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Research paper

A new theoretical model to characterize the densification behavior of tableting materials

Katharina M. Picker*

Martin-Luther-University Halle-Wittenberg, Institute of Pharmaceutical Technology and Biopharmacy, Halle/Saale, Germany

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Abstract

The purpose of the study was to develop a new three-dimensional model using force, time and displacement to characterize the densification behavior of tableting materials. Normalized time (x), displacement converted to $\ln(1/1 - D_{rel})$ according to Heckel (y) and force presented as pressure (z) were used to plot a graph. A twisted plane was fitted to this three-dimensional plot. This plane was characterized by three parameters d, the slope over time called 'time plasticity', e, the slope over pressure called 'pressure plasticity' and ω, the angle of rotation called 'fast elastic decompression'. These parameters were used to characterize the densification behavior of the well-known materials microcrystalline cellulose, dicalcium phosphate dihydrate, theophylline monohydrate, cellulose acetate and hydroxypropyl methylcellulose at different $\rho_{rel,\,max}$. It could be shown that brittle, elastic and plastic compression properties could be very well distinguished and differentiated. Further on, it could be shown whether these properties were due to pressure or time. Thus this model has the prevailing advantage to characterize tableting materials in one step according to time and pressure and it is a useful tool to develop tablet formulations or new excipients.

Keywords: Tablets; Compaction; Data modeling; Curve-fitting; Excipients

1. Introduction

The characterization of tableting excipients is of special importance for the use of pharmaceutical excipients in the development and production of tablets. Tableting excipients have been characterized according to their predominating deformation and densification behavior by treatment of compaction data with mathematical methods [1–11]. Establishing a compaction data bank with the most important parameters derived from several models for different tableting machines is an ultimate goal for the pharmaceutical industry [12]. The data presentations for analysis used up to now are the porosity–pressure plot, the pressure–displacement plot and the pressure–time plot. From these graphs by application of different mathematical models several parameters have been derived: the slope of the Heckel-function [2] or the yield strength, fitting parameters to describe the form of the pressure time plot [7,11] or the ratio of areas under the curve for the pressure–time plot [5,9] as well as under the pressure-displacement plot [4,13,14]. The parameters try to describe the ductile, brittle and elastic behavior of the excipients even when these plots are mainly used as 'fingerprints' for the special tableting materials. However, since always only two of the three gained measured values are used for the analysis of the data plots, a part of valuable information is lost in each of these models. Therefore using these models, it is of importance to use parameters calculated from different models and to combine the different results. Another possibility is to use the parameters got from calculations of viscoelasticity [6,15]. They include displacement, force and time but the final models can get rather complicated, and they end up in a lot of parameters for description of the compaction behavior of one tableting material. The aim of this study is therefore to find a model which uses all three variables force, time and displacement at the same time for the calculation of only two or three significant parameters which can describe as comprehensive as possible the compaction properties.

2. Theoretical development

2.1. The model

With the software available today it is possible to create three-dimensional data plots. The independent variable is time, the dependent variables are force and displacement. With such a data plot it is now possible to combine the

* Martin-Luther-University Halle-Wittenberg, Institute of Pharmaceutical Technology and Biopharmacy, Wolfgang-Langenbeck-Strasse 4, 06120 Halle/Saale, Germany. Tel.: +49-345-552-5138; fax: +49-345-552-7029.
E-mail address: picker@pharmazie.uni-halle.de (K.M. Picker)

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information from one compaction cycle in one single data plot. First aim was to find a mode of characterization of this graph which presents as much information as possible. Since the porosity–pressure plot according to Heckel [2] includes the densification process (porosity), it was decided to present the displacement data as $\ln(1/1 - D_{rel})$. Force is presented as pressure to get more independent from the size of the tablet tooling. Time stays as time. It was normalized to compare the shape of the curves more easily. The second step was then to find a possibility to model this three-dimensional data plot (Fig. 1), either with a function or another model. The disadvantage of a function is the dependency of the variables and their complexity. Thus, a fitting function would result in many parameters for characterization. However, in a three-dimensional space a simple figure is a plane which can be differently situated. Every plane is characterized by three parameters: the slopes of 'z over x' and 'y over x' and the intersection of the y-axis by the plane. Since the data plot in its upper part, the most important part for the deformation of the material, seems to fit a plane, it was decided to fit a plane to the data. Another criterion was that the plane had to include the maximum pressure. In Fig. 2 an example is given. The function for this plane is

$$y = \ln\frac{1}{1 - D_{rel}} = d{\cdot}t + e{\cdot}p + f \tag{1}$$

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

$$d = \frac{\partial\left(\ln\left(\frac{1}{1 - D_{rel}}\right)\right)}{\partial t}, \qquad e = \frac{\partial\left(\ln\left(\frac{1}{1 - D_{rel}}\right)\right)}{\partial p} \text{ and}$$

$$f = \ln\left(\frac{1}{1 - D_{rel}}\right)$$

For this plane it had to be tested which percentage of the

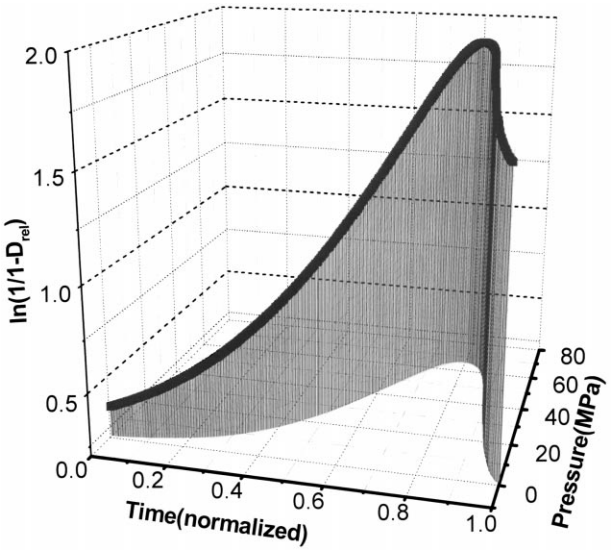

Fig. 1. Three-dimensional data-plot for one compaction cycle of microcrystalline cellulose at $\rho_{rel,\,max}$ of 0.850.

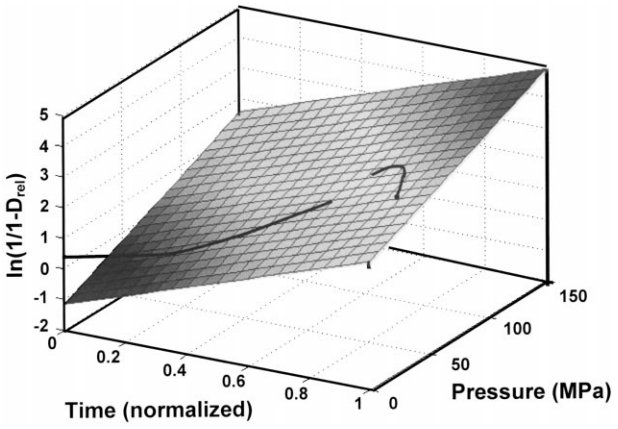

Fig. 2. Three-dimensional data-plot for one compaction cycle of microcrystalline cellulose with a fitted plane according to the three-dimensional model without twisting (Eq. (1)).

data had to be used for analysis and which percentage could be neglected to gain a better fit. The best fit was got by neglecting 70% of the data referring to maximum pressure. The error of residues increased from 0.0125 to 0.0480 going from 30 to 50% of the data ($n = 25$, five different materials). However from a pharmaceutical point of view, it seemed necessary to include more data, especially to include the most important parts of a compaction cycle. It was decided to use 50% of the data referring to maximum pressure which means that only data with more than half of the maximum pressure were used for fitting. Since deformation of the particles mainly happens during the period of the compaction event it is regarded to be legitimate to use only this part of the data for comparison. A further loss of fitting quality was not regarded as helpful. The most important part of the compaction event is taking place during this time. This is in accordance with models used by Vogel and Schmidt [9].

Since the fit of this plane was not satisfying, because the data plot is more twisted than a simple plane the fitting plane was twisted by an axis which includes the maximum pressure and cuts at this pressure the time axis. The error of residues was reduced from 0.0429 to 0.0186 ($n = 81$, six different materials). An example is given in Fig. 3. The used function is

$$y = \ln\left(\frac{1}{1 - D_{rel}}\right) = \left((t - t_{max})(d + \omega{\cdot}p_{max} - p)\right) + \left(e{\cdot}p\right) + \left(f + d{\cdot}t_{max}\right) - \omega \tag{2}$$

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

$$d = \frac{\partial\left(\ln\left(\frac{1}{1 - D_{rel}}\right)\right)}{\partial t}, \qquad e = \frac{\partial\left(\ln\left(\frac{1}{1 - D_{rel}}\right)\right)}{\partial p},$$

$$f = \ln\left(\frac{1}{1 - D_0}\right)$$

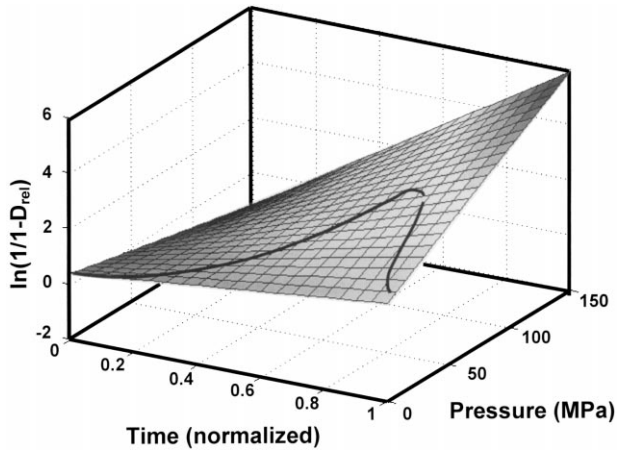

Fig. 3. Three-dimensional data-plot for one compaction cycle of microcrystalline cellulose with a fitted plane according to the three-dimensional model including the angle of rotation (Eq. (2)).

t_{max} = time at maximum pressure, p_{max} = maximum pressure and ω = angle of rotation.

2.2. The parameters

The four parameters derived from the twisted plane could now be used to interpret the compaction cycle and following that the predominating deformation and densification behavior of the materials. The parameter $d = (\ln(1/1 - D_{rel}))/t$ is the densification over the time and was called 'time plasticity'. It describes the extent of densification over time. A fast deforming material has a high value of d, a slow deforming material has a low value of d. The value of d is reduced as well when a fast deforming material shows a lot of decompression. The parameter $e = (\ln(1/1 - D_{rel}))/p$ is the densification of a material over pressure and was called 'pressure plasticity'. An easily without a lot of pressure deforming material shows a high value of e, a material which needs a lot of pressure shows a low value of e. This parameter is similar to the slope of the Heckel function at 'zero pressure' [2]. However it cannot be directly compared to the slope of the Heckel function since another range of fitting has been chosen. e shows only plastic deformation because it is reduced as well when an easily deforming material shows a lot of decompression. The slope of the decompression under load is 'subtracted' from the slope of compression and thus the slope e of the plane is for more elastic materials lower than the slope of the Heckel function 'at pressure' [1]. The parameter f is the intersection with the y-axis $\ln(1/1 - D_{rel})$. It contains both the influences of d and e. A fast and easily deforming material has a low value of f, a slowly and with higher pressure deforming material has a high value of f. Combinations exist in between. Therefore this parameter is more difficult to interpret than both the others. Finally the twisting angle ω has to be interpreted. ω describes the angle of rotation at an axis at the time of the maximum pressure. Thus it describes the twist of compression to decompression phase and thus the extent of decompression. It was called 'fast elastic decompression'. It is the correction of d in dependence of pressure. Thus ω completes the information provided by d and e, and decides whether the material shows decompression or not. ω has the dimension of an angle. Since the plane is only plane when the slope over compression is in accordance with the slope over decompression, ω is positive when the material does not show decompression and becomes negative when the material shows a lot of decompression.

3. Materials and methods

3.1. Materials

Dicalcium phosphate dihydrate (Emcompress®, Lot # R 19 K, Mendell, Patterson, NY), microcrystalline cellulose (Avicel® PH 101, Lot # 14204, FMC Corporation, Princeton, NJ), hydroxypropyl methylcellulose (Metolose® 90 SH, Lot # 506825, Shin-Etsu, Tokyo, Japan), cellulose acetate (Lot # AC-62505, Eastman Chemical Company, Kingsport, TN) and theophylline monohydrate (Lot # 4072.2, Roth GmbH, Karlsruhe, Germany) were used as materials with different deformation mechanisms. The materials were used as obtained. Moisture content was determined by thermogravimetrical analysis (TG, Netzsch Gerätebau, Selb, Germany) and sorption isotherms were recorded gravimetrically to ensure that no moisture uptake happened during compression. The true density of the materials was determined by helium-pycnometry (Accupyc1330, Micromeritics, Norcross, GA).

3.2. Methods

Tableting was performed on an instrumented single punch 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 five different maximum relative densities of the tablets, $\rho_{rel,\,max}$: 0.750, 0.800, 0.850, 0.900 and 0.950 ($\pm$0.001) with

$$\rho_{rel,\,max} = \frac{\rho_{max}}{\rho_{true}} \quad (3)$$

with $\rho_{rel,\,max}$ = maximum relative density, ρ_{max} = density at minimum height of the tablet under load and ρ_{true} = true density.

The tablet height and therefore the volume at maximum densification under load was held constant at 3.000 $\pm$ 0.001 mm (corrected for elastic deformation of the punches). This precision is valid for the absolute tablet height. Displacement of the punch faces was measured using an inductive transducer (W 20 TK, Hottinger Baldwin Meßtechnik, Darmstadt, Germany). Elastic deformation was measured by punch to punch deformation. The calculated error was 6 μm. The transducer was calibrated with slip gauges of 2, 3

and 5 mm height. Throughout the tableting cycle the remaining error was estimated to be 10 μm. Forces were measured by the calibrated strain gauges. The depth of filling was held constant at 13 mm. The production rate was 10 tablets per minute. Lubricant (0.5 % magnesium stearate) was only used in case of dicalcium phosphate dihydrate to avoid its influence on the microstructure of the tablet. The amount of material necessary for each tablet with a given $\rho_{rel,\ max}$ and always the same apparent density was calculated. The powder was manually filled into the die and one compaction cycle was performed.

Five single tablets were produced at each condition. Data acquisition was performed by a DMC-plus system (Hottinger Baldwin Meßtechnik, Darmstadt, Germany) and data were stored by BEAM-Software (AMS-Flöha, Germany). Fitting of the plane was performed by the least-squares method according to Levenberg–Marquard. Results were similar when using the method of Gauss–Newton. For fitting results for d, e and ω of the five compaction cycles at one tableting condition (material and a given $\rho_{rel,\ max}$) means and standard deviations were calculated.

4. Results and discussion

4.1. Theoretical application of the model

To evaluate the model extreme values had to be chosen and the different cases have to be discussed. Following that, this cases have to be applied to different tableting materials. Since f is not really independent, combinations of the other three parameters were chosen for description. In Table 1 minimal and maximal values for d, e and ω are given, calculated from 90 different compaction conditions. The theoretical cases are given in Table 2.

When ω is high this means that there is no elastic recovery during the decompression cycle. For this case we have four possibilities.

Case I a. A low d and e, meaning that this material needs a lot of time and a lot of pressure for deformation. Such a material does not deform easily, therefore it probably fractures under pressure after some deformation, and therefore shows no elasticity. Practically, most materials will show little elastic recovery in this case. An example is dicalcium phosphate dihydrate at low stages of densification (Table 3). However, ω is not really high, and thus it is more Case I b with a low ω.

Table 1
Minimal and maximal values for the parameters d, e and ω calculated at 90 different compaction conditions including 18 different tableting materials (not all presented in the paper)

Parameter	Minimum	Maximum	Mean SD
d	0.20	4.50	0.03
e	0.0050	0.0210	0.0003
ω	−0.0400	0.0500	0.0005

Table 2
Different combination of parameters from the fitting function for description of different cases compaction cycles

Case	d	e	ω
I a	Low	Low	High
II a	High	High	High
III a	High	Low	High
IV a	Low	High	High
I b	Low	Low	Low
II b	High	High	Low
III b	High	Low	Low
IV b	Low	High	How

Case II a. A high d and e, meaning that this material deforms easily by low pressure without fast recovery. Such a material has to be a totally plastic material, a ductile material which is not too voluminous. An example is difficult to find because all tableting materials showed a low ω.

Case III a. A high d and a low e, meaning that this material deforms during a short time, but needs a lot of pressure. Such a material will most probably be a material which fractures totally (short time, fast densification), but needs a lot of pressure for that. Practically such a material does not exist, it would need more time.

Case IV a. A low d and a high e, meaning that this material needs time for a deformation at low pressure. Such materials have a voluminous powder bed, they consume time, but the densification is totally plastic. A good example is theophylline monohydrate at low densification (Table 3).

These four cases will be different when ω is low. In this case, the material shows a lot of fast recovery.

Case I b. A low d and e: The material is not only fracturing, a lot of its deformation is elastic and therefore it shows elastic recovery and thus a high ω. A very brittle material will never show very low values of ω. Dicalcium phosphate dihydrate may again serve as an example (Table 3).

Case II b. A high d and e: This material is not only deforming plastically, the plastic deformation is combined with elastic deformation, and this results in elastic recovery shown by a low ω. A good example is cellulose acetate at high densification (Table 3).

Case III b. A high d and a low e: Thus the pressure needed is high but the time for deformation is short, and a lot of fast expansion occurs shown by the low ω. Such a material is as unlikely as Case III a.

Case IV b. A low d and a high e: Only little pressure is needed and it takes time for densification by showing fast recovery. Such materials will not be very likely or ω is extremely high. The material is mainly deforming plastically but the particles show some elasticity shown by a low ω. An example can be theophylline monohydrate at higher densification (Table 3).

Following that, eight cases exist which can be theoretically combined with either a low or a high f. However, according to the position of the plane in the three-dimensional space a high f will only exist in Case I a and b and a

Table 3
Different combination of parameters from the fitting function for description of compaction cycles of different tableting materials (n =5, means and SD) at different maximum relative densities $\rho_{rel,\ max}$

Case	Material	$\rho_{rel,\ max}$	d	e	ω
IV a	Theophylline monohydrate	0.750	0.2021 (0.0035)	0.0171 (0.0003)	0.0466 (0.0005)
I b	Dicalcium phosphate dihydrate	0.750	0.2305 (0.0188)	0.0074 (0.0002)	0.0150 (0.0008)
II b	Cellulose acetate	0.950	4.2731 (0.0867)	0.0198 (0.0001)	−0.0384 (0.0014)
IV b	Theophylline monohydrate	0.950	1.6209 (0.0210)	0.0185 (0.0001)	0.0019 (0.0003)

low f in Case II a and b, when d or e will be both high or low. Since f is dependent on d and e, it can only contribute little to interpretation. For the characterization of the materials it can be neglected. In the following only the parameters d, e and ω are discussed and used for the characterization of tableting materials. These three parameters can be presented in an three-dimensional graph for which an example is given by Fig. 4. For this graph, the values of substances from Table 3 were used.

4.2. Practical application of the model

The theoretical discussion of the model showed that only few tableting conditions can be described with the eight extreme cases discussed. Therefore in Fig. 5 a,b typical plots for five tableting materials at different $\rho_{rel,\ max}$ with different tableting behavior are shown. The corresponding values are given in Table 4.

Microcrystalline cellulose showed medium to high values of d which are increasing with $\rho_{rel,max,}$ e was medium to high as well and slightly increasing. Thus, microcrystalline cellulose showed quite a lot pressure- and time-plasticity which increased especially due to time with increasing $\rho_{rel,\ max}$. Simultaneously, ω decreased, which means that fast elastic decompression increased. This may be an indication for viscoelasticity. ω is medium which indicates that this material is more plastic than elastic.

Contrary, dicalcium phosphate dihydrate showed very low values for d and e even when $\rho_{rel,\ max}$ was increasing. This means that this material is not plastic, it needs a lot of pressure and time for deformation. Whether it behaved brittle or elastic during compression can be interpreted as well. At low $\rho_{rel,\ max}$ ω is high, the material showed only little fast

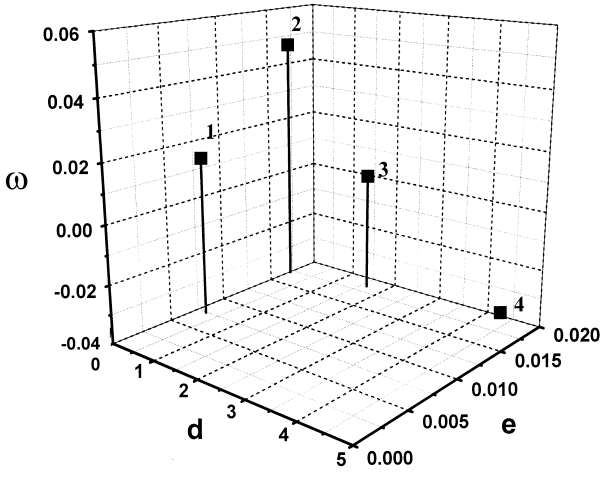

Fig. 4. Presentation of the fitting parameters time plasticity d, pressure-plasticity e and fast elastic decompression ω in a three-dimensional graph for four different tableting conditions: dicalcium phosphate dihydrate at $\rho_{rel,\ max}$ of 0.750 (1), theophylline monohydrate at $\rho_{rel,\ max}$ of 0.750 (2), theophylline monohydrate at $\rho_{rel,\ max}$ of 0.950 (3) and cellulose acetate at $\rho_{rel,\ max}$ of 0.950 (4).

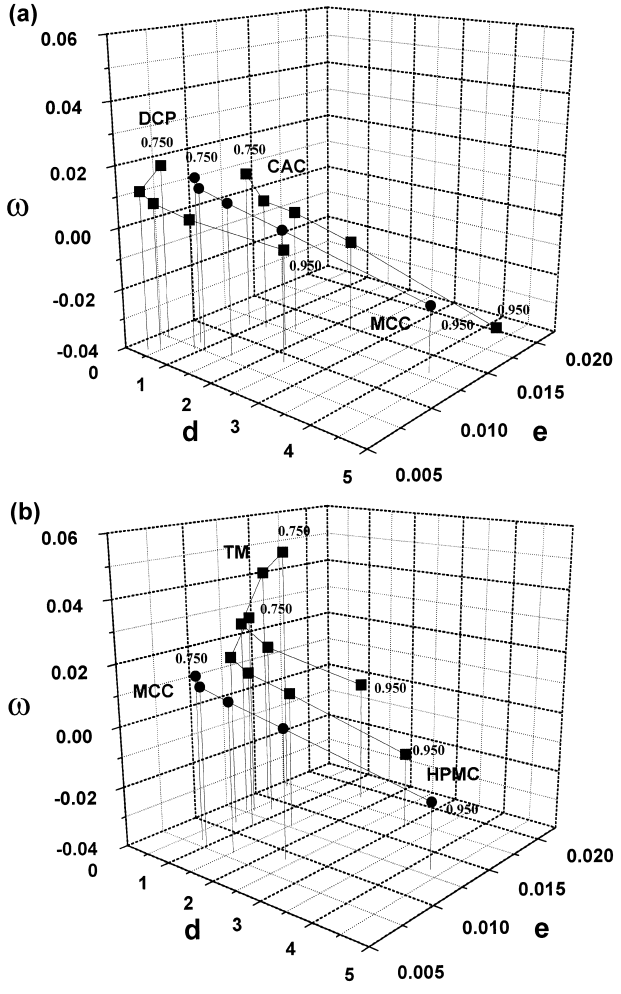

Fig. 5. Parameter plot for different tableting materials at different graded $\rho_{rel,\ max}$ 0.750, 0.800, 0.850, 0.900 and 0.950 (a) microcrystalline cellulose (MCC), dicalcium phosphate dihydrate (DCP), cellulose acetate (CAC) and (b) microcrystalline cellulose (MCC), theophylline monohydrate (TM) and hydroxypropyl methylcellulose (HPMC).

Table 4
Different combination of parameters from the fitting function for description of compaction cycles of different tableting materials (n =5, mean and SD) at different maximum relative densities $\rho_{rel,\ max}$

Material	$\rho_{rel,\ max}$	d	e	ω
Microcrystalline cellulose	0.750	0.7828 (0.0102)	0.0081 (0.0005)	0.0151 (0.0002)
	0.800	1.0700 (0.0297)	0.0075 (0.0001)	0.0134 (0.0004)
	0.850	1.5320 (0.0307)	0.0080 (0.0001)	0.0097 (0.0004)
	0.900	2.3416 (0.0594)	0.0092 (0.0000)	0.0028 (0.0001)
	0.950	4.3016 (0.0399)	0.0131 (0.0003)	−0.0180 (0.0004)
Dicalcium phosphate dihydrate	0.750	0.2305 (0.0188)	0.0074 (0.0002)	0.0150 (0.0008)
	0.800	0.3342 (0.0127)	0.0056 (0.0001)	0.0122 (0.0008)
	0.850	0.5080 (0.0119)	0.0060 (0.0001)	0.0084 (0.0002)
	0.900	0.8843 (0.0061)	0.0073 (0.0000)	0.0029 (0.0002)
	0.950	1.9240 (0.0368)	0.0108 (0.0000)	−0.0077 (0.0003)
Theophylline monohydrate	0.750	0.2021 (0.0035)	0.0171 (0.0003)	0.0466 (0.0005)
	0.800	0.3100 (0.0023)	0.0150 (0.0004)	0.0411 (0.0010)
	0.850	0.4475 (0.0051)	0.0127 (0.0002)	0.0260 (0.0002)
	0.900	0.7658 (0.0220)	0.0137 (0.0002)	0.0179 (0.0008)
	0.950	1.6209 (0.0210)	0.0185 (0.0001)	0.0019 (0.0003)
Cellulose acetate	0.750	0.8653 (0.0357)	0.0116 (0.0001)	0.0065 (0.0004)
	0.800	1.1755 (0.0233)	0.0119 (0.0001)	0.0040 (0.0001)
	0.850	1.6237 (0.0334)	0.0128 (0.0001)	0.0005 (0.0003)
	0.900	2.3623 (0.0467)	0.0147 (0.0006)	−0.0092 (0.0005)
	0.950	4.2731 (0.0867)	0.0198 (0.0001)	−0.0384 (0.0014)
Hydroxypropyl methylcellulose	0.750	0.5728 (0.0025)	0.0129 (0.0001)	0.0282 (0.0005)
	0.800	0.6838 (0.0022)	0.0110 (0.0001)	0.0173 (0.0001)
	0.850	0.9978 (0.0048)	0.0113 (0.0001)	0.0129 (0.0003)
	0.900	1.5478 (0.0117)	0.0126 (0.0000)	0.0063 (0.0002)
	0.950	2.9763 (0.0921)	0.0169 (0.0001)	−0.0149 (0.0005)

elastic decompression. With increasing $\rho_{rel,\ max}$ e increased which means less plasticity even when d and e remained the same. This is the sign for brittle fracture. With further increasing $\rho_{rel,\ max}$ mainly d, less e increased and ω decreased. This indicates that with increasing plasticity, more time- than pressure-plasticity, elastic decompression was increasing as well. Only when a $\rho_{rel,\ max}$ of 0.950 was reached, pressure–plasticity was predominant. Summarizing, dicalcium phosphate dihydrate showed a totally different densification behavior compared to microcrystalline cellulose.

Typical for theophylline monohydrate were very high values of ω, which indicate only very little fast elastic decompression. e was higher than for microcrystalline cellulose and dicalcium phosphate dihydrate indicating a lot of pressure-plasticity. Since e was generally low, time–plasticity was lower. Following that, theophylline monohydrate is an easily compactible material which needs only little pressure for deformation. It fractured at lower $\rho_{rel,\ max}$, because d decreased. At higher $\rho_{rel,\ max}$ it finally deformed more plastically.

Cellulose acetate deformed similar to microcrystalline cellulose. However, its values of ω were lower showing a lot of fast elastic decompression. d-values were similar and e-values were slightly higher. Thus pressure–plasticity was higher for this material even when its fast elastic decompression was a lot higher. This indicated a very viscoelastic material.

Hydroxypropyl methylcellulose showed higher values of e compared with microcrystalline cellulose indicating more pressure-plasticity. The e-value was a little lower. Thus this material was less easily deforming due to time. ω was similar to microcrystalline cellulose indicating some fast elastic decompression as sign of viscoelasticity. At low $\rho_{rel,\ max}$ e decreased, thus some brittle fracture is occurring. Generally hydroxypropyl methylcellulose is a very plastic material.

5. Conclusions

The practical application of the model showed that by combination of d, e and ω at different $\rho_{rel,max,}$ it is possible to differentiate brittle and plastic deformation and elastic decompression and in combination viscoelasticity. Further on, this three-dimensional analysis enables to differentiate between plasticity due to pressure or time, thus the reason of plastic behavior can be located. The advantage is that it is now possible to quantify densification behavior of materials due to pressure and time simultaneously. No longer the use of two different models is necessary. Thus this new three-

dimensional model will help for an advanced characterization of the densification behavior of new and well-known tableting materials and mixtures of tableting substances and following that to model tableting excipients. In the galenical development of pharmaceutical industry it will be a useful tool to modify tablet formulations.

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