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TRANSIENT DSC, A NOVEL AND RAPID METHOD FOR ASSESSING PHARMACEUTICAL POWDER COMPACTS

R. Ozao[1*], *M. Ochiai*[1], *Y. Ichimura*[2], *H. Takahashi*[2] *and T. Takano*[3]

[1]North Shore College of SONY Institute, Atsugi, 243-8501
[2]Seiko Instruments Inc., Chiba 261-8507
[3]Waseda University, Tokyo 169-8555, Japan

Abstract

The previously described method involving the use of transient DSC was applied to pharmaceutical powder compacts and to ceramic powder compacts. The samples were prepared by compressing powders of pentaerythritol tetraacetate and two kinds of alumina powder (differing in particle size distribution) up to a pressure of 20 MPa by using a jig. For pentaerythritol tetraacetate, a linear relationship was obtained between the parameter obtained by DSC and the compaction pressure.

Keywords: alumina, aluminum oxide, compact, DSC, particles, pentaerythritol tetraacetate, pharmaceuticals, powder, thermal resistance, transient state

Introduction

When powder compacts are produced by applying pressure to a system consisting of numerous particles, there are changes in the pore size, the contact area between the particles, the particle size and shape, the particle size distribution, etc. An almost linear relationship was earlier found between the electrical conductivities and the strengths of metal powder compacts [1], which was then found to be not always true, due to various uncontrollable factors [2]. The process of compaction is so complicated that the changes cannot be explained by a single mechanism; they also depend on the nature of the material, e.g. whether it is plastic or brittle [2]. Various methods known for the characterization of a powder system, e.g. mercury porosimetry, permeametry, gas adsorption methods, etc., should be used in combination to acquire an adequate understanding of the details of the compaction process. However, from a practical viewpoint, it is sometimes necessary to know the average or macroscopic character of the powder compact quickly without specifying what is responsible for the overall change.

On the other hand, the present-day sophisticated technology and innovations have permitted the development of elaborate TA instruments. For instance by comparing the 1990 and 1997 specifications for the DSC produced by Perkin Elmer [3], it can be understood that the accuracy in measuring temperature remains the same, namely ±0.1°C, but that the error is improved by one digit, i.e. from ±0.1°C in 1990 to

* Author for correspondence: e-mail: ozao@ei.shohoku.ac.jp

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Kluwer Academic Publishers, Dordrecht

±0.01°C in 1997. As concerns the scanning rate, it can now be controlled in 0.01°C min^{-1} steps from 0.01 to 500°C, which can be contrasted with the 0.1°C min^{-1} steps from 0.1 to 200°C in 1990. If the instrument is well maintained and operated properly, the above fact allows the discussion of a change of e.g. 1°C in the measured temperature as a sample-dependent change, which might have been difficult 10 years ago. In other words, this shows that DSC is usable as an instrument to detect changes, or to check for a defective sample from a lot consisting of numerous samples [4].

Thus, the present authors proposed a method based on a novel concept involving the use of DSC [5]; it positively utilizes the transient state instead of the steady state typically used in an ordinary thermal analysis, in which a physical property of the sample is directly related to temperature. The average or macroscopic character of the entire sample can be obtained, e.g. a parameter which represents the compressive force applied to a powder compact [6].

The present paper reports results obtained on compacts of a pharmaceutical powder, pentaerythritol tetraacetate, and compares these with results on alumina powders.

Experimental

Samples

Reagent grade pentaerythritol tetraacetate ($C(CH_2OOCCH_3)_4$, molecular mass 304.30; produced by Tokyo Kasei Kogyo K. K.) was used as received. Also used were commercially available white alumina (α-Al_2O_3) (containing $Al_2O_3 \geq 98.0\%$, $Fe_2O_3 \leq 0.1\%$, and $SiO_2 \leq 1.0\%$; produced by Soegawa Rikagaku K. K.) samples WA220 and WA2500, differing in sample size distribution. WA2500 consists of particles with diameter not greater than 16 μm, with 97% or more not greater than 14 μm, 50% or more not greater than 5.5±0.5 μm, and 94% or more not smaller than 3.0 μm. WA220 consists of particles that all pass through by 106 μm sieve, 15% over 75 μm, 40% over 53 μm and 60% between 53 and 45 μm. For pentaerythritol tetraacetate, the particle size distribution was obtained by using a SALD-2200 laser diffraction particle size analyzer (manufactured by Shimadzu Corporation). The sample was dispersed in water by using a surfactant (detergent) as a dispersant and applying ultrasonic vibration. For pentaerythritol tetraacetate, it was found that 10% of the particles are below 7.86 μm, 50% below 21.84 μm, and 90% below 45.20 μm, with an average particle diameter of 19.63 μm.

Thus, the particle size distributions of the samples are given in the Rosin-Rammler diagram as shown in Fig. 1. The literature value [7] for pentaerythritol tetraacetate is also shown in the Figure.

Preparation of powder compacts for use in DSC measurements

A jig for applying pressure was machined from a micro-pelletizing jig for use in IR analysis. Aluminum sample pans 5 mm in diameter and having the same mass were carefully selected, and 20 mg of each powder sample was placed in the sample pans. The samples were set in the jig and the pressure applied to them was changed to prepare samples differing in compression pressure: 0, 40, 80, 160 and 200 kg cm^{-2} [0 to 20 MPa].

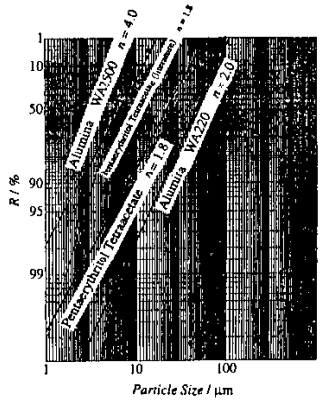

Fig. 1 Particle size distribution of the samples (white alumina WA2500, WA220 and pentaerythritol tetraacetate) expressed in the Rosin-Rammler diagram. A literature value [7] for pentaerythritol tetraacetate is also shown in the Figure

DSC runs

DSC runs were performed by using a DSC6200 (manufactured by Seiko Instruments, Inc.). Aluminum sample pans were mounted on the sample holders by using a robot. The precision expressed by the reproducibility was about 0.75%. For pentaerythritol tetraacetate, the heating started from 20°C. Thus, the samples were each held sufficiently long (15 min) at 20°C in gaseous N_2 flowing at a rate of 30 ml min^{-1}, and heating was then started at a rate of 20 K min^{-1}. To ensure precision, automatic cooling was applied to obtain stable results at room temperature.

For the alumina samples, heating was performed after they had been kept isothermally at 350°C.

All of the samples were each scanned more than three times to ensure repeatability. DDSC peak values were used for the analysis.

Once the method is established less than 10 min in total was necessary for the run of a single sample, inclusive of the time necessary for sample preparation.

Results and discussion

DSC and DDSC curves for pentaerythritol tetraacetate

Figure 2 shows DSC curves and DDSC curves obtained when heating was started from room temperature. It can be seen that, although samples of the same mass are used, the DSC curve is steeper for the powder compacts obtained under a higher compaction pressure, except for that pressed at 15.70 MPa (160 kg cm^{-2}). Accordingly, the DDSC peak value increases with increasing compaction pressure. Table 1 summarizes the results obtained from the DSC runs. The DDSC peak values were read directly and the errors are given in the Table.

Similarly as with the method described previously [8, 9], the DDSC peak value corresponds approximately to $\Delta T/R^2C$, where ΔT is the temperature difference be-

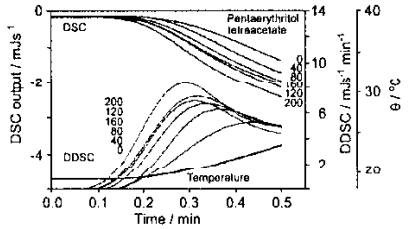

Fig. 2 DSC curves and DDSC curves obtained when heating is started from room temperature for pentaerythritol tetraacetate powder compacts obtained by applying pressures of 0, 40, 80, 120, 160 and 200 kp cm^{-2}

Table 1 Relation between compaction pressure and DDSC peak value

Compaction pressure/		DDSC peak values/ mJ s^{-1} min^{-1}		Deviation/ %
MPa	Kg cm^{-2}			
0.00	0	5.28	5.26	0
3.92	40	6.37	6.27	2
7.85	80	6.87	6.73	2
11.77	120	7.36	7.32	1
15.70	160	6.85	6.96	−2
19.62	200	7.22	8.35	−14

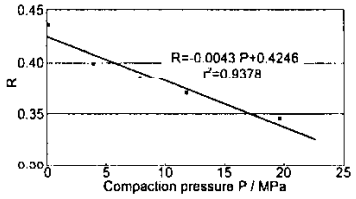

Fig. 3 Change in R with increasing compaction pressure in pentaerythritol tetraacetate powder compacts

tween the sample and the heat bath (source), which is unknown, but is the same for all samples at starting heating, provided that the same heating rate is selected; R is the thermal resistance between the heating source and the sample; and C is the heat capacity of the sample. Since the same heating rate and the same quantity of sample are used, ΔT and C are the same for all the samples. Thus, the DDSC peak value reflects the difference in R. Figure 3 schematically outlines the change in R with increasing compaction pressure. More specifically, the ordinate is R taken as a function of the compaction pressure. It can be seen that R decreases with increasing compaction pressure. Osborne [7] demonstrated that the total intrusion volume decreases approximately linearly with log$P$, where P is the compaction pressure (MPa), and that the median pore size s (μm) decreases as a function expressed by $s=P^n$ up to a

compaction pressure of about 20 MPa. Since the intrusion volume can be related linearly to porosity φ, φ can be expressed by

$$\varphi = c\log P \tag{1}$$

where c is a constant.

According to Woodside and Mesmer [10], the effective thermal conductivity of an unconsolidated particle system can be expressed by $k=k_f^{\varphi}k_s^{1-\varphi}$, where k_f is the thermal conductivity of the fluid (gas) and k_s is the thermal conductivity of the solid. Since the thermal resistance per unit area, the thermal resistivity, is the inverse of conductivity, $R=k^{-1}$, i.e., $R=k_f^{-\varphi}k_s^{\varphi-1}$,

$$\log R = \varphi(\log k_s - \log k_f) - \log k_s$$

or

$$\log R = c'\varphi + c'' \tag{2}$$

where c' and c'' are constants. From Eqs (1) and (2), the following relation can be obtained:

$$R = c''P^{c*}$$

where R is the thermal resistance, P is the compaction pressure, and c'' and c^* are constants. Thus, by assuming $c^*\approx 1$, the relation obtained in Fig. 2 can be understood to be valid.

DSC of white alumina

The particle size distribution of white alumina indicates that WA2500 consists of fine particles, but that there is a deviation from a self-similar particle size distribution. In contrast WA220 exhibits self-similarity in its particle size distribution. Figures 4 and 5 depict the DSC and DDSC curves for WA2500 and WA220, respectively. It can be seen that no systematic relation is observed between the compaction pressure and the DDSC results. This is assumed to be due to the difference in compaction mechanism [2]. Furthermore, it can be seen that consistent results are obtained for WA220. This is consistent with the result obtained previously [5], and confirms the conclusion given therein. Details on alumina powders will be reported elsewhere.

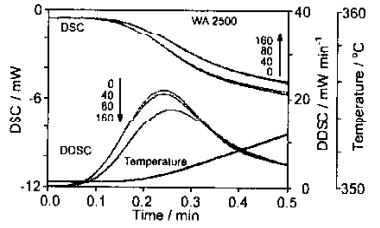

Fig. 4 DSC curves and DDSC curves for WA2500 (alumina)

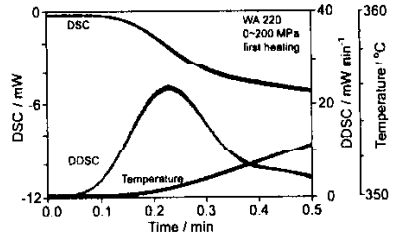

Fig. 5 DSC curves and DDSC curves for WA220 (alumina)

Conclusions

Transient DSC is novel in concept in that a different type of information is acquired from the DSC signal by taking it as a function of time in the transient state of heat flow, and is advantageous in that it takes far less time for the scan and allows the use of a conventional DSC instrument.

In the present case, a linear relationship was obtained between the DDSC peak value and the compaction pressure up to about 20 MPa (with a deviation of 2% or less). This suggests that the compaction pressure is related to the porosity, and indicates that DSC is effective in detecting porosity.

The method is not universal for all types of powders and pressure ranges; applicable ones and ranges should be chosen before this method is employed.

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