ELSEVIER

Journal of Pharmaceutical and Biomedical Analysis
23 (2000) 1065–1071

JOURNAL OF
PHARMACEUTICAL
AND BIOMEDICAL
ANALYSIS

www.elsevier.com/locate/jpba

Short communication

Variable heating rate thermogravimetric analysis as a mechanism to improve efficiency and resolution of the weight loss profiles of three model pharmaceuticals

Michael B. Maurin *, Anita Taylor [1]

Pharmacy Research and Development, DuPont Pharmaceuticals Company, P.O. Box 80400, Wilmington, DE 19880-0400, USA

Received 2 November 1998; received in revised form 20 April 2000; accepted 28 April 2000

Abstract

The effect of variable heating rates on the efficiency or resolution of the derivative of the thermogravimetry profiles of three model pharmaceutical compounds was investigated. The variable heating system utilized computer controlled algorithms for the evaluation of crystalline sodium warfarin, DuP 532 and hydrated DuP 925 as model compounds with one, two and three step weight loss profiles, respectively. As the heating modes were increased through each of the eight settings, the minimum heating rate decreased while the efficiency and resolution and the analysis times increased. The observed weight loss remained relatively constant for each of the model compounds as the heating modes were increased. The efficiency of the derivative of the weight loss profile of crystalline sodium warfarin increased from 121 to 621 as the heating mode increased. The resolution between the two steps of the derivative of the weight loss profile of DuP 532 increased from 1.73 to 3.88 as the heating mode increased. For hydrated DuP 925, the resolution increased from 1.49 to 5.46 between steps 1 and 2 of the derivative of the weight loss profile and from 1.87 to 3.24 between steps 2 and 3 of the derivative of the weight loss profile. Variable heating rates provided a valuable aid in obtaining high efficiency/resolution thermograms. The enhanced efficiency/resolution permitted greater separation of the volatilization process, especially for samples with multi-step weight loss profiles. Increasing the heating mode afforded higher efficiencies/resolutions that typically reached a maximum value at mode 6. © 2000 Dupont Pharmaceuticals Company. Published by Elsevier Science B.V. All rights reserved.

Keywords: Thermogravimetric analysis; Variable heating rate; Thermal resolution

1. Introduction

Thermogravimetric analysis (TGA) follows the weight of a sample as a function of temperature and has been applied to a variety of pharmaceuticals [1]. The application of TGA to the analytical

* Corresponding author. Tel.: +1-302-9925000.
[1] Present address: School of Pharmacy, Campbell University, Buies Creek, NC, USA.

PII: S0731-7085(00)00368-X

fingerprinting of pharmaceutical formulation components has been proposed as a method to confirm the similarity of complex dosage forms [2]. Critical to the analytical fingerprinting by TGA is the optimization of the resolution of the weight loss profile of the complex mixture. Some variables affecting the resolution that can be obtained with TGA include the size of the sample, the nature of the purge gas and the rate of heating. It is generally accepted that smaller sample weights, low heating rates and purge gases with high thermal conductivity enhance the resolution that can be obtained by TGA. Low heating rates suffer from the drawback of often lengthy analysis times. An alternative is a variable heating rate that decreases only when weight loss begins.

The utilization of variable heating rates has been previously reported as a means to improve resolution [3–6]. The dehydration of cobalt sulfate hydrate and calcium hydroxide mixtures and a mixture of aluminum, magnesium and calcium hydroxides was described by Rouquerol [3]. In the dehydration studies, the balance pressure was maintained constant thereby permitting indirect control of the heating rate.

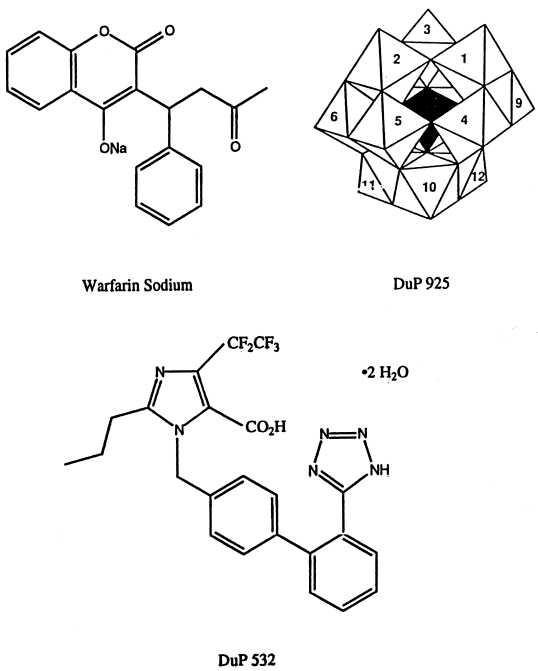

Fig. 1. Chemical structures of sodium warfarin and DuP 532 and the Keggin ion structure of DuP 925.

Quasi-isothermal TGA permitted variable heating rate control by coupling the balance to a galvanometer which produced a light signal that impinged upon a pair of photocells that led to the heating rate control mechanism as described originally by Paulik and Paulik [4]. The quasi-isothermal TGA of the decomposition of potassium bicarbonate to potassium carbonate, carbon dioxide and water had an increased selectivity when comparing to conventional TGA [4]. The quasi-isothermal TGA of non-stoichiometric cerium oxides permitted characterization of the subphases as well as further support that the processes were diffusion-controlled [5].

Ethylene–vinyl acetate (EVAc) copolymer, a rate controlling membrane for several pharmaceuticals, with a vinyl acetate content of 40% was examined using a variable heating rate TGA [6]. The method permitted determination of the vinyl acetate content of the copolymer and maximized the resolution of the derivative of the two step weight loss profile by varying the heating rate in response to the weight loss. The resolution was increased from 1.45 at a constant heating rate of 40°C/min to a maximum of 3.89 with the variable heating rate.

The objective of the present work was to evaluate the effect of a variable heating system that utilizes computer controlled algorithms [7] on the efficiency and resolution of the derivative of the weight loss profile of three model compounds. The model compounds were crystalline sodium warfarin, DuP 532 (4(pentafluoroethyl)-2-*n*-propyl-l-[2′-(1H-tetrazol-5-yl)-biphenyl-4-yl-methyl] imidazole-5-carboxylic acid dihydrate) and hydrated DuP 925 (hexapotassium-α-vanado-11-tungstoborate) (Fig. 1) which display one, two and three step weight loss profiles, respectively.

2. Materials and methods

2.1. Materials

Crystalline warfarin sodium was used as received. DuP 532 and DuP 925 were prepared by the Chemical Process R&D Section of the DuPont Merck Pharmaceutical Company at Cham-

Table 1
Thermogravimetric analysis of crystalline sodium warfarin[a]

Mode	Weight loss (%)[a]	Efficiency[a]	Minimum heating rate (°C/min)	Analysis time (min)	Standard analysis time (min)
Traditional	8.49 (0.02)	125 (1)	10.0	22	23
1	8.40 (0.08)	121 (2)	9.4	21	24
2	8.39 (0.05)	122 (1)	8.8	22	26
3	8.37 (0.02)	133 (5.0)	7.4	23	30
4	834 (0.06)	205	4.3	28	53
5	8.27 (0.05)	370 (10)	1.8	44	130
6	8.11 (0.02)	592	0.50	85	450
7	8.03 (0.09)	595	0.15	270	1500
8	8.15 (0.1)	621	0.05	950	4200

[a] Mean (standard deviaiton), $n = 3$.

bers Works, Deepwater, NJ. DuP 532 was used as received. Prior to analysis, DuP 925 was hydrated by incubating for 3 weeks at 85% RH. The 85% RH was maintained in a sealed chamber (Dry Keeper, Samplatec Corporation) with a saturated aqueous solution of potassium chloride in contact with excess potassium chloride.

2.2. Thermal analysis

Thermogravimetric analysis (TGA 2950 Thermogravimetric Analyzer, TA Instruments, New Castle, DE) was employed to characterize the weight loss profiles.

Samples ranging from 10 to 20 mg were weighed directly into a 1.0-cm diameter platinum pan, lowered into a furnace and heated under a stream of dry nitrogen. The samples were heated initially at 10°C/min from 25°C to 250°C (traditional mode). Subsequent analyses employed each of eight heating modes (Hi-Res™ TGA, TA Instruments, New Castle, DE). The samples were analyzed in triplicate at each heating mode. The efficiency and resolution were calculated from the derivative of the weight loss profile with standard methods [8]. The efficiency (E) is defined as:

$$E = 5.54(t_R/t_{W-1/2})^2 \quad (1)$$

where t_R is the retention time and $t_{W-1/2}$ is the band width at half-height. The resolution (R) is defined as:

$$R = \frac{(t_2 - t_1)}{(1/2)(t_{W2} + t_{W2})} \quad (2)$$

where t_2 and t_1 are the t_R values for the second and first peaks of the derivative, respectively, and t_{W1} and t_{W2} are the band width values for the first and second peaks of the derivative profile, respectively.

3. Results and discussion

Crystalline warfarin sodium, a 2-propanol clathrate, was prepared by crystallizing amorphous warfarin sodium from isopropyl alcohol (IPA) to eliminate a degradation product [9]. It presented a single step weight loss due to the evolution of 2-propanol. As the heating modes were increased through each of the eight settings, the observed weight loss remained relatively constant and the efficiencies and the analysis times increased. The onset of weight loss decreased as the heating mode increased due to the kinetic phenomena of having a greater time temperature exposure as the heating mode increased. The results of the analyses of the crystalline sodium warfarin are provided in Table 1. The efficiency increased from 121 at mode 1 to 621 at mode 8, a 410% increase. Table 1 also indicates that the minimum rate of heating in the analyses of crystalline sodium warfarin decreased from 9.4°C/min at mode 1 to 0.05°C/min at mode 8, while the analysis time increased from 21 to 950 min. The

standard analysis time is the time required to obtain a thermogram. employing the minimum heating rate as a constant rate of heating with the minimum heating rate determined from the derivative plot of temperature versus time. The standard analysis times for crystalline sodium warfarin increased from 24 min at mode 1 to 4200 min at mode 8.

DuP 532, a dihydrate of a carboxylic acid [10], provided a two step weight loss due to the release of water and subsequent decomposition leading to the release of carbon dioxide (Fig. 2) [11]. The observed weight loss for each step of the DuP 532 profile remained relatively constant throughout the eight different heating modes (Table 2). The resolution between steps 1 and 2 increased from 1.73 at mode 1 to 3.88 at mode 8, a 120% increase (Table 2). The minimum rate of heating decreased

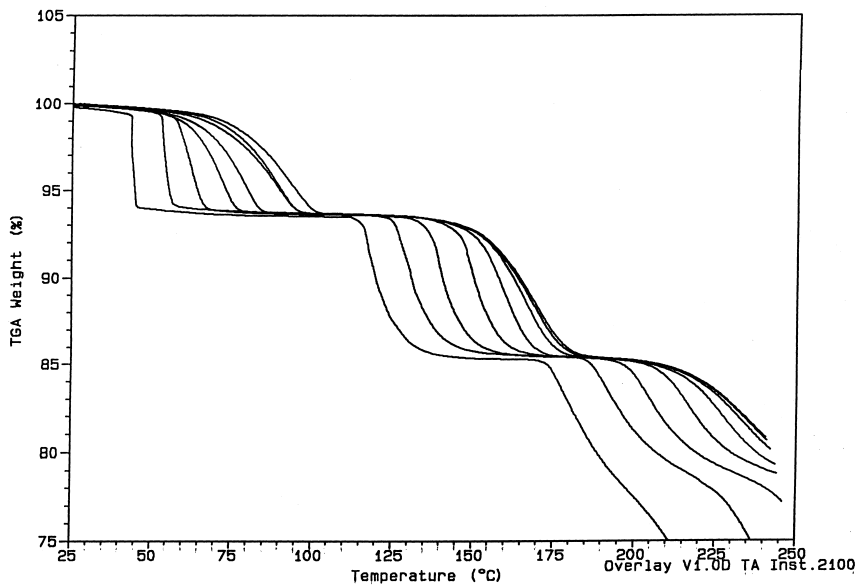

Fig. 2. Percentage weight versus temperature for the thermal dehydration and decomposition of DuP 532 as a function of heating mode. The heating modes 1–8 are presented from right to left.

Table 2
Thermogravimetric analysis of DUP 532

Mode	Observed weight loss (%)[a]		Resolution[a]	Minimum heating rate	Analysis time (min)	Standard analysis time (min)
	First step	Second step				
Traditional	6.35 (0.01)	831 (0.03)	1.81 (0.05)	10.0	22	23
1	6.41 (0.03)	8.29 (0.02)	1.73 (0.09)	9.4	23	24
2	6.36 (0.02)	8.28 (0.01)	1.84 (0.09)	8.7	24	26
3	6.36 (0.01)	8.29 (0.01)	2.04 (0.05)	6.0	27	39
4	6.34 (0.02)	8.30 (0.01)	2.67 (0.06)	2.8	38	79
5	6.29 (0.01)	8.27 (0.01)	3.18 (0.2)	1.0	67	230
6	6.32 (0.03)	831 (0.08)	3.65 (0.2)	0.3	160	790
7	6.32 (0.2)	8.28 (0.06)	3.83 (0.2)	0.05	490	4800
8	6.13 (0.09)	8.42 (0.07)	3.88 (0.2)	0.02	1600	11 000

[a] Mean (standard deviation), $n = 3$.

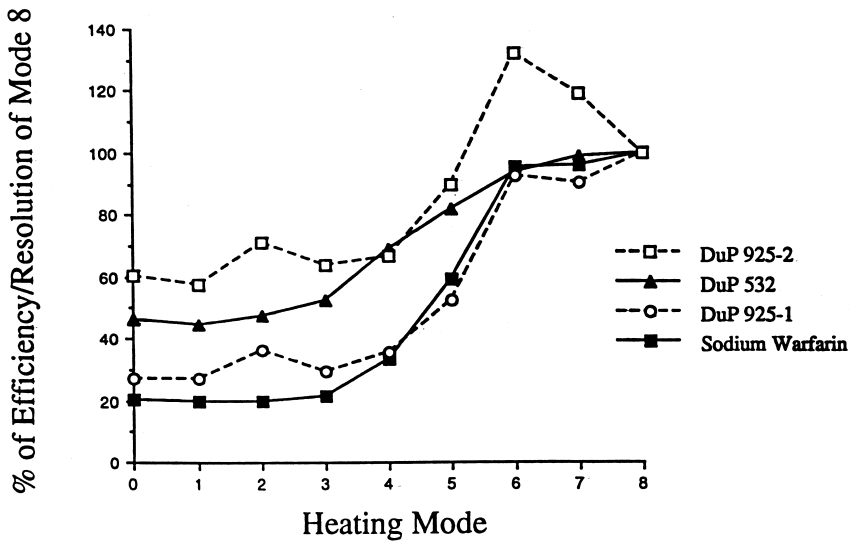

Fig. 3. Percentage of mode 8 resolution versus resolution mode for crystalline sodium warfarin, DuP 532, the first and second steps of hydrated DuP 925 (DuP 925-1) and the second and third steps of hydrated DuP 925 (DuP 925-2). The data points represent the mean of three replicates.

from 9.4°C/min at mode 1 to 0.02°C/min at mode 8. The analysis time increased from 23 to 1600 min while the standard analysis time increased from 24 to 11 000 min.

Hydrated DuP 925, a heteropolyanion, provided a three step weight loss following incubation at 75–85% RH due to the release of water [12]. The observed weight loss of DuP 925 remained relatively constant for each of the three steps (Table 3). The resolution increased from 1.49 to 5.46 between steps 1 and 2, a 270% increase, on reaching mode 8. The resolution between steps 2 and 3 increased from 1.87 to 4.28 at mode 6, representing a 130% increase (Table 3). The analysis times increased from 23 min at mode 1 to 310 min at mode 8 and the standard analysis times increased from 23 min at mode 1 to 54 000 min at mode 8, while showing a decrease in the minimum rate of heating from 9.9°C/min at mode 1 to 0.004°C/min at mode 8 (Table 3).

Variable heating rate control provided a valuable aid in obtaining high efficiency/resolution thermograms. The enhanced efficiency and resolution permitted greater separation of the volatilization process especially for samples with multi-step weight loss profiles. The quantitative weight loss remained relatively constant across the eight heating modes for these model compounds. The relative efficiency of changing heating mode was normalized by dividing the efficiency or resolution at a: given mode by the efficiency or resolution at mode 8 to permit cross-comparison of the model compounds. The data are presented in Fig. 3. Increasing the heating mode afforded higher efficiencies/resolutions of the derivative weight loss profiles that reached greater than 90% of the maximum value at mode 6 and increased slightly through mode 8 for crystalline sodium warfarin, DuP 532 and the resolution between the first and second weight loss step of hydrated DuP 925. The resolution of the derivative weight loss profile between the second and third weight loss step of hydrated DuP 925 reached a maximum value at mode 6 and decreased subsequently at modes 7 and 8. The resolution decrease at modes 7 and 8 was due to a significant tailing that occurred in the derivative of the third weight loss step of DUP 925 that was a result of decomposition that began with the prolonged heating exposure that accompanied modes 7 and 8.

As the efficiencies/resolutions were increased, the minimum rate of heating was decreased which

Table 3
Thermogravimetric analysis of hydrated DUP 925

Heating mode	Observed weight loss (%, w/w)[a]			Resolution[a]		Minimum heating rate (°C/min)	Analysis time (min)	Standard analysis time (min)
	First step	Second step	Third step	First/second step	Second/third step			
Traditional	3.28 (0.1)	2.27 (0.02)	0.83 (0.10)	1.49 (0.1)	1.96 (0.09)	10.0	23	23
1	3.15 (0.2)	2.31 (0.04)	0.88 (0.02)	1.49 (0.03)	1.87 (0.04)	9.9	23	23
2	3.33 (0.04)	2.31 (0.03)	0.94 (0.07)	1.96 (0.4)	2.31 (0.4)	9.4	23	24
3	3.33 (0.04)	2.28 (0.03)	0.96 (0.01)	1.62 (0.3)	2.07 (0.2)	7.6	25	30
4	336 (0.04)	2.28 (0.02)	0.88 (0.03)	1.93 (0.2)	2.16 (0.09)	5.6	29	41
5	3.56 (0.03)	2.25 (0.1)	0.79 (0.01)	2.86 (0.5)	2.91 (0.30)	1.8	40	120
6	3.26 (0.05)	2.24 (0.04)	1.05 (0.02)	5.06 (0.3)	4.28 (0.1)	0.06	66	3800
7	3.23 (0.04)	2.33 (0.07)	1.00 (0.03)	4.95 (0.1)	3.85 (0.40)	0.02	130	15 000
8	3.12 (0.1)	2.33 (0.03)	1.02 (0.03)	5.46 (0.07)	3.24 (0.5)	0.004	310	54 000

[a] Mean (standard deviation), $n = 3$.

corresponded to an increased analysis time. However, the increased analysis times were substantially less, 0.6–20% of the time that would have been required by traditional TGA at heating mode 8 if the minimum rate of heating was employed as a constant. The data indicate that mode 6 provides the best balance between maximized resolution and minimized analysis time.

The variable heating rate method was quite reproducible with average coefficients of variation of 1.4% for the 48 weight loss steps and 5.9% for the 32 efficiency/resolution determinations of the three compounds across the eight heating modes. Overall, the technique provides a powerful tool for optimizing the efficiency and resolution of thermogravimetric analysis profiles.

References

[1] J.L. Ford, P. Timmins, Pharmaceutical Thermal Analysis. Techniques and Applications, Series in Pharmaceutical Technology, Ellis Horwood, 1989.
[2] T. Layloff, Pharm. Technol. 15 (1991) 146–148.
[3] J. Rouquerol, Mem. Soc. Chim. 31 (1964) 31–32.
[4] J. Paulik, F. Paulik, Anal. Chim. Acta 56 (1971) 328–331.
[5] O.T. Sorensen, J. Thermal Anal. 13 (1978) 429–437.
[6] M.B. Maurin, J.W.C. Pang, M.A. Hussain, Thermochim. Acta 209 (1992) 203–207.
[7] C.J. Lundgren, Am. Lab. 24 (1992) 49–52.
[8] L.R. Snyder, J.J. Kirkland, Introduction to Modern Liquid Chromatography, second ed., Wiley Interscience, New York, 1979, pp. 31–34.
[9] C.F. Hiskey, V. Melnitchenko, J. Pharm. Sci. 54 (1965) 1298–1302.
[10] M.E. Pierce, D.J. Carini, G.F. Huhn, G.J. Wells, J.F. Arnett, J. Org. Chem. 58 (1993) 4642–4645.
[11] L.-S. Wu, Personal communication (1989).
[12] M.B. Maurin, R.D. Vickery, W.A. Bryant, III, M.A. Hussain, Pharm. Res. 9 (1992) 570–574.