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RESEARCH PAPER

Formulation and Development of Tablets Based on Ludipress and Scale-Up from Laboratory to Production Scale

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ABSTRACT

In spite of the wealth of experience available in the pharmaceutical industry, tablet formulations are still largely developed on an empirical basis, and the scale-up from laboratory to production is a time-consuming and costly process. Using Ludipress® greatly simplifies formulation development and the manufacturing process because only the active ingredient Ludipress and a lubricant need to be mixed briefly before being compressed into tablets. The studies described here were designed to investigate the scale-up of Ludipress-based formulations from laboratory to production scale, and to predict changes in tablet properties due to changes in format, compaction pressure, and the use of different tablet presses. It was found that the tensile strength of tablets made of Ludipress increased linearly with compaction pressures up to 300 MPa. It was also independent of the geometry of the tablets (diameter, thickness, shape). It is therefore possible to give an equation with which the compaction pressure required to achieve a given hardness can be calculated for a given tablet form. The equation has to be modified slightly to convert from a single-punch press to a rotary tableting machine. Tablets produced in the rotary machine at the same pressure have a slightly higher tensile strength. The rate of increase in pressure, and therefore the throughput, has no effect on the tensile strength of Ludipress tablets. It is thought that a certain minimum dwell time is responsible for this difference. The production of tablets based on Ludipress can be scaled up from one rotary press to another without problem if the powder mixtures are prepared with the same mixing energy. The tensile strength curve determined for tablets made with Ludi-

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press alone can also be applied to tablets with a small quantity (<10%) of an active ingredient.
Key Words: *Compaction pressure; Direct compression; Ludipress; Scale-up; Tablet geometry; Tensile strength.*

INTRODUCTION

In direct compression, the demands made of the tablet press and of the product to be made into tablets are particularly high. A modern direct compression excipient therefore must have a wide range of properties. The main properties required are good flowability, the ability to form interactive mixtures (i.e., low tendency to segregate), low hygroscopicity, low dust, and good compressibility (1). Good compressibility means that the product must form tablets that are hard, have low friability, and are stable in storage after being compressed with the compaction pressures typically used in the pharmaceutical industry. Ludipress is a multipurpose excipient based on lactose, Kollidon 30, and Kollidon CL (Table 1) (2). The properties of the powder and its compaction properties have already been investigated by Schmidt and Rubensdörfer (3).

In spite of intensive research work, tablet formulations today are still largely developed on an empirical basis and scaled up from laboratory to production scale in a time-consuming and costly process. Ludipress simplifies the development of formulations because usually only three components are required: active ingredient, Ludipress, and a lubricant (4). The technical literature also contains many references to the behavior of materials based on lactose in tableting (5–12).

The objective of the studies was to determine whether the tablet properties, mainly the hardness and tensile strength (13), can be calculated from such data as the compaction pressure and the dimensions of the tablet (14–21). This would further simplify the development of formulations for production. Many drugs are sold in different dosages. Direct compression offers the special advantage that one and the same formulation can be used for different dosages by varying the weight and format of the tablets. This makes it possible to reduce the amount of validation work and to ensure bioequivalence. Initial trials were conducted with tablets of pure Ludipress. Subsequently, it was determined whether tablets with a low drug dosage can also be produced under similar conditions. We chose glibenclamide and hydrochlorothiazide as the drugs to be added in low dosages.

An additional question was the scale-up behavior of tablets based on Ludipress. The suitability of laboratory formulations for full-scale production was determined using single-punch and rotary tablet presses. So far, there are no in-depth studies in the literature on this wide-ranging subject.

Table 1

Composition of Ludipress

Component	Concentration (%)	Function
α-Lactose monohydrate	93.0 ± 2.0	Filler
Kollidon 30	3.5 ± 0.5	Binder
Kollidon CL	3.5 ± 0.5	Disintegrant

EXPERIMENTAL

Materials

The following ingredients were used: Ludipress, batches 86-3111, 67-0457, and 77-0456, BASF AG, Ludwigshafen, Germany; glibenclamide, batches 9406001/01, 9406006/02, and 9504005/02, Arzneimittelwerk Dresden GmbH, 01445 Radebeul, Germany; magnesium stearate, batch MF 1930482, Bärlocher Company, Munich, Germany; and hydrochlorothiazide, batch 1132044, Chemag (Frankfurt, Germany).

Methods and Apparatus

Product Characterization

The following physical properties of the Ludipress used in the studies were determined:

1. True density, using an AccuPyk 1330 (Micromeritics, Mömchemgladbach, Germany)
2. Water, Karl Fischer method
3. Bulk density, DIN 53 912
4. Tap density, DIN 53 194, using an Engelsmann Type STAV 2003 tap density apparatus (Ludwigshafen, Germany)
5. Angle of repose, DIN 53916, using a Pfrengle funnel (H.W. Schmidt, Mainz, Germany)
6. Particle size distribution, using an Engelsmann JEL 200/80 classifier; the fines were also determined in an Alpine A 200 L-S air-jet classifier

The sieve analysis was evaluated by the method of Rosin, Rammler, Sperling, and Bennett (RRSB), using the formula

$$R = 100 \cdot e^{-(d/d')^n}$$

where R is the retained fraction, d is the particle size, d' is the mean particle size, and n is the gradient of the curve (width of the distribution).

For comparison, the Ludipress was also measured by Fraunhofer diffraction in a Malvern Mastersizer X (Malvern Instruments, Herrenberg, Germany). The powder injection equipment was used.

Formulations and Production of the Direct Compression Mixtures

The powder mixture used in the single-punch press consisted of Ludipress with 0.5% magnesium stearate that had previously been passed through a 500-µm sieve. These were mixed in a 500-ml glass bottle in an Engelsmann tumbler mixer for 10 min at 29 min^{-1}. For the laboratory rotary tableting machine, the Ludipress and magnesium stearate were mixed in a T 2 C Turbula mixer (Willy A. Bachofen AG, Maschinenfabrik, Basel, Switzerland) at 42 min^{-1} for 10 min. The large quantity of tableting powder required for the production-scale rotary machine was prepared in a V 50 Diosna mixer (Dierks and Sons, Osnabrück, Germany) using different mixing times.

Tableting

The tablets were produced on an instrumented Korsch EK 0 single-punch tablet press (Korsch, Berlin, Germany). The forces in the upper and lower punches were measured with strain gauges applied to the punch holders, while the displacement was measured inductively. The signals were amplified with 5-kHz carrier frequency amplifiers (Hottinger KWS 3072, HBM Meßtechnik, Darmstadt, Germany). The results were recorded using a National Instruments AT MIO 16 AD converter card (National Instruments, Munich, Germany). The characteristic values discussed below were calculated from these values. The single-punch press used achieves outputs of 9–50 tablets per min. A Korsch PH 106 laboratory rotary tableting press with CRS (Compression Research System) instrumentation and a small Kilian LX 20 production-scale rotary tablet press (Kilian, Köln, Germany) were used for the scaling-up experiments. The laboratory rotary tablet press achieves its highest output of 540 tablets/min at a speed of 90 rpm. The compaction and ejection forces of the upper and lower punches and the speed of the die table were measured during tableting. Outputs of 600–1800 tablets per min were achieved with the production-scale rotary tablet press.

The compaction pressure was increased in steps up to the highest pressure commonly used in production of 300 MPa. In addition, tableting speed and the output also were varied. The same rates of increase in pressure were achieved in all the presses.

Assessment of the Tablets and of the Tableting Process

The physical characteristics of the tablets (weight, height, diameter), as well as the hardness, were determined with the aid of a Pharmatest Apparatebau type WHT-1 automatic tablet tester (Hainburg, Germany).

A program developed at BASF AG was used to calculate the characteristic data that describe the compression behavior from the force and displacement curves of the upper and lower punches and the geometric dimensions of the tablet.

The disintegration time of the tablets was determined with a Krämer type DES-4AS disintegration tester (Krämer, Darmstadt, Germany), and the friability was determined with an Erweka type TAR-20 friabilator (Erweka, Heusenstamm, Germany).

A Pharmatest PTWS paddle-type dissolution tester filled with pH 7.4 phosphate buffer was used to test the glibenclamide tablets at 75 rpm, and a rotating-basket-type dissolution tester filled with 0.1 N HCl was used to test the hydrochlorothiazide tablets at 150 rpm.

Tablet Geometry

The tablet geometry can differ in terms of diameter, thickness, and shape. All the parameters were systematically varied, keeping the other two the same. Flat, flat beveled-edge, and convex tablets (Fig. 1) were tested. The capsule form was not tested.

Different tablet diameters, ranging from 6 mm to 12 mm, and thicknesses, ranging from 2 mm to 5 mm, were used. Only beveled-edge and convex forms were made

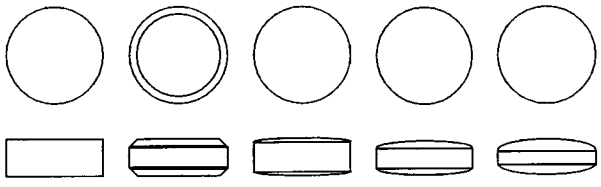

Figure 1. Tablet shapes (from left to right): flat; flat bevel edge; slightly convex; standard convex; for sugar coating.

in the rotary presses as the edges of flat tablets tend to crumble. The tablet mass was kept constant.

RESULTS AND DISCUSSION

Granulation and Tableting Properties of Ludipress

The product properties given in Table 2 show that Ludipress is a direct compression auxiliary with medium porosity and good flow properties. The product is not particularly sensitive to vibration, as can be seen by comparing the bulk and tap densities.

The particle size distribution of Ludipress (Fig. 2 and Table 3) and the low proportion of fines give it good flow properties. The mean particle size according to RRSB is 269 μm with a narrow distribution ($n = 2.59$), and the proportion of fines (i.e., the proportion <50 μm) is 4.0%. The proportion of coarse particles (>600 μm) is also low, 0.9%. The mean particle sizes determined in the classification column and by Fraunhofer diffraction agree surprisingly well.

In compaction at 155 MPa pressure (Table 4), Ludipress shows medium plasticity at 84% and also medium resistance to compaction at 5.7. The individual granules are relatively robust and offer resistance to the punches, although they are destroyed and densely packed at higher pressures. The elastic recovery of the tablets is small, with the result that their structure is not weakened. The residual porosity of about 10.4% ensures rapid disintegration as enough water can still penetrate the tablet.

For the calculation of the tensile strength of convex tablets, an empirically derived equation was used.

Influence of Shape

Figures 3 to 5 show the tensile strength σ_t of the tablets as a function of the compaction pressure p for tablets of different diameters (Fig. 3), different thicknesses (Fig. 4), and different shapes (Fig. 5) made with Ludipress on the single-punch press. In these tests, only one of the parameters was varied in each case.

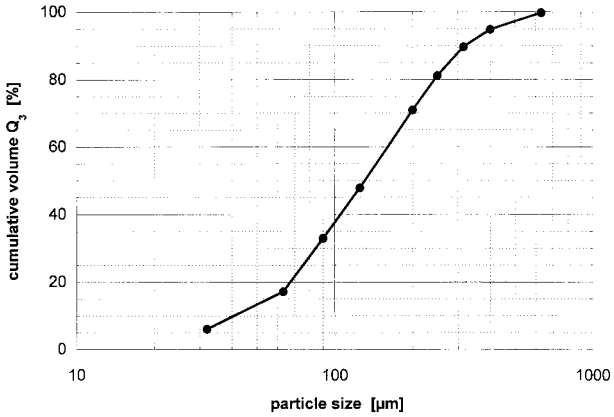

Figure 2. Particle size distribution of Ludipress determined by sieve analysis.

In the pressure range studied, the tensile strength increased linearly with the compaction pressure. The minimum porosity (Fig. 6) was almost reached at the highest pressure (300 MPa) commonly used in production. Figures 3 to 5 show clearly that the tensile strength profile does not depend on the diameter, thickness, or outer form. It can be described for all shapes and sizes of tablets by the following formula:

$$\sigma_t = 0.012 \times p - 0.4 \qquad \text{single-punch press}$$

in which p and σ_t are measured in MPa. This equation can be used to calculate the compaction pressure required to achieve a particular tensile strength or hardness.

However, the tests did show that tablets with a small radius of curvature (normal convex or cores for sugar coating) and a small tablet thickness (<2 mm) gave lower tensile strength values. The small thickness results in overcompression around the circumference of these tablets, which reduces their overall tensile strength. To avoid this, thicknesses greater than 2 mm were used for these forms of tablet.

Table 2

Physical Properties of Ludipress

Product	True Density (g/ml)	Moisture Content (%)	Bulk Density (g/ml)	Tap Density (g/ml)	Ratio of Tap Density to True Density = 1 Porosity	Angle of Repose (Degrees)
Ludipress	1.51	5.5	0.53	0.63	0.42	29.6

Table 3

Particle Size Distribution of Ludipress

Fraunhofer Diffraction		Classification Column Evaluation According to RRSB		Air-Jet Classification	
D (4.3) (μm)	250	*d′* (μm)	269	Fines (% <50 μm)	4.0
d (0.5) (μm)	223	*n*	2.59		
d (0.1) (μm)	99	Regression coefficient	0.9905		
d (0.9) (μm)	432	Coarse fraction >600 μm (%)	0.9		
Span	1.5				

If it is possible to guarantee adequate thickness, the superficial form chosen for production depends only on other requirements, such as a possible coating, the friability, or marketing strategies and consumer wishes.

Scale-Up from Single-Punch to Rotary Press

Rotary presses are usually used in commercial tablet production. In the past, it has been found that the change from single-punch to rotary press presents considerable difficulties, necessitating extensive testing (22). The first tablets were therefore produced on the Korsch PH 106 laboratory rotary tablet press at relatively low rates. Figure 7 shows the hardness profile of the tablets made in the rotary press. Here, too, the tensile strength increased linearly with the compaction pressure. It can be seen clearly that the speed of the rotary press and, therefore, the output had no effect on the tensile strength of the tablets.

Figure 8 shows the tensile strength profiles of Ludipress tablets made in the single-punch press and the rotary press. With the same compaction pressure, the rotary press gave tablets with higher tensile strength than the single-punch press. The difference in tensile strength was particularly marked at very high compaction pressures. This requires an adjustment of the constants in the design equation:

$$\sigma_t = 0.012 \times p - 0.4 \qquad \text{single-punch press}$$

$$\sigma_t = 0.018 \times p - 0.3 \qquad \text{rotary press}$$

This difference in the hardness profiles of tablets obtained with the different machines cannot be attributed to differences in rates of increase in pressure.

Figure 9 shows that the tensile strength of Ludipress tablets was independent of the rate of increase in compaction pressure. It was always higher for tablets produced on rotary machines than on single-punch presses at the same compaction pressure and rate of pressure increase. The great difference between single-punch presses and rotary machines is that, in single-punch presses, the tablet is exposed to the highest pressure for an extremely short time. As Ludipress has pronounced plastic properties, the difference in dwell time could explain why rotary machines produce harder tablets. The material has more time for plastic flow, and the particles can bond more strongly (23,24).

Effect of Additives (Drugs)

Tablets were prepared with two active ingredients to determine whether the results obtained with the excipient alone can be applied to low-dose active tablets. Ludipress tablets were prepared with glibenclamide and hydrochlorothiazide on the Korsch PH 106 laboratory rotary tablet press. Their tensile strength profiles are plotted together with that of pure Ludipress tablets in Fig. 10.

As can be seen, the tensile strength profile obtained with pure Ludipress tablets can be applied approximately to low-dose active tablets. Here, too, the tensile strength of the tablets was independent of the speed of the rotary tablet press (i.e., throughput). The tensile strength values of the active tablets are slightly lower than those of the pure Ludipress tablets, but the difference is only small at the dosages tested. The difference increases with the dosage, amounting to approximately 0.5 MPa for 2.5% glibenclamide and approximately 1 MPa for 6.25% hydrochlorothiazide at a compaction pressure of 350 MPa in each case. Thus, trials with pure Ludipress can be extrapolated to provide the mechanical properties of low-dose active tablets.

Table 5 shows that the hydrochlorothiazide and glibenclamide tablets also have good values for other properties. Their friability was almost zero; the relative stand-

Table 4

Data Characterizing the Compaction Process (Evaluated with BASF Software)

p	Compaction pressure $p = \left(\frac{F_u + F_L}{2} \Big/ \pi \cdot \frac{D^2}{4} \right)$	155 MPa
F_u/F_L	Ratio of upper and lower punch forces (measure of friction losses in compaction)	93.1%
k value	Resistance to compaction $k = \frac{\lg p_1 - \lg p_0}{\lg \rho_1 - \lg \rho_0}$	5.7
E_p	Plastic energy: Energy absorbed in the permanent deformation of the tablet	11.02 J
E_e	Elastic energy: Work that the tablet performs against the punch when it is withdrawn	2.09 J
E_{sp}	Specific tablet energy $E_{sp} = \frac{E_p}{m}$	22.1 J/g
Plasticity	Plasticity $= \frac{E_p}{(E_p + E_e)}$	84.1%
$\sigma_{tensile}$	Tensile strength flat tablets $\sigma_{tensile} = \frac{2 \cdot F_{failure}}{\pi \cdot D \cdot H}$ Tensile strength convex tablets $\sigma_{tensile} = \frac{2 \cdot F_{failure}}{\pi \cdot A_{cross\text{-}sectioned\ area}}$	3.06 MPa
$\rho_{apparent,\ wl}$	Apparent density, without load, average tablet mass divided by the volume	1.37 g/cm^3
$\rho_{apparent,\ ul}$	Apparent density under load, average tablet mass divided by the volume at maximum compaction pressure	1.40 g/cm^3
ε_{wL}	Porosity without load $\varepsilon_{wl} = 1 \frac{\rho_{apparent,\ wl}}{\rho_{solid}}$	10.4%
ε_{ul}	Porosity under load $\varepsilon_{ul} = 1 \frac{\rho_{apparent,\ ul}}{\rho_{solid}}$	8.3%

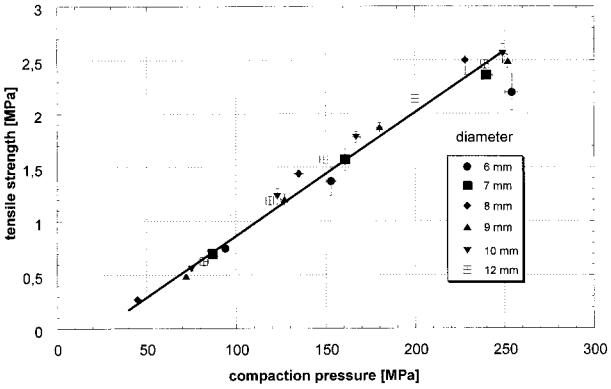

Figure 3. Tensile strength profile of Ludipress flat bevel-edge tablets 3.5 mm thick with different diameters.

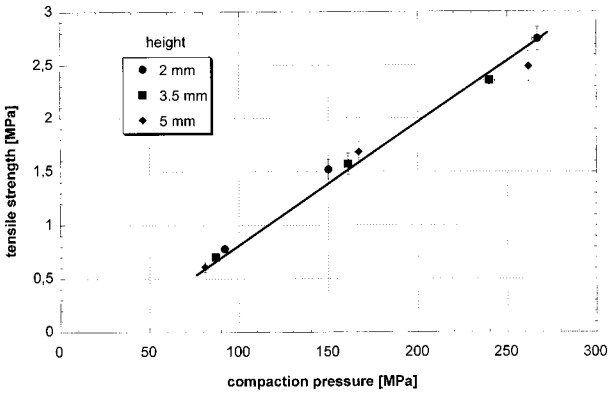

Figure 4. Tensile strength profile of Ludipress flat bevel-edge tablets 7 mm in diameter with different thicknesses.

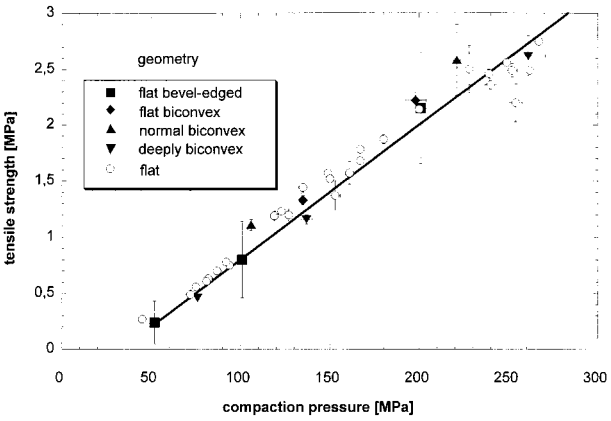

Figure 5. Tensile strength profile of Ludipress tablets of different shapes.

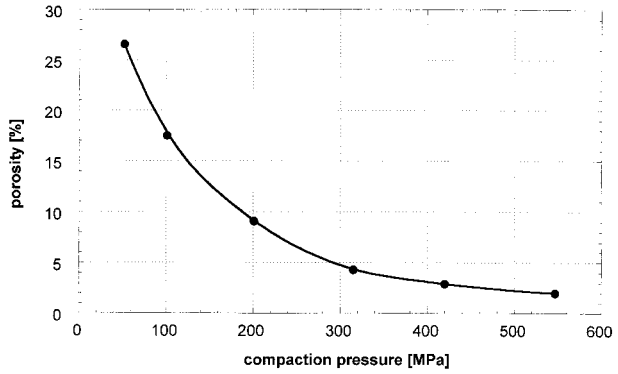

Figure 6. Porosity profile of Ludipress tablets.

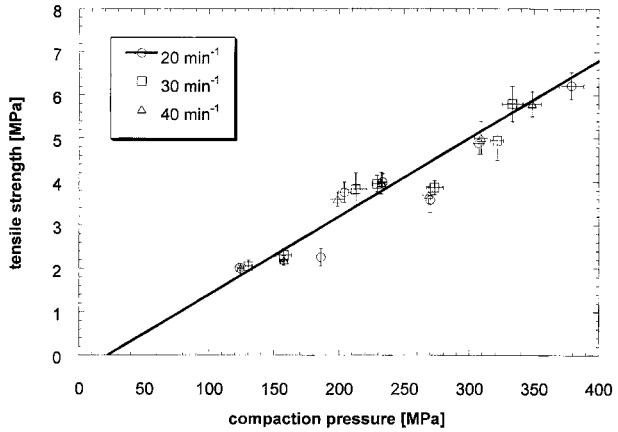

Figure 7. Tensile strength profile of rotary press operated at different speeds and with different punches.

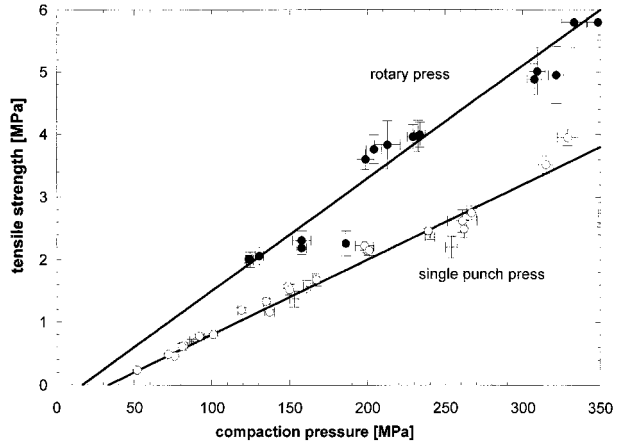

Figure 8. Tensile strength profile of Ludipress: comparison of single-punch press and rotary press.

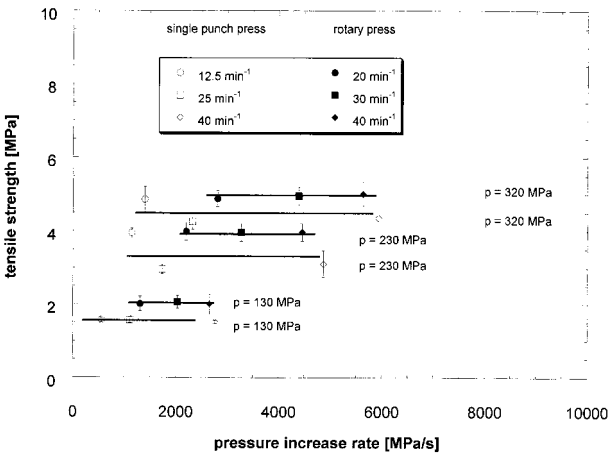

Figure 9. Tensile strength independent of compaction pressure for Ludipress, 8 mm diameter, flat bevel-edge tablets.

ard deviation for the weight was less than 1% and that of the content was approximately 3%; the disintegration time was 3 to 4 minutes; and drug release was rapid.

Scale-Up to Production Rotary Tablet Presses

To check how well the formulation can be scaled up for use in rotary presses with a higher output, the drug formulation of Ludipress plus 2.5% glibenclamide was also run on a Kilian LX 20 rotary tablet press with an output of 600 to 1800 tablets/min. Figure 11 shows the hardness profiles of the tablets produced on the Korsch PH 106 laboratory machine compared to the Kilian LX

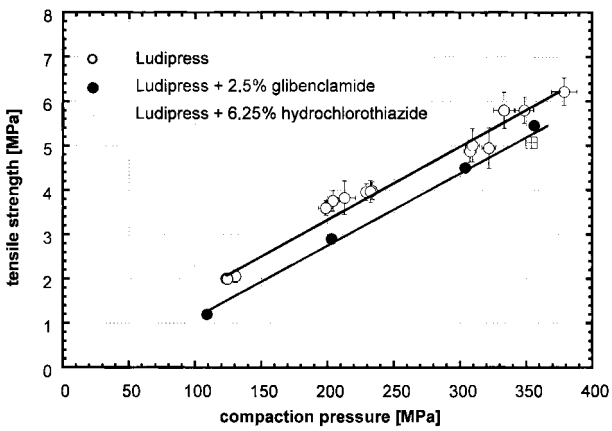

Figure 10. Tensile strength profiles of tablets made with the excipient alone and with low dosages of drugs for comparison.

Table 5

Properties of Glibenclamide and Hydrochlorothiazide 8-mm Diameter Tablets Made on the Korsch PH 106 Rotary Tableting Machine

	Hydrochorothiazide 12.5, Ludipress 186.5, Magnesium Stearate 1.0	Glibenclamide 5.0, Ludipress 194, Magnesium Stearate 1.0
Average weight (mg)	202.0	198.3
S rel (%)	0.7	0.9
Hardness (N)	175	187
Tensile strength (MPa)	5.07	5.46
Friability (%)	0.01	0.02
Content uniformity s rel. (%)	2.3	3.4
Disintegration in 0.1 N HCl (min:s)	3:18	3:46
Release after 30 min (%)	93.4	70.0

20 production machine. It must be noted, though, that the values determined for the tablets produced on the Kilian LX 20 only apply if the mixing time for the powder mixture in the Diosna mixer is very short (30 to 60 sec). The mixing energy is then similar to that developed by the Turbula mixer in preparing the powder mixture for the Korsch PH 106 laboratory rotary press. With longer mixing times (providing higher mixing energy), the tensile strength of the tablets decreases as the particles become too strongly coated with magnesium stearate and are no longer able to form intimate bonds (25). Thus, the proportion of magnesium stearate must be reduced if longer mixing times are used.

Again, the tensile strength proved independent of the tablet form and the compressing speed (i.e., throughput).

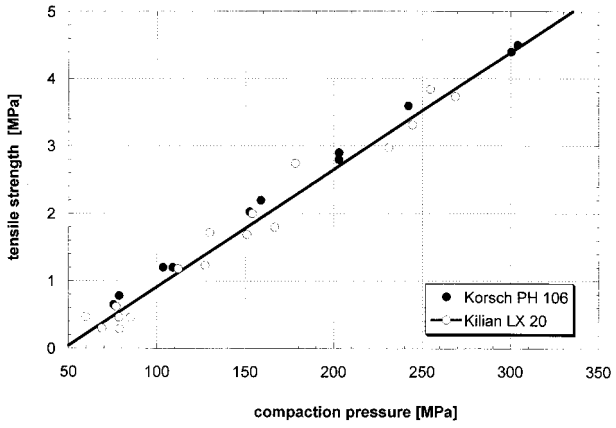

Figure 11. Scale-up from a laboratory rotary press (Korsch PH 106) with an output of 180 and 360 tablets/min to a production machine (Kilian LX 20) with outputs of 600, 1200, and 1800 tablets/min: tensile strength profile.

Thus, no problems are encountered in scaling up low-dose active tablets based on Ludipress from one rotary press to another as long as the powder mixtures are prepared in the same manner with the same mixing energy.

The effect of precompacting the tablets was not investigated. However, it must be expected that this would give slightly harder tablets.

SUMMARY

The development of tablet formulations and their transfer from laboratory to production scale frequently involves a high work load. However, the tests and results described in this report should help to make future tablet development easier. It was found that it is possible to calculate the tensile strength, and thus the hardness, of tablets made of pure Ludipress and formulations with low drug dosages directly from the compaction pressure.

Furthermore, as the tensile strength of the tablets depends only on compaction pressure and not on tablet form, it is possible to compare different tablet shapes. A comparison of tablets made on single-punch presses and on different size rotary presses indicates that it is possible to scale-up low-dose Ludipress formulations without difficulty. However, formulation mixing energies must remain constant at the different scales as it is well known that longer mixing using magnesium stearate reduces the tensile strength of tablets. Tablets produced on rotary presses are slightly harder than those made on single-punch presses. As the tensile strength of Ludipress tablets is independent of the rate of increase in compaction pressure, it is thought that this is attributable to dwell time under pressure, during which Ludipress undergoes plastic

distortion. It was also shown that tablet production rate had no effect on tablet properties. Overall, it was found that formulations with a low active ingredient dosage based on Ludipress are simple to develop, easy to put into production, and that they had tablet properties that could be predicted reliably.

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