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Note

Assessment of tableting properties using infinitesimal quantities of powdered medicine

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Abstract

In the early stage of new drug candidate development, the available quantity of drug substance is limited. In order to carry out preformulation studies of tablets in this stage, a static compression test was carried out with infinitesimal quantity of powder sample using the new Micro Powder Characterizer device. Aspirin, phenacetin, ascorbic acid and ethenzamide were used as model drugs. In this study, the possibility of use of the Micro Powder Characterizer as a device for estimating the tableting properties of each powder sample such as stress displacement curves, tablet tensile strength, stress relaxation rate, and ejection energy was evaluated. In addition, the differences between the Micro Powder Characterizer and the traditional large-scale compression testing machine were compared.

It was found that tableting properties could be estimated by the Micro Powder Characterizer, and that the quantity required to estimate tableting properties was approximately 10 mg per measurement. The results were nearly equal to those obtained with the traditional large-scale compression testing machine. This technique thus appears to be useful for early-stage preformulation studies of new drug candidates.

Keywords: Infinitesimal quantity; Tableting properties; Preformulation; Tablet; Tensile strength

The importance of early-stage preformulation study for accelerating new drug development has been recognized in recent years. In tablet development, estimation of the tableting properties of the drug substance itself is performed in preformulation studies (Graffner et al., 1985; Suiko et al., 2001). However, since the supply of test sample is generally restricted in this stage, the volume provided for estimation of tableting properties is very small. Hence, a drug's own tableting properties must be estimated using infinitesimal quantity of it. The purpose of this study was to examine the possibility of estimating tableting properties using infinitesimal quantities of drug with a new compression machine, the Micro Powder Characterizer.

Aspirin (ASP), phenacetin (PHE), ascorbic acid (VC) and ethenzamide (ETZ) were used as model drugs. ASP, PHE and VC were purchased from Wako Pure Chemicals in Japan and ETZ was purchased from Iwaki Pharmaceutical in Japan. Each sample was classified using sieve apertures of 38 and 75 μm in order to adjust particle size, and samples between 38 and 75 μm were used for experiments. Each sample was used for the test after drying for six hours at 50 °C with a ventilation drier (WFO-450ND,

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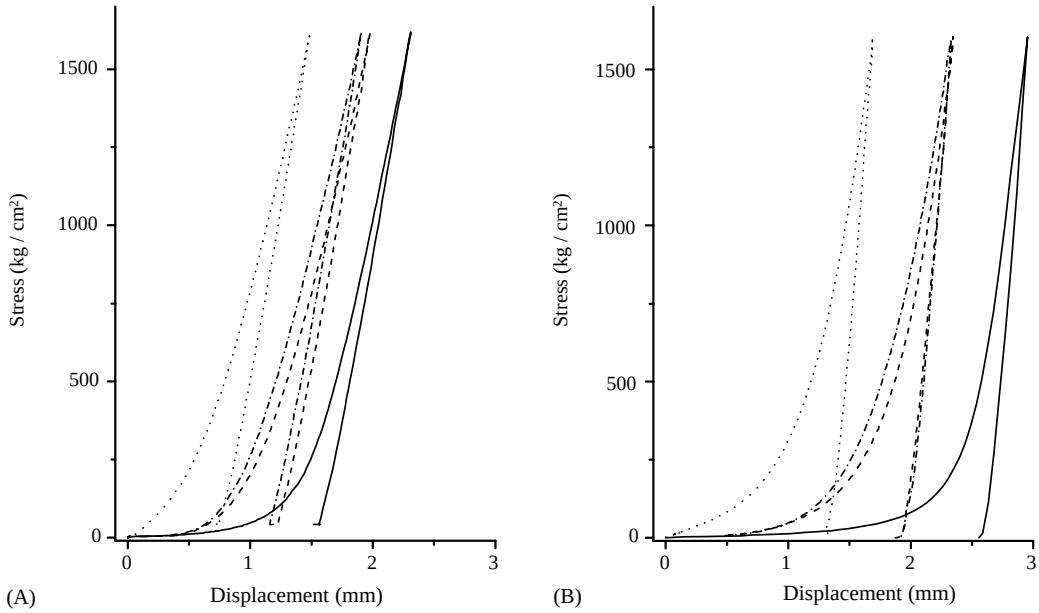

Fig. 1. Stress displacement curves of samples determined by MPC (A) and AG-G (B): (—) ASP; (- - -) PHE; (· · ·) VC; (- · - · -) ETZ.

YAMATO, Japan). The tests were performed using two static compression testing machines, the Micro Powder Characterizer (MPC-100, Okada, Japan) and the Auto Graph (AG5000G, Shimadzu, Japan). For the MPC-100 (MPC) test, a 3 mm diameter flat-faced punch and 11 mg of sample were used, and a 6 mm diameter flat-faced punch and 90 mg of sample were used in tests with the AG5000G (AG-G). Each test was carried out under the same constant conditions, with a compression load of 1600 kg/cm^2 and compression, unloading and an ejection speed of 10 mm/min. All tests were carried out five times. No lubricant was added to estimate drug substance properties. The stress displacement curves of the four model drugs obtained by compression using the MPC and AG-G are shown in Fig. 1. The shape of the stress displacement curve for each drug corresponded to that with AG-G. measurement. Accordingly, MPC measurement with infinitesimal quantity of powder sample was considered useful for estimation of compression properties. In addition, analysis with Cooper's equation (Cooper and Eaton, 1962) indicated that the curve patterns for the MPC and AG-G were almost similar. These results supported that the compression properties of each drug could be estimated in MPC measurement. Then, each tablet was ejected after compression, and ejection energy (area under the ejection stress displacement curve) was calculated referring to the technique described in a previous report (Antikainen and Yliruusi, 1997; Graffner et al., 1985). The ejection energy is shown in Fig. 2 as an absolute value. The rank order of ejection energy of each sample measured by MPC was similar to that measured by AG-G. Furthermore, the absolute value of the ejection energy for each sample measured by MPC would nearly corresponded to the value measured by AG-G if these values were corrected with the size of tablets and die. Accurate elasticity recovery cannot be calculated by the systems of the MPC and AG-G. For this reason, correction for the contact area between the die wall and the tablet was not carried out. It thus appeared that MPC measurement enabled estimation of the ejection force of each drug in infinitesimal quantity. A stress relaxation test was then performed as another method to estimate tableting properties. The punch was halted when the axial force reached the required load, and decay in axial force was recorded for periods up to 120 s. The stress relaxation rate was calculated by a method described in a previous report (Salem et al., 1984) using the stress relaxation curves. The stress

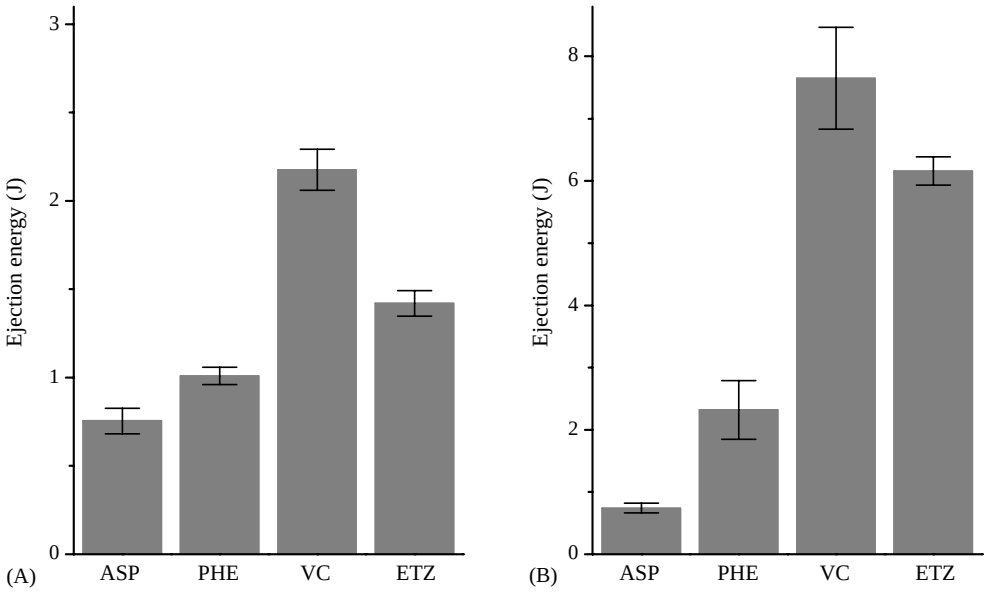

Fig. 2. Ejection energy of samples determined by MPC (A) and AG-G (B).

relaxation rates are shown in Table 1. The relaxation rates for each device suggested that ASP and ETZ readily underwent plastic deformation since their relaxation rates were large, and that VC and PHE were very brittle since their relaxation rates were smaller. The range of the relaxation rate measured with MPC is smaller than that of AG-G. However, it was possible to detect the differences among samples, and the rank order of relaxation rates were similar with that obtained with AG-G measurements. MPC was thus considered useful for estimating a drug's properties in a similar fashion to the traditional large-scale compression testing machine. The hardness of each sample in the diametrical direction was measured. Hardness was determined by a particle hardness tester (GRANO, Okada, Japan) for tablets compressed by MPC, while a motorized tablet hardness tester (Type 6D, SCHLEUNIGER, Switzerland) was used for tablets compressed by AG-G. The thickness and diameter of tablets were determined by a micrometer (Model No.293, Mitutoyo, Japan). The tensile strength of tablets was calculated from Eq. (1) (Summers et al., 1977). Fig. 3 shows the tablet tensile strength of each sample. In MPC compression, it became clear that the rank order of tensile strength of each

$$\mathrm{TS} = \frac{2P}{\pi D t} \tag{1}$$

where TS is the tensile strength (kg/cm^2), P is the tablet hardness (kg), D is the diameter (cm), t is the thickness (cm). Tablet compressed with MPC was the same as that compressed with AG-G. ASP tablet had the highest tensile strength, and PHE and VC tablets had lower tensile strength, indicating that ASP has good compressibility and that PHE and VC have poor compressibility. This result suggested that the interior structure of tablets compressed by the MPC with infinitesimal sample quantity was similar to that of tablets compressed by the AG-G. Each tablet was ejected after compression. Fig. 4. show the thickness

Table 1
Stress relaxation rates determined from plots of stress remaining against log time

Device	Sample	Rate (kg/cm^2) (mean ± s.d.)
MPC	ASP	16.1 ± 1.6
	PHE	14.1 ± 1.6
	VC	8.2 ± 1.2
	ETZ	24.3 ± 1.0
AG-G	ASP	68.7 ± 2.8
	PHE	31.3 ± 1.0
	VC	16.0 ± 0.6
	ETZ	70.2 ± 0.9

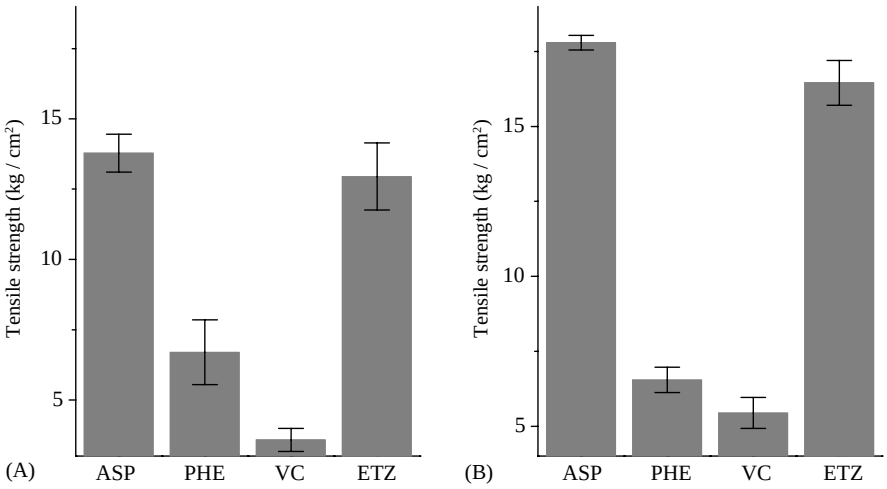

Fig. 3. Tensile strength of tablets compressed by MPC (A) and AG-G (B).

of tablets after elastic recovery. The thickness of each tablet compressed by MPC was almost half of that of the same tablet compressed by AG-G. With both devices, it appeared that the void fraction of each tablet was similar.

The findings of this study suggested that the tableting properties of drugs could be estimated in MPC tests with infinitesimal quantities of sample (only about 10 mg per measurement), while about 90 mg per measurement was needed in the AG-G test. The MPC appeared to be similar in function to the traditional large-scale compression testing machine. Assuming five measurements with the MPC, the quantity of sample needed is about 50 mg. This technique appears to be useful for preformulation studies in early stages of drug development.

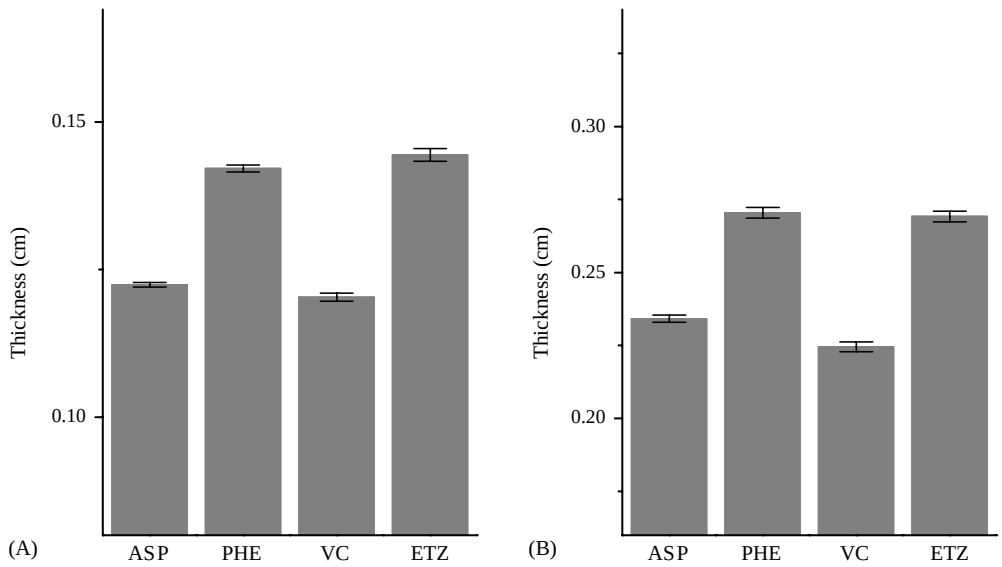

Fig. 4. Thickness of tablets ejected after compression by MPC (A) and AG-G (B).

References

Antikainen, O.K., Yliruusi, J.K., 1997. New parameters derived from tablet compression curves. Part II. Force–displacement curve. Drug Dev. Ind. Pharm. 23, 81–93.

Cooper, A.R., Eaton, L.E., 1962. Compaction behavior of several ceramic powders. J. Am. Ceram. Soc. 45, 97–101.

Graffner, C., Johansson, M.E., Nicklasson, M., Nyqvist, H., 1985. Preformulation studies in a drug development program for tablet formulations. J. Pharm. Sci. 74, 16–20.

Salem, M.S., Fell, J.T., Alkaysi, H.N., Muhsin, N.A., 1984. Stress relaxation of pharmaceutical powders. Acta Pharm. Technol. 30, 312–316.

Suiko, E., Lehto, V.P., Ketolainen, J., Laine, E., Paronen, P., 2001. Dynamic solid-state and tableting properties of four theophylline forms. Int. J. Pharm. 217, 225–236.

Summers, M.P., Enever, R.P., Carless, J.E., 1977. Influence of crystal form on tensile strength of compacts of pharmaceutical materials. J. Pharm. Sci. 66, 1172–1175.