

Physics of Tablet Compression XV

Thermodynamic and Kinetic Aspects of Adhesion Under Pressure

By ALBERT S. RANKELL and TAKERU HIGUCHI*

A theoretical analysis has been made of the processes by which interparticle adhesion can occur during the compression of tablet granulations in the absence of added fluid adhesives. A reasonable explanation for the development of adhesion in these systems is based on the occurrence of either partial fusion or partial dissolution at the surfaces of the particles induced by energy added during the compression. The possibility that these phenomena do occur gains partial support from an examination of the thermodynamics and kinetics of surface processes that may take place. The Clapeyron equation cannot be applied directly to these processes, but must be modified to take into account the nonuniformity of the pressures exerted on the particles during compression. Another factor which may affect particle adhesion is the production of highly localized frictional heat and slow diffusion of this heat from the particle surfaces into their interior.

THE PROCESSES by which powder particles are made to adhere by compression in a tablet press are not well understood. Pharmaceutical literature concerning the mechanism of interparticle bonding in compressed tablets is not extensive, and most studies applicable to this area are found in the literature of powder metallurgy and of solid friction (1, 2). This report is concerned with theoretical examination of physical processes that may be responsible for compressive bonding of ingredients of pharmaceutical tablets.

In a summary of existing theories of bonding and sintering in powder metallurgy, Goetzl (3, 4) finds three proposed mechanisms to be worthy of extended discussion: (a) interatomic forces (surface adhesion, cold-welding, and surface tension), (b) liquid surface cements, and (c) mechanical interlocking. The liquid surface cement mechanism, which attributes adhesion to the presence of thin films of liquid at the interface between the particles being compressed, has much to recommend it in the analysis of binding in tablets.

Tablet triturates obviously require the presence of liquid at the interparticular interface during their production. The use of solutions of polymeric materials as binding agents for compressed tablets is common knowledge (5, 6) as is the importance of granulation humidity (7, 8). It is possible, however, to compress some materials into tablets without the addition of a binding

agent. For such materials, the liquid cement mechanism would indicate that the cementing film is the product of fusion or solution at the particle surface induced by the energy added during the compression.

The reason why substantial melting has not been observed during the compression of commonly tableted materials can be made clear by consideration of a single case. It has been shown that the energy expended in the compression of a 400-mg. sulfathiazole tablet is in the order of 2 calories (9). Assuming that all of the energy expended appears as heat, the resultant temperature rise of the tablet would be only about 5°. This temperature is nowhere near the normal melting point of the material being tableted.

EFFECT OF STRESS DISTRIBUTION ON MELTING POINT

During the compression process, however, conditions at the surfaces of the particles are radically different from those in the particle interior. The load applied by the upper and lower punches is exerted only on particles directly in contact with the punch surfaces. The stresses on the rest of the particles in the mass are the result of particle-to-particle contact. The irregular surface of the particles causes each individual point of contact to have a very small area; thus, the pressures involved are extremely large.

The relative magnitude of these effects is demonstrated by a measurement of the real area of contact between two flat steel plates under pressure (10). It was found that when the surfaces were pressed together under a load equivalent to 4.6 Atm., the true area of contact was only 1/2000 of the apparent macroscopic area. Thus, the pressure at the points of contact was actually 9200 Atm.

Clapeyron Equation—The high pressure at the points of contact have a definite effect on the melting point of the substance being compressed. A relationship between pressure and melting point derived from thermodynamic considerations is the

Received August 11, 1967, from the School of Pharmacy, University of Wisconsin, Madison, WI 53706

Accepted for publication October 13, 1967.

Presented to the Basic Pharmaceutics Section, APHA, Academy of Pharmaceutical Sciences, Las Vegas meeting, April 1967.

This investigation was supported in part by grant GM-05830 from the National Institutes of Health, U. S. Public Health Service, Bethesda, Md., American Chicle Co., Warner-Lambert Pharmaceutical Co., Long Island, N. Y.

Previous paper: Higuchi, T., Shimamoto, T., Eriksen, S. P., and Yashiki, T., *J. Pharm. Sci.*, **54**, 111 (1965).

* Present address: 314 Malott Hall, Lawrence, KS 66045

Clapeyron equation (11):

$$dT/dP = T(V_L - V_S)/\Delta H \quad (\text{Eq. 1})$$

where: dT/dP is the change in melting point with pressure, T is the absolute temperature, V_L is the volume per mole of the liquid melt, V_S is the volume per mole of the solid, and ΔH is the molar latent heat of fusion.

The latent heat of fusion is positive, thus, the Clapeyron equation predicts that for a solid which expands on melting ($V_L > V_S$), the melting point is increased by raising the pressure, while for a solid which contracts on melting ($V_L < V_S$), the melting point is lowered by increasing the pressure. Except for a few substances, such as water, most solids expand on melting.

Thus, Eq. 1 would indicate that during tablet compression, the rise in melting point with pressure for most substances would make it highly unlikely that fusion could take place. The Clapeyron equation, however, is derived for an ideal process in which the solid is exposed to uniform hydrostatic pressure, and which is thermodynamically reversible. In the case of tablet compression, on the other hand, the process is essentially nonreversible, and the pressure exerted on each particle is far from uniform.

Thermodynamics of Stressed Solids—Thermodynamic relationships for particles being compacted in a tablet press must take into account the stress distributions induced by the point pressures involved. The Clapeyron equation is derived by equating the Gibbs free energies of the two phases of the equilibrium:

$$\text{liquid } (V_L) \rightleftharpoons \text{solid } (V_S) \quad (\text{Eq. 2})$$

At constant temperature and pressure, the equation is of the form:

$$dF_L = dF_S = V_L dP - S_L dT = V_S dP - S_S dT \quad (\text{Eq. 3})$$

which reduces to Eq. 1. If the system is not under constant pressure, but is subjected to nonhomogeneous stress, the free energy, dF , is a function of the strain, and must be represented in a suitable form, such as that suggested by Li and co-workers (12):

$$dF = \int (\epsilon_i \sigma_i d\epsilon_i) dV - S dT \quad (\text{Eq. 4})$$

where: σ_i is one of the six components of the stress, and ϵ_i is the corresponding strain component. In such a case, the derivation of an equation corresponding to the Clapeyron equation would be quite involved.

Stressed Beam Analogy—The effect of stress distribution on particle melting points during compression can be more easily illustrated by the following analogy. Consider a crystal which is supported at each end and which is subjected to a point pressure on its upper surface, as shown in Fig. 1. For ease in mathematical treatment, the

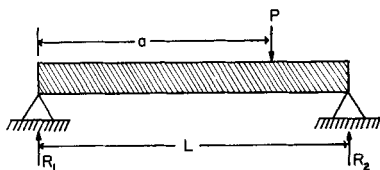


Fig. 1—Point loading on a simply supported beam.

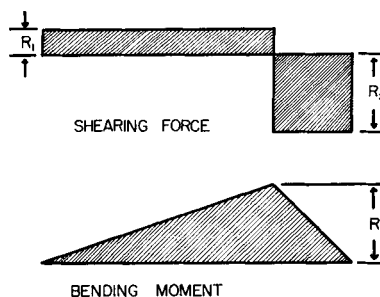


Fig. 2—Shearing force and bending moment diagrams for point loading on a simply supported beam.

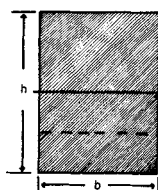


Fig. 3—Cross-sectional view of a beam showing the neutral axis.

crystal can be considered to be a beam with rectangular cross-section. The point pressure p is opposed by the resultant forces R_1 and R_2 , producing both shear and bending stresses, as shown in Fig. 2. The shearing force is uniform on either side of the point of application of p , but the bending moment increases to a maximum at the point of application of p .

The bending stress on a cross section of the beam can be shown to be (13):

$$\sigma_n = My/I \quad (\text{Eq. 5})$$

where: σ_n is the normal stress (force/unit area); M is the bending moment (force \times length); y is the distance from the neutral axis of the beam (length); and I is the moment of inertia of the cross-sectional area about the neutral axis (length³). The moment of inertia for a rectangular cross-section is

$$I = bh^3/12 \quad (\text{Eq. 6})$$

where: b is the thickness of the beam, and h is the height, as shown in Fig. 3. Thus, the bending stress is

$$\sigma_n = 12(My/bh^3) \quad (\text{Eq. 7})$$

The range of values for y is

$$-h/2 \leq y \leq +h/2 \quad (\text{Eq. 8})$$

and the variation of stress over the depth of the beam can be plotted as shown in Fig. 4. It can be seen that there is no stress at the neutral axis, and that the stress is greatest at the surfaces of the beam. The nature of the stress is different on each side of the neutral axis; while the upper surface of the beam is being compressed, the lower surface is under tension, or negative pressure.

Referring once more to the Clapeyron equation (Eq. 1), it may be seen that while the right-hand side of the equation is positive for substances which expand on melting, the left-hand side is negative for those portions of the solid which are under tension. In these areas the melting point will be lowered when point pressure on the opposite side of the crystal is increased. Thus, under the conditions

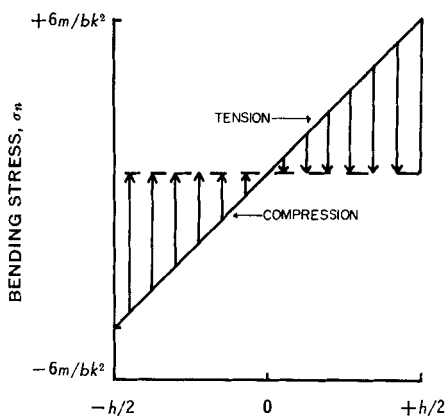


Fig. 4—Stress distribution for point loading on a simply supported beam.

of tablet compression there will be a reduction of melting point on some portion of the surface of each particle, whether the material in question expands or contracts on melting.

Skotnicky Equation—A more recent derivation of the relationship between melting point and pressure is that of Skotnicky (14). The change of equilibrium temperature (melting point) for each phase in the system of Eq. 2 can be shown to be:

$$(\partial T/\partial P)_F = V/S = TV/H \quad (\text{Eq. 9})$$

If a pressure P_L acts on the liquid, and a pressure P_S acts on the solid, then the molar latent heat of fusion, ΔH , can be expressed as a function of the change of equilibrium temperature with pressure:

$$\Delta H = H_L - H_S = TV_L(\partial P_L/\partial T)_F - TV_S(\partial P_S/\partial T)_F \quad (\text{Eq. 10})$$

For an ideal process, in which the system is exposed to a uniform hydrostatic pressure ($P_L = P_S = P$), Eq. 10 reduces to the usual form of the Clapeyron equation (Eq. 1). However, if a point pressure is exerted on the solid only, and the liquid is subjected to a constant atmospheric pressure P_L , then Eq. 10 reduces to:

$$dT/dP_S = -V_S T/\Delta H \quad (\text{Eq. 11})$$

For such a system, the isolated pressure acting locally on the solid always lowers the melting point regardless of the expansion or contraction of the solid on melting.

Skotnicky showed that Eq. 11 agrees qualitatively with the experimentally observed lowering of the melting point of naphthalene under point pressure. This substance, which expands on melting, would be expected to show a rise in melting point with increased pressure by the usual Clapeyron equation.

EFFECT OF STRESS DISTRIBUTION ON SOLUBILITY

The reasoning employed in the analysis of point pressure effects on melting point can also be extended to changes in solubility of solids with pressure. It can be shown that the variation in solubility of a solid with uniform hydrostatic pressure is of the form (15):

$$(\partial \ln x/\partial P)_T = -(V_L - V_S)/RT \quad (\text{Eq. 12})$$

where $\ln x$ is the natural logarithm of the mole fraction of the solid in saturated solution, and R is the gas law constant. This equation predicts that if the solid expands on melting ($V_L > V_S$), an increase in pressure will diminish its solubility. Conversely, if the solid contracts on melting ($V_L < V_S$), an increase in pressure will increase the solubility.

A consideration of the stress distribution resulting from point pressures under the conditions of tablet compression leads to the conclusion that there will be an increase in the solubility on some portion of the particle surface whether the material in question expands or contracts on melting. The liquid in which solution takes place is usually the film of moisture adsorbed on the particle surface.

The essentially nonadherent nature of most insoluble materials and the ease of compaction of water-soluble substances would seem to indicate that pressure-induced solubilization plays an important role in adhesion of tablet particles. The importance of adsorbed moisture is pointed up by studies on the relationship of tablet compacting properties to granulation moisture content (5, 6). Generally, granulations which are absolutely dry have poor compacting properties (16).

EFFECT OF HEAT TRANSFER KINETICS ON FUSION

A basic requirement for the occurrence of surface fusion, regardless of changes in melting point, is the formation of localized high-temperature areas, or "hot spots," on the particle surface. If the temperature of these hot spots reaches the melting point of the substance being compressed, surface fusion will occur. The temperature reached is a function of the balance between the heat transferred to the surface of the particle and the heat transferred away from the surface by conduction into the interior of the particle.

The heat transferred to the surface of the particle is produced by the conversion of the mechanical energy of compression to thermal energy and is essentially independent of temperature. The rate of heat conduction into the interior of the particle is a function of the specific heat and thermal conductivity of the solid and of the particle geometry. The surface temperature reached cannot be determined exactly because of the time-dependent nature of the heat transfer rates and the complicated geometry of the average particle. However, qualitative estimates can be made by the use of a simplified equation.

The average rate of heat transfer to the particle surface can be estimated by dividing the energy of compression by the total time of compression. The rate of heat transfer into the particle interior can be estimated by neglecting the effects of particle geometry and calculating on the basis of one-dimensional heat transfer into a slab of semi-infinite thickness. A suitable equation for heat transfer under these conditions has been derived by Carslaw and Jaeger (17), and is of the form:

$$\Delta T = (2q/Ak)(kt/c\rho\pi)^{0.5} \quad (\text{Eq. 13})$$

where: ΔT is the rise in surface temperature, q is the rate of heat transfer to the surface per unit time, A is the surface area, k is the thermal conductivity of the solid, t is the heating time, c is the specific

heat, and ρ is the density of the solid.

The above equation can be applied to the case of the compression of the 400-mg. sulfathiazole tablet mentioned previously. The properties of the granulation particles can be estimated from the published data (7, 18) as: $A_i = 1800 \text{ cm.}^2/\text{Gm.}$, $k = 0.01 \text{ cal. sec.}^{-1} \text{ cm.}^{-1} \text{ deg.}^{-1}$, $c = 0.75 \text{ cal.-Gm.}^{-1} \text{ deg.}^{-1}$, and $\rho = 1.58 \text{ Gm.-cm.}^{-3}$. The heating time, t , can be estimated from typical tablet compression times (19) as 0.1 sec., and the heat added is 2 cal. The true area of contact can be represented as the product $f \cdot A_T$, where f is the fraction of area in actual contact, and A_T is the total surface area. Substituting these values into Eq. 13 yields:

$$\Delta T = 0.046/f \quad (\text{Eq. 14})$$

Thus, for values of f in the range 10^{-3} to 10^{-4} , the surface temperature of the granules will reach the melting point of commonly tableted organic materials and surface fusion will take place.

The existence of high local surface temperatures produced by the conversion of mechanical energy to thermal energy has been demonstrated by several investigators. Bowden and Ridler (20) measured the temperature of the contact points of dissimilar metals sliding over each other by thermoelectric methods, and found temperatures reaching the melting point of the lower melting metal. In the case of metals with high melting points, transient temperatures of 500–1000° were obtained. Smekal (21) found that when glass was scratched by carborundum, a eutectic melt of $\text{Na}_2\text{OSiO}_2\text{Al}_2\text{O}_3$ was produced, indicating that a surface temperature of 700° had been reached.

SUMMARY

The mechanism of interparticle bonding during tablet compression has not been satisfactorily explained as yet, although a number of theories have been advanced. The liquid surface cement theory is compatible with known facts about tableting, although it has not been proven experimentally. The possibility of formation of a liquid film at the particle surface is supported by thermodynamic analysis of the effects of stress distribution on melt-

ing point and solubility, and by heat transfer kinetics at the surface.

REFERENCES

- (1) Evans, A. J., and Train, D., "A Bibliography of the Tableting of Medicinal Substances," The Pharmaceutical Press, London, England, 1963.
- (2) Evans, A. J., "A Bibliography of the Tableting of Medicinal Substances, First Supplement," The Pharmaceutical Press, London, England, 1964.
- (3) Goetzel, C. G., "Treatise on Powder Metallurgy," vol. I, Interscience Publishers, Inc., New York, N. Y., 1949, pp. 259–312.
- (4) *Ibid.*, vol. II, 1950, pp. 797–861.
- (5) Seth, P. L., and Munzel, K., *Pharm. Industrie*, **21**, 417 (1959).
- (6) Egorova, V. I., and Vikul'eva, E. I., *Med. Prom. SSSR*, **15**, 37(1961).
- (7) "Binders for Tablet Making," Laboratory Information Bulletin No. 2, F. J. Stokes Machine Co., Philadelphia, Pa., 1955.
- (8) Donaghy, L. S., *Drug Cosmetic Ind.*, **83**, 304(1958).
- (9) Nelson, E., Busse, L. W., and Higuchi, T., *J. Am. Pharm. Assoc., Sci. Ed.*, **44**, 223(1955).
- (10) Bowden, F. P., and Tabor, D., "Friction and Lubrication," John Wiley and Sons, Inc., New York, N. Y., 1956, p. 18.
- (11) Wall, F. T., "Chemical Thermodynamics," 2nd ed., Will Freeman and Co., San Francisco, Calif., 1965, p. 158.
- (12) Li, J. C. M., Oriani, R. A., and Darken, L. S., *Z. Physik. Chem.*, **49**, 271(1960).
- (13) Nash, W. A., "Theory and Problems of Strength of Materials," Schaum Publishing Co., New York, N. Y., 1957, pp. 110–137.
- (14) Skotnický, J., *Czechoslov. J. Phys.*, **3**, 225(1953).
- (15) Wall, F. T., *op. cit.*, p. 353.
- (16) Smith, A. N., *Pharm. J.*, **163**, 194(1949).
- (17) Carslaw, H. S., and Jaeger, J. C., "Conduction of Heat in Solids," 2nd ed., Oxford University Press, London, England, 1959, p. 75.
- (18) Higuchi, T., Rao, A. N., Busse, L. W., and Swintosky, J. V., *J. Am. Pharm. Assoc., Sci. Ed.*, **42**, 194(1953).
- (19) Knoechel, E. L., Sperry, C. C., Ross, H. E., and Lintner, C. J., *J. Pharm. Sci.*, **56**, 109(1967).
- (20) Bowden, F. P., and Ridler, K. E. W., *Proc. Roy. Soc. (London)* **A151**, 610(1936).
- (21) Smekal, A., *Powder Met. Bull.*, **4**, 120(1949).



Keyphrases

Tablet compression
 Particle bonding—tablet compression
 Thermodynamics—stressed solids
 Stress distribution, solids—solubility
 Heat transfer kinetics—fusion