Energy Relations in Compression of Polymeric Materials and Granulations

HATEM FESSI *, JEAN-PAUL MARTY *, F. PUISIEUX *, and J. T. CARSTENSEN ‡x

Received February 25, 1980, from the **Faculte de Pharmacie, Universite de Paris-Sud, 92290 Chatenay-Malabry, France*, and the ‡*School of Pharmacy, University of Wisconsin, Madison, WI 53706.* Accepted for publication February 12, 1981.

Abstract □ In tablet compression, a force, F, is exerted on a punch penetrating into a tablet die. For a stationary bottom punch, the force on the upper punch is a function, $F = f(x)$, of penetration and this value was previously determined empirically. Since differential energy is force, $f(x)$, multiplied by distance, dx, the integral $\int f(x)dx$ between limits should give the energy input into the tablet. The integral yields an expression where energy input is a linear function of the logarithm of the maximally applied pressure, F^*, a fact substantiated by the data presented.

Keyphrases □ Tablet compression—energy relations, polymeric materials and granulations □ Energy relationships—tablet compression, polymeric materials and granulations □ Parmentier–Führer equation—energy relations in tablet compression, polymeric materials and granulations

Many tablet properties (hardness, disintegration, dissolution, and thickness) are a function of the pressure at which the tablets are made, which essentially is the maximum pressure in the compression cycle. The energy input into the tablet is a more logical parameter for correlation with tablet properties but is less easily derived. The intent of this study was to obtain the pertinent correlations between the maximally applied pressure during the compression cycle and the energy imparted to the tablet in the compression step.

EXPERIMENTAL

The tablet compositions listed in Table I were used. The polymers were polyvinyl alcohol[1], polyvinyl chloride[2], and a copolymer[3] of the two. Their respective particle sizes were 250–400 μm, <5 μm, and 80–125 μm. The three polymers were compressed first without additives and then as a granulation with the following composition: 20% diphenhydramine hydrochloride, 50% polymer, 1.5% povidone, and a quantity of tribasic calcium phosphate, *qs*. In the last three formulas listed, the polymer quantity was varied (to 60 and 70%) and the amount of tribasic calcium phosphate was reduced.

The granulations were made by mixing the tribasic calcium phosphate and the polymer and granulating with a 3.75% solution of povidone in isopropanol, except in one case where methylene chloride was used. The alcohol-wet granulations were dried in a small fluid bed drier[4] for 20 min at 60° and then were passed through an oscillating granulator through a 1-mm opening. The mesh fraction between 200 and 800 μm was obtained by sieving and was used for compression. Compression was carried out on a single-punch tablet machine[5] equipped with strain gauges for measuring upper and lower punch pressures and punch displacement. Compressions then were effected at a speed corresponding to one-sixtieth of a second per cycle, with upper punch pressures, P, of approximately 2, 3, 4, 5, and 6 tons, accurately monitored; 12-mm flat-faced punches were used.

RESULTS AND DISCUSSION

In a tablet operation, powder first is introduced into the tablet die in loose packing (Fig. 1*a*) since it flows into the die and simply attains its cascaded density. Ideally, the penetration, x, of the upper punch starts at this point, denoted $x = -a$ (Fig. 2). The particles then rearrange to their closest packing (Fig. 1*b*), after which they are deformed elastically by further penetration of the upper punch. At a particular point ($x = 0$ in Fig. 2), the limit of elasticity is reached. From $x = -a$ to $x = 0$, the force, F, exerted by the upper punch is assumed here to be proportional to x (although this assumption is not crucial).

At $x = 0$, the force has achieved a value of F_0; *i.e.*, up to the elastic limit, one may write:

$$F = F_0(x + a)/a \qquad -a \leqq x \leqq 0 \qquad \text{(Eq. 1)}$$

Beyond the elastic limit (1–10), substantial amounts of work, A, are required for further penetration of the upper punch, and particle fracture and/or plastic deformation take place (Fig. 1*c*). The deepest penetration is denoted $x = q$ (Fig. 2).

Parmentier (1) and Führer (2) suggested a force–displacement relationship that is hyperbolic; if it is confined to the $x \geqq 0$ region, it may be expressed as follows:

$$F = F'/(b - x) \qquad 0 \leqq x < b \qquad \text{(Eq. 2)}$$

where F' is a constant and b is an upper limit for x. It then follows

Table I—Compounds Used and Least-Squares Fit Parameters from Fitting Areas of Energy Loop to Eq. 8

Formula	Correlation Coefficient	Slope, F_0b	Intercept, $-F_0b \ln F_0$	$F_0 \times 10^{-3}$, N
Polyvinyl chloride	0.995	14.6	−126	5.35
Polyvinyl chloride + excipients[a]	0.991	20.2	−182	8.21
Polyvinyl alcohol	0.99	25.0	−226	8.63
Polyvinyl alcohol + excipients	0.98	15.9	−141	7.02
Polyvinyl alcohol–polyvinyl chloride copolymer	0.97	21.3	−196	10.1
Copolymer (50%) + excipients	0.99	18.8	−168	7.61
Copolymer (60%) + excipients	0.98	16.5	−144	6.21
Copolymer (70%) + excipients	0.96	25.5	−234	9.58
Copolymer (50%) + excipients + methylene chloride	0.96	19.1	−170	7.68

[a] Excipients denote presence of diphenhydramine, povidone, and tribasic calcium phosphate; granulated with isopropanol unless otherwise stated.

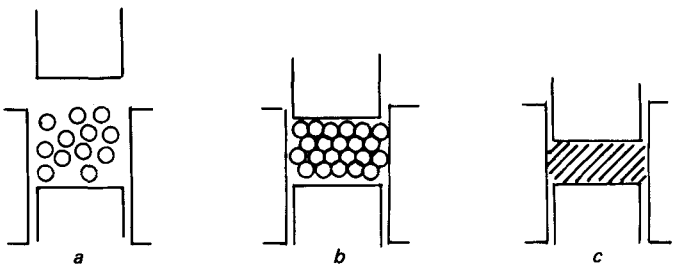

Figure 1—*The three basic steps in the tableting process: filling of die at cascaded density (a), rearrangement (b), and situation after plastic deformation and/or brittle fracture (c).*

[1] Rhodopas H, Rhone-Poulenc, France.
[2] Pevikon, 637P, Seppic, Paris, France.
[3] 15PVA/85PVC, Solvic, Solvay, France.
[4] Glatt, Basel, Switzerland.
[5] Frogerais type AO, Societe Edmond Frogerais, Vitry-sur-Seine, France.

0022-3549/81/0900-1005$01.00/0

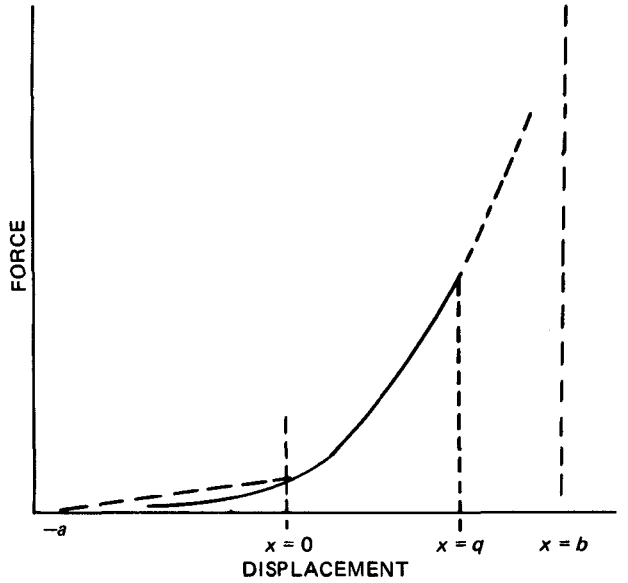

Figure 2—*Schematic of force–displacement cycle,* F = f(x).

that:

$$F' = F_0 b \qquad \text{(Eq. 3a)}$$

$$F = F_0 b/(b - x) \qquad \text{(Eq. 3b)}$$

The largest applied force, F^* (corresponding to $x = q$), is given by:

$$F^* = F_0 b/(b - q) \qquad \text{(Eq. 4)}$$

The ideal graph then is as shown in Fig. 2. A typical experimental *F versus* x plot is shown in Fig. 3.

In relating such data to the Parmentier–Führer equation (Eq. 2), it is noted that the value of b is not known and the data in Fig. 3*b* are in the form:

$$\ln F = -Q \ln (b - x) + P \qquad \text{(Eq. 5)}$$

where Q and P are constants. If Eq. 2 holds, then Q should equal −1. A best value of b can be found by iteration as the value giving the least sum

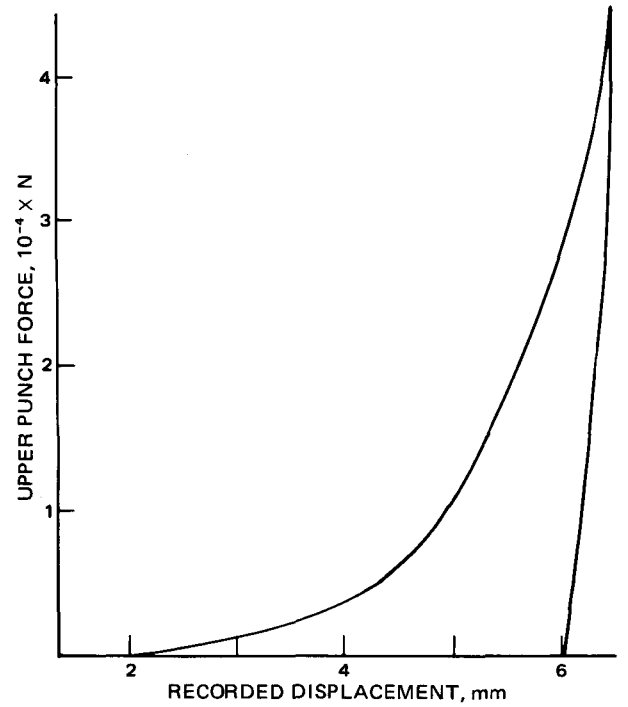

Figure 3—*Force–displacement cycle of granulation of polyvinyl acetate–polyvinyl chloride copolymer (50%) plus excipients. Compression maximum is 5 tons.*

Table II—Data in Fig. 3 Treated According to Eq. 5

x, mm	F, 10^{-4} N	$\ln F \times 10^{-4}$, y	$\ln (b - x)$ b = 6.7	b = 6.5	b = 6.45	b = 6.55	b = 6.6	b = 6.9
3.65	0.28	−1.27	1.05	0.98	0.96	0.99	1.01	1.12
5.50	1.4	0.34	0.18	0	−0.05	0.05	0.095	0.34
5.95	2.28	0.82	−0.29	0.60	−0.69	−0.51	−0.43	−0.05
6.3	3.44	1.24	−0.92	−1.61	−1.90	−1.39	−1.20	−0.51
6.35	4.48	1.50	−1.05	−1.90	−2.30	−1.61	−1.39	−0.60
$(n-2)s^2_{yx}$ [a]			0.21	0.42	0.54	0.26	0.29	0.68
Slope α			−1.25	−0.89	−0.77	−0.99	−1.08	−1.08
Intercept			0.27	−0.03	−0.09	0.04	1.11	0.42
Correlation coefficient			−0.98	−0.95	−0.94	−0.96	−0.97	−0.93

[a] Sum of deviations squared, *i.e.*, $(n-2)s^2_{yx} = \Sigma(y - \bar{y})^2 - \alpha^2(\Sigma\{x - \bar{x}\}^2)$.

of squares of ln F regressed on ln $(b - x)$. This procedure is shown in Table II for the data of the type shown in Fig. 3. It is noted from Table II that the sum of squares is not exceedingly sensitive to the chosen value of b; *i.e.*, there is a broad minimum in the value of the sum of squares for b values ranging from 6.45 to 6.7. The data treated according to Eq. 5 are shown graphically in Fig. 4. Based on the best-fit criteria, it would be somewhat difficult to choose one b value over another in this range; what is important is that the range entails the slope $Q = -1$, which is the one dictated by Eq. 2.

The experimental zero point for x is chosen judiciously but nevertheless arbitrarily. However, since the value of b is obtained by iteration, this fact does not matter. If $x' = 0$ is chosen where x is actually 2, then b by iteration also would increase by a value of 2, and $(b - x)$ would have the same value as if x had been accurately chosen.

The value of b is related to (but not identical to) the true density, ρ, of the nonporous solid composition. True correspondence would exist if ρ were pressure independent; however, ρ is a function of F.

In compression (Figs. 1*b* and 1*c*), the work, A, done by the upper punch as it moves an infinitesimal distance, dx, against the powder mass is given by:

$$dA = F\,dx \qquad \text{(Eq. 6)}$$

The total work (energy imparted to the tablet during the compression step but excluding the decompression step) then is obtained by integration from zero to $x = q$, *i.e.*:

$$A = \int_0^q F_0 b/(b - x)dx = F_0 b[\ln b/(b - q)] \qquad \text{(Eq. 7)}$$

Introducing Eqs. 3*b* and 4 gives:

$$A = F_0 b \ln F^* - F_0 b \ln F_0 \qquad \text{(Eq. 8)}$$

As mentioned earlier, due to the floating nature of b, Eqs. 7 and 8 are independent of the experimental choice of $x = 0$.

Equation 8 predicts that a plot of the energy, A, as a function of ln F should be linear and that the ratio of the slope to the intercept should be $-\ln F_0$. These energies were obtained as the areas under the curves of the type shown in Fig. 3. The data are indeed linear, as shown in Fig. 5, and the least-squares fit values of all formulas tested are shown in Table

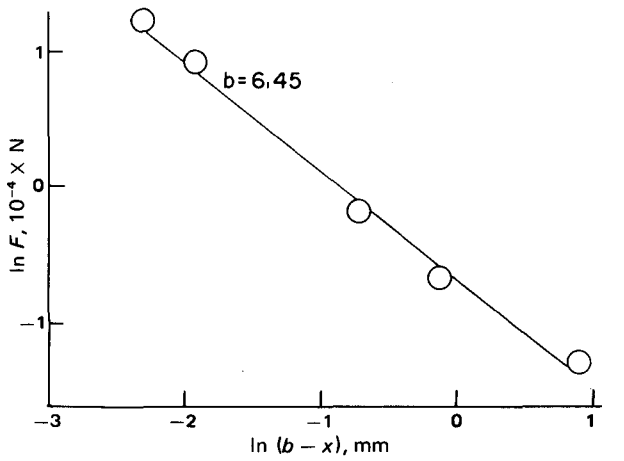

Figure 4—*Data in Fig. 3 (upper curve) treated according to Eq. 5.*

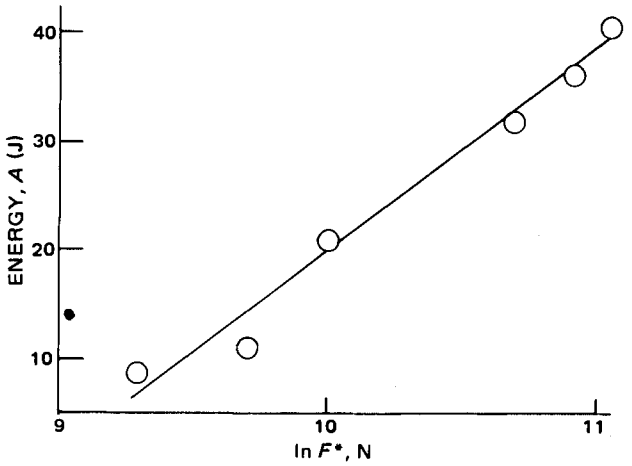

Figure 5—*Areas from plots of the type in Fig. 3 at six different pressures, plotted as a function of maximal pressure according to Eq. 6.*

I. The last column gives the F_0 value that is the smallest force necessary for actual displacement beyond the rearrangement step. It is seen from Table I that, for example, for "excipient + copolymer (50%)" (the case shown in Fig. 3), F_0b ln F_0 = 168 J and F_0b = 18.8 J. In other words, ln F_0 = 168/18.8 = 8.94, or F_0 = 6610 N. This value corresponds to an ordinate of 0.66 in Fig. 3, which corresponds to a "recorded" abscissa value (with arbitrary zero) of 4.5 mm.

Since F_0b = 18.8, it follows that b = 18.8/F_0 = 0.0028 m = 2.8 mm. Hence, in Fig. 3, the final asymptote would be at a recorded abscissa value of 4.5 + 2.8 = 7.3 mm (again recalling that the zero is somewhat arbitrary). At this point, the distance between the upper and lower punch would be 2.4 mm[6]. If the solid achieves its true density at b, then the true density can be deduced. The die has a diameter of 12 mm; *i.e.*, the volume between the upper and lower punch is equal to [π (1.2^2/4) 0.24] = 0.27 cm^3.

[6] This value is obtained from knowledge of the lower punch position in relation to the arbitrary zero and does not account for possible compression of the presumably static lower punch.

The weight of the solids is 500 mg, so the true density would have a value of 0.5/0.27 = 1.84 g/cm^3, which is reasonable. Since compression can possibly (and presumably does) produce densities that are higher than the true densities at atmospheric pressure, the calculated figure only has interest in that it is of a reasonable magnitude. Furthermore, Eq. 8 deals with the energy input and assumes that the relaxation trace in Fig. 3 (the recovery) is vertical. This approximation becomes poorer the more pronounced the recovery after upper punch release.

SUMMARY

The present study shows that the Parmentier–Führer equation for the value of the upper punch force as a function of displacement is useful and can be used to deduce mathematically energy *versus* maximum force relationships for energy input. These relationships were validated experimentally. The plots provide an estimate of the point in the displacement of the upper punch where the powder or granulation was rearranged to its closest packing.

REFERENCES

(1) W. Parmentier, Ph.D. thesis, Technical University Carolo-Wilhemina zu Braunschweig, Braunschweig, West Germany, 1974, pp. 1–90.

(2) C. Führer, *Dtsch. Apoth.-Ztg.*, **105**, 1150 (1965).

(3) P. Toure, Ph.D. thesis, University of Paris-Sud, Chatenay-Malabry, France, 1979, p. 102.

(4) P. Toure, D. Duchene, F. Puisieux, and J. T. Carstensen, *Powder Technol.*, **26**, 213 (1980).

(5) J. T. Carstensen: "Rate Processes and Mechanical Properties in Solid Pharmaceutics," Academic, New York, N.Y., 1980, pp. 187–214.

(6) W. M. Long, *Powder Metall.*, **6**, 73 (1960).

(7) S. Leigh, J. E. Carless, and B. W. Burt, *J. Pharm. Sci.*, **56**, 888 (1967).

(8) J. J. Windheuser, J. Misra, S. P. Eriksen, and T. Higuchi, *ibid.*, **52**, 767 (1963).

(9) A. Obiorah, *Int. J. Pharm.*, **1**, 249 (1978).

(10) K. Marshall, "The Physics of Tablet Compression, 12th Arden House Conference, Feb. 2, 1977, Conference Notes," Colorcon, West Point, Pa., pp. 15, 16.

Mevalonic Acid Analogs as Inhibitors of Cholesterol Biosynthesis

C. ROWAN DeBOLD * and J. C. ELWOOD ˣ

Received September 26,1980, from the *Department of Biochemistry, State University of New York, Upstate Medical Center, Syracuse, NY 13210.* Accepted for publication February 20, 1981. *Present address: Department of Medicine, Division of Endocrinology, Vanderbilt University School of Medicine, Nashville, TN 37232.

Abstract □ A series of 20 mevalonic acid analogs was synthesized and tested for their ability to inhibit cholesterol biosynthesis from [2-^{14}C]-mevalonate in rat liver homogenates. Removal of the 5-hydroxyl group from mevalonic acid produced an active inhibitor, 3-hydroxy-3-methylpentanoic acid. Removal of the 3-hydroxyl group, addition of an aromatic group in the 3-position, or insertion of a double bond reduced inhibitory activity. Compounds with an aromatic group or halide on the 5-position were active inhibitors. The most active inhibitor was 5-phenylpentanoic acid, with 50% inhibition at 0.064 m*M*.

Keyphrases □ Mevalonic acid—analogs synthesized as potential cholesterol biosynthesis inhibitors □ Cholesterol—inhibitors, synthesis and testing of mevalonic acid analogs □ Structure–activity relationships—mevalonic acid analogs as inhibitors of cholesterol biosynthesis

Considerable progress has been made in understanding the biosynthesis of cholesterol (1, 2). Mevalonic acid, the product of the major rate-limiting reaction of cholesterol biosynthesis, is converted to isopentenyl pyrophosphate by three enzymes, each requiring Mg^{2+} and ATP. The first step is phosphorylation at position 5 by mevalonate kinase (EC 2.7.1.36). Next, 5-pyrophosphomevalonate is formed by phosphomevalonate kinase (EC 2.7.4.2). This product is decarboxylated and dehydrated by pyrophosphomevalonate decarboxylase (EC 4.1.1.33), possibly involving 3-phospho-5-pyrophosphomevalonate as an intermediate.

Interest has focused on these reactions for various reasons. For example, the role of cholesterol in atherosclerosis prompted a search for inhibitors of these reactions with the prospect of decreasing cholesterol synthesis (3–7). It also has been suggested that the decreased brain cholesterol levels seen in phenylketonuria may be due to inhibition of these steps by elevated levels of phenylalanine

0022-3549/81/0900-1007$01.00/0