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EVALUATION OF LUDIPRESS AS A "MULTIPURPOSE EXCIPIENT" FOR DIRECT COMPRESSION
PART II:
INTERACTIVE BLENDING AND TABLETING WITH MICRONIZED GLIBENCLAMIDE

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ABSTRACT

In the second part of this publication the differing interactions of micronized glibenclamide during mixing with four filler/binders for direct compression were studied. The excipients used were: Ludipress, Cellactose, Avicel PH 200 and Karion Instant. In order to prepare interactive mixtures, increasing amounts of micronized glibenclamide were blended with filler/binder fractions of 125 to 500 µm. The degree of interactivity was determined by air jet sifting of the mixes, comparing drug content in the mixes before and after sieving. Cellactose showed the highest adhesion tendency for glibenclamide due to the large cavities in the particles, leading to a reagglomeration within these cavities. Tablets containing 1.75, 3.50, 5.00 and 10.00 mg of glibenclamide per tablet were compressed with Cellactose and Ludipress. As previously reported (1) for Cellactose based placebo tablets, Cellactose also showed a tremendous increase in

disintegration time and a prolonged dissolution rate at compaction pressures above 100 MPa. The corresponding values of Ludipress were not influenced. Therefore in terms of a multipurpose-excipient, Ludipress should be given preference in the formulation of low dosed drugs.

INTRODUCTION

One of the major problems in the manufacture of low dosed single unit dosage forms such as tablets and capsules is the homogeneous distribution of the active ingredient in the powder blend.

The concept of random powder mixing has largely been explored in the past by Stange (2,3,4) and Poole (5) and has been applied to pharmaceutical blending by Johnson (6, 7). The equations developed by these authors make it possible to calculate the random homogeneity of a powder blend.

In 1975 Hersey (8) presented a new "disorder to order" concept in powder mixing, where due to the cohesive nature of most pharmaceutical blends "ordered mixtures" result. As a result of the particle-particle interaction between coarse granules and fine drug particles, stable blends are formed. The physical interactions are caused by electrostatic or van-der-Waals forces, which by a decreasing particle size increase allowing the smaller particles to adhere to larger surfaces (9). Egermann (10) suggested the term *interactive mixtures* instead of *ordered mixtures* as blending operations are, in practice, processes of disordering rather than ordering, and as such are unlikely to produce ordered mixes.

The mechanisms of the physical interactions during the mixing of a drug and excipient particles and its effect upon the homogeneity of a blend have been discussed widely and have been subject to further investigations (11, 12, 13). Schmidt and Benke (14) for example showed that the rough surface of Karion Instant, a large size sorbitol granule, enhanced the adherence of micronized B-vitamins to the coarse carrier particles, thus preventing segregation and providing a high degree of homogeneity of the blends.

This paper and the investigations presented in it stems from a comparative evaluation of Ludipress, Cellactose, Avicel PH 200 and Karion Instant as carrier materials for micronized glibenclamide and its effect upon homogeneity and tablet properties including the dissolution of glibenclamide.

MATERIALS

In addition to materials cited in Part I (1) glibenclamide (Guidotti, I-Pisa, Italy; batch no. 89/008) and Karion Instant (E. Merck, D-Darmstadt, Germany, batch no. M 363 040) were used.

METHODS

The preparation and testing procedure of the glibenclamide-carrier blends are depicted in FIGURE 1 and were carried out according to the conditions optimized by Walter (15).

Preblending was performed in a metal bowl with a metal shovel for 1 min.

Blending parameters: Batch size: 25.000 g. Drug concentration: 1.75, 3.50, 5.00 and 10.00 mg per 125 mg-sample. Mixer: Turbula (W. A. Bachhofen, CH-Basle, Switzerland), 42 rpm. Mixing time: 30 min. Relative humidity: 30 ± 5 %. Temperature: 22.5 ± 2.5 °C.

The displacement of adherent glibenclamide from carrier granules was carried out by sieving through an Air Jet Sifter (type 200 LS, Alpine AG, D-Augsburg, Germany). From each 25g-blend of micronized glibenclamide and coarse excipient, 5 x 1.00 g was sampled and submitted to air jet sifting. The determination of the remaining glibenclamide adhering to the carrier granules was performed by sampling each time 1 x 125 mg of a 1.00 g sieved sample.

Air jet sifting parameters: Sieve: 63 µm. Sieving time: 2 min. Pressure: 50 mm H_2O. Mass: 1.00 g. Relative humidity: 25.0 ± 3.0 %. Temperature: 22.5 ± 1.5 °C.

Sample preparation and analysis of glibenclamide content. 20 ml 0.1 M hydrochloric acid in methanol were added to mixtures of approx. 125 mg glibenclamide containing either *Avicel PH 200 or Karion Instant.* In the course of 5 min the drug was dissolved at 60 °C. After cooling down to room temperature, sufficient 0.1 M hydrochloric acid in methanol was added to produce 50 ml and the absorbance of the resulting solution was measured at 300.5 nm using a spectrophotometer (type 16 UV/VIS, Bodenseewerk Perkin-Elmer GmbH, D-Überlingen, Germany). With blends containing the water-insoluble Avicel PH 200, a clear suspension resulted which after decanting could be used directly in

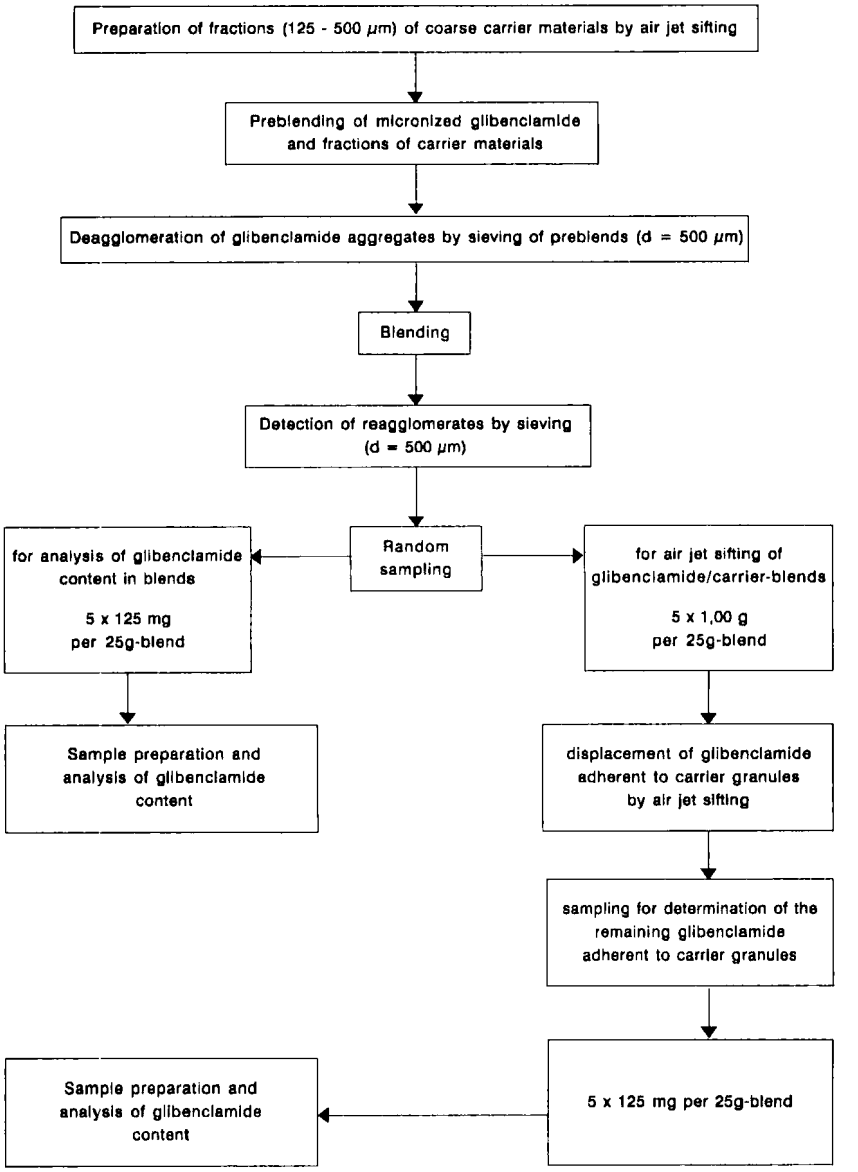


FIGURE 1:
Preparation and testing of glibenclamide/carrier-blends.

order to determine glibenclamide content. Due to the composition of *Ludipress* and *Cellactose*, another extraction procedure had to be used to determine glibenclamide content. 10 ml 0.1 M hydrochloric acid in methanol was added to the samples. During 5 min the drug was dissolved at 60 °C. The resulting suspension was centrifuged for 10 min at 5000 rpm (Minifuge 2, Heraeus, D-Hanau, Germany). The extraction was repeated again using 10 ml 0.1 M hydrochloric acid in methanol. The combined, cooled extracts were diluted to 50 ml using 0.1 M hydrochloric acid in methanol. All of the values are the mean results of 5 determinations.

Scanning electron microscopy and particle size analysis were performed as reported in Part I (1).

Preparation of tableting blends. The tablet weight was 125 mg with glibenclamide concentrations of 1.75, 3.50, 5.00 and 10.00 mg. In all cases the batch size was 500 g. Magnesium stearate was passed through a 315 µm sieve and added to the glibenclamide/excipient preblend by coarse mixing. In order to break down drug agglomerates, the blends were passed through a 500 µm sieve. The mixing parameters were previously reported in Part I (1). The magnesium stearate concentration was 0.4 percent.

Tableting. 7 mm flat face bevelled edge tablets were compressed on an instrumented 3-station Korsch Pharmapress rotary press (E. Korsch OHG, D-Berlin, Germany) equipped with a one die-and-punch assembly at a machine speed of 20 rpm. Die filling was performed by a force feeder.

Tablet testing. For the determination of radial crushing strength and tablet disintegration time see Part I (1).

The uniformity of content test was carried out according to USP XXII with 10 tablets per lot. The sample preparation and analysis of drug content was performed as with glibenclamide blends containing either Ludipress or Cellactose. The tablet had, beforehand, been powdered with a glass stick.

The dissolution rates were determined by BASF AG (D-Ludwigshafen, Germany) using a fully automized paddle-dissolution tester (type PTW S, Pharma Test Apparatebau, D-Hainburg, Germany) interfaced with a computerized HPLC-system. Six tablets per lot were tested in 900 ml phosphate buffer pH 7,4 USP XXII at 37.0 ± 0.1 °C and at a paddle speed of 75 rpm. Samples were drawn after 3, 6, 10, 15, 20, 30 and 60 minutes respectively

RESULTS AND DISCUSSION

The determination of glibenclamide adhesion to coarse carrier particles

To evaluate the adhesion of a micronized drug to coarse carrier granules, a blend of the two components is submitted to air jet sifting, determining the drug content before and after sieving (16). The sieve used must permit the passage of the largest drug particles and at the same time retain the smallest carrier granules. Therefore, in order to avoid overlapping of the particle size distributions of drug and excipient, a coarse fraction of the excipient has to be used. The corresponding particle size data are given in Table 1 and FIGURE 2. According to the d_{10} and d_{90}-values all carrier fractions were well within the limits of 125 and 500 μm, thus not interfering with glibenclamide particle size distribution as depicted in FIGURE 3.

To visualize the interactions between the carrier particles and the drug, scanning electron micrographs were taken before blending and after air jet sifting respectively. In FIGURE 4 A to D single excipient granules are shown. Ludipress, Cellactose and Avicel PH 200 granules are ball shaped and have irregular surfaces, thus enhancing adhesion of fine drug particles. The morphology and composition of these excipients have been described previously (1). Karion Instant (see FIGURE 4 D, E), a spray-dried sorbitol granule, exhibits a needle-like surface with a high adhesion capacity for micronized drugs (14, 15, 17). A 7000 times magnification of glibenclamide particles is depicted in FIGURE 4 F. During mixing, these particles were entrapped in the numerous cavities on the surface of the carrier granules. Adhesion forces were strong enough to prevent segregation by air jet sifting, a certain percentage of the drug, was therefore, retained in the cavities of the excipient granules as depicted in FIGURE 5. The highest adhesion of drug after sieving was found for Cellactose, whereas the other excipients showed similar adhesion ratios (see FIGURE 6). At a drug concentration of 10 mg per 125 mg-sample, almost double the amount of glibenclamide could be detected in Cellactose blends compared to blends with Ludipress, Avicel PH 200 and Karion Instant. Apparently this phenomenon is caused by the voluminous cavities of Cellactose granules where *intraparticulate reagglomeration* of glibenclamide particles takes place as depicted in FIGURE

TABLE 1
Particle size distribution data of carrier fractions 125-500 µm and glibenclamide.

	d_{10}[a] (µm)	d_{50}[a] (µm)	d_{90}[a] (µm)
Ludipress	153	233	340
Cellactose	157	244	357
Avicel PH 200	160	252	364
Karion Instant	176	279	408
Glibenclamide	1.45	6.07	17.90

[a] Volume diameter

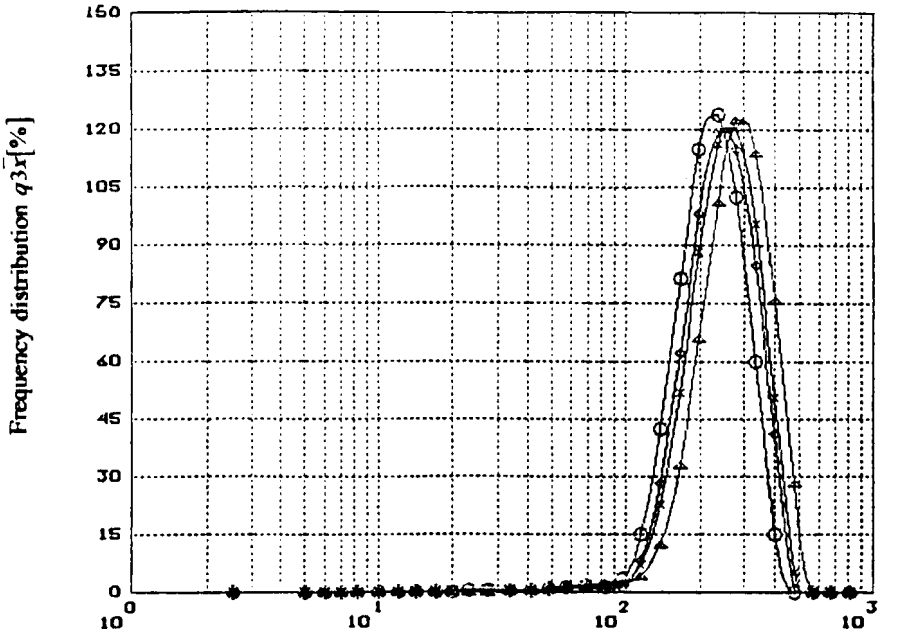


FIGURE 2:
Particle size frequency distribution by volume of carrier fractions 125-500 µm. --x-- Avicel PH 200; --◊-- Cellactose; --Δ-- Karion Instant;--o-- Ludipress.

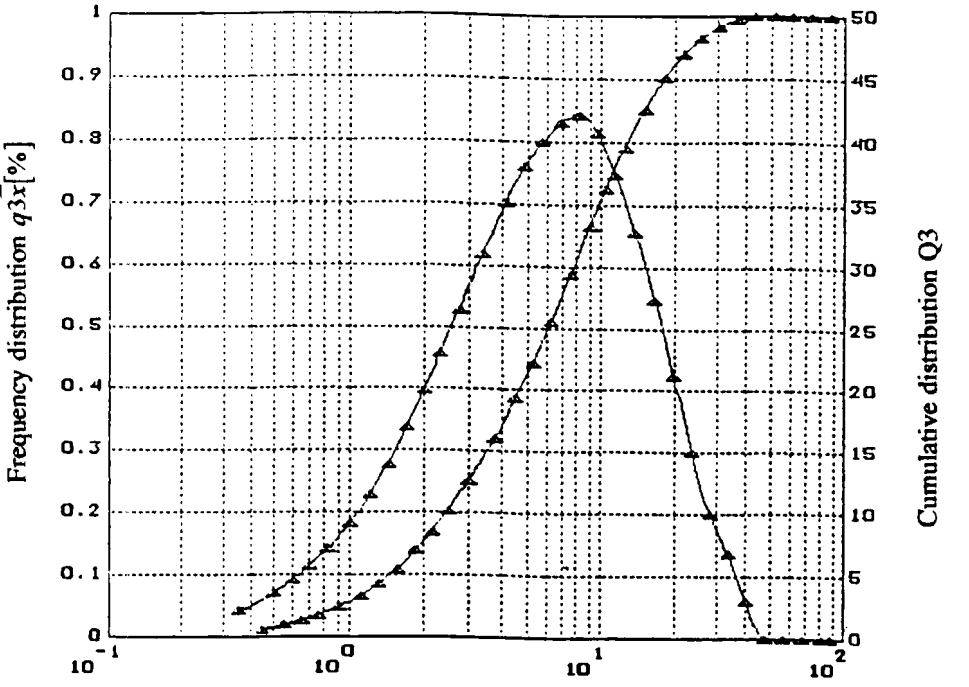


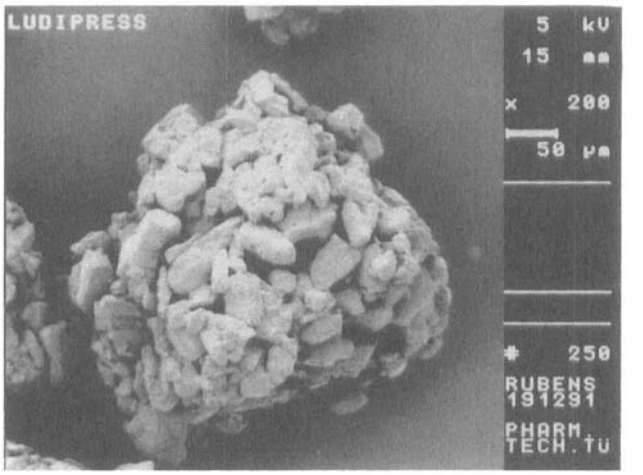
FIGURE 3:
Particle size data as frequency distribution by volume of micronized glibenclamide.

7 A. Inverting the picture in FIGURE 7 B the depth of the cavity and the high amount of reagglomerated glibenclamide becomes even more obvious.

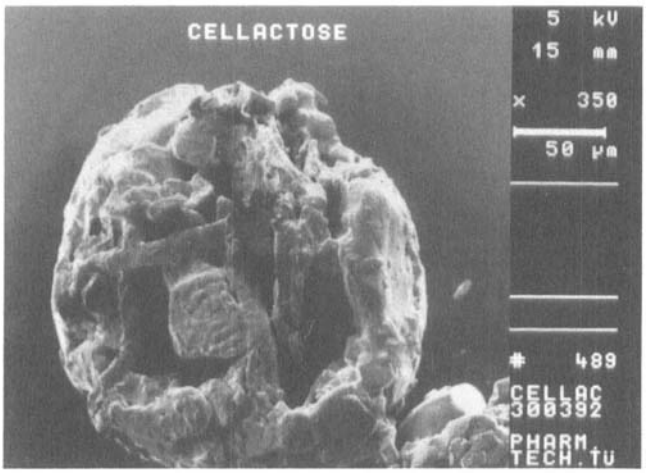
The homogeneity of Glibenclamide Carrier Blends

When producing low dosed drugs in single unit solid dosage forms, micronized drugs are mixed with other excipients. Due to the cohesive nature of the fine drug particles, the limiting factor in preparing a homogeneous blend is the break-down of drug agglomerates which can be achieved in different ways.

Firstly, by prolonged mixing (18). Nevertheless, drug agglomerates may still exist in the powder blend, which may cause drastic over-dosage in some samples.



A

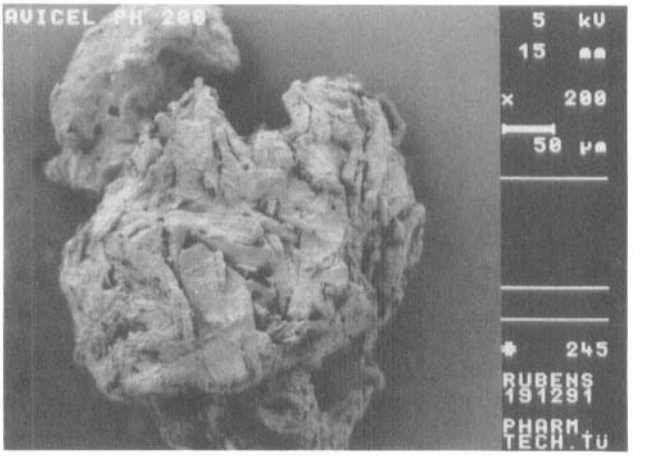


B

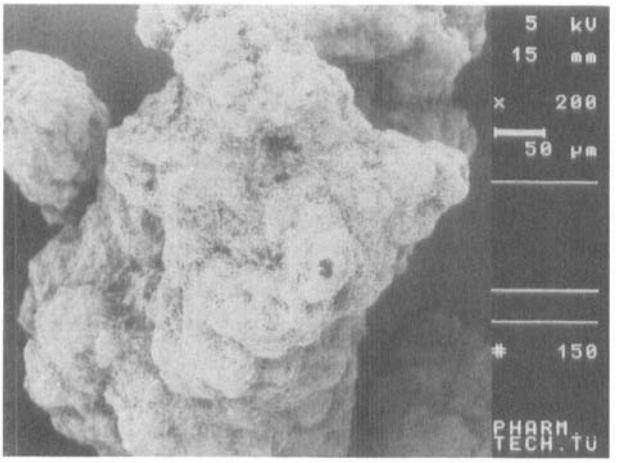
FIGURE 4:

A: Ludipress, magnification: x200. **B:** Cellactose, magnification x350. **C:** Avicel PH 200, magnification x200. **D:** Karion Instant, magnification x200. **E:** Karion Instant, magnification x2000. **F:** Glibenclamide, magnification x7000.

(continued)



C



D

FIGURE 4. Continued

Secondly, by applying high-performance mixers (18), here, it must be recognised that elevated shear forces can also break down coarse excipients, thus decreasing the flowability of the powder mix.

Thirdly, by adding flow adjuvants (19) like Aerosil®, the addition of another fine constituent, however, may have a negative effect upon interaction between micronized drug and coarse carrier particles (20, 21).

Fourthly, by presieving the drug, despite this in such cases reagglomeration of drug particles may occur.

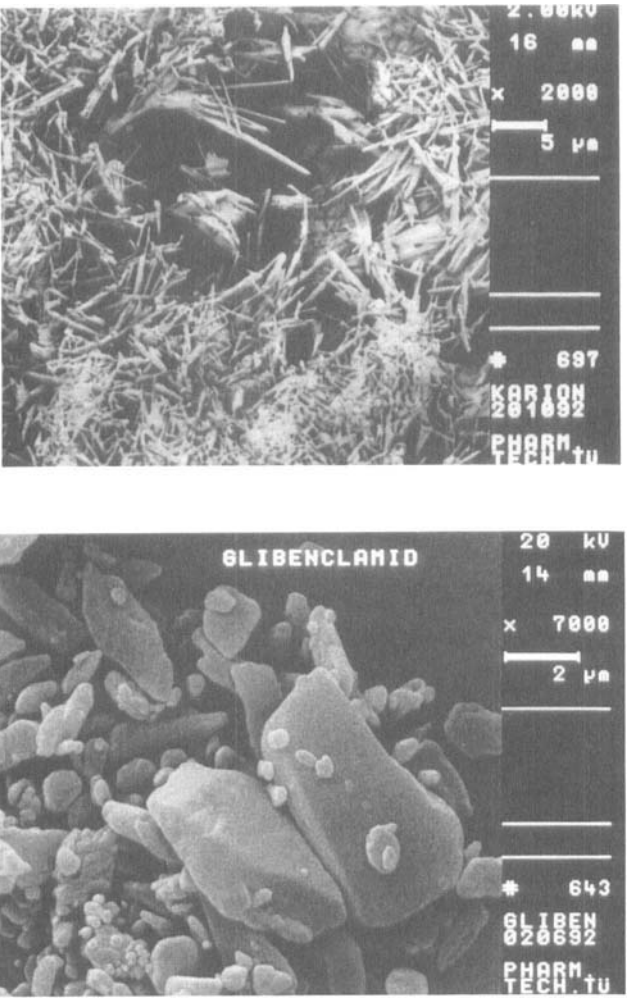


FIGURE 4. Continued

According to Egermann (22) reagglomeration can be hindered by sieving an interactive preblend of drug and excipient instead of the sole drug, as cohesive forces between drug particles then also have to compete adhesion from the coarse carrier granules. To ensure a homogeneous blend a limitation of the maximum mass of drug agglomerates (m_{max}) of 5 percent of the drug concentration per unit was suggested as sufficient. Supposing a spherical shape and an agglomerate density (ρ_{Agg}) of 0.5 g/cm^3, the corresponding sieve size (d) can be calculated

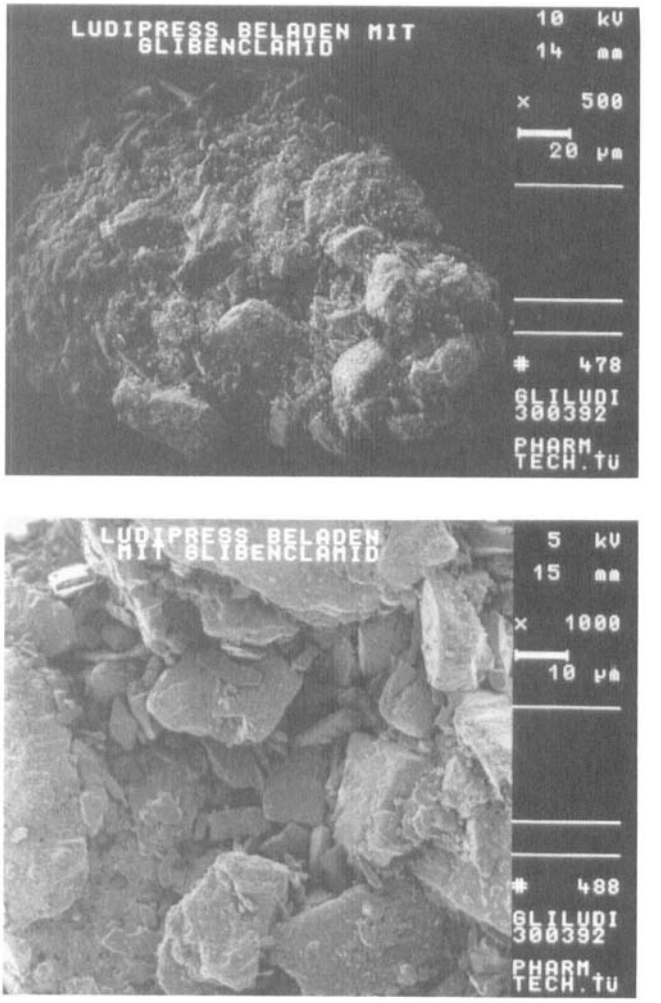
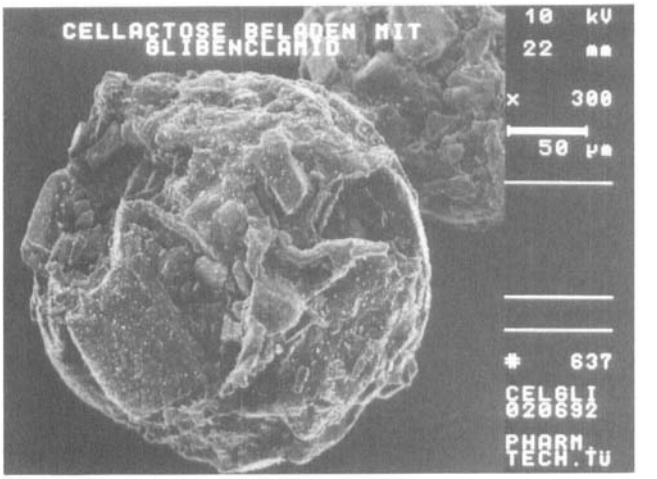


FIGURE 5/1:
Micrographs of carrier materials (fraction 125-500 µm) loaded with glibenclamide after air jet sifting. **A:** Ludipress, magnification: x500. **B:** Ludipress, magnification: x1000. **C:** Cellactose, magnification x300. **D:** Cellactose, magnification x3000.

C



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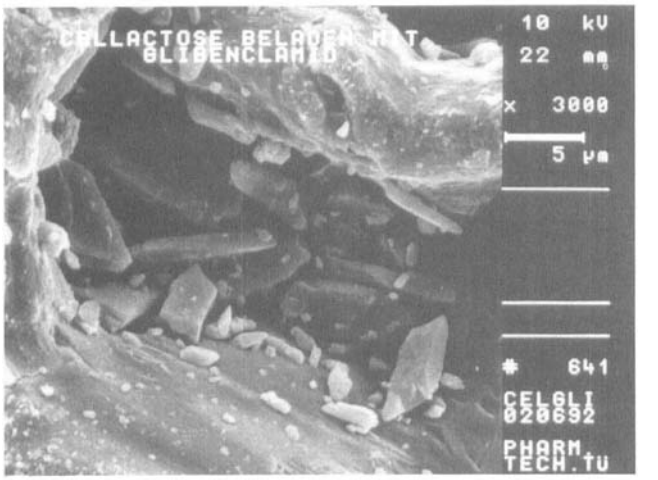


FIGURE 5/1. Continued

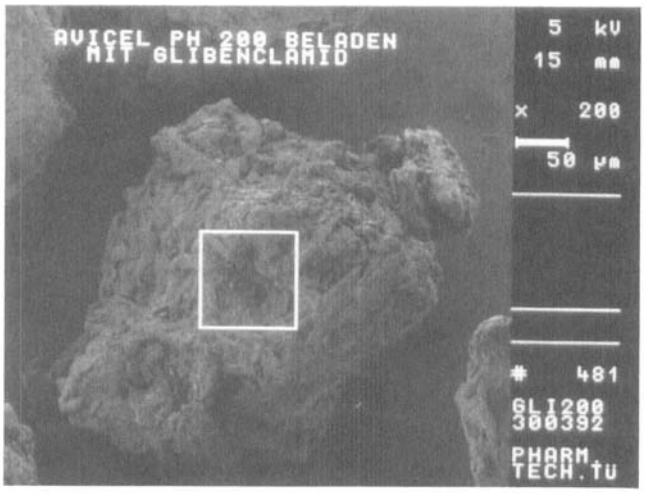
applying Egermann's equation (22):

$$d = \sqrt[3]{\frac{m_{max} * 6}{\rho_{Agg} * \pi}}$$

m_{max} = 0,05 * mass of drug per dosage unit

According to this formula a 694 µm-sieve should be adequate to prepare drug/carrier blends containing 1.75 mg glibenclamide per unit. To ensure suffi-

E



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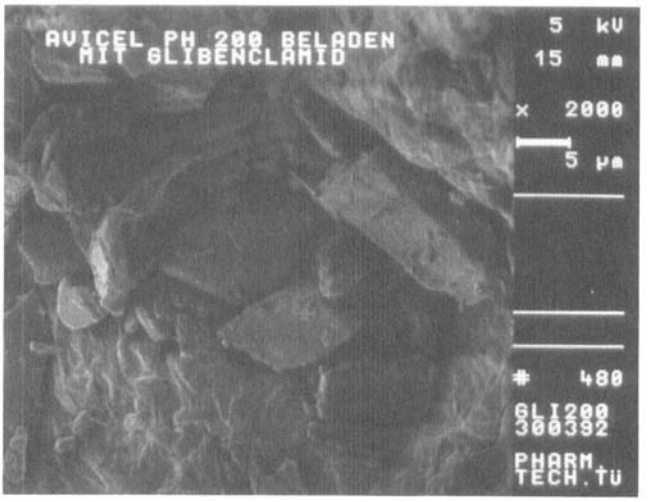
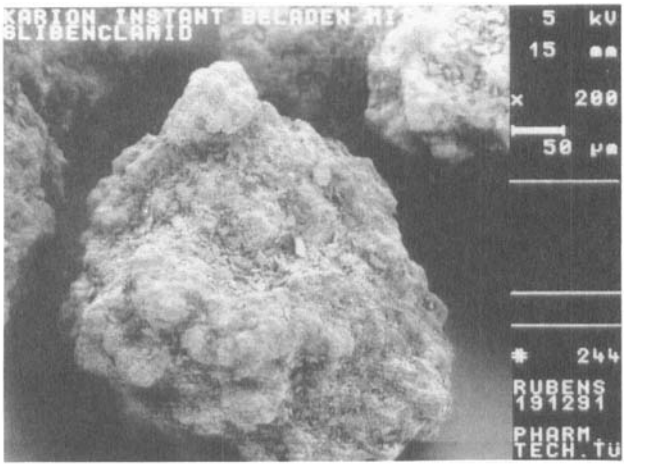


FIGURE 5/2:
E: Avicel PH 200, magnification x200. **F:** Avicel PH 200, magnification x2000. **G:** Karion Instant, magnification x200. **H:** Karion Instant, magnification x1000.



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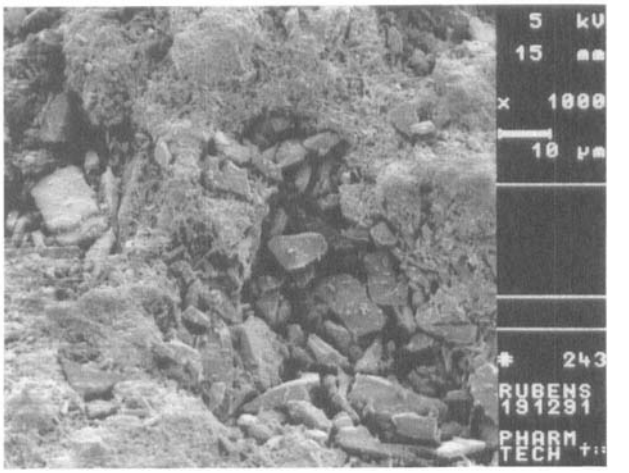

H

FIGURE 5/2. Continued

cient size reduction of drug agglomerates a 500 µm sieve was used for all blends as depicted in FIGURE 1. The reagglomeration of glibenclamide particles was checked by sieving the blends again after blending in the Turbula mixer. In 16 blends no reagglomerates could be detected.

The powder blend homogeneity was evaluated by determining the coefficient of variation of 5 samples per blend before and after air jet sifting respectively. As previously reported by Steffens (23) and Staniforth (24), it is

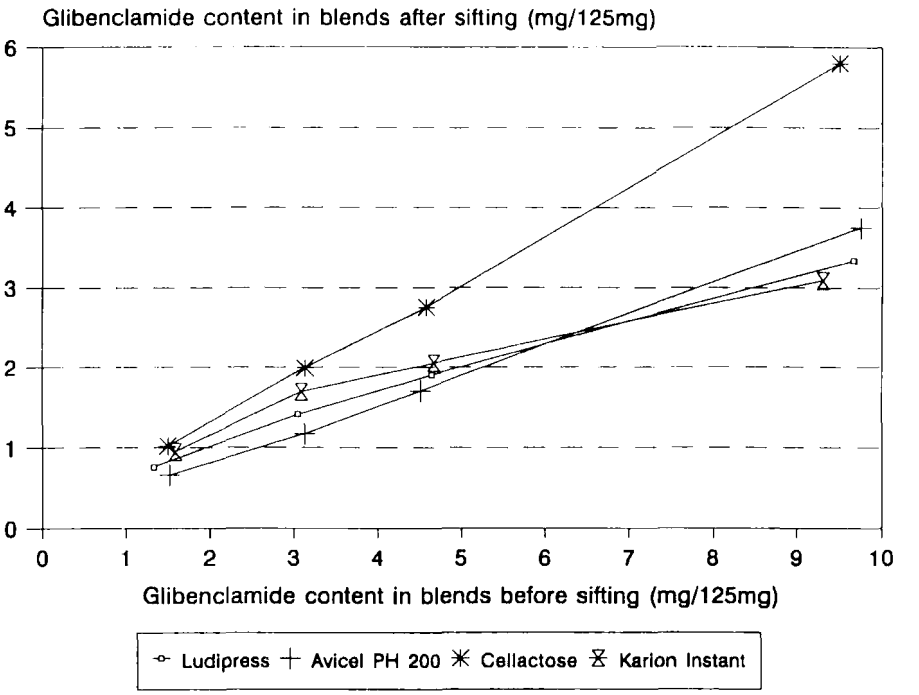

FIGURE 6:
Adhesion of glibenclamide to carrier materials.

possible to obtain a sufficient degree of homogeneity in direct compression of low dosed tablets by using coarse carrier materials. By simply blending, micronized drug particles are forced to adhere to the surface of excipient granules. This interaction does not necessarily yield order as a multi-layer adhesion takes place before mono-layer adhesion is completed (see FIGURE 5). Adhesion is fundamentally a mechanism of interaction, but not of order, it stabilizes the degree of *disorder* obtained in a blend by impeding segregation of the micronized drug particles from coarse carrier granules. Therefore, the degree of homogeneity of a blend is limited by the random mixture of the constituents.

Calculation of the coefficient of variation for interactive binary random mixes was carried out applying Johnson's equation (6) in the extended form by Egermann (25).

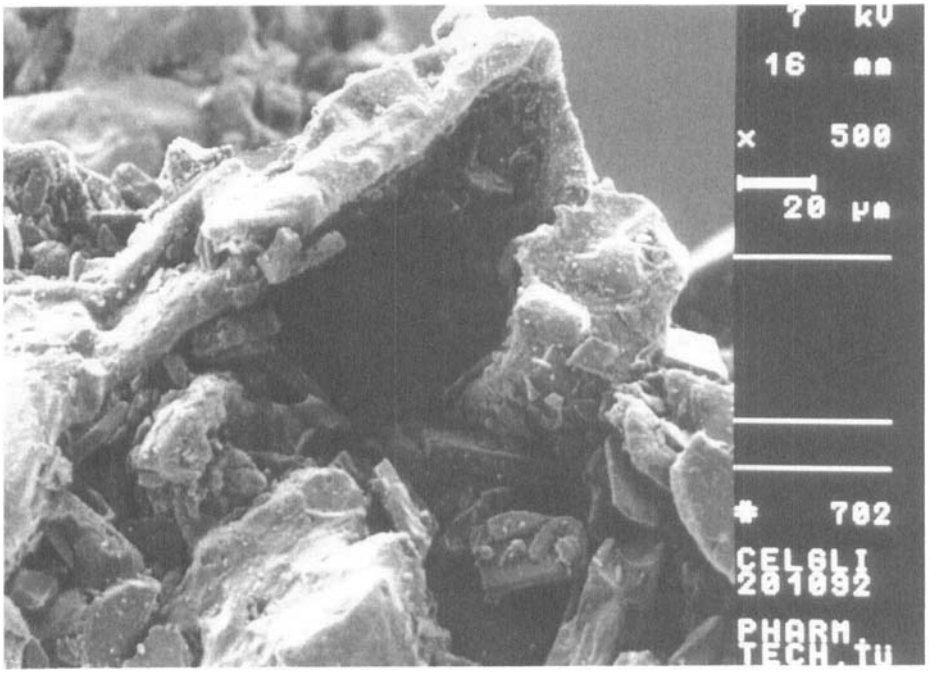

FIGURE 7A:
Intraparticulate reagglomeration of glibenclamide in Cellactose cavities, magnification x500.

FIGURE 7B:
Inverted picture of FIGURE 7A.

$$\sigma_{R\%x} = 100 * \sqrt{\frac{\overline{m}_x}{G}} \qquad \text{(I)}$$

$\sigma_{R\%x}$: coefficient of variation of the drug content per sample of the random mixture (%)

$\overline{m}_x$ volume-weighted mean particle weight (mg)
= mean particle volume $\overline{v}$ * particle density ρ (density of glibenclamide =1.36 g/cm^3)

G : mean weight of drug content per sample (mg)

Mean particle volume $\overline{v}$ was calculated by equation II.

$$\overline{v} = \frac{d_v^3 * \pi}{6} \qquad \text{(II)}$$

d_V : volume-weighted mean diameter of glibenclamide particles (d_{50}-value = 6.07 μμm as depicted in Table 1)

Corresponding values are depicted in Table 2. Calculated coefficients of variation were between 0.013 and 0.030 percent, a degree of homogeneity which cannot be quantified by common analytical methods. The coefficient of variation for blends before air jet sifting was lowest for Karion Instant blends and approx. 1-2 percent for the other excipients. The deviating values for the 1.75 mg Ludipress and 3.50 mg Cellactose sample respectively might be caused by electrostatic charge during air jet sifting. Increasing amounts of glibenclamide decreased electrostatic charge of the blends. Homogeneity after air jet sifting was approx. at the same level for all excipients not exceeding 6 percent. This is remarkable as air jet sifting is normally used for the determination of particle size distribution of powders, thus representing a drastic method for the separation of particle size classes.

Tableting of glibenclamide.

Since blending and determination of homogeneity was carried out under artificial conditions, for example using carrier fractions between 125 and

TABLE 2
Coefficients of variation of glibenclamide-content

Carrier	Glibenclamide concentration (mg/125 mg)	Coefficient of variation (%)		
		before air jet sifting a)	after air jet sifting a)	random mixtures b)
Ludipress	1.75	4.67	4.36	0.030
	3.50	1.73	2.63	0.021
	5.00	0.46	2.92	0.018
	10.00	1.23	2.16	0.013
Cellactose	1.75	2.22	3.19	0.030
	3.50	3.59	5.99	0.021
	5.00	0.70	3.48	0.018
	10.00	0.78	1.29	0.013
Avicel PH 200	1.75	1.11	1.93	0.030
	3.50	2.02	3.90	0.021
	5.00	1.63	5.33	0.018
	10.00	0.95	2.53	0.013
Karion Instant	1.75	1.00	2.50	0.030
	3.50	0.97	1.15	0.021
	5.00	1.70	4.75	0.018
	10.00	0.60	2.46	0.013

a) values calculated with 5 samples per blend
b) values calculated by equation (I)

500 µm, tableting of glibenclamide was performed with unfractioned Cellactose and Ludipress respectively. Blends were prepared containing 1.75, 3.50, 5.00 and 10.00 mg at a tablet weight of 125 mg and a magnesium stearate concentration of 0.4 percent. The test to assess the content uniformity of glibenclamide tablets was carried out according to USP XXII with 10 tablets per lot. The corresponding

TABLE 3
Content uniformity of glibenclamide tablets according to USP XXII with 10 tablets

Excipient	Glibenclamide concentration (mg/tablet)		Coefficient of variation (%)
	Declaration	Mean	
Ludipress	1.75	1.83	1.00
	3.50	3.68	0.74
	5.00	4.96	1.11
	10.00	10.02	0.90
Cellactose	1.75	1.83	0.97
	3.50	3.48	0.88
	5.00	5.13	0.72
	10.00	10.11	0.74

Note: All tablets were within 85-115% of the declaration

values are depicted in Table 3. Tablets of all Ludipress and Cellactose samples were within the range of ±15 % from the mean. Coefficients of variation were approx. 1 percent, thus showing a homogeneity superior even to blends which were prepared with fractions between 125 and 500 μm.

To compare Cellactose and Ludipress as multipurpose excipients in direct compression, physical testing of the resulting tablets was undertaken. Within a compaction load range of approx. 60-550 MPa crushing strength (FIGURE 8) and disintegration time (FIGURE 9) of the compacts were determined. The values obtained correlated with the results previously reported in Part I. I.e.; a compaction pressure optimum at approx. 100 MPa with Ludipress and increasing tablet disintegration time for Cellactose compacts at mid range compression forces was observed.

For tablets containing 5 mg glibenclamide, dissolution rates were determined at 3 different compaction loads as depicted in FIGURE 10. As glibenclamide is not very soluble in water, dissolution rates were just 75 percent

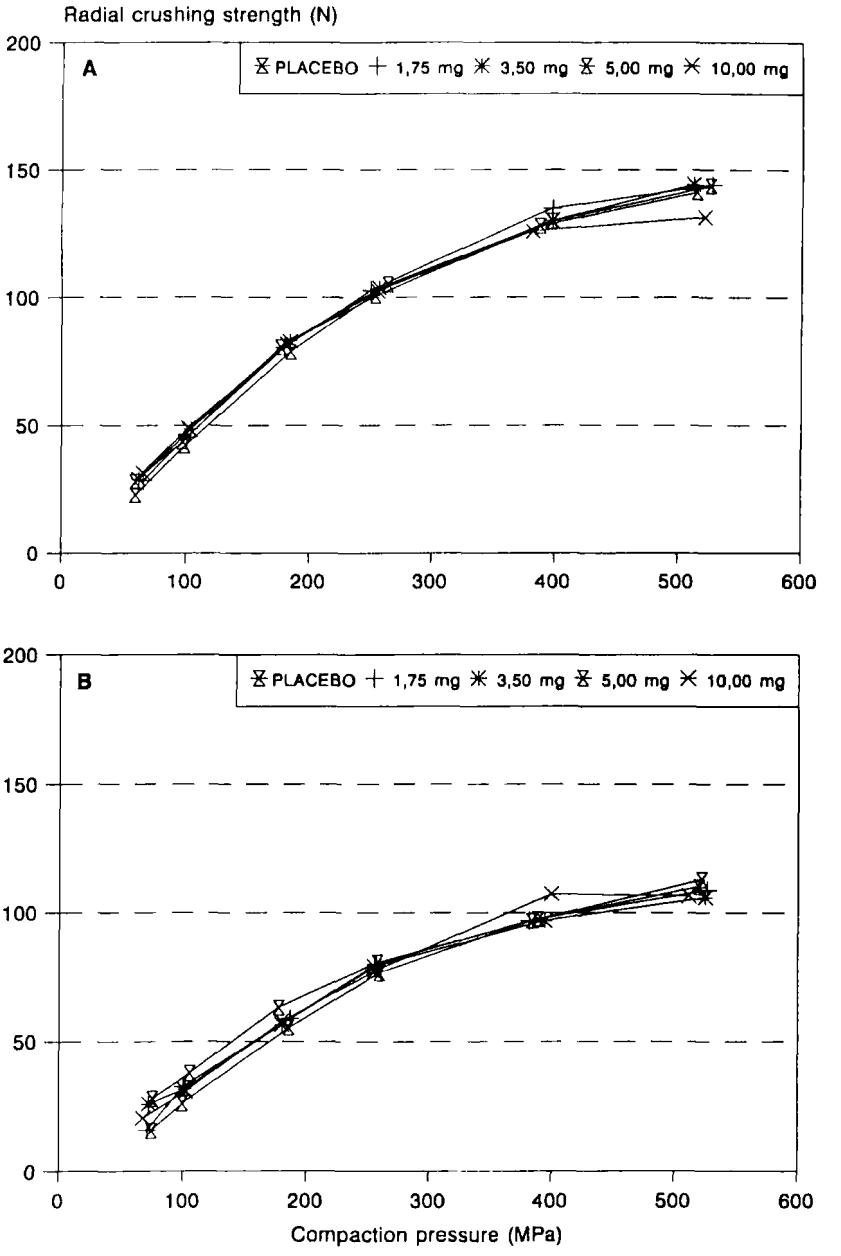

FIGURE 8
Radial crushing strength versus compaction pressure of Cellactose (**A**) and Ludipress (**B**) compacts with increasing amounts of glibenclamide.

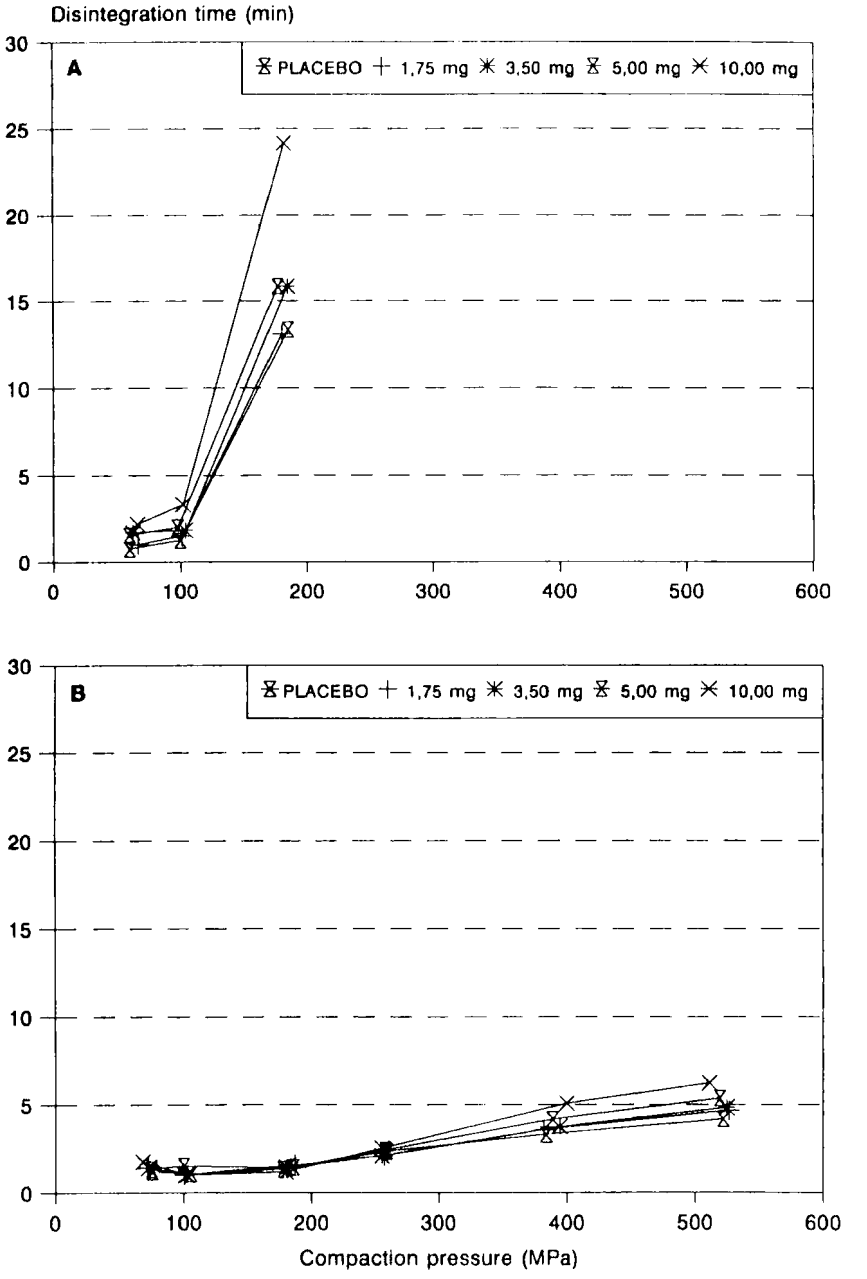

FIGURE 9
Disintegration time versus compaction pressure of Cellactose (**A**) and Ludipress (**B**) compacts with increasing amounts of glibenclamide.

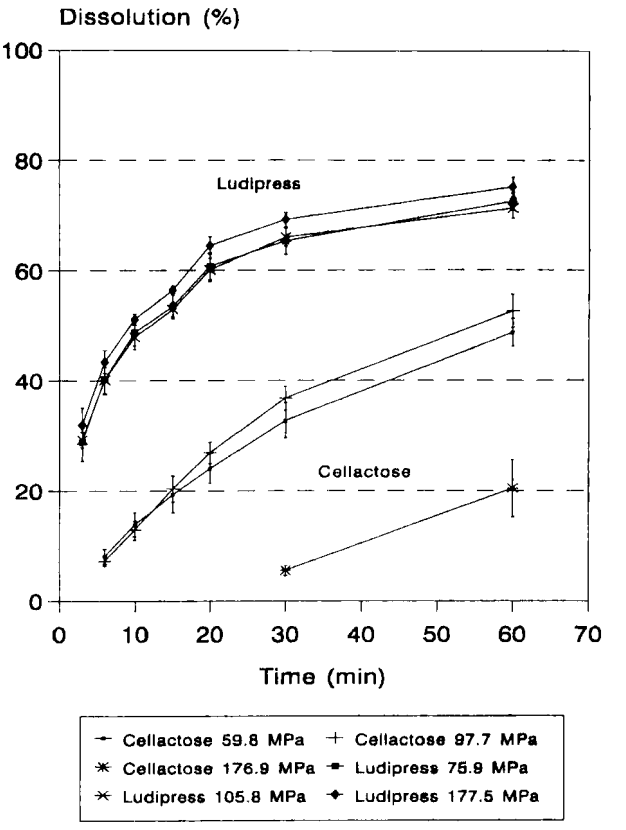

FIGURE 10
Dissolution of glibenclamide from Cellactose and Ludipress compacts at increasing compaction loads. Glibenclamide concentration is 5 mg / tablet.

after 60 minutes. In compressing more soluble drugs, Ludipress can be used without difficulties as recently reported by Senjkovic and co-workers (26).

Augmenting compaction pressures hardly altered the dissolution rates of Ludipress compacts, whereas the increase from 100 to 175 MPa had a deleterious effect on drug dissolution from Cellactose tablets. Also at lower compaction pressures dissolution was also significantly higher with Ludipress. This might be due to intraparticulate reagglomeration of glibenclamide particles in the voluminous cavities of Cellactose granules as depicted in FIGURE 7.

Apparently the high adhesion capacity of Cellactose causes more negative results. Therefore, in order to obtain a suitable carrier for low dosed

drugs a certain irregularity of the granule surface is favourable, but voluminous cavities should be avoided as fine drug particles may be entrapped, thus decreasing dissolution rates.

CONCLUSIONS

According to the investigations presented in Part I and this paper, Ludipress is an advantageous multipurpose excipient for direct compression. Due to the irregular surface of the granules, interactive blending with micronized drugs is possible leading to a high degree of homogeneity in tableting blends. Tablets of mid dosage range can also be manufactured with Ludipress at moderate compaction loads exhibiting a disintegration time optimum and almost compaction load independent dissolution rates, whilst increasing compaction loads had a negative effect on glibenclamide dissolution from Cellactose compacts. Therefore, in order to obtain disintegration and dissolution qualities of Ludipress tablets the addition of disintegrants would be necessary for compacts prepared with Cellactose as a sole excipient besides the lubricant.

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