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The 3-D Model: Does Time Plasticity Represent the Influence of Tableting Speed?

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ABSTRACT

The objective of this study is to test the hypothesis that time plasticity (parameter *d* from 3-D modeling) is influenced by tableting speed. Tablets were produced at different maximum relative densities ($\rho_{rel, max}$) on an instrumented eccentric tableting machine and on a linear rotary tableting machine replicator. Some 3-D data plots were prepared using pressure, normalized time, and porosity according to Heckel. After fitting of a twisted plane, the resulting parameters were analyzed in a 3-D parameter plot. The materials used were dicalcium phosphate dihydrate (DCPD), spray-dried lactose, microcrystalline cellulose (MCC), hydroxypropyl methylcellulose (HPMC), κ-carrageenan (CAR), and theophylline monohydrate (TheoM). The results show that tableting speed especially influences the parameter *d* (time plasticity) of the 3-D model for plastically and viscoelastically deforming materials such as MCC, HPMC, CAR, and TheoM. For more plastically deforming materials such as MCC, HPMC, and TheoM, a subtle influence on ω is also visible. The stages of higher densification are affected more than the stages of lower densification. Brittle materials such as DCPD exhibit no influence of tableting speed. The influence of speed on spray-dried lactose is minor. The results are valid for data obtained from an eccentric tableting machine and also for data from a linear rotary tableting machine replicator. Thus, the empirically derived parameter time plasticity *d* really represents the influence of time.

KEYWORDS: rotary tableting machine simulator, eccentric tableting machine, tableting speed, excipients, compression

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INTRODUCTION

The 3-D model has been successfully used to characterize the densification mechanisms of tableting materials using 3-D parameter plots.[1-3] It can be used for data from eccentric tableting machines as well as from rotary tableting machines (here, the linear rotary tableting machine replicator).[2] When the compression wheels from different rotary tableting machines are mounted on the linear rotary tableting machine replicator, different results are exhibited and, depending on the size of the compression wheels the different processes can be distinguished.[2] However, the relation of the derived parameter values to each other is the same for different excipients.[2] Three parameters are derived by 3-D modeling: *d* (time plasticity), *e* (pressure plasticity), and ω (the twisting angle, indicating fast elastic decompression). Materials that deform quickly show high *d* values, and materials that deform easily and with low pressure show high *e* values. Elastically deforming materials already possess a great degree of decompression during tableting, and the ω-values are low.

However, the parameters are mathematically derived, and even when the results obtained are in accordance with those from 2-D models[3] there should be a direct experimental basis. Thus, the aim of this study is to test whether time plasticity *d* actually represents the influence of time. To evaluate this, tableting is performed at different production rates and thus machine speeds on an eccentric tableting machine and also on the linear rotary tableting machine replicator. The change of the parameters with the tableting speed is studied at different stages of densification.

The term "tableting speed" as used in this article refers not to the real speed of the punches, which changes during one compression cycle, but to the production rate. For definition of the real speed of the punches and details, refer to Armstrong and Palfrey.[4] Since the speeds of different machines are not directly compared in this article and the increase of speed is applied for just one machine, it is deemed to be legitimate to apply the term "tableting speed," taking this precondition into account.

Table 1. True Densities of the Materials*

Material	True Density (g/cm^{-1}), mean (SD)
MCC	1.574 (0.001)
HPMC	1.331 (0.001)
Spray-dried lactose	1.544 (0.002)
DCPD	2.342 (0.003)
CAR	1.744 (0.011)
TheoM	1.469 (0.001)

*MCC indicates microcrystalline cellulose; HPMC, hydroxypropyl methylcellulose; DCPD, dicalcium phosphate dihydrate; CAR, κ-carrageenan; and TheoM, theophylline monohydrate. n = 3.

Speed's effect on deformation and densification properties is generally known for plastically and viscoelastically deforming materials.[5-12] Examples for this are microcrystalline cellulose (MCC),[9] polyethylene glycol,[10-11] hydroxypropyl methylcellulose (HPMC),[12] and polystyrene.[13] Little effect has been found for materials that predominantly fracture and show brittle compaction behavior—for instance, dicalcium phosphate dihydrate (DCPD), lactose, or DC calcium lactate.[14-16] When the deformation behavior for very differently deforming materials is analyzed, an effect caused by speed should be exhibited for plastically and viscoelastically deforming materials. This influence could be especially visible in changes of the parameter *d* (time plasticity).

Consequently, the particular aim of this study is to test whether time plasticity *d* really does represent the influence of time.

MATERIALS AND METHODS

Materials

The materials used were MCC (Avicel PH 101, lot 14204, FMC Corp, Princeton, NJ), HPMC (15 000; Metolose 90 SH, lot 506825, Shin-Etsu, Tokyo, Japan), spray-dried lactose (FlowLac 100, lot S0047, Meggle GmbH, Wasserburg, Germany), DCPD (Emcompress, lot R 19 K, Mendell, Patterson, NY), κ-carrageenan (CAR; Gelcarin GP-911 NF, lot ZC 502, FMC Corp, Princeton, NJ), and theophylline monohydrate (TheoM; lot 4072.2, Roth GmbH, Karlsruhe, Germany). Magnesium stearate (lot 93810410, Caelo GmbH, Fröhlingsdorf, Germany) was used for internal lubrication.

Methods

True Density

The true density (ρ_{true}) of the materials was determined by helium pycnometry (Accupyc 1330, Micromeritics, Norcross, GA). The results are given in **Table 1**. The method described by Picker and Mielck[17] was used to determine the true density of the equilibrated materials containing some moisture.

Tableting and Data Analysis Using an Eccentric Machine

Tablets were produced on an instrumented eccentric tableting machine (EK0/DMS, No. 1.0083.92, Korsch GmbH, Berlin, Germany) with 11-mm-diameter flat-faced punches (Ritter GmbH, Hamburg, Germany). Equal true volumes of the substances were tableted to 5 different maximum relative densities ($\rho_{rel,\ max}$) of the tablets (precision 0.001) between 0.70 and 0.90. The amount of material necessary for tablets with a given $\rho_{rel,\ max}$ was calculated. The powder was manually filled into the die, and 1 compaction cycle was performed.

The tablet height at maximum densification under load was adjusted to 3 mm. The actual height of the powder bed was determined using an inductive transducer (W20 TK, Hottinger Baldwin Meβtechnik, Darmstadt, Germany), and the measured displacement values were corrected for elastic deformation of the punches. The accuracy of displacement measurement was 0.002 mm. For calibration, refer to Picker.[18] The filling depth was held constant at 13 mm. The production rate was 10, 20, 30, or 40 tablets per minute. Lubricant (0.5% magnesium stearate) was used for only DCPD to avoid having it influence the microstructure of the other tablets.

Five single tablets were produced under each condition. Force, time, and displacement of the upper punch were recorded[2]; normalized time, pressure, and ln $(1/1 - D_{rel})$ according to Heckel[19,20] were calculated, and the data were presented in a 3-D data plot. To this 3-D data plot, a twisted plane was fitted by the least-squares method according to Levenberg-Marquard (Matlab, MathWorks Inc, Unterföhrung, Germany) with the following equation. The mean goodness of fit (R^2) was 0.0060 ± 0.0038.

Table 2. Different Combination of Parameters From the Fitting Function for Description of Compaction Cycles of Different Tableting Materials (n = 5, mean [SD]) at Different Maximum Relative Densities $\rho_{rel,\,max}$ and Different Tableting Speeds

Material	$\rho_{rel,\,max}$	Tablets/min	*d*	*e* (MPa^{-1})	ω
Hydroxypropyl methylcellulose	0.73	10	0.5262 (0.0022)	0.0106 (0.0002)	0.0291 (0.0005)
	0.82		0.8085 (0.0031)	0.0073 (0.0001)	0.0167 (0.0003)
	0.90		1.3958 (0.0511)	0.0065 (0.0001)	0.0113 (0.0005)
	0.73	20	0.4489 (0.0042)	0.0117 (0.0002)	0.0185 (0.0003)
	0.82		0.8591 (0.0044)	0.0090 (0.0001)	0.0133 (0.0001)
	0.90		1.5556 (0.0862)	0.0068 (0.0001)	0.0097 (0.0005)
	0.73	30	0.4511 (0.0088)	0.0116 (0.0001)	0.0174 (0.0004)
	0.82		0.8936 (0.0062)	0.0082 (0.0002)	0.0141 (0.0004)
	0.90		1.7130 (0.0148)	0.0066 (0.0000)	0.0098 (0.0003)
	0.73	40	0.4737 (0.0069)	0.0112 (0.0004)	0.0171 (0.0004)
	0.82		0.9010 (0.0114)	0.0077 (0.0001)	0.0145 (0.0007)
	0.90		1.7892 (0.1175)	0.0066 (0.0001)	0.0098 (0.0001)
Dicalcium phosphate dihydrate	0.72	10	0.1933 (0.0135)	0.0026 (0.0001)	0.0126 (0.0010)
	0.79		0.3123 (0.0066)	0.0012 (0.0000)	0.0074 (0.0002)
	0.84		0.4978 (0.0076)	0.0007 (0.0000)	0.0039 (0.0002)
	0.72	20	0.1861 (0.0008)	0.0026 (0.0001)	0.0135 (0.0001)
	0.79		0.3040 (0.0059)	0.0012 (0.0000)	0.0072 (0.0002)
	0.84		0.4360 (0.0029)	0.0007 (0.0000)	0.0036 (0.0001)
	0.72	30	0.1861 (0.0034)	0.0026 (0.0000)	0.0135 (0.0001)
	0.79		0.2998 (0.0117)	0.0012 (0.0000)	0.0069 (0.0006)
	0.84		0.4409 (0.0058)	0.0007 (0.0000)	0.0036 (0.0001)
	0.72	40	0.1948 (0.0112)	0.0026 (0.0001)	0.0132 (0.0006)
	0.79		0.3120 (0.0054)	0.0012 (0.0000)	0.0070 (0.0010)
	0.84		0.4399 (0.0073)	0.0007 (0.0000)	0.0033 (0.0001)

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

where $d = \frac{\delta\, ln(1/(1 - Drel))}{\delta t}$, $e = \frac{\delta\, ln(1/(1 - Drel))}{\delta p}$, $f = ln(\frac{1}{1 - D0})$, D_{rel} is relative density; t is normalized time; t_{max} is normalized time at maximum pressure; p_{max} is maximum pressure; p is pressure; ω is the twisting angle at t_{max}; and D_0 is the relative density at $t = 0$.

The resulting parameters d, e, and ω of the 5 compaction cycles under each tableting condition (material, a given $\rho_{rel,\,max}$, and production rate) were averaged, and means and standard deviations were calculated (**Tables 2** and **3**).

Tableting Using the Presster

Additionally, tableting was performed on the Presster (Metropolitan Computing Corporation, East Hanover, NJ). This single-station linear rotary tableting machine replicator has been described elsewhere.[2] In this case, the mean goodness of fit, r^2, was 0.0084.

The equipment is instrumented with inductive displacement transducers (Macro Sensors, Pennsauken, NJ) for the upper (model CD375-100) and the lower (model CD375-250) punch, which were calibrated separately inside the machine. The accuracy of displacement measurement for the upper punch was 4.5 μm and for the lower punch 6.5 μm. Forces were measured by strain gauges (N2A-06-T031P-350, Measurements Group Inc, Raleigh, NC) mounted at the upper compression roll pin. (For details, see Picker.[2]) Compression rolls with the geometries of the high-speed rotary tableting machine Fette PT 2090 (Fette GmbH, Hamburg,

Table 3. Different Combination of Parameters From the Fitting Function for Description of Compaction Cycles of Different Tableting Materials (n = 5, mean [SD]) at Different Maximum Relative Densities $\rho_{rel,\,max}$ and Different Tableting Speeds

Material	$\rho_{rel,\,max}$	Tablets/min	*d*	*e* (MPa^{-1})	ω
Microcrystalline cellulose	0.72	10	0.6702 (0.0008)	0.0047 (0.0000)	0.0145 (0.0003)
	0.80		1.1120 (0.0103)	0.0045 (0.0003)	0.0135 (0.0004)
	0.88		1.7590 (0.0311)	0.0041 (0.0000)	0.0120 (0.0001)
	0.72	20	0.7575 (0.0079)	0.0051 (0.0002)	0.0137 (0.0002)
	0.80		1.1190 (0.0078)	0.0041 (0.0001)	0.0123 (0.0002)
	0.88		1.9709 (0.0105)	0.0049 (0.0002)	0.0079 (0.0003)
	0.72	30	0.7421 (0.0485)	0.0047 (0.0001)	0.0129 (0.0004)
	0.80		1.1498 (0.0106)	0.0040 (0.0001)	0.0116 (0.0001)
	0.88		1.8574 (0.0296)	0.0037 (0.0002)	0.0090 (0.0002)
	0.72	40	0.7388 (0.0374)	0.0046 (0.0001)	0.0129 (0.0007)
	0.80		1.1662 (0.0359)	0.0040 (0.0001)	0.0117 (0.0005)
	0.88		1.9049 (0.0865)	0.0037 (0.0001)	0.0091 (0.0009)
Theophylline monohydrate	0.74	10	0.1883 (0.0033)	0.0115 (0.0002)	0.0374 (0.0005)
	0.82		0.3672 (0.0033)	0.0061 (0.0002)	0.0219 (0.0003)
	0.90		0.7489 (0.0186)	0.0042 (0.0001)	0.0149 (0.0002)
	0.74	20	0.1161 (0.0168)	0.0088 (0.0005)	0.0362 (0.0025)
	0.82		0.4012 (0.0166)	0.0059 (0.0001)	0.0201 (0.0008)
	0.90		0.8880 (0.0176)	0.0043 (0.0001)	0.0156 (0.0003)
	0.74	30	0.2293 (0.0033)	0.0086 (0.0002)	0.0247 (0.0007)
	0.82		0.4450 (0.0306)	0.0073 (0.0001)	0.0172 (0.0029)
	0.90		0.8819 (0.0205)	0.0043 (0.0001)	0.0156 (0.0002)
	0.74	40	0.2039 (0.0018)	0.0077 (0.0002)	0.0288 (0.0008)
	0.82		0.4660 (0.0123)	0.0055 (0.0004)	0.0182 (0.0014)
	0.90		0.8518 (0.0426)	0.0044 (0.0001)	0.0151 (0.0005)

Germany) were used for simulation. Dwell time was set to 16.9 ms referring to 35 rpm, 10.6 ms referring to 55.8 rpm, and 7.9 ms referring to 75 rpm of the original machine.

Standard PCT B tooling with 10-mm flat-faced punches was used throughout the study. Internal lubrication (0.5% magnesium stearate) was used for tableting only DCPD and spray-dried lactose to avoid having it influence the microstructure of the other tablets. Feeding of the die was performed by using a feeding shoe with gravimetric force. The height of the tablets at maximum densification was held constant at 3 mm (accuracy: 25 μm). Equal true volumes of the substances were tableted to different $\rho_{rel,\,max}$ between 0.75 and 0.95. The weight of the final tablets was recorded. Tablet weight, true density, tablet height under load, and the diameter of the die were used to calculate the $\rho_{rel,\,max}$ of the final tablets.

The 3-D modeling technique was applied as for the data obtained with the eccentric machine. The resulting parameters *d*, *e*, and ω were plotted in a 3-D coordinate system. A quadratic polynomial regression in the 3-D space was performed using the least-squares method according to Levenberg-Marquard. A 3-D parameter plot resulted. In the 3-D parameter plot, the calculated parameters *d*, *e*, and ω as well as the resulting values after polynomial fitting were given.

RESULTS AND DISCUSSION

Influence of Speed Using an Eccentric Tableting Machine

In **Figure 1**, the 3-D parameter plots of 4 well-known materials tableted on an eccentric tableting machine are shown: HPMC, DCPD, MCC, and TheoM. These materials were tableted at 4 different speeds between 10 and 40 revolutions per minute. Even though these speeds were low compared to those of fast rotary machines, a subtle effect should be visible for plastically and viscoelastically deforming materials.

Figure 1A shows the densification behavior of HPMC at different machine speeds. HPMC is a high plastically deforming material.[2,12] Time plasticity *d*, pressure plasticity *e*, and the twisting angle ω are high in comparison to those of the other materials. For the different speeds, different 3-D parameter plots result. With increasing speed, time plasticity *d*, in particular, increases ($\alpha = 0.01$). This influence is

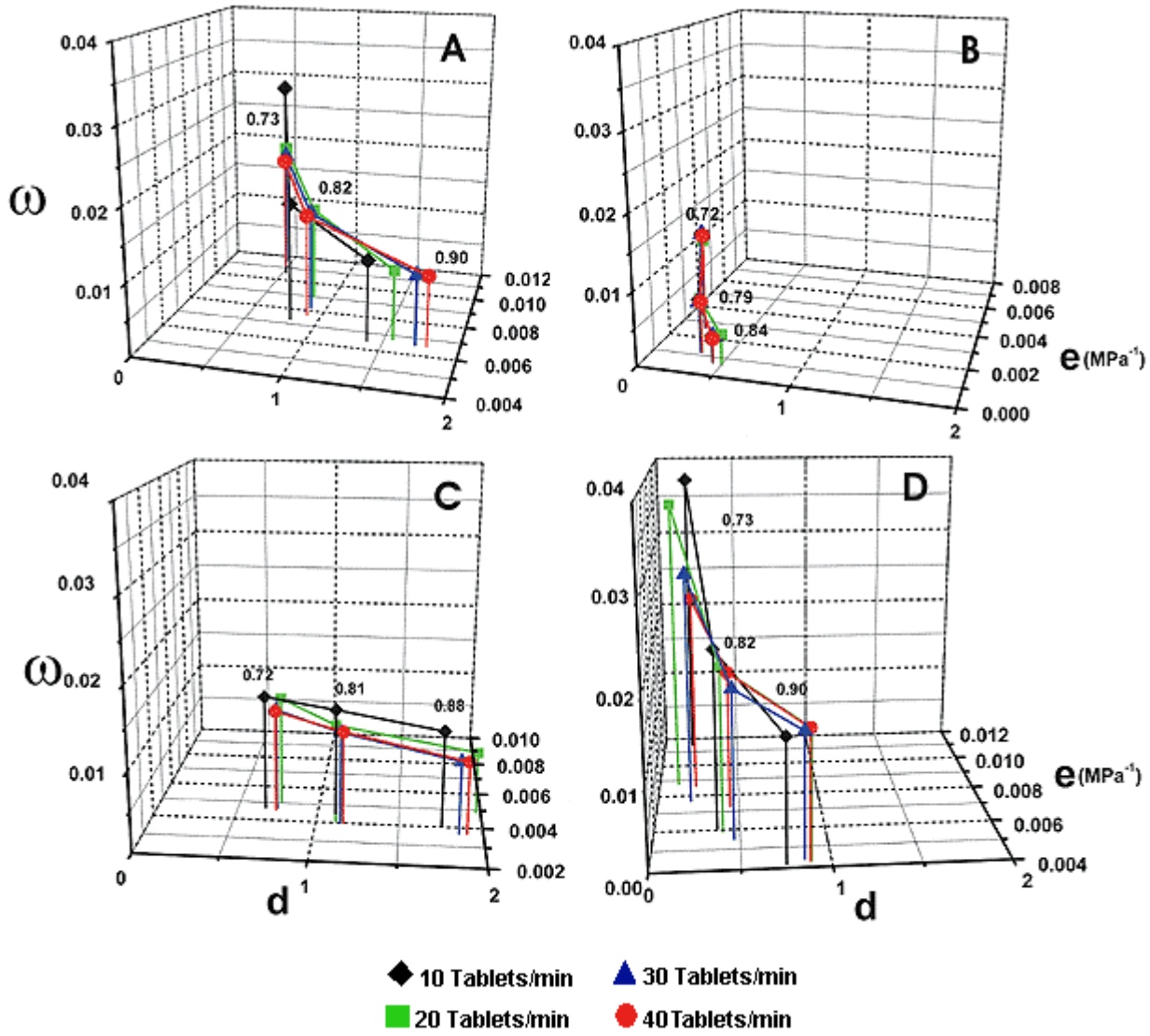

Figure 1. A 3-D parameter plot of (A) HPMC, (B) DCPD, (C) MCC, and (D) TheoM at different tableting speeds and at different graded $\rho_{rel,\ max}$ for data obtained with an eccentric tableting machine.

mostly visible at the highest $\rho_{rel,\ max}$. This is due to the fact that with increasing speed, the time interval used for relaxation of the material during tableting is low. However, pressure plasticity *e* for the same densification remains the same. In conclusion, the influence of speed and thus time is mainly expressed in *d*.

Figure 1B exhibits the 3-D parameter plots of DCPD. This brittle material does not readily deform, and pressure plasticity *e* as well as time plasticity *d* are low. With increasing $\rho_{rel,\ max}$, pressure plasticity *e* decreases and time plasticity *d* increases. However, as expected, the effect of tableting speed is subtle. The parameter values do not differ significantly ($\alpha = 0.01$). This result is in accordance with results from Armstrong and Palfrey,[5] Roberts and Rowe,[6] and Rees and Rue.[14] These authors interpreted porosity-pressure and compactibility plots.

In **Figure 1C** the MCC 3-D parameter plots are shown. As for HPMC, but to a lower extent, time plasticity *d* increases slightly as the machine speed increases (between 10 and 20, 10 and 30, and 10 and 40 rpm). However, here the influence of speed is here more complicated, since ω is also affected at the same stage of densification. The increase in fast elastic decompression (decrease in ω) demonstrates that decompression is higher in relation to compression; the fitted plane is less twisted.

Finally, **Figure 1D** shows the influence of speed on TheoM, which plastically deforms easily: the twisting angle ω is high in comparison to that of the other materials, and thus

fast elastic decompression is very low. Concerning TheoM, the tableting speed affects *d* at medium and high $\rho_{rel, max}$. At low $\rho_{rel, max}$ ω is also influenced as for MCC (α = 0.01).

In summary, concerning the eccentric machine, speed has no visible effect on brittle materials, and for plastically and viscoelastically deforming materials, the effect of speed is expressed in time plasticity *d*. In some cases ω is affected as well. For the analyzed materials, the ranking order for the influence of speed on the parameter *d* is as follows:

HPMC > MCC ≥ TheoM > DCPD = 0.

Influence of Speed Using a Linear Rotary Tableting Machine Replicator

Since the production rate is very low when using an eccentric tableting machine, the influence of tableting speed should also be studied when using a linear rotary tableting machine replicator, which allows for much higher production rates. The 3-D parameter plots produced with data of this tableting machine simulator exhibit the same relation of the parameter values for different materials as those produced with an eccentric tableting machine.[2]

In **Figure 2**, the 3-D parameter plots of five different tableting materials are shown: HPMC, MCC, CAR, DCPD, and spray-dried lactose. The tableting speed was set to different speeds: 35, 55.8, and 75 rpm. When these conditions, simulating a fast rotary tableting machine, are used, the influence of tableting speed (here production rate) on the parameters of 3-D modeling should be visible as well.

Figure 2A exhibits the HPMC 3-D parameter plots at different tableting speeds. The dwell time decreased from 16.9 to 7.9 ms. With increasing speed and decreasing dwell time, time plasticity *d* increased. Furthermore, ω decreased, indicating that decompression was higher in relation to compression, and thus fast elastic decompression increased.

The same is valid in the case of MCC (**Figure 2B**) when the tableting speed was increased from 35 to 55.8 rpm. Time plasticity *d* increased and the twisting angle ω decreased. At a maximum speed of 75 rpm, the 3-D parameter plot appeared bent and the results could not be clearly interpreted. However, this might have been due to a low number of parameter values for the final polynomial fitting in the 3-D parameter plot. In this case, the highest $\rho_{rel, max}$ was only 0.89.

Figure 2C shows the 3-D parameter plot for the viscoelastically deforming polymer CAR.[21-23] As expected, the *d* values were clearly increased and speed appeared to have no effect on ω.

Neither HPMC nor MCC and CAR 3-D parameter plots exhibited an effect caused by speed on the parameter *e*.

In addition to these plastically and viscoelastically deforming materials, 2 materials that predominantly deform by brittle fracture were investigated. **Figure 2D** exhibits the 3-D parameter plots of DCPD. When the experimental error was taken into account, speed produced no visible effect on *d*, *e*, or ω. This is in accordance with the results obtained with the eccentric tableting machine (see above).

For the spray-dried lactose (**Figure 2E**) the influence of tableting speed was minor. A slight increase in the parameter *d* (time plasticity) might have been present, but this is difficult to determine with the existing experimental error.

In summary, it can be stated that for predominantly fracturing materials such as DCPD and spray-dried lactose, hardly any effect of speed on deformation properties can be detected.

When a linear rotary tableting machine replicator is used and one takes into account that in some cases ω is affected as well, the materials can be ranked as follows with regard to the effect of speed on *d*:

CAR > HPMC ≥ MCC >> spray-dried lactose ≥ DCPD = 0.

Comparison of 3-D Modeling of Eccentric and Linear Rotary Tableting Machine Replicator

For both the eccentric and rotary tableting machines (in this study simulated), an influence of speed on the parameters of the 3-D model was visible when plastically or viscoelastically deforming materials were tableted. The 3-D parameter plots exhibited different values, and the influence for the eccentric tableting machine and the linear rotary tableting machine replicator was similar but not identical. This is due to the fact that the 3-D data plots have a different shape. Plots for the eccentric tableting machine were narrower than those of the linear rotary tableting machine replicator, which showed a plateau at maximum pressure. Accordingly, the 3-D fitting of the twisted plane exhibited different results.

Overall, the higher stages of densification are more greatly influenced than the lower stages of densification. Time plasticity *d* increases strongly with increasing speed; in some cases, fast elastic decompression slightly decreases. The order for the effect is the same for both machine types.

CONCLUSION

From the above-given discussion of the results, it can be concluded that the empirically derived parameter time plasticity *d* truly represents the influence of time and can be used in further interpretations of the densification due to

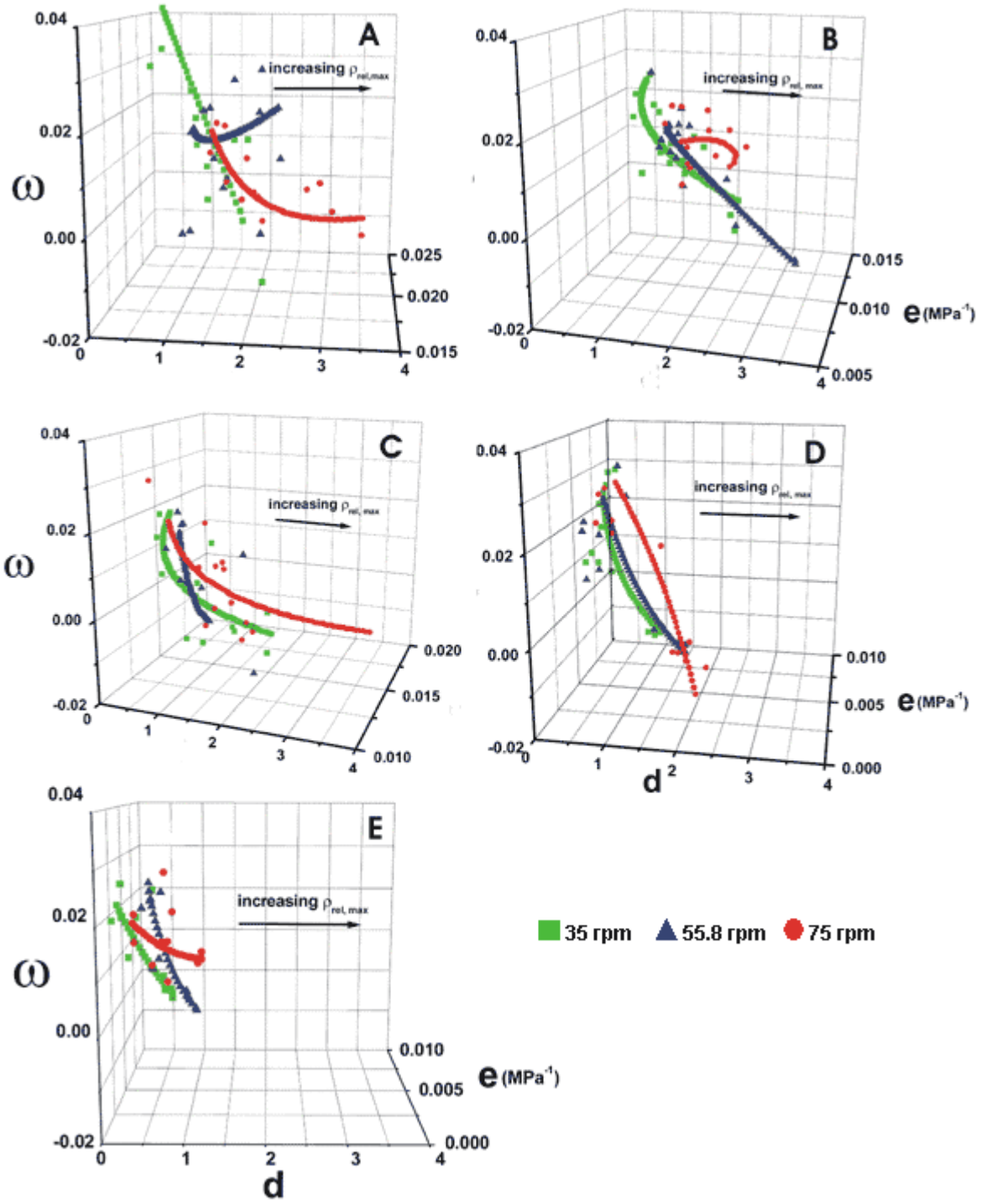

Figure 2. A 3-D parameter plot of (A) HPMC, (B) MCC, (C) CAR, (D) DCPD, and (E) spray-dried lactose at different tableting speeds and increasing $\rho_{rel,\ max}$ for data obtained with the linear rotary tableting machine replicator.

time. This is worthwhile to know for further investigations of new excipients. It also enables this technique to be used for scale-up either when tableting speed has to be increased to increase production rates or when scale-up using different sizes of tableting machines is necessary. In this respect, 3-D modeling aids in formulation development and scale-up.

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