Pharmaceutical Research, Vol. 16, No. 9, 1999

Determination of the Glass Transition Temperatures of Some New Methyl Methacrylate Copolymers Using Modulated Temperature Differential Scanning Calorimetry (MTDSC)

**M. C. Ferrero,[1] M. V. Velasco,[2] J. L. Ford,[2,3]
A. R. Rajabi-Siahboomi,[2] A. Muñoz,[1] and
M. R. Jiménez-Castellanos[1]**

Received March 25, 1999; accepted May 26, 1999

Purpose. The purpose of this study was to determine the glass transition temperatures of new graft copolymers using Modulated Temperature Differential Scanning Calorimetry (MTDSC), and to assess the differences between starch and cellulosic derivatives of methyl methacrylate and between two different drying methods used in their preparation.
Methods. Graft copolymers of methyl methacrylate were synthesized and dried by oven or freeze-drying. Surface area measurements and different thermal analysis techniques (Differential Scanning Calorimetry (DSC), Thermogravimetric analysis (TGA) and MTDSC) were used to characterize these copolymers.
Results. DSC was not sensitive enough to identify the T_gs of the copolymers, however they were clearly identifiable by MTDSC. T_g values obtained may depend on the method of preparation that also altered their physical characteristics e.g. specific surface area. Cellulose derivatives showed lower T_gs than starch derivatives. The results also depended on the drying method used, thus, freeze dried products had slightly lower T_gs than oven dried products.
Conclusions. MTDSC represents a useful thermal technique that allows the identification of glass transitions in these new copolymers with higher sensitivity and resolution than conventional DSC, separating the transition from overlapping phenomena such as decomposition or dehydration. The T_g of this new class of copolymers appeared to be dependent on polymer composition and drying method used.

KEY WORDS: dynamic differential scanning calorimetry; thermogravimetric analysis; methyl methacrylate; surface area; graft copolymers.

INTRODUCTION

Glass transition is a consequence of an increase in segmental motions in a material and is accompanied by an increase in heat capacity, and possibly a relaxation endotherm (1). The glass transition of a polymer is a critical factor in pharmaceutical processes such as compaction (2–3) and film formation during coating (4–6).

Differential Scanning Calorimetry (DSC), amongst thermal techniques, is most used to evaluate the glass transition temperatures (3,5–8). However, thermal techniques may not be sensitive enough to identify T_gs or require preconditioning of the sample (9–11) to evaluate a T_g.

Modulated Temperature Differential Scanning Calorimetry (MTDSC) is a thermoanalytical technique whereby a sample is subjected to a repetition of programmed steps. In the modified Perkin Elmer DSC 7 calorimeter, which uses a branch of MTDSC termed Dynamic DSC (DDSC), the programmed temperature is modulated with a linear stepwise temperature change and Fourier analysis is used for the evaluation of the data. From analysis of the heat flow response, the specific heat capacity (C_p) can be determined independently of continuous long term enthalpy effects. This represents an important advance on conventional DSC, which involves the use of a linear heating program and does not allow the separation of the signal into component responses. MTDSC is, therefore, a software development rather than a change in the basic DSC equipment.

MTDSC has a number of advantages over conventional DSC including higher resolution without loss of sensitivity and T_g detection. The main disadvantage is that a longer scanning time is required and a new baseline for each operating condition must be run (12).

The development of new polymers for controlled release is becoming increasingly important. Graft copolymers of methyl methacrylate (MMA) on various substrates (hydroxypropyl starch, carboxymethyl starch and hydroxypropyl cellulose) have been introduced as matrix-forming excipients for oral sustained dosage forms (13–17). Several controlled release formulations incorporating these new copolymers have been reported (14–15,17). Moreover, the characterization of these copolymers in terms of morphology, powder flowability, moisture uptake, compaction behavior and rheological properties (13–14,16) has been carried out since these factors may strongly influence the release properties of drugs from their matrix tablets. The amorphous nature of the graft copolymers used in this study has been confirmed using X-ray diffraction (16) and a characteristic glass transition therefore might be expected. These polymers have been previously characterized by NMR-techniques to determine the structure of the organic compounds and by IR spectrophotometry to identify the functional groups. The thermal analysis of these polymers has not been reported previously.

The aim of this study is to evaluate the usefulness of MTDSC as a tool for the study of the glass transition of several recently synthesized graft copolymers in comparison with DSC, and to assess if the T_g was modified by the manufacturing process. The specific surface areas were also measured since they may depend on the preparation of the copolymers.

MATERIALS AND METHODS

The copolymers were synthesized by graft copolymerization of cellulose and starch derivatives with methyl methacrylate (MMA) and dried either in an oven to constant weight under vacuum at 50°C or freeze-dried in a lyophilization apparatus

---

[1] Departamento de Farmacia y Tecnología Farmacéutica, Facultad de Farmacia, C/Tramontana s.n., 41012 Sevilla, Spain.
[2] School of Pharmacy and Chemistry, Liverpool John Moores University, Byrom Street, Liverpool L3 3AF, United Kingdom.
[3] To whom correspondence should be addressed. (e-mail: j.l.ford@livjm.ac.uk)

ABBREVIATIONS MTDSC, modulated temperature differential scanning calorimetry; T_g, glass transition temperature; DSC, differential scanning calorimetry; TGA, thermogravimetric analysis; HS-MMA, hydroxypropyl starch-methyl methacrylate; CS-MMA, carboxymethyl starch-methyl methacrylate; HC-MMA, hydroxypropyl cellulose-methyl methacrylate; OD, oven-dried; FD, freeze-dried; ΔC_p, specific heat capacity change; PMMA, polymethyl methacrylate.

(FD-154D, Varian) at −20°C during 24 hours followed −50°C at 100 millitorrs of pressure until powdered product was obtained. In both cases a similar product was obtained but in two different states: as a glassy mass in the oven-dried products or as a powder in the freeze-dried products. The oven-dried products were crushed in a hand mill to obtain powdery products (13). Three pairs of products were produced: hydroxypropyl starch-methyl methacrylate (HS-MMA), carboxymethyl starch-methyl methacrylate (CS-MMA) and hydroxypropyl cellulose-methyl methacrylate (HC-MMA).

Surface Area Measurements

Surface area measurements were carried out using a surface area analyzer (Quantachrome Nova 2000, Florida, USA). The samples were carefully weighed (Model WA 205, Oertling, England) into the sample cell and the outgassing process was conducted using vacuum and a temperature of 50°C over 18 hours. In the case of HS-MMA copolymers, the samples were previously dried in an oven in order to remove the excess of water; 2 g of each sample were placed in Petri dishes and dried at 50°C for 24 hours prior to the outgassing process. The specific surface areas were calculated using a multiple point BET (Brunauer, Emmet and Teller) method (18) from the mean of two replicates.

Thermal Analysis

Differential Scanning Calorimetry

Differential Scanning Calorimetry (DSC) measurements were performed using a Perkin-Elmer DSC 7 (Beaconsfield, UK) controlled by a Perkin-Elmer TAC 7/DX. Liquid nitrogen was used as coolant and nitrogen gas as purge gas. The instrument was calibrated for temperature at each heating rate using the standard references, indium and zinc. Samples of copolymers (8–16 mg) were carefully weighed (Model WA 205, Oertling, England) into 40 μL aluminum pans with a pin-hole in the lid to allow evaporation of volatile materials. The samples were scanned from −40°C to 240°C at a heating rate of 10°C min^{-1}. Duplicate scans were made for each copolymer.

As heating rate influences the nature of the thermoanalytical curves, DSC measurements were also carried out, in duplicate, at a heating rate of 1.5°C min^{-1} over a temperature range of 40 to 200°C. The slow rate would result in a higher resolution between events which occur over similar temperature ranges but with lower sensitivity (1).

Modulated Temperature Differential Scanning Calorimetry

A Perkin-Elmer DSC 7 Differential Scanning Calorimeter was used. Samples (9–13 mg) were weighed (Model WA 205, Oertling, England) into 40 μL aluminum pans, and sealed with pin-holed lids to avoid sample expansion and warping. A dynamic heat-cool program was used, scanning from 40°C to 200°C using a heating rate of 6°C min^{-1}, followed by cooling at 3°C min^{-1}, each for 40 s, repeating 80 times. Liquid nitrogen and nitrogen gas were used as coolant and purge gas respectively. A new baseline was constructed for each operating condition. Values of specific heat capacity (ΔC_p) and T_g were determined in duplicate. T_gs were determined by the half-C_p method, where the specific heat (C_p) change is half of the change of the complete transition. Tan delta curves were calculated as the ratio between the storage and loss signals.

Thermogravimetric Analysis

Thermogravimetric analysis (Perkin-Elmer TGA 7, Beaconsfield, UK) was carried out using samples of 5–10 mg in open pans at a scan rate of 10°C min^{-1} over a temperature range of 20 to 200°C.

RESULTS AND DISCUSSION

Surface Area Measurements

The specific surface areas for the copolymers were obtained by fitting the data to BET equation, with correlation coefficients between 0.9979 and 0.9995 (Table 1). Higher specific surface areas were observed for polymers dried by freeze-drying. In the cases of CS-MMA and HC-MMA derivatives, the value for the freeze-dried copolymer was almost double that of the oven-dried copolymer. The least difference in the surface area between freeze-dried products and oven-dried products was in HS-MMA samples.

These results agree with the morphological differences described previously between oven-dried and freeze-dried products. Scanning electron microscopy showed a more porous structure in freeze-dried samples (13,16). Oven-dried products showed smoother surfaces which may be due to the milling process carried out after drying.

Thermogravimetric Analysis

TGA was used to assess weight loss, due either to moisture loss or decomposition so as to relate to the DSC scans and T_g values. Although free/bound water may exist in these copolymers, their identification is not the objective of this work. Figure 1 illustrates weight loss occurred over a broad temperature range (20–200°C). Moisture loss was assumed to be complete by 120°C. Subsequent weight loss was attributed to decomposition.

Differential Scanning Calorimetry

Table 2 summarizes the endotherm and exotherm peaks of the copolymers obtained from DSC studies at heating rates of 10 and 1.5°C min^{-1}. Figure 2 shows examples of the conventional DSC scans of CS-MMA copolymers freeze-dried and

Table 1. Specific Surface Area (m^2/g) (Mean and S.D. of Two Experiments) of the Copolymer Samples

Copolymer	Specific surface area (m^2/g)
HC-MMA (OD)	1.55 ± 0.04
HC-MMA (FD)	2.86 ± 0.04
HS-MMA (OD)	1.18 ± 0.05
HS-MMA (FD)	1.26 ± 0.11
CS-MMA (OD)	4.13 ± 0.03
CS-MMA (FD)	8.34 ± 0.04

Note: FD: freeze-dried OD: oven-dried.

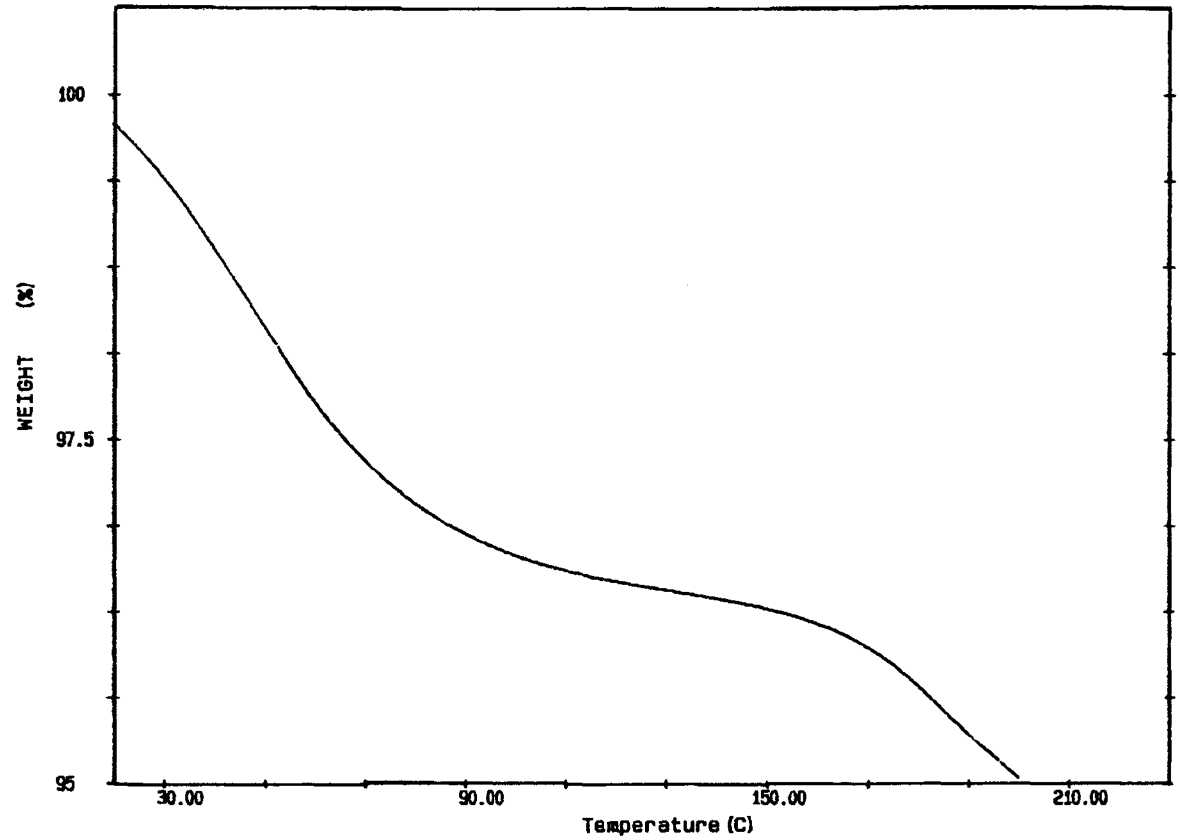

Fig. 1. TGA scan of CS-MMA oven-dried (6.514 mg) at 10°C min^{-1}.

oven-dried obtained at a heating rate of 10°C min^{-1}. The endotherms and exotherms may be due to dehydration and decomposition respectively. T_gs were not apparent in any of the DSC scans for the copolymers, possibly because they overlapped the decomposition and dehydration processes.

With the purpose of obtaining a better resolution, the DSC scans were repeated at a slower heating rate (1.5°C min^{-1}). However, the heat flow through the sample was not enough to identify any glass transitions (Fig. 3), and the transitions were moved to lower temperatures (Table 2) for each specimen examined.

Table 2. Approximate Peak Temperatures of Endotherms and Exotherms Obtained in the DSC (at 10°C min^{-1} and 1.5°C min^{-1}) and MTDSC Scans of the Copolymers

	DSC (10°C min^{-1})		DSC (1.5°C min^{-1})		MTDSC	
Copolymer	endo	exo	endo	exo	endo	exo
HC-MMA (OD)	115	135	55	110	60	106
HC-MMA (FD)	115	130	50	110	70	110
HS-MMA (OD)	120	—	70	125	70	120
HS-MMA (FD)	112	180	70	110	65	110
CS-MMA (OD)	140	190	70	170	70	170
CS-MMA (FD)	120	190	70	110	70	120

Note: FD, freeze-dried; OD, oven-dried.

Modulated Temperature Differential Scanning Calorimetry

Preliminary MTDSC studies were carried out using fully sealed pans; however these did not produce scans stable enough to determine T_g values because of the accumulation of volatile materials in the pan, leading to warping of the sample pans and variable, inconsistent scans. MTDSC carried out in pans fitted with pin-hole lids allowed stable heat flow signals to be obtained.

The selection of encapsulation methods illustrates the inevitable problem of determining a T_g via thermal analysis. If hermetically sealed pans are used, water or volatiles will be lost from the polymer to the space within the pan. With pinholed samples the water is completely lost from the polymer: only water strongly bound to the polymer will be retained. Neither encapsulation technique allows the determination of the T_g of the sample in its condition prior to the scan. It is assumed in this study that most of the water will be lost from the polymers and that glass transitions reflect the solid state at the temperature at which the T_g occurs. Additionally the TGA data indicate that the samples were not particularly stable and that decomposition, as evidenced by weight loss, occurred at temperatures in excess of ~140°C.

Figures 4 and 5 show typical MTDSC scans obtained for CS-MMA samples, freeze-dried and oven-dried respectively. Table 3 shows the T_g values and changes in C_p for the different copolymers.

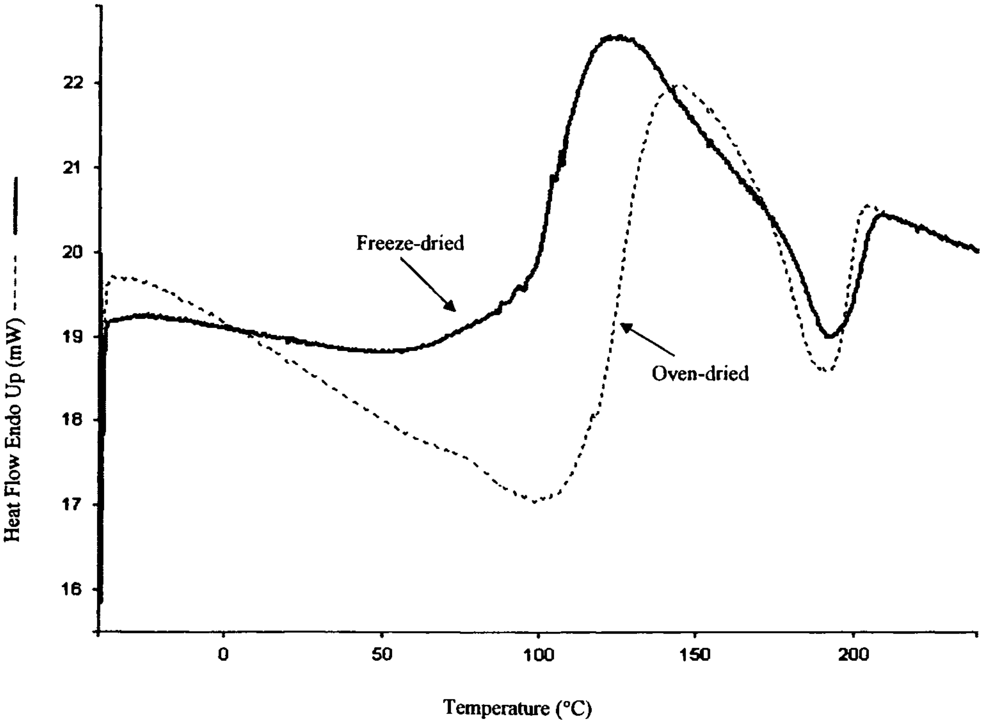

Fig. 2. DSC scans at a heating rate of 10°C min^{-1} for CS-MMA freeze-dried and oven-dried samples.

Heat flow MTDSC curves displayed similar trends to the DSC curves obtained at the similar overall heating rate of 1.5°C min^{-1}, but these events were shifted to lower temperatures than the ones obtained by DSC at 10°C min^{-1} (Table 2). Loss specific heat curves, which represent the dynamic specific heat that is out of phase with the temperature change, showed small capacity changes at 100–140°C. However, the T_gs were clearly identified in storage specific heat curves occurring from ~80°C to ~130°C (Figs. 4 and 5). The results are presented in Table 3. To confirm these results, the tan delta curves were produced. The presence of a clear peak in the tan delta curve represents a higher storage signal, i.e., a transition change in this temperature range is due to the movement of the polymer molecules, and a glass transition (Figs. 4 and 5).

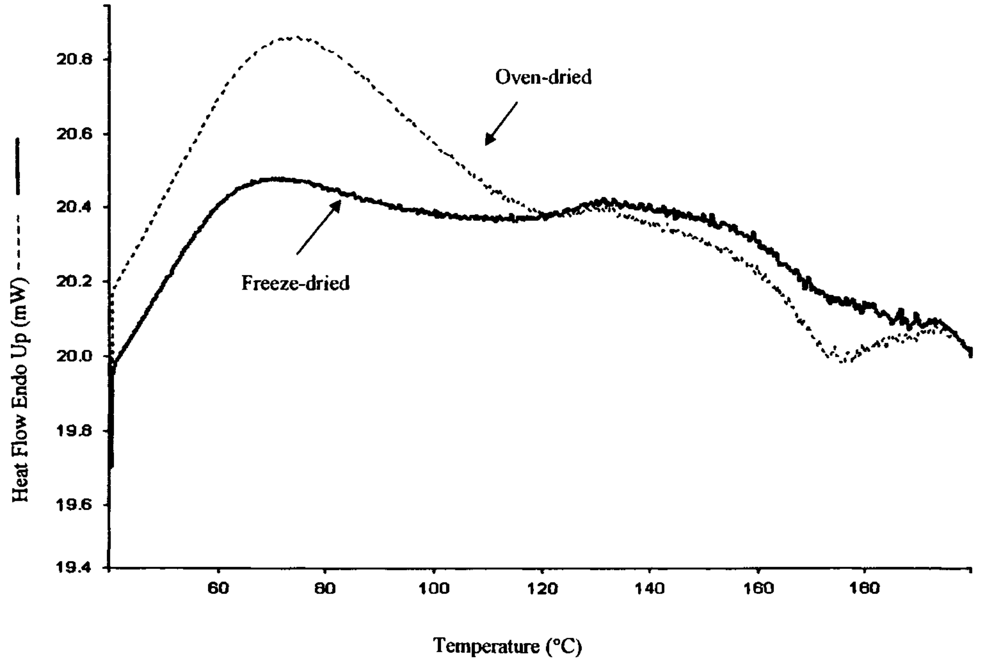

Fig. 3. DSC scans at a heating rate of 1.5°C min^{-1} for CS-MMA freeze-dried and oven-dried samples.

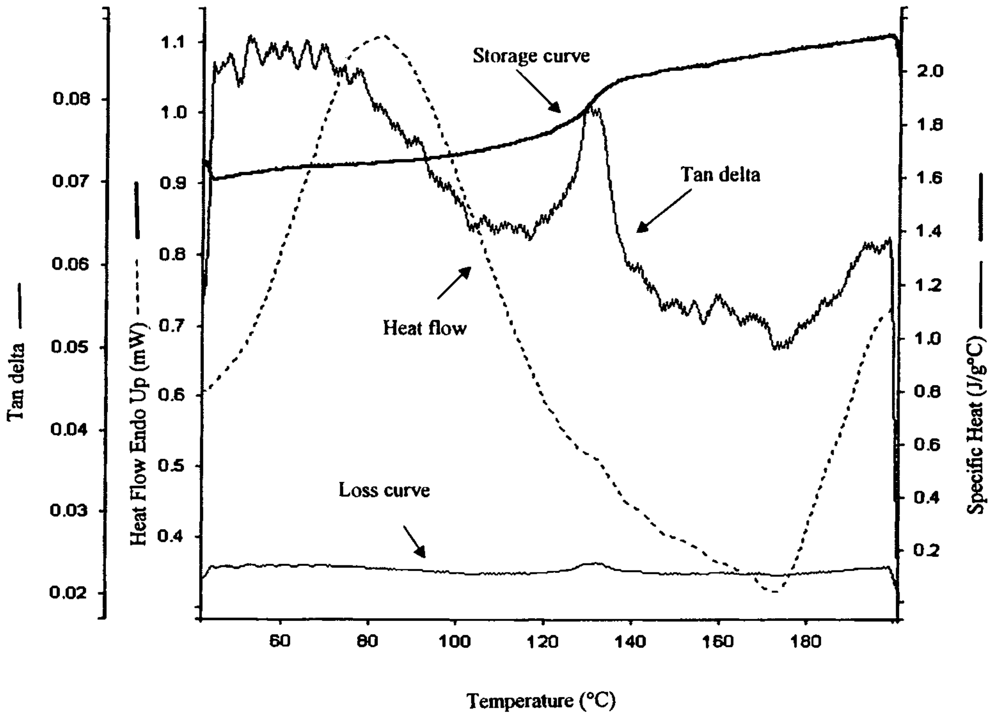

Fig. 4. MTDSC scan for CS-MMA freeze-dried samples with pin-hole lids.

The cellulose derivatives showed smaller T_g and ΔC_p values than the starch derivatives (Table 3). These differences could be justified by the synthesis that consisted of a copolymerization reaction (13). The substitution grade of the initial carbohydrate is higher in the cellulosic carbohydrate (HC) than in the starch carbohydrates (CS and HS). However, the cellulosic derivatives present the highest yield in the graft copolymerization reaction (13), so this seems to indicate that HC-MMA is constituted from long PMMA chains separated from each other. This structure could avoid the formation of hydrogen bonds and therefore the polymers could present a loose structure with lower T_g. Starch derivatives, with lower substitution grades, may present

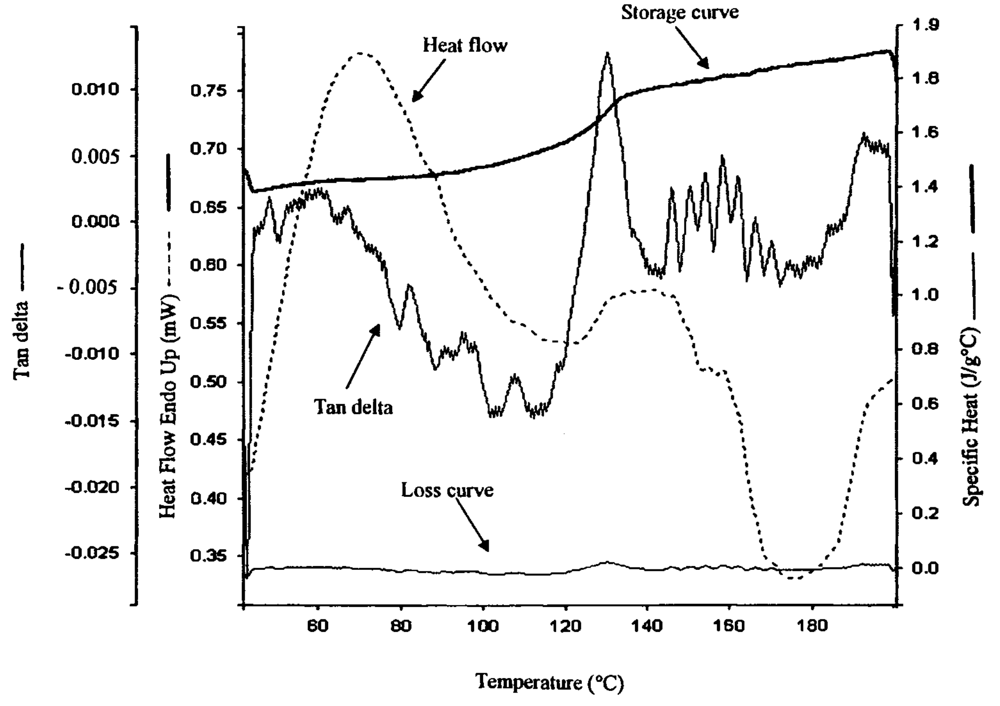

Fig. 5. MTDSC scan for CS-MMA oven-dried samples with pin-hole lids.

Table 3. Glass Transition Temperatures (T_g (°C)) and ΔC_p(J/g°C) Derived from MTDSC Scans (Mean and S.D., n = 2)

Copolymer	T_g(°C)	ΔC_p(J/g°C)
HC-MMA (OD)	116.2 ± 1.3	0.171 ± 0.008
HC-MMA (FD)	110.1 ± 3.5	0.155 ± 0.015
HS-MMA (OD)	128.3 ± 0.9	0.197 ± 0.025
HS-MMA (FD)	126.8 ± 0.3	0.231 ± 0.019
CS-MMA (OD)	126.5 ± 0.6	0.210 ± 0.032
CS-MMA (FD)	124.6 ± 0.8	0.213 ± 0.029

Note: FD, freeze-dried; OD, oven-dried.

closer chains of PMMA and free hydroxyl groups. Hydrogen interactions will be possible and will lead to a rigid structure with higher T_g.

The smallest difference between the T_gs in freeze-dried and oven-dried products was for the starch derivatives. These results may indicate that the drying method had less influence on the starch derivatives.

The freeze-dried products appeared to have slightly lower T_gs than the oven-dried samples (Table 3). These results may partly be explained by the differences reported in the physical performances of the oven-dried and freeze-dried products (13). The oven-dried products were glassy in nature following preparation (13). Although surface area may not be a major factor in influencing the glass transition temperature, in particles with higher specific surface area a higher heat transfer is enhanced and this may shift the glass transition to lower temperatures. Oven-dried products had lower surface areas (Table 1) as well as higher T_gs (Table 3) than freeze-dried products.

The heat capacity associated with the glass transition process is also shown in Table 3. MTDSC uses a saw-tooth function as a temperature profile and a discrete Fourier transformation for evaluation to calculate C_p (19). Cellulose derivatives showed lower heat capacity than starch derivatives. In the starch derivatives (HS-MMA and CS-MMA), the heat capacity is higher in the freeze-dried products than in the oven-dried products. These differences in the energy involved in the transition from the glassy to the rubbery state may be due to different physical characteristics of the copolymers.

MTDSC, rather than DSC, allowed differentiation of the T_gs of methyl methacrylate copolymers. Moisture loss, through the lid pin-holes, was not controlled and might have influenced the absolute values of the data.

ACKNOWLEDGMENTS

This work has been founded by a project of Acciones Integradas-British Council between the University of Seville (Spain) and Liverpool John Moores University (U.K.). MVV works in Liverpool John Moores University as part of a European Community Training Project (Biomed Program). The authors wish to thank Dr. Tim Mann (Perkin Elmer) for his helpful suggestions in the discussion of MTDSC results and the research group from the University of San Sebastian (Spain) for the synthesis of the graft copolymers.

REFERENCES

1. N. J. Coleman and D. Q. M. Craig. Modulated temperature differential scanning calorimetry: a novel approach to pharmaceutical thermal analysis. *Int. J. Pharm.* **135**:13–29 (1996).
2. K. Van der Voort Maarschalk, K. Zuurman, M. J. Van Steenbergen, W. E. Hennink, H. Vromans, G. K. Bolhuis, and C. F. Lerk. Effect of compaction temperature on consolidation of amorphous copolymers with different glass transition temperatures. *Pharm. Res.* **14**:415–419 (1997).
3. K. Van der Voort Maarschalk, H. Vromans, G. K. Bolhuis, and C. F. Lerk. Influence of plasticizers on tableting properties of polymers. *Drug Dev. Ind. Pharm.* **24**:261–268 (1998).
4. T. Keshikawa and H. Nakagami. Film formation with coating systems of aqueous suspensions and latex dispersions of ethylcellulose. *Chem. Pharm. Bull.* **42**:656–662 (1994).
5. A. O. Okhamafe and P. York. Studies of interactions phenomena in aqueous-based film coatings containing soluble additives using thermal analysis techniques. *J. Pharm. Sci.* **77**:438–443 (1988).
6. A. O. Okhamafe and P. York. Thermal characterization of drug/polymer and excipient/polymer interactions in some film coating formulation. *J. Pharm. Pharmacol.* **41**:1–6 (1989).
7. J. Ford and P. Timmins. The use of thermal analysis in the development of solid dosage forms. In J. L. Ford and P. Timmins (eds.), *Pharmaceutical Thermal Analysis, Techniques and Applications.* Ellis Horwood, Chichester, UK, 1989, pp. 180–200.
8. J. Kerč and S. Srčič. Thermal analysis of glassy materials. *Thermochim. Acta* **248**:81–95 (1995).
9. E. Selinger and C. J. Brine. Use of thermal analysis in the optimization of polymeric diffusion barriers in controlled release delivery systems. *Thermochim. Acta.* **134**:275–282 (1988).
10. J. C. Seferis, I. M. Saliri, P. S. Gill, and M. Reading. Characterization of polymeric materials by modulated differential scanning calorimetry. *Proceedings of the Greek Academy of Sciences*, Nov., 1992, pp. 310–346.
11. C. A. Entwistle and R. C. Rowe. Plastification of cellulose ethers used in the film coating tablets. *J. Pharm. Pharmacol.* **31**:269–272 (1979).
12. J. E. K. Schawe. A comparison of different evaluation methods in modulated temperature DSC. *Thermochim. Acta* **260**:1–16 (1995).
13. I. Castellano, M. Gurruchaga, and I. Goñi. The influence of the drying method on the physical properties of some graft copolymers for drug delivery systems. *Carbohyd. Polym.* **34**:83–89 (1997).
14. I. Castellano, I. Goñi, M. Gurruchaga, M. V. Velasco, A. Muñoz, and M. R. Jiménez-Castellanos. Contribution to the study of new graft copolymer matrices for drug delivery systems. Technological study. *Int. J. Pharm.* **146**:71–79 (1997).
15. M. C. Ferrero, M. V. Velasco, A. Muñoz, M. R. Jiménez-Castellanos, I. Castellano, M. Gurruchaga, and I. Goñi. Drug release from a new family of graft copolymers of methyl methacrylate. *Int. J. Pharm.* **149**:233–240 (1997).
16. M. C. Ferrero, A. Muñoz, M. V. Velasco, M. C. Monedero, and M. R. Jiménez-Castellanos. Comparative study on compaction mechanism of a new family of graft copolymers of methyl methacrylate. *16th Pharm. Techn.* **1a**:585–598 (1997).
17. M. V. Velasco, A. Muñoz, M. R. Jiménez-Castellanos, I. Castellano, I. Goñi, and M. Gurruchaga. In vitro evaluation of sustained-release matrix tablets prepared with new modified polymeric carbohydrates. *Int. J. Pharm.* **136**:107–115 (1996).
18. S. Brunauer, P. H. Emmet, and E. Teller. Adsorption of gases in multimolecular layer. *J. Am. Chem. Soc.* **60**:309–619 (1935).
19. B. Schenker and F. Stäger. Influence of the thermal conductivity on the C_p-determination by dynamic methods. *Thermochim. Acta* **304/305**:219–228 (1997).