Plastic Flow during Compression of Directly Compressible Fillers and Its Effect on Tablet Strength

S. T. DAVID * and L. L. AUGSBURGER ˣ

Abstract □ The effects of the duration of the overall compression cycle and of the duration of the maximum compressive force on tablet strength were studied using an instrumented rotary tablet press. Various direct compression fillers were evaluated. Increasing the overall compression cycle duration to 10 sec resulted in significantly greater tablet tensile strengths with microcrystalline cellulose and compressible starch fillers but not with lactose or compressible sugar. Increasing the duration of the maximum compressive force to 20 sec significantly increased the tensile strength in all cases, but microcrystalline cellulose and compressible starch tablets were affected more than lactose or sugar tablets. The maximum compressive force decayed with time for all fillers but at a greater rate with microcrystalline cellulose and compressible starch. This behavior was attributed to differences in the extent of plastic flow. The decay curves were analyzed using the Maxwell model.

Keyphrases □ Tablets—plastic flow during formation, effect of duration of compression cycle and maximum compressive force on tensile strength □ Plastic flow—during tablet formation, effect of duration of compression cycle and maximum compressive force on tensile strength □ Compression cycle—tablet formation, effect of duration and maximum force on tablet tensile strength □ Dosage forms—tablets, effect of duration of compression cycle and maximum compressive force on tensile strength □ Tensile strength—tablets, effect of duration of compression cycle and maximum compressive force

In the mid-1950's, Train (1) formulated a hypothesis on the mechanics involved in tablet formation. The consolidation process was divided into stages. Stage I takes into account interparticulate slippage of the powder particles, which leads to a decrease in the relative volume of the compact. The formation of temporary struts, columns, and vaults due to the increased resistance of the powder to compression is manifested in Stage II. Failure of these structures, brought about by increasing the compression forces on the powder material, is obtained in Stage III. Here the structure failure is a result of the crushing of particles or plastic flow. In Stage IV, rebonding is taking place more quickly than particle fracture, and the decrease in the relative volume of the compact becomes quite small as compared to the former stages.

As stated by Train, one event reported to occur during the formation of tablets is plastic deformation, which results from the crushing or fracturing of particles or by plastic flow. Plastic flow in various materials has been evaluated by comparing their stress relaxation behavior under constant load (2, 3).

The purpose of this study was to investigate plastic flow, with particular reference to its effect on tablet tensile strength. Therefore, the effects of the duration of the total compression cycle and of the duration of the maximum compressive force on tablet strength were investigated. Directly compressible fillers were chosen, because there is much interest today in materials and formulas that permit the manufacture of tablets without the traditional and costly granulating step.

EXPERIMENTAL

Tablet Preparation—Tablets were prepared on a rotary tablet press[1], which had been instrumented with resistance strain gauges after the manner of Wray *et al.* (4) to monitor compression and ejection forces. The instrumentation of this machine was described in detail previously (5). Only a single station was used to help minimize tooling errors. The same circular, flat-faced punches and die, 1.588 cm in diameter, were used throughout the study.

Tablet weights were held constant at 750 mg, unless otherwise stated. When a lubricant was necessary, it was first prescreened through an 80-mesh screen to facilitate blending. Lubricated blends (500-g batches) were prepared by mixing in a 1.92-liter (2-qt) twin-shell blender[2] for 12 min, with the intensifier bar running for only the final 2 min. All tableting was conducted in a room where temperature and relative humidity were maintained at 26 ± 1° and 35 ± 5%, respectively.

Tablet Tensile Strength—Tablet tensile strength was determined from the force required to fracture tablets by diametral compression on a motorized tablet hardness tester[3]. Rather than report tablet strength as hardness (*i.e.*, fracture force), force readings were converted to tensile strength in the manner of Fell and Newton (6), because tensile strength is independent of tablet dimensions and is a measure of the strength of the "as compacted" material (7, 8). The equation used to compute tensile strength was:

$$\sigma_0 = \frac{2F}{\pi dt} \qquad \text{(Eq. 1)}$$

where σ_0 is the tensile strength, F is the force needed to cleave the tablet, d is the diameter of the tablet, and t is the tablet thickness. Care was taken to use only the fracture forces generated when tablets failed in tension, as evidenced by their uniform splitting into halves. Tablet dimensions were determined using an inch measure[4]. All tensile strengths reported are based on 10 determinations.

Effect of Duration of Compression Cycle—Compression cycle durations were varied from 0.09 to 10 sec for the following directly compressible materials: lactose[5] USP, direct compressible sugar[6] USP, microcrystalline cellulose[7] NF, and compressible starch[8] (pregelatinized starch USP). The first two materials each contained 0.50% magnesium stearate[9] USP as a lubricant to facilitate ejection of the compacts from the die cavity. In most cases, machine speed could be altered by making a mechanical adjustment to vary the time of the compression cycle; however, the 10-sec time was achieved by rotating the flywheel of the press manually at a relatively constant rate.

Ten tablets, representing each cycle duration, were evaluated for tensile strength (Table I). Increasing the duration of the compression cycle did not result in significantly different tensile strengths for the lactose or sugar tablets; however, the microcrystalline cellulose and compressible starch tablets were significantly stronger when the compression cycle was increased to 10 sec (5% level).

Effect of Duration of Maximum Compressive Force—The ef-

[1] Stokes model RB-2.
[2] Patterson-Kelly, Stroudsburg, Pa.
[3] Heberlein model 2E/106, series 7203, Key Industries, Farmingdale, N.Y.
[4] Model C815, Federal Products Corp., Wayne, Pa.
[5] Fast-Flo lactose, Foremost Dairies Inc., San Francisco, Calif.
[6] DiPac, Amstar Corp., Brooklyn, N.Y.
[7] Avicel PH101, F.M.C. Corp., American Viscose Division, Newark, Del.
[8] StaRx 1500 starch, A. E. Staley Manufacturing Co., Decatur, Ill.
[9] Ruger Chemical Co., New York, N.Y.

Table I—Effect of Duration of the Compression Cycle on Tablet Strength for a Few Directly Compressible Fillers

Filler	Compression Force, kg	Duration of Compression Cycle, sec	Tablet Tensile Strength kg/cm²	S[a]	t[b]
Compressible	938	0.11	10.0	0.72	—
lactose with 0.50%	938	0.13	10.2	0.68	0.639
magnesium stearate	938	10	10.1	0.70	0.314
Compressible	1619	0.11	11.6	0.69	—
sugar with 0.50%	1619	0.12	11.6	1.01	—
magnesium stearate	1619	10	11.6	0.50	—
Microcrystalline	203	0.10	13.6	0.51	—
cellulose	203	0.12	13.6	0.52	—
	203	10	14.2	0.69	2.21[c]
Compressible	643	0.10	8.0	0.32	—
starch	643	0.12	8.0	0.41	—
	643	10	8.7	0.50	3.72[c]

[a] Standard deviation, based on 10 determinations. [b] Student t statistic for difference comparing shortest cycle with each longer cycle. [c] Significant difference (5% level).

fect of the duration of the maximum compressive force on tablet tensile strength was examined using compressive forces required to make tablets of acceptable hardness. The same compressible materials used in the preceding study were again examined. The lactose and sugar contained 0.50% magnesium stearate.

Initially, samples were compressed utilizing a rotary tablet machine speed of 25 rpm where the duration of the compression force was less than 0.1 sec. Additional samples of the fillers were compressed on the same machine with the same maximum force but the duration of the force was prolonged. This change was accomplished by manually rotating the flywheel at approximately 0.5 rpm until the maximum compressive force was observed on a strip-chart recorder tracing. The position of the flywheel was held constant for 20 sec, and then the compressional force was released.

Tensile strengths were determined on 10 tablets produced on each run (Table II). Tablet strengths for these compacts increased significantly (5% level) in all cases when the duration of the maximum compressive force was increased to 20 sec.

Plastic Flow—In the previous experiment, increasing the duration of the maximum compressive force resulted in increased tablet tensile strength. However, of the four fillers tested, microcrystalline cellulose and compressible starch were affected to a markedly greater extent than compressible lactose and sugar. The compaction forces used in making these tablets were presumably in the range of Train's Stage III of compression, in which plastic flow and fracture take place. The differences could have been due to differences in the extent of plastic flow. To test this possibility, an experiment was designed to evaluate the role of plastic flow in the compaction of these materials.

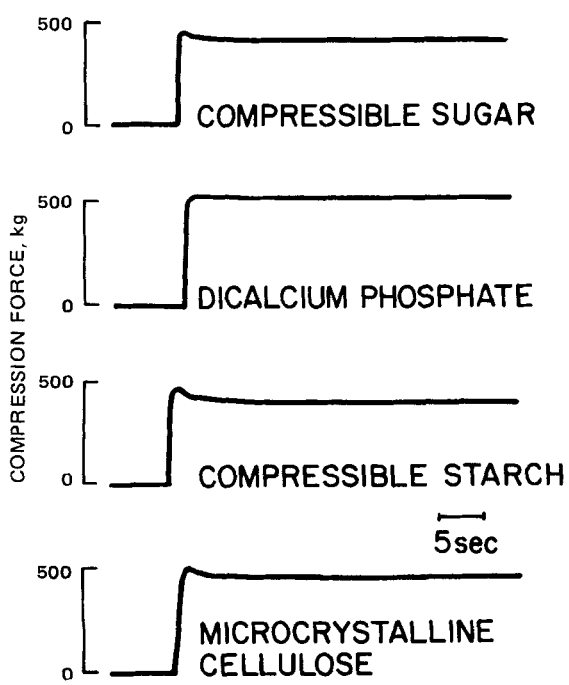

Figure 1—*Typical compression force decay curves.*

In the previous experiment, it was observed from the recorder tracings that during the extended times in which the compression cycle was halted at the point of maximum compressive force, this force tended to decay with time. This observation both supported the proposed role of plastic flow and suggested the instrumented rotary press as an experimental tool to evaluate this phenomenon. Thus, tablets were compressed manually on the instrumented rotary press by turning the flywheel by hand at an approximate rate of 0.5 rps until the maximum compressive force was observed on the recorder tracing. The flywheel was halted at this point, but the recorder was permitted to run, thus producing a continuous tracing of the compressive force.

Compressible starch, microcrystalline cellulose, dicalcium phosphate dihydrate[10] USP, and compressible sugar were evaluated. In all cases, maximum decay appeared to be reached within about 10 sec. The lactose used in the previous study was not used since a change had taken place in the material. Although microcrystalline cellulose and starch do not require a lubricant when tableted alone (9, 10), 0.30% magnesium stearate was added to each of the four fillers to keep the experimental conditions the same in all cases. Tablet weights for each blend were adjusted carefully to produce tablets with the same thickness of 0.300 ± 0.001 cm. Typical tracings appear in Fig. 1.

The data were treated in a manner similar to that of Shlanta and Milosovich (2). These substances were treated as materials showing both an elastic and a plastic nature during deformation. A linear, Hookean stress-strain relationship is combined in series with a linear, Newtonian viscous relationship to describe the material's behavior

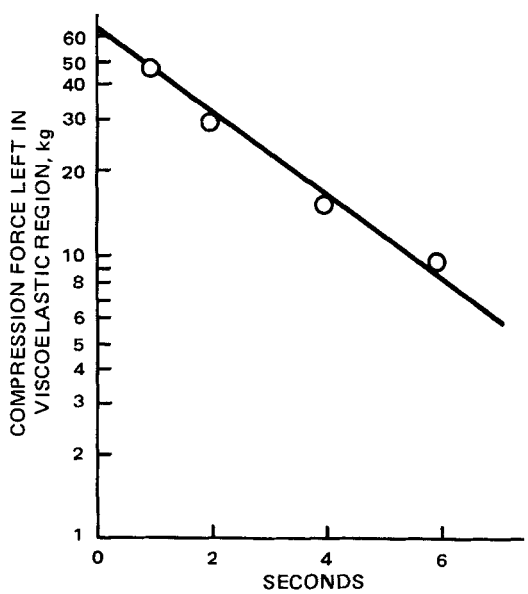

Figure 2—*Effect of time on the compression force observed for a compressible starch containing 0.30% magnesium stearate. Slope = 0.336 sec^{-1}. Intercept = 63 kg.*

[10] Unmilled, Stauffer Chemical Co., Chicago Heights, Ill.

Table II—Effect of Duration of the Maximum Compressive Force on Tablet Strength for a Few Directly Compressible Fillers

Filler	Compression Force, kg	Duration of Maximum Compressive Force, sec	Tablet Strength		
			kg/cm²	S^a	t^b
Compressible lactose with 0.50% magnesium stearate	826	<0.1	16.3	0.48	—
	826	20	18.8	0.77	8.71
Compressible sugar with 0.50% magnesium stearate	826	<0.1	10.0	0.42	—
	826	20	12.3	0.29	14.4
Microcrystalline cellulose	203	<0.1	13.6	0.62	—
	203	20	18.7	0.60	18.2
Compressible starch	643	<0.1	8.0	0.30	—
	643	20	18.8	0.44	63.5

[a] Standard deviation, based on 10 determinations. [b] Student t statistic comparing each pair. All differences are significant at the 5% level.

under real conditions. Thus, the plastic flow concept is treated mathematically as the Maxwell model under constant strain (11, 12), which involves combining one viscous parameter and one elastic parameter. The Hookean element is given by:

$$\sigma_1 = Ee_1 \qquad \text{(Eq. 2)}$$

From Newton's law of flow, the plastic or viscous relationship is:

$$\sigma_2 = n\frac{de_2}{dt} \qquad \text{(Eq. 3)}$$

where σ is the stress, e is the amount of powder constriction, de/dt is the rate of constriction with time, E is Young's modulus, and n is a viscosity coefficient. Since:

$$\sigma = \sigma_1 = \sigma_2 \qquad \text{(Eq. 4a)}$$

and:

$$e = e_1 + e_2 \qquad \text{(Eq. 4b)}$$

then:

$$\frac{de}{dt} = \frac{de_1}{dt} + \frac{de_2}{dt} = \frac{1}{E}\frac{d\sigma}{dt} + \frac{\sigma}{n} \qquad \text{(Eq. 4c)}$$

When a fixed constriction is applied to the powder mass at time t = 0 and held constant, one can express stress as a function of time. Therefore, de/dt is equal to zero so:

$$E^{-1}\frac{d\sigma}{dt} + \frac{\sigma}{n} = 0 \qquad \text{(Eq. 5a)}$$

and after integration:

$$\ln\frac{\sigma}{\sigma_0} = -Et/n \qquad \text{(Eq. 5b)}$$

or:

$$\Delta\sigma = \Delta\sigma_0 e^{-Et/n} \qquad \text{(Eq. 5c)}$$

The symbol Δ in front of the σ symbol represents the total range of compressive stresses located in the viscoelastic region in question. Since the area of contact between powder and punches was constant throughout, Eq. 5c becomes:

$$\Delta F = \Delta F_0 e^{-Et/n} \qquad \text{(Eq. 6)}$$

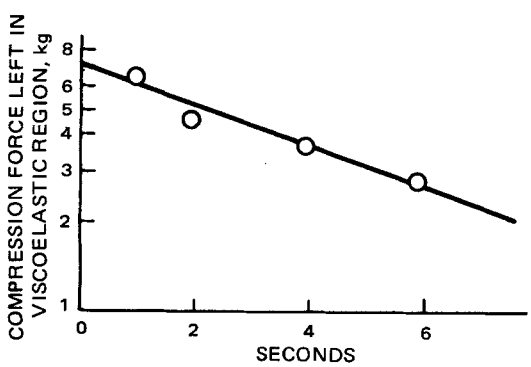

Figure 3—*Effect of time on the compression force observed for dibasic calcium phosphate containing 0.30% magnesium stearate. Slope = 0.182 sec^{-1}. Intercept = 7 kg.*

where ΔF is the amount of the compressional force left in the viscoelastic region at time t, and ΔF_0 is the total magnitude of this force at t = 0. Thus, according to Eq. 6, the decay of compression force with time from the continuous trace recordings can be treated as a first-order rate process. The logarithmic form of Eq. 6 is:

$$\ln \Delta F = \ln \Delta F_0 - kt \qquad \text{(Eq. 7)}$$

where the first-order rate constant, k, equals E/n and is the viscoelastic slope. Accordingly, compressive force data were obtained from tracings of the force decay curves of each filler. Data points were obtained and plotted in accordance with Eq. 7 on semilogarithmic paper. The first-order plots appear in Figs. 2–5. The data, including the first-order rate constants and the total magnitude of compression force decay, ΔF_0, appear in Table III. Results are based on three separate determinations for each filler.

RESULTS AND DISCUSSION

Although increasing the duration of the compression cycle did not result in statistically significant changes in the strength of the sugar or lactose tablets, the microcrystalline cellulose and starch tablets were significantly stronger (5% level) when a compression cycle of 10 sec was utilized (Table I). Plastic deformation results from fracture of particles and/or plastic flow. If plastic flow is an important factor affecting the compressibility of a substance, a prolongation of the compression cycle would be expected to increase the strength of tablets produced from such a substance, since more surface contact for interparticulate bonding would be produced through plastic flow.

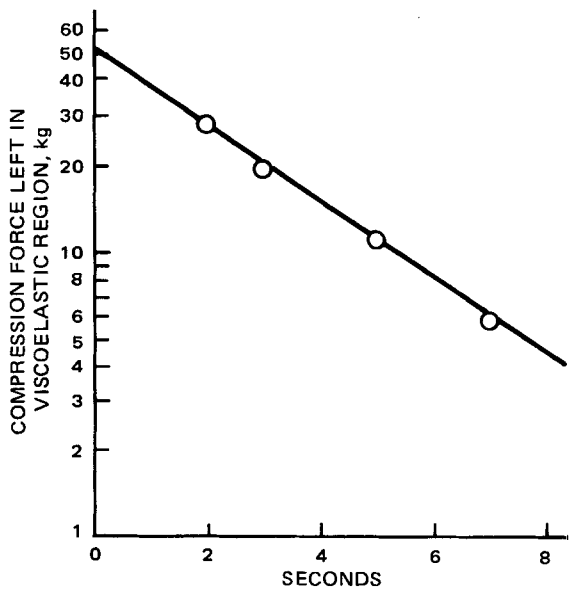

Figure 4—*Effect of time on the compression force observed for microcrystalline cellulose containing 0.30% magnesium stearate. Slope = 0.332 sec^{-1}. Intercept = 53 kg.*

Table III—Effect of Time on the Compression Force Observed for a Few Directly Compressible Fillers, All Containing 0.30% Magnesium Stearate

Filler	Seconds	Compression Force Observed, kg			Mean Viscoelastic Slope (k)	Mean Total Compression Force Lost in Viscoelastic Region, kg
Compressible starch	0	476	461	461	0.336	63
	1	454	441	432		
	2	439	425	419		
	4	425	417	406		
	6	419	412	403		
	12	412	403	394		
Microcrystalline cellulose	0	476	465	480	0.332	53
	1	463	454	463		
	2	450	441	450		
	3	441	436	443		
	5	432	425	436		
	7	425	421	432		
	12	421	416	425		
Compressible sugar	0	430	434	436	0.281	37
	1	425	423	425		
	2	410	414	414		
	3	406	410	410		
	5	403	404	406		
	7	401	402	403		
	12	392	399	397		
Dicalcium phosphate	0	529	507	531	0.182	7
	1	529	507	531		
	2	527	505	529		
	4	525	502	529		
	6	522	502	529		
	12	518	500	527		

To investigate further the role of the basic deformation properties of materials on compressibility, the effect of the duration of the maximum compressive force on tablet strength was examined. Increasing the duration of the maximum compressive force resulted in significantly greater tablet strengths in all cases (Table II). However, the differences appeared relatively greater with microcrystalline cellulose and compressible starch. These results, together with the findings of the experiment in which the overall compression cycle times were varied, give evidence that plastic flow may play a more important role in particle–particle bonding in the microcrystalline cellulose and starch tablets than in the lactose and compressible sugar tablets.

In the experiment in which the effect of the duration of the maximum compressive force on tablet tensile strength was studied, this compressive force decayed with time. As this result was no doubt due to plastic flow (3), this observation suggested that plastic flow data could be obtained by treating these compressive force decay curves viscoelastically using the Maxwell element. Accordingly, viscoelastic slopes, based on compressive force decay curves, were determined for compressible starch, microcrystalline cellulose, compressible sugar, and dicalcium phosphate. Dicalcium phosphate was included as an example of an inorganic compound.

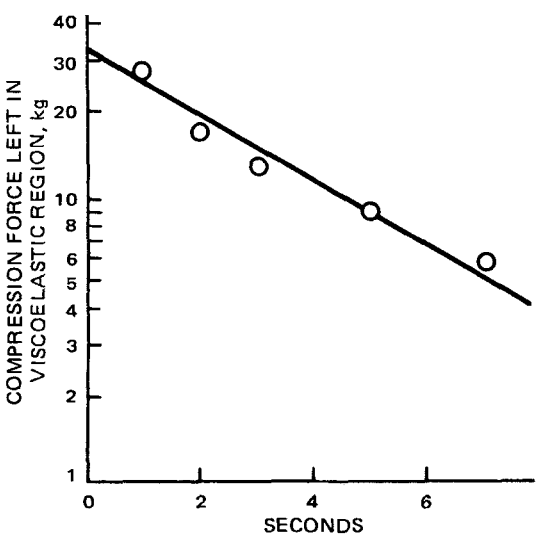

Figure 5—*Effect of time on the compression force observed for compressible sucrose containing 0.30% magnesium stearate. Slope = 0.281 sec^{-1}. Intercept = 37 kg.*

If the previous finding that plastic flow is more predominant in the compaction of compressible starch and microcrystalline cellulose and not as dominant in the compaction of sugar is correct, the viscoelastic slope, k, may be expected to be greater for the former two materials than for sugar. Furthermore, the total amount of compressive force decay, ΔF_0, should be less with sugar than with microcrystalline cellulose or compressible starch, as was found to be the case. The order of decreasing slopes and decreasing ΔF_0's (Figs. 2–5) is as follows: compressible starch > microcrystalline cellulose > compressible sugar > dicalcium phosphate. The viscoelastic plot for compressible sugar (Fig. 5) seems to deviate from linearity. One possible explanation is that, instead of a linear Newtonian element being applied, a nonlinear viscous relationship or a combination of the two may be involved.

The Maxwell element was used to determine the qualitative nature of polymers under stress, since it is generally unable to describe truly polymer properties quantitatively (11, 12). Vincent (12) pointed out that more complex models would be more suitable, but the behavior of the more complex models becomes "less easy to picture, as well as more difficult to analyze." However, since the Maxwell element is used to determine the qualitative behavior of polymers, the same treatment may be expected to help understand the important compressibility characteristics of various pharmaceutical materials during tablet compression. For example, Rees and Shotton (13) found that the tablet strength of sodium chloride tablets increased up to 100% or more 1 hr after tablet compression. This result was attributed to "stress relief of the crystals and interparticulate bonds" due to plastic flow. Therefore, a similar type of mathematical treatment, as described utilizing the Maxwell element, may become a useful tool in explaining unusual shifts in tablet hardness with time.

These results suggest that direct compression fillers can be classified according to their degree of plastic flow under compaction. Furthermore, these results help explain the phenomenon in which the compressibility of either microcrystalline cellulose or compressible starch is reduced to a much greater extent by the presence of lubricants than is observed with spray-dried lactose or sugar. It was suggested (5) that crystal fracture and the creation of new surfaces under compression may be more predominant factors in the bonding of tablets formed from lactose and sugar fillers than from microcrystalline cellulose or compressible starch. Thus, in the former cases, more new surfaces uncontaminated with lubricant would be formed which could participate essentially unhindered in bonding. Although plastic flow would be expected to increase the true area of contact

between particles, a lubricant initially present at particle surfaces would still exist at the interfaces formed by plastic flow where it could interfere with particle–particle bonding. The results of the present study help support this thesis, since microcrystalline cellulose and compressible starch appeared to exhibit a greater degree of plastic flow under compression than did sugar.

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* American Foundation for Pharmaceutical Education Fellow, 1971–1973. Present address: Mead Johnson Research Center, Evansville, IN 47721

[x] To whom inquiries should be directed.

Zero-Order Drug Delivery System: Theory and Preliminary Testing

D. BROOKE [x] and R. J. WASHKUHN *

Abstract □ A new approach to zero-order drug delivery that includes geometric factors is described. An experimental device based on the theory was tested by following the release of stearic acid into ethanol. Three separate trials indicated that the solid was released *via* a zero-order process in a reproducible manner.

Keyphrases □ Drug delivery—zero-order system, geometric factors considered, experimental device tested □ Delivery, drug—zero-order system, geometric factors considered, experimental device tested □ Stearic acid—release into ethanol, zero-order drug delivery system, experimental device tested

Roseman and Higuchi (1) and, more recently, Roseman (2) treated the subject of drug release from silicone polymer matrixes containing suspended particulate drug. They developed equations for drug release from both planar and cylindrical surfaces (1). Roseman (2) showed that the fraction of drug release from a matrix with a planar surface was linear—not with time but with the square root of time. This finding confirmed an expectation published earlier (3). Roseman (2) also showed that the initial portion of a similar plot for a matrix of cylindrical shape was similar to that for the planar case. However, as more drug was released, the slope for the fraction *versus* square root of time plot decreased.

A study of these results indicates that polymer devices might be useful in dispensing drug to tissues or body cavities at fairly constant rates over reasonable periods of time. However, the ideal of a zero-order drug delivery system cannot be realized from planar or cylindrical devices of silicone polymer containing suspended particulate drug.

BACKGROUND

The planar case of a drug suspended in a polymer matrix fails as a zero-order drug delivery system because, as the drug is released, the boundary in the matrix at which drug dissolution occurs recedes from the surface from which the drug is released. The problem is one of a decreasing release rate due to an increasing drug diffusion path length within the matrix. For the cylindrical case, the situation is more complicated. Here, the diffusion path increases and the drug core within the matrix decreases in area.

The reduction of an effective dissolution surface, given a constant diffusion barrier, and its effect on drug dissolution, *e.g.*, from implants, are fairly well understood. In their derivation of the well-known "cube root law," Hixson and Crowell (4) showed an appreciation for the decreasing area of a single particle that maintained its shape during the dissolution process. Ballard and Nelson (5) related the rate of absorption from spherical implants to size. The same investigators (6) developed a graphical method of estimating the area of subcutaneously implanted cylindrical drug pellets.

More recently, Rippie and Johnson (7) attempted to regulate the dissolution behavior of drug pellets by controlling their geometry. However, their work involved dissolution in a turbulent flow, so that transport of the drug from the surface could not be considered limited to diffusion across a constant diffusion barrier.