Pergamon

0731-7085(94)00112-X

Journal of Pharmaceutical & Biomedical Analysis, Vol. 13, No. 2, pp. 103–110, 1995
Elsevier Science Ltd
Printed in Great Britain

The combined use of DSC and TGA for the thermal analysis of atenolol tablets

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Abstract: The New York Regional Laboratory's forensic pharmaceutical group used thermal analysis (TA) to ensure adherence to batch formulations by drug manufacturers. TA in our laboratory consisted of differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA). DSC and TGA were used to analyse finished dosage forms and their components. In this study the components of atenolol formulations were qualitatively identified by analysing individual components and comparing with the finished product. DSC and TGA were used together to develop a profile of batch formulations, with each analytical technique giving complementary types of information. For example, the excipient sodium starch glycolate was identified by DSC and confirmed by TGA. These experimental results demonstrated the use of TA for the characterization of finished dosage forms and the qualitative identification of some of the individual components in batch formulations.

Keywords: *Thermal analysis; thermogravimetric analysis; differential scanning calorimetry; atenolol tablets.*

Introduction

Thermal analysis (TA) of pharmaceuticals was routinely used as a screening method for drug-excipient interactions, purity determinations, quantification of volatile components, and for the characterization of excipients and active ingredients [1–4]. Researchers have used differential scanning calorimetry (DSC) to characterize the physical properties of pharmaceutical materials including melting points, specific heat capacities, heats of fusion, glass transitions, vapour pressures and solubilities [5–8]. One study showed that TA can be used to demonstrate the differences of complex mixtures, by using specific heat capacities [9]. Analytical work in the area of TGA included compositional analysis of drugs, the volatile components of substances, effects of water vapor on the stability of crystalline drugs and excipients, and the determination of the water content, both free and bound, of a wide variety of materials [10].

The purpose of this study was to investigate the combined use of (DSC) and thermogravimetric analysis (TGA), to develop profiles of finished dosage forms. The different types of data generated by the two analytical techniques were used to maximize the detection of differences in the composition of finished dosage forms. Support for this approach comes from the general belief that the thermal properties of the finished products would roughly equal the sum of the properties of the finished product's components if the excipients and active ingredients had no interactions [11]. In cases where there may be interactions between the active ingredient and excipients it was important to be able to monitor the magnitude of the effect in finished dosage forms. One good example was magnesium stearate which was reported to affect dissolution profiles [12].

Materials and Methods

Apparatus

The following apparatus were used during the current analysis: Shimadzu Corporation DSC-50 Differential Scanning Calorimeter; Shimadzu Corporation TGA-50 Themogravimetric Analyzer; Shimadzu Corporation TA-501 Thermal Analyzer; Shimadzu Corporation Thermal Analysis Software TA-50; and Crescent WIG-L-BUG vortex mixer.

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Materials

The following materials were used during the current analysis: aluminium pans and caps and platinum sample pans (Shimadzu Corporation); indium (99.999% purity) and lead (99.99% purity) (Perkin–Elmer); nickel (99.999% purity), Trafoperm (99.99% purity) and nickel metal powder (National Institute of Standards and Technology, Gathersburg, MD, USA); permanent magnet (VWR Corp.); atenolol tablets (100 mg) containing atenolol BP (active ingredient) (Prodesfarma Corp., Spain); sodium starch glycolate (Anebe Corp., the Netherlands); povidone K 29/32 (GAF Corp., NJ, USA); microcystalline cellulose (FMC Corp., DE, USA); magnesium stearate (Whitaker, Clark & Daniels, Inc., NJ, USA); and nitrogen (99.99% purity).

Calibration

The heating rates were kept the same at 10°C min^{-1} to better integrate the information generated by both DSC and TGA. The DSC scans were from ambient to 335°C, while the TGA run parameters were from ambient room temperature to 600°C. Both instruments had the same nitrogen purge gas and flow rate of 20 ml min^{-1}. It was important that the rates of heating and purge gas flows be the same to allow for direct comparison of thermal events in both systems.

The DSC was calibrated using indium (m.p. 156°C) and lead (m.p. 327°C) on the same run. Once crimped in aluminium pans, the indium was put on the sample side and the lead was put on the reference side. All sample analyses were conducted with the crimped lead pan on the reference side of the furnace, which acted as an internal temperature standard that in no way interacted with the samples, giving each DSC thermogram a downward spike at the melting point of lead. This internal standard ensured the instrument was calibrated. It was also possible to direct the software that calculated the enthalpy to check the energy of the lead standard on each analysis. This further ensured the energy measuring capabilities of the instrument were always calibrated. The TGA was calibrated using the Curie points of the metals nickel and trafoperm.

Nickel became paramagnetic at 353°C, roughly the mid-point of most of the analyses and trafoperm had a Curie point at 754°C. The calibration of the balance part of the instrument utilized calcium oxalate as the standard, which had three well documented weight loss transitions. As a further check, traceable calibrating weights were also used. The nature of regulatory work dictates strict adherence to instrument calibrations as related to our total quality assurance programs.

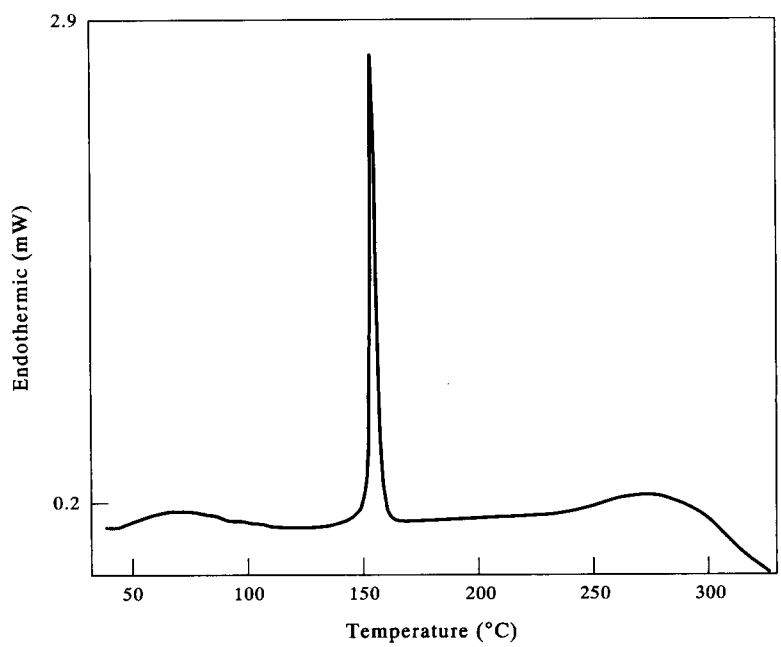

Figure 1
DSC thermal trace of finished dosage form.

Sample preparation

The materials analysed had various physical forms, from tablets to finely ground powders. Finished dosage forms had their coatings (if present) removed using a scalpel, and the cores ground in a mortar and pestle, the resulting powders were put through a 60 mesh screen. The powdered active ingredients and powdered excipients were also put through a 60 mesh screen. The analysed materials all had to be the same physical form, so that the most direct comparison between the different instrumental data could be made. For the DSC analysis, the samples after preparation if any, were crimped in aluminium pans. Care was taken to keep the weights of samples between 0.8 and 1.2 mg. For TGA, the samples were placed in an open pan platinum cup and introduced into the instrument. The weights used for this TGA instrument ranged from 8 to 12 mg. Synthetic mixtures, which consisted of pulverized finished dosage form and one of the excipients, were prepared. These were simple additions by weight, followed by vortex mixing for 30 s.

Results

Differential scanning calorimetry (DSC)

The finished dosage form was analysed first in order to ascertain if there were any interactions between the active ingredient and the

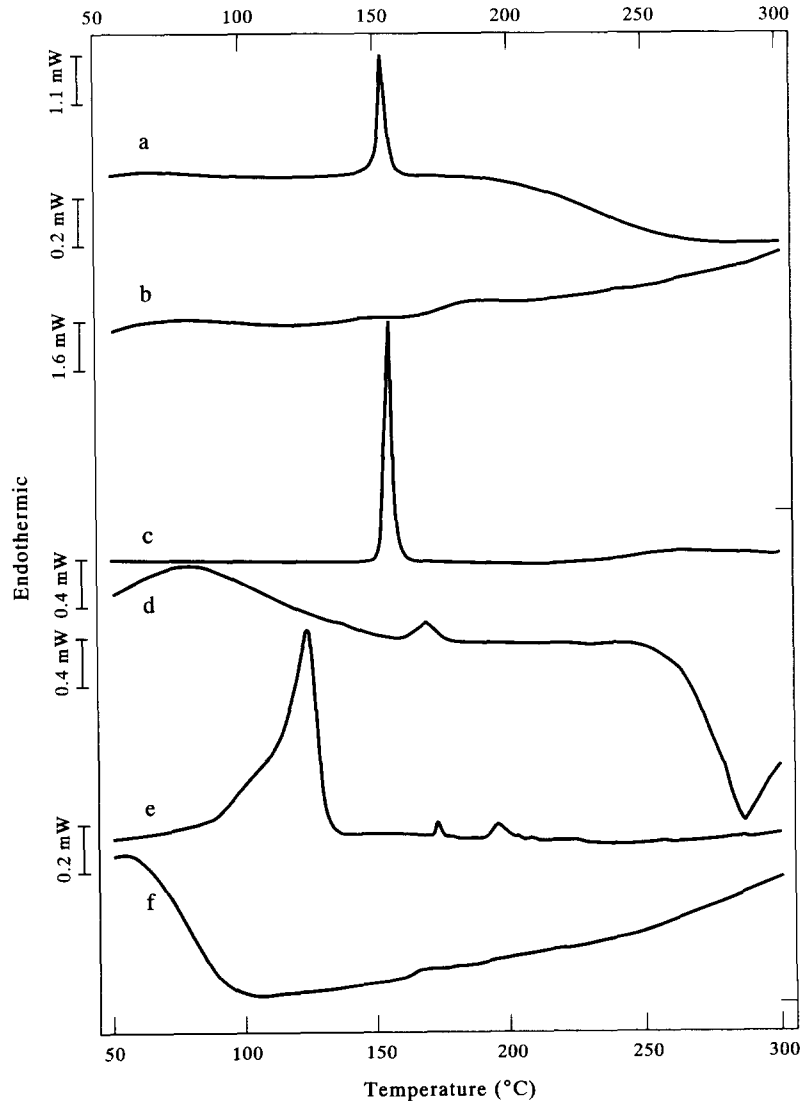

Figure 2
Stacked overlay of DSC thermal traces: (a) finished dosage form; (b) microcrystalline cellulose; (c) active ingredient atenolol; (d) sodium starch glycolate; (e) magnesium stearate; (f) Povidone K 29/32.

excipients. It was customary for this laboratory to begin an analysis using the tablet and then analyse the components of the tablet. The DSC thermogram showed several distinct features (see Fig. 1). The first thermal event was a broad, rounded endothermic transition at the temperature range where water would boil off. The next most prominent feature was a large sharp endothermic peak. That was assigned to the active ingredient atenolol melting at 153.2°C. This main peak was followed by a broad exothermic transition which dominated the higher temperature features between 290 and 330°C.

The stacked overlay (Fig. 2) of DSC curves consisted of the finished dosage form (trace 2a), and the ingredients, microcrystalline cellulose (trace 2b), atenolol (trace 2c), sodium starch glycolate (trace 2d), magnesium stearate (trace 2e) and povidone (trace 2f). This figure showed some of the effects of the components on the tablet. The microcrystalline cellulose had very little interactive effect on the finished dosage form. The sodium starch glycolate had a large sharp exothermic transition in the temperature range from 250 to 300°C, which was present in the finished dosage form but at a slightly higher temperature range. The active ingredient's melting endotherm corresponded to the sharp peak in the finished dosage form trace. The magnesium stearate had no visible effect that was immediately apparent. The povidone also had no effect that was readily discernable.

Figure 3 shows the effects of the addition of magnesium stearate to a finished dosage form. It was possible to shift the melting point of the active ingredient (trace 3a) from 154.4°C to

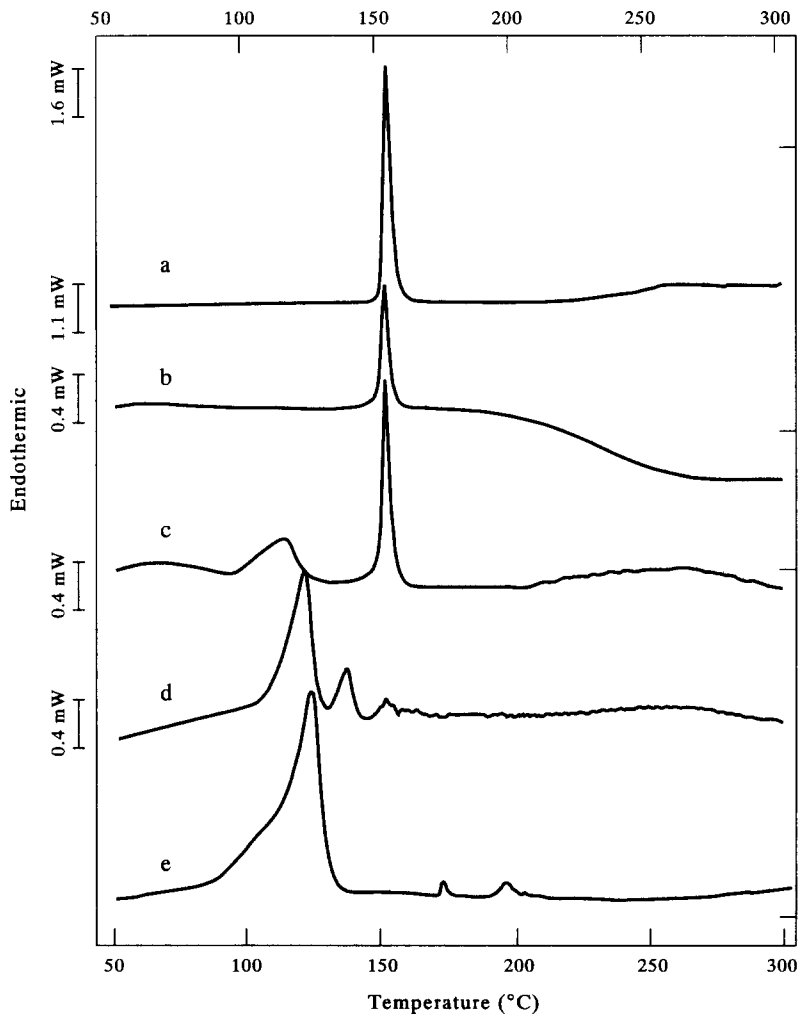

Figure 3
Stacked overlay of DSC thermal traces of the affects of varying the amounts of magnesium stearate in the mixtures. (a) atenolol active ingredient; (b) finished dosage form; (c) 70% finished dosage form/30% magnesium stearate; (4) 50% finished dosage form/50% magnesium stearate; (e) magnesium stearate.

lower temperatures ranging from 153.2°C in the finished dosage form (trace 3b) to 153.1°C in the 70% finished dosage/30% magnesium stearate mixture (trace 3c) and finally to 137.6°C in the 50% finished dosage form/50% magnesium stearate mixture (trace 3d), while pure magnesium stearate had a melting peak at 124.5°C (trace 3e). In this same figure the shape and size of the peaks for the ingredients magnesium stearate and atenolol changed along with the temperatures. Magnesium stearate by itself had a broad based sharp peak which had a shoulder on the lower temperature range. This peak got smaller and shifted to lower temperatures as the amount of magnesium stearate in the mixture decreased. This same phenomenon held true for the atenolol melting peak. It got smaller and shifted to lower temperatures as the percentage of active ingredient decreased. The pure active ingredient's melting endotherm was sharp and narrow, and as the percentage of active decreased the peaks became broader and smaller.

Thermogravimetric analysis (TGA)

A TGA trace normally consists of a weight loss curve and a derivative curve. One axis was plotted with the actual weight or percentage of weight left in the sample pan and the other axis was plotted with the temperature or time.

The finished dosage was analysed first to obtain a general idea about the decompositional nature of the complex matrix (Fig. 4). The atenolol tablet TGA trace had several distinct weight loss transitions. In the lower temperature range there was a small weight loss that indicated moisture or low boiling point solvents evolving out of the matrix. The major weight loss transition occurred between 200 and 380°C. The derivative curve peak had a shoulder on it that indicated that more than one material was decomposing. The final weight loss transition from 400 to 550°C was smaller and broad in nature.

The individual components were analysed and a plot of the derivative curves was compared to that of the finished dosage form (Fig. 5a). Microcrystalline cellulose had a single weight loss transition that corresponded to the main weight loss transition seen on the finished dosage form (trace 5b). Sodium starch glycolate had a large singular weight loss transition that matched the temperature range of the shoulder on the main weight loss transition of the atenolol tablet (trace 5c). Magnesium stearate had a large decomposition peak in the

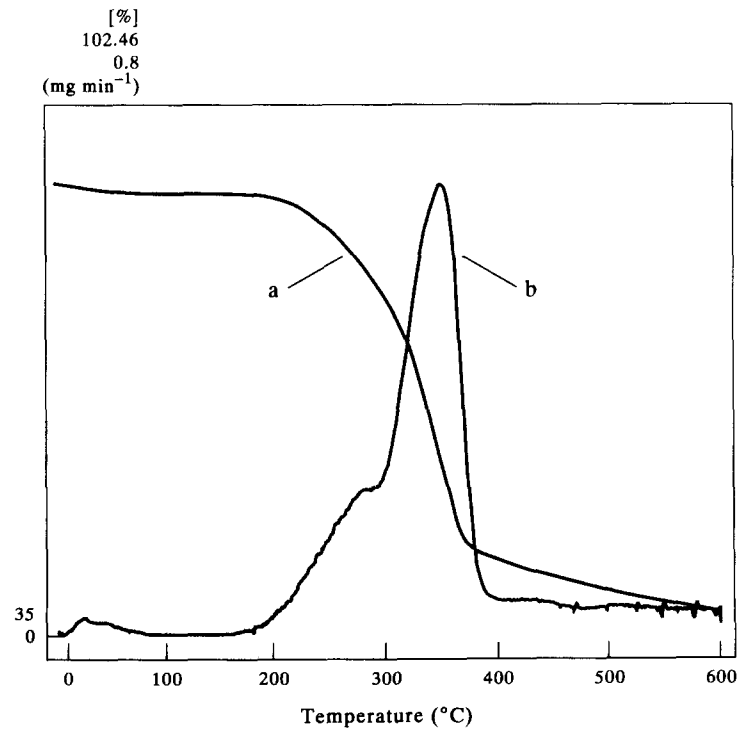

Figure 4
TGA thermal trace of the finished dosage form. Curve (a) is the weight loss curve, curve (b) is the derivative curve ($\Delta\omega/\Delta T$).

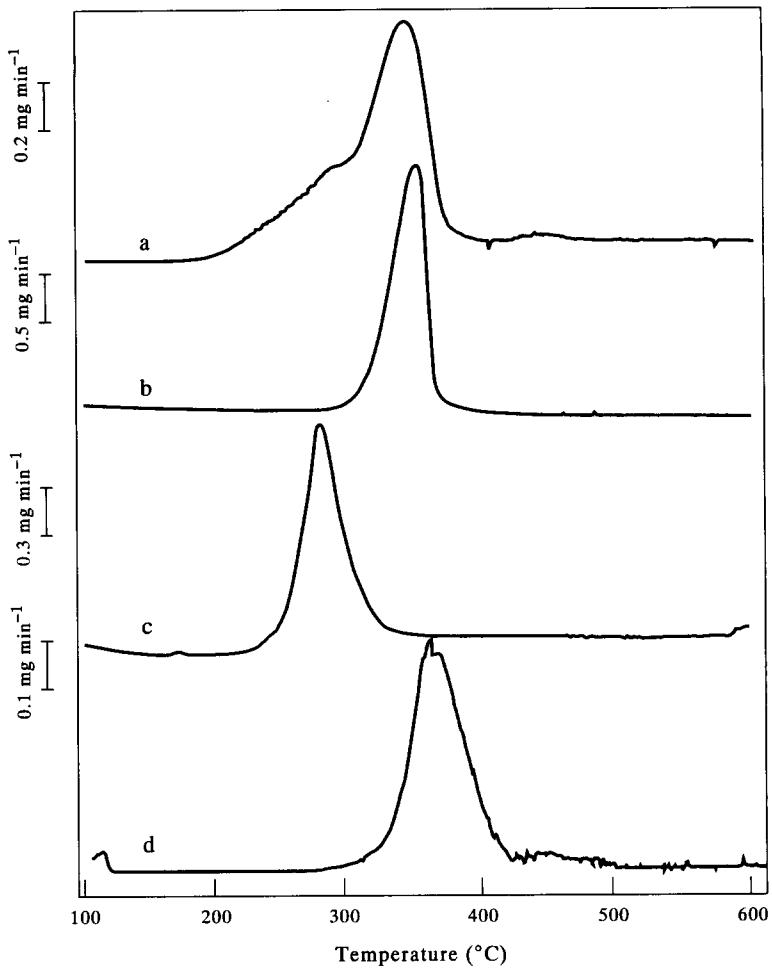

Figure 5
Stacked overlay of the TGA derivative curves of the components. (a) Finished dosage form; (b) microcrystalline cellulose; (c) sodium starch glycolate; (d) magnesium stearate.

area of the high temperature weight loss transition of the finished dosage form (trace 5d).

Figure 6 is an overlay of the derivative curves of the finished dosage form and the excipients sodium starch glycolate and microcrystalline cellulose. Derivative curves were presented because they demonstrated the differences in the weight loss transitions. This figure allowed for the comparison of the decomposition temperature ranges of excipients and the finished dosage form. The sodium starch glycolate peak corresponded to the shoulder on the finished dosage form main peak. The microcrystalline cellulose peak matched the main peak of the finished dosage form. It was easier to see which component was causing a particular weight loss transition when the thermal traces were overlaid in such a manner.

To confirm our prediction of being able to use simple comparisons of decomposition temperature ranges from individual components and apply them to finished dosage forms, a spiked sample was created using the finished dosage form and pure excipient. Figure 7 was an overlay of the derivative curves of the finished dosage form TGA trace and a spiked sample made up of 50% sodium starch glycolate and 50% finished dosage form. The spiked sample had an increased area which corresponded to the temperature range of the shoulder on the main weight loss peak of the finished dosage form. This showed that the weight loss transition associated with the shoulder on the main peak of the finished dosage form was due to sodium starch glycolate.

Discussion

This series of thermal analysis experiments

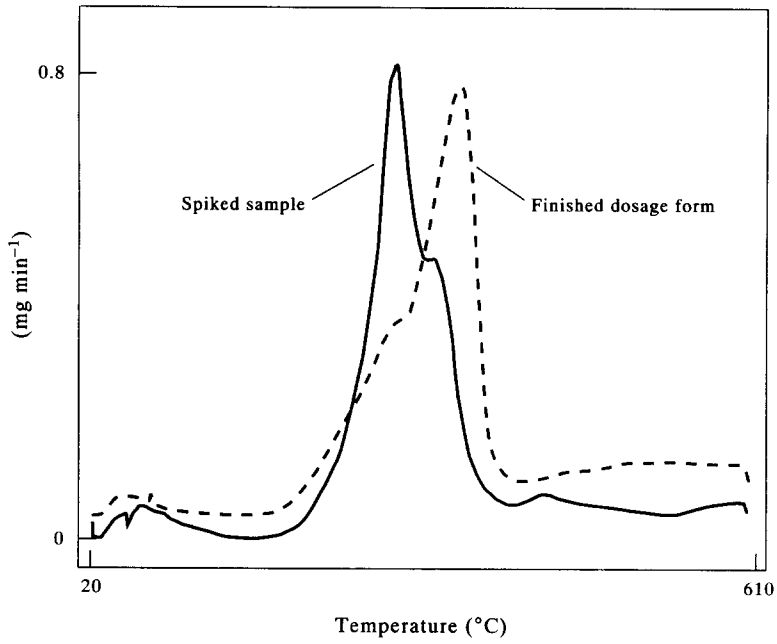

Figure 6
Overlay of derivative curves of finished dosage form, microcrystalline cellulose and sodium starch glycolate.

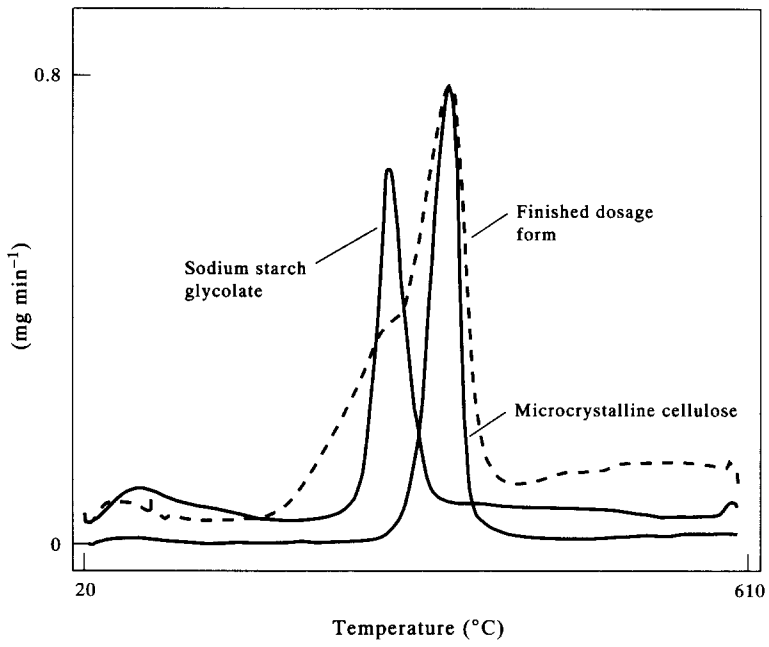

Figure 7
Overlay of derivative curves of finished dosage form and spiked sample consisting of 50% finished dosage form/50% sodium starch glycolate.

qualitatively confirmed some of the components in the finished dosage form including moisture, sodium starch glycolate, microcrystalline cellulose, magnesium stearate and the active ingredient atenolol. This research enabled us to get a rapid idea about the relative amounts of magnesium stearate in an atenolol tablet. Magnesium stearate was reported to affect dissolution profiles and the ability to monitor its amount in finished dosage forms rapidly with little or no preparation was of significant value to our forensic group.

The analytical techniques of DSC and TGA were used together as a dual detection system

to obtain important information about the batch formulation and to confirm some of the components of atenolol tablets. When the DSC thermograms were reviewed there were indications of sodium starch glycolate in the finished dosage form, and this was confirmed by the breakdown product and subsequent weight loss transition seen on the TGA thermogram. The first thermal transition seen on DSC was suspected to be moisture and TGA showed a weight loss transition in the same temperature range. This added proof to the belief that the transition seen on the DSC curve was indeed water being vaporized from the sample matrix. In general, the two techniques were complementary with one confirming the results of the other.

Acknowledgement — Special thanks to Ted M. Hopes, Director, Drug Chemistry Branch, Northeast Regional Laboratory, Food and Drug Administration, for all his help and support.

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[*Received for review 4 February 1994; revised manuscript received 10 May 1994*]