though this result was biased by the 12- and 24-hr time points. Oleic acid was not investigated further in this study, although Noguchi *et al.* (17) concluded that oleic acid may be a useful vehicle to sustain the release of poorly water-soluble drugs, thus, prolonging their effects.

In the last series of this study, the oral availability of triamterene was evaluated from peanut oil and aqueous suspensions in which the dosing volume was reduced to 20 μl. Peanut oil was selected for comparison with the aqueous vehicle based on results from the initial study. In that study, the peanut oil vehicle provided a similar peak plasma level as the aqueous suspension, although peak levels occurred somewhat later. The decline from peak levels was slower for peanut oil than for the aqueous suspension, resulting in a larger overall *AUC* for peanut oil suspensions. Finally, the intersubject variability in the initial study was smallest with the peanut oil suspensions. It was thus concluded that peanut oil might be a promising vehicle for formulating triamterene and improving its oral availability.

The results (Tables III and IV and Fig. 1) of the two-way crossover study, comparing peanut oil and aqueous suspensions of triamterene, did not confirm the initial optimism regarding peanut oil as a vehicle when administered in realistic dosage form vehicle volumes. A weighted unpaired *t*-test revealed no significant differences between the aqueous and peanut oil vehicles with respect to peak plasma concentration, peak time, or *AUC* ($\alpha = 0.05$). These results suggest that any enhanced availability in the peanut oil vehicle, which was suggested by the initial study, may have been due to physiological effects on the GI tract caused by the relatively large vehicle volume used. Such effects appeared to be eliminated when the dosage form vehicle volumes were used.

A further aspect of these studies is the comparison of the doses used in both the large and small volume experiments. In the 1-ml administered volume study, each rat received ~2.5 mg of triamterene; in the 20-μl volume study, the administered dose was ~0.9 mg. The *t*-test revealed that neither peak height nor peak time was significantly different between these two studies ($\alpha = 0.5$). However, with the aqueous suspension, the *AUC* for the 20-μl dose volumes was greater ($p < 0.05$) than with the 1-ml volume. With the peanut oil suspensions, the *AUC* for the 20-μl dose volume was significantly less than with the 1-ml volume ($p < 0.001$) but, in absolute terms, was reduced by one-third compared with the dosage reduction of a factor of ~3. Clearly, the larger dose volumes for both peanut oil and aqueous suspensions adversely affected the oral availability of triamterene. The precise mechanism of this effect is unexplained, although it is probably due to some alteration of physiological processes within the GI tract caused by the large vehicle volumes.

The results indicated that the methodology used to evaluate the effects of various vehicles on the GI absorption of drugs must be carefully considered. The results of *in situ* perfusion studies and those employing large vehicle volumes may not be directly applicable to an actual dosage form. With triamterene, a drug poorly soluble in both aqueous and lipid vehicles, a large volume of lipid vehicle may provide some enhancement of oral availability when compared to aqueous vehicles. At least with peanut oil, however, when the vehicle volume is reduced to a realistic dosage form volume, the potential advantage is lost. Furthermore, small vehicle volumes result in better relative oral availability for triamterene than do large vehicle volumes. Such a finding might be considered with regard to the administration of triamterene in conjunction with some foods.

REFERENCES

(1) R. G. Crounse, *J. Invest. Dermatol.*, **37**, 529 (1961).

(2) M. Kraml, J. Dubue, and D. Beall, *Can. J. Biochem.*, **40**, 1449 (1962).

(3) P. J. Carrigan and T. R. Bates, *J. Pharm. Sci.*, **62**, 1476 (1973).

(4) J. G. Wagner, E. S. Gerard, and D. G. Kaiser, *Clin. Pharmacol. Ther.*, **7**, 610 (1966).

(5) D. G. Kaiser, E. M. Glenn, R. H. Johnson, and R. L. Johnson, *J. Pharmacol. Exp. Ther.*, **155**, 174 (1967).

(6) S. E. Swenson, W. L. DeLorenzo, R. Engelberg, M. Spooner, and L. O. Randell, *Antibiot. Med.*, **2**, 148 (1956).

(7) D. C. Bloedow and W. L. Hayton, *J. Pharm. Sci.*, **65**, 328 (1976).

(8) J. A. Grisafe and W. L. Hayton, *ibid.*, **67**, 895 (1978).

(9) V. Stella, J. Haslam, N. Yata, H. O'Kada, S. Lindenbaum, and T. Higuchi, *ibid.*, **67**, 1375 (1978).

(10) J. Kreuter and T. Higuchi, *ibid.*, **68**, 451 (1979).

(11) V. Alvisi, C. Longhini, B. Bagni, F. Portaluppi, M. Ruina, and C. Fersini, *Arzneim-Forsch.*, **29**, 1047 (1979).

(12) Y. Yamahira, T. Noguchi, H. Takenaka, and T. Maeda, *J. Pharmacokinet. Dyn.*, **1**, 160 (1978).

(13) Y. Yamahira, T. Noguchi, T. Noguchi, H. Takenaka, and T. Maeda, *ibid.*, **2**, 52 (1979).

(14) Y. Yamahira, T. Noguchi, H. Takenaka, and T. Maeda, *Int. J. Pharm.*, **3**, 23 (1979).

(15) S. Sved, J. A. A. Sertie, and I. J. McGilveray, *J. Chromatogr.*, **162**, 474 (1979).

(16) A. W. Pruitt, J. S. Winkel, and P. G. Dayton, *Clin. Pharmacol. Ther.*, **21**, 610 (1977).

(17) T. Noguchi, K. Taniguchi, S. Muranishi, and H. Sezaki, *Chem. Pharm. Bull.*, **25**, 434 (1977).

ACKNOWLEDGMENTS

Supported by grants from R. P. Scherer Corp. and Inter$_x$ Research Corp.

Compression Properties of Granulations Made with Binders Containing Different Moisture Contents

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Received June 27, 1980, from the *Institute of Pharmaceutical Sciences, Syntex Research, Palo Alto, CA 94304.* Accepted for publication March 5, 1981.

Abstract □ The role of the granulation moisture content on compression properties of granules made with selected binders was studied. The results suggested that, at lower pressures, higher moisture-containing granules were slightly more compressible than lower moisture-containing granules. However, at higher pressures, the reverse was true because of the water lubrication effect. At lower moisture levels, the crushing strength of the tablets was dependent on the binder; at higher moisture levels, binder differences became less significant.

Keyphrases □ Compression—effect of moisture content on granulations made with various binders □ Granulations—effect of moisture content on compression properties, various binders □ Binders—various, effect of moisture content on compression properties of granulations

The compression behavior of four pharmaceutical powders of widely different particle-size distribution and shape was reported previously (1). It was shown that the Heckel (2) and Cooper–Eaton (3) equations can be used

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Table I—Tablet Formulations [a]

Ingredient	Formulation A	B	C	D	E
Ticlopidine hydrochloride	250	250	250	250	250
Lactose	91.25	91.25	91.25	91.25	99.05
Starch	39.00	39.00	39.00	39.00	39.00
Magnesium stearate	1.95	1.95	1.95	1.95	1.95
Methylcellulose	7.8	—	—	—	—
Povidone	—	7.8	—	—	—
Pregelatinized starch	—	—	7.8	—	—
Hydroxypropyl methylcellulose	—	—	—	7.8	—

[a] Milligrams of ingredient per tablet.

to quantify the compression parameters of powders, provided that various experimental conditions are considered.

The relative density *versus* pressure plots of the granulations made with powder mixtures by wet granulation did not give a typical relationship (4), as previously explained (2). A break in the linear portion of the Heckel plots at a pressure range of ~1200–1900 kg/cm^2 was explained largely on the basis of the water lubrication effect at higher pressures. At lower pressures, where the water lubrication effect did not occur, the relative density–pressure plots (2) and the Cooper–Eaton plots (3) were used to calculate the apparent material constants and the coefficients of the Cooper–Eaton equation. Excellent correlation between the apparent material constant (C_1) of the Heckel equation and the coefficient (k_2) of the Cooper–Eaton equation and the tablet crushing strength suggested the usefulness of these studies for proper binder selection when designing tablet formulations.

This paper reports the role of moisture content on compression properties of granulations made with selected binders.

EXPERIMENTAL

Materials—Ticlopidine hydrochloride[1] (I) was at least 98% pure. The excipients, crystalline lactose[2], starch[3], magnesium stearate[4], povidone[5], methylcellulose[6], hydroxypropyl methylcellulose[7], and pregelatinized starch[3], were all USP grade.

Granulation—The formulations are listed in Table I. Compound I and lactose were mixed together in a small planetary mixer for 5 min. For Formulation C, pregelatinized starch was also mixed with I and lactose and granulated with purified water by mixing for 5 min. For Formulations A, B, and D, the binder was dispersed or dissolved in the same amount of water as was used in granulating Formulation C. The I–lactose mixture (39 g) was granulated with 15 ml of the granulating solution by mixing for 5 min.

For Formulation E, the I–lactose mixture was granulated with 15 ml of purified water. The wet granulation was passed through a 1.4-mm aperture and dried in a forced-air oven at 40° until the desired moisture levels were obtained. The dried granulation was screened through a 1.2-mm aperture. Starch and magnesium stearate then were blended with the granulation for 5 min.

Compression—For each compression, 390 mg of the granulation was used[8]. The die and punches were 10.32 mm in diameter, and the punches were flat-faced. The contact time of the upper punch with the granulation was less than 5 sec. Immediately after compression and ejection, the height of the compact was measured accurately and the volume and density of the compact were calculated. Three determinations were made for each data point. The mean volumes of compression, along with the standard deviations at given pressures for granulations made with the selected binders, are given in Table II.

Tablet Crushing Strength—The compact hardness was determined[9] immediately after compression. For each hardness determination, three compacts were tested and the mean was calculated.

Moisture Determination—An aluminum dish was dried in a forced-air oven at 60° for 30 min. The dish was then equilibrated to room temperature, and the sample was accurately weighed into the dish and

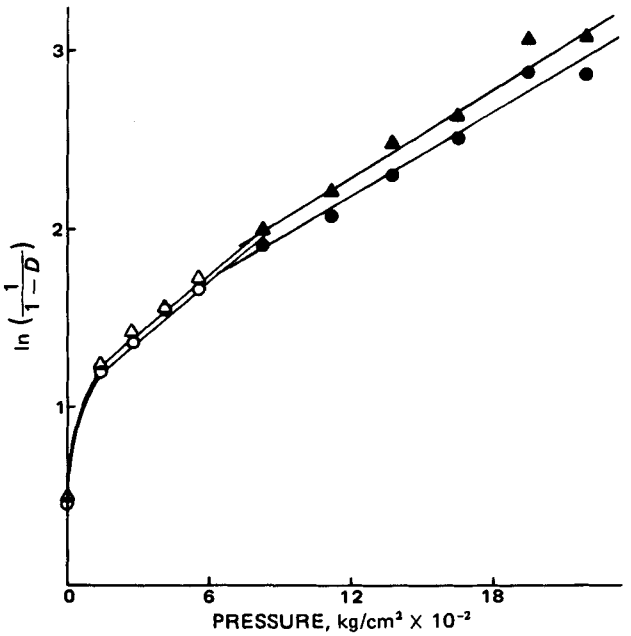

Figure 1—*Plots of ln[1/(1 − D)] versus pressure using granulations made with povidone (△,▲) and methylcellulose (○,●) as binders. The moisture contents at the time of compression were 1.12% for povidone granules and 0.89% for methylcellulose granules.*

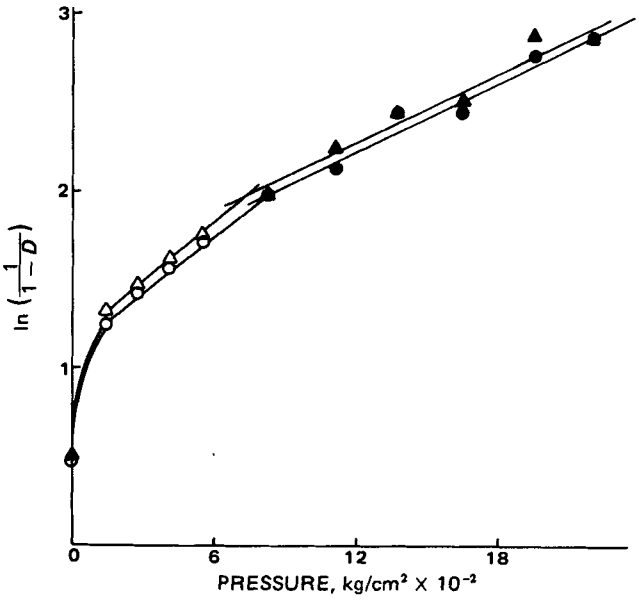

Figure 2—*Plots of ln[1/(1 − D)] versus pressure using granulations made with pregelatinized starch (○, ●) and without a binder (△,▲). The moisture contents at the time of compression were 0.79% for pregelatinized starch granules and 0.77% for granules made without a binder.*

[1] 5-(o-Chlorobenzyl)-4,5,6,7-tetrahydrothieno-[3,2-c]pyridine hydrochloride, Sanofi Research Co., New York, NY 10019.
[2] Regular grade, Foremost Co., San Francisco, CA 94104.
[3] Staley Manufacturing Co., Decatur, IL 62525.
[4] Mallinckrodt Chemical Co., St. Louis, MO 63134.
[5] GAF Corp., New York, NY 10020.
[6] Methocel A-15, Dow Chemical Co., Midland, MI 48640.
[7] Pharmacoat 606, Shinetsu Chemical Co., Tokyo, Japan.
[8] Model b Carver laboratory press, Fred S. Carver Inc., Summit, NJ 07901.
[9] Schleuniger-2E hardness tester, Vector Corp., Marion, IA 52302.

Table II—Mean Volumes [a] of Compression for Granulations Made with Selected Binders Containing Different Moisture Contents

Pressure, kg/cm²	Methylcellulose		Povidone		Pregelatinized Starch		Hydroxypropyl Methylcellulose			No Binder	
	2.44% Moisture	0.89% Moisture	2.23% Moisture	1.12% Moisture	2.02% Moisture	0.79% Moisture	3.35% Moisture	2.32% Moisture	0.75% Moisture	1.95% Moisture	0.77% Moisture
135.9	0.395 ± 0.004	0.414 ± 0.002	0.393 ± 0.000	0.405 ± 0.002	0.399 ± 0.004	0.401 ± 0.002	0.389 ± 0.002	0.401 ± 0.000	0.412 ± 0.002	0.389 ± 0.004	0.382 ± 0.002
271.9	0.369 ± 0.000	0.389 ± 0.002	0.365 ± 0.004	0.380 ± 0.004	0.369 ± 0.002	0.380 ± 0.002	0.367 ± 0.002	0.378 ± 0.006	0.384 ± 0.002	0.372 ± 0.002	0.361 ± 0.002
407.8	0.355 ± 0.002	0.367 ± 0.002	0.350 ± 0.002	0.365 ± 0.000	0.352 ± 0.000	0.363 ± 0.002	0.352 ± 0.002	0.357 ± 0.002	0.369 ± 0.002	0.357 ± 0.002	0.346 ± 0.002
543.7	0.346 ± 0.000	0.357 ± 0.002	0.340 ± 0.002	0.350 ± 0.000	0.342 ± 0.002	0.350 ± 0.002	0.340 ± 0.002	0.350 ± 0.002	0.361 ± 0.000	0.346 ± 0.002	0.338 ± 0.002
815.6	0.331 ± 0.002	0.340 ± 0.002	0.321 ± 0.002	0.333 ± 0.002	0.329 ± 0.002	0.333 ± 0.002	0.329 ± 0.004	0.333 ± 0.002	0.342 ± 0.000	0.331 ± 0.002	0.325 ± 0.002
1359.3	0.314 ± 0.002	0.321 ± 0.004	0.310 ± 0.004	0.314 ± 0.002	0.312 ± 0.000	0.314 ± 0.002	0.314 ± 0.002	0.316 ± 0.002	0.321 ± 0.002	0.314 ± 0.002	0.312 ± 0.000
1631.2	0.310 ± 0.002	0.314 ± 0.002	0.306 ± 0.002	0.310 ± 0.002	0.308 ± 0.002	0.314 ± 0.002	—	0.312 ± 0.002	0.312 ± 0.002	0.312 ± 0.000	0.306 ± 0.000
2174.9	0.304 ± 0.002	0.360 ± 0.000	0.299 ± 0.002	0.301 ± 0.000	0.306 ± 0.002	0.304 ± 0.000	0.360 ± 0.002	0.308 ± 0.002	0.308 ± 0.002	0.304 ± 0.002	0.304 ± 0.002

[a] In cubic centimeters (mean ± *SD*).

dried in the oven at 60° until it reached a constant weight. The moisture content was calculated from the sample weight before and after drying.

Bulk Density—The powder was slowly sifted into a 50-ml graduated cylinder through a plastic funnel. The powder weight (W) and volume (V) were recorded to calculate the bulk density ($\gamma_b = W/V$).

True Density—The true density of the granules was calculated from the true density of the individual components in the formulation. The method of density matching (5) was used to determine the true density of individual components. A few milligrams of the powder was added to the test tubes containing different combinations of carbon tetrachloride and hexane mixtures. The powder–solvent mixture was shaken on a vortex mixer, centrifuged, and allowed to stand for 30 min. The true density of the powder was the same as the density of the solvent mixture in which the powder remained suspended. The density of the solvent mixture was determined with a pycnometer at 23° using water to calibrate the volume.

RESULTS AND DISCUSSION

The relative density *versus* pressure plots of the granulations made with selected binders at different moisture levels are given in Figs. 1 and 2 (moisture content, 0.77–1.12%) and 3 and 4 (moisture content, 1.95–2.44%). The relative density *versus* pressure plots of the granulations made with hydroxypropyl methylcellulose at different moisture levels are given in Fig. 5.

As reported previously (4), the relative density *versus* pressure plots of the granulations made with powder mixtures do not give a typical relationship, as explained by Heckel (2). According to the Heckel equation (Eq. 1), plots of $\ln [1/(1-D)]$ *versus* pressure (P) give, on extrapolation, the material constant (C), which is identified with the reciprocal yield pressure of the material, and the intercept (I), which is identified with the movement of particles during the initial stages of compaction:

$$\ln\left(\frac{1}{1-D}\right) = CP + I \qquad \text{(Eq. 1)}$$

where D (relative density of the compact) is obtained by dividing the bulk density at a given pressure by the true density (calculated). However, bulk density was determined on granules before compression (no pressure).

The break in the relative density *versus* pressure plots (Figs. 1–5) could be attributed largely to the water lubrication effect. At higher pressures, the small amount of water in the granulation is squeezed out to the surface of the die wall and thus reduces the die wall friction. However, at lower pressures, the small amount of water in the granules remains in the

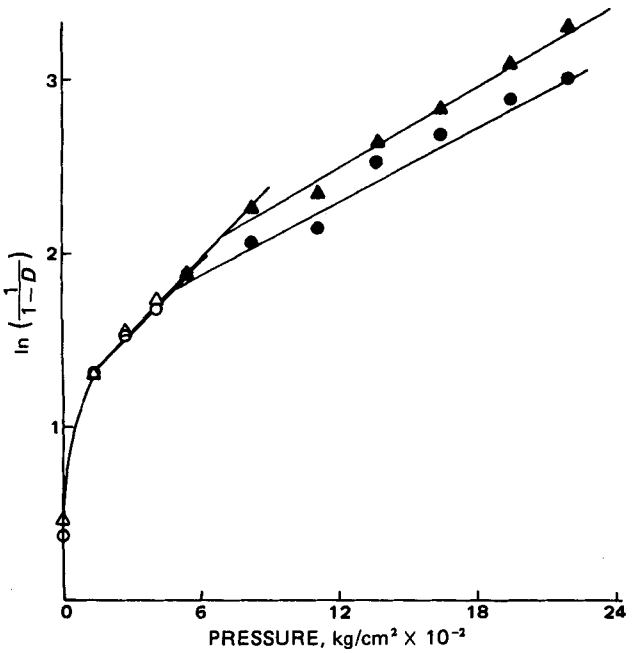

Figure 3—*Plots of ln[1/(1 − D)] versus pressure using granulations made with povidone (△,▲) and methylcellulose (○,●) as binders. The moisture contents at the time of compression were 2.23% for povidone granules and 2.44% for methylcellulose granules.*

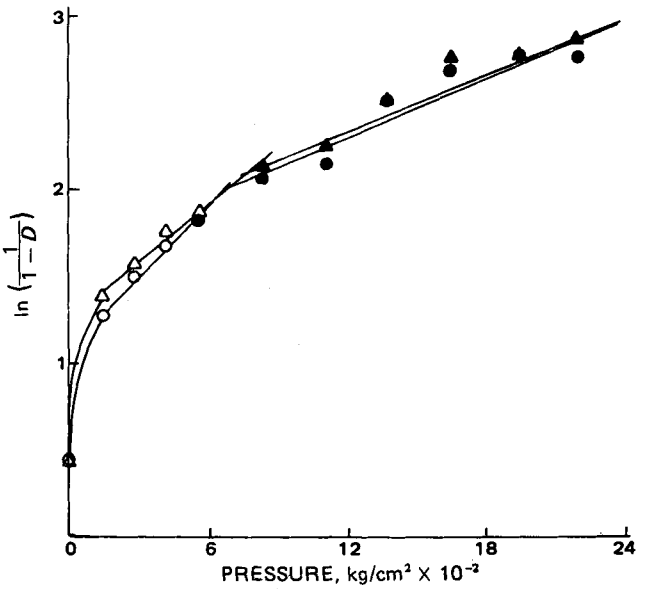

Figure 4—*Plots of ln[1/(1 − D)] versus pressure using granulations made with pregelatinized starch (○,●) and without a binder (△,▲). The moisture contents at the time of compression were 2.02% for pregelatinized starch granules and 1.95% for granules made without a binder.*

Table III—Values of Bulk Density, Calculated True Density, and Densification of the Granules Made with Selected Binders Containing Different Moisture Contents

Binder	Moisture Content, %	Bulk Density, g/ml	Calculated True Density	D_0	D_a	D_b
None	0.77	0.538	1.357	0.396	0.702	0.306
	1.95	0.490	1.354	0.362	0.723	0.361
Methyl-	0.89	0.490	1.355	0.362	0.647	0.285
cellulose	2.44	0.420	1.348	0.312	0;692	0.380
Povidone	1.12	0.521	1.348	0.386	0.671	0.285
	2.23	0.512	1.345	0.381	0.690	0.309
Pregelatinized	0.79	0.516	1.357	0.380	0.669	0.289
starch	2.02	0.477	1.351	0.353	0.695	0.342
Hydroxypropyl	0.75	0.499	1.355	0.368	0.688	0.320
methylcellulose	2.32	0.457	1.348	0.339	0.677	0.338
	3.35	0.446	1.346	0.331	0.696	0.365

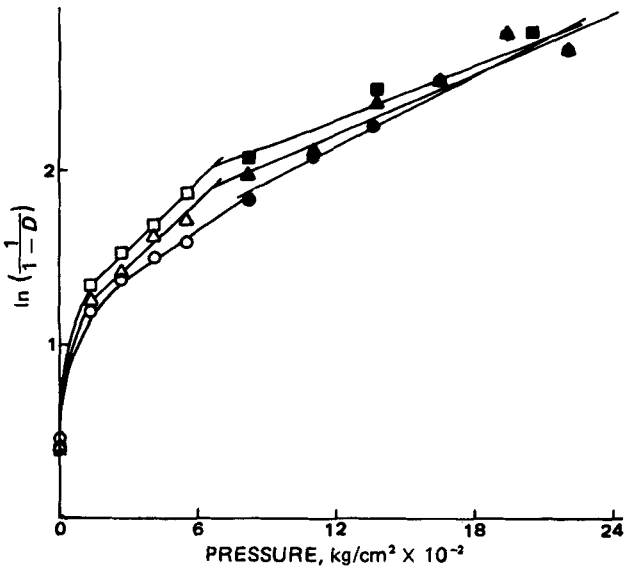

Figure 5—*Plots of ln[1/(1 − D)]* versus *pressure using granulations made with hydroxypropyl methylcellulose as a binder. The moisture contents at the time of compression were 3.35% (□,■), 2.32% (△,▲), and 0.75% (○,●).*

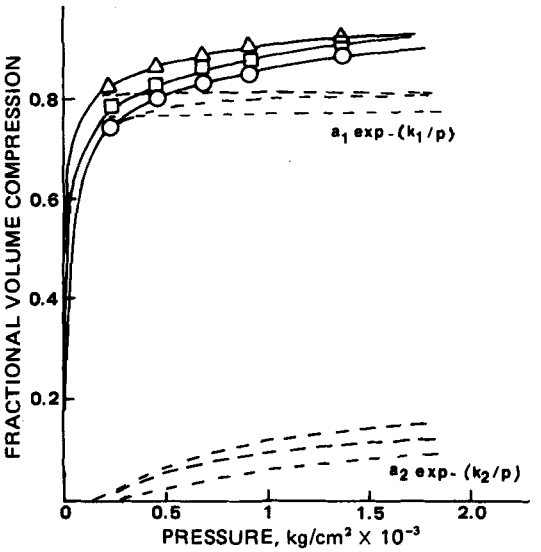

Figure 6—*Fractional volume compression* versus *pressure plots of the granulation made with hydroxypropyl methylcellulose dried to different moisture contents. Key: ○, 0.75% moisture; □, 2.32% moisture; and △, 3.35% moisture. Dotted lines indicate calculated results of Eq. 4.*

granulation and the powder mixtures behave as a single material. In view of the water lubrication effect, the first part of the relative density–pressure plots could be analyzed by the Heckel equation.

Table III gives the values of the bulk density and the calculated true density of the granules made with selected binders containing different moisture contents and the three-stage densification values, D_0, D_a, and D_b. These values represent the three-stage densification process that takes place: filling the die (D_0), individual particle movement and rearrangement (D_b), and particle deformation after interparticle bonding becomes appreciable (D_a).

The D_a value was obtained from the measured intercept value, I (Eq. 1), and the relationship:

$$D_a = 1 - e^{-I} \qquad \text{(Eq. 2)}$$

The D_b value was obtained from the experimental bulk density, D_0:

$$D_b = D_a - D_0 \qquad \text{(Eq. 3)}$$

In agreement with previous results (1, 2, 4), D_a values were higher than D_b values, indicating that more densification occurred by granule deformation than by rearrangement and granule movement. However, these values did not show significant effect due to differences in the type of binder or the percent moisture content. The concentration of binders in these formulations was even lower than that used previously (4).

At lower moisture levels (0.75–1.12%), the values of the apparent material constant, C_1 (Table IV), suggest that granules made with methylcellulose, povidone, and pregelatinized starch are more compressible than granules made with hydroxypropyl methylcellulose and without a binder. However, at higher moisture levels (1.95–2.44%), the values of the ap-

Table IV—Values of the Apparent Material Constants, C_1 and C_2, and Intercept I of Compacts Made from Granules Containing Different Binders

Binder	Moisture Content, %	C_1, $(kg/cm^2)^{-1} \times 10^4$	I	Correlation Coefficient	C_2, $(kg/cm^2)^{-1} \times 10^4$	Correlation Coefficient
None	0.77	10.11	1.212	0.999	6.77	0.979
	1.95	11.07	1.282	0.994	5.99	0.968
Methylcellulose	0.89	11.33	1.042	0.994	7.68	0.984
	2.44	11.98	1.179	0.991	7.59	0.986
Povidone	1.12	11.41	1.111	0.999	8.98	0.983
	2.23	14.10	1.170	0.995	8.96	0.992
Pregelatinized	0.79	11.26	1.107	1.000	6.89	0.982
starch	2.02	11.73	1.186	0.987	6.83	0.969
Hydroxypropyl	0.75	8.24	1.164	0.998	7.31	0.963
methylcellulose	2.32	11.96	1.129	0.989	6.58	0.956
	3.35	13.31	1.190	1.000	5.92	0.988

Table V—Values of a_1, a_2, k_1, and k_2 of the Compacts Made from Granulations Containing Different Binders

Binder	Moisture Content, %	a_1	a_2	k_1, kg/cm^2	k_2, kg/cm^2
None	0.77	0.77	0.23	2.05	482.37
	1.95	0.82	0.17	3.03	355.76
Methylcellulose	0.89	0.76	0.24	4.25	386.61
	2.44	0.83	0.14	2.63	245.97
Povidone	1.12	0.74	0.27	1.00	393.22
	2.23	0.82	0.15	9.53	324.32
Pregelatinized starch	0.79	0.75	0.25	0.71	420.18
	2.02	0.82	0.16	7.53	315.87
Hydroxypropyl methylcellulose	0.75	0.80	0.17	10.10	469.58
	2.32	0.81	0.18	2.55	392.55
	3.35	0.82	0.19	0.07	368.38

Table VI—Crushing Strength Change after Overnight Exposure to Ambient Room Conditions in Tablets Compressed at 815 kg/cm^2

Binder	Moisture Content, %	Initial Crushing Strength, Strong–Cobb units	Crushing Strength after Overnight Exposure, Strong–Cobb units
Pregelatinized starch	2.02	7.77 ± 0.55	7.73 ± 0.32
Povidone	2.23	7.6 ± 0.6	10.77 ± 0.38
Methylcellulose	2.44	7.77 ± 2.59	10.93 ± 0.42
Hydroxypropyl methylcellulose	2.32	7.80 ± 0.17	9.33 ± 0.68
None	1.95	5.27 ± 1.06	4.27 ± 0.86

parent material constant, C_1 (Table IV), suggest that granules made with povidone are more compressible than granules made with other binders.

The C_2 values, representing the slope of the second linear region (Table IV), were obtained under the assumption that the compact above a certain pressure (P) compresses under the water lubrication effect, thus giving a higher yield pressure. At lower moisture content, the C_2 values suggest that the granules made with methylcellulose and povidone are more compressible than granules made with other binders. At higher moisture contents, the C_2 values suggest that methylcellulose and povidone are also slightly more compressible than granules made with other binders.

In general, the C_1 values indicate that the granulations containing lower moisture levels are slightly less compressible than those containing higher moisture levels. However, the C_2 values suggest that the lower moisture-containing granules are slightly more compressible than the higher moisture-containing granules. At higher applied pressures, granules containing more moisture may exhibit a barrier to compression due to the water lubrication effect, thus making these granules more difficult to compress.

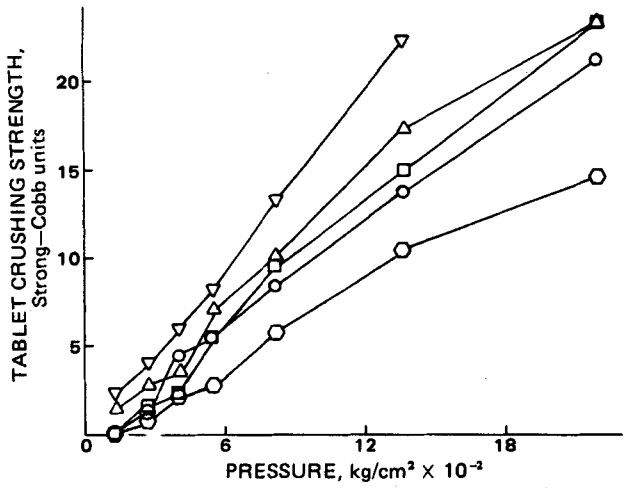

Figure 7—*Tablet crushing strength* versus *pressure profiles of tablets compressed from granulations made with different binders. The moisture contents of the granules at the time of compression were 0.89% (methylcellulose) (▽); 0.79% (pregelatinized starch) (△); 1.12% (povidone) (○); 0.75% (hydroxypropyl methylcellulose) (○); and 0.77% (no binder) (□).*

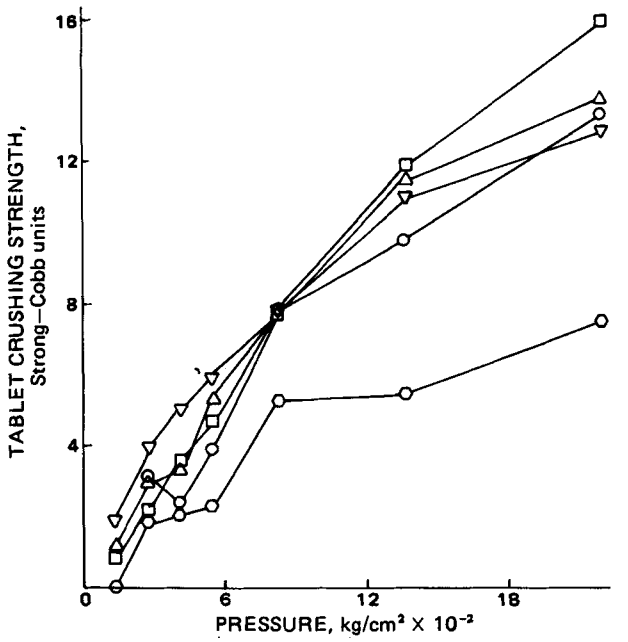

Figure 8—*Tablet crushing strength* versus *pressure profiles of tablets compressed from granulations made with different binders. The moisture contents of the granules at the time of compression were 2.23% (povidone) (□); 2.02% (pregelatinized starch) (△); 2.32% (hydroxypropyl methylcellulose) (○); 2.44% (methylcellulose) (▽); and 1.95% (no binder) (○).*

Cooper and Eaton (3) analyzed compression behavior of ceramic powders by assuming two largely independent probabilistic processes, the filling of large holes and the filling of small pores. The Cooper–Eaton equation (Eq. 4) relates the fractional value compression, V^*, to the applied pressure, P:

$$V^* = \frac{V_0 - V}{V_0 - V_\infty} = a_1 \exp - (k_1/P) + a_2 \exp - (k_2/P) \quad \text{(Eq. 4)}$$

where:

V_0 = initial total volume when no holes are filled
V = compact volume
V_∞ = compact volume when all holes of all types are filled
a_1 and a_2 = dimensionless coefficients indicating a fraction of the theoretical compression that would be achieved at infinite pressure by each particular process
k_1 and k_2 = coefficients with units of pressure where the particular process is most probable

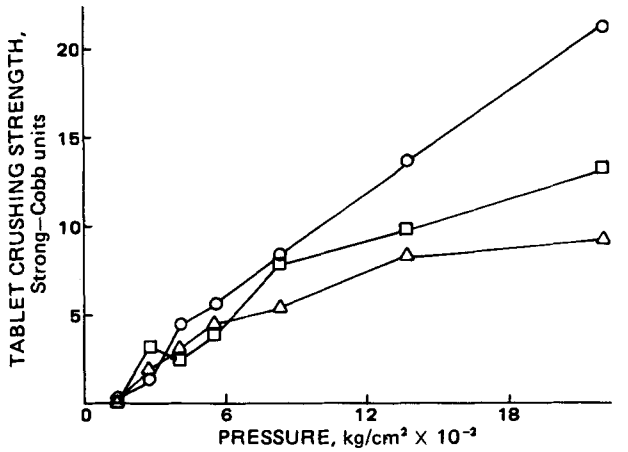

Figure 9—*Tablet crushing strength* versus *pressure profiles of tablets compressed from granulations made with hydroxypropyl methylcellulose. The moisture contents of the granules at the time of compression were 0.75% (○), 2.32% (□), and 3.55% (△).*

The fractional volume compression *versus* applied pressure plots up to the first linear region of the relative density *versus* pressure plots were used to calculate the coefficients of the Cooper–Eaton equation (Table V). Figure 6 gives the fractional volume compression *versus* pressure plots of the granulation made with hydroxypropyl methylcellulose and dried to different moisture contents. The experimental data were fitted to the results of the calculations using Eq. 4. The values of the coefficients were obtained from the best-fit curves.

The larger values of the dimensionless coefficient a_1 compared to a_2 (Table V) suggest that a large percentage of compression was achieved by filling large holes. The sum of coefficients a_1 and a_2 ranged from 0.97 to 1.01, indicating that compression is achieved by the two probabilistic processes of filling large and small holes by rearrangement, fragmentation, and plastic flow.

The coefficient k_1 gives the pressure needed to fill the large holes. This process occurs primarily by particles sliding past one another, which may require elastic deformation or even slight fracturing or plastic flow of particles. This process occurs at low pressures and is reflected in small k_1 values (Table V).

The coefficient k_2 indicates the pressure needed to fill small voids that are substantially smaller than the original particles. These voids can be filled by plastic flow or by fragmentation. This process requires high pressure, which is reflected in large k_2 values (Table V). Thus, k_2 provides more information about granulation compressibility since, during the rearrangement process, granules do not produce hard compacts. The k_2 values given in Table V indicate that, at lower moisture contents, methylcellulose- and povidone-containing granules are more compressible than granules made with the other binders. At higher moisture contents, methylcellulose-containing granules are more compressible than granules made with other binders. The k_2 values also suggest that the higher moisture-containing granules are more compressible than those of lower moisture content. This finding is in complete agreement with the C_1 values of the Heckel plots (Table IV), which suggest that the high moisture granules compress more easily than the low moisture ones.

The tablet crushing strength *versus* pressure profiles of granulations made with the selected binders containing different moisture contents are given in Figs. 7–9. At lower moisture contents (0.75–1.12%), methylcellulose-containing tablets gave higher crushing strengths than those made with granules containing other binders. The tablets made from granules without a binder were lower in crushing strength than the tablets made from granules containing binders.

At higher moisture levels (1.95–2.44%), differences in tablet crushing strength due to the binders were small (Fig. 8). Povidone-containing granules were better in crushing strength only at high pressure. Granules without a binder showed lower tablet crushing strengths compared to those with different binders.

Figure 9 compares the tablet crushing strength *versus* pressure profiles of the tablets compressed from granulations made with hydroxypropyl methylcellulose at different moisture levels. These results clearly show that the lower moisture-containing granules gave a higher crushing strength compared to the higher moisture-containing granules and that these differences became more pronounced as pressure was increased.

At higher moisture levels, it is important to consider the moisture-induced crushing strength increase phenomenon (6). Table VI gives the initial crushing strength and the crushing strength after a 24-hr exposure to ambient room conditions of tablets compressed at a given pressure. The crushing strength of tablets containing povidone, methylcellulose, and hydroxypropyl methylcellulose increased after overnight exposure to ambient room conditions. Pregelatinized starch-containing tablets did not show any change in crushing strength after overnight exposure to ambient room conditions. In the absence of a binder, the tablet crushing strength actually decreased after overnight exposure to ambient room conditions.

REFERENCES

(1) Z. T. Chowhan and Y. P. Chow, *Int. J. Pharm.*, **5**, 139 (1980).

(2) R. W. Heckel, *Trans. Metall. Soc. AIME*, **221**, 671, 1001 (1961).

(3) A. R. Cooper and L. E. Eaton, *J. Am. Ceram. Soc.*, **45**, 97 (1962).

(4) Z. T. Chowhan and Y. P. Chow, *Int. J. Pharm. Technol. Prod. Manuf.*, **2**, 29 (1981).

(5) G. Oster and M. Yamamoto, *Chem. Rev.*, **63**, 257 (1963).

(6) Z. T. Chowhan and L. Palagyi, *J. Pharm. Sci.*, **67**, 1385 (1978).

Leaching of 2-(2-Hydroxyethylmercapto)benzothiazole into Contents of Disposable Syringes

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Received November 17, 1980, from the **Perinatal Pharmacology Laboratory, Foundation 41, The Women's Hospital, Crown Street, Surry Hills, 2010 Australia*, and the ‡*Department of Pharmacy, University of Sydney, Sydney, Australia.* Accepted for publication March 6, 1981.

Abstract □ A contaminant was found to leach into the contents of two brands of disposable syringes. It was identified as 2-(2-hydroxyethylmercapto)benzothiazole and is believed to be formed during manufacture of the syringes as a result of a reaction between 2-mercaptobenzothiazole, a rubber vulcanization accelerator, and ethylene oxide, used for sterilization. The contaminant was isolated from the rubber plunger-seal and identified using mass, NMR, and UV spectroscopic methods. The amount of contaminant appearing in the contents of syringes was measured; up to 140 μg was found under clinically relevant conditions. This finding has important implications with respect to the use of these syringes for drug administration and for the collection of blood for drug analyses.

Keyphrases □ 2-(2-Hydroxyethylmercapto)benzothiazole—leaching into contents of disposable syringes, isolation, identification, and quantitation □ Syringes, disposable—leaching of 2-(2-hydroxyethylmercapto)benzothiazole, isolation, identification, and quantitation □ Contaminants—2-(2-hydroxyethylmercapto)benzothiazole, leaching from disposable syringes

Several previous reports described the problems associated with the leaching of compounds from plastic infusion bags and giving sets and from blood collection tubes. The measurement of drug levels in blood and plasma samples for toxicological, therapeutic monitoring, or pharmacokinetic purposes may be hampered by such contaminants. In addition, the accumulation of plasticizers in patients' organs after transfusion of blood from plastic storage bags was reported (1).

Recently, contamination of blood collected in evacuated

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