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Paper

Compression force/time-profiles of microcrystalline cellulose, dicalcium phosphate dihydrate and their binary mixtures—a critical consideration of experimental parameters[1]

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Abstract

Compression force/time-profiles of microcrystalline cellulose and dicalcium phosphate dihydrate and mixtures thereof were compared on a modern rotary press by three different methods of compression: compression to a constant tablet weight, compression to a constant tablet height and compression from a constant filling depth. Compression was carried out at three different compression force levels. The differences obtained by analysing the area under the curve in the compression, dwell and decompression phase could be explained by differences of the in-die working density of the powders and their respective compression behaviour. From data of the compression phase as well as from the area-quotient-index obtained from the dwell time it was possible to estimate the percolation threshold of dicalcium phosphate dihydrate in a mixture with microcrystalline cellulose to ~ 50% (w/w) corresponding to 30% (v/v). © 1997 Elsevier Science B.V.

Keywords: Compression; Compression force/time profiles; Microcrystalline cellulose; Dicalcium phosphate dihydrate; Binary mixtures; Rotary tablet press; Dwell time coefficient; Plasticity index; In-die-working density

1. Introduction

Compression force/time-profiles are used to characterise the compression behaviour of active ingredients, excipients and even formulations in tableting with respect to their elastic and plastic properties. The compression/time-curve is more than a fingerprint of the product under investigation and can be a useful tool to choose excipients for direct compression and binders for granulation.

In the past various attempts were made to characterise compression force/time-profiles from single punch as well as from rotary tablet presses. Jones [1] defined the consolidation time as the time to reach the maximum force, the dwell time as the time at the maximum displacement of the punches and contact time as the time for compression and decompression. Parameters to characterise the shape of the curves were developed by several authors. Schwartz [2] and later on Chilamkurti et al. [3] used the area under the curve, the peak height, the peak width, the peak width at half height, the time and the height of the inflexion point of the compression phase, and the time of the force maximum to characterise the compression behaviour of powders. Emschermann and Müller [4] divided the area under the curve along the abscissa at the point of the

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[1] Dedicated to Professor Dr Karl Thoma on the occasion of his 65th birthday.

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force maximum. Due to the prolonged dwell time on a rotary press this method is mainly applicable on eccentric presses.

Besides these more or less phenomenological evaluations other authors applied mathematical models to describe compression/time-curves. Dietrich and Mielck [5] after mirror-converting of the force/time-curve took the Weibull function and were able to extract two parameters: γ, describing the skewness and β, describing the width of the curve. Recently, Juppo et al. [6] applied the 3rd and 4th statistical moment to describe the skewness and kurtosis of a compression/time-curve. In both cases it is questionable, whether or not a statistical function which is based on a frequency distribution could be used to describe an experimental curve.

Another evaluation method deals with mechanical models, first described by Rippie and Danielson [7] and later on developed by Müller and Caspar [8], Paronen and Müller [9] and Sutanto [10]. Combining spring and dashpot elements it is possible to fit a given compression/time-profile. For a good fit a relatively high number of elements is necessary though the interpretation becomes more difficult.

Most of the work referred to so far dealt with single substances. The compression characteristics of mixtures were rarely investigated. The combination of dicalcium phosphate dihydrate and microcrystalline cellulose was studied earlier by Wells and Langridge [11]. In addition to tablet properties they determined the binding capacity for microfine paracetamol and also studied the stress relaxation behaviour of dicalcium phosphate dihydrate/microcrystalline cellulose mixtures. Stress relaxation was high for microcrystalline cellulose and low for dicalcium phosphate dihydrate while the mixtures were in between. Chilamkurti et al. [12] studied the same system with and without the addition of a soluble (amitriptyline hydrochloride) and a sparingly soluble (hydrochlorothiazide) drug using their compression indices developed earlier [3]. For the soluble amitriptyline they found a significant influence on the disintegration time of the tablets when the dicalcium phosphate dihydrate/microcrystalline cellulose ratio was varied. Garr and Rubinstein [13] compared mixtures of 25% cellulose and 75% dicalcium phosphate dihydrate with those containing 75% microcrystalline cellulose and 25% dicalcium phosphate dihydrate and found a decrease of tablet strength for the latter when increasing the compression speed. Holman and Leuenberger [14] and Holman [15] studied mixtures of dicalcium phosphate dihydrate and microcrystalline cellulose on the basis of the percolation theory, introduced by Stauffer [16]. Ilkka and Paronen [17] investigated the compression behaviour of the same mixtures by Heckel plots and found that a plastically deforming material had a greater effect on the percolation threshold than a fragmenting one. A correlation between compaction pressure and tablet hardness using an equation similar to the Heckel equation was used by Castillo-Rubio and Villafuerte-Robles [18] to investigate mixtures of dicalcium phosphate dihydrate and microcrystalline cellulose. The highest compactibility was found again for microcrystalline cellulose, the lowest for dicalcium phosphate dihydrate and the mixtures were in between.

In our previous work [19,20] we used a descriptive method to characterise pharmaceutical substances by compression/time profiles. An external trigger marks that point of the compression/time-curve where the middle of the plane area of the punch head is exactly under the centre of the upper compression roller, enabling calculation of the dwell time and providing the possibility to divide the compression force/time-curve into an exactly defined compression-, dwell- and decompression-phase. From the compression phase data information on the rearrangement and densification of the powder bed can be drawn. The duration of this phase is influenced by the untapped and tapped bulk densities and mainly by the so called in-die-working density, which is the density of the powder in the die after the filling operation by the force feeder. The shape of the force curve during the dwell time gives information about the plastic and brittle properties of the material and the decompression phase could be used to detect the initial elastic recovery of the tablet before ejection. For a number of single substances these data were reported and in addition the influence of the compression force was investigated [21]. With powder mixtures, depending on the quantitative composition, a change in untapped and tapped bulk densities as well as in in-die-working density will be observed. When compressing different mixtures to a constant tablet weight, changes in tablet height and duration of the compression phase will result. In addition, other tablet parameters like tablet height and hardness will vary also.

The aim of this study was therefore, to quantify these influences using binary mixtures as models. The mixtures were composed of the plastically deforming microcrystalline cellulose and the brittle dicalcium phosphate dihydrate. Thus, the compression to a constant tablet weight, compression to a constant tablet height and compression of a constant powder volume in the die and their influence on the compression parameters have been investigated.

2. Materials and methods

2.1. Materials

Avicel® PH 102 (Lehmann and Voss, Hamburg, Germany), a microcrystalline cellulose, and Emcompress® DH (E. Mendell GmbH, Uetersen, Germany), a dicalcium phosphate dihydrate, were used as received. Mag-

nesium stearate, Type Pharma (Otto Bärlocher GmbH, München, Germany) was used as a lubricant.

2.2. Preparation of mixtures

Besides the pure substances binary mixtures were prepared of 20, 30, 50, 70 and 90% of Emcompress® DH and the corresponding amount of Avicel® PH 102 to give 100%. The components were first sieved through a 2 mm sieve and then mixed for 5 min at 40 rpm in a 10 l drum mixer type Röhnrad in amounts giving a total filling volume in the mixer between 40 and 60%. The mixtures were sieved through an 800 μm sieve and mixed again for an additional 5 min. One part of magnesium stearate was sieved through a 355 μm sieve onto 99 parts of the mixtures and mixed for 5 min under the same conditions. The pure components Avicel® PH 102 and Emcompress® DH were separately mixed with magnesium stearate without prior mixing and sieving steps.

2.3. Powder density determinations

Untapped and tapped bulk densities were determined according to German Pharmacopoeia 10, 2nd Addendum as a mean of three determinations using an Engelsmann apparatus (type JEL ST2, Engelsmann, Ludwigshafen, Germany).

The working densities of the single components and the mixtures in the die were calculated from the filling volume of the die and the powder mass filled into the die by the force feeder during operation. To simplify the determination of the powder mass the tablet weight after compression was taken as the powder mass in the die.

2.4. Calibration of the tablet machine

A Korsch PH 230/17 DMS rotary tablet press (Korsch Pressen GmbH, Berlin, Germany) was used throughout the study. The machine was instrumented with four strain gauges type 6/120 LY11 (Hottinger Baldwin Meßtechnik, Darmstadt, Germany) each at the rockers of the lower and upper main compression roller in a full Wheatstone bridge. In this study the upper rocker instrumentation was used to measure the main compression force. Primary signals were amplified by a 5 kHz frequency carrier bridge (Type K 52, Hottinger Baldwin Meßtechnik, Darmstadt, Germany) and converted by an A/D-converter board (RTI 860, Analog Devices, Norwood MA, USA). Data acquisition was controlled by a software package called Turbo-Lab® (Stemmer PC-Systeme GmbH, Puchheim, Germany).

The force calibration of the machine is described elsewhere [22]. All experiments were done on the basis of a static force calibration.

2.4.1. Calibration of the filling depth hand wheel

The calibration of the hand wheel to adjust the filling depth was carried out against a plane lower punch using a depth micrometer (type 129, Mitutoyo, Osaka, Japan) which was mounted onto the die table. Eleven different filling depths ranging between 2 and 13 mm were adjusted in equidistant intervals. The true filling depth was calculated by linear regression to give:

$$y = 0.98x + 0.10 \quad (1)$$

where y is the true filling depth and x is the filling depth value shown on the hand wheel.

The regression coefficient R, was 0.99996.

2.4.2. Calibration of tablet thickness hand wheel

The tablet thickness was adjusted by a handwheel acting on the lower wing carrying the lower compression roller. To calibrate the tablet thickness, eleven polished flat faced steel tablets of 9.5 mm in diameter and varying in height from 3.0 to 3.5 mm in 0.05 mm steps were used. The true height of the steel tablets was measured with an accuracy of 0.01 mm. The steel tablets were fixed between one pair of flat, type B punches under compression force control. The value for the tablet height was considered as correct when there was just no compression force visible at the oscilloscope. This position was read from the handwheel scaling and taken as the x-value for the linear regression. The linear regression was calculated from the eleven values as follows:

$$y = 0.91x + 0.16 \quad (2)$$

where y is the true filling depth and x is the readout of the filling depth at the hand wheel.

The regression coefficient R, was 0.99990.

2.5. Compression and data collection

Compression was carried out on the Korsch Pharma 230. Four of the 17 punch stations (positions no. 3, 7, 11, 15) were active, equipped with 10 mm flat faced bevelled edge B-tooling with an overall length of 133.6 mm and a punch head curvature type 'Manesty'. The punch head flat diameter was 10 mm. The machine was run at 25 rpm. The speed of the force feeder was 25 rpm, and the penetration depth of the upper punch into the die was set to 4 mm while the hydraulic overload was fixed between 100 and 105 bar. All experiments were done at room temperature and ambient humidity. Tablets were compressed at approximately 2.5, 5, 7.5 and 10 kN. From these four levels data were linearly interpolated to 3, 6 and 9 kN in order to compare results at exactly the same compression force level. When compressing to a constant weight, the tablet height was adjusted to correspond to the force levels stated above. For a constant tablet height the tablet

mass was adjusted, and when starting from a constant filling depth, the tablet height was varied until the desired compression force levels were obtained.

Compression events were recorded over a time period of 6.3 s at 25 rpm. With four punches installed on the machine nine to ten complete compression events were recorded during that time interval and used for further calculations. The area A_1 under the compression/time-curve and the quotient A_6/A_5 were calculated according to Schmidt and Vogel [20]. The t-values for the calculation of the confidence limits of all parameters were approximated using the 95%-level for a given degree of freedom (DF) as follows [23]:

$$t_{95}\% = 1.96 + \frac{3.012}{DF} - \frac{1.273}{DF^2} - \frac{8.992}{DF^3} \quad (3)$$

2.6. Tablet parameters

Twenty four hours after production, the mass (balance AE 200, Mettler-Toledo GmbH, Gießen, Germany), the thickness (0.01 mm micrometer, Mitutoyo, Kyoto, Japan) and the crushing strength (model 6D, Dr Schleuniger AG, Solothurn, Switzerland) were measured for 10 tablets. Tensile strength values were calculated according to Frocht [24]:

$$s = \frac{2 \cdot F}{\pi \cdot D \cdot h} \quad (4)$$

where F is the crushing strength, D is the tablet diameter and h is the tablet height.

3. Results and discussion

3.1. Powder densities and tablet properties

The untapped and tapped bulk densities and the in-die-working density of the pure components and their mixtures are presented in Fig. 1. The increase of all three densities with increasing amount of dicalcium phosphate dihydrate is nonlinear. The in-die-working density over the whole range of the mixtures lies in between the untapped and tapped bulk densities and approaches the tapped density of pure Avicel® PH 102 for low amounts of Emcompress® DH in the mixture. With higher amounts of Emcompress® DH this curve approaches the untapped density of that material. This could be explained as follows: the densification by the force feeder is lower for Emcompress® DH as compared to Avicel® PH 102 due to the excellent flow properties and higher true density of this material. Avicel® PH 102 on the other hand is a non free flowing excipient due to its fibrous structure it exhibits lower untapped and tapped bulk densities and hence densification during filling of the die.

In Fig. 1 there are no visible percolation thresholds. Due to the fact that percolation is not a mass but a volume controlled phenomenon [17], the mass proportions of the mixtures were transformed into volumes. However, after replacing the mass based abscissa in Fig. 1 by a volume-based equivalent, there was also no percolation threshold visible. The volume based proportions in the mixtures were calculated via the in-die-working densities of the pure components. The volume of Emcompress® DH V_E in 1 g of a mixture can be calculated from the mass proportion m_E and the in-die-working density ρ_E of pure Emcompress® DH according to:

$$V_E = m_E/\rho_E \quad (5)$$

In the same way the volume V_A for Avicel® PH 102 is calculated. The total volume V_{tot} of 1 g of a mixture is therefore:

$$V_{tot} = V_A + V_E \quad (6)$$

The volume fraction of Emcompress® DH in a mixture V_{EM} is now:

$$V_{EM} = \frac{V_E}{V_E + V_A} \quad (7)$$

The calculated volume fraction of Emcompress® DH in mixtures with Avicel® PH 102 and the resulting densities are presented in Fig. 1.

Fig. 2 shows the tensile strength of the tablets prepared by the three methods as related to the amount of Emcompress® DH (w/w) in the mixture. As expected for any of the methods used the tablets with a higher Avicel® PH 102 content show a higher strength. Moreover, it is interesting to note that the tensile strengths of the tablets vary with method of preparation and amount of Avicel® PH 102 in the mixture. This may appear to be contradictory to the fact that the calculation of tensile strength values should not show differences. This discrepancy could be explained by a deformation of these tablets before crushing occurs. Under these circumstances the assumptions made by Frocht [20] and Fell and Newton [25] for the calculation of tensile strength values are no longer valid. The brittle material Emcompress® DH behaves more ideally during tablet crushing. Therefore, the tensile strength calculation is valid, which is also demonstrated by the congruent curves for different preparation methods at given force levels and higher Emcompress® DH fractions. From Fig. 2 it could be concluded that Emcompress® DH in an amount of 50 to 100% in the tablet dominates the crushing behaviour of these tablets. Therefore, a percolation threshold could be assumed at ~ 50% (w/w) of Emcompress® DH.

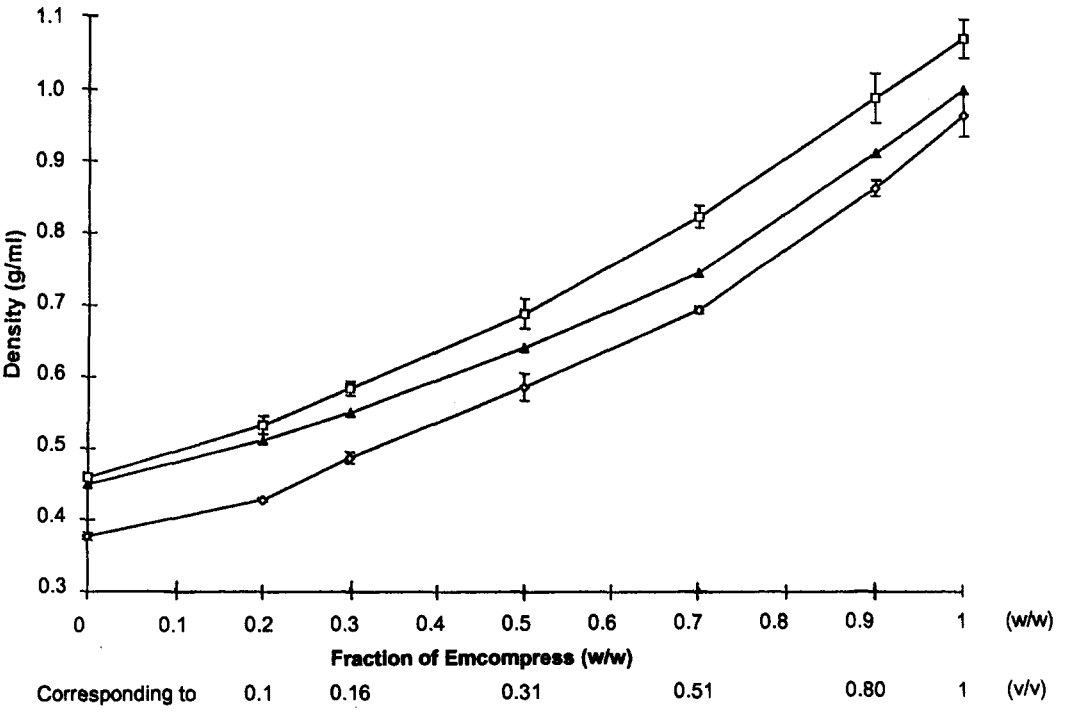

Fig. 1. Densities of the pure components and their binary mixtures (-□-tapped bulk density; -▲- in-die-working density; -◇- untapped bulk) with mean ($n = 3$) and 95%-confidence limits. The confidence limits of the in-die-working density are smaller than the symbols. With increasing amounts of Emcompress in-die-working density approaches the untapped bulk density line.

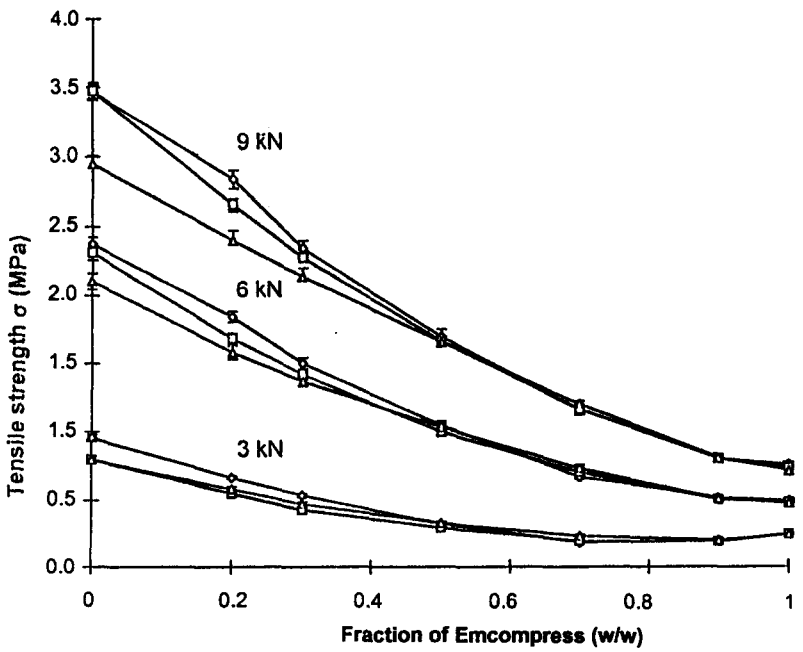

Fig. 2. Tensile strength of the tablets at three compression force levels against fraction of Emcompress in the mixture as related to the three methods of preparation (-◇- 300 mg tablet mass; -□- 1.25 mm tablet height; -△- 6 mm filling depth).

3.2. Evaluation of compression/time-profiles

The compression event on an eccentric press can be divided into the compression and decompression phase. A real so called 'dwell time' does not exist due to the fact that the lower punch does not move actively during tablet formation and the upper punch being at any time in an up- or downward movement. In contrast on a rotary press there is a dwell time because the punches do not move actively in a vertical direction when they are with their plane punch head area under the compression rollers. This situation is demonstrated in Fig.

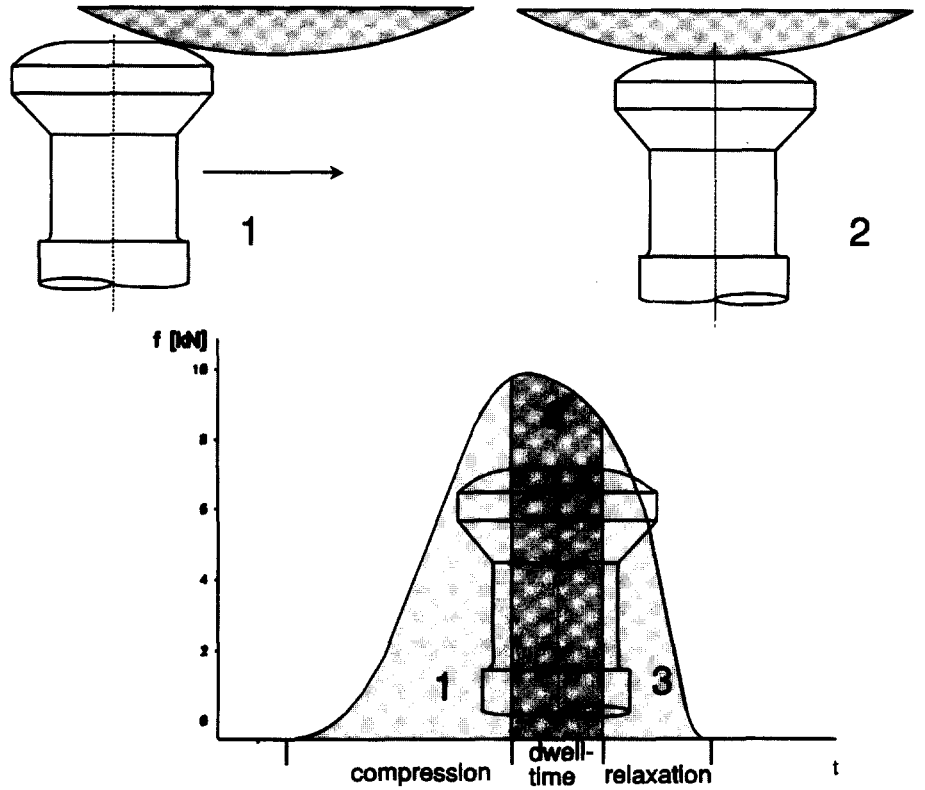

Fig. 3. Phases of the compression event on a rotary tablet press: (1) Compression phase: punch moving in horizontal and vertical direction. (2) Dwell time: punch movement in a horizontal direction only. The punch head is with its plane surface under the compression roller. (3) Decompression phase: punches moving away from the upper and lower surfaces; initial relaxation of the tablet.

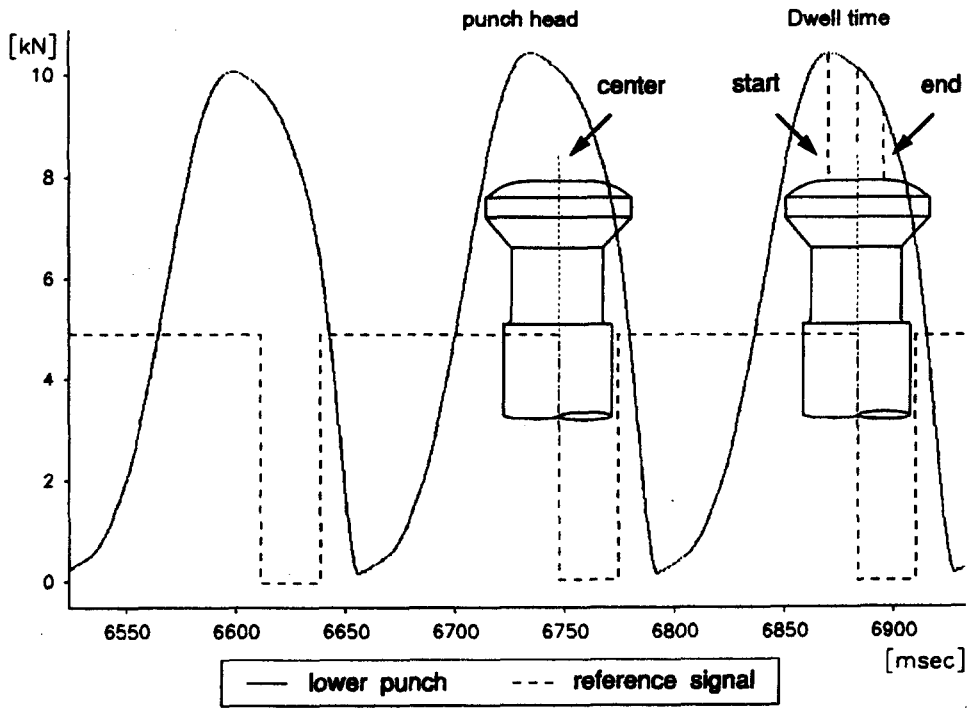

Fig. 4. Force signal of the lower punch and reference signal indicating the mid of the punch head under the compression roller. The dwell time is shown on the right side of the figure.

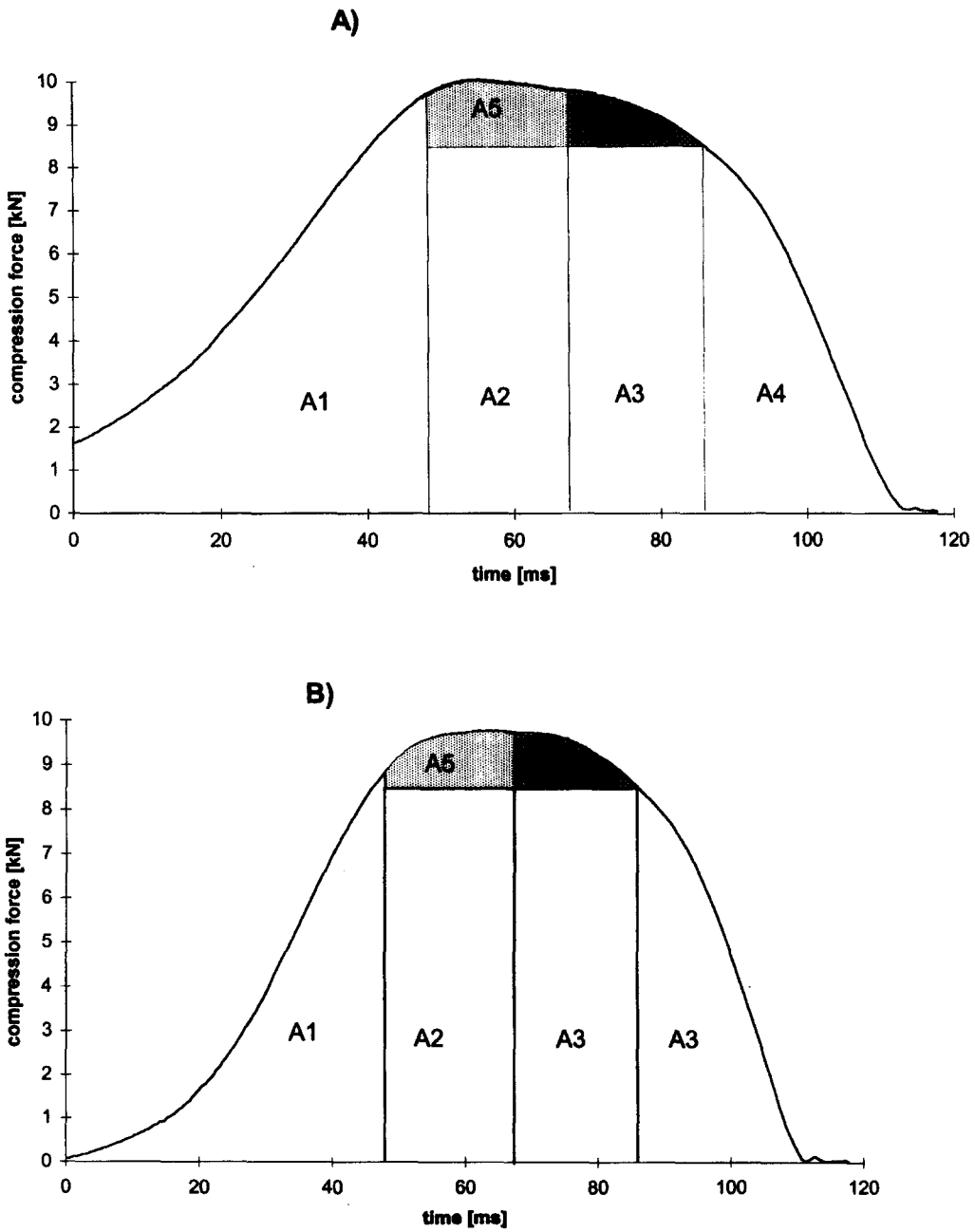

Fig. 5. The compression/time curve of (A) Avicel PH102 and (B) Emcompress DH showing the compression phase (A_1), the dwell phase ($A_2 + A_3$) and the decompression phase (A_4).

3. At the beginning of the compression event the upper punch is hitting against the compression roller (phase 1 in Fig. 3). After reaching its lowest position the dwell time starts (phase 2 in Fig. 3). Decompression occurs when the punch rises again. The duration of the dwell time is dependent on

the diameter of the plane surface of the punch head,
the speed of the machine,

and can be defined according to Armstrong and Palfrey [26].

The middle of the flat punch head under the deepest point of the compression roller was detected by a reference signal as shown in Fig. 4. from which the dwell time can be calculated for any given machine speed.

The compression/time-curve of Avicel® PH 102 and Emcompress® DH can be divided into a compression phase, a dwell time or dwell phase and a decompression phase as shown in Fig. 5. The area under the curve A_1 represents the compression phase, the sum of A_2 and A_3 gives the dwell phase and A_4 depicts the decompression phase. At a given tablet weight A_1 is small for powders showing a high in-die-working density, e.g. dicalcium phosphate dihydrate and high for those having a low in-die working density, e.g. Avicel® PH 102. Within the dwell phase the areas A_5 and A_6 are obtained by drawing a line parallel to the x-axis from the starting

Table 1
Constant and variable parameters to adjust compression force in different tableting modes

Compression of tablets	Adjustment of compression force by	Additional parameter change for different mixtures
To constant tablet weight (300 mg)	Tablet thickness	Filling depth
To constant tablet height (1.25 mm)	Tablet mass	Filling depth
From constant filling depth of the die (6 mm)	Tablet thickness	Tablet mass and height

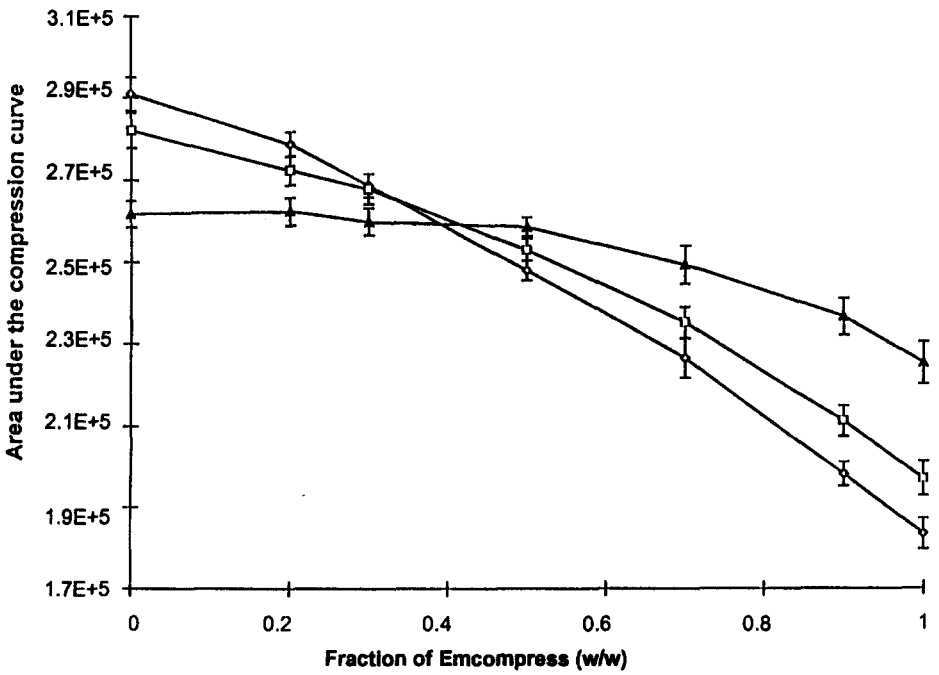

Fig. 6. Area under the force/time-curve A_1 for the compression phase against the fraction of Emcompress. Up to 50% (w/w) there is no change in A_1 indicating the percolation threshold for Emcompress (-◇- 300 mg tablet mass; -□- 1.25 mm tablet height; -△- 6 mm filling depth).

point to the end of the dwell phase. Avicel® PH 102 shows a force decrease over the dwell time, while Emcompress® DH shows a more or less constant plateau. The force decrease of Avicel® PH 102 can be related to the plastic behaviour of this material, while the constant plateau observed for Emcompress® DH can be due to the absence of plastic deformation during the dwell phase. Therefore, the parameter A_6/A_5 can be used as a measure for plasticity of a substance or a mixture.

It might be of interest to find out how different methods of adjusting a tablet machine would influence the parameters described above. For this reason the methods given in Table 1 were examined. The results obtained with the pure materials and different mixtures are presented in Fig. 6.

The experimental method has a considerable influence on the area under the compression curve A_1. When the tablet mass is constant a decrease in A_1 with increasing Emcompress® DH content is observed. This decrease is somewhat smaller when the tablet height is held constant. With a constant filling depth A_1 remains constant up to 50% (w/w) Emcompress® DH and decreases slightly thereafter. The differences shown in Fig. 6 could be explained in combination with Table 2 as follows:

(1) In the case of constant tablet weight an increase of the percentage of Emcompress® DH in the mixture leads to a decrease in filling depth due to the higher density of Emcompress® DH and therefore to a lower degree of compression resulting in a reduction of A_1 for geometrical reasons.

(2) Compression to a constant tablet height reduces again the time of the compression phase and therefore A_1.

(3) For a constant filling depth one should expect only a small change in A_1 over the whole range of mixtures, because the height of the powder column in the die is nearly constant. This is valid up to 50% (w/w) Emcompress® DH in the mixture, but at higher Emcompress® DH contents a significant decrease of A_1 is observed. This could be attributed to the formation of a percolating Emcompress® DH cluster at higher contents. The compression phase is now controlled by

Table 2
Filling depth (mm), tablet mass (mg), tablet height (mm) and compression time t_v (ms) for the pure components Avicel® and Emcompress® at 9 kN compression force

Experimental mode	Parameter	Avicel®	Emcompress®	Change in per cent (Avicel® = 100%)
Tablet mass ~300 mg	Filling depth	8.15	3.57	
	Tablet mass	298	300	
	Tablet height	1.53	0.83	
	t_v	77	50	−35
Tablet height ~1.25 mm	Filling depth	7.49	4.44	
	Tablet mass	274	368	
	Tablet height	1.33	1.29	
	t_v	74	52	−30
Filling depth ~6 mm	Filling depth	6.28	6.31	
	Tablet mass	235	513	
	Tablet height	1.02	2.22	
	t_v	70	59	−16

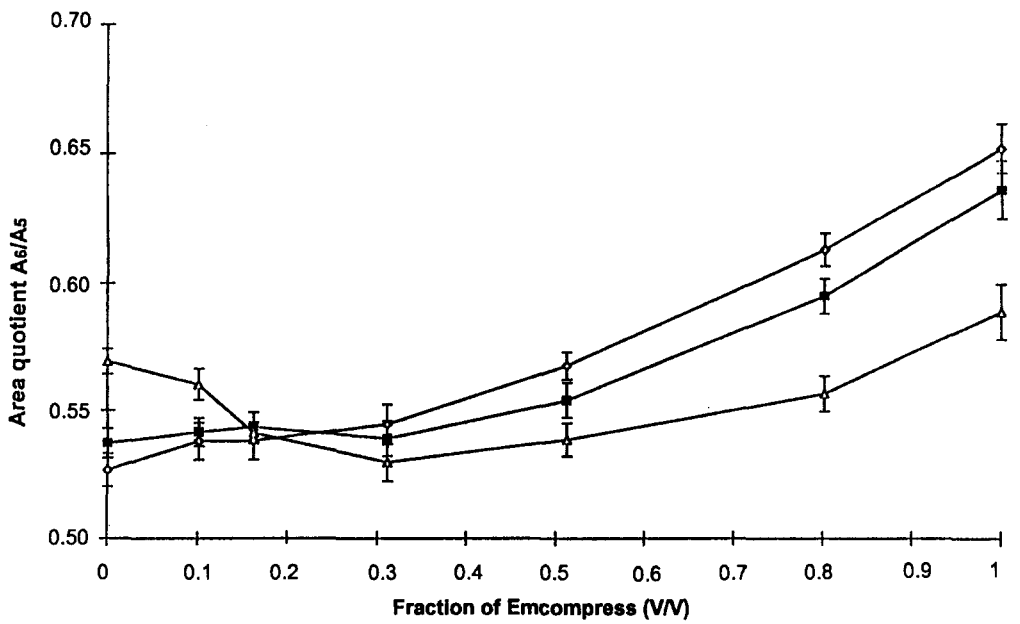

Fig. 7. Dwell time coefficient A_6/A_5 against fraction of Emcompress for the three experimental modes. Percolation threshold could be estimated at ~50% (w/w) Emcompress (-◇- 300 mg tablet mass; -■- 1.25 mm tablet height; -△- 6 mm filling depth).

Emcompress® DH which requires a lower densification to reach a certain force level due to its high in-die-working density and its lower deformability. Therefore, the percolation threshold for Emcompress® DH could be estimated to ~50% by weight corresponding to ~30% by volume which is in good agreement with literature values of 0.25 to 0.31 reported by Leuenberger et al. [27].

The dwell time coefficient A_6/A_5 is also influenced by the experimental mode as shown in Fig. 7. The highest increase in that parameter is observed for tablets compressed to a constant mass. A similar curve is obtained for tablets with a constant tablet height. Again the behaviour of tablets prepared from a constant filling volume is different. To obtain a compression force of 9 kN (Table 2) the machine parameter 'tablet height' has to be increased due to the low compressibility of Emcompress® DH. This is accompanied by an increase in the contact area between the tablet band and the die leading to a higher die wall friction and thereby lowering the force transmission onto the material. The parameter A_6/A_5 is decreasing up to an Emcompress® DH content of 50% (v/v). Now percolation of Emcompress® DH takes place and dominates the compression behaviour, leading to a higher A_6/A_5-value. When the tablet mass is constant, the band height of the tablet and the die wall friction are decreasing with increasing amount of Emcompress® DH. The force transmission onto the material becomes more and more efficient and this together with the percolation effect of Emcom-

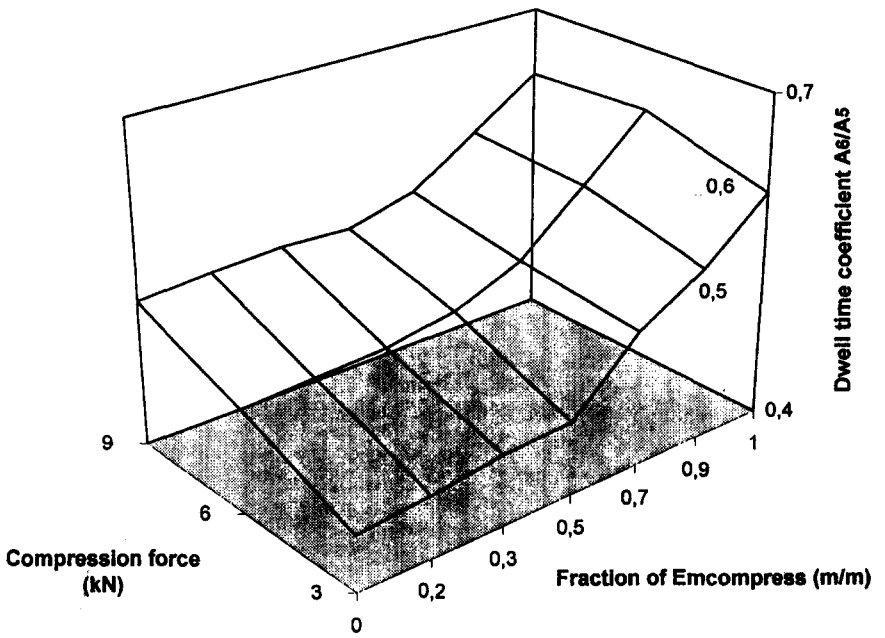

Fig. 8. Dwell time coefficient A_6/A_5 as related to compressional force and fraction of Emcompress. At all three compression force levels an increase of the dwell time coeffiecient above 50% (w/w) of Emcompress is observed indicating the formation of a percolating Emcompress cluster.

press® DH leads to the highest increase of the dwell time coefficient A_6/A_5. The best figure is obtained, when tablets are compressed to a constant tablet height because in this case the die wall friction remains constant. Up to 50% Emcompress® DH the area parameter does not change but starts to rise thereafter due to the percolation of Emcompress® DH.

Fig. 8 shows the area quotient A_6/A_5 for a band height of 1.25 mm at the three compression levels as influenced by the amount of Emcompress® DH. At all the three compression force levels an increase in the dwell time coefficient above 50% (w/w) of Emcompress® DH is observed indicating the percolation level in the range of 50% (w/w).The effect is more pronounced at lower compression forces and is predominant for tablets containing a high amount of Avicel® PH 102.

4. Conclusions

From the results it is apparent that the compression behaviour of Avicel® PH 102 and Emcompress DH® alone and their mixtures can be explained by compression/time-profiles obtained on a rotary tablet press. A percolation threshold in the range of 50% (w/w) Emcompress® DH was found from tensile strength measurements of the tablets, from the area A_1 under the compression/time-curve obtained at constant filling depth of the die and as well as from the area quotient A_6/A_5 obtained at constant height of the tablet.

In pharmaceutical development and production tablets are always compressed to constant tablet weight. To characterise the compression behaviour of pure substances and their mixtures from constant tablet weight alone should not be the method of choice because differences in the compression behaviour of the components are interfering with the differences of the in-die-working density and volume reduction ratio during the compression phase. That is the reason why Koch [28] and Ilkka and Paronen [17] did not find percolation thresholds for mixtures of microcrystalline cellulose and dicalcium phosphate dihydrate when compressing tablets to a constant weight. A constant filling depth of the die in combination with the area under the curve during the compressional phase or compression to a constant tablet height when using the dwell time coefficient A_6/A_5 is suggested to be more indicative for percolation.

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