[Chem. Pharm. Bull.]
36(7) 2531—2537(1988)

The Effect of Particle Size on the Compaction Properties and Compaction Mechanism of Sulfadimethoxine and Sulfaphenazole¹⁾

NOBUYOSHI KANENIWA,* KANJI IMAGAWA, and JUN-ICHI ICHIKAWA

*School of Pharmaceutical Sciences, Showa University,
1-5-8 Hatanodai, Shinagawa-ku, Tokyo 142, Japan*

(Received October 9, 1987)

The effect of particle size on compaction properties and compaction mechanism was investigated by using sulfadimethoxine (SD) and sulfaphenazole (SP) as model drugs. The plots of log(mean compaction pressure) against the thickness of the powder bed for SD and SP showed that the compaction proceeded biphasically (primary and secondary compaction) except in the case of the larger particle size fraction (42/48 mesh) for SD, and the compaction process of SD was much more markedly affected by particle size than that of SP. Analysis based on Janssen's equation suggested that the compaction proceeded by a repetitive process of structure formation and fracture. The tensile strength of SP tablets was higher than that of SD tablets, and the change in the fractional voidage indicated that all particle size fractions of SP gave tablets having the same structure. On the other hand, for SD, the larger particle size fractions showed higher tensile strength than the smaller particle size fractions in the initial compression pressure region, and measurement of the compaction energy indicated that the binding between the particles in the larger particle fractions was more effective than that of the smaller particle size fractions in that region. These results suggested that the compaction process of SD involves particle fragmentation, while that of SP involves mainly plastic deformation.

Keywords—tablets; tensile strength; compaction; particle size; fragmentation; plastic flow; energy; sulfadimethoxine; sulfaphenazole

Introduction

The mechanism of compaction of pharmaceutical particulate materials is of importance in relation to the friability, disintegration, and dissolution behavior. It is known that the compaction properties are affected by the particle size,²⁻⁷⁾ shape,^{2,3,8)} the material species,⁹⁾ *etc.* Different stages of compaction have been distinguished^{10,11)} and the classification of compaction properties of materials¹²⁻¹⁶⁾ has been attempted in order to obtain information on the mechanism of the compaction. Concerning the binding between particles, it has been proposed that sintering and asperity melting take place locally at the contact points between asperities on particles.^{14,17-21)} The purpose of the present study was to investigate the effect of the particle size on the compaction properties and compaction mechanism of sulfadimethoxine (SD) and sulfaphenazole (SP) as model drugs.

Experimental

Materials—SD and SP (Dainippon Seiyaku Co., Ltd.) were used. The materials (SD and SP) were each separated, by the use of J.I.S. sieves (42—200 mesh) on a sonic sieve tester made in this laboratory, into nine different particle size fractions.

Compression Apparatus and Procedures—Figure 1 shows a schematic diagram of the compression apparatus. Tablets were prepared by using a single-punch eccentric tableting machine (type KS-2; Nichiei Seiko Co., Ltd.) with a flat-faced punch of 10 mm diameter. The lower punch was fixed. One side of the upper punch carried a load cell

Fig. 1. Block Diagram of the Compression Apparatus

Fig. 2. Schematic Diagram of the Apparatus for the Measurement of Tablet Hardness

(LC/2C; Shinkoh Co., Ltd.), and four strain gauges (type B-FAE-1S-12 T11; Shinkoh Co., Ltd.) were fixed around the shank of the lower punch and connected as a Wheatstone bridge. Variation of electric resistance during the compression was converted to a change of voltage by a strain amplifier (upper punch 6M56A, lower punch 6M52; San-ei Sokki Co., Ltd.), and the amplified signal was recorded on a magnetic oscillograph (5L31; San-ei Sokki Co., Ltd.). Displacement of the upper punch was measured by using a noncontact displacement transducer (Shin Nippon Sokki Co., Ltd.). The punch distance was converted to electric voltage by an amplifier (6L5; San-ei Sokki Co., Ltd.) and was also recorded on a magnetic oscillograph. The upper and lower punches and the die wall were thoroughly cleaned with acetone, then lubricated with 5% stearic acid solution in chloroform, and dried before each compression. The powder (200 mg) was put into the die and compressed using a range of upper punch pressures at a machine speed setting of one tablet/21 s. The thickness of the tablet was measured with a micrometer. The fractional voidage of the tablet was obtained from the dimensions of the ejected tablet.

Tensile Strength—Tablet hardness was determined by the application of the diametrical compaction test. The apparatus was made in our laboratory and the loading rate was 20 g/s. Figure 2 shows a schematic diagram of the apparatus. In order to compare the strength of tablets of different thickness and porosity, the tablet hardness was recalculated with respect to tensile strength in accordance with Newton *et al.*²²⁾ Tensile strength of a tablet is given by:

$$\text{tensile strength} = \frac{2P}{\pi Dt(1-\varepsilon)} \quad (1)$$

where P is the force applied diametrically at fracture and D , t , and ε are the diameter, thickness, and porosity, respectively, of the tablet.

Compaction Energy—The upper punch work was calculated by integration of upper punch pressure *versus* upper punch displacement.²³⁾ The expansion work was estimated from the decompression curve. Jarvinen and Juslin²⁴⁾ found that the particle displacement depends linearly on the distance from the lower punch and that axial force distribution decreases exponentially from the upper punch to the lower punch, and they proposed the following equation for the frictional work at the die wall

$$W = \int_{h_1}^{h_2} (P_U - (P_U - P_L)/\ln(P_U/P_L)) dh \quad (2)$$

where the height of the powder column changes from h_1 to h_2 during the compaction. Accordingly, the compaction energy is obtained by subtracting from the upper punch work both the expansion work and the friction work evaluated by Eq. 2.

Size Analysis—For size analysis of the intact powder of SD or SP, the powder was added to ethylene glycol-water solution saturated with SD or SP. The suspension was subjected to size analysis in a micron photosizer (model SKN 500) of Seishin Kigyo Co., Ltd. For size analysis of the tableted SD or SP, the tablet was added to ethylene

glycol–water solution saturated with SD or SP, and the aggregates were broken mechanically with a scalpel. The suspension was then dispersed with an ultrasonic probe for 30 s and subjected to size analysis. The viscosity of the solution was measured with a Ubbelohde-type viscometer (Kusano Kagaku Kikai Seisakusho Co., Ltd.).

Results and Discussion

Compression Curve and Transmission of Compression Pressure

Bal'shin²⁵⁾ examined various materials and observed a logarithmic relationship of the form

$$\log P_a = C_1 V_r + C_2 \quad (3)$$

where C_1 and C_2 are constants, V_r is the relative volume of the tablet, and P_a is applied pressure. Train¹⁰⁾ made a detailed study on the effect of pressure on V_r and concluded that the consolidation proceeded in four stages. Equation 3 may be rewritten in the form:

$$\log P_a = -C_3 t + C_4 \quad (4)$$

where C_3 and C_4 are constants and t is the thickness of the powder bed. Figure 3 presents plots of $\log P_a$ versus t for SD and SP, respectively. The plots indicated that the compaction process was biphasic, proceeding through linear primary and secondary compaction stages except in the case of the largest size fraction (42/48 mesh) for SD. For both SD and SP, the smaller the particle size was, the higher the compression pressure needed to produce the same thickness of powder bed. The compaction process for SD was more markedly dependent on particle size than was that for SP. The plots of the slope of Eq. 4 against the particle size in the two compaction stages of both SD and SP are shown in Fig. 4. In the primary compaction stage,

Fig. 3. Relation between Common Logarithm of Compression Pressure and Thickness of the Powder Bed

(A) SD, (B) SP. ○, -42+48 mesh; △, -48+60 mesh; ▽, -80+100 mesh; □, -170+200 mesh.

Fig. 4. Effect of Particle Size on the Slope of the Plot of Common Logarithm of Compression Pressure against Thickness of Powder Bed

△, primary compaction stage of SD; ○, secondary compaction stage of SD; ▽, primary compaction stage of SP; □, secondary compaction stage of SP.

Fig. 5. Relation between Natural Logarithm of the Ratio of Lower to Upper Punch Pressure and Thickness of the Powder Bed

(A) SD, (B) SP. $\circ$, -42+48 mesh; ∇ , -80+100 mesh; $\square$, -170+200 mesh.

Fig. 6. Relation between Tensile Strength of Tablets and Mean Compression Pressure for SP

$\circ$, -42+48 mesh; ∇ , -80+100 mesh; $\square$, -170+200 mesh.

Fig. 7. Relation between Tensile Strength of Tablets and Mean Compression Pressure for SD

$\circ$, -42+48 mesh; $\triangle$, -48+60 mesh; —, -60+65 mesh; ----, -80+100 mesh; - · -, -170+200 mesh.

the slopes for both SD and SP were almost the same and were independent of particle size. On the other hand, in the secondary compaction stage, the slope for SD was steeper than that for SP; further, the slope of SP was independent of particle size, whereas that of SD increased with particle size. These results suggest that SP is a ductile material, that is, the compaction process of SP involves mainly plastic deformation, since it was little affected by the particle size. On the other hand, the compaction process of SD may involve mainly particle fragmentation.

Janssen²⁶⁾ examined the transmission of the compression pressure when powder was compressed from one side of a cylindrical container, and presented the following equation

$$P_L/P_U = \exp(-4\mu KH/D) \quad (5)$$

P_L is the lower punch pressure, P_U is the upper punch pressure, μ is the coefficient of die wall friction, K is the ratio of the horizontal pressure to the normal pressure, H is the powder bed thickness and D is the diameter of the die. In Eq. 3, both μ and K are assumed to be constant. The plots of the pressure-transmission ratio against the tablet thickness for SD and SP are shown in Fig. 5. The ratio of P_L/P_U for each powder did not increase monotonously, but

showed a wavelike increase with increase of the compression pressure. This result seems to suggest that the compaction process proceeded by repetitive structure formation and fracture. However, Fig. 5 did not reveal a clear distinction of compaction properties between SD and SP.

Tensile Strength

The relationships between tensile strength of tablet and mean compression pressure (calculated as the average of the upper and lower punch pressure) for various particle size fractions of SP and SD are shown in Figs. 6 and 7, respectively. Tensile strength increased linearly with the compression pressure in all particle size fractions of SP, and a decrease in the particle size resulted in an increase in the tensile strength of the tablet for a given applied pressure. The tensile strength of SP tablets was higher than that of SD tablets. Further, for larger particle size fractions of SD (42/48 and 48/60 mesh), the relationship was no longer linear, and higher tensile strength than for the smaller particle size fractions was obtained in

Fig. 8. Relation between Tensile Strength of Tablets and Fractional Voidage

(A) SD, (B) SP. $\circ$, -42+48 mesh; $\triangle$, -48+60 mesh; ∇ , -80+100 mesh.

Fig. 9. Relation between Compaction Energy and Mean Compression Pressure

(A) SD, (B) SP. $\circ$, -42+48 mesh; $\triangle$, -80+100 mesh; $\square$, -170+200 mesh.

Fig. 10. Relation between Compaction Energy and Tensile Strength

Symbols: as in Fig. 9.

the low range of applied pressure. It may be considered that the compression pressure and binding force per contact point were larger for the large particle size fraction in that pressure region, since the numbers of contact points were relatively few compared with the smaller particle size fractions. Figure 8 shows plots of the tensile strength of tablets against fractional voidage for SD and SP. Tensile strength of tablets prepared from larger particle size fractions (42/48 and 48/60 mesh) of SD showed a rather consistent increase with decreasing fractional voidage, while tablets from the small particle size fraction (80/100 mesh) of SD showed a precipitous increase at below a certain fractional voidage. These effects of particle size indicated that the main deformation mechanism for SD was fracture of the initial particles. On the other hand, no particle size dependence was seen in the case of SP, and the tensile strength of tablets of SP increased logarithmically with decrease of fractional voidage. This is expected for a material that deforms by a mechanism involving plastic flow.

Compaction Energy

Figure 9 shows plots of the compaction energy against the compression pressure for SD and SP. For SP, the relationship was almost independent of particle size, and the compaction energy increased linearly with increase of the compression pressure. For SD, on the other hand, a decrease in the particle size resulted in an increase in the compaction energy for a given applied pressure. The plots of the compaction energy against tensile strength for SD and SP are shown in Fig. 10. Particle size had little effect on the relationship in the case of SP at lower compaction energies (lower compression pressures). However, in the case of SD, the larger particle size fraction (42/48 mesh) gave a higher tensile strength than the smaller particle size fraction for the same compaction energy in the lower compression pressure region. This result suggested that the binding between the particles of the larger particle size fraction (42/48 mesh) was far more effective than that of the smaller particle size fraction in that region. However, the compaction energy for the larger particle size fraction (42/48 mesh) increased steeply with increasing tensile strength at the next compaction stage. This suggests that the compaction energy was mainly consumed for the fracture of particles at this compaction stage. Consequently, it is considered that SD is compacted by a mechanism of brittle fracture, whereas SP is compacted mainly plastic deformation, that is, SP is a ductile material. Furthermore, SP tablets showed higher tensile strength than SD tablets at the same compaction energy, suggesting that the compaction energy for SP was more effectively consumed for binding between the particles, compared with the case of SD.

Fig. 11. Relation between Ratio of Particle Size after to before Compression and Mean Compression Pressure for SD

○, -42+48 mesh; △, -48+60 mesh; ▽, -80+100 mesh; □, -170+200 mesh.

Particle Size Change after Compression

The changes in particle size of SD after compression are shown in Fig. 11. The particle size of SP after compression could not be measured because SP mainly underwent plastic deformation, and the particles could not be separated. This is of significance in tablet dissolution, as an increase in surface area will increase the rate of dissolution of tablets made from drugs of low solubility. The particle size of the 42/48 and 48/60 mesh fractions decreased, whereas the particle size of the 170/200 mesh fraction increased with increase of the compression pressure. It is clear that the larger size fractions are crushed, while the smaller size fractions are agglomerated. This implies the existence of a critical size of SD particles where the effects of binding and fragmentation counterbalance each other, and this critical size lies in the vicinity of 80/100 mesh.

References and Notes

- 1) Presented at the 101st Annual Meeting of the Pharmaceutical Society of Japan, Kumamoto, April 1981.
- 2) O.Y. A. Alpar, J. A. Hersey, and E. Shotton, *J. Pharm. Pharmacol.*, **22**, Suppl., 1S (1970).
- 3) C. A. Walton and N. Pilpel, *J. Pharm. Pharmacol.*, **24**, 10P (1972).
- 4) Coy L. Huffine and C. F. Bonilla, *J. A. I. Chem. E.*, **8**, 490 (1962).
- 5) Y. B. G. Varma and D. Venkateswarlu, *Chemical Process. Eng.*, **48**, 77 (1967).
- 6) A. M. Sakr, H. M. El-Sabbagh, and M. S. Mesiha, *Manuf. Chem. Aerosol News*, **44**, 29 (1973).
- 7) J. E. Carless and A. Sheak, *J. Pharm. Pharmacol.*, **28**, 17 (1976).
- 8) M. P. Summers, R. P. Enever, and J. E. Carless, *J. Pharm. Sci.*, **66**, 1172 (1977).
- 9) E. T. Cole, J. E. Rees, and J. A. Hersey, *Pharm. Acta Helv.* **50**, Nr. 1/2, 28 (1975).
- 10) D. Train, *J. Pharm. Pharmacol.*, **8**, 745 (1956).
- 11) T. Anmo, M. Washitake, T. Kurashige, M. Naritomi, H. Ono, and M. Asno, *Yakugaku Zasshi*, **88**, 857 (1968).
- 12) J. Okada and Y. Fukumori, *Chem. Pharm. Bull.*, **23**, 326 (1975).
- 13) S. Leigh, J. E. Carless, and B. W. Burt, *J. Pharm. Sci.*, **56**, 888 (1967).
- 14) P. York and N. Pilpel, *J. Pharm. Pharmacol.*, **25**, Suppl., 1P (1973).
- 15) J. S. Hardman and B. A. Lilley, *Nature (London)*, **228**, 353 (1970).
- 16) J. A. Hersey and J. E. Rees, *Nature (London)*, **230**, 96 (1971).
- 17) A. S. Rankell and T. Higuchi, *J. Pharm. Sci.*, **57**, 574 (1968).
- 18) P. York and N. Pilpel, *J. Pharm. Pharmacol.*, **24**, Suppl., 47P (1972).
- 19) N. Pilpel and S. Esezobo, *J. Pharm. Pharmacol.*, **29**, 389 (1977).
- 20) J. R. Britten and N. Pilpel, *J. Pharm. Pharmacol.*, **30**, 673 (1978).
- 21) R. C. Rowe, P. H. Elworthy, and D. Ganderton, *J. Pharm. Pharmacol.*, **25**, Suppl., 12P (1973).
- 22) J. M. Newton, G. Rowley, J. T. Fell, D. G. Peacock, and K. Ridgway, *J. Pharm. Pharmacol.*, **23**, Suppl., 195S (1971).
- 23) N. Kaneniwa, K. Imagawa, and M. Otsuka, *Chem. Pharm. Bull.*, **32**, 4986 (1984).
- 24) M. J. Jarvinen and M. J. Juslin, *Farm. Aikak.*, **83**, 1 (1974).
- 25) M. Yu. Bal'shin, *Vestnik Metalloprom.*, **18**, 124 (1938).
- 26) H. A. Janssen, *Z. V. D. I.*, **39**, 1045 (1895).