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VISCOELASTIC BEHAVIOR OF PHARMACEUTICAL MATERIALS DURING COMPACTION

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Introduction

It is well established in pharmaceutical literature that time dependent processes are involved in mechanisms of tablet formation. Simplistically, one can divide the process into three parts. Consolidation of the powder bed where particles are brought into intimate contact, formation of interparticulate bonds, and structural and dimensional changes in the tablet during stress unloading.[1-4] It is the intention here, to give the reader an idea of work that has been done to investigate time dependent phenomena throughout these parts of tablet formation. This article will focus on investigations made during tablet formation, rather than tests and investigation of mechanical and time dependent properties of ejected tablets.

Background in Viscoelasticity

A viscoelastic material is one that exhibits a relationship between stress and strain having both elastic and viscous components. Elastic behavior is modeled by

an ideal spring whose behavior obeys the equation:

$$\sigma = E\epsilon \tag{1}$$

where σ is the stress on the spring, ε is the strain, and E is the proportionality constant often called Young's modulus. Viscous behavior is modeled by a dashpot which can be visualized as a piston moving in a cylinder where between the piston wall and the cylinder there is a viscous lubricant. A stress is required to displace the piston. A dashpot's behavior obeys the equation:

$$\sigma = F\frac{d\epsilon}{dt} \tag{2}$$

where $d\varepsilon/dt$ is the strain rate, and F is the viscous proportionality constant. These two idealized elements can be combined to model viscoelastic behavior. If a spring and a dashpot are combined in series, the material is known as a Maxwell fluid. It's mechanical behavior is described by the equation:

$$\frac{d\sigma}{dt} + \frac{E}{F}\sigma = E\frac{d\epsilon}{dt} \tag{3}$$

where $d\sigma/dt$ is the stress time derivative, and the other symbols are as above. If the two elements are combined in parallel, the material is known as a Kelvin solid having the equation:

$$\sigma = E\epsilon + F\frac{d\epsilon}{dt} \tag{4}$$

Note, that when a Kelvin solid is subjected to a strain profile, the resultant stress will be a linear combination depending on the magnitude of the strain and the

magnitude of the **strain rate**. Therefore, it will behave like a spring when strained slowly. When subjected to a large rate of strain, the behavior of the dashpot will predominate.

Any number of more complicated models can be constructed by combining more of these two fundamental elements in series and/or parallel. It can be shown[5,6] that any possible viscoelastic model can be expressed as a collection of Maxwell bodies connected in parallel, or a collection of Kelvin bodies connected in series. The differential equation for this general model has the form:

$$\sigma + p_1\frac{d\sigma}{dt} + p_2\frac{d\sigma^2}{d^2t} + \cdots = q_0\epsilon + q_1\frac{d\epsilon}{dt} + q_2\frac{d^2\epsilon}{dt^2} + \cdots \quad (5)$$

where the p and q coefficients are algebraic combinations of the proportionality constants of the individual spring and dashpot elements comprising the model. These ordinary, linear, differential equations with constant coefficients are easily solved given appropriate, specified, initial conditions. Regression analysis of experimental data can also be done to determine spring and dashpot proportionality values of elements within a proposed model.

Visualize a number of Kelvin solids connected in series where they are rank ordered according to the magnitude of the dashpot constant. Now, this body is subjected to an intermediate strain rate with respect to the viscous constants. Dashpots with very low viscous constants will not retard the strain of their individual unit significantly. These units will appear to be an uncoupled spring. Dashpots with a very high viscous constant will undergo negligible strain. Only Kelvin units with dashpots with a viscosity of an intermediate value will undergo significant time

dependent deformation. Therefore, the strain rate that was selected determined which of the Kelvin units in the body we would see deform in a time dependent manner. In a very real sense, we see what we look for experimentally.

One often sees the word "plasticity" or the term "plastic deformation" used in the literature on tablet compaction. These terms are used to describe a state of material where the elastic strain limit has been exceeded, and non-recoverable deformation occurs. A material in this state is able to support exactly it's yield stress value. If stress on the material falls below the yield stress value, the material reverts to a non-plastic state. Conceptually, it is understood that the extent of non-recoverable deformation depends on the amount of time that the material is under yield stress. However, descriptions of plasticity do not deal with quantitating this time dependence. Plasticity theory does not deal with the relationship between the strain rate of the material in a plastic state and the stress needed to produce that strain rate. Viscoelastic theory is needed to examine this phenomena.

Stress Relaxation

Some early work examining time dependent behavior of tablets as they were being formed used stress relaxation measurements.[1] David and Augsburger[7] modeled pharmaceutical materials as a Maxwell fluids. Stress relaxation data was fit to a linearized form of the equation which describes the stress decay of a Maxwell fluid under constant strain as follows:

$$\ln\sigma = \ln\sigma_0 - \left(\frac{E}{F}\right)t \qquad (6)$$

The first order rate constant which they termed the viscoelastic slope is a ratio of the spring constant to the dashpot constant. In other words, the driving force divided by the retarding viscosity. Larger values for this slope were found for microcrystalline cellulose and starch than for sugar and dicalcium phosphate. Some deviation from linearity of the data for sugar was noted. This result is unexpected, since one would expect the elastic/viscous ratio to be smaller in the case of microcrystalline cellulose and starch where plastic flow is more extensive. Rees and Rue[8] performed stress relaxation experiments on these materials in a reciprocating tablet machine and found the Maxwell model inadequate to characterize the stress relaxation behavior of the materials. In the limiting case of infinite time, it is clear that the Maxwell equation for stress relaxation is unable to describe the behavior. The stress will always drop to zero at infinite time. This will not happen to a solid confined in a die under constant strain. Another model such as a standard linear solid (a Kelvin solid and a spring in series) might be better suited. Rees and Rue[8] also compared Heckel[9] plots obtained using different contact times to assess a material's time dependent consolidation behavior. The linearized Heckel equation is:

$$\ln\left(\frac{1}{1-D_{rel}}\right) = KP + A \qquad (7)$$

where D_{rel} is the relative density of the compact, P is the applied pressure, and K and A are constants. The slope, K, of the line is sometimes called the Heckel constant.

Roberts and Rowe[10] used a compaction simulator to generate pressure - density data for Heckel analysis. Individual tablets were compressed at constant punch velocity. The effect of punch velocity on yield pressure as obtained from the inverse of the Heckel constant[11] was examined. A strain rate sensitivity (SRS) value was calculate as follows:

$$SRS = \frac{P_{Y2} - P_{Y1}}{P_{Y2}} x\ 100 \qquad (8)$$

where P_{y1} is the yield pressure at a punch velocity of 0.033 mm/sec. and P_{y2} is the yield pressure at a punch velocity of 300 mm/sec. Values of SRS for materials ranged from 1% to over 50%. Materials were ranked in terms of their brittle and ductile behaviors. In an extension of this study,[12] these authors looked at the effect particle size had on the SRS. In general a smaller particle size decreased the SRS. The extent to which this happens can give information about the importance of particle size control for a given material.

Casahoursat[13,14] and coworkers used a more complex viscoelastic model to describe stress relaxation. Their bi or tri-exponential equation for stress decay is analogous to two or three Kelvin solids and an individual spring in series or the same number of Maxwell element and an individual spring in parallel. Relaxation times of their measurements were in the one second range or greater.

Viscoelasticity of Tablets

Work thus far discussed has dealt with only the loading part of the compression event. The mathematical relationships employed can be thought of as one-dimensional relating scalar quantities.

Rippie and Danielson[15,16] used a three-dimensional viscoelastic model to describe tablet behavior during the unloading portion of the compression event. For a three dimensional situation, the state of stress of a tablet must be expressed by a tensor (σ_{ij}) of the form:

$$\sigma_{ij} = \begin{pmatrix} \sigma_{xx} & \sigma_{xy} & \sigma_{xz} \\ \sigma_{yx} & \sigma_{yy} & \sigma_{yz} \\ \sigma_{zx} & \sigma_{zy} & \sigma_{zz} \end{pmatrix} \tag{9}$$

where σ_{zz} is the axial (punch) stress, σ_{xx} and σ_{yy} are the radial (die) stresses and the other quantities are the shear stresses. For convenience, this can be split into two tensors

$$\begin{pmatrix} \sigma_{xx} & \sigma_{xy} & \sigma_{xz} \\ \sigma_{yx} & \sigma_{yy} & \sigma_{yz} \\ \sigma_{zx} & \sigma_{zy} & \sigma_{zz} \end{pmatrix} = \begin{pmatrix} S & 0 & 0 \\ 0 & S & 0 \\ 0 & 0 & S \end{pmatrix} + \begin{pmatrix} S_{xx} & S_{xy} & S_{xz} \\ S_{yx} & S_{yy} & S_{yz} \\ S_{zx} & S_{zy} & S_{zz} \end{pmatrix} \tag{10}$$

where $s = (1/3)(\sigma_{xx} + \sigma_{yy} + \sigma_{zz})$ and the elements in the second tensor on the right side of this equation are such that when the same terms of the two tensors on the right side of this equation are added, they give the term in the original stress tensor. The first tensor on the right side of equation (10) is called the dilational tensor, since it alone would cause only a volume change in a body. The second tensor on the right side of equation (10) is called the distortional tensor and will cause only a shape change in a body. Analogous separation can be done with the strain tensor ε_{ij}.

This splitting of the stress and strain tensors allows one to relate the dilational stress and strain and the distortional stress and strain separately by their

own viscoelastic model independent of each other. For the case of tablet compression where there is applied uniaxial strain in a well lubricated die it can be shown that the following equations hold:[5]

$$(P'Q'' + 2P''Q')\,e_{zz} = 3P'P''\sigma_{zz} \tag{11}$$

$$(P'Q'' - P''Q')\,e_{zz} = 3P'P''\sigma_{yy} = 3P'P''\sigma_{xx} \tag{12}$$

where P", P', Q", and Q' are model dependent linear differential operators. The double prime superscript indicates dilation and the single prime indicates distortion. In general, for an elastic material, P = 1 and Q = q_0. For a Kelvin solid, P = 1 and Q = $q_0 + q_1$ d/dt. Assuming a material which behaves as a Kelvin solid in both dilation and distortion, substituting into (11 and 12), doing the operations, setting the radial strain rate equal to zero and rearranging, equations for the punch and die stress become:

$$\sigma_{zz} = \frac{1}{3}(q_0'' + 2q_0')\,e_{zz} + \frac{1}{3}(q_1'' + 2q_1')\,\frac{de_{zz}}{dt} + \frac{2}{3}(q_0'' - q_0')\,e_{xx} \tag{13}$$

$$\sigma_{xx} = \frac{1}{3}(q_0'' - q_0')\,e_{zz} + \frac{1}{3}(q_1'' - q_1')\,\frac{de_{zz}}{dt} + \frac{1}{3}(2q_0'' + q_0')\,e_{xx} \tag{14}$$

where q_0'' is the elastic dilational constant, q_0' is the elastic distortional constant, q_1'' is the viscous dilational constant and q_1' is the viscous distortional constant. If the material is modeled as behaving elastically in dilation and as a Kelvin solid in distortion the equation is the same except that q_1'' is zero. Multiple linear regression of the punch stress and die wall stress data and algebraic rearrangement allow for determination of the viscoelastic constants.

After punch liftoff, decay of radial die wall stress can be derived:

$$\sigma_{xx} = [\sigma_{xx}(0) - C_1] e^{-(C_2 t)} + C_1 \quad (15)$$

$$C_1 = \frac{3 q_0' q_0'' e_{xx}(0)}{2 q_0' + q_0''} \quad (16)$$

$$C_2 = \frac{(2 q_0' + q_0'')}{2 q_1'} \quad (17)$$

The initial condition, $\sigma_{xx}(0)$, is the radial stress at punch liftoff. Non-linear regression is done to obtain the equilibrium radial stress, C_1, and the first order stress decay rate constant, C_2. Individual viscoelastic constants cannot be resolved since there are four unknowns and only two equations.

The values of the q's indicate the mechanical behavior of the tablet during the period of punch unloading. The q_0's represent the average elastic properties, both in dilation and distortion. The elastic q's bear a relation to the instantaneous strain during unloading. The q_1's represent the time dependence of the distortional and dilation properties of the tablet. These latter q's are related in the analysis to the strain rate. During unloading, the strain rate of the tablet in the axial direction is positive and increasing. Therefore, any departure of the stresses from what would be predicted by the elastic parameters and the strain alone is related to this strain rate. There is a correlation, but not necessarily a cause and effect relation, between the strain rate and the apparent viscosity as reflected by the q_1's. In relating the values of the viscoelastic parameters to the behavior of the tablet, it must be remembered that a tablet is not a fully dense body. The heterogeneity of the tablet

means only spatial averages of viscous and elastic properties can be measured, rather than the uniform intensive properties of a fully dense material. Therefore these parameters represent structural and configuration alterations in the tablet as well as behavior of the particles themselves. Consider the following data:

Viscoelastic Parameters of Tablets Punch at 125 MPA[15-17]

MATERIAL	q_0'' (MPa)	q_0' (MPa)	q_1' (MPa • sec)	C_1 (MPa)	C_2 (sec^{-1})
Spray-Processed Lactose	2120	1180	3.79	9.2	310
Microcrystalline Cellulose	685	132	0.85	5.4	230
Starch USP	317	-22	0.78	2.1	175

Contrasted here are data of a brittle material, lactose, a plastic material which compresses well, microcrystalline cellulose, and a poorly compressible material, starch. Microcrystalline cellulose shows smaller elastic parameters than lactose. It sustains a lower residual die wall pressure (C_1) than lactose and relaxes more slowly (C_2). Microcrystalline cellulose also has a lower viscous parameter than lactose. The magnitude of the viscous constant involves both the amount of material within the tablet in a plastic state, and the effective viscosity of that material. It is possible that even though microcrystalline cellulose has a lower yield stress, the conditions within the lactose tablet are such that what lactose does exist in the plastic state offers a greater strain rate dependent resistance. Immediately noticeable is the negative value for the distortional elastic parameter for starch. An isolated compressed spring with a negative modulus would exert an increased force with a decrease in compression. A phenomena within a tablet that would have this same

effect is the release of internally bound elastic energy due to fracture of interparticulate bonds as punch withdrawal creates a sufficient volume to allow for bond fracture. This is not to say that starch itself has a negative elastic modulus. It is only the tablet as a fracturing structure under these unloading conditions that exhibits this behavior in distortion.

Recently,[18] this same type of analysis was done on the loading portion of the compression cycle. It was shown mathematically, that for a rotary tablet machine, punch pressure maxima must precede maximum insertion of the punches into the die. Also, that the die pressure maximum will occur after the punch pressure maxima and may or may not occur before maximum insertion of the punches into the die. This was verified experimentally.

Hoag[19] used three-dimensional viscoelastic analysis during unloading to examine the conversion of elastically stored energy into force-displacement work and dissipated dilational and distortional energy during unloading. As given previously,[15] the equation for punch and

die wall stress during unloading is:

$$\sigma_{zz} = \frac{1}{3}(q_0'' + 2q_0')e_{zz} + \frac{1}{3}(q_1'' + 2q_1')\frac{de_{zz}}{dt} + \frac{2}{3}(q_0'' - q_0')e_{xx} \tag{13}$$

$$\sigma_{xx} = \frac{1}{3}(q_0'' - q_0')e_{zz} + \frac{1}{3}(q_1'' - q_1')\frac{de_{zz}}{dt} + \frac{1}{3}(2q_0'' + q_0')e_{xx} \tag{14}$$

The rate of work done on the punch is:

$$\frac{dW}{dt} = \sigma_{zz}\frac{de_{zz}}{dt} \tag{18}$$

This can be resolved into distortional and dilational parts[20] as was done earlier with the stress tensor. Making appropriate substitutions of (13) and (14) into (18) and integrating, one can get expressions for the four types of viscoelastic energy. We get:

$$W_0'' = \frac{1}{3}\int_\alpha^\beta q_0'' e_{zz}\frac{de_{zz}}{dt} + 2q_0'' e_{xx}\frac{de_{xx}}{dt}d\tau \tag{19}$$

$$W_0' = \frac{2}{3}\int_\alpha^\beta q_0' e_{zz}\frac{de_{zz}}{dt} - q_0' e_{xx}\frac{de_{xx}}{dt}d\tau \tag{20}$$

$$W_1'' = \frac{1}{3}\int_\alpha^\beta q_1''\left(\frac{de_{zz}}{dt}\right)^2 d\tau \tag{21}$$

$$W_1' = \frac{2}{3}\int_\alpha^\beta q_1'\left(\frac{de_{zz}}{dt}\right)^2 d\tau \tag{22}$$

Values over a given unloading interval for these four types of work are obtained using numerical methods.[19]

Examination of the relative proportion of elastic potential energy which is used to do force-displacement work on the punches versus that which is dissipated can give information on the extent of plastic deformation occurring during unloading. It can be particularly effective in evaluating the effect of compression rate on tableting behavior of a given formulation. Changes in this ratio may indicate a change in mechanical behavior of the tablet during unloading. Consider the following table from Hoag.[19]

Force-Displacement Work / Dissipated Energy Ratios						
Tablet machine angular velocity	Acetaminophen		Calcium Oxalate		Avicel	
	Max Press 150 Mpa	Max Press 210 MPa	Max Press 150 Mpa	Max Press 210 MPa	Max Press 150 MPa	Max Press 210 MPa
2.4 rad/sec	0.36	0.43	0.26	0.22	0.23	0.21
5.7 rad/sec	0.24	0.26	0.25	0.22	0.17	0.17

Avicel is well known to undergo extensive plastic flow during compression[21]. Acetaminophen has been observed to exhibit both brittle fracture and considerable time-dependent strain recovery and stress decay under constant strain.[22-24] Calcium oxalate is extremely brittle in nature.

Energy ratio's for these three materials during unloading are given for two maximum punch pressures at two different machine speeds. Calcium oxalate values are not affected by machine speed. Avicel is affected somewhat, and acetaminophen undergoes the greatest change as a result of increasing tablet machine speed. It is likely that the effect on acetaminophen is greater than Avicel because, even though Avicel is more plastic in nature than acetaminophen, there is a **transition** in behavior toward failure due to viscous flow as machine speed increases.

Tablet Bonding

In recent work,[25,26] Hiestand models the processes involved in tablet bonding considering the effect that viscoelastic properties of the material have on the strength of bonding. He states that "viscoelastic properties increase the strength because of the effects on the work done during the separation of surfaces and on the radius of

curvature of the surfaces in contact." He distinguishes between two mechanisms of bond separation. One is a brittle mechanism where separation of surfaces is treated as crack growth. The other, called ductile extension, involves "plastic deformation of the contacting surfaces during both the unloading of elastic stresses and the application of tensile stresses." Through a rather complex derivation he arrives at a number of equations which shed light on the factors involved in the formation and strength of an interparticulate bond. He describes the bond strength between two identical viscoelastic particles where ductile extension does not occur:

$$f_a'' = -\frac{2e_t H_0 \Delta\gamma}{e_\infty e_0 H_t}\left(\frac{f_c}{\pi H_c}\right)^{\frac{1}{2}} \tag{23}$$

and the bond strength where it does occur:

$$f_{ad} = -H_t \pi a_d^2 = -\left(\frac{64}{\pi H_t^3}\right)\left(\frac{H_0 \Delta\gamma}{e_0}\right)^2 \tag{24}$$

Note that the meaning for all symbols is listed below.

Criteria for ductile extension are:

$$f_c < \frac{256 H_c}{\pi}\left[\frac{e_\infty H_0 \Delta\gamma}{e_T e_0 H_t^2}\right]^2 \tag{25}$$

$$R < \frac{64 H_0 \Delta\gamma}{3\pi^2 e_t e_0 H_t^2} \tag{26}$$

Definitions:

a_d maximum chordal radius of contact for ductile extension

f_a'' pull off force; spherical surfaces; brittle mechanism; viscoelastic material

f_{ad} pull off force; spherical surfaces, ductile extension of surfaces

f_c compression force; spherical surfaces

H_0 indentation hardness for instantaneous process

H_t indentation hardness for viscoelastic materials where strain rate is based on the process rate using time t

H_c indentation hardness of particles at strain rate used for the compression of the compact

R the harmonic mean radius of the two contacting spherical surfaces

$\Delta\gamma$ change of surface energy going from free surface to solid solid interface

ε_0, ε_t, ε_c strain indices, subscripts refer to strain rate as in definitions of H's

Note from inequality (25) that ductile extension occurs at lower compression forces. However, a low compression force alone is not enough to assure ductile extension. Inequality (26) states that R must be below a maximum value for ductile extension to occur. Since R after plastic deformation must always be greater than R from the initial particle radii, particle size may prohibit this mechanism.

In his analysis of uniaxial tensile strength of a compact, the weakest bonding case occurs in the absence of viscoelasticity. Any time-dependent deformation behavior increases tablet tensile strength.

This bonding theory was examined experimentally. It was found that sorbitol underwent a ductile to brittle mechanism transition with increasing compression forces. It was found that phenacetin's behavior was consistent with a single brittle mechanism.

Conclusion

Studies have shown that viscoelastic phenomena are involved throughout the entire cycle of tablet compaction. Time dependent processes occur during loading, dwell time where tablet strain is at a maximum, and during punch pressure unloading. The nature of particle viscoelastic behavior is fundamental in determining the strength of particle-particle bonds.

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