DSC method gives us quantitative information about the purity of the compound, makes it possible to establish the melting temperature interval for the drug and study the phenomenon of polymorphism characteristic of this drug [1–3]. In the present work the above mentioned possibilities of thermal analysis have been utilized for the control of quality and for standardization of two drugs: lipoic acid and progesterone. Lipoic acid-6,8-dithiooctanoic acid (I) – is a drug that functions as a co-enzyme. Progesterone (pregn-4-en-3,20-dion) (II) – is assigned to the group of synthetic steroid hormones.

Among the indices characterizing the quality of I and II and included in scientific and engineering specifications, the melting temperature is one of the most important.

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Experimental

The objects of investigation were the samples of several batches of I and II of pharmacopoeic quality and those obtained by additional recrystallization of the substance from cyclohexane and freon (I) or acetone (II) and a WHO standard of II.

Melting curves were obtained on a DSC-20 instrument (Mettler TA-3000 thermoanalytical system) with a nitrogen flow rate of 20 $ml \cdot min^{-1}$, heating rates of 1.5–20 $deg \cdot min^{-1}$. The samples (1–3 mg) were weighed to an accuracy of 0.001 mg. The recording of the melting temperature, and calculation of enthalpy and other parameters were performed automatically by processing the thermoanalytical curve with Mettler's programs. Indium of 99.99% purity was used as standard.

For detecting polymorphic modifications the sample of II was heated at a rate of 10–20 $deg \cdot min^{-1}$ till it was completely transformed into the molten state (to a temperature 5°–10°C higher than the melting point), thus the endothermic melting peak of the principal modification was obtained. The crucible with the sample was then cooled to room temperature and heated again at the same or lower rate (1.5–5 $deg \cdot min^{-1}$). The appearance of a melting temperature lower than the initial one points to the formation on another polymorphic modification.

Spectrophotometric measurements were carried out using a Specord M-40 spectrophotometer (GDR).

The semi-quantitative analysis of admixtures in II was conducted by thin-layer chromatography (TLC) on Silufol, using chloroform-ethyl acetate mixture.

Results

Lipoic acid

The melting curves taken of several industrial batches of I indicate the presence of admixtures with the registered melting temperature of about 286°C along with a clear-cut endothermic melting peak observed within the temperature range 59.5°–62°C (Fig. 1). The value of the peak area (when equal samples of the same specimen lot are analyzed) depends on the heating rate: the slower the heating the greater is the peak area. The presence of the second peak on the melting curve of I is explained by the specimen property of polymerization upon melting. This feature is more pronounced in samples that have higher melting temperatures, i.e. that are of higher purity. The polymeric product formation during the melting of I is characteristic of the specimen which hinders the determination of

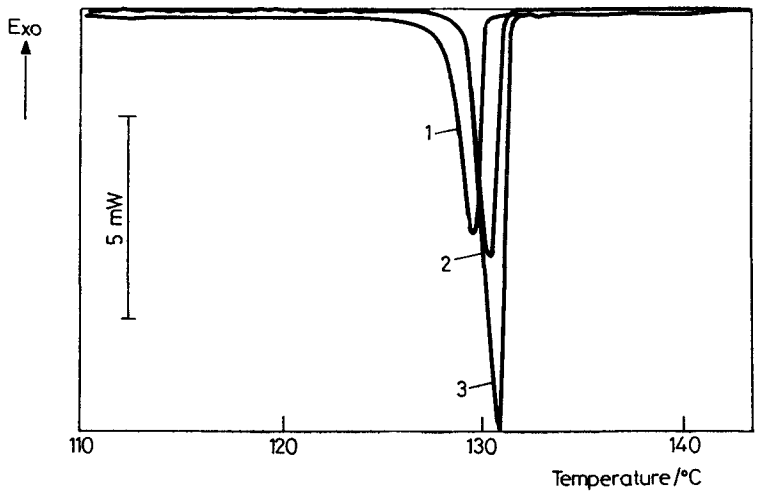

Fig. 1 DSC melting curve of lipoic acid containing a polymer admixture

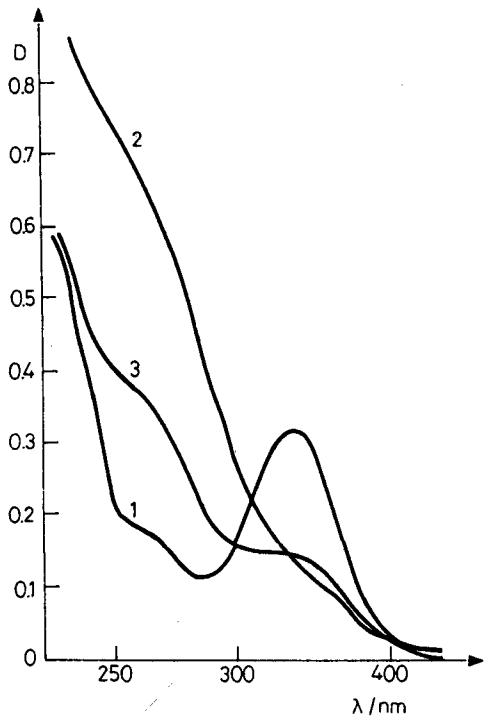

Fig. 2 UV and visible spectra of lipoic acid (1), polymerization product (2) and their mixture (3)

the melting temperature by the pharmacopoea methods [4] and requires special heating conditions for determining the index concerned.

The specimen can initially contain a polymeric product admixture or accumulate it during storage. This is confirmed by spectrophotometry. In Fig. 2 are presented the ultraviolet and visible absorption spectra of the specimen practically free from polymer (1), of the one with increased polymer content (3) and the absorption spectrum of the polymeric product (2), which was isolated during the heating of I to the melting temperature. The comparison of the above spectra shows that the increase in the polymeric product content of the specimen leads to a reduction in the absorbance of I at the maximum (333 ± 2 nm) and to an increase in the polymer absorption maximum (about 255 nm). Thus an absorbance ration (D_{333}/D_{255}) can be regarded as one of the indices of the specimen quality, which, with appropriate standardization, may be used to restrict the polymer admixture content of the specimen. The results of analysis of a number of I

Table 1 Physico-chemical characteristics of lipoic acid

Specimen characteristic	No	Content/ %	D333/D255	Melting temperature / °C (heating rate 2 deg·min^{-1})
Initial substance	1	98.2	2.00	60.7
	2	98.8	2.03	60.7
	3	98.5	2.09	61.0
After recrystallization from cyclohexane	1	99.4	2.11	61.1
	2	99.4	2.21	60.8
	3	99.6	2.31	61.2
After recrystallization from freon	1	99.4	2.27	61.6
	2	99.6	2.31	61.9
	3	100.0	2.35	61.7

specimens shows the three indices of the specimen quality to be in agreement with one another: recrystallized I specimens have the higher percentage, melting temperature and D_{333}/D_{255} ratio; the I specimens recrystallized from freon being pure [Table 1].

Progesterone

Studies on several series of II by DSC method have shown that within the temperature range of 30° to 170°C the melting curves in all cases have only one distinct endothermic melting peak with ΔH = 80–82 J/g. At a heating rate of 1.5 deg·min^{-1} the melting of the drug begins at 127.4°–128.3°C and ends at 128.9°–129.3°C with the temperature interval for the samples lying within 0.9° to 1.5°C (Fig. 3).

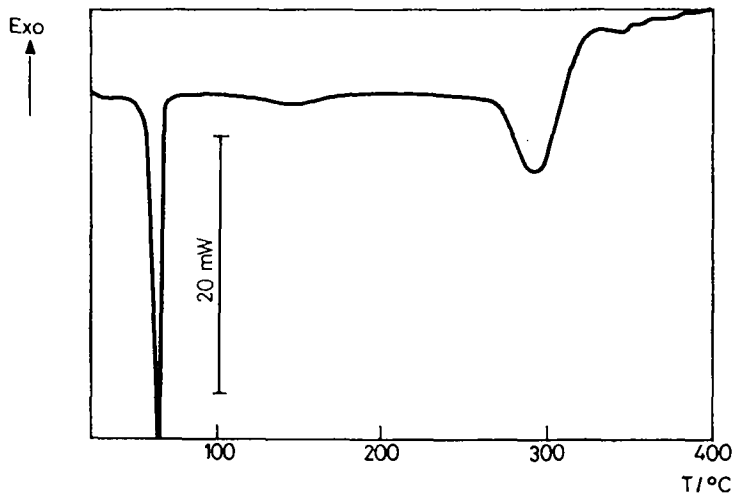

Fig. 3 DSC-melting curve of the progesterone (heating rate 1.5 deg·min^{-1}): 1 - industrial batch ; 2 - industrial batch upon recrystallization; 3 - WHO-standard

The melting curves for the WHO standard and for the samples of II purified by additional recrystallization from acetone differ from the above-described curves by a higher melting point (129.4°–129.7°C at the beginning of melting and 129.9°–130.0°C at the end of melting at a heating rate of 1.5 deg·min^{-1}) and by considerably narrower melting temperature interval (0.3°–0.5°C).

As the rate of heating increases to 10 deg·min^{-1}, the melting point of II increases by about 1.0°C irrespective of the quality of the sample. The absence of additional endothermic peaks on the melting curve obtained by the DSC method for all the analyzed samples of II indicates the fact that the drug exists only in one crystalline modification with the melting point lying between 127° and 130°C. This modification which is thermodynamically stable at room temperature is named in the literature as the high-melting or α-form [5, 6].

A special technique has been developed which enables the drug's ability to form other metastable polymorphous modifications with lower melting points known in the literature to be confirmed. For this purpose, the substance is melted under normal conditions and is then rapidly cooled; in this case most of the melt is crystallized in the form of the β-modification which is revealed at the repeated melting of the sample by the new endothermic peak with a melting point of 121°–123°C (Fig. 4, curve 2).

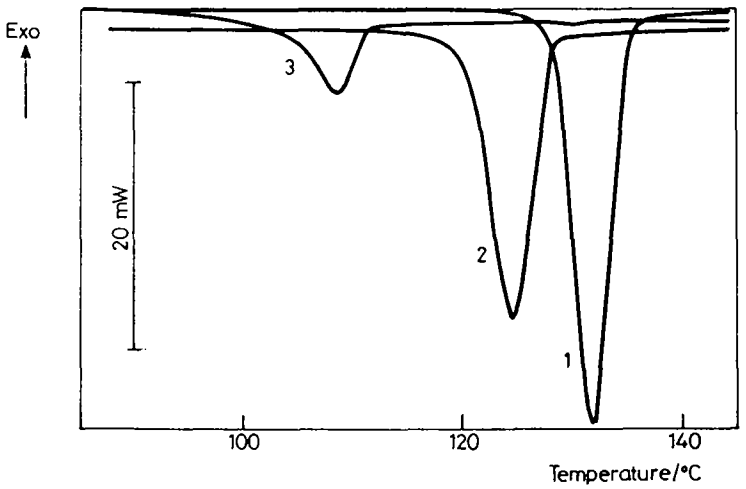

Fig. 4 Detection of polymorphic modifications of progesterone by the DSC method: 1 - first heating; 2 - second heating; 3 - third heating.

Another low-melting metastable form of progesterone β^1 with a melting point of about 108°C has been found during the third melting of the sample that was kept for a few hours at room temperature (Fig. 4, curve 3). In this case, on the melting curves of one of the batches two peaks are seen at once: one clearly-defined peak of the β^1-form and the second weak peak of the α-form with a melting point of 129°–130°C.

One of the important fields of the application of the DSC-method in pharmaceutical analysis is the determination of the overall concentration of admixtures [1, 2]. This has been estimated for the α-form of II with various purification degrees. At the same time, the parallel analysis for the foreign admixtures was conducted by the semi-quantitative method of TLC. The concentration of admixture determined by the DSC-method corresponds to the quality of the drug: for the substance- 0.4–0.7%, for the recrystallized substance- 0.1–0.3% and for the WHO standard- 0.1%. The TLC-method allows detection (total) of: 1.0 to 1.2% (3 admixtures) in the substance and 0.2 to 0.3% (1 admixture) in the purified sub-

stance. In the WHO standard no admixture have been detected. Pairwise comparison of the results of determination by the two different methods has shown that for the purified samples of II the parameters being determined are practically the same.

The results of the present investigation have been used for working out the scientific and engineering specification for the substances I and II of different quality categories.

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Zusammenfassung — Gemeinsam mit anderen Methoden der pharmazeutischen Analyse (Spektrofotometrie, TLC) wurde DSC zur Abschätzung der Güte und Normierung von zwei Wirkstoffen eingesetzt: Liponsäure (Polymerisierung beim Schmelzen, Reinheit) und Progesteron (Schmelztemperatur, Polymorphie).