Unloading and Postcompression Viscoelastic Stress *versus* Strain Behavior of Pharmaceutical Solids

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Abstract □ The viscoelastic properties of several compacts composed of drugs and direct compression excipients have been measured during the stress unloading and postcompression phases of the tablet compression process. Measurements of applied strains and the resultant stresses, generated in the tablet structure under compaction, were made using a rotary press. The press was instrumented to measure punch and die wall stresses at normal operating speeds. The three-dimensional viscoelastic theory, used in data analysis, provides for the separate characterization of tablet behavior into its dilation and distortion components. The tablets investigated were found to behave elastically in dilation, but to have both viscous and elastic contributions to their stress/strain relaxation in distortion. This latter behavior could be modeled well as a Kelvin solid. Data derived from an elastic-in-dilation, Kelvin-in-distortion analysis of tablets, compressed at similar machine speeds but at various peak pressures, were found to vary widely depending on tablet composition. Dependence of the viscous and elastic parameters on compression conditions was found to be predictive of conditions under which capping or lamination of the compact would occur.

Keyphrases □ Viscoelastic behavior—of compacts of drugs and direct compression excipients □ Tablet formulation—viscoelastic behavior of compacts during stress unloading and postcompression, parameters predictive of capping and lamination □ Compression—viscoelastic behavior of tablets, conditions predictive of capping and lamination

The physical properties of pharmaceutical tablets are of practical interest not only because they dictate manufacturing methodology and determine resistance to physical damage in handling, but also because they can influence drug bioavailability through the processes of tablet disintegration and dissolution. These properties or physical parameters can be categorized roughly in terms of those which may be observed under either changing or static conditions, or both. Viscoelastic properties of solids can be elucidated fully only if measurements of the dynamic relationships between stress and strain are made.

BACKGROUND

Effects of the time-dependent viscoelastic behavior of compressed tablets have been observed under a variety of transient conditions (1–6) and are distinguishable from the hysteretic effects, due to plastic failure, observed in radial *versus* axial pressure cycles measured under quasistatic or equilibrium conditions (3, 7, 8).

The successful formation of a pharmaceutical tablet by the compression of solid particulate matter depends on interparticulate bonding across particle–particle interfaces. The areas of virtual contact, necessary for bonding, are both formed and destroyed during the compression and decompression phases, and possibly also during ejection from the die. The net area of such interparticulate contacts, during and after compression, is expected to depend on the time-dependent flow of material which occurs in conjunction with instantaneously responding elastic deformations. Coupling of these processes results in the viscoelastic behavior observed during the compression of tablets at normal production speeds and, often, at slower speeds. The viscoelastic parameters of tablets and their components, therefore, are expected to be indicative of the relative sensitivity of tablet formation to the rates of compression and decompression, and the rate and nature of ejection from the die. More fundamentally, these parameters provide for insight into the kinetically controlled formation and destruction of interparticulate bonds and the resultant changes in internal structure which occur during and after these periods.

THEORETICAL

The temporal relationships between stress and strain which are exhibited by many materials can be described and analyzed in terms of viscoelastic theory and its related mathematical models. The elements of such models consist of springs, representing elastic behavior, and dashpots, corresponding to viscous flow characteristics.

The simplest application of this theory is to fully dense materials, either fluids or solids, in which voids do not occur. However, the presence of crystal dislocations, grain boundaries, or other structural irregularities in such solids can have a significant effect on their mechanical properties. Provided the test process does not in itself change these material properties, the viscoelastic constants determined by a given test procedure will be independent of the test and are true material constants. In applications such as powder metallurgy or pharmaceutical tablets, however, the structure under study is not fully dense. In these cases, the nature of the pores, crevices, or other voids is a significant part of the structure and is reflected in the measured viscoelastic parameters. Thus, these parameters are a function of the architecture of the tablet as well as the characteristics of the units of which it is constructed. Further, both the nature of the architecture and the material comprising the units can be expected to depend on the strain *versus* time profile of the compaction process; *i.e.*, the compression stress *versus* strain event as a function of time, together with the material constants of the tablet components (which are themselves likely to be dependent on the compression event), determine the viscoelastic parameters of the tablet proper. In the remainder of this paper when material behavior is discussed, the material referred to is the compact and not individual particles of its component substance(s).

The theory of linear three-dimensional viscoelasticity (9, 10) permits the dynamics of tablet compression to be mathematically separated into two components: isostatic contraction/dilation and distortion at constant volume. The former process occurs because the volume occupied by the tableted material is substantially reduced during compression and then increases slightly due to rebound. Because the tablet is confined radially by the die, the majority of this volume change occurs in the axial direction causing a change in the tablet height–diameter ratio, resulting in a distortion in shape.

Several three-dimensional viscoelastic models have been developed to describe the behavior of various materials in a rotary press and were tested against experimental stress/strain data collected during and after compression. Among those tested, four models were found to provide a good statistical fit to the data: Kelvin-in-dilation/Kelvin-in-distortion, elastic-in-dilation/three parameter solid-in-distortion, elastic-in-dilation/four parameter solid-in-distortion, and elastic-in-dilation/Kelvin-in-distortion. The latter was selected since it was the simplest model that fit the data.

Three sets of equations representing this model were developed (11). The first two sets describe the time dependence of axial stress (σ_{zz}) and radial stress (σ_{xx}) during the period of stress unloading:

$$\sigma_{zz} = A_1 - A_2[(r_1 + r_2)^2 - (r_3 \sin \omega t - x_2)^2]^{1/2} + \frac{A_3 \omega r_3 \cos \omega t (r_3 \sin \omega t - x_2)}{[(r_1 + r_2)^2 - (r_3 \sin \omega t - x_2)^2]^{1/2}} \quad \text{(Eq. 1)}$$

where the macroconstants are defined by:

$$A_1 = (2/3)[(q_0'' - q_0')\epsilon_{xx} + (2q_0' + q_0'')|z_0|/L] \quad \text{(Eq. 2)}$$

$$A_2 = (2/3)(2q_0' + q_0'')/L \quad \text{(Eq. 3)}$$

$$A_3 = (4/3)q_1'/L \quad \text{(Eq. 4)}$$

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Table I—Viscoelastic Constants [a] for Unloading and Postcompression Phases of Tablet Compression [b]

Viscoelastic Constant	Macroconstants [c]	Peak Punch Pressure, MPa 125	208	333
		Mannitol		
q_0'	A_1B_1	87.1 ± 4.1	152 ± 5	714 ± 12
q_0''	A_2B_2	88.9 ± 4.2	154 ± 5.1	716 ± 13
q_0''	A_1B_1	1540 ± 73	2180 ± 72	2780 ± 49
q_0''	A_2B_2	1550 ± 74	2180 ± 72	2780 ± 49
q_1'	$A_1B_1C_2$	3.35 ± 0.11	5.09 ± 0.14	10.1 ± 0.22
q_1'	$A_2B_2C_2$	3.38 ± 0.11	5.10 ± 0.14	10.1 ± 0.22
		Dextrose		
q_0'	A_1B_1	698 ± 21	1260 ± 19	1210 ± 18
q_0''	A_2B_2	700 ± 21	1270 ± 20	1220 ± 18
q_0''	A_1B_1	2070 ± 63	2920 ± 45	3340 ± 50
q_0''	A_2B_2	2070 ± 63	2920 ± 45	3350 ± 50
q_1'	$A_1B_1C_2$	6.74 ± 0.19	12.0 ± 0.22	10.1 ± 0.19
q_1'	$A_2B_2C_2$	6.75 ± 0.19	12.1 ± 0.22	10.1 ± 0.19
		Sucrose		
q_0'	A_1B_1	859 ± 24	1070 ± 17	1590 ± 21
q_0''	A_2B_2	860 ± 24	1070 ± 17	1590 ± 21
q_0''	A_1B_1	1810 ± 51	2450 ± 38	3200 ± 43
q_0''	A_2B_2	1810 ± 51	2450 ± 38	3210 ± 43
q_1'	$A_1B_1C_2$	4.23 ± 0.10	6.52 ± 0.14	8.84 ± 0.21
q_1'	$A_2B_2C_2$	4.23 ± 0.10	6.52 ± 0.14	8.85 ± 0.22
		Dextrate		
q_0'	A_1B_1	219 ± 4	652 ± 24	761 ± 16
q_0''	A_2B_2	221 ± 4	654 ± 24	765 ± 16
q_0''	A_1B_1	1160 ± 43	1950 ± 72	2580 ± 54
q_0''	A_2B_2	1160 ± 43	1960 ± 72	2590 ± 54
q_1'	$A_1B_1C_2$	3.09 ± 0.24	3.62 ± 0.15	14.0 ± 0.47
q_1'	$A_2B_2C_2$	3.09 ± 0.24	3.63 ± 0.15	14.1 ± 0.47
		Starch USP		
q_0'	A_1B_1	−23.4 ± 1.8 [d]	101 ± 8.3 [d]	−215 ± 68 [d]
q_0''	A_2B_2	−21.0 ± 1.6	104 ± 8.3	−207 ± 87
q_0''	A_1B_1	315 ± 24	364 ± 30	−76.7 ± 24
q_0''	A_2B_2	319 ± 25	370 ± 30	−61.2 ± 21
q_1'	$A_1B_1C_2$	0.766 ± 0.037	1.69 ± 0.087	−1.42 ± 0.24
q_1'	$A_2B_2C_2$	0.791 ± 0.038	1.720 ± 0.087	−1.34 ± 0.24
		Sulfanilamide		
q_0'	A_1B_1	698 ± 17	204 ± 6.4	209 ± 7.4
q_0''	A_2B_2	699 ± 17	207 ± 6.4	213 ± 7.5
q_0''	A_1B_1	2110 ± 52	1630 ± 51	1950 ± 69
q_0''	A_2B_2	2120 ± 52	1630 ± 51	1960 ± 69
q_1'	$A_1B_1C_2$	9.08 ± 0.21	5.54 ± 0.15	7.26 ± 0.19
q_1'	$A_2B_2C_2$	9.11 ± 0.21	5.55 ± 0.15	7.32 ± 0.19
		Sulfamerazine		
q_0'	A_1B_1	−374 ± 40 [e]	284 ± 10	229 ± 5.5
q_0''	A_2B_2	−372 ± 40	286 ± 10	232 ± 5.6
q_0''	A_1B_1	1300 ± 140	2320 ± 80	2410 ± 58
q_0''	A_2B_2	1300 ± 138	2330 ± 80	2410 ± 58
q_1'	$A_1B_1C_2$	0.791 ± 0.057	4.47 ± 0.20	3.45 ± 0.11
q_1'	$A_2B_2C_2$	0.797 ± 0.057	4.49 ± 0.20	3.45 ± 0.11
		Acetylsalicylic Acid		
q_0'	A_1B_1	−776 ± 38 [f]	−374 ± 12 [f]	−288 ± 9.6 [f]
q_0''	A_2B_2	−775 ± 37	−373 ± 12	−286 ± 9.4
q_0''	A_1B_1	3390 ± 164	4130 ± 130	3710 ● 124
q_0''	A_2B_2	3400 ± 163	4140 ± 128	3730 ± 123
q_1'	$A_1B_1C_2$	3.63 ± 0.11	6.26 ± 0.15	4.96 ± 0.15
q_1'	$A_2B_2C_2$	3.66 ± 0.11	6.29 ± 0.15	5.00 ± 0.14
		Salicylamide		
q_0'	A_1B_1	−632 ± 40 [f]	−252 ± 5.8 [f]	−117 ± 2.7 [f]
q_0''	A_2B_2	−631 ± 39	−251 ± 5.8	−115 ± 2.7
q_0''	A_1B_1	2820 ± 178	4610 ± 106	4310 ± 101
q_0''	A_2B_2	2820 ± 175	4620 ± 106	4320 ± 102
q_1'	$A_1B_1C_2$	3.60 ± 0.14	7.81 ± 0.14	7.78 ± 0.15
q_1'	$A_2B_2C_2$	3.61 ± 0.14	7.83 ± 0.14	7.81 ± 0.15
		Salicylic Acid		
q_0'	A_1B_1	−755 ± 185 [f]	−245 ± 8.8 [f]	−618 ± 26 [f]
q_0''	A_2B_2	−753 ± 183	−243 ± 8.7	−613 ± 25
q_0''	A_1B_1	2280 ± 560	3780 ± 136	4060 ± 173
q_0''	A_2B_2	2280 ± 553	3780 ± 136	4070 ± 169
q_1'	$A_1B_1C_2$	1.76 ± 0.23	7.55 ± 0.20	5.47 ± 0.20
q_1'	$A_2B_2C_2$	1.77 ± 0.23	7.56 ± 0.20	5.51 ± 0.20
		Acetaminophen		
q_0'	A_1B_1	−425 ± 33 [d]	136 ± 4.7	−1270 ± 28 [d,e]
q_0''	A_2B_2	−423 ± 31	138 ± 4.8	−1270 ± 27
q_0''	A_1B_1	2420 ± 188	4570 ± 158	4020 ± 894
q_0''	A_2B_2	2420 ± 179	4580 ± 158	4030 ± 854
q_1'	$A_1B_1C_2$	2.80 ± 0.13	8.84 ± 0.22	2.85 ± 0.35
q_1'	$A_2B_2C_2$	2.81 ± 0.13	8.86 ± 0.22	2.87 ± 0.34
		Phenacetin		
q_0'	A_1B_1	−629 ± 32 [d,e]	166 ± 3.0 [d]	−1320 ± 154 [d,e]
q_0''	A_2B_2	−627 ± 32	167 ± 3.1	−1320 ± 150
q_0''	A_1B_1	2890 ± 149	3920 ± 73	3700 ± 431
q_0''	A_2B_2	2900 ± 148	3920 ± 73	3720 ± 422
q_1'	$A_1B_1C_2$	3.49 ± 0.12	10.9 ± 0.18	2.51 ± 0.16
q_1'	$A_2B_2C_2$	3.52 ± 0.12	11.0 ± 0.18	2.56 ± 0.16

[a] Calculated from mean macroconstants derived from triplicate compressions. [b] Units are MPa for q_0' and q_0'' and MPa sec for q_1' (±*SE*). [c] Macroconstants used in calculation of viscoelastic constants. [d] Weak friable tablets. [e] Frequent capping and lamination on ejection. [f] Occasional capping and lamination on ejection.

and:

$$\sigma_{xx} = B_1 - B_2[(r_1 + r_2)^2 - (r_3 \sin \omega t - x_2)^2]^{1/2} - \frac{B_3 \omega r_3 \cos \omega t (r_3 \sin \omega t - x_2)}{[(r_1 + r_2)^2 - (r_3 \sin \omega t - x_2)^2]^{1/2}} \quad \text{(Eq. 5)}$$

where the macroconstants are defined by:

$$B_1 = (1/3)[(2q_0'' + q_0')\epsilon_{xx} + 2(q_0'' - q_0')|z_0|/L] \quad \text{(Eq. 6)}$$

$$B_2 = (2/3)(q_0'' - q_0')/L \quad \text{(Eq. 7)}$$

$$B_3 = (2/3)q_1'/L \quad \text{(Eq. 8)}$$

In the above equations: q_0' and q_0'' are the elastic microconstants in distortion and dilation, respectively; q_1' is the viscous microconstant in distortion; ϵ_{xx} is the radial strain; z_0 is the vertical punch displacement at separation from the tablet; ω is the turret angular velocity; x_2 is the horizontal distance between the vertical center line of the upper punch and the center of vertical curvature of the punch head rim; r_1 and r_2 are the radii of the compression roller and punch head rim, respectively; r_3 is the radial distance between the turret and punch axes; and L is the tablet thickness.

Following compression and prior to tablet ejection, the radial stress can be expressed as:

$$\sigma_{xx} = [\sigma_{xx}(0) - C_1] \exp(-C_2 t) + C_1 \quad \text{(Eq. 9)}$$

where:

$$C_1 = \frac{3q_0' q_0'' \epsilon_{xx}(0)}{2q_0' + q_0''} \quad \text{(Eq. 10)}$$

$$C_2 = (2q_0' + q_0'')/2q_1' \quad \text{(Eq. 11)}$$

and the microconstants are as defined above.

EXPERIMENTAL

Materials—Twelve substances, including drugs and popular organic excipients, were chosen to represent a broad spectrum of physical properties. Materials were selected which comprise a substantial volume fraction of tablets in which they appear, and whose tableting characteristics are generally well known. These range from brittle to plastic, from highly to poorly cohesive, and from highly crystalline to mixed partially amorphous monomers and polymers derived from natural sources.

Substances were dried in an oven for 14 hr at 70° and stored over anhydrous calcium sulfate prior to compression. Except for drying, all materials were used as received and were not mixed with a lubricant or other substance prior to compression. Because of a tendency to cake, dextrate[1] was not dried by heating. Other excipients included starch USP[2], sucrose[3], dextrose[4], mannitol[5], and sulfanilamide[6], sulfamerazine[7], salicylic acid[8], salicylamide[5], acetylsalicylic acid[4], acetaminophen[5], and phenacetin[9].

Methods—Details of the experimental setup and methodology have been reported previously (11) and are outlined here. Tablets were compressed on a rotary tablet machine[10] using 9.525-mm flat-faced punches. Punch and die wall stresses were measured using resistance strain gauges during and after compression. Signals displayed on an oscilloscope were photographed for later analysis. Because of the difficulty in mounting displacement transducers, punch displacements were calculated as a function of time from the known mechanical geometry of the machine. All tablets were compressed in the same location in the instrumented die, at the same angular velocity ($\omega = 2.76$ rad/sec) of the die table, and at the same punch settings. The die wall was lubricated prior to each compression by swabbing with a 10% slurry of magnesium stearate in ethanol. Compressions were ~70–80 msec in duration from punch contact to punch separation; experiments were conducted in triplicate at each of three peak punch pressures (125, 208, and 333 MPa). Pressures were adjusted by control of the fill weight of individually weighed charges.

Numerical data obtained by electronic digitization of scope photographs were analyzed in terms of Eqs. 1–11 using statistical regression programs (12, 13). Viscoelastic constants corresponding to elastic behavior in dilation and to Kelvin solid behavior in distortion were calculated from the regression coefficients in Eqs. 1 and 5. These equations describe punch and die stresses during the punch stress unloading phase of compression where the elastic contributions predominate. The viscous constant relating to distortion was obtained from the postcompression data using the exponential regression coefficient of Eq. 9, expressed as Eq. 11, together with previously determined elastic constants. The rationale for this method of viscoelastic microconstant calculation from the regression macroconstants has been discussed previously (11).

RESULTS AND DISCUSSION

Within the categories of drugs and excipients studied here, there was a degree of correlation between overall viscoelastic behavior and chemical composition. With the exception of starch, the carbohydrates (mannitol, dextrose, sucrose, and dextrate) were found to produce hard, well-formed tablets. As shown in Table I, all three viscoelastic parameters were seen to increase with increasing peak pressure, except for dextrose. In this latter case, the distortional constants decreased slightly at a peak pressure of 333 MPa. These compacts showed increased internal structural strength with increased pressure, as reflected by their viscoelastic properties. This is characteristic of readily compressible materials, and these carbohydrates are useful as binders when included in tablet formulations. It should be noted that the higher pressures employed in these studies were somewhat above those normally used in production. They were chosen to reveal the pressure sensitivity of viscoelasticity and to include the range of slugging pressures.

Before discussing starch and the remaining materials, it is necessary to consider the meaning of negative elastic and viscous microconstants in relation to internal tablet structure. Positive or negative elasticity can be related to the behavior of a simple spring. Consider the elastic behavior of a tablet in response to the confinement imposed on it by the die and punches. This condition corresponds to that of a spring under compression. A normal spring, *i.e.*, one having a positive modulus, would exert a decreased force on the die and punches with a decrease in its degree of compression. Conversely, a spring having a negative modulus would exert an increased force with a decrease in compression. Tablets undergoing unloading, following the application of the peak pressure, are springing back toward their final dimensions. This entails both an expansion in volume and a distortion in shape, since the diameter is held constant by the die. If, in the generation of increased voids produced by this process, sufficient interparticulate bonds are broken, internally borne stresses residing in elastically deformed particles will be transferred to the die wall. This behavior corresponds to a negative elastic modulus and reflects a disruption of internal structure. These constants are not solely a reflection of the nature of the materials comprising the tablet, but are strongly influenced by the efficiency of survival of the bonded areas within the tablet during elastic recovery. These bonds, which are formed during compaction, are a consequence of molecular forces acting across interfaces in zones of true interparticulate contact. If sufficient plastic deformation occurs at the bonded areas (or elsewhere in the structure) so that the stresses developed by elastic recovery do not exceed bond strength, the bonds will survive. However, if the disruption is sufficient, the integrity of the tablet will be destroyed.

Further, consider the case of a plastic body subjected to a shear stress sufficient to produce flow. In materials possessing positive coefficients of viscosity, an increase in the flow rate implies an increase in the applied stress. In such a system, the greater the rate of shear imposed, the greater the thrust or drag produced by the flow. Again (as seen with negative elasticity) an increasing breakdown of internal structure with increasing shear rates may be indicated. It must be emphasized that the substances which comprise compacts exhibiting negative viscoelastic parameters do not in themselves have negative elastic or viscous properties. Instead, it is the destruction of bonds within the structure of the tablet during elastic recovery that leads to such behavior. The viscoelastic constants reported here must be considered to reflect the behavior of the compact itself and are not primary constants related to the individual fully dense components only. This conclusion is supported further by the observed dependence of the viscoelastic parameters on pressure. Tablet microstructure can be expected to depend on compaction forces, and changes in structure resulting from changes in the compression process will be manifested by changes in the parameters.

Starch, as shown in Table I, exhibited all negative microconstants at a peak compaction pressure of 333 MPa. This was the only material–pressure combination of those studied which showed this behavior; an intact tablet could not be made at this pressure. A crumbled tablet also resulted at 125 MPa peak pressure, on ejection. Only at the intermediate pressure were intact, although fragile, tablets obtained. Their weak character is reflected by the very low values of the microconstants.

The sulfas are brittle crystalline materials which are noted for tablet-making difficulties due to lamination and capping. Sulfanilamide produced intact tablets at all pressures while sulfamerazine capped and laminated at 125 MPa.

Fracture and splitting of the tablets made from the salicylates was a common occurrence. Despite lubrication of the die and punches, die wall and punch face adhesion could not be avoided totally. Acetaminophen and phenacetin also are known for the difficulties experienced in forming tablets from them. Their general behavior was similar to that of the salicylates, with frequent capping and lamination.

Although the 12 materials studied exhibited diverse viscoelastic behavior, as shown by the wide range in the numerical value of their microconstants, they may be separated into two distinct groups: those having negative distortional elastic moduli and those which do not. While all tablets in the former group did not laminate on ejection, they could be laminated easily with the fingernail. Moreover, all tablets which laminated showed negative q_0' values.

The group of materials exhibiting positive microconstants, over the range of pressures reported, could be divided further into two categories: those showing increased viscoelastic parameters with increased pressure and those with decreasing or relatively constant parameters at high pressures. Of the materials reported, only sulfanilamide fell in the latter category. These materials were compressed at peak pressures above 333 MPa to observe their tendency to laminate. Because of the danger to the instrumented die posed by these pressures (up to ~425 MPa), a standard die was used, and therefore, viscoelastic data are not available. A substantial fraction of the tablets in the second category capped and/or laminated, whereas this was a rare occurrence with the first four materials listed in Table I. The rate at which the compacts relax their stresses following compaction can be seen from Eq. 11 to be dependent not only on the viscous constant but also on the elastic constants. The latter constants serve to drive the plastic flow and also, in conjunction with the lateral strain, determine the residual die wall stress.

When tablets are ejected from the die, they are subjected to a transverse shearing stress at the point where they emerge from the die. This results from externally unsupported radial stresses in the portion of the tablet above the die face. The transverse shearing stress builds to a limit as progressively more of the tablet extends above the die and the tablet is ejected. Structural failure due to this stress, coupled with an

[1] Emdex; Edward Mendell Co., Inc., Carmel, N.Y.
[2] Sta-Rx 1500; S. E. Stanley Mfg. Co., Decatur, Ill.
[3] American Crystal Sugar, East Grand Forks, Minn.
[4] Mallinckrodt Inc., St. Louis, Mo.
[5] Sigma Chemical Co., St. Louis, Mo.
[6] Eastman Organic Chemicals, Rochester, N.Y.
[7] Matheson Co., Norwood, Ohio.
[8] Fisher Scientific Co., Fair Lawn, N.J.
[9] Merck & Co., Inc., Rahway, N.J.
[10] Colton model 216; Cherry-Burrell Corp., Park Ridge, Ill.

inadequate tablet shear strength, is thought to be the principal cause of capping and lamination, although there is some disagreement on this point (7). In support of this view (4), tablet formulations found to consistently laminate or cap were satisfactorily made with a press utilizing flexible die walls which retreat from the tablet prior to ejection.

In any case, it is apparent that the ejection of the tablet from the die subjects it to significant shear stresses. It is likely, therefore, that some internal strutural changes occur even in tablets that survive ejection and appear intact. For this reason, viscoelastic microconstants, when considered together with die wall stress, indicate the mechanical properties of the tablet within the die cavity and reflect the ability of the tablet to withstand ejection. In many, if not all, cases these parameters will not apply to the ejected tablet even though it has escaped gross fracture.

Because tablets were allowed to remain in the die for an extended period (several minutes in many cases) before being ejected manually by prying up the lower punch, the ejection event was atypical and did not reproduce production conditions. Studies utilizing an instrumented ejection cam to produce normal ejections are in progress to investigate this and other aspects of tablet viscoelasticity.

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Inhibition of Oral Lead Absorption in Rats by Phosphate-Containing Products

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Abstract □ Recent studies indicate that elevated blood lead levels in children are largely a result of exposure to this metal *via* the oral route. A logical approach to decrease or prevent lead intoxication would be to reduce its absorption as soon as lead ingestion is known or suspected. Presently, however, there are no readily available products recommended to accomplish this goal. It was found that a phosphate-buffered, saline laxative reduced lead absorption over 50% in rats administered a single oral lead acetate dose, presumably by promoting the formation of less soluble lead salts. A popular phosphate-containing carbonated beverage also decreased lead absorption ~30% after oral lead acetate or lead-based paint doses, possibly by decreasing solubility, dissolution rate and/or GI motility. It is possible that these household products, and those with similar ingredients, may be safely used to reduce lead absorption in humans.

Keyphrases □ Lead absorption—reduction *in vivo* in rats by administration of phosphate-containing products □ Phosphate—lowering of blood lead levels in rats after oral administration of lead acetate or lead-based paint.

Ingested lead is the major source of the body burden of lead for most people (1). Children are exposed to lead from household dust (2), paint (3), and hand-to-mouth activity (4). Because they absorb a greater percentage of ingested lead than do adults (5), children have a higher risk of lead intoxication. Children with pica may be prone to chronic and repeated lead intoxication (6). Therapeutic intervention is not initiated, however, until blood-lead concentrations become elevated or symptoms of lead toxicity appear. It is recognized that subtle effects of lead on behavior and intelligence may occur in children at levels of exposure which do not produce elevated blood-lead concentrations or symptoms of lead intoxication (7). Prevention of lead exposure is therefore extremely important. Reduction of environmental lead and maintenance of sufficient dietary mineral intake partially achieve this objective. Presently there are no methods recommended to prevent or reduce the absorption of ingested lead.

A logical biopharmaceutical approach to reduce the extent of intestinal lead absorption, and thereby lead intoxication, is to decrease its solubility and dissolution rate in the GI tract. For some compounds, the extent of oral absorption is directly related to the absorption rate (8), which in turn may be limited by the rate of dissolution of the solid compound in the gut fluids (9). Dissolution rate is proportional to solubility, among other factors (10). Since the solubility products of lead phosphate and hydroxide are very low (Ksp $Pb_3(PO_4)_2 = 8 \times 10^{-43}$, Ksp of $Pb(OH)_2 = 1.2 \times 10^{-15}$) (11), it is possible that products containing phosphate or hydroxide ions might significantly reduce the extent of lead absorption by promoting the formation of insoluble lead phosphate and hydroxide salts in the GI tract. Since several household products contain

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