Compression of Pharmaceutical Powders I

Theory and Instrumentation

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Considering that compression of a powder bed involves time dependent flow, it is reasonable to expect that this process would exhibit viscoelastic properties. To test this concept, an instrument was developed to measure stress relaxation of a powder bed under constant strain. Preliminary relaxation data obtained on several powders indicated correlation with physical properties of the compacts. Tests of factors known to influence tablet capping, hardness, and friability showed that these factors also had marked effect on relaxation data.

THE RECENT DEVELOPMENT of special feeding devices for tableting presses has made it possible to compress powders directly into uniform tablets without the usual granulation steps. The obvious savings in equipment, labor, and time effected by this processing shortcut, including better dose uniformity and smaller dosage size, make the ability to tablet all pharmaceutical powders directly highly desirable. However, many of these materials cannot be compressed into suitable tablets without prior treatment. At the present time the lack of basic knowledge of tableting mechanism has seriously hindered the elucidation and solution of this problem.

A great majority of the published work on pharmaceutical tableting has been directed toward the evaluation of excipients such as binders, lubricants, and disintegrants. Only recently have systematic efforts been made to define the mechanism of compression (1–9), but the majority of these studies have dealt with the behavior of granules under pressure. Considerable investigation into powder compression has been conducted in other applications, notably in the fields of powder metallurgy and ceramics. The types of materials studied, however, have few physical properties in common with most pharmaceutical powders.

Huffine (10), using the methods pioneered by Walker and Balshin, obtained correlations between quasi-equilibrium pressure-volume behavior and principle compression mechanisms for a number of powders, including some of pharmaceutical interest. He postulated a general theory for powder compaction based on the existing literature and his results. Assuming that this theory is valid, compaction may be visualized as a composite of several processes: particle diffusion into void space, fracture, elastic deformation, plastic deformation, and cohesion between particle surfaces. It is probable that these processes occur simultaneously, although not necessarily to the same degree, at any stage in the compression cycle. Also, in practice, tablets are formed by a process more closely related to impact loading, and the degree of air expulsion during initial pressure loading may have a pronounced effect on tablet quality. This effect was not considered by Huffine since it is not likely to be important in equilibrium studies, except in rare instances.

Considering that all of these processes depend on flow and thus are probably time dependent, it would be unrealistic to expect quantitative correlation between equilibrium studies and tablets produced under nonequilibrium conditions. Thus, the effect of one process may predominate in very short compression times, yet could be completely overshadowed when longer experimental times are used. In fact, it is probable that compression data can have physical meaning in terms of a tableting process only if they are obtained in equivalent time periods and with equivalent loading rates.

Nonequilibrium data are necessary to investigate these concepts. Such data on non-Newtonian flow systems are usually obtained through the measurement of stress relaxation under constant strain and creep under constant

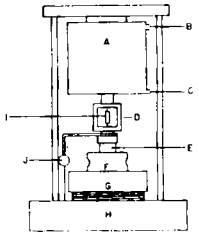

Fig. 1.—Apparatus for studying powder bed stress relaxation under constant strain. Key: A, cylinder and piston; B, compressed air; C, port used to raise piston; D, force transducer; E, tablet punch; F, tablet die, 0.5 in. i.d.; G, adjustable platen; H, base; I, signal from transducer; J, dial micrometer.

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stress (11). It was felt that such techniques could be employed advantageously for the study of powder compression. This communication reports the results obtained in the initial exploration of these considerations.

EXPERIMENTAL

Instrumentation.—A Carver press formed the nucleus of the apparatus shown schematically in Fig. 1. A piston driven by compressed air was used in place of the hydraulic loading system to obtain pressure loading rates approaching more closely those of high-speed rotary presses. The maximum rate obtained with this equipment using a $^1/_2$-in. punch was 10^4 p.s.i./second, giving a maximum pressure of 18000 p.s.i. in 1.8 seconds. Dimension was such that the piston was forced against the bottom of the cylinder when the force on the piston top exceeded the force on the powder bed. This insured a fixed movement of the upper punch so that data at constant strain could be obtained. Pressure on the powder bed as a function of time was obtained by installing a Daytronic model 140-5K force transducer between the piston ram and the upper punch. The demodulated signal (Daytronic model 200H) was recorded on a Varian G-14 recorder. Movement of the upper punch was measured by fastening a dial micrometer to the upper punch assembly. All studies were made using dies lubricated with stearic acid.

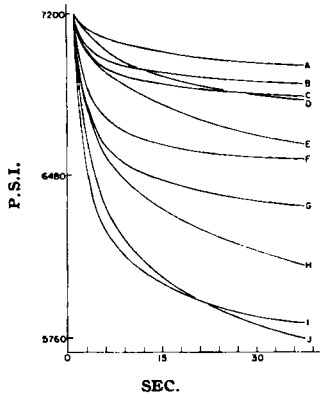

Fig. 2.—Relaxation curves for powder beds. Key: A, 70/100-mesh glass spheres; B, sulfathiazole I; C, crystalline lactose; D, aspirin crystals; E, sodium *p*-aminosalicylate; F, spray dried lactose; G, amorphous lactose; H, sodium chloride crystals; I, cornstarch; J, magnesium trisilicate.

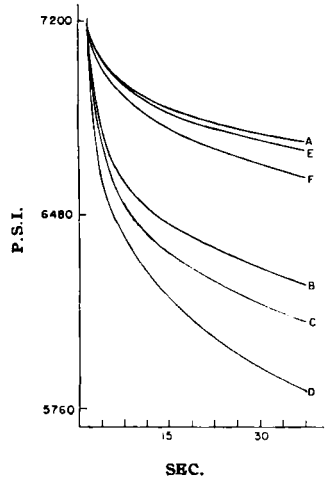

Fig. 3.—Effect of particle size and size distribution on relaxation curves. Key: A, 20/40 salicylamide; B, micronized salicylamide; C, 80/120 sodium chloride; D, <230 sodium chloride; E, 80/120 sodium PAS; F, 40/200 sodium PAS.

Stress Relaxation Results.—Several pharmaceutical powders were chosen on the basis of varied tableting properties for initial stress relaxation measurements. No attempt was made to control such known variables as particle size, size distribution, or moisture since only qualitative information was sought. Consequently, these powders were tested directly as received from respective suppliers, the only modification being the incorporation of 1% stearic acid. Preliminary compression tests were used to determine the weight of each material required to form a tablet or compressed bed of fixed thickness at 7200 p.s.i. Stress relaxation data for all of these materials were then obtained by suitable adjustment of the bottom platen to give a maximum recorded pressure of 7200 p.s.i. Figure 2 shows that the results of this series varied widely between the small relaxation of relatively incompressible 70/100-mesh glass spheres to the large relaxation of starch and magnesium trisilicate. In either of these two extremes, a suitable tablet was not formed. Except for aspirin, those materials forming good tablets by direct compression all showed medium relaxation. The relaxation of aspirin was in the same low range as that obtained for materials giving poor tablets. All of these materials except the glass sample were compressed at three pressures and three compression speeds on a Colton 216 rotary press equipped with a Colton force feed attachment.

Since particle size and size distribution are known to affect the tablet forming properties of powders, relaxation measurements were made on 80/120 and <230-mesh sodium chloride, 20/40-mesh and micronized salicylamide, and 80/120 and 40/200-mesh sodium PAS. Figure 3 shows that for each material the degree of relaxation was dependent upon the size or size distribution.

Sodium PAS samples were equilibrated at five relative humidities and relaxation data were obtained. Figure 4 shows the effect of humidity on relaxation for this series. Qualitative correlation with physical properties of the resulting compacts showed increasing hardness and decreasing friability with decrease in moisture.

Because strain could not be applied instantaneously, the effect of loading rate on relaxation was investigated. The equation describing the relationship between stress, P, strain, $\Delta V/V$, and time, t, for viscoelastic compression is

$$\frac{P_t}{(\Delta V/V)_t} = \sum_{i=1}^{n} \frac{P_i}{(\Delta V/V)_i} e^{-t/\tau_i} \quad \text{(Eq. 1)}$$

where the subscript i refers to the ith element relaxing from an initial stress and strain. Differentiating with respect to time gives

$$\frac{-dp}{dt} = \sum_{i=1}^{n} \frac{P_i}{\tau_i} e^{-t/\tau_i} \quad \text{(Eq. 2)}$$

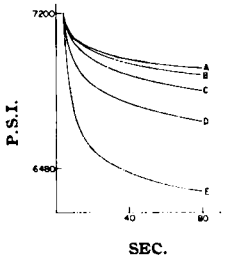

Fig. 4.—Effect of moisture on relaxation curves for sodium PAS stored at various relative humidities. Key: A, 85%; B, 75%; C, 33%; D, 22%; E, ~0%.

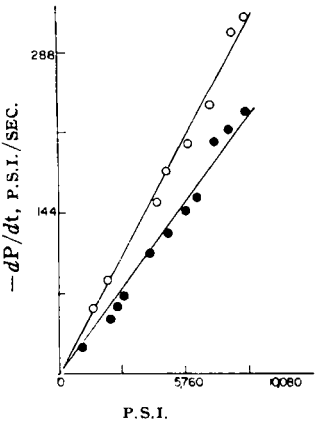

Fig. 5.—Effect of maximum pressure on initial relaxation slope for sodium chloride. Key: O, 1.8 seconds loading time; ●, 3.4 seconds loading time.

for the case $\Delta V/V$ constant. For a specific time period, a, the exponentials are constant and

$$\frac{-dp}{dt} = \sum_{i=1}^{n} \frac{e^{-a/\tau_i}}{\tau_i} P_i \qquad \text{(Eq. 3)}$$

Equation 3 reduces to

$$\frac{-dp}{dt} = k P \qquad \text{(Eq. 4)}$$

for all elements relaxing from an initial pressure P at fixed time. Accordingly, relaxation data for sodium chloride samples compressed at several pressures (weight and platen adjusted to keep $\Delta V/V$ constant) were obtained at two loading rates. Figure 5 is a plot of initial $-dp/dt$ against maximum pressure obtained at 1.8 seconds for 1.8-second loading time and 3.4 seconds for 3.4-second loading time.

DISCUSSION AND CONCLUSIONS

These preliminary studies were conducted to ascertain the feasibility of using stress relaxation data to investigate powder compaction. On the basis of the results obtained, the techniques appear to be valuable. Even though instrumentation was crude, evidence was obtained to show that factors known to affect tableting also had effects on stress relaxation data. The fact that seemingly anomalous behavior appears in some of these results is undoubtedly due to lack of experimental control or inadequate knowledge of the compression mechanism.

Certainly, correlation between tablet quality and bonding strength, surface area and porosity of the tablet, elastic compressibility, relaxation, particle size and shape, bulk density and flow properties of the powder may be expected. The technique reported in this communication is useful for studying elastic compressibility, relaxation, and flow under pressure. These important properties have received little attention in past studies on pharmaceutical powders; their measurement should help in understanding powder compression.

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Notes

Mode of Action of Endomycin-Neomycin Synergism

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The mode of action for endomycin-neomycin synergism against *Candida albicans* was postulated to be an action of endomycin which influences permeability of the cell membrane and facilitates the entry of neomycin in the cell. A neomycin-resistant strain was also found to be resistant to endomycin, but the combination of antibiotics was still synergistic. The permeability hypothesis of endomycin was strengthened by data showing that the cell membrane barrier was less resistant to increasing osmotic pressure in the presence of endomycin.

ENDOMYCIN is an antifungal and antibacterial complex of agents first described by Gottlieb, *et al.* (1). Endomycins A and B were reported to be synergistic with neomycin against *Candida albicans* UC1392 (2). Because endomycin lowers the surface tension of water and hence acts like a detergent, a cell wall permeability change has been postulated to be a factor in the synergism of endomycin and neomycin; presumably endomycin facilitates the passage of neomycin through the cell membrane. A precedent for this detergent type of synergistic activity was reported by Sokolski, *et al.* (3), and by Karaila (4).

One approach to show that endomycin affects the cell wall permeability was to use an organism which was resistant to neomycin. According to our hypothesis, the resistant organism should be sensi-

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