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THE THERMAL CHARACTERIZATION OF TERFENADINE POLYMORPHS IN A SUSPENSION

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ABSTRACT

A procedure was developed to monitor the polymorphic form of Terfenadine when formulated as a suspension for pediatric use. Terfenadine was separated from the suspension components, then examined with Differential Scanning calorimetry and Hot-Stage microscopy. The thermal data were used to classify the Terfenadine isolate as either Form II, the low melting form or Form I, the high melting form.

INTRODUCTION

Terfenadine, an antihistaminic drug may be formulated as a suspension. Problems are often encountered in preparing physically stable suspensions when the active is polymorphic, as is terfenadine. This study was undertaken to evaluate the applicability of thermal techniques to the problem of monitoring a

polymorphic suspension. Both Differential Scanning calorimetry and Hot-stage microscopy were applied.

EXPERIMENTAL

The suspension formulations evaluated consisted of terfenadine (30 mg/5 mL) suspended in an aqueous medium which contained a suspending agent, surfactant, flavor, sweetener and preservative. Batches of suspension were prepared using terfenadine which was predominately Form I, a mixture of forms, or predmoninately Form II.

A sequential separation procedure was used to remove the suspension excipients. An aliquot of the suspension containing 30 mg of terfenadine was mixed with 50 mL of water, then centrifuged to separate solid and liquid phases. The residue was mixed with 0.1M sodium hydroxide, centrifuged, and separated. The separation procedure was repeated with water, then hexane, each time carrying the residual solid forward. The final residue was dried in a vacuum oven overnight at 50°C.

The differential scanning calorimetric data were obtained under a nitrogen atmosphere using a Perkin Elmer DSC-2C thermal analysis system. The sample container was an aluminum volatile sample pan and cover. The cover was pierced with a needle to create a small pin hole. The heating range was from 130° to 155°C with a heating rate of 1.25°C/min. Indium was used to calibrate the temperature scale.

The hot-stage microscopy observations were made with a Mettler FP52 hot-stage system, and an American Optical Series 20 polarized light microscope. Samples were mounted in silicone oil and observed after one minute of isothermal heating at 147.5°C.

RESULTS AND DISCUSSION

The suspension was first examined with DSC. The resulting curves were so broad that the polymorphic forms could not be differentiated. Isolation of the suspended solid was therefore attempted. The isolation sequence was designed to protect the physical state of the solid phase while removing the suspending agents. The procedure was validated by analyzing synthetic samples prepared with terfenadine which had been authenticated with x-ray crystallography to be pure Form I, pure Form II, or a mixture of forms. The polymorphic mixture was composed of about 14% form I. The mixture was chosen so that the polymorphic stability of Form II, in the case where Form I is available to seed crystal growth, could be observed. The hot-stage and DSC data for suspensions prepared from the pure polymorphic forms of terfenadine was in good agreement with the data obtained for non-formulated authentic samples of Form I and Form II.

Suspensions prepared from mixtures of forms were more difficult to evaluate since the melting ranges for samples of the pure polymorphs differ by only 3°. The proximity of the two melting ranges resulted in an overlapping of the DSC curves.

The overlapping peaks for mixtures observed with DSC precluded our reliance on DSC alone for the evaluation of the polymorphic form of suspension samples. Therefore, we developed a classification scheme based on a combination of hot-stage microscopy and DSC data.

The DSC component of the classification used the peak shape and the temperature of the maxima. Curves displaying a single endotherm with a maxima corresponding to the maxima of either Form II or Form I were classed accordingly. When multiple transitions were evident, the area due to Form I was estimated by superimposing the curve for an authentic sample of Form I on the curve for the mixture and hypothecating an area for Form I. In

TABLE 1. QUANTITATIVE DATA FOR TERFENADINE RAW MATERIALS

SAMPLE	% FORM I		
Technique:	X-Ray	DSC	Hot-Stage
Authentic Form I	64	75	≥75%
Authentic Form II	not detected	6	≤25%
Mixed Form	15	18	≤25%

the case where Form II predominated, the curve for an authentic sample of Form II was used as an overlay. The resulting areas were measured with a planimeter.

Hot-stage observations were used to confirm the DSC quantitation. The melting of these polymorphic mixtures occurs in steps; melt, pause at 147.5°C, crystallization (a very slow process for terfenadine), finally the complete liquification of the sample. In mixed samples, the amount of Form I, the unmelted sample at 147.5°C, was estimated visually.

Based on the thermal evaluation, samples were grouped as predominately low melting, ≥75% Form II; mixed melting, ≥25% Form II ≤75% Form II; and high melting, ≤25% Form II. Results of the classification scheme for the raw material samples used in the suspension studies as compared with x-ray powder data are presented in Table I.

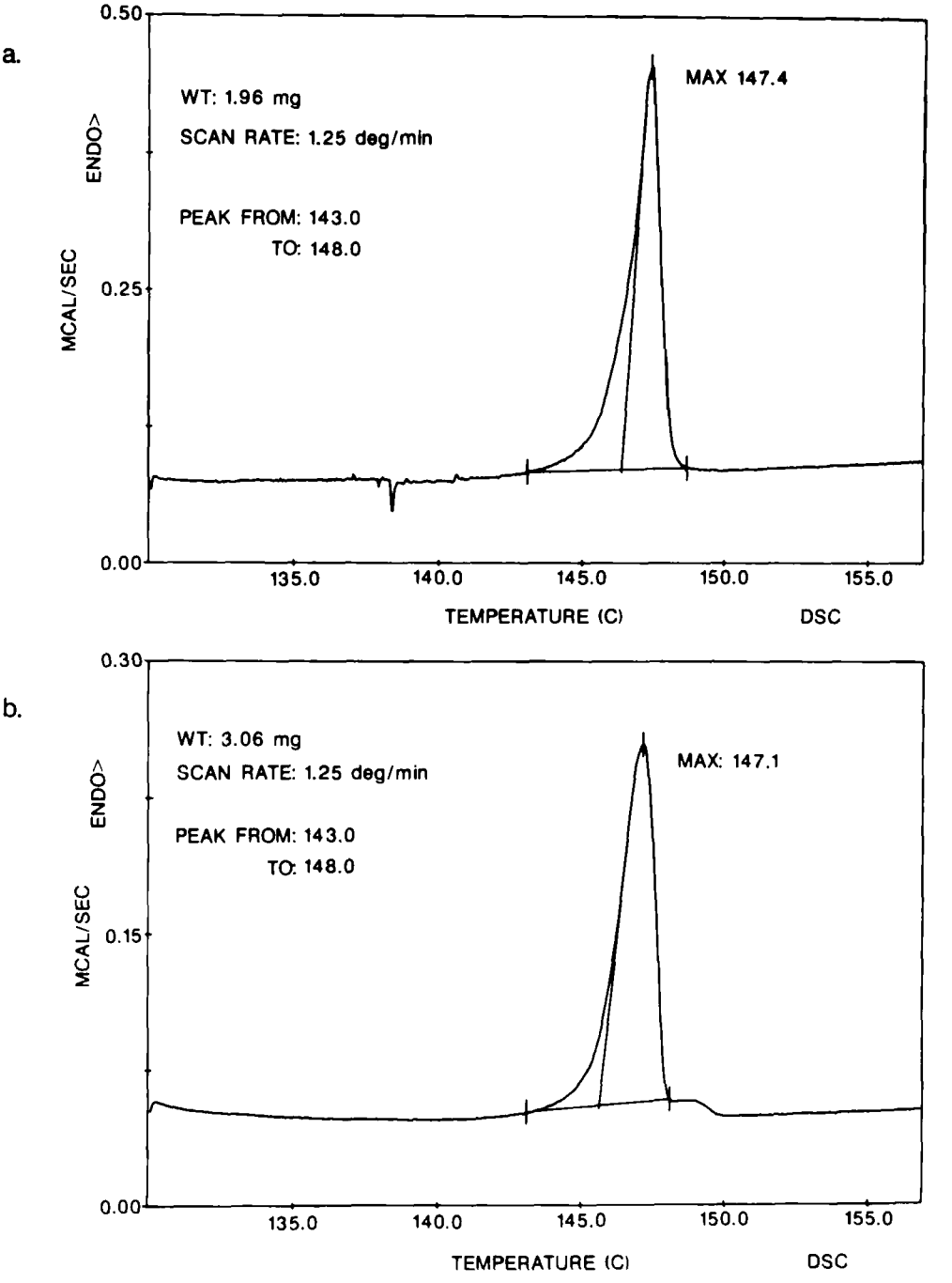

Figure 1. DSC SCAN OF THE AUTHENTIC SUSPENSION

(a) FORM II, "AS RECEIVED",

(b) FORM II, SUSPENSION AFTER EXTRACTION

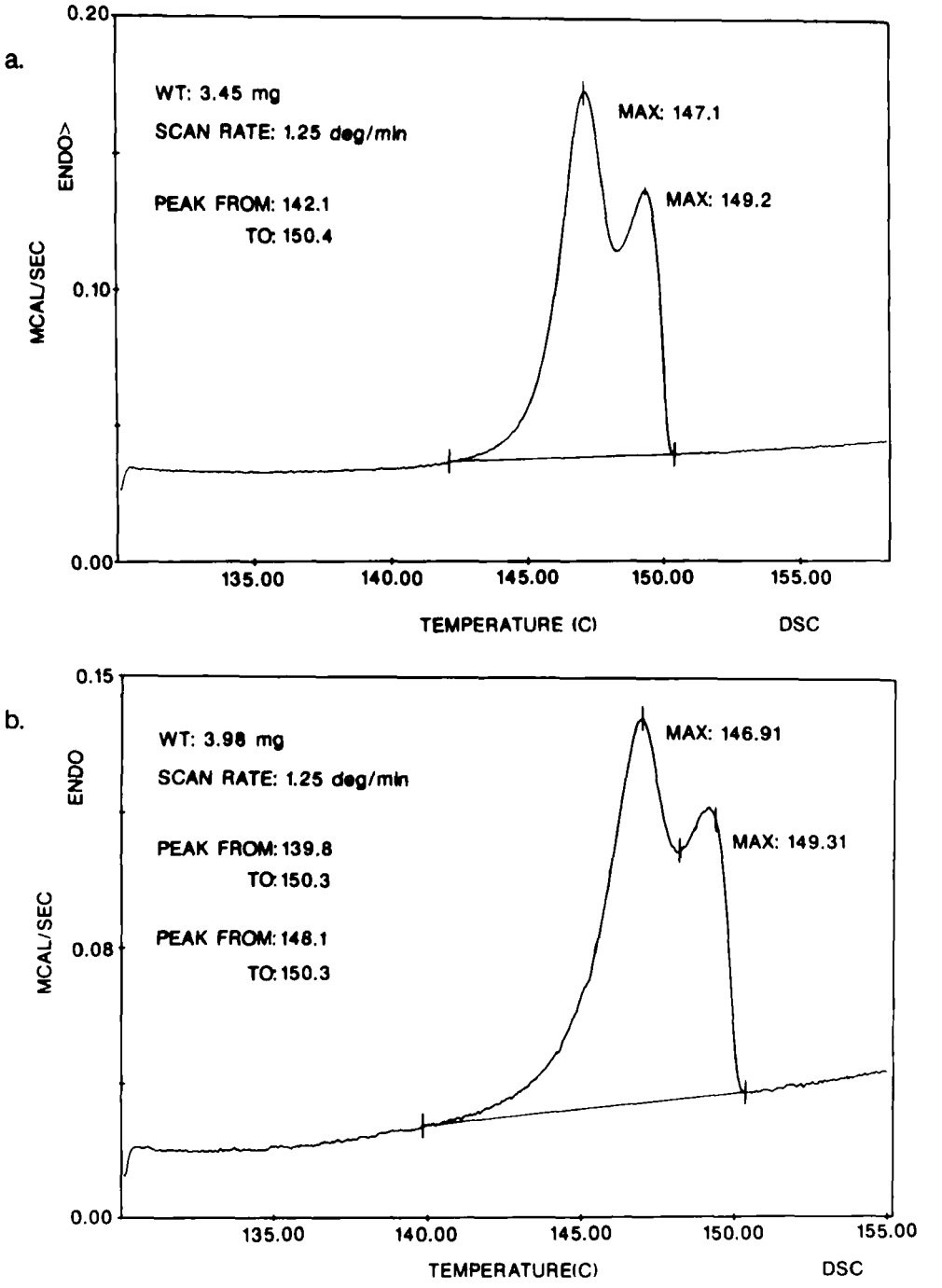

Figure 2. DSC SCAN OF THE AUTHENTIC SUSPENSIONS;

(a) MIXED FORM, "AS RECEIVED"

(B) MIXED FORM SUSPENSIONS AFTER EXTRACTION

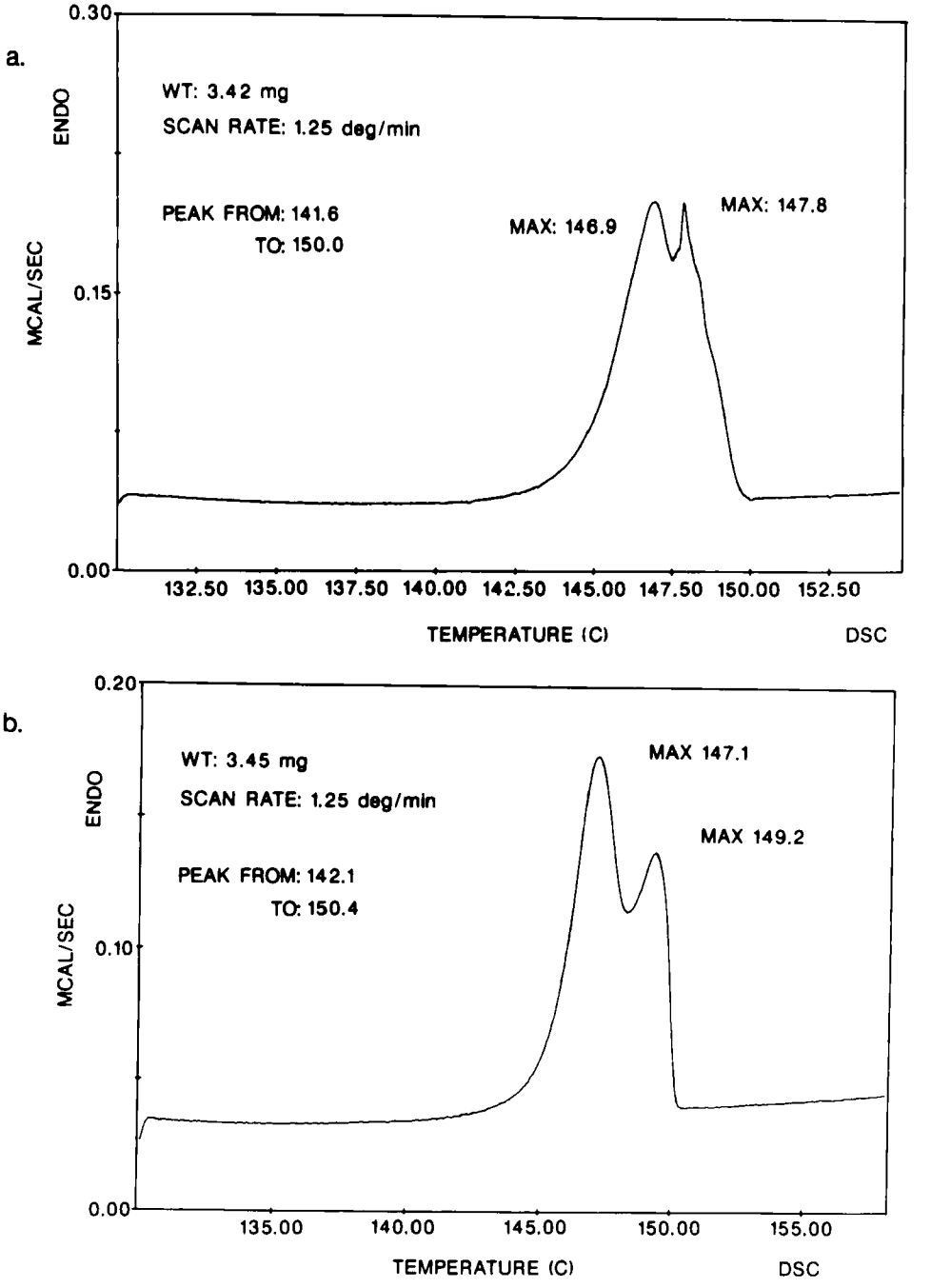

Figure 3. DSC SCAN OF THE AUTHENTIC SUSPENSION; STABILITY SAMPLE FOR THE MIXED FORM

(a) INITIAL SUSPENSIONS

(B) AFTER 2 YEARS AT RT

The separation procedure was applied to authentic suspension samples prepared from form I, Form II and for the mixed form sample. Figure 1 presents data for Form II, the lower melting form. While Figure 2 presents similar data for the mixed form sample. Our classification scheme relying on both the DSC and Hot-stage observations indicates that the mixed form suspension isolate is equivalent to the "as received" raw material.

Stability considerations with regard to the rate of transformation of Form II to Form I led to repetitive evaluation of the DSC patterns for the suspensions. Data obtained for the mixed form sample after approximately 2 years of storage at room temperature are presented in Figures 3. No significant change is noted.

CONCLUSIONS

This study demonstrates the applicability of thermal techniques to the study the polymorphism in pharmaceutical suspensions. An isolation sequence which relies on the insolubility of the solid phase can provide the means to obtain a sample which is suitable for characterization with thermal analysis techniques. Thermal analysis can provide an initial estimate of the polymorph content and generate physical stability data.

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