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Research paper

# Investigation of the pellet-distribution in single tablets via image analysis

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**Abstract**

The influence of five different microcrystalline cellulose filler-binders on the pellet-distribution in tablets was investigated under production-scale conditions. Coloured coated pellets were tableted on an instrumented high speed rotary tablet press at four machine speed levels. The pellet-distribution on the upper and the lower tablet surfaces was detected via image analysis and correlated with the disintegration time and the crushing strength of the tablets. Filler-binders with a large surface area and a fibrous texture, like Avicel PH 101, enable the production of disintegrating tablets with an approximately homogeneous pellet-distribution within a large range of machine speeds, while pellet-containing tablets prepared with coarse microcrystalline cellulose granules showed an inhomogeneous pellet-distribution, depending on machine speed. © 1999 Elsevier Science B.V. All rights reserved.

*Keywords:* Pellet; Pellet-distribution; Image-analysis; Microcrystalline cellulose; Tableting

## 1. Introduction

Oral controlled release multiple unit dosage forms are becoming more and more important due to their improved bioavailability and safety of drug release. After disintegration of the tablets in the stomach, pellets with a particle size below 2 mm behave like liquids [1] and have a short transit time through the stomach. The spreading of the multiparticulates across large sections of the intestine results in less variations in drug release [2].

Pellets as multiple unit dosage forms are often filled into hard gelatin capsules. Less frequently, they are compressed into tablets. Advantages of tablets compared to capsules comprise cost effectiveness and dividability. With pellets, sustained release can be achieved with matrix-type pellets or through the coating of the pellets with polymers. In case of delayed release (e.g. enteric systems), only coated pellets are possible.

For the tableting of coated pellets without damage of the coating, the choice of suitable coating polymers [3,4], pellet size [5,6], pellet properties [7–10], pellet amount [10,11], filler-binders [5,10,12,13] and the conditions during production are important.

Non-segregating mixtures of coated pellets and filler-binders are necessary to obtain tablets of uniform weight and drug content. A threshold of at least 50% w/w pellet content has to be reached [14] and the size of the filler-binders should be similar to the size of the pellets [9,11,15]. Haubitz et al. [16] found that mixtures consisting of 70% w/w theophylline pellets and Avicel PH 101 ($X_{50}$ = 50 $\mu$m) have less tendency to segregate upon tableting than those containing cellactose ($X_{50}$ = 200 $\mu$m), depending on the shape of the excipient. Investigating binary random powder mixtures, Egermann and Frank [17] showed that despite large differences in particle size, shape and bulk density of the constituents, significant segregation did not occur during mixing and further processing of the powders into tablets.

Using plastically deforming filler-binders like polyethylene glycol 3350 or microcrystalline cellulose, damage of the pellets was minimised by absorbing the compression energy [13]. Disintegration time and crushing strength can be optimised using microcrystalline cellulose or derivates [14].

Damages of pellets and coatings during tableting increase upon increasing the pellet content of the mixture [11]. The

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maximum achievable pellet content is reached by a rhombic lattice and is 71% v/v. This is the maximum pellet density using regular spheres. Inhomogeneous distributions may lead to deformation even at lower pellet contents in the tablet. Tableting of coloured pellets (60% w/w) on a single punch tablet press has been shown to be possible without pellet deformation and segregation within the tablet matrix [11]. However, there are no publications investigating the segregation of pellets within the die using a high speed rotary press.

The aim of this work was to elucidate the behaviour of pellets during tableting under production-scale conditions.

## 2. Materials and methods

### 2.1. Materials

4110 D, a new aqueous 30% polymer dispersion based on polymethacrylates, Tween 80® and triethyl citrate were supplied by Röhm GmbH (Darmstadt, Germany), Cutina GMS® (Glyceryl monostearate) by Henkel KGaA (Düsseldorf, Germany), Bayferrox 130®, a red iron oxide pigment by Bayer AG (Leverkusen, Germany), Aerosil 200® by Degussa AG (Frankfurt/M., Germany), Silicon antifoam emulsion SE 2® by Wacker-Chemie GmbH (München, Germany), Kollidon 90 F® (povidone) and Kollidon CL® (crosspovidone) by BASF AG (Ludwigshafen, Germany), Avicel PH 101® by FMC Corp./Lehmann and Voss and Co. (Hamburg, Germany), Magnsium stearate by Bärlocher GmbH (Munich, Germany), Vivacel-granules, an excipient for direct compression, were prepared at the Department of Pharmaceutical Technology of the University of Tübingen, Germany [18]. Placebo pellets, type 08430 (90% within 850–1000 $\mu$m), were purchased from Hanns G. Werner GmbH (Tornesch, Germany).

### 2.2. Preparation of coloured pellets

The pellets were coated in a fluid-bed coater (Uniglatt®, Glatt GmbH, Binzen, Germany) by top-spraying. Batches of 1000 g placebo pellets were coated with 12.5% pigment-coloured polymer dispersion 4110 D. The coloured dispersion contained 3% glycerol monostearate as a glidant, 5% triethyl citrate as a plasticiser [14] and Bayferrox 130® as a pigment based on the amount of pure polymer. Bayferrox 130® was wet milled using a colloid mill type MZ-50/R (Fryma, Rheinfelden, Germany) for 5 min at a rotor/stator-distance of 0.3 scaling. The spraying conditions were: inlet temperature 47°C, outlet temperature 27°C, atomising pressure 1.2 bar, aperture of the nozzle 10 mm (Schlick, Coburg, Germany), time of coating 40 min, preheating 12 min.

### 2.3. Preparation of filler granules

The Avicel® filler-granules were prepared by wet granulation in a mixer-granulator (Rapid 3Z, F. Herbst, Neuss, Germany). Avicel PH 101 and Kollidon CL were blended for 5 min, the binder-solution (Kollidon 90 F® 5% w/w in water) was added at a rate of 320 g/min, the wet mass was mixed for another 3 min and granulated by sieving through a 2 mm sieve (SKM, Alexanderwerk, Germany). Finally the granules were dried at 60°C using a tray dryer (Memmert GmbH + CoKG, Schwabach, Germany) until a relative humidity of 60% was reached. After a second sieving step through a 1.4 mm screen (FGM/500, ERWEKA, Heusenstamm, Germany), the granules were dried for 10 h at 25°C and classified by passing through a 850 $\mu$m and 350 $\mu$m sieve, respectively. The Vivacel®-granules were prepared in a fluid-bed granulator (WSG5, Glatt, Binzen, Germany) according to Hühne [18]. For further details of the filler granules see Table 1.

### 2.4. Characterisation of the components

The true density was determined using a Beckman air comparison pycnometer (model 930, Beckman Instruments, Inc., Fullerton, USA).

The surface area was determined using a BET-instrument (SA 3100, Coulter, Krefeld, Germany).

Table 1
Properties and composition of the filler-binders

| Type number | Avicel granules | | | Vivacel granules | Avicel PH 101 |
|---|---|---|---|---|---|
| | Nr. 1 | Nr. 2 | Nr. 3 | Nr. 4 | Nr. 5 |
| Composition | Avicel PH 101<br>Kollidon CL 3.5%<br>Kollidon 90F 5.0% | | | Vivacel 10<br>Kollidon CL 3.5%<br>Kollidon 90F 5.0% | – |
| $X_{90}$ ($\mu$m) | 1220 | 852 | 342 | 400 | 121 |
| $X_{50}$ ($\mu$m) | 1055 | 621 | 194 | 179 | 54 |
| Surface (BET) ($m^2/g$) | 0.272 (±0.015) | 0.502 (±0.0115) | 0.802 (±0.020) | 0.905 (±0.028) | 1.076 (±0.047) |
| True density ($g/cm^3$) | 1.487 (±0.003) | 1.495 (±0.002) | 1.507 (±0.006) | 1.504 (±0.020) | 1.544 (±0.004) |

Confidence intervals (95%) are in parentheses.

The granule size distribution was determined by sieve analysis (Retsch, F. Kurt Retsch GmbH and Co. KG, Haan, Germany).

### 2.5. Blending and tableting

One thousand gram coated pellets (70% w/w of the mixture) were blended for 10 min with 10 g Aerosil immediately after the coating-process, using a gyro-wheel-mixer. Kollidon CL® (86 g) and 326 g filler-binder were added and blended for 10 min. Finally, 0.5% w/w magnesium stearate was passed through a 315 $\mu$m sieve onto the mixture and blended for an additional 5 min. Batches of 1429 g each were prepared.

Tablets of 400 ± 30 mg were compressed on an instrumented rotary tablet press Korsch PH230/17 (Korsch Pressen GmbH, Berlin, Germany). The die table diameter of the press was 195 mm. Eight of the 17 punch stations were equipped with 10 mm flat face bevelled edge B-tooling for the upper punches and with 10 mm flat face B-tooling for the lower punches. One of the lower-punches was guided and marked on one edge by a notch. Thus, the upper and lower surface of the tablets could be distinguished and the exact position of the tablet in the die could be determined. For filling, a gravity feeder (Art. Nr. 8590052, Korsch Pressen GmbH, Berlin, Germany) was used. Rotating speed levels were set to 26, 50, 75 and 100 rpm while compressing at 20 kN. Each of the five filler-binders were processed at all conditions. Data acquisition and processing were performed by the Compression Research System (Korsch Pressen GmbH, Berlin, Germany).

### 2.6. Tablet parameters

The mass (AE 200 balance, Mettler-Toledo GmbH, Gießen, Germany), thickness (0.01 mm micrometer, Mitutoyo Co. Ltd, Japan) and the crushing strength (model 6D, Dr. Schleuninger Pharmatron AG, Solothurn, Switzerland) of 10 tablets were measured. Disintegration time of six tablets was determined according to Ph. Eur. (Pharma Test, Hainburg, Germany). Disintegration time was defined as the time needed for separation of the filler-binder from the pellets. Whenever there were agglomerates of pellets on the sieve of the tester, a note on their size was added to the disintegration time data.

### 2.7. Evaluation of the pellet-distribution via image-analysis

The distribution of pellets at the upper and lower surfaces of the tablet was determined by image analysis using those tablets marked by the notch. For each tablet type (5 filler-binders × 4 rotating speeds = 20 samples), photographs of the upper and lower surfaces of 25 marked tablets were taken using a LEICA reprocamera (Leitz, Wetzlar, Germany). The pictures were digitised as greyscale pictures using a flat bed scanner (Aashima GmbH, Kleve, Germany) on an IBM compatible PC (75 MHz Pentium, 16 MB RAM, 850 Mb hard disk drive) with fixed brightness and contrast conditions at 256 greyscales (Software: Image Pals 2 GO, Ulead Systems Inc., Torrance, Canada). The greyscale data were row-calibrated using a standard photographic grey scale bar, which was added to each photograph. The obtained data-files were imported to an image-analysis-software (NIH-Image 1.60, US National Institutes of Health) on an Apple Macintosh computer (PM 6100, Apple, Cupertino, CA, USA). For each tablet surface, the 25 images were cut into identical circles and averaged. Thus, a statistically averaged optical density of the upper and the lower surface of each tablet type was obtained. The basic idea of the method is to use coloured pellets and a white filler-binder. The probability to find pellets at the tablet surface depends on the percentage of pellets being present in the mixture and on the distribution of the pellets within the die or the tablet, respectively. For a low number of pellets at the tablet surface, the optical density of the photograph would be low. On the other hand, a high number of pellets would increase the probability of finding pellets at the surface of the tablet, resulting in a higher optical density. The relationship between pellet distribution and optical density is approximated by the following considerations. To correlate the optical density with the pellet-distribution (pellet density), it has to be assumed that the coloured pellets are spheres. A pellet touching the surface without deformation can be seen as a single point, producing a low optical density on the surface of the tablet. A sphere-section, e.g. caused by deformation of the pellet by the punch will give a much higher optical density on the surface of the tablet, depending on the degree of deformation (see Fig. 1). To correlate the optical

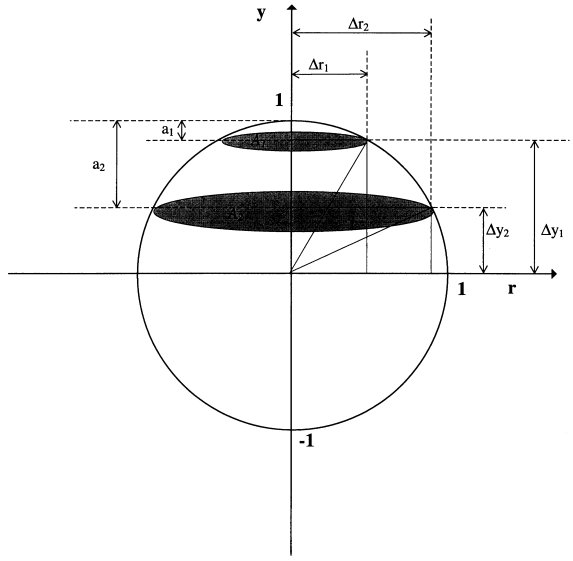


Fig. 1. Correlation between sphere section areas ($A_1$ and $A_2$), circle radius ($\Delta r_1$ and $\Delta r_2$), distance of the section from the middle of the sphere ($\Delta y_1$ and $\Delta y_2$) and sphere-deformation ($a_1$ and $a_2$) within a standard sphere ($r = 1$). Correlation between $A$ and a is leading to the non-linear calibration model (Fig. 2).

density with the pellet distribution on the tablet surface, a calibration model between section area ($A$) and deformation (a) was developed within a standard sphere ($r = 1$). The section area ($A$) depends on the circle radius ($\Delta r$) shown in Eq. (1).

$$A = \pi * \Delta r^2 \quad (1)$$

Minimum deformation (a = 0) causes a minimum section area ($A_{min}$) having the lowest optical density (Eq. (2))

$$A_{min} = \pi * 0^2 \hat{=} 0 \text{ units of optical density } \hat{=} a = 0 \quad (2)$$

Maximum deformation (a = 1) causes a maximum section area ($A_{max}$) having the highest optical density (Eq. (2)) according to the optical density of the pure coloured pellet.

$$A_{min} = \pi * 1^2 \hat{=} 200 \text{ units of optical density } \hat{=} a = 1 \quad (3)$$

The function for the section area ($A$) between minimum and maximum deformation ($0 \leq a \leq 1$) was derived as follows (Eqs. (4)–(9)).

$$\Delta r^2 + \Delta y^2 = 1 \quad (4)$$

$$\Delta r = \sqrt{1 - \Delta y^2} \quad (5)$$

$$\Delta y = 1 - a \quad (6)$$

(6) in (5)

$$\Delta r = \sqrt{1 - (1-a)^2} \quad (7)$$

(7) in (1)

$$A = \pi * (1 - (1-a)^2) \quad (8)$$

Eq. (8) was normalised by dividing by $\pi$ leading to a non-linear calibration model according to Eq. (9) and shown in Fig. 2.

$$A_{STAND.} = 1 - (1-a)^2 \quad (9)$$

Using this calibration model, each averaged tablet image (lower and upper surface) was transformed. The normalized optical densities are now directly correlated to the pellet densities of the tablets. The ideal case would be a pair of images of upper and lower surfaces of a tablet having an equal and homogeneously distributed grey scale intensity.

## 3. Results and discussion

### 3.1. Pellet distribution

The distribution of pellets within the tablet depends on the machine speed and on the properties of the filler-binder. Fig. 3 shows images of tablets produced with Avicel-granules of different size but equal production conditions (Nrs. 1–3). Tablets produced with the coarse granules (Nr. 1),

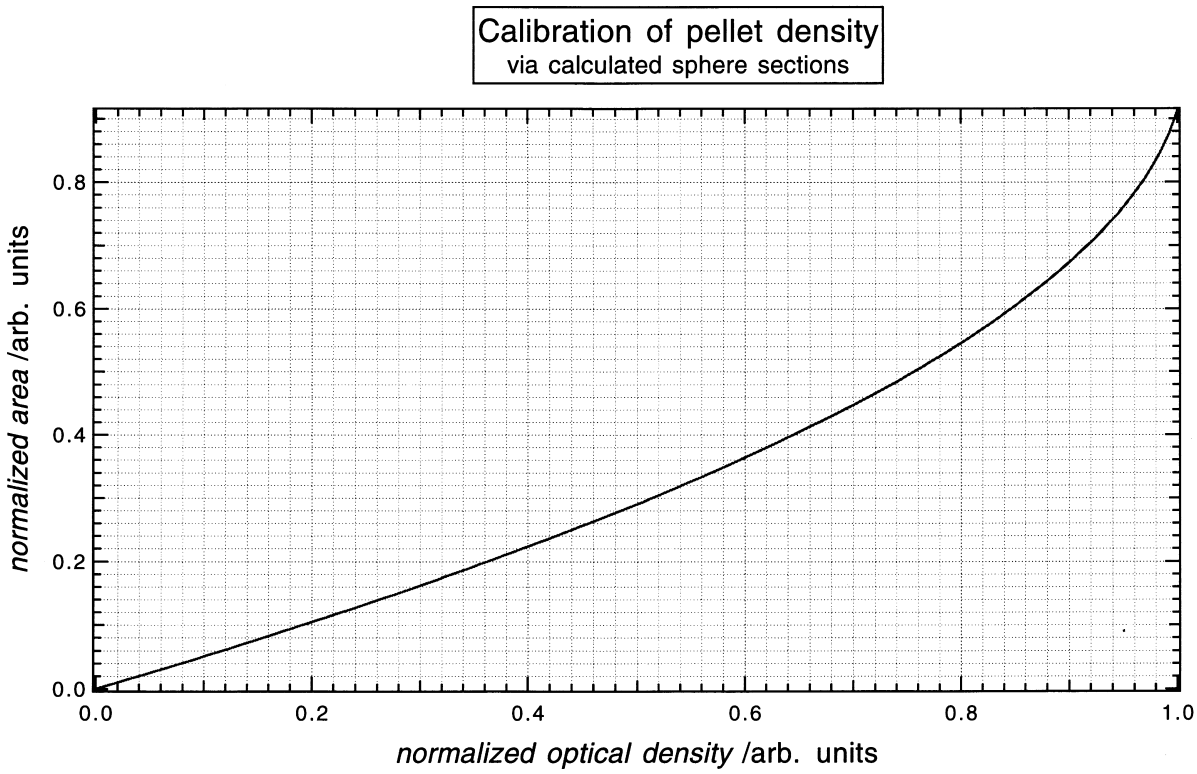


Fig. 2. Calibration model to correlate the optical density of the tablet surface obtained from photographic pictures and the corresponding sphere areas of the pellets.

which are approximately equal in size to the coated pellets showed the most inhomogeneous pellet distribution. A high pellet density was found on the lower surface of the tablet at a low machine speed (26 rpm), while a high pellet density was found at the upper surface of the tablet at high machine speeds (75 and 100 rpm). This indicated an almost complete vertical segregation of the pellets at the higher machine speeds. With smaller Avicel granules (Nrs. 2 and 3), similar but less extensive effects were observed. Upon decreasing the diameter of the filler-binder and thereby increasing the surface, the pellet density on the lower outer surface of the tablet decreased at a machine speed of 26 rpm. At 75 rpm, the horizontal segregation changed first to a vertical segregation to the upper right surface of the tablet and only at a high speed of 100 rpm a much higher pellet density on the whole upper surface compared to the lower one was obtained. Thus, among the three Avicel granules, only Nr. 3 gave tablets with a homogeneous pellet distribution at an intermediate machine speed (50 rpm).

Using filler-binders of similar size (Nr. 3 and Nr. 4) but prepared with different methods and accordingly different surfaces, has the same effect as increasing the surface area of the Avicel granules (Fig. 4). Even at a low machine speed

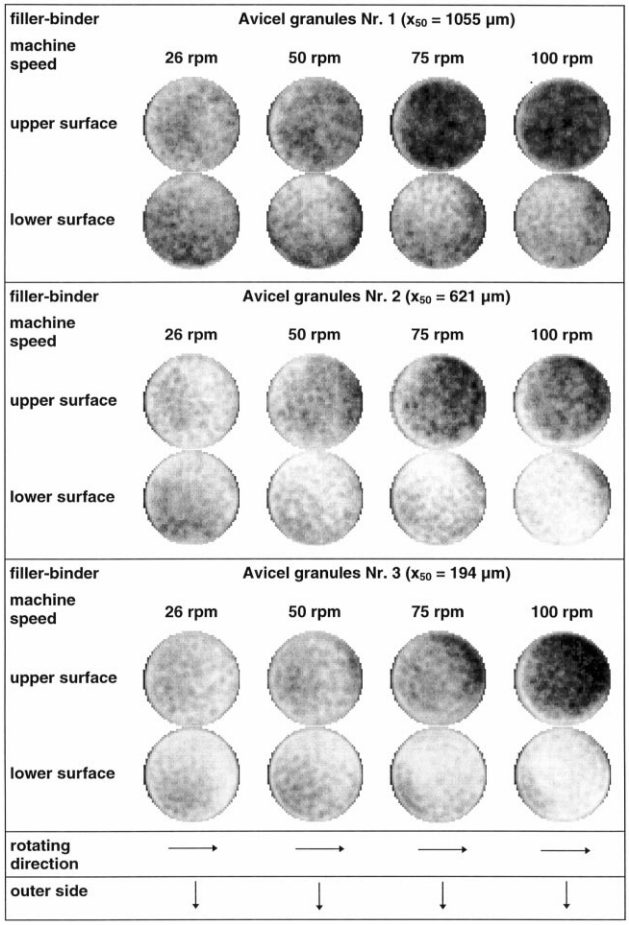


Fig. 3. Normalised pellet densities of upper and lower tablet surfaces using Avicel granules of different sizes but equal production method as filler-binder.

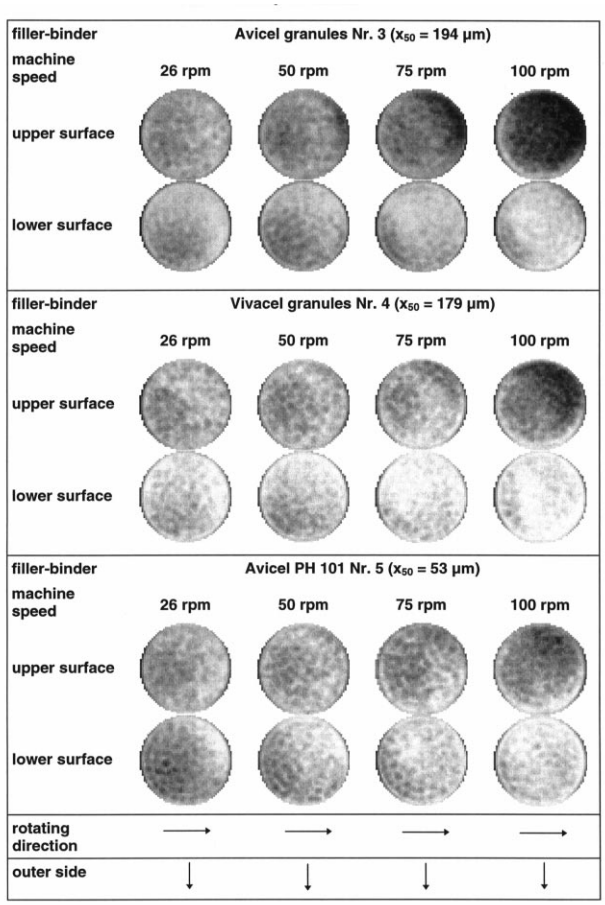


Fig. 4. Normalised pellet densities of upper and lower tablet surfaces with microcrystalline cellulose granules of different sizes and different production methods as filler-binders.

(26 rpm), tablets prepared with the Vivacel granules (Nr. 4) showed no increased pellet density on the lower surface of the tablet and an almost homogeneous distribution. At a high machine speed (100 rpm), a significant increase in pellet density on the upper right surface of the tablets was detected. The most homogeneous distribution of the pellets, particularly at intermediate and high machine speeds, was achieved with Avicel PH 101 (Fig. 4). A small increase in pellet density was observed on the lower surface only at a low machine speed and on the upper inner surface at a high machine speed.

The segregation tendency of pellets during tableting using different microcrystalline cellulose granules could be correlated with the surface area of the respective filler-binders. Granules or pure microcrystalline cellulose like the Vivacel granules or Avicel PH 101 having a large surface area and a fibrous surface texture built a close percolating infinite cluster stabilising the pellets at their location in the mixture.

The changes of pellet distribution as a function of the machine speed might be a consequence of the different shapes of pellets and filler-binder. The powder flow through the scrapers of the gravity feeder and the vibrations of the machine increase with increasing the machine speed. These

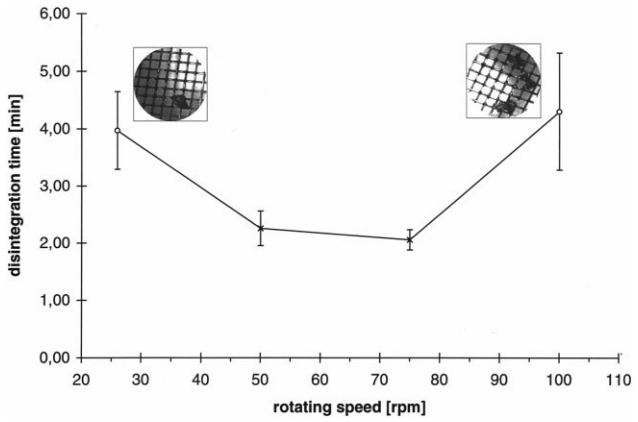


Fig. 5. Disintegration time of pellet-tablets containing Avicel PH101 Nr. 5 ($X_{50}$ = 53 $\mu$m) as a filler-binder depending on the machine speed. Size of pellet agglomerates after disintegration: (○) 2–10 pellets. Error bars represent the 95% confidence interval.

forces lead to a flotation of the round pellets, while the anisometric filler-binder particles descend, depending on the surface and flow properties of the filler-binder. Thus, the coarse Avicel granules (Nr. 1) with a small surface area and good flow properties show a higher segregation tendency, which increases with higher machine speed.

### *3.2. Disintegration time*

The disintegration time of tablets (without any residue on the screen of the tester) is fixed to 15 min by most Pharmacopeias. Pellet-tablets compressed with the Vivacel granules (Nr. 4) did not disintegrate within 15 min and even after 72 min the major part of the pellet matrix was not disintegrated. Coarse Avicel granules (Nr. 1) had a disintegration time of 17 min, leaving pellet agglomerates of about 20 pellets sticking together on the screen of the disintegration tester.

For tablets prepared with the other filler-binders (Nr. 2, Nr. 3 and Nr. 5), disintegration times were achieved correlating well with the pellet distribution data. Depending on

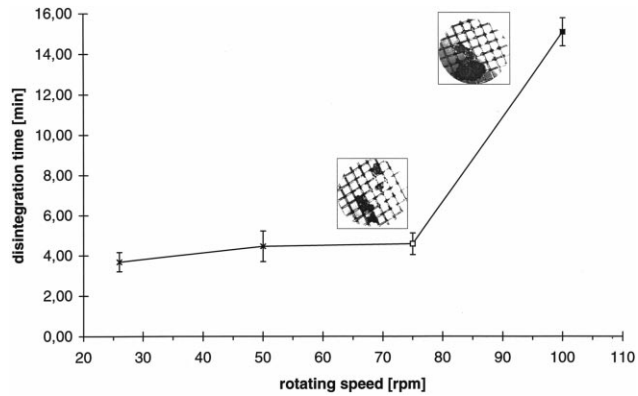


Fig. 6. Disintegration time of pellet-tablets containing Avicel granules. Nr. 3 ($X_{50}$ = 194 $\mu$m) as a filler-binder depending on the machine speed. Size of pellet agglomerates after disintegration: (○) 2–10 pellets, (□) 11–20 pellets, (■) >20 pellets. Error bars represent the 95% confidence interval.

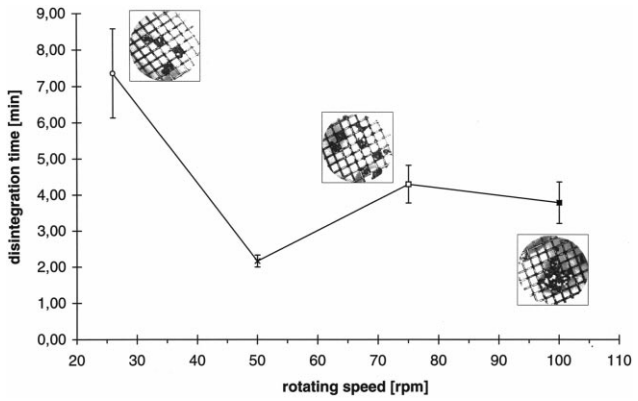


Fig. 7. Disintegration time of pellet-tablets containing Avicel granules ($X_{50}$ = 621 $\mu$m) as a filler-binder depending on the machine speed. Size of pellet agglomerates after disintegration: (○) 2–10 pellets, (□) 11–20 pellets, (■) >20 pellets. Error bars represent the 95% confidence interval.

the machine speed, tablets with a homogeneous pellet-distribution resulted in the shortest disintegration time and complete disintegration, while inhomogeneous pellet-distributions lead to longer disintegration times and non-disintegrating agglomerates of coated pellets (Figs. 5, 6, and 7). These agglomerates consisted of coated pellets, which exceeded the critical volume (71% v/v) at several locations within the tablet. The pellets were deformed and formed a non-disintegrating pellet-matrix, as shown on the photographs (Figs. 5, 6, and 7). The average true pellet-volume in the tablets was between 62% (v/v) and 66%(v/v), thus the critical volume of 71% (v/v) was easily exceeded by an inhomogeneous pellet-distribution. Pellets coated with brittle polymers would loose their drug release controlling properties, while with an elastic coating polymer, a damage could be prevented, although there could be an increased possibility of adhesion of coated pellets. The best results in disintegration were obtained by tableting pellets with Avicel PH 101. Little tendency of forming pellet-agglomerates and a complete and short disintegration at machine speeds of 50−75 rpm confirms the data obtained from the image

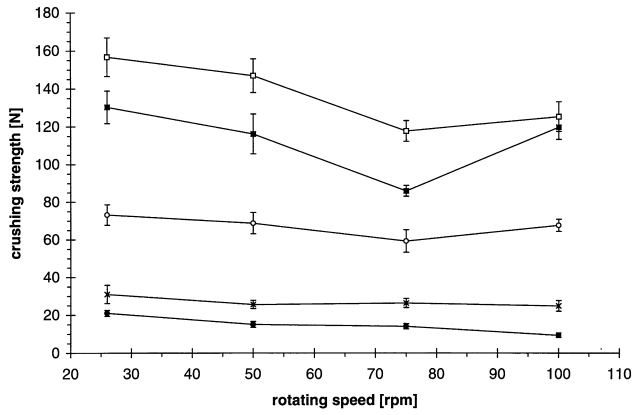


Fig. 8. Crushing strength of pellet-tablets depending on the machine speed and different types of filler-binders: (□) Vivacel granules Nr. 4, (■) Avicel PH 101 Nr. 5, (○) Avicel granules Nr. 3, (●) Avicel granules Nr. 2, (X) Avicel granules Nr. 1. Error bars represent the 95% confidence interval.

analysis (Fig. 5). A complete disintegration of tablets prepared with the Avicel granules (Nr. 2 and Nr. 3) as a filler-binder was only achieved at a machine speed of 50 rpm for granules Nr. 2 (Fig. 6) and 26–50 rpm for granules Nr. 3 (Fig. 7). Increasing machine speed lead to an increasing size of pellet-agglomerates.

### *3.3. Crushing strength*

The crushing strength of the pellet-containing tablets did not depend on the machine speed and the pellet-distribution. However, the filler-binders showed significant differences in the resulting crushing strength. Tableting pellets with the coarse Avicel granules (Nr. 1 and Nr. 2) no suitable tablets with a crushing strength below 40 N were obtained (Fig. 8). Tablets processed with the other filler-binders showed an adequate (Nr. 3) or high (Nr. 4 and Nr. 5) crushing strength (Fig. 8). Vivacel granules (Nr. 4) of approximately the same size as the Avicel granules (Nr. 3), but being processed in a fluid bed granulator, lead to a very high crushing strength, even higher than the pure microcrystalline cellulose Avicel PH 101. A larger surface area and higher plastic deformation of the granules prepared by fluid bed granulation when compared to the granules processed by conventional wet granulation are probable reasons for these effects.

## 4. Conclusions

Tableting of pellets into dividable tablets requires a homogeneous distribution of the pellets within each tablet. Variations in machine speed and filler-binders lead to different pellet-distributions in the tablet and therefore have to be considered for each formulation, especially during the scale-up process. Filler-binders with a large surface area and a fibrous surface texture like Avicel PH 101, enable the production of disintegrating tablets containing 70% w/w of pellets with an approximately homogeneous pellet-distribution within a large range of machine speeds.

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