DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 20(18), 2899-2925 (1994)

# EVALUATION OF LUDIPRESS AS A "MULTIPURPOSE EXCIPIENT" FOR DIRECT COMPRESSION
## PART I:
## POWDER CHARACTERISTICS AND TABLETING PROPERTIES

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## ABSTRACT

The powder characteristics and tableting properties of Ludipress, a lactose-based, free flowing granule containing povidone and crospovidone have been evaluated and compared to the physical blend of the base materials in Ludipress and to other filler/binders including Cellactose and Avicel PH 200.

The data were determined in order to evaluate flowability, bulk density, tapped density, Hausner ratio, angle of repose and particle size distribution. The particle morphology and constitution were examined using scanning electron microscopy (SEM). Differential scanning calorimetry (DSC) was used to detect differences between lactose based products.

Several Ludipress samples exhibited a good batch-to-batch uniformity and flow characteristics compared to the physical blend and other excipients investigated.

The tableting parameters tested were crushing strength, friability and disintegration time. The ability to form coherent compacts was similar for Ludipress, Cellactose and Avicel PH 200, whereas tablets made from the physical blend resulted significantly softer. Determination of tablet disintegration time revealed a disintegration time minimum at about 100 MPa for Ludipress compacts. By augmenting compaction load from 100 to 185 MPa Cellactose showed an increase in disintegration time to more than 20 minutes. The disintegration times of Avicel PH 200 compacts were nearly constant and were also the shortest in the compaction load range examined.



## INTRODUCTION

Direct compression is a technology which was developed in the 1960's. Due to the intensive research in tableting machinery and the development of new, potent excipients over the last three decades, direct compression has become an interesting alternative for the tablet manufacturer. Apart from the economic point of view and the simplicity of the process, direct compression offers many advantages compared with techniques such as pre-compression or wet granulation in terms of an improved process reliability and product stability (1). For example, thermolabile substances and active ingredients liable to hydrolysis can be tableted without difficulty.

The poor flowability of the powder mixes and the limited dilution potential of the filler/binders available form the main problems with direct compression. Furthermore segregation of the drug can occur, debasing the content uniformity of low dosage forms. Despite these difficulties, by choosing the correct equipment and machinery, the majority of the drugs can be tableted via direct compression (2).

To ensure proper tableting properties, a direct compression blend has to contain several ingredients besides the drug and the lubricant. These are basically fillers, binders, glidants and disintegrants. Alternatively a "multipurpose excipient" (MPE) combining the properties of these adjuvants in one single excipient can be used. The advantages are obvious:

- Problems in terms of batch-to-batch variation of tableting excipients are reduced to the lubricant and the MPE,
- the extent of analysis and storage of base materials is reduced and

- fewer interactions between the single tablet components are possible, which produces greater clarity in the manufacturing procedure, facilitating the detection of possible problems.

As a consequence the costs involved in high-quality production decrease.

Based on these advantages the number of MPEs is increasing since the second half of the last decade. In 1986 Ludipress (3), a α-lactose monohydrate based, free-flowing granule was introduced into the pharmaceutical market. The components of Ludipress are listed in Table 1.

Lactose, the main constituent of Ludipress, is probably the oldest and most frequent filler/binder in tableting (4). The other components povidone and crospovidone increase compactibility and provide a certain swelling activity.

Due to this composition, Ludipress should be able to act as a MPE for direct compression.

## MATERIALS

The base materials used are shown in Table 2.

## METHODS

*Scanning electron microscopy (SEM).* A DSM 940 A scanning electron microscope (Carl-Zeiss, D-Oberkochen, Germany) was employed. Samples were attached to pin-type mounts which had been previously covered with double-coated tape.

The samples were sputtered with gold (Sputter Coater Type E 5100, BIO-RAD GmbH, D-München, Germany). Photographs from the scanning electron microscope were taken with a Contax camera Type 167 MT (YASHICA Kyocera GmbH, D-Hamburg, Germany) using Ilford Pan F 135 (50 ASA) film.

*Differential scanning calorimetry (DSC).* The DSC thermograms were obtained using a Mettler TA 3000 - DSC 20 thermal analysis system interfaced with a TC 10 A processor. All measurements were performed with an open pan.

*Particle size analysis.* The particle size distribution parameters were determined using a HELOS laser scattering particle sizer (Sympatec GmbH, D-Clausthal-Zellerfeld, Germany) interfaced with a Hewlett-Packard Vectra ES/12

TABLE 1
Ludipress: Attributes and concentration of the constituents

| Constituent | Concentration (%) | Attribute |
|---|---|---|
| α-Lactose-monohydrate | 93.0 ± 2.0 | Filler, binder |
| Kollidon 30 (povidone) | 3.5 ± 0.5 | Binder |
| Kollidon CL (crospovidone) | 3.5 ± 0.5 | Disintegrant |

TABLE 2

| Base material | Batch numbers | Supplier |
|---|---|---|
| Avicel PH 101 (microcrystalline cellulose) | 6803 | FMC Corporation, Philadelphia PA, provided by Lehmann & Voss & Co., D-Hamburg, Germany |
| Avicel PH 200 (microcrystalline cellulose) | X 119 | |
| Cellactose (one-body compound of α-lactose-monohydrate and cellulose) | 521 | Meggle GmbH & Co. KG, D-Wasserburg, Germany |
| Kollidon 30 (povidone) | 42-4217 | BASF AG, D-Ludwigshafen, Germany |
| Kollidon CL (crospovidone) | 26-3079 | |
| Ludipress (agglomerate of α-lactose-monohydrate, Kollidon CL and Kollidon 30) | 06-2521, 94-9157, 98-0011 [a] | |
| Magnesium stearate | 0 1040 703 | Otto Bärlocher GmbH, D-München, Germany |
| Sanaq 101 L (microcrystalline cellulose) | MC 900412 | Wei Ming Pharmaceutical Mfg. Co., Ltd., Taiwan, provided by Pharmatrans SANAQ AG, Basel, Switzerland |
| Tablettose (α-lactose-monohydrate granule) | 011 | Meggle GmbH & Co. KG, D-Wasserburg, Germany |

[a] other batches used are indicated in figures and tables

computer. Calculation of particle size data was performed using Sympatec HELOS-software. All samples were tested in duplicate.

*Powder flow properties.* The angle of repose θ was measured by pouring the powder through a 1000 µm sieve and allowing it to fall onto a cylinder, 50 mm in diameter, measuring the height (h) attained. Mean values are calculated by 5 measurements with $\tan\theta = h * r^{-1}$ (r = 25 mm).

The bulk density was determined by pouring 100 ± 0,1 g of the powder through a funnel into a graduated 250 ml glass cylinder (German Standard DIN 53912). With powders of low bulk densities, a smaller amount of powder was used. Tapped density was determined using an Engelsmann type volumenometer (JET ST 2, Engelsmann AG, D-Ludwigshafen, Germany) according to German Standard DIN 53194. The minimum volume was generally attained after 2 times 1250 tamps. Mean values were calculated by 3 measurements. The Hausner ratio is defined as the ratio between the tapped and bulk density of powders.

*Preparation of tableting blends.* Magnesium stearate was passed through a 315 µm sieve and blended with the excipients. To ensure agglomerate-free tableting powders, the blends were passed through a 800 µm sieve. Mixing was performed in a Turbula mixer ( Type T2C, Willy Bachhofen AG, Basel, Switzerland) at 42 rpm for 10 minutes using original 2 litre-Turbula glass vessels. For all magnesium stearate-excipient blends 500 g samples were prepared, providing a 35-65 % filling load of the vessels. Magnesium stearate concentration was 1 %.

*Compaction of blends.* 11 mm flat face bevelled edge tablets of 500 mg were compressed on an instrumented 3-station Korsch Pharmapress 103 rotary press (E. Korsch OHG, D-Berlin, Germany). This was equipped with one die-and-punch assembly at a machine speed of 20 cycles/min. Die filling was performed by a force feeder. The tablets shown in the micrographs were compressed with 7 mm flat faced bevel edged punches under the same conditions.

*Tablet testing.* The radial crushing strength of tablets was measured 24 hours after compaction using a Schleuniger hardness tester (Model 2 E, Dr. K. Schleuniger, Solothurn, Switzerland). Results are the mean of 10 runs. Friability was evaluated from the weight loss of 20 tablets tumbled for five minutes in a Pharma Test friability tester (Type PTF 1, Pharma Test Apparatebau GmbH, D-Hainburg, Germany) at 25 rpm. Disintegration testing (6 tablets per lot) was carried out according to German Pharmacopoeia (DAB 10) in a Type PTZ 1

Pharma Test disintegration tester at 37.0 ± 0.1 °C. For tablets containing povidone no discs were used.

## RESULTS AND DISCUSSION

### Morphology and Constitution of Ludipress

Scanning electron microscopy (SEM) is a very useful tool for evaluating the morphology and and functionality of tablet excipients (5, 6). Figure 1A shows Ludipress in a 100x magnification. The spherical shape of the granules indicates the good flowability of this excipient. Apart from the larger granules with a mean diameter of approx. 200 µm, smaller agglomerates and little crystals of lactose could be detected. The 5000x magnification of a granule surface in figure 1B makes the inner structure of this excipient visible. In the lower part of the micrograph a broken lactose crystal of approx. 10 µm, is depicted. The single crystals are held together by amorphous components. These are mainly povidone, crospovidone and amorphous lactose ("lactose glass"), which is generated during the production process.

Lactose glass can be detected by differential scanning calorimetry (DSC) (7) as shown in figure 2. Over a range from 50-250 °C Ludipress, the base lactose in Ludipress and Tablettose were compared. All materials tested showed a typical α-lactose monohydrate DSC-thermogram. Dehydratation takes place between 100 and 150 °C, followed by an exothermic transition at 160 °C indicating recrystalization of amorphous lactose. The lactose melts at approx. 220 °C.

As lactose glass undergoes plastic deformation during compaction, it increases the binding capacity of lactose (7). Therefore, in order to achieve a high dilution potential, a lactose based tableting excipient should contain a high amount of lactose glass.

### Powder Flow Properties of Ludipress

Of primary importance to the formulator, when designing a new excipient, is an assessment of the flow properties. These can be evaluated simply using the bulk density measurements and the angle of repose (θ). An increase in crystal

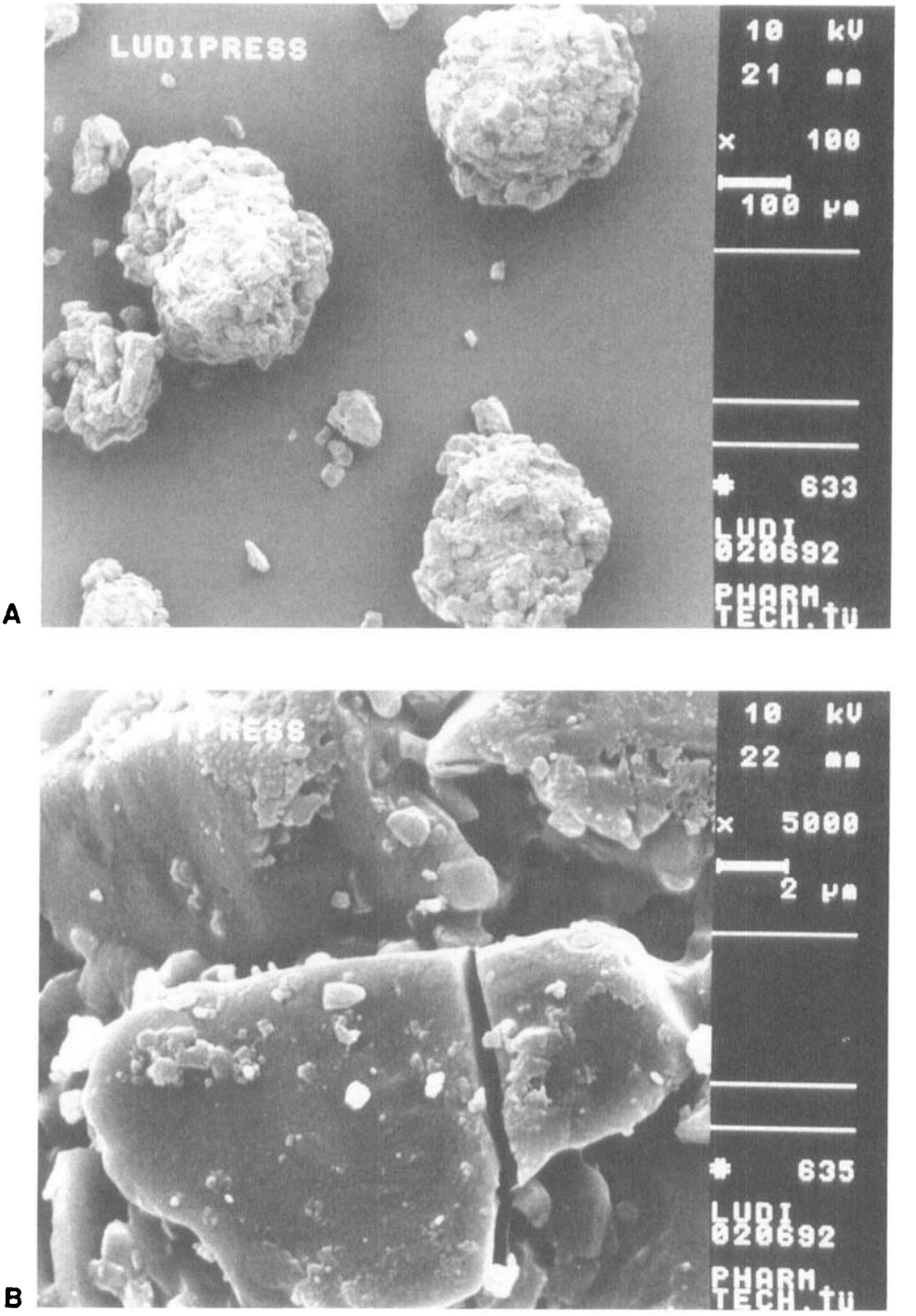



FIGURE 1:
Micrographs of Ludipress. **A**: Magnification x100. **B**: Magnification x5000.

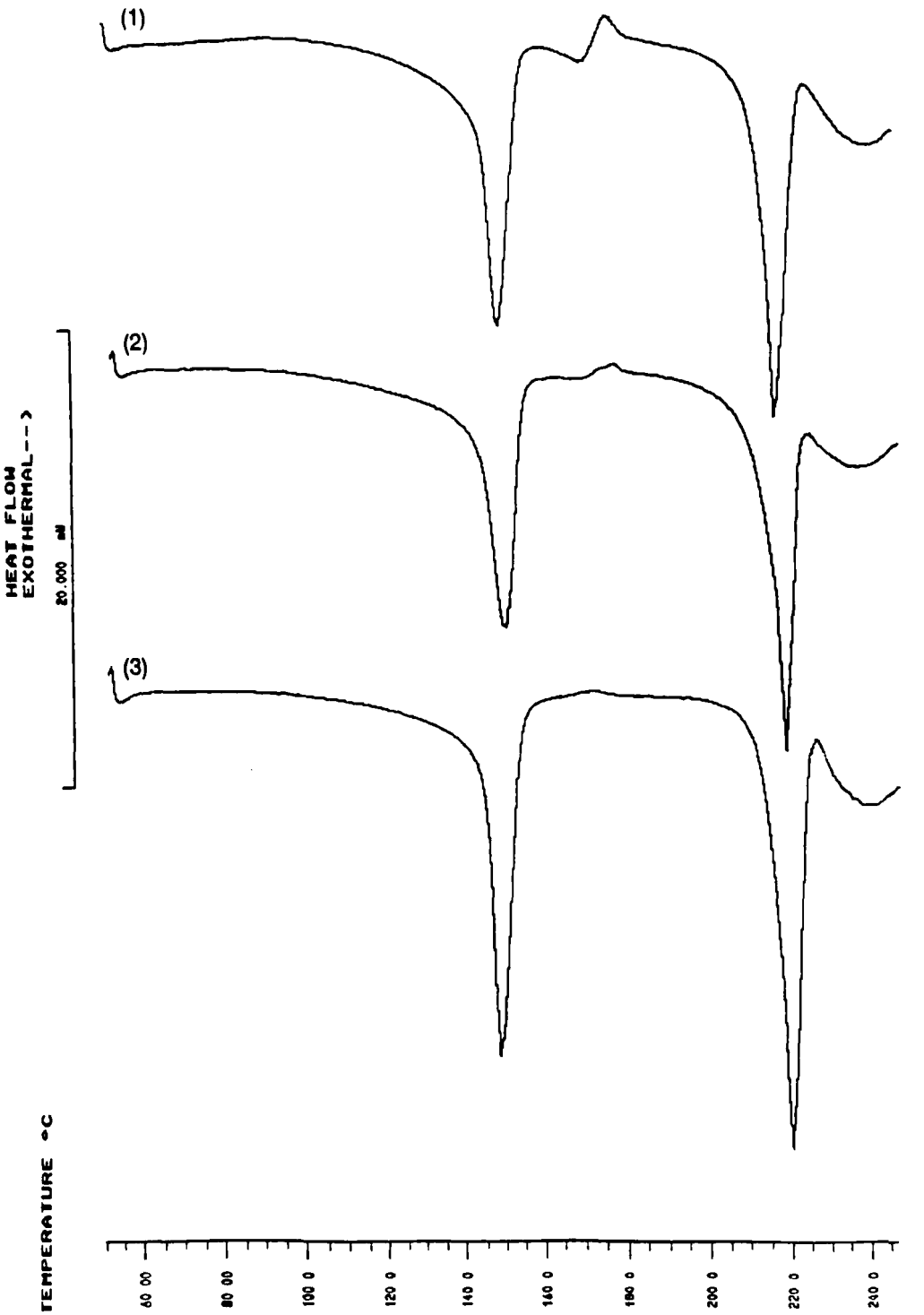



FIGURE 2:
DSC-thermograms of Ludipress **(1)**, base lactose in Ludipress **(2)** and Tablettose **(3)**. Range: 50-250 °C; heating rate: 10 K/min at 50 ml $N_2$/min; sample size: 5,4 mg. Transitions: 100-150 °C: dehydratation; approx. 160 °C: recrystallization of amorphous lactose; approx. 220 °C: melting point.

shape or a more uniform shape will lead to a smaller angle of repose indicating a better flowability of the powder. In 1967 Hausner (8) developed a simple test to evaluate flowability by comparing both the initial (bulk) density and the final (tapped) density and the rate of packing down. The Hausner ratio is defined by tapped density / bulk density, where values < 1.25 indicate good and values > 1.5 poor flow properties.

In Table 3 the powder flow properties of 3 Ludipress samples are compared to the blend of the base materials (Blend I). Blend II contains Tablettose, a free flowing α-lactose-monohydrate granule instead of the fine lactose used in the production of Ludipress .

All Ludipress samples and Blend II have good flow properties exhibiting similar bulk densities, Hausner ratios of approx. 1.2 and angles of repose of around 30. Due to the finer structure of the base lactose in Ludipress, internal bridging occurs and the angle of repose of Blend I increases to 60.4. Its Hausner ratio of 1.423 is also significantly higher than the Hausner ratios of the other samples. The good flow properties of Ludipress have been reported previously by Baykara and other authors (9-11).

In order to estimate the manufacturing uniformity of Ludipress, a routine bulk analysis of 13 batches was carried out. Particle size data are listed in Table 4. There were two different types of particle size distributions as depicted in Figure 3. 9 of 13 lots were found to have a Type 1 tight frequency distribution. Type 2 with a higher proportion of the smaller fraction was detected for 2 batches and a intermediate Type 1-2 was found for another 2 of the lots tested. These results demonstrate a high batch-to-batch uniformity for Ludipress.

## Tableting Characteristics of Ludipress

Figure 4 shows the compaction load/hardness profiles of 3 Ludipress batches compared to Tablettose and Blend II. Because of its poor flow properties, Blend I could not be tableted on the rotary press used. The profiles obtained correlate with the results of the evaluation of the powder flow properties. Firstly, there is a high batch-to-batch uniformity with Ludipress. Secondly, Ludipress has significant advantages compared to the blend of the base materials in Ludipress. Taking the entire compaction load range into consideration Ludipress tablets are harder compared to tablets prepared from Blend II and Tablettose respectively.

TABLE 3
Powder flow properties of 3 Ludipress samples compared to blends of base materials in Ludipress.

| | Angle of repose (θ) | Tapped density (g/ml) | Bulk density (g/ml) | Hausner ratio |
|---|---|---|---|---|
| Lot No. 06 2521 | 30.3 | 0.618 | 0.517 | 1.195 |
| Lot No. 94 9157 | 30.5 | 0.608 | 0.501 | 1.214 |
| Lot No. 98 0011 | 32.8 | 0.692 | 0.571 | 1.212 |
| Blend I [a] | 60.4 | 0.757 | 0.532 | 1.423 |
| Blend II [b] | 30.3 | 0.684 | 0.563 | 1.215 |

[a] Blend I: 93.0 % base lactose in Ludipress, 3.5 % Kollidon 30, 3.5 % Kollidon CL

[b] Blend II: 93.0 % Tablettose, 3.5 % Kollidon 30, 3.5 % Kollidon CL

The higher compactibility of Ludipress was previously reported by the manufacturer taking a Blend I analogue as reference (12). Obviously, there is a great difference between just mixing the single components and co-processing a mix of various excipients. Admixing of further components can even decrease compactibility of a powder as shown with Tablettose. Tablets made of Blend II containing 3.5% povidone and 3.5% crospovidone, both adjuvants, which perform plastic deformation, are softer than compacts with just Tablettose as a filler binder. It could be the case that bonding mechanisms here are disturbed by the additional ingredients.

The improved compactibility becomes even more evident if the friability of the compacts is checked. Corresponding profiles are depicted in Figure 5. At a compaction pressure of 100 MPa friability of Ludipress compacts was approx. 0.2 percent. To obtain similar values for tablets prepared with Blend II and Tablettose respectively, a compaction load of 200 MPa was necessary.

The results of tablet disintegration testing are shown in Figure 6. The fastest disintegration was measured for tablets of Blend II, whereas Tablettose

TABLE 4
Particle size distribution data of 13 Ludipress batches

| Batch numbers | $d_{10}$[a] (μm) | $d_{50}$[a] (μm) | $d_{90}$[a] (μm) | Type of distribution [b] |
|---|---|---|---|---|
| 06 2521 | 113 | 226 | 357 | 1 |
| 20 0827 | 84 | 195 | 339 | 1 |
| 27 0047 | 96 | 226 | 375 | 1 |
| 44 0013 | 80 | 206 | 370 | 1-2 |
| 45 0844 | 94 | 190 | 313 | 1 |
| 48 9155 | 105 | 225 | 360 | 1 |
| **50 0048** | 54 | 181 | 349 | **2** |
| 56 0191 | 90 | 216 | 360 | 1 |
| 57 0015 | 86 | 205 | 360 | 1-2 |
| 68 0845 | 125 | 228 | 361 | 1 |
| 71 9156 | 96 | 194 | 305 | 1 |
| 94 9157 | 110 | 210 | 338 | 1 |
| **98 0011** | 72 | 187 | 360 | **2** |

[a] Volume diameter [b] Type of distribution see Figure 3

compacts produced the highest disintegration times. This is due to the absence of a swelling agent in Tablettose so that disintegration must occur by dissolving the tablet from the surface. Ludipress compacts showed intermediate disintegration times, just exceeding 5 minutes at a compaction pressure of 300 MPa. Furthermore a disintegration time minimum at approx. 100 MPa could be detected. Higher and lower compaction loads provoked increasing disintegration times of the tablets.

A disintegration or dissolution optimum at a certain compaction load of a lactose based granule containing povidone and crospovidone has been reported

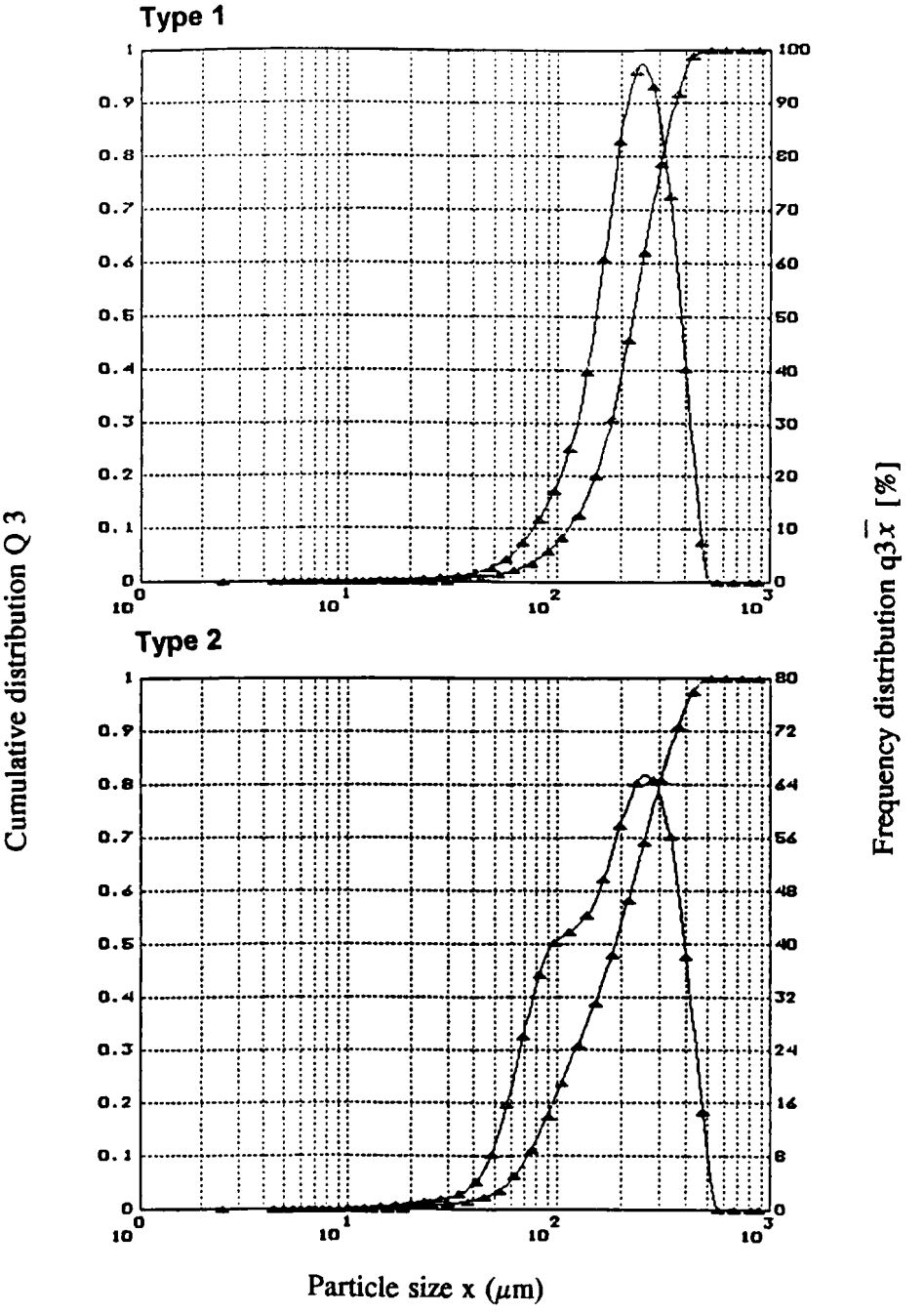



FIGURE 3:
Particle size data as cumulative and frequency distribution by volume. **Type I**: tight frequency distribution, e.g. batch no. 06 2521. **Type II**: higher proportion of the smaller fractions, e.g. batch no. 98 0011.

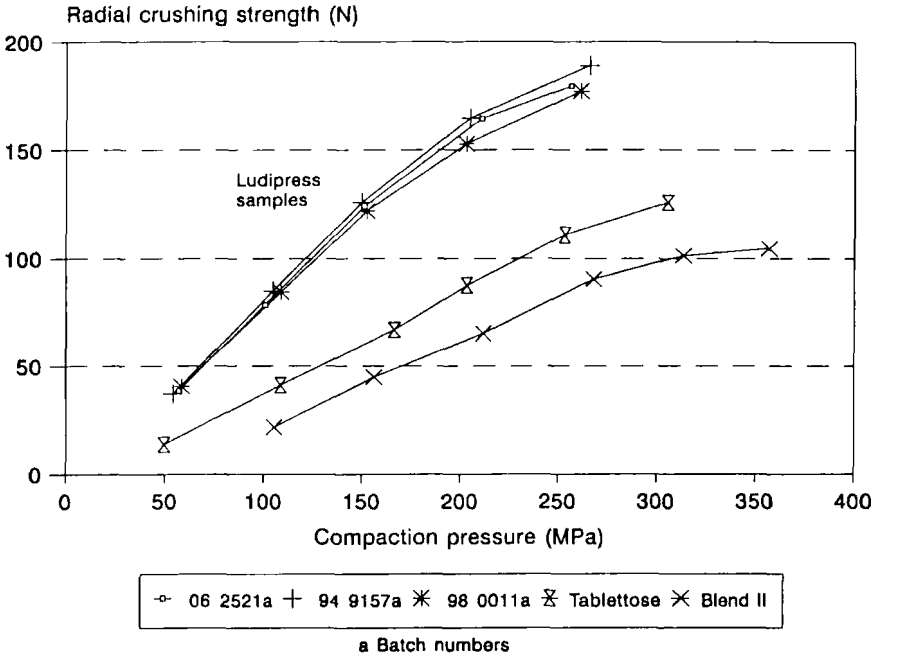



FIGURE 4
Crushing strength versus compaction pressure for 3 batches of Ludipress in comparison to Tablettose and Blend II. For composition of Blend II see Table 3.

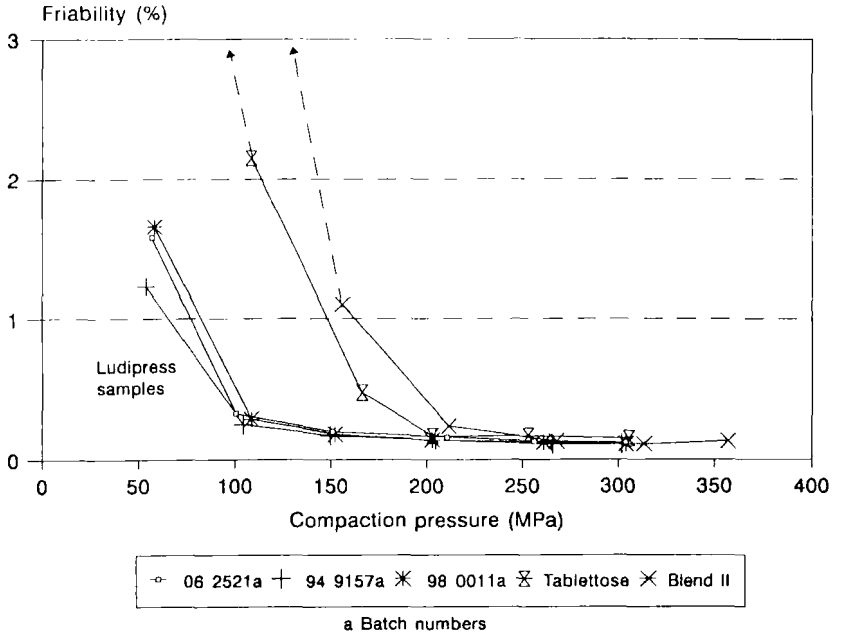



FIGURE 5:
Friability versus compaction pressure. Blend II see Table 3.

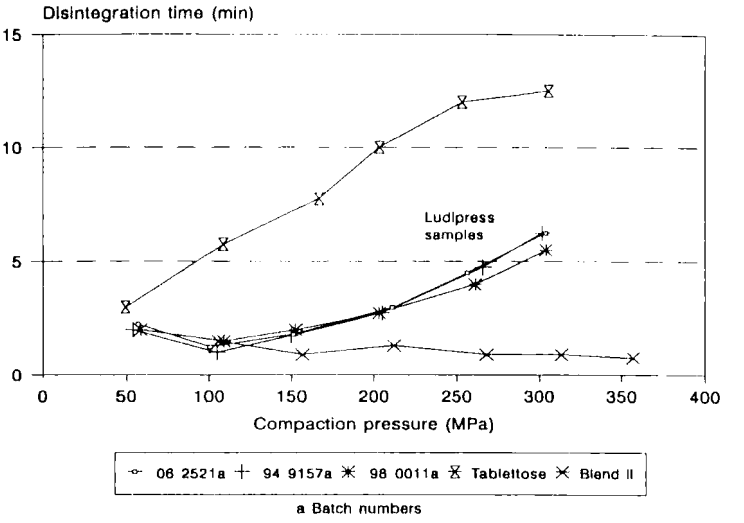



FIGURE 6:
Disintegration time versus compaction pressure. Blend II see Table 2.

earlier by Khan and Rooke (13). This phenomenon can be explained by the packing density of the tablet and visualised with the aid of scanning electron microscopy.

Figure 7 shows micrographs of the fracture surface at increasing compaction loads in two different magnifications. At 75,1 MPa (Figure 7A) packing of the tablet is loose. Intact lactose crystals and amorphous constituents can be detected clearly. Magnification of the frame in Figure 7A (Figure 7B) reveals a typically popcorn-shaped crospovidone particle. During water uptake the swelling of this cross-linked, insoluble polymer will lead to tablet disintegration. Due to the loose packing of the tablet, a certain amount of swelling volume will vanish into the numerous voids of the compact causing prolonged disintegration. By increasing the compaction load up to 100 MPa, plastic deformation of the amorphous constituents occurs providing optimal tablet properties . The single crystals are "glued" together (Figure 7C, D) leading to a significant reduction in friability (see Figure 5). Due to the augmented packing density, the interparticulate volume decreases thus enabling the crospovidone in Ludipress to establish its swelling activity properly. A further increase of the compaction pressure causes a more brittle fracture of the lactose crystals and a strong decrease

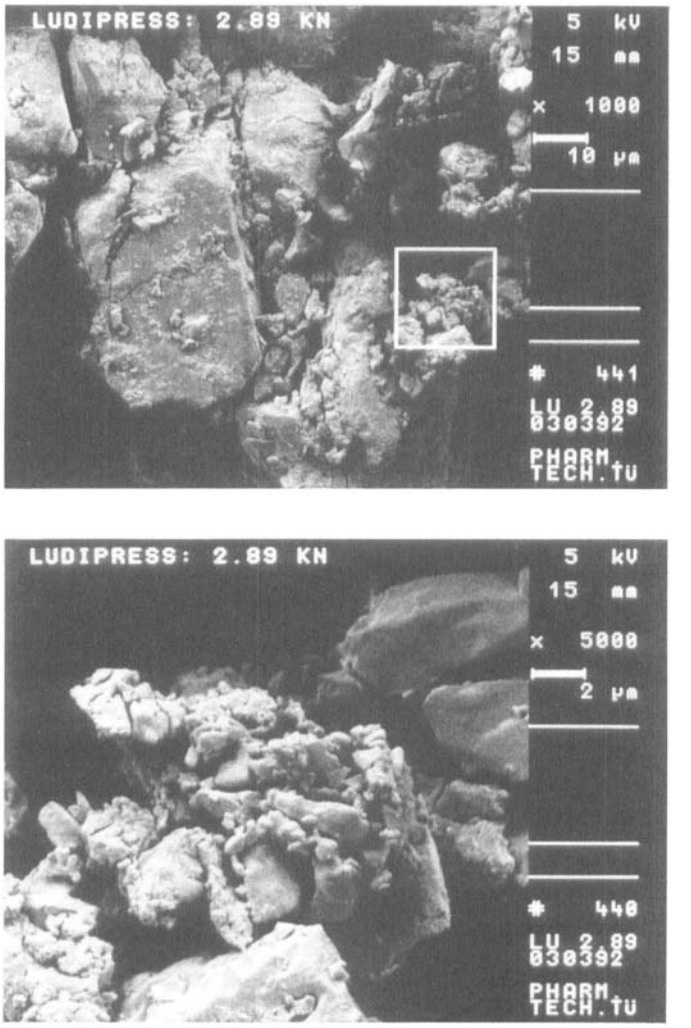
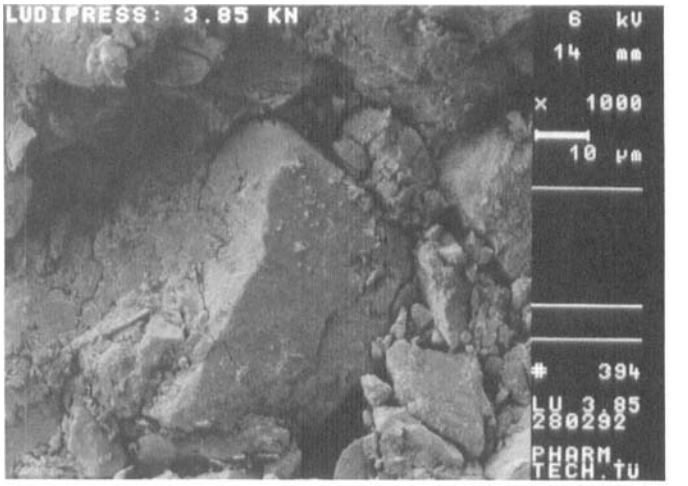
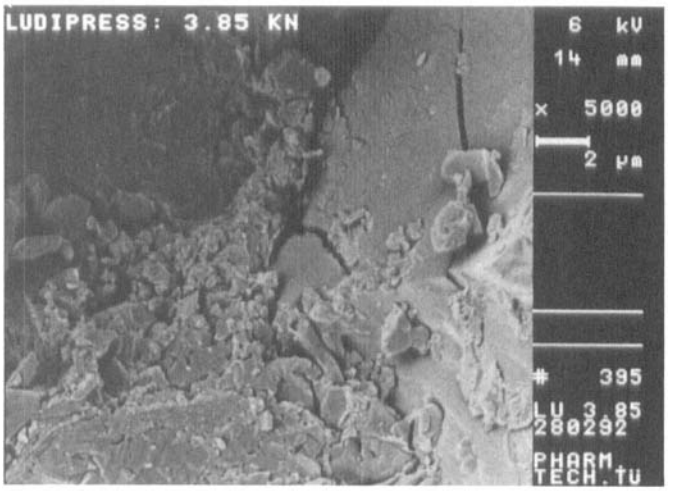



FIGURE 7:
Micrographs of 7 mm Ludipress compacts. Fracture surfaces at different compaction loads. **A**, **B**: Compaction load 75.1 MPa (2.89 kN). **C**, **D**: Compaction load 100.1 MPa (3.85 kN). **E**, **F**: Compaction load 185.8 MPa (7.15 kN).

*(continued)*




C




D

FIGURE 7. Continued

of tablet porosity as depicted in Figure 7E and 7F. Consequently water uptake is impeded and disintegration time increases.

Comparison with Other Direct Compression Excipients

Figure 8 and 9 show micrographs of two recently introduced direct compression excipients *Cellactose* and *Avicel PH 200.*

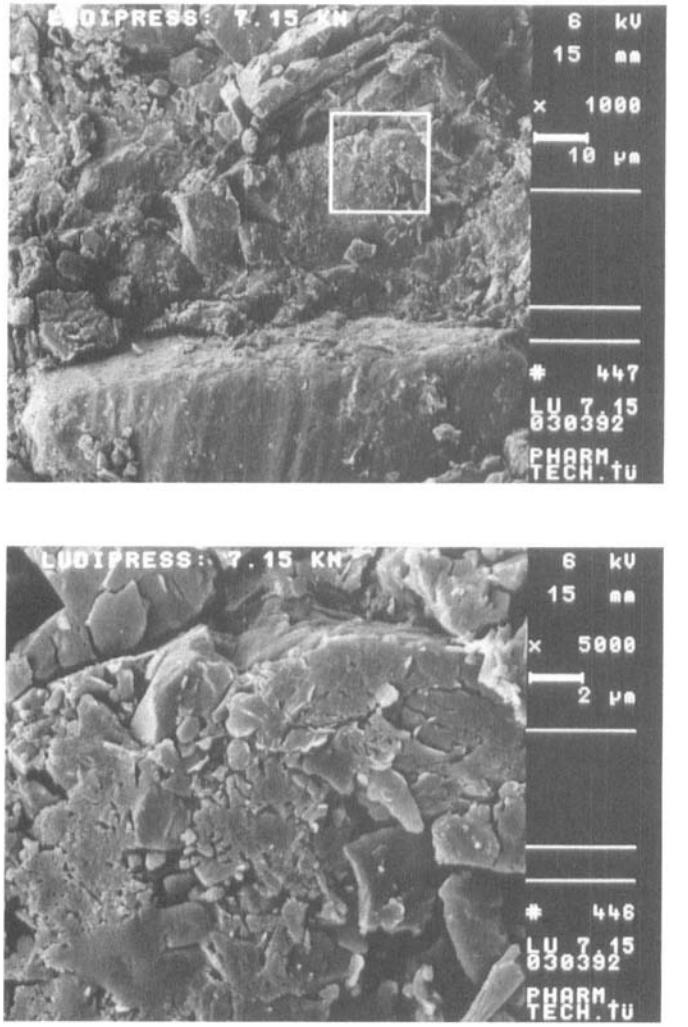
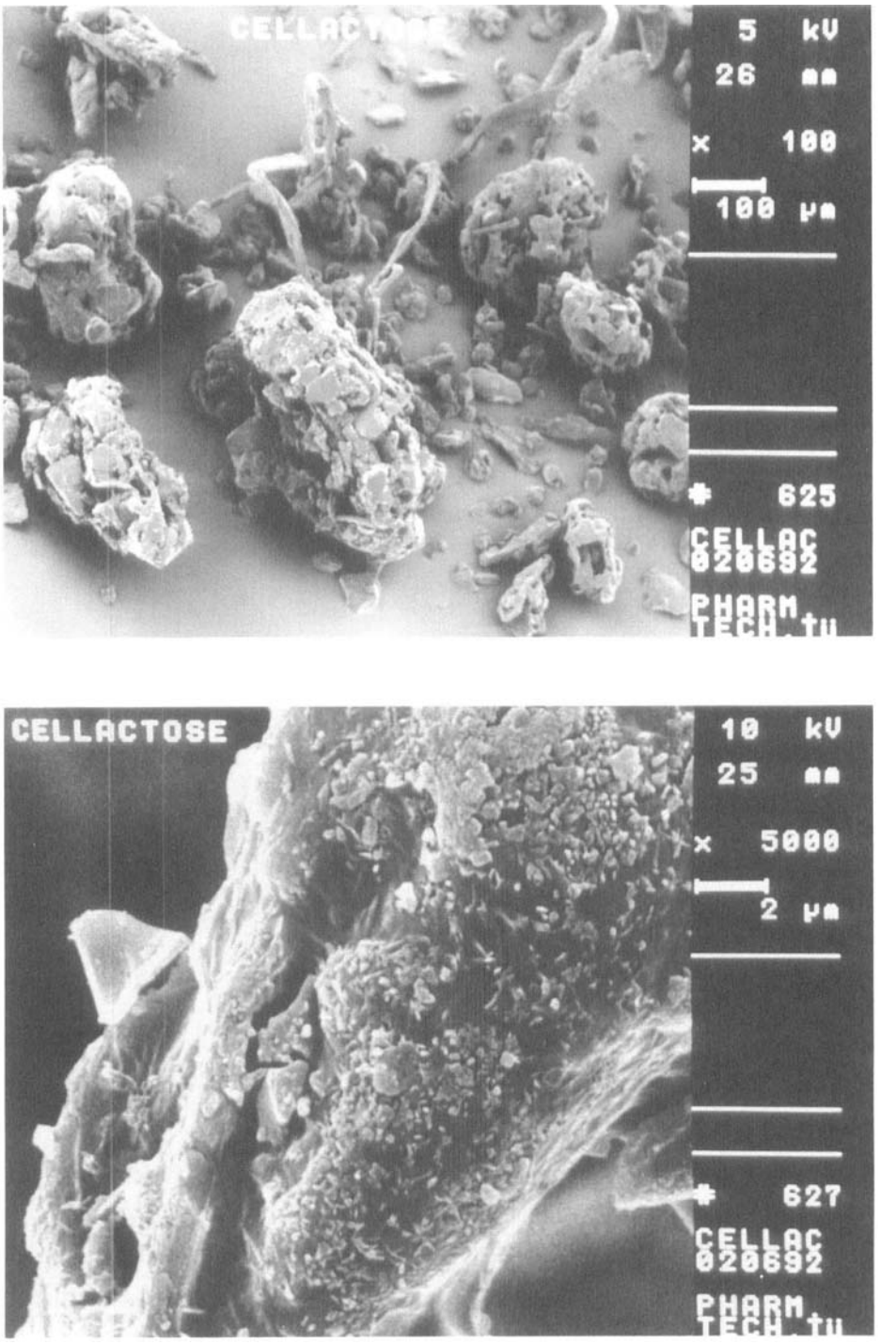



FIGURE 7. Continued

*Cellactose* is a one-body compound of 25% cellulose and 75% $\alpha$-lactose-monohydrate. The 100x magnification in Figure 8A shows spherical agglomerates, small lactose crystals and loose cellulose fibres. The 5000x magnification of a Cellactose fibre depicted in Figure 8B indicates significant differences compared to the pure microcrystalline cellulose (see Figure 9B). Apart from small crystals, amorphous lactose can be detected on the fibre surface.




A

B

FIGURE 8:
Micrographs of Cellactose. A: Magnification x100. B: Magnification x5000.

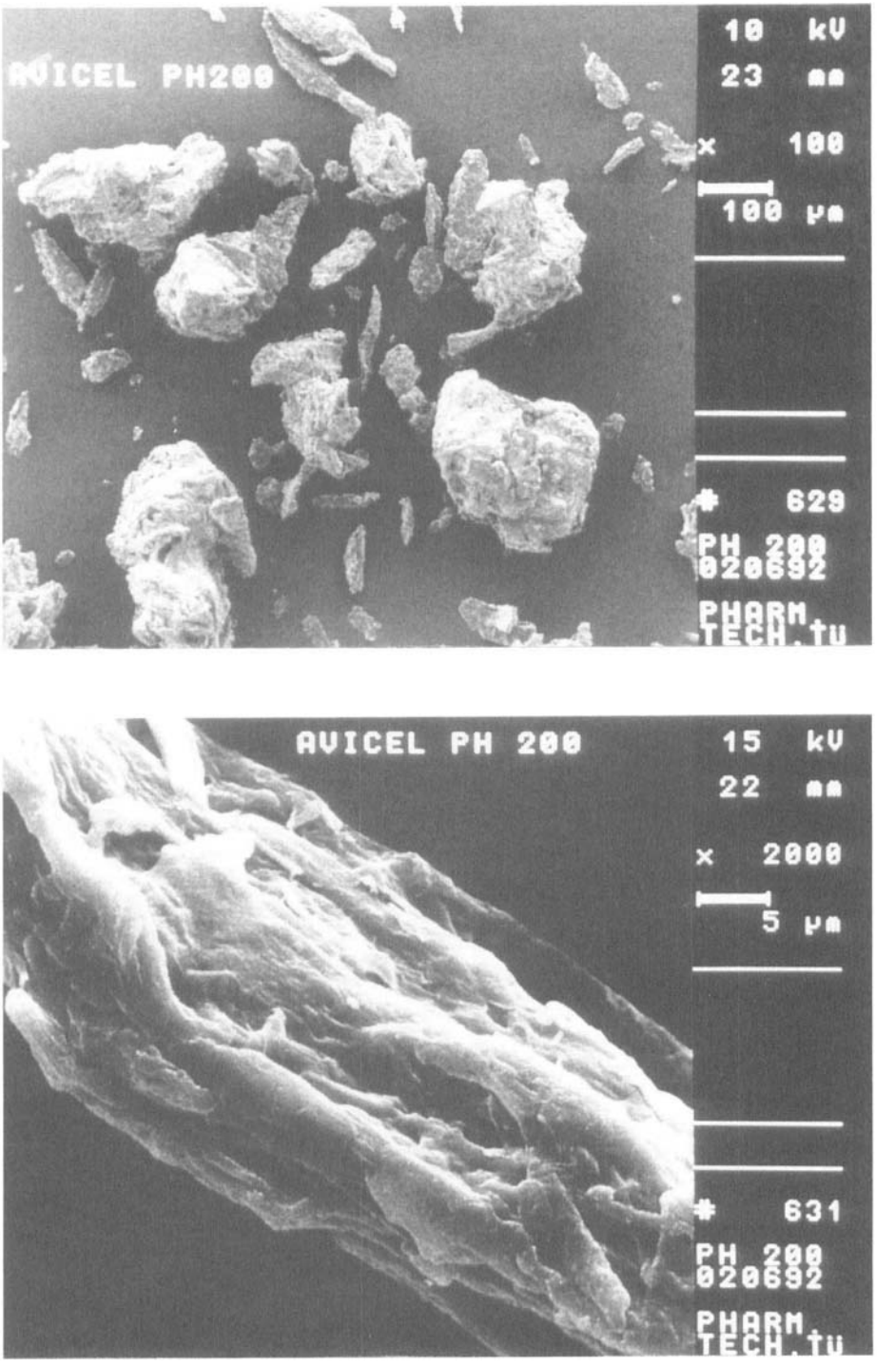



FIGURE 9:
Micrographs of Avicel PH 200. **A**: Magnification x100. **B**: Magnification x2000.

*Avicel PH 200* is a large particle size microcrystalline cellulose (MCC), which was designed to improve flow properties of Avicel. Examination by SEM indicates that Avicel PH 200 is composed of microcrystalline aggregates exhibiting a ball-like shape and loose fibres, which are typical of Avicel PH 101, as probably the most intensively investigated excipient in direct compression.

Table 5 shows comparative flow properties of the direct compression excipients used in this study. The lowest angle of repose was detected for Ludipress, while Cellactose, Avicel PH 200 and Tablettose exhibited similar flowability. Apart from these large particle size excipients, two finer celluloses, Avicel PH 101 and Sanaq 101 L were evaluated. Due to their fibrous shape, internal bridging was enhanced resulting in higher angles of repose. Discrepancies were also found with respect to the bulk density and Hausner ratios. The highest values for bulk and tapped density were measured for excipients containing lactose. Ludipress, Cellactose and Tablettose also featured similar packing properties leading to Hausner ratios of approx. 1.2. For the different grades of MCC Hausner ratios of 1.3 to more than 1.4 for Sanaq 101 L were measured.

The particle size frequency distributions of the coarse excipients are depicted in Figure 10. The lowest $d_{50}$-value and the broadest frequency distribution was detected for Tablettose, whereas Ludipress, Cellactose and Avicel PH 200 exhibited similar frequency distributions. Thus, the better flow properties of Ludipress compared to Cellactose and Avicel PH 200 must be due to the ball like shape of the granules and the lack of fibres in Ludipress. Complete particle size data for all excipients are given in Table 6.

In order to estimate the compactibility of the large particle size excipients, placebo tablets were compressed and a comparative evaluation with Avicel PH 101 and Sanaq 101 L was carried out. The corresponding compaction load/hardness profiles are depicted in Figure 11.

The highest compactability was detected for Avicel PH 101. Interparticulate bonding results in the formation of robust compacts, even under comparatively low compaction pressures. With the exception of Tablettose there were only limited differences between the other excipients in a compaction range from 50 to 150 MPa. By further elevation of the compaction load an almost linear increase in tablet hardness was detected for Ludipress and Cellactose, whilst increasing compaction pressure could not augment hardness of Avicel PH 200

TABLE 5
Powder flow properties of direct compression excipients

| | Angle of repose ($\theta$) | Tapped density (g/ml) | Bulk density (g/ml) | Hausner ratio |
|---|---|---|---|---|
| Ludipress [a] | 30.5 | 0.608 | 0.501 | 1.214 |
| Cellactose | 36.2 | 0.462 | 0.380 | 1.216 |
| Avicel PH 200 | 35.7 | 0.359 | 0.276 | 1.301 |
| Tablettose | 36.0 | 0.724 | 0.602 | 1.203 |
| Avicel PH 101 | 46.2 | 0.414 | 0.313 | 1.323 |
| Sanaq 101 L | 55.9 | 0.461 | 0.323 | 1.427 |

[a] Lot No. 94 9157

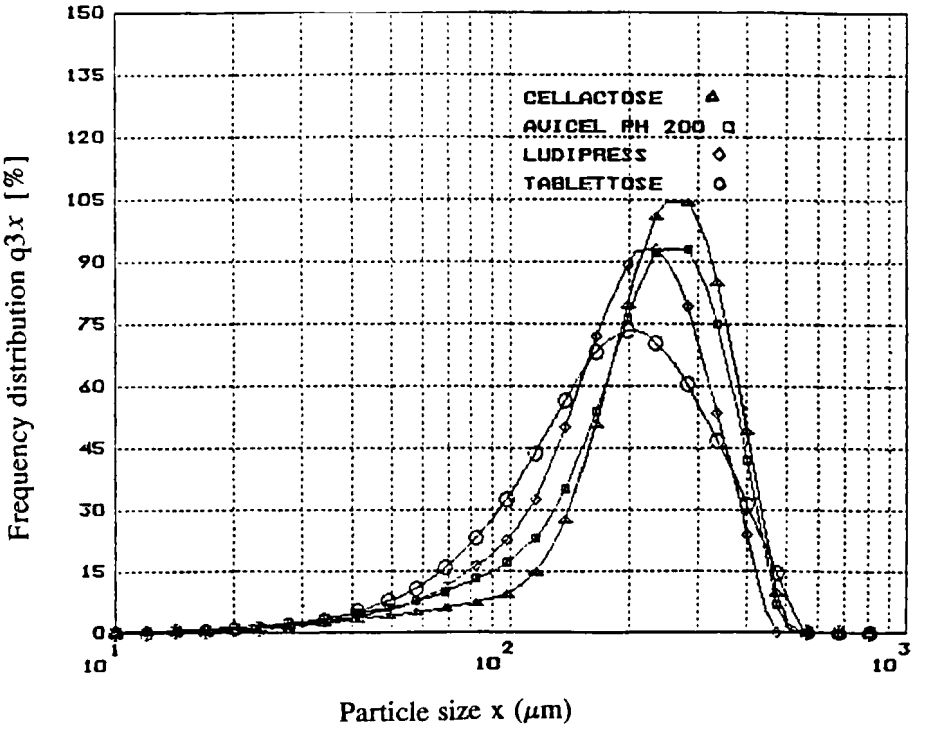



FIGURE 10:
Particle size data as frequency distribution by volume of coarse direct compression excipients.

TABLE 6
Particle size distribution data of direct compression excipients

| | $d_{10}$[a] (μm) | $d_{50}$[a] (μm) | $d_{90}$[a] (μm) |
|---|---|---|---|
| Ludipress | 110 | 210 | 338 |
| Cellactose | 115 | 238 | 364 |
| Avicel PH 200 | 93 | 226 | 358 |
| Tablettose | 81 | 186 | 350 |
| Avicel PH 101 | 11 | 44 | 97 |
| Sanaq 101 L | 12 | 47 | 110 |

[a] Volume diameter



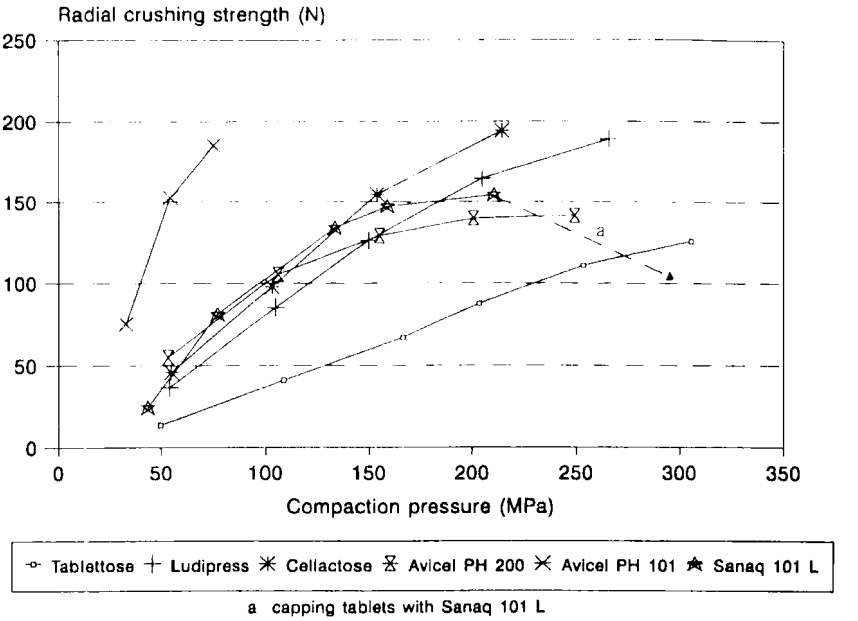



FIGURE 11:
Crushing strength of tablets of various direct compression excipients versus compaction pressure.

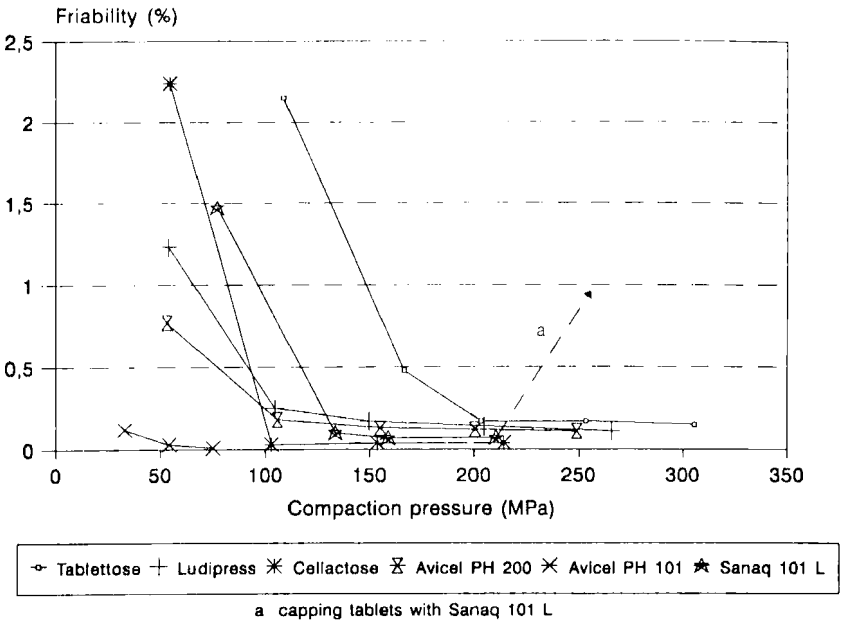



FIGURE 12:
Friability of placebo tablets of various direct compression excipients versus compaction pressure.

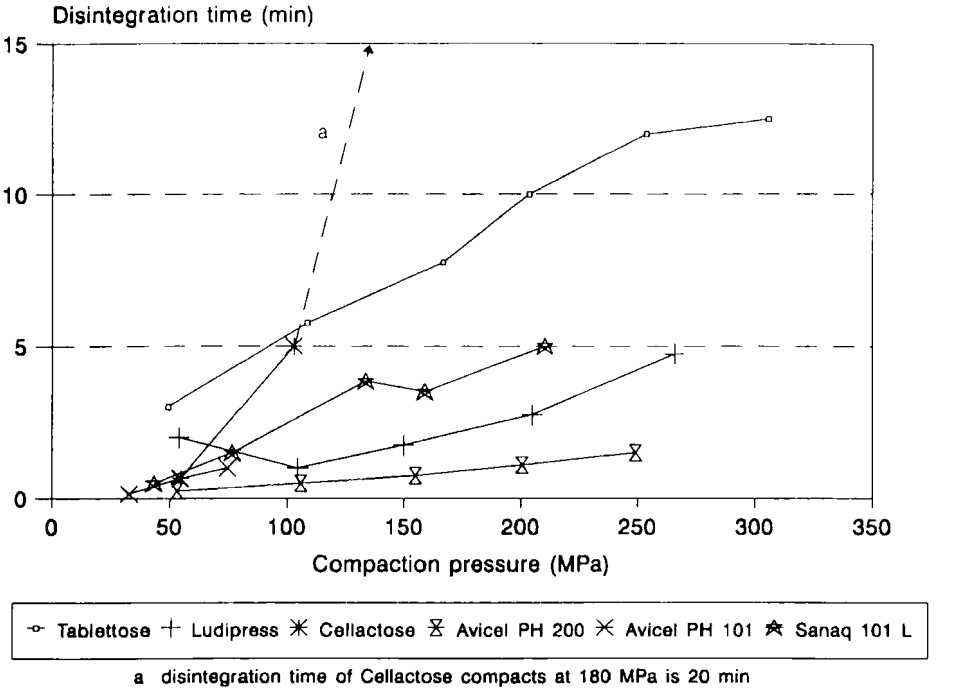



FIGURE 13:
Disintegration time of placebo tablets of various direct compression excipients versus compaction pressure.

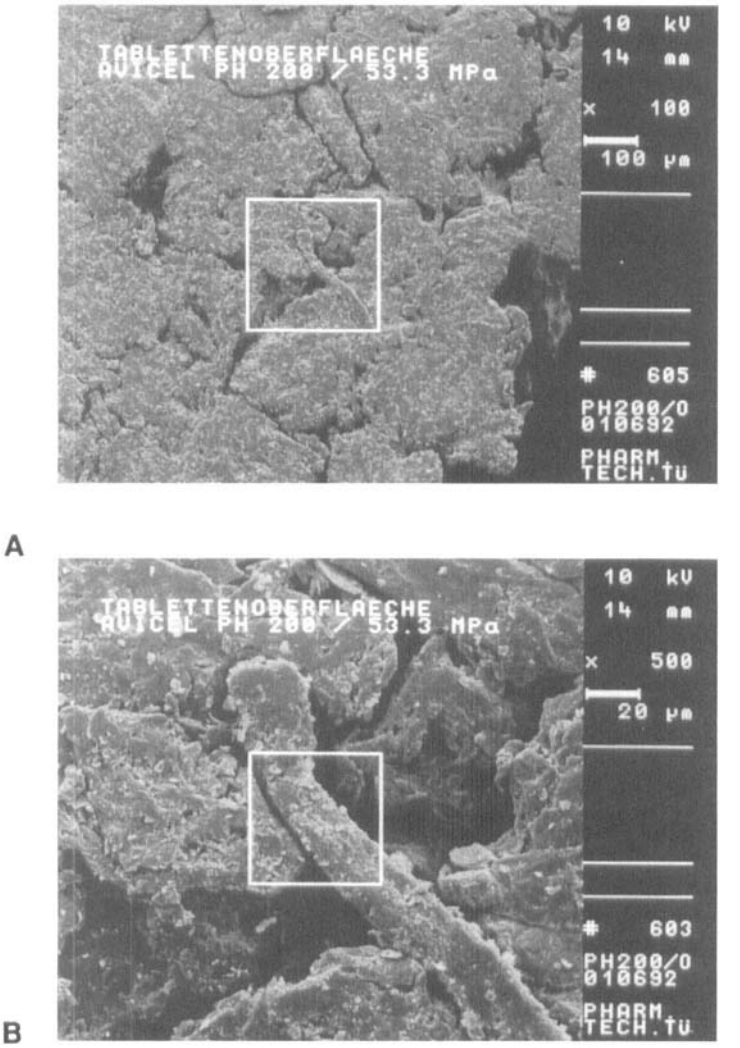
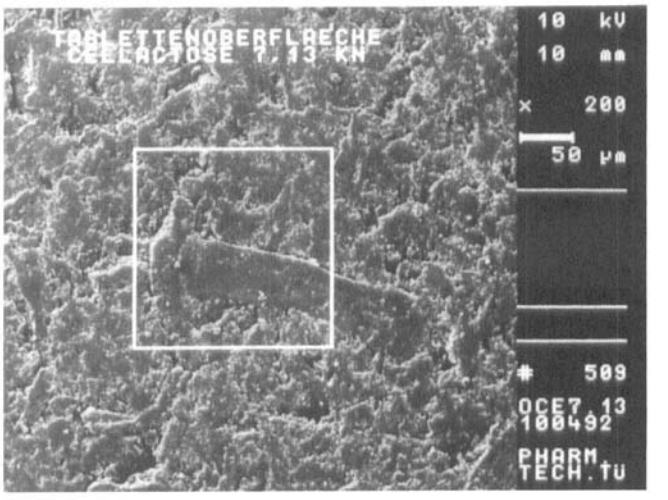



FIGURE 14:
Micrographs of tablet surfaces. **A**, **B**: Avicel PH 200, compaction load 53.3 MPa (2.05 kN). **C**, **D**: Cellactose, compaction load 185.3 MPa (7.13 kN).
Tablet diameter: 7 mm.




C


D

FIGURE 14. Continued

tablets and had a deleterious effect on Sanaq 101 L compacts. At 200 MPa capping of tablets took place during compaction, which is also documented by the high friability values as depicted in Figure 12. The lower binding capacity of this Avicel PH 101 analogue was earlier reported in a comparative investigation of different types of MCC by Doelker and co-workers (14). At a compaction load of approx. 50 MPa Avicel PH 200 compacts exhibited the lowest friability compared to the other coarse direct compression excipients. This can be explained by the

morphology of this cellulose type. Apart from hydrogen bonding, mechanical interlocking occurs as shown in Figure 14A and 14B. The depicted tablet surface reveals partially deformed granules and smaller cellulose fibres, which act like "bridges" between the larger agglomerates.

Results of tablet disintegration testing are given in Figure 13. In general terms even robust MCC compacts exhibited rapid disintegration. The corresponding mechanism is the capillary uptake of water, which subsequently disrupts interparticulate hydrogen bonding. With Sanaq 101 L this effect is less pronounced than for the Avicel types which produced the comparatively fastest tablet disintegration. However, the disintegration properties of formulations containing cellulose are significantly affected by the nature of the other constituents. For example, by increasing compaction load from 100 to 185 MPa for Cellactose, disintegration time was drastically elevated to more than 20 minutes, exceeding the European Pharmacopoeia limit. This phenomenon can be explained by the internal structure of the Cellactose compacts as depicted in Figure 14C and 14D. The micrograph in Figure 14C shows a condensed tablet surface with a bone like cellulose fibre in the middle. Magnification of the frame in Figure 14C depicted in Figure 14D helps to understand why disintegration time was elevated with Cellactose. The combination of plastic deformation of the cellulose and the tendency to brittle fracture of the lactose in Cellactose leads to highly condensed compacts even at intermediate compaction pressures. As a consequence the pores are obstructed by broken crystals thus impeding water penetration.

## CONCLUSION

The results indicate that Ludipress as a single adjuvant can substitute various tablet ingredients thereby acting as a "multipurpose excipient" for direct compression of tablets. Compared to its physical blend, Ludipress exhibited significant advantages. Powder flow properties are excellent and superior to the competitive large particle size excipients Cellactose and Avicel PH 200, whereas compactibility is similar in a compaction load range from 50 to 150 MPa. In terms of tablet disintegration Avicel PH 200 came first followed by Ludipress and Cellactose. The latter featured strongly elevated tablet disintegration times at even intermediate compaction pressures. Further evaluation of Ludipress will be

published in a second paper, which comprises the investigation of interactive mixing and direct compression using glibenclamide as a model substance.

## ACKNOWLEDGMENTS

The authors wish to thank BASF AG for the financial support of the investigations and companies, Meggle, SANAQ, AG, Basel and Lehmann&Voss for the supply with tablet excipients.

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