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THERMAL CHARACTERIZATION OF LAPACHOL BY MEANS OF TG AND DSC COUPLED TO A PHOTOVISUAL SYSTEM

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Abstract

Thermal characterization is proposed as analytical methodology for the purity assay of lapachol, and for determination of the quality parameters of capsules containing this molecule. The TG data revealed that lapachol is more stable in the presence of adjuvants, showing the good quality of the formulation. The kinetic parameters obtained were lower for lapachol drug than for the formulated lapachol. The DSC data demonstrated good compatibility between lapachol drug and the adjuvant in the formulated lapachol, and did not reveal impurities such as secondary products of the isolation and recrystallization processes. The data were confirmed by the DSC-photovisual findings.

Keywords: DSC-photovisual system, lapachol, TG

Introduction

Lapachol, 2-hydroxy-3-(3-methyl-2-butenyl)-1,4-naphthalenedione, a natural compound found in several vegetable families, e.g. *Bignoniaceas*, is used in oncotic therapy [1]. Lapachol has been marketed in solid dosage forms such as capsules, but the pharmaceutical assays used in the identification and purity tests are not sufficiently sensitive to detect polymorphic changes in the crystal, or organic impurities, or secondary products resulting from the extraction, isolation and recrystallization processes applied to the natural products.

Thermal analysis is a powerful tool for purity assay, stability determination, and drug-excipient compatibility studies [2, 3]. A number of thermal studies have been performed on substances from plants and their products [4, 5]. DSC coupled to a photovisual system is an auxiliary technique which reveals processes that can not be detected when the conventional DSC technique alone is used.

The present work reports on the use of TG and DSC coupled to a photovisual system for the thermal characterization of lapachol and as analytical methodology in

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the purity assay and determination of the quality parameters of capsules containing this molecule.

Experimental

Lapachol capsules were donated by the Laboratório Farmacêutico do Estado de Pernambuco: they had the composition lapachol dried extract: 62.5, mannitol; 37.5%. Lapachol drug was obtained from the lapachol capsules by extraction with ethanol and recrystallization from benzene [1]. The lapachol drug and capsules were sieved to 60 mesh and conditioned in an amber flask.

Calorimetric studies

The DSC apparatus temperature was calibrated via the melting points of indium (156.6±0.2°C) and zinc (419.5±0.3C°) standards. The heat flow and enthalpy were calibrated via the heat of fusion of indium (28.58±0.30 J g^{-1}) under the same conditions as for the samples. The correction factors were calculated in accordance with the procedures and specifications of Shimadzu.

The DSC studies were carried out with a Shimadzu model DSC-50 calorimeter, in a nitrogen atmosphere at a flow rate of 50.0 ml min^{-1}, at a heating rate of 10.0°C min^{-1}, up to 500.0°C. The sample mass was 2.00 mg. The sample and reference were in hermetically sealed aluminium cells. The DSC was coupled to a photovisual system involving an Olympus Microscope connected to a Sanyo model VCC-D520 camera with a high-resolution image.

Thermogravimetric studies

The TG studies on the lapachol drug and capsules were performed in a Shimadzu model TGA-50H thermobalance, in air atmosphere at a flow rate of 20.0 ml min^{-1}, at heating rates of 10.0, 12.5, 15.0 and 20.0°C min^{-1}, up to 900.0°C. The sample mass was 4.00–4.50 mg. The TGA-50H thermobalance was calibrated with calcium oxalate monohydrate under the same conditions.

The activation energy (E), pre-exponential factor (Z) and order of reaction (n) were calculated from the TG curves by using the integral methods of Coats–Redfern (CR) [6], and Madhusudanan–Ninam (MD) [7], the approximation methods of Horowitz–Metzger (HM) [8] and van Krevelen–Hutjens (VK) [9] and the Ozawa model (OZ) [10].

Results and discussion

Calorimetric studies

The DSC curve of lapachol drug displayed only a melting point, at 141.7°C. The heat of fusion, 132.58 J g^{-1} and the purity of 98.6% demonstrated the good quality of the extraction and purification processes of this drug. Mannitol gave a melting point of

168.1°C and a heat of fusion of 294.96 J g^{-1}. The lapachol capsule presented two-phase transition peaks: at 141.9°C, with a heat of fusion of 82.47 J g^{-1}, and at 167.5°C, with a heat of fusion of 101.44 J g^{-1}. The lower heat of fusion for the lapachol capsule was due to the dilution of the drug by mannitol: 62.2% lapachol drug and 37.8% mannitol (Fig. 1).

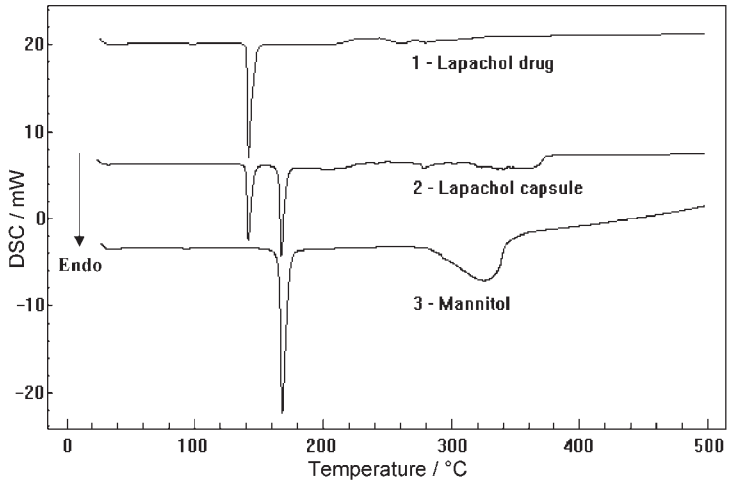

Fig. 1 DSC curves of lapachol drug (1), capsules (2) and mannitol (3) at 10°C min^{-1}

DSC coupled to the photovisual system confirmed the melting point of the lapachol drug at 141.7°C (Fig. 2B), in accordance with the literature [1, 11], followed by a change in colour from yellow to dark-red. The initial decomposition was observed at 185.0°C, in agreement with the TG profile. Figure 2C revealed partial decomposition of the drug at 212.0°C, corresponding to the end of the first stage in the TG profile.

The lapachol capsule exhibited two melting points: the first, at 141.9°C, corresponded to the presence of lapachol (Fig. 3B), while the second, at 167.6°C (Fig. 3C), was due to the presence of the mannitol excipient, which melts at 166.0–168°C according to the literature [11], with a change in colour from yellow to yellowish-red. At this latter melting point instability and thermal decomposition were observed, with the formation of a brown residue, this decomposition being confirmed by the TG profile.

The DSC curves showed the good technological quality of the lapachol formulation. The DSC-photovisual results on the lapachol capsule confirmed the presence of additional substance in the manufacturing process. This points to the need for the quality control of phytopharmaceuticals so as to obtain products with better therapeutic quality and improved safety.

The calorimetric data allowed the differentiation of lapachol drug from its mixture. This technique could be used to monitor lapachol purification and the manufacturing process (Figs 2 and 3).

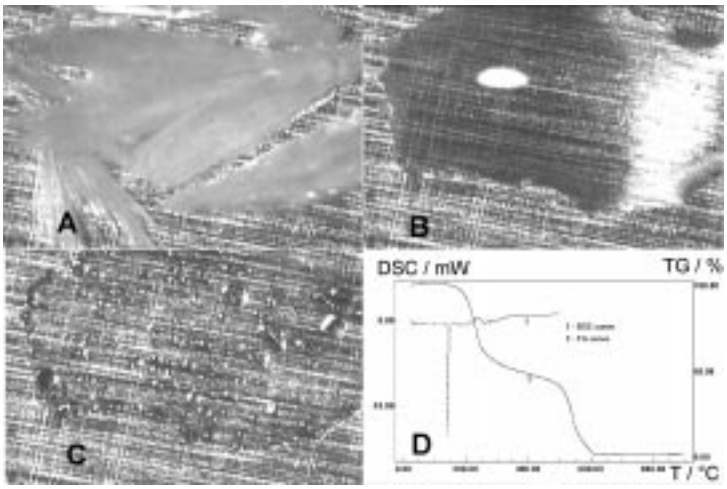

Fig. 2 DSC-photovisual pictures of lapachol drug; A – room temperature, B – 141.7°C, C – 212.0°C, D – TG/DSC curves at 10°C min^{-1}

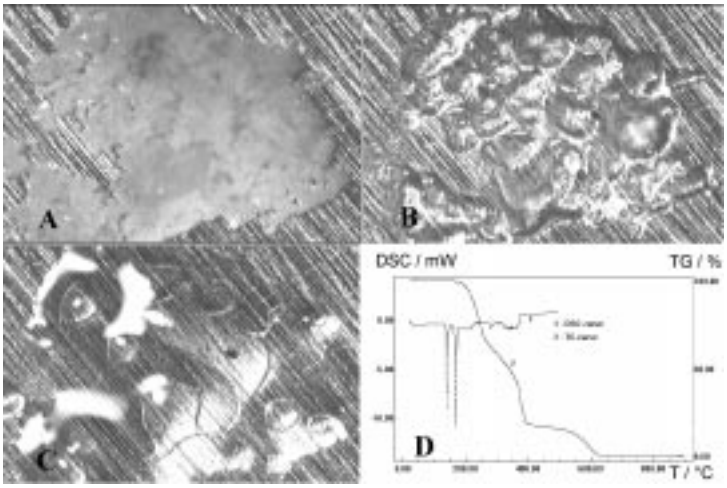

Fig. 3 DSC-photovisual pictures of lapachol capsules; A – room temperature, B – 141.7°C, C – 212.0°C, D – TG/DSC curves at 10°C min^{-1}

Thermogravimetric studies

The TG curve of lapachol drug presented three thermal decomposition stages: the first in the temperature interval 145.1–256.8°C, with a mass of 38.8%. The TG curve of the lapachol capsule presented four thermal decomposition stages, the first stage being similar to that for lapachol drug, in the interval 154.5–257.9°C, with a mass loss of 31.8%, suggesting that the pharmaceutical adjuvant somewhat delays the thermal decomposition of lapachol.

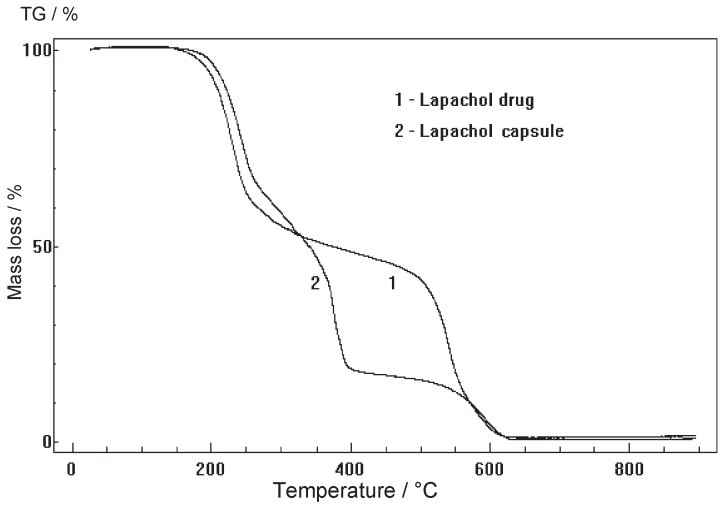

Fig. 4 TG curves of lapachol drug (1) and capsules (2) at 10°C min^{-1}

The TG curves of lapachol drug and the capsules demonstrated an increased decomposition temperature when the drug was associated with mannitol in this formulation (Fig. 4). The presence of the adjuvant in the formulation altered its decomposition rate.

Kinetic studies

The activation energies obtained with the integral methods were smaller than those found with the approximation methods. The OZ values differ from the others, obtained at different heating rates. The activation energies obtained were smaller for lapachol drug than for the lapachol capsule (Table 1).

Table 1 Kinetic characteristics of lapachol drug and capsule

	Kinetic parameters	Methods				
		OZ	CR	MD	HM	VK
Drug	N	0.2	0.8	0.8	0.9	0.9
	E/kJ mol^{-1}	58.1	91.9	91.8	109.8	105.9
	Z/s^{-1}	$2.7 \cdot 10^5$	$2.0 \cdot 10^7$	$2.1 \cdot 10^7$	$2.1 \cdot 10^9$	$1.8 \cdot 10^{14}$
Capsule	N	0.6	0.9	0.8	1.1	0.8
	E/kJ mol^{-1}	69.7	102.0	99.8	123.7	110.6
	Z/s^{-1}	$5.0 \cdot 10^6$	$1.6 \cdot 10^8$	$9.9 \cdot 10^7$	$3.8 \cdot 10^{10}$	$3.5 \cdot 10^{14}$

The kinetic data revealed that it was possible to differentiate qualitatively the lapachol drug and capsules, indicating that mannitol influences the thermal behaviour of lapachol drug.

Conclusions

The DSC-photovisual and kinetic studies allowed detection of the technological quality of lapachol capsules and their differentiation from lapachol drug.

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