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DETERMINATION OF CODEINE PHOSPHATE AND CODEINE IN THERMAL CHARACTERIZATION BY DIFFERENTIAL SCANNING CALORIMETRY

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Abstract

Thermal behaviour of codeine phosphate and codeine crystallized at the several solvents system was studied by DSC, and then, the kinetic parameters and thermochemical data have been obtained. We have found that codeine phosphate and codeine exist in a number of polymorphic formes which may inflicence the bio-availability.

Keywords: codeine, codeine phosphate, DSC, kinetic parameters, polymorphism

Introduction

The authors used DSC previously as a screening technique for assessing the purity of some chemical drugs, reference substances and identification of polymorphism of cimetidine. This was achieved by comparing the DSC curves of codeine and codeine phosphate. This is a very useful approach to determine the kinetic parameters and thermochemical data. It has been found that codeine can exist in a number of polymorphic forms that may influence its bioavailability.

Experimental

Materials: codeine phosphate, codeine and the chemical reference substances; all from our Institute. All the solvent are of the analytically pure grade.

Preparation: (a) Codeine was dissolved in 85% Ethanol, a mixture of benzene-petroleum ether in appropriate proportions, and crystallized at low temperature and then air-dried respectively. (b) Codeine phosphate was dissolved in a mixture of ether and crystallized at low temperature and air-dried.

Instrument: Perkin-Elmer (DSC-4) differential scanning calorimeter with a model 3600 data station. Samples (2–5 mg) were weighed after being finely powdered and encapsulated in flat-bottom aluminium pans with crimped-on lids. The sample was heated in an atmosphere of nitrogen and curves were ob-

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tained by heating at a constant heating rate of 10 deg·min^{-1} and a constant range setting of 10 mcal per second over the temperature range of 50~300°C. The area under the differentical scanning calorimetric heating curve was measured by using a computer.

Table 1 Thermodynamic characterization of codeine and its phosphate salt

	Codeine		Codeine phosphate		
	85% Ethanol	Benzene-Petroleum Ether		S*	R. S**
Onset °C	a 90.55		a'	179.84	177.51
	b 173.87	154.84	b'	236.23	236.83
	c 231.88				
Peak max °C	a 98.10		a'	181.61	180.00
	b 176.75	157.11	b'	239.23	239.74
	c 234.09				
Enthalpy / J·g^{-1}	a 15.80		a'	16.97	11.51
	b 15.18	79.52	b'	56.33	84.32
	c 35.90				

S* sample
R. S** Reference Substance

The experimental conditions and results are summarized in Table 1.

Result and discussion

The DSC curve of codeine (EtOH 85%) showed three endothermic peaks. The first one with an aqueous transition temperature range form 85 to 100°C with a maximum peak of transition at 90.55°C which corresponds to the first

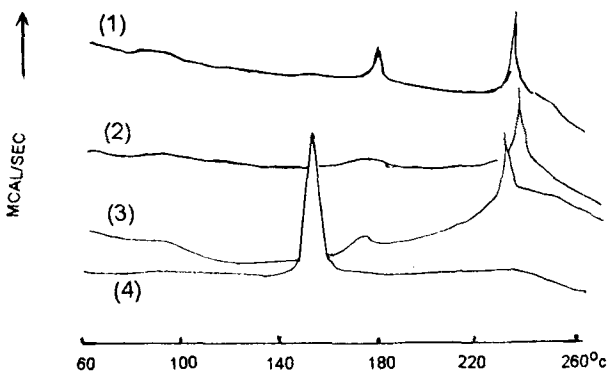

Fig. 1 (1) Codeine Phosphate; (2) Codeine Phosphate References Substances; (3) Codeine Crystallized in 85% Ethanol; (4) Codeine Crystallized in Benzene-Petroleum-ether

peak of codeine phosphate. The second peak is a new transition of polymorphism. The enthalpy change (J/g) of the first was found to be 22.4% of codeine value, calculated from the exact percentage contribution of codeine and of the total enthalpy change of the mixture. The DSC curve of codeine phosphate showed also three-endothermic peaks. The transition temperature shifted to higher temperature and the two main peaks corresponding to 181.61 and 239.23°C are more distinct.

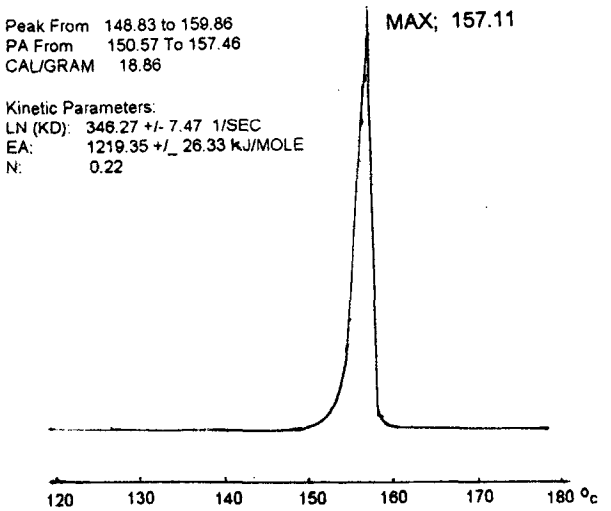

Fig. 2 Thermodynamic characterization of codeine; weight=3.9 mg; scan rate: 10 deg·min^{-1}

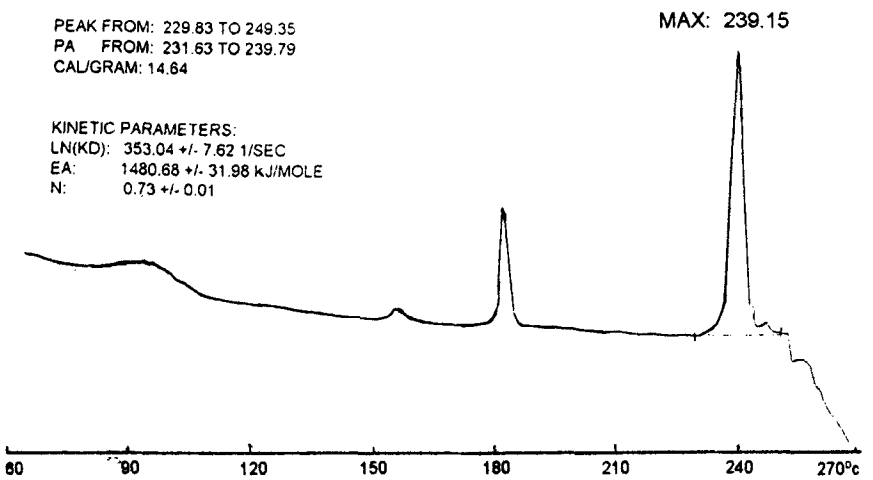

Fig. 3 Kinetic parameters of codeine phosphate

A single peak is observed with a maximum at 157.11°C.

We have estimated stability characteristics and found that a single temperature programmed DSC experiment can be used to calculate the Arrhenius pre-exponential factor. Activation energy and the order of the reaction were determined within a few hours on the basis of the mathematical model suggested in this paper. The kinetic parameters and the molar enthalpy (ΔHf) of a single-substrate reaction can be calculated with the curve data simultaneously.

It has been found codeine can exist in a number of polymorphic forms that may influence its bio-availability.

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Reference

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Zusammenfassung — Mittels DSC wurde die thermische Charakterisierung von aus verschiedenen Lösungsmitteln kristallisiertem Kodeinphosphat und Kodein getätigt und anschließend die kinetischen Parameter und thermochemischen Angaben ermittelt. Es wurde festgestellt, daß Kodeinphosphat und Kodein in einer Reihe von polymorphen Formen existieren, welche die Bioverfügbarkeit beeinflussen können.