The 3-D Model: Experimental Testing of the Parameters *d*, *e*, and ω and Validation of the Analysis

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ABSTRACT: The aim of the study was to evaluate the parameters d, e, and ω for their significance in compression data analysis. Materials with predominantly different compression properties were used and tableting data were obtained with an instrumented eccentric and rotary tableting machine. The parameters time plasticity (d), pressure plasticity (e), and the twisting angle (ω), an indicator of fast elastic decompression, were derived by 3-D modeling. The Peak-Offset-Time, the pressure–time function parameters, the Heckel slope, normalized compaction ($E2_{norm}$) and elastic energy ($E3_{norm}$), and fast elastic recovery (FER), which are well known tableting parameters, were calculated from the tableting data. The plastic microhardness of the tablets was determined from using microindentation. The results revealed that d is influenced by speed, e correlates with microhardness, and ω correlates with the Elastic modulus (E). Thus, for all three 3-D model parameters an experimental basis is given. The validation showed that d correlates with the Peak-Offset-Time and the pressure–time function parameters, e correlates with the Heckel slope and $E2_{norm}$, and ω correlates with $E3_{norm}$ and FER of the tablets. The significance of the three parameters is fully given. It is no longer necessary to use two separate methods to differentiate between time- and pressure-dependent deformations.
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Keywords: compression; tablet formation; 3-D model; production speed; microhardness; Elastic modulus; experimental testing

INTRODUCTION

The 3-D model was developed in order to rapidly and distinctly characterize the tableting properties of direct compression materials in one step.[1,2] It is the only compression model which is based on all of the three important variables necessary to characterize the tableting process namely time, force, and displacement.

Three-dimensional modeling uniquely characterizes the three variables during the tableting process (normalized time, pressure, and density) simultaneously. To the data a twisted plane is fitted which is characterized by the three parameters—d, e, and ω.

$$z = \ln\left(\frac{1}{1-D_{rel}}\right) = ((t - t_{max})(d + \omega p_{max} - p)) + (ep) + (f + dt_{max}) \quad (1)$$

where D_{rel} = relative density, t = time, p = pressure,

$$d = \frac{\delta \ln(1/(1-D_{rel}))}{\delta t}, \quad e = \frac{\delta \ln(1/(1-D_{rel}))}{\delta p}, \quad f = \ln\left(\frac{1}{1-D_{rel}}\right),$$

t_{max} = time at maximum pressure, p_{max} = the maximum pressure, and ω = twisting angle at t_{max}.

Time plasticity (d), describes the plastic deformation with respect to time. Increasing time

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plasticity indicates faster deformation during tableting. Pressure plasticity (e), describes the relationship between density and pressure. Large pressure plasticities are observed with materials that require only a small amount of pressure for deformation. The twisting angle (ω), is a measure for the elasticity of the material. Elasticity decreases with increasing ω. can be interpreted as the ratio between compression and decompression and thus describes indirectly fast instantaneous elastic decompression during the decompression process. Pressure- and time-dependent deformation can be clearly distinguished and separated from elasticity using this method. Furthermore, brittle fracture and plastic deformation can also be differentiated. The 3-D modeling technique is applicable to data from rotary and eccentric tableting machines and from tableting machine simulators[3] and the method has been successfully used in characterizing materials with very different deformation mechanisms,[4,5] as well as, those with similar deformation mechanisms.[6,7] This method has already been applied to characterize mixtures[8] and is a valuable tool in testing excipients for their usefulness in soft tableting,[9] that is for tableting pressure-sensitive materials without damage.

So far, the utility and validity of this technique has only partially been tested, that is the influence of speed on time plasticity.[10] The result shows that time plasticity increases with increasing speed of the tableting machine. This has been shown for eccentric tableting machines and for tableting machine simulators. However, the parameters pressure plasticity and fast elastic decompression have not been tested for correlation with physical parameters. Furthermore a complete validation in comparison with other well-established analysis techniques has not been performed.

Thus, the aim of the study is to test the parameters d, e, and ω for their significance and applicability and to validate the parameters in comparison with other well-established characterization methods. Excipients and drugs known to have distinctly different deformation properties were used as test materials.

EXPERIMENTAL

Materials

The materials used were spray-dried lactose, LAC (FlowLac® 100, Lot #S0047, Meggle GmbH, Wasserburg, Germany), microcrystalline cellulose, MCC (Avicel® PH 101, Lot #14204, FMC Corporation, Princeton, NJ), hydroxypropyl methylcellulose (HPMC 15.000, Metolose® 90 SH, Lot #506825, Shin-Etsu, Tokyo, Japan), cellulose acetate, CAC (CA 398-10, Lot #AC-632505, Eastman Chemical Company, Kingsport, TN), dicalcium phosphate dihydrate, DCPD (Emcompress®, Lot #R 19 K, Mendell, Patterson, NY), theophylline monohydrate, TM (Lot #4072.2, Roth GmbH, Karlsruhe, Germany), pregelatinized starch, STARCH (Starch 1500®, lot #606009, Colorcon West Point, PA), granulated mannitol, MANN (Pearlitol SD 200®, Lot #69-65-8, Roquettes Frères, Lestrem, France), and sodium chloride, NaCl (pure (99,9%), Lot #30940440, Roth). Magnesium stearate (Lot #93810410, Caelo GmbH, Fröhlingsdorf, Germany) was used for internal lubrication.

Test Conditions

All materials and tablets were equilibrated, produced and stored between 35% and 45% RH. Tableting was performed in a special climate controlled room which was set to $23 \pm 1^{\circ}C$ and $45 \pm 2\%$ RH.

Water Content

The water content was determined by thermogravimetric analysis using TGA 209 (Netzsch Gerätebau GmbH, Selb, Germany) in triplicate. The results are given in Table 1. The powder was heated up to 150°C with a rate of 10 K min^{-1} and water loss was determined. For materials which loos already crystal water at this temperature the water loss was determined at 60°C for several hours.

Particle Size Determination

Particle size distribution was determined by sieve analysis according to DIN 66165 (Retsch sieving machine, Type Vibrio, No. 12189031, Retsch GmbH und Co. KG, Haan, Germany) in triplicate. In cases where the particles were too small, laser light diffractometry using a dry feeder (Sympatec Rodos, Type 12SR, pressure 3.5 bar, injection pressure 85–90 mbar) was applied (MCC, HPMC, CAC, TM), also in triplicate. The mean volume particle size distribution was calculated and median particle size determined (Tab. 1).