

## PŮVODNÍ PRÁCE

**A study of the properties of tablets from coprocessed dry binders composed of  $\alpha$ -lactose monohydrate and different types of cellulose**

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## SUMMARY

**A study of the properties of tablets from coprocessed dry binders composed of  $\alpha$ -lactose monohydrate and different types of cellulose**

The paper evaluates the differences between the properties of tablets from two coprocessed dry binders based on  $\alpha$ -lactose monohydrate and cellulose, MicroceLac®100 and Cellactose®80. The substances differ in the type of contained cellulose; MicroceLac®100 contains 25% of microcrystalline cellulose, Cellactose®80, 25% of powdered cellulose. The properties under study included the tensile strength and disintegration time in dependence on compression force, addition of two concentrations of the lubricant sodium stearyl fumarate (Pruv) and a 50% addition of the active ingredients ascorbic acid and acetylsalicylic acid. Using one of the compression forces, the effect of Pruv and magnesium stearate on the above-mentioned properties were compared. In the compression forces of 6 and 8 kN the strength of the compacts from pure Cellactose®80 was lower than that of those from MicroceLac®100 both without and with the lubricant. The lubricant sensitivity of dry binders depended on compression force. Pruv decreased the strength of compacts less than magnesium stearate. The tablets from Cellactose®80 possessed a longer disintegration time than those from MicroceLac®100, excepting the tableting materials containing 0.4 Pruv with a compression force of 6 kN. Disintegration time was prolonged with the use of sodium stearyl fumarate and it was increased with compression force much more markedly in the case of Cellactose®80. In the presence of ascorbic acid, the strength of tablets was decreased in the case of both dry binders, but it was higher with MicroceLac100, disintegration time was very short and independent of the type of the dry binder. In the case of acetylsalicylic acid, the strength of tablets was higher with a lesser influence of the type of the dry binder, and disintegration time was longer and especially in the case of Cellactose®80 increased with increasing concentration of Pruv.

**Key words:** MicroceLac®100 – Cellactose®80 – sodium stearyl fumarate – magnesium stearate – ascorbic acid – acetylsalicylic acid – tensile strength of tablets – disintegration time of tablets

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## SOUHRN

**Studium vlastností tablet ze směsných suchých pojiv složených z  $\alpha$ -laktosy monohydrátu a různých typů celulosy**

V práci je hodnocen rozdíl mezi vlastnostmi tablet ze dvou směsných suchých pojiv na bázi  $\alpha$ -laktosy monohydrátu a celulosy, a to MicroceLacu®100 a Cellactosy®80. Látky se liší typem

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obsažené celulosy, v MicroceLacu®100 je 25 % mikrokrytalické celulosy, v Cellactose®80 25 % práškové celulosy. Studovanými vlastnostmi tablet byla pevnost a doba rozpadu v závislosti na lisovací síle, přidavku dvojí koncentrace mazadla stearylufumarátu sodného (Pruvu) a 50 % přidavku účinných látek kyseliny askorbové a kyseliny acetylsalicylové. Při jedné lisovací síle se porovnával také vliv Pruvu a stearanu hořečnatého na uvedené vlastnosti. Při lisovacích silách 6 a 8 kN byla pevnost tablet z čisté Cellactose®80 nižší než z MicroceLacu®100 bez i s mazadlem. Citlivost suchých pojiv na přídavek mazadla závisela na lisovací síle. Pruv snižoval pevnost tablet méně než stearan hořečnatý. Tablety z Cellactose®80 měly delší dobu rozpadu než z MicroceLacu®100, vyjma tablet s 0,4 % Pruvu při lisovací síle 6 kN. Doba rozpadu byla prodloužena stearylufumarátem sodným a rostla s lisovací silou a to mnohem výrazněji v případě Cellactose®80. V přítomnosti kyseliny askorbové se pevnost tablet snížila v případě obou suchých pojiv, ale vyšší byla s MicroceLacem®100, doba rozpadu byla velmi krátká a nezávislá na typu použitého suchého pojiva. V případě kyseliny acetylsalicylové byla pevnost tablet vyšší s menším vlivem typu suchého pojiva, doba rozpadu byla delší a především v případě Cellactose®80 rostla s rostoucí koncentrací Pruvu.

**Klíčová slova:** MicroceLac®100 – Cellactose®80 – stearylufumarát sodný – stearan hořečnatý – kyselina askorbová – kyselina acetylsalicylová – pevnost tablet v tahu – doba rozpadu tablet

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### Introduction

Derivatives of cellulose with  $\alpha$ -lactose monohydrate are a widely used combination of dry binders in the manufacture of tablets with the use of direct compression. This combination stresses advantageous properties of the individual substances and suppresses their negative characteristics. Cellulose is well-compressible and produces strong tablets with low abrasive wear, but due to their insolubility they disintegrate poorly in water. The compressibility of lactose is worse, but tablets disintegrate very quickly <sup>1)</sup>. In addition, this substance, in contrast to cellulose, is not sensitive to added lubricants, which may decrease tablet strength. This is due to the mechanism of compression, which is fragmentation, in contrast to plastic deformation of cellulose <sup>2)</sup>. Both substances are components of commercially produced dry binders Cellactose®80 and MicroceLac®100, which are coprocessed dry binders and differ only in the type of cellulose contained.

Cellactose®80 (further on referred to as Cellactose) is a spray-dried agglomerated product, consisting of 75% of  $\alpha$ -lactose monohydrate and 25% of cellulose powder. Spray-drying makes it possible to achieve the optimal size of particles and their uniform distribution, which very positively influences the flowability of the material. The flow properties and compressibility of Cellactose are thus better than in the case of a mixture of agglomerated lactose with powdered cellulose alone <sup>3)</sup>. The substance possesses excellent binding capacity and produces strong tablets. Good compressibility is attributed to the action of fragmented lactose connected with plastic deformability of cellulose <sup>1)</sup>. Good disintegration properties are due to the presence of cellulose fibres in macroporous particles. As cellulose is covered with lactose, moisture sorption is much lower than in microcrystalline cellulose alone <sup>4)</sup>. Tablets

from Cellactose possess higher strength, lower abrasive wear, and a shorter disintegration period than those from the mixtures of lactose and cellulose <sup>5)</sup>. Cellactose is not markedly sensitive to the added lubricant, as it would be in the case of the mechanism of compression with the use of purely plastic deformation <sup>2)</sup>.

In a comparative evaluation of directly compressible substances Cellactose,  $\alpha$ -lactose monohydrate, and a mixture of 25% microcrystalline cellulose with 75% calcium phosphate dihydrate, Cellactose shows excellent compressible properties and yields tablets of the best prescribed quality. Tablet strength is not diminished with increasing compression rate <sup>1)</sup>. Tablets from Cellactose obtained with the use of a compression pressure which considerably eliminates macropores possess better properties, but much worse disintegration than tablets from the mixtures of the same composition, particle size, and right density. Their tensile strength and disintegration time are rapidly decreased with lowering of compression pressure <sup>6)</sup>.

MicroceLac®100 is a substance similar to Cellactose®80 with one difference – instead of powdered cellulose it contains microcrystalline cellulose. Due to the spray-drying technology, during which porous spherical agglomerates are formed, the flowability of the substance is excellent again. It is also well compressible and a constant ratio of lactose and microcrystalline cellulose results in constant strength of tablets. The compressibility of MicroceLac is better than that of a physical mixture of spray-dried lactose and microcrystalline 102 type cellulose, the tablets possessing better mass uniformity. The substance exerts reliable compression properties at different compression rates and an increased dilution potential for active ingredients <sup>7)</sup>. Sensitivity to added lubricants is again suppressed by high representation of fragmenting lactose.

MicroceLac®100 was compared with physical

mixtures of three different lactoses with microcrystalline cellulose in the formulation of tablets with folic acid. The study resulted in the design of a tablet composed of folic acid with MicroceLac as the dry binder, which improved the functionality of the contained ingredient, and showed better flow properties and binding properties. In addition, good adhesiveness of folic acid to MicroceLac particles decreased demixing and segregation <sup>8)</sup>.

The present paper aimed to evaluate the differences between the tableting properties of MicroceLac<sup>®</sup>100 and Cellactose<sup>®</sup>80. The properties under study included the tensile strength and disintegration time of compacts in dependence on compression force, addition of two different concentrations sodium stearyl fumarate, magnesium stearate, and 50% addition of model active ingredients ascorbic acid and acetylsalicylic acid.

## EXPERIMENTAL

### Materials

*MicroceLac<sup>®</sup>100* – 75%  $\alpha$ -lactose monohydrate and 25% microcrystalline cellulose (Meggler GmbH, Wasserburg, Germany); particle size distribution: max. 15% < 32  $\mu$ m, 45–70% < 160  $\mu$ m, at least 90% < 250  $\mu$ m; *Cellactose<sup>®</sup>80* – 75%  $\alpha$ -lactose monohydrate and 25% cellulose powder (Meggler GmbH, Wasserburg, Germany); particle size distribution: max. 20% < 32  $\mu$ m, 35–65% < 160  $\mu$ m, at least 80% < 250  $\mu$ m; *sodium stearyl fumarate* – *Pruv<sup>®</sup>* (J. Rettenmaier & Söhne GmbH+Co, Rosenberg, Germany); specific surface area: 1.2133 m<sup>2</sup>/g; *magnesium stearate* (Acros Organics, New Jersey, USA); specific surface area: 1.6083 m<sup>2</sup>/g; *ascorbic acid* (Northeast General Pharmaceutical Factory, Shenyang, China); *acetylsalicylic acid* (Merck KGaA, Darmstadt, Germany).

### Preparation of tableting materials and tablets

A list of tableting materials evaluated in the study:

- MicroceLac<sup>®</sup>100, Cellactose<sup>®</sup>80
- MicroceLac<sup>®</sup>100 with 0.4% sodium stearyl fumarate, Cellactose<sup>®</sup>80 with 0.4% sodium stearyl fumarate
- MicroceLac<sup>®</sup>100 with 0.8% sodium stearyl fumarate, Cellactose<sup>®</sup>80 with 0.8% sodium stearyl fumarate
- MicroceLac<sup>®</sup>100 with 0.4% magnesium stearate, Cellactose<sup>®</sup>80 with 0.4% magnesium stearate
- MicroceLac<sup>®</sup>100 with 0.8% magnesium stearate, Cellactose<sup>®</sup>80 with 0.8% magnesium stearate
- MicroceLac<sup>®</sup>100 with 50% ascorbic acid and 0.4% sodium stearyl fumarate, Cellactose<sup>®</sup>80 with 50% ascorbic acid and 0.4% sodium stearyl fumarate
- MicroceLac<sup>®</sup>100 with 50% ascorbic acid and 0.8% sodium stearyl fumarate, Cellactose<sup>®</sup>80 with 50% ascorbic acid and 0.8% sodium stearyl fumarate
- MicroceLac<sup>®</sup>100 with 50% acetylsalicylic acid and 0.4% sodium stearyl fumarate, Cellactose<sup>®</sup>80 with 50% acetylsalicylic acid and 0.4% sodium stearyl fumarate
- MicroceLac<sup>®</sup>100 with 50% acetylsalicylic acid and 0.8% sodium stearyl fumarate, Cellactose<sup>®</sup>80 with 50% acetylsalicylic acid and 0.8% sodium stearyl fumarate

The mixtures were prepared by mixing in a stainless mixing cube KB 15S (Erweka GmbH, Hausenstamm, Germany). Dry binders were mixed with lubricants for 5 minutes. If a mixture with an active ingredient was made, then the dry binder was first mixed with the active ingredient for 5 minutes and finally the lubricant was added for another period of 5 minutes. The mixing rate was 17 revolutions per minute, the total amount always being 30 g.

Of all tableting materials, 16 tablets were compacted on a material-testing machine T1-FRO 50 TH.A1K Zwick/Roell (Zwick GmbH & Co, Ulm, Germany). A special matrix with an upper and a lower punch was employed for tablet compacting using this apparatus. The compression proper took place by applying the pressure on the upper punch. The tablets were of cylindrical shape without facets, diameter 13 mm and weight 0.5g $\pm$ 0.0010 g. Compression rate was 40 mm/min and compression forces 6, 8, and 10 kN. Mixtures with magnesium stearate were pressed by a compression force of 6 kN and mixtures with active ingredients were pressed by a compression force of 8 kN.

### Measurement of tensile strength of tablets and evaluation of the lubricant sensitivity of tableting materials

Tensile strength was always evaluated in 10 tablets, first no sooner than 24 hours after compression. Measurements were performed on a Schleuniger apparatus (Dr. Schleuniger Pharmatron AG, Solothurn, Switzerland), which measured tablet sizes accurate to 0.01 mm and destruction force in N. Tensile strength of tablets was calculated according to Eq. [1]:

$$P = \frac{2F}{\pi \cdot d \cdot h}, \quad [1]$$

where P is tensile strength of tablets (MPa), F is destruction force (N), d is tablet diameter (mm), and h is thickness of the tablet (mm) <sup>9)</sup>.

LSR (lubricant sensitivity ratio) values, which make it possible to quantify and mutually compare the lubricant sensitivity of tableting materials, were calculated according to Eq. [2]:

$$LSR = \frac{(C_{su} - C_{sl})}{C_{su}}, \quad [2]$$

where C<sub>su</sub> is the crushing strength of tablets without an added lubricant and C<sub>sl</sub> is the crushing strength with a lubricant. The more this value approaches 1, the more the dry binder is sensitive to an added lubricant from the viewpoint of decreased strength of compacts <sup>10)</sup>. In the present paper, the values of tensile strength, not those of crushing strength, are used in the equation.

### Measurement of disintegration time of tablets

Disintegration times were determined 24 h after compression in water of 37  $^{\circ}$ C  $\pm$  1  $^{\circ}$ C using the Ph. Eur. apparatus. The test was carried out without discs using the procedure described in the chapter *Pharmaceutical Technical Procedures* in the Ph. Eur. 2005. The tablet was considered disintegrated at the moment when there was no residue on the net.

### Statistical treatment of results

The results of strengths and disintegration times were statistically processed by means of the computer programmes Excel and Qcexpert. Elementary data analysis yielded the mean values with standard deviations, which were plotted into dependences on compression force. In the cases of unclear significance of differences in the values, unpaired t-test at a level of significance of 0.05 was employed.

## RESULTS AND DISCUSSION

The paper deals with the evaluation and comparison of the properties of tablets from two coprocessed dry binders, differing only in the type of cellulose contained. The combination of  $\alpha$ -lactose monohydrate and cellulose, which composes the examined substances MicroceLac®100 and Cellactose®80, should guarantee well compressible tablets with a short disintegration time and suitable strength, which is little influenced by added lubricants. Both substances are spray-dried agglomerated products, which ensures their better flowability and compressibility than in the case of physical mixtures of contained substances.

The tablet properties under study were tensile strength and disintegration time. The influential factors were compression force, the type and concentration of the lubricant, and the type of the active ingredient. Compression forces were 6, 8 and 10 kN and they were adjusted in such a way as to allow the tensile strengths of tablets to vacillate as much as possible within the optimal range, i.e. 0.56–1.11 MPa<sup>11)</sup>. The effects of magnesium

stearate and Pruv were compared only at a compression force of 6 kN, mixtures with the active ingredient were compacted with a compression force of 8 kN. The concentrations of lubricants under study were 0.4 and 0.8%, the concentrations of the active ingredients ascorbic acid and acetylsalicylic acid were 50% (i.e. 250 mg in one tablet).

Figure 1 represents the dependence of tensile strength of tablets on compression force for MicroceLac®100 and Cellactose®80 both without and with the lubricant sodium stearyl fumarate. The strength of tablets from both substances increases with compression force, and it is lower in the case of Cellactose, which is due to the presence of powdered cellulose, which possesses smaller binding capacity than microcrystalline cellulose<sup>12)</sup>. Addition of the lubricant sodium stearyl fumarate produces in both dry binders a decrease in strength, which is intensified with increasing concentration of the lubricant. This fact corresponds with the composition of coprocessed dry binders, which contain mainly fragmenting lactose as well as plastically deforming cellulose<sup>2)</sup>.

Figure 2 presents the dependence of disintegration time of tablets on compression force. Disintegration time increases with compression force and it is longer for tablets from Cellactose, excepting the tableting

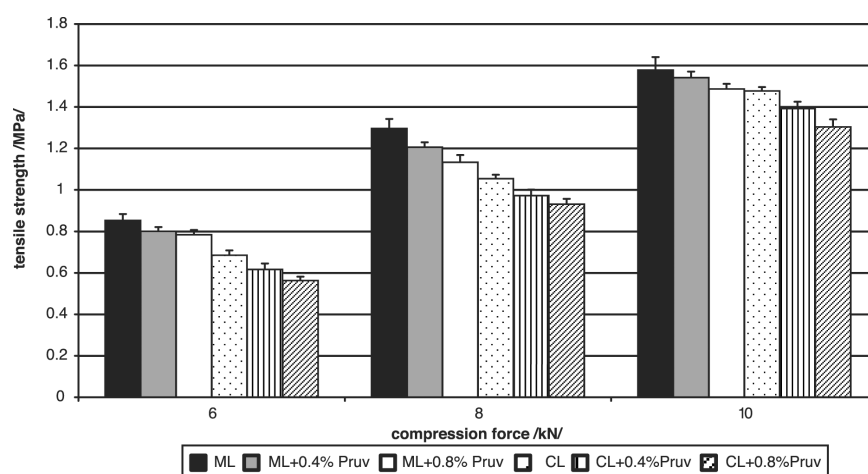


Fig. 1. Tensile strength of tablets in function of compression force: MicroceLac®100 and Cellactose®80 without and with Pruv

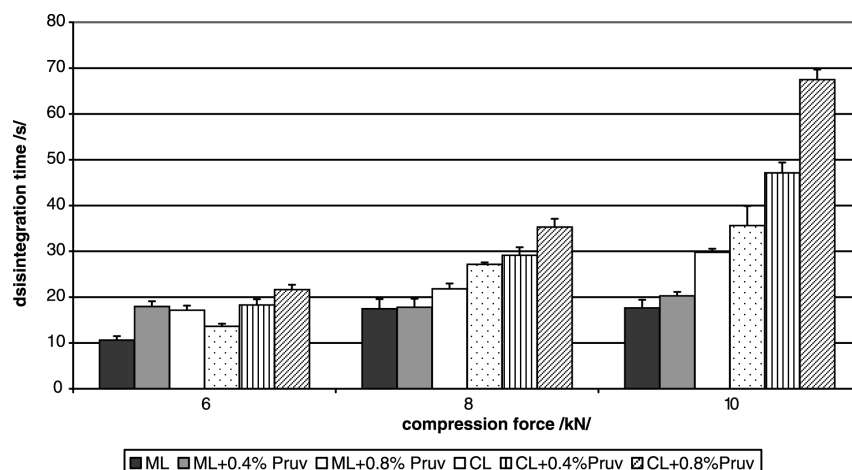


Fig. 2. Disintegration time in function of compression force: MicroceLac®100 and Cellactose®80 without and with Pruv



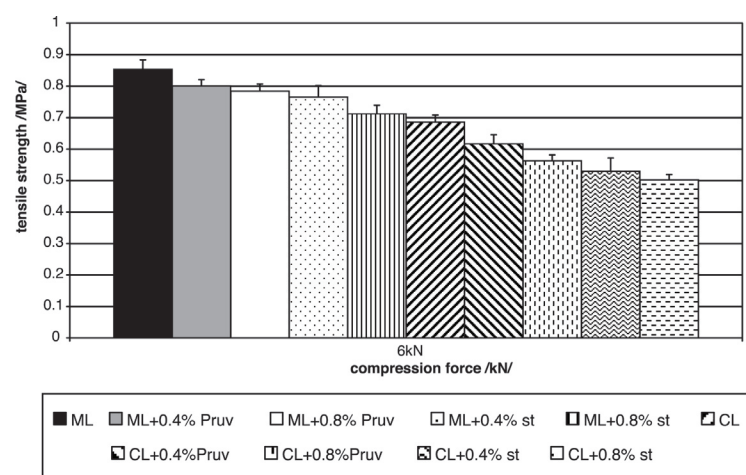


Fig. 3. Tensile strength of tablets – MicroceLac®100 and Cellactose®80 without and with Pruv and magnesi stearas

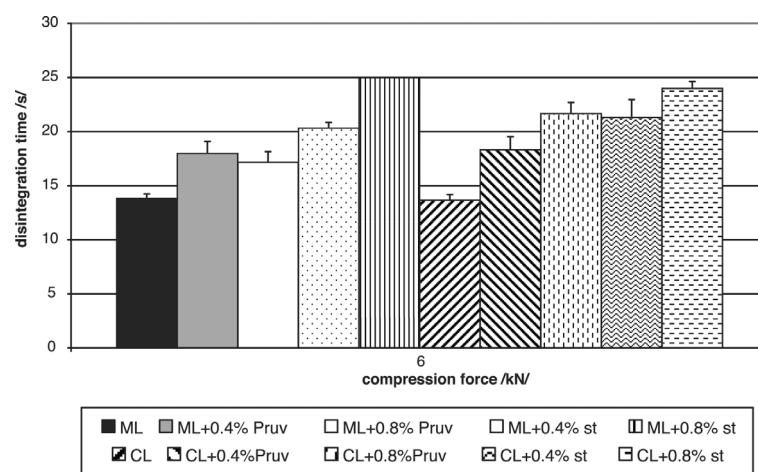


Fig. 4. Disintegration time of tablets – MicroceLac®100 and Cellactose®80 without and with Pruv and magnesi stearas

materials containing 0.4 % of Pruv with compression force of 6 kN. In all cases it is relatively short, which is due to the prevailing amount of passively disintegrating lactose <sup>13</sup>. Microcrystalline cellulose in MicroceLac forms a capillary net, which absorbs water. Penetration of the liquid is accompanied by the development of force, which results from the swelling of material and thus causes more rapid disintegration of compacts; it is so-called active disintegration <sup>13</sup>. This disintegration effect is stronger than in the case of powder cellulose in Cellactose, which does not swell in water. Therefore, though the tablets from Cellactose are less strong, they disintegrate more slowly. The presence of a hydrophobic lubricant prolongs disintegration time.

With a compression force of 6 kN the effects of sodium stearyl fumarate and magnesium stearate on the strength and disintegration time of compacts from both dry binders were compared. Figure 3 shows the values of tensile strength of tablets, the values for MicroceLac with the stearate are taken from a different paper <sup>14</sup>. It shows a more marked intervention of magnesium stearate into the strength of tablets from both dry binders. This fact seems to be connected with a larger specific area of magnesium stearate, which thus produces a more

perfect film on the particles of the dry binder, thus decreasing the strength of bonds between its particles <sup>15</sup>. Disintegration time of tablets from the above-mentioned mixtures made at a compression force of 6 kN is represented in Fig. 4. A more hydrophobic character of the stearate produces longer disintegration periods, which is clearer in the case of MicroceLac. In the case of Cellactose, there is no statistically significant difference between the values of disintegration times of compacts with 0.8% Pruv and 0.4% magnesium stearate.

Sensitivity of dry binders to added lubricants was evaluated by means of the lubricant sensitivity ratio (LSR) values and it is represented in Figure 5. With a compression force of 6 kN also the values for the mixtures with the stearate are shown. Higher values of LSR for the mixtures of dry binders with the stearate confirm a greater decrease in the strength of tablets due to the effect of this lubricant, resulting from its larger surface area. It is also of interest that there is no statistically significant difference between the values for the mixture of MicroceLac with 0.4% of the stearate and Cellactose with 0.4% of Pruv. This does not hold true of a lubricant concentration of 0.8%; the difference in the values is statistically significant, though it is not too high again. Unambiguously the highest LSR values

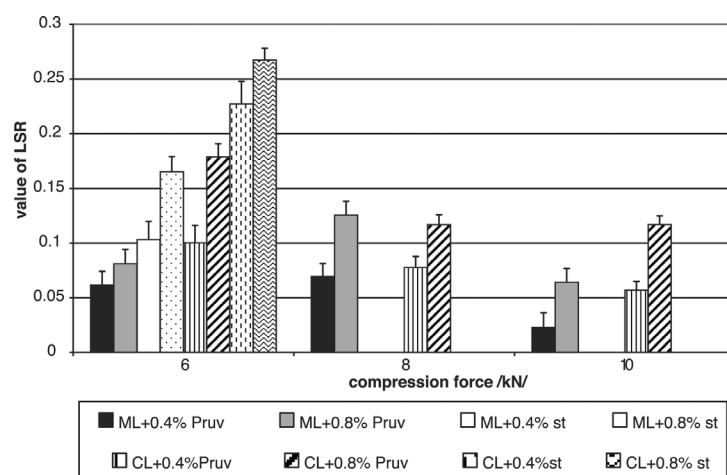


Fig. 5. Values of LSR for MicroceLac®100 and Cellactose®80

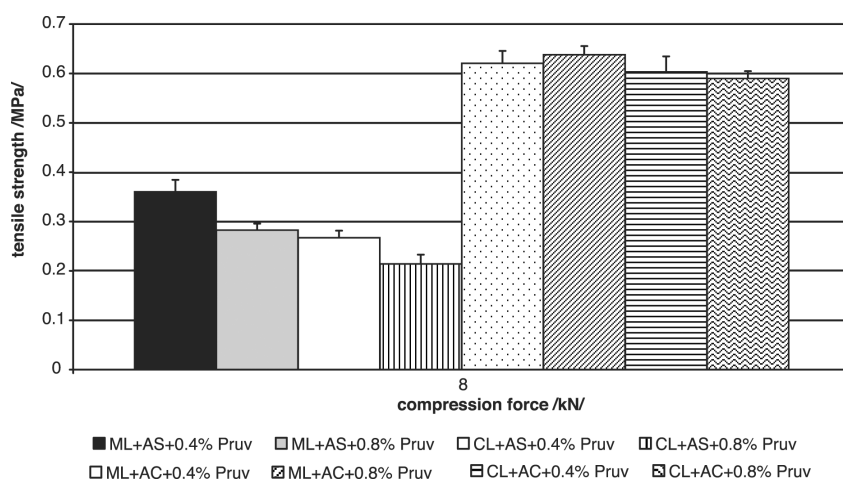


Fig. 6. Tensile strength of tablets – MicroceLac®100 and Cellactose®80 with 50% active ingredients

were observed in Cellactose with the stearate; in this case thus there occurs the greatest softening of tablets due to the effect of the lubricant. With compression forces of 8 and 10 kN, the values with the stearate are not shown, as with these compression pressures the effect of the stearate was not evaluated. Due to the effect of compression force there is an evident decrease in LSR values and therefore lesser influence of Pruv on the softening of tablets, excepting the mixture of Cellactose with 0.8% of Pruv, where there is no statistically significant difference between the values with compression forces of 8 and 10 kN. In the case of MicroceLac, there is a higher difference of values between the employed concentrations of Pruv than in a compression force of 6 kN.

Figures 6 a 7 show the values of the strengths and disintegration times of tablets with the active ingredients ascorbic acid and acetylsalicylic acid. The active ingredients were selected with regard to the different mechanism of compression and different solubility in an aqueous medium. Acetylsalicylic acid is compressed by plastic deformation, ascorbic acid by particle fragmentation<sup>4)</sup>. Tablets with the active ingredients were

obtained using a compression force of 8 kN.

Figure 6 is a column graph showing the values of tensile strengths of tablets. They clearly show a markedly lower tensile strength of tablets containing ascorbic acid in combination with both dry binders. The values are below the lower limit of optimal strength, i.e. below 0.56 MPa<sup>11)</sup>. The strength decreases with increasing concentrations of Pruv, and it is lower in the case of Cellactose. The values of the strength of tablets containing acetylsalicylic acid are higher and more uniform within the framework of the type of the dry binder and the Pruv concentration employed. There is no statistically significant difference between the strengths of tablets containing 0.4 and 0.8% of Pruv in MicroceLac as well as Cellactose; there is no statistically significant difference between the values with a concentration of 0.4% of Pruv in both dry binders either. Only the difference between the values for 0.8% Pruv is significant, where the strength in Cellactose is lower. The intervention of the lubricants into the strength of tablets containing active ingredients is interesting, as theoretically a contrary effect would be more likely expected, i.e. more profound intervention of

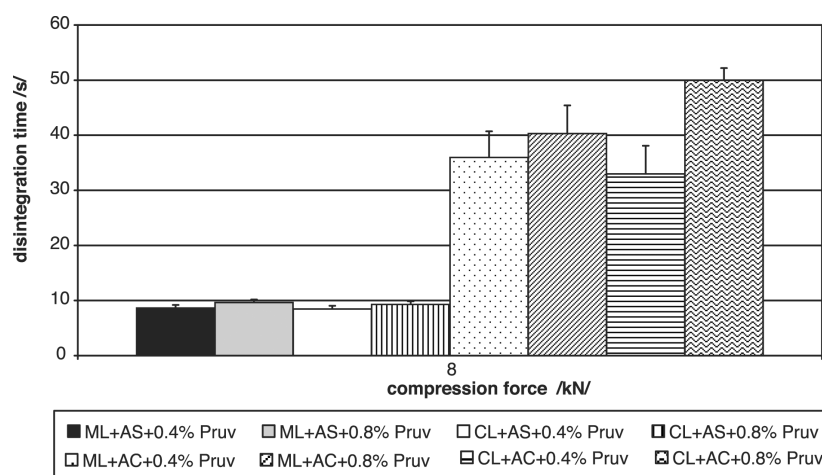


Fig. 7. Disintegration time of tablets – MicroceLac®100 and Cellactose®80 with 50% active ingredients

Explanations of the abbreviations used in Figures: ML – MicroceLac 100; CL – Cellactose 80; st – magnesii stearas; AS – ascorbic acid; AC – acetylsalicylic acid

lubricants into the strength of tablets containing acetylsalicylic acid, which is better compressible due to the mechanism of compression mainly by plastic deformation.

Figure 7 presents the disintegration times of tablets from the mixtures of dry powders and active ingredients. The tablets containing ascorbic acid possess a very short disintegration time, in all cases below 10 s. With higher concentrations of Pruv, the disintegration times are slightly increased, but for both concentrations of the lubricant no statistically significant differences were demonstrated within the framework of the type of the dry binder. The tablets containing acetylsalicylic acid possess a several times longer disintegration time, the higher concentration of the lubricant prolongs it especially in the case of Cellactose 80. In a concentration of 0.4% of Pruv, no statistically significant difference was demonstrated within the framework of the type of the dry binder. A longer disintegration period is due to a higher strength of tablets as well as primarily to poor solubility of acetylsalicylic acid in water, in contrast to ascorbic acid, which is well soluble.

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