PŮVODNÍ PRÁCE

# A study of the properties of tablets from the mixtures of directly compressible starch and directly compressible lactitol

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SUMMARY

**A study of the properties of tablets from the mixtures of directly compressible starch and directly compressible lactitol**

The paper deals with the evaluation of tablets from the mixtures of directly compressible starch Starch 1500® and directly compressible lactitol Lacty®-Tab in a ratio of 3:1 and 1:1. The examination included the tensile strength and disintegration time of tablets in dependence on compression force, addition of two concentrations of sodium stearyl fumarate (Pruv) as the lubricant, and a 50% content of the model active ingredient acetylsalicylic acid. Tensile strength of tablets increased with compression force and the effect of Pruv decreased it in both mixtures. Tablets from the mixture of dry binders in a ratio 1:1 without the lubricant possessed highest values of tensile strength. After an addition of the lubricant, no statistically significant difference was found in this mixture between interventions of 0.5 and 1% Pruv concentrations into strength. Disintegration time increased with compression force; it was the shortest in tablets with 1% Pruv in the case of the mixture of Starch 1500 and lactitol 3:1; in the case of the mixture 1:1 it was the longest. Tablets containing acetylsalicylic acid possessed higher values of tensile strength in the case of the mixture of dry powders in a ratio of 1:1, the strength decreasing with increasing Pruv concentration. Tablets from this mixture also possessed a longer period of disintegration time which increased with increasing Pruv concentration.

**Key words:** Starch 1500® – Lacty®-Tab – sodium stearyl fumarate – acetylsalicylic acid – tensile strength of tablets – disintegration time *Má*

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SOUHRN

**Studium vlastností tablet ze směsí přímo lisovatelného škrobu a přímo lisovatelného laktitolu**

Práce se zabývá hodnocením výlisků ze směsí přímo lisovatelného škrobu Starch 1500 a přímo lisovatelného laktitolu Lacty-Tabu v poměru 3:1 a 1:1. Studovala se pevnost tablet v tahu a doba rozpadu v závislosti na lisovací síle, přídavku dvojí koncentrace stearylfumarátu sodného (Pruvu) jako mazadla a 50% obsahu modelové účinné látky kyseliny acetylsalicylové. Pevnost tablet rostla s lisovací silou, vlivem Pruvu se snížila u obou směsí. Výlisky ze směsi suchých pojiv v poměru 1:1 bez mazadla byly nejpevnější, po přídavku mazadla nebyl u této směsi statisticky významný rozdíl mezi zásahem 0,5 a 1% koncentrace Pruvu do pevnosti. Doba rozpadu rostla s lisovací silou, u výlisků s 1% Pruvu byla v případě směsi Starch 1500 a laktitol 3:1 nejkratší, v případě směsi 1:1 byla

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nejdelší. Výlisky s kyselinou acetylsalicylovou byly pevnější v případě směsi suchých pojiv v poměru 1:1, pevnost klesala s rostoucí koncentrací Pruvu. Tablety z této směsi měly také delší dobu rozpadu, která rostla s rostoucí koncentrací Pruvu.
**Klíčová slova:** Starch 1500® - Lacty®-Tab – stearylfumarát sodný – kyselina acetylsalicylová – pevnost tablet v tahu – doba rozpadu

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### *Introduction*

Dry binders, or directly compressible fillers, are auxiliary substances necessary for the performance of the technology of direct compression of tablets. When using an individual raw material, however, completely optimal properties of the tableting material or compressed tablets can never be achieved. For this reason, advantageous combinations of dry binders are searched for, which are either a physical mixture of substances, or they are commercially manufactured as the so-called coprocessed dry binders. The principal requirements for these raw materials include good flowability, compressibility, low sensitivity to lubricants, good strength of tablets, and optimal disintegration and release of the active ingredient [1].

The present paper tests the mixtures from directly compressible starch Starch 1500® and directly compressible lactitol Lacty®-Tab in ratios of 1:1 and 3:1. Starch 1500 is pre-swollen, partially hydrolyzed maize starch, whose modification has improved its compression and flow properties, thus making it possible to use it as a directly compressible filler. It can be plastically deformed with a high share of the elastic component, which is the reason for low strength of tablets, which is, in addition, very markedly influenced by added alkaline stearate lubricants. Starch 1500 alone can be compressed without lubricants, but in the presence of other substances lubricants are necessary [2].

Lactitol monohydrate, or ß-galactosido-sorbitol, is a sugar alcohol, which is employed mainly in chewing tablets. The directly compressible form is a water-granulated product of microcrystalline aggregates [3]. Its advantage is good compressibility and strength of tablets, which is not influenced by added alkaline stearates [4, 5]. When used alone, it does not exert lubricant effects, thus it cannot be compressed without a lubricant. Anhydrous lactitol is in a 5% share a component of the commercially manufactured coprocessed dry binder Pharmatose DCL 40, where in combination with anhydrous ß-lactose it improves the strength and compressibility of tablets [6].

Different compression properties of these raw materials made the present author test their tableting properties in mixtures with the above-mentioned proportional representation.

## EXPERIMENTAL

### *Materials*

*Starch 1500®* – partially pregelatinized maize starch (Colorcon, Great Britain); *Lacty®-Tab* – directly compressible lactitol monohydrate (Purac biochem, Gorinchem, The Netherlands)

*Acetylsalicylic acid* (Schűtz and Co. GmbH, Hamburg, Germany); *Pruv®* – sodium stearyl fumarate (J. Rettenmaier & Söhne GmbH+Co, Rosenberg, Germany)

### *Preparation of tableting materials and tablets*

A list of tableting materials evaluated in the study:
- Starch 1500 and Lacty-Tab 3:1
- Starch 1500 and Lacty-Tab 1:1
- Starch 1500 and Lacty-Tab 3:1 with 0.5 % Pruv
- Starch 1500 and Lacty-Tab 1:1 with 0.5% Pruv
- Starch 1500 and Lacty-Tab 3:1 with 1 % Pruv
- Starch 1500 and Lacty-Tab 1:1 with 1% Pruv
- Starch 1500 and Lacty-Tab 3:1 with 50% acetylsalicylic acid
- Starch 1500 and Lacty-Tab 1:1 with 50% acetylsalicylic acid
- Starch 1500 and Lacty-Tab 3:1 with 0.5 % Pruv and 50% acetylsalicylic acid
- Starch 1500 and Lacty-Tab 1:1 with 0.5% Pruv and 50% acetylsalicylic acid
- Starch 1500 and Lacty-Tab 3:1 with 1 % Pruv and 50% acetylsalicylic acid
- Starch 1500 and Lacty-Tab 1:1 with 1% Pruv and 50% acetylsalicylic acid

The substances were mixed gradually always 5 minutes in a stainless cube KB 15S (Erweka GmbH, Hausenstamm, Germany). In multicomponent mixtures, the dry binders were mixed first, then the active ingredient, and finally the lubricant sodium stearyl fumarate were added.

All tableting materials were used to produce 16 tablets compressed with the use of a special die with an upper and a lower punch on a material testing equipment T1 – FRO 50 TH.A1K Zwick/Roell (Zwick GmbH & Co, Ulm, Germany). The tablets were of a cylindrical shape without facets with a diameter of 13 mm and weight 0.5±0.0010g. Compression velocity was 40 mm/min and compression forces of 12, 16, and 20 kN. Mixtures including acetylsalicylic acid were compressed using only a compression force of 20 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 compaction. 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]:

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

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) [7].

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]:

$$LSR = \frac{Csu - Csl}{Csu}, \quad [2]$$

where Csu is the crushing strength of tablets without an added lubricant and Csl 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 tablets [8]. In the present paper, the values of tensile strength, not those of crushing strength, are used in the equation.

***Measurements of the disintegration time of tablets***

Disintegration times of tablets were evaluated earliest 24 hours after compaction always in 6 tablets. Measurements were performed on an apparatus for the determination of disintegration time following the method of Ph.B. MMV in the medium of purified water tempered to 37 °C ±1 °C. The tablet was considered disintegrated at the moment when there was no remainder on the net [9].

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 examined mixtures of pre-swollen maize starch Starch 1500 and granulated lactitol Lacty-Tab aiming to find their mutual influence manifested in the properties of tablets. Of the two substances, lactitol yields stronger tablets; strength is not negatively affected by added lubricants. Disintegration time from lactitol without the lubricant is very short and it is markedly affected by the presence of a hydrophobic lubricant [5]. These characteristics do not held true for Starch 1500 [10].

The properties of examined tablets from mixtures of Starch 1500 and Lacty-Tab in ratios of 3:1 and 1:1 included their tensile strength and disintegration time in dependence on compression force, additions of two concentrations of the lubricant sodium stearyl fumarate (0.5 and 1%), and a 50% addition of the active ingredient acetylsalicylic acid. Acetylsalicylic acid possesses good compression properties and is compressed mainly by plastic deformation [11]. It can negatively affect disintegration time due to its poor solubility in aqueous media. Compression forces were adjusted to make the compacts from the mixtures without the lubricant and the active ingredient vacillate as much as possible within the range of the optimal strength of tablets (i.e. 0.56–1.11 MPa) [12].

Figure 1 presents the dependences of tensile strength of tablets on compression force for the mixture of Starch 1500 and lactitol in a ratio of 3:1 with varying Pruv concentrations. The dependences are linear, the strength increases with compression force and it markedly decreases with increasing Pruv concentration. A sharp decrease in strength by the action of the lubricant is due to the prevailing amount of starch in the mixture. In the case of the mixture of Starch 1500 and lactitol in a ratio of 1:1 it is otherwise. Dependences again grow linearly, Pruv produces a sharp decrease in the strength of tablets, but there is no statistically significant difference in the values for the mixtures with 0.5 and 1% of Pruv. In the case of this mixture there are not so many intersurfaces between the particles of pure starch, which are plastically deformed, and therefore a 1% Pruv concentration produces an identical decrease in strength as a 0.5% concentration. These facts are presented in figure 2.

For the sake of comparison, figure 3 shows the

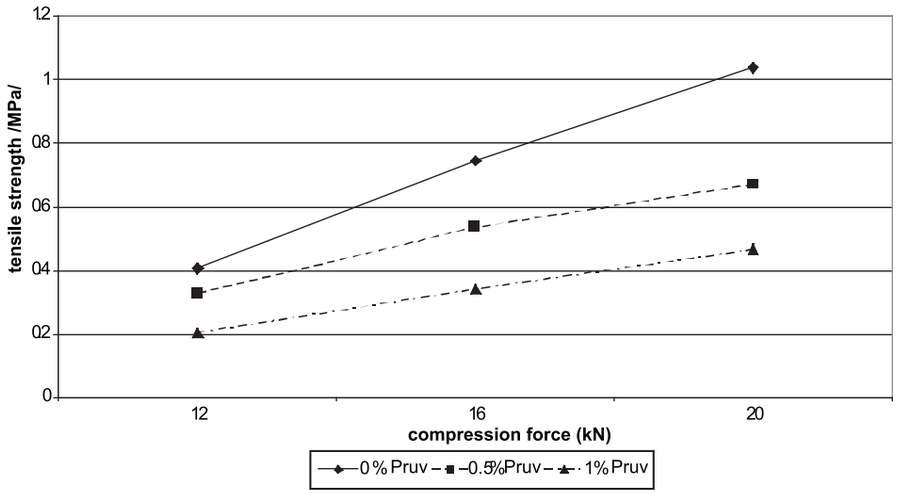


*Fig. 1. Tensile strength of tablets in function of compression force: Starch 1500 and Lacty – Tab 3:1 with various Pruv concentrations*

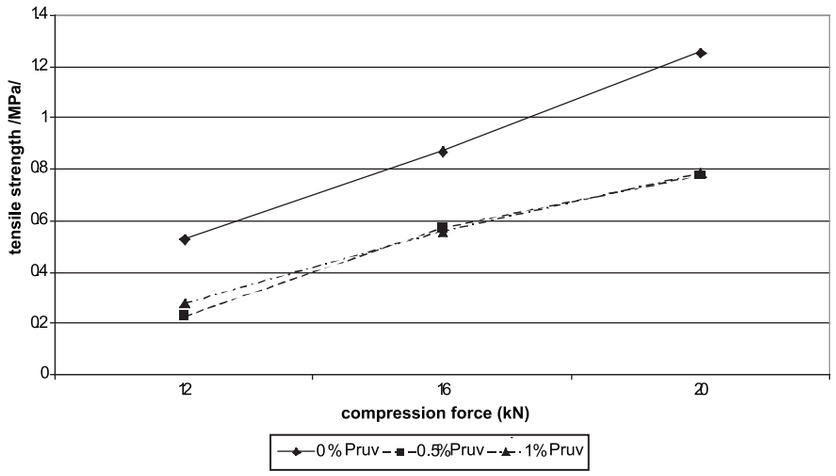


*Fig. 2. Tensile strength of tablets in function of compression force: Starch 1500 and Lacty – Tab 1:1 with various Pruv concentrations*

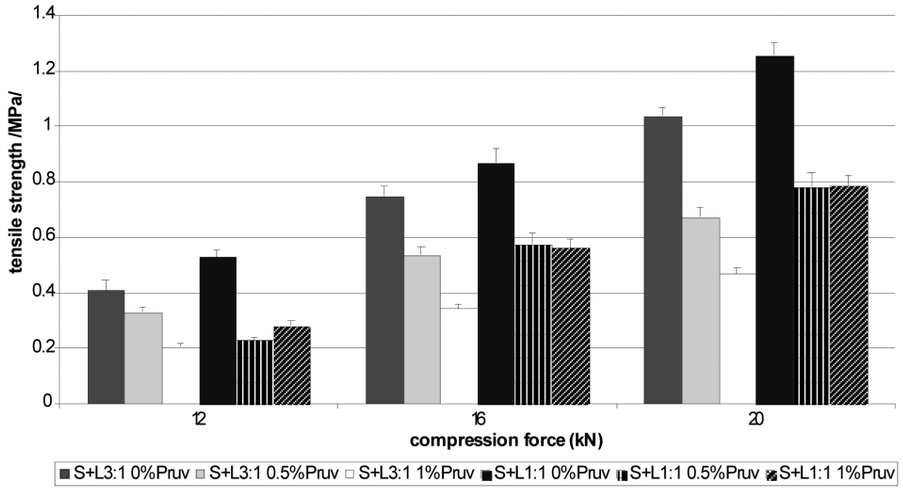


*Fig. 3. Comparison of tensile strength of tablets*
*Mixtures of Starch 1500 and Lacty – Tab with various Pruv concentrations*

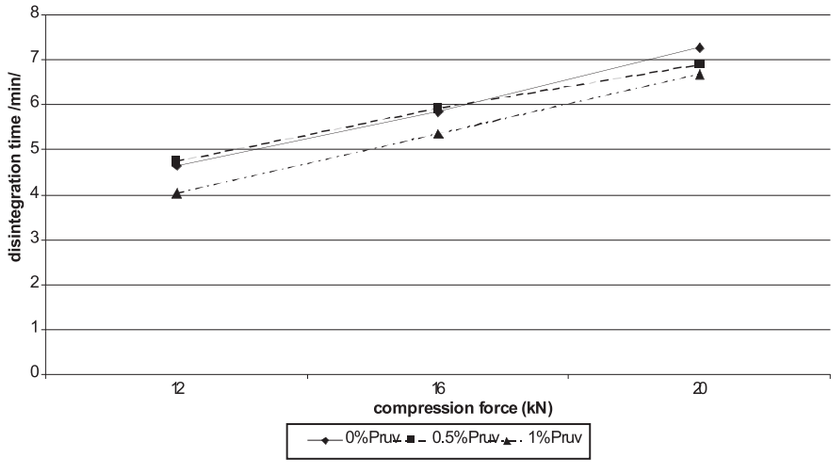


*Fig. 4. Disintegration time in function of compression force: Starch 1500 and Lacty – Tab 3:1 with various various Pruv concentrations*

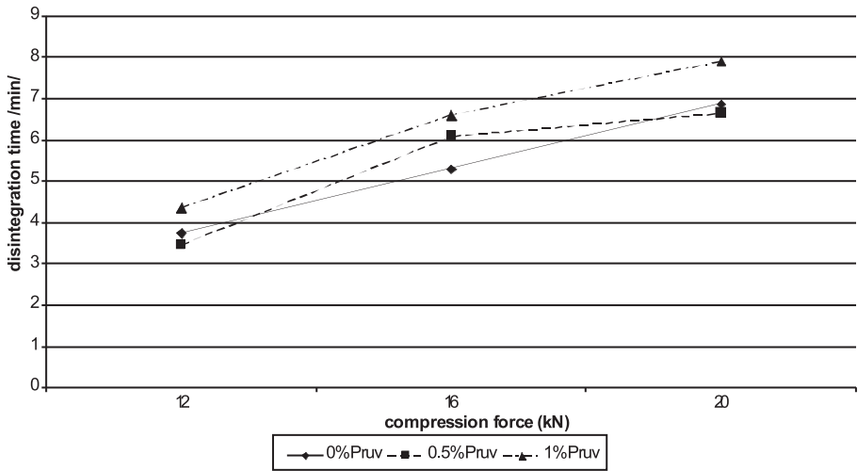


*Fig. 5. Disintegration time in function of compression force: Starch 1500 and Lacty – Tab 1:1 with various various Pruv concentrations*

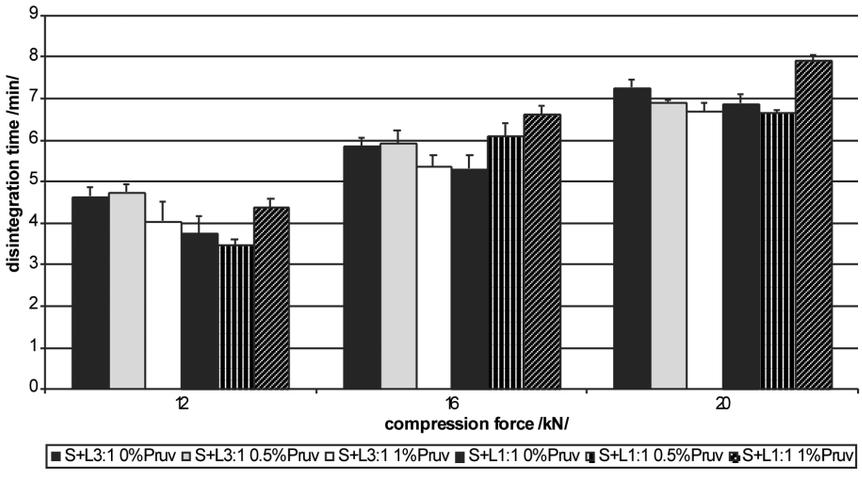


*Fig. 6. Comparison of disintegration time of tablets*
*Mixtures of Starch 1500 and Lacty – Tab with various Pruv concentrations*

strengths of tablets from both mixtures. It follows that the tablets with the higher values of tensile strength are yielded by pure mixtures without the lubricant, the highest strength is found in the compacts from the mixture of Starch 1500 and lactitol 1:1. In the mixture of Starch 1500 and lactitol in a ratio of 3:1, there is a significant difference in the values of strength for tableting materials with different concentrations of the lubricant in comparison with the mixture with a ratio of the substances 1:1; a 1% addition of Pruv in this case intervenes into the strength much more.

Figure 4 is a graphic representation of the dependence of disintegration time on the compression force for the mixture Starch 1500 and lactitol in a ratio of 3:1 with varying Pruv concentrations. The shortest disintegration time was found in the tablets with 1% of Pruv, which were also least strong. For the concentrations of 0 and 0.5% of Pruv there is no statistically significant difference between the values of disintegration times in compression forces of 12 and 16 kN; in a compression force of 20 kN there is a shorter period of disintegration time in the mixture with 0.5% of Pruv. The hydrophobic character of sodium stearyl fumarate therefore did not negatively affect disintegration time. Figure 5 shows an identical dependence for the mixture of substances in a ratio of 1:1. In this case the compacts from the mixtures with 1% Pruv show, on the other hand, the longest period of disintegration time. The result for two more mixtures is ambiguous, as with compression forces of 12 and 20 kN the disintegration time is shorter in the mixtures with 0.5% Pruv, with a compression force of 16 kN it is the shortest for the mixtures with 0% of Pruv. Figure 6 compares the disintegration times for both mixtures. It could be theoretically assumed that disintegration times will be always longer in the mixtures with a higher share of Starch 1500, as in this substance it is active disintegration via swelling, whereas lactitol disintegrates passively by dissolution [13]. This holds true for compression forces of 12 and 20 kN excepting the mixtures with 1% of Pruv. In a compression force of 16 kN the period of disintegration time is longer in the mixtures with a smaller share of Starch 1500, excepting the mixtures without Pruv.

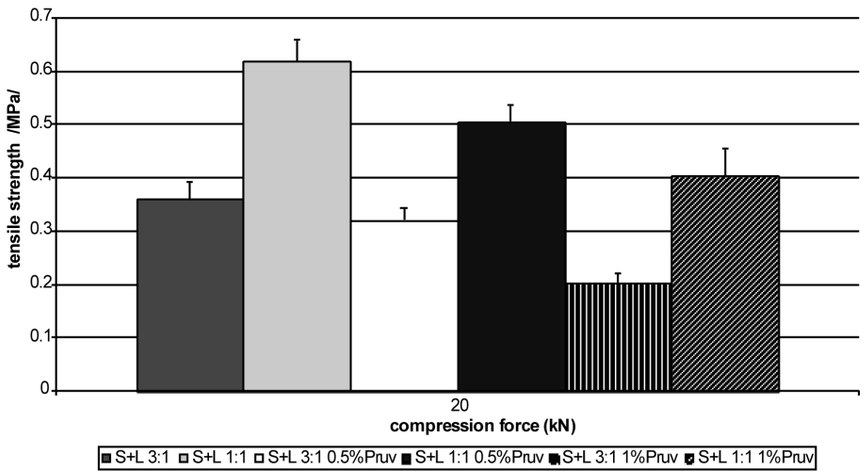


*Fig. 7. Tensile strength of tablets*
*Mixtures of Starch 1500 and Lacty-Tab with 50% acetylsalicylic acid*

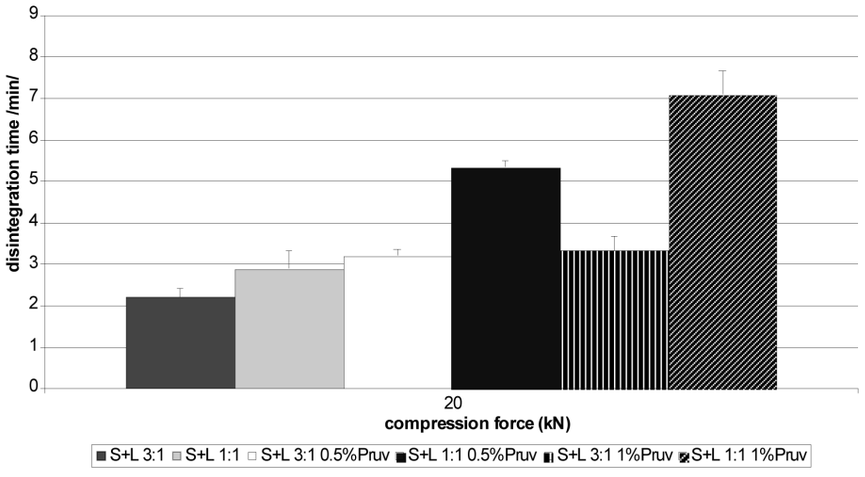


*Fig. 8. Disintegration time of tablets*
*Mixtures of Starch 1500 and Lacty-Tab with 50% acetylsalicylic acid*

*Tab. 1 Values of LSR*

| Compression force (kN) | S : L 3:1 0.5%P | S : L 1:1 0.5%P | S : L 3:1 1 %P | S : L 1:1 1 %P | S : L 3:1 0.5%P 50%ACA | S : L 1:1 0.5%P 50%ACA | S : L 3:1 1 %P 50%ACA | S : L 1:1 1 %P 50%ACA |
|---|---|---|---|---|---|---|---|---|
| 12 | 0.1921 | 0.5627 | 0.4944 | 0.4665 | | | | |
| 16 | 0.2787 | 0.3392 | 0.5389 | 0.3540 | | | | |
| 20 | 0.3514 | 0.3793 | 0.5488 | 0.3730 | 0.1121 | 0.1825 | 0.4380 | 0.3469 |

S – Starch 1500, L – Lacty-Tab, P – Pruv, ACA – acetylsalicylic acid

The column graph in figure 7 represents the values of strengths for the mixtures with acetylsalicylic acid. Higher values of the strength of tablets containing acetylsalicylic acid are achieved in the mixtures of Starch 1500 and lactitol in a ratio of 1:1, the strength decreasing with increasing Pruv concentration. The highest value is thus in the mixture without Pruv and it is found still in the optimal range of strength of tablets. In the mixtures in a ratio of 3:1, the disintegration time of tablets also decreases with increasing Pruv concentrations. Disintegration times of tablets are shown in column figure 8; they are longer in the tablets from the mixture of dry binders in a ratio of 1:1 and they increase with increasing Pruv concentrations. This fact is also connected with a higher strength of these tablets.

Table 1 shows the LSR values for the mixtures without and with the active ingredient. In the case of 0.5% concentration of Pruv, a higher lubricant sensitivity was observed in the mixture of Starch 1500 and lactitol in a ratio of 1:1, which is most probably caused by a smaller specific surface area of particles in the mixture. In the case of 1% concentration of Pruv, a higher sensitivity was recorded in the mixture of Starch 1500 and lactitol 3:1. This corresponds to plastic deformation of starch, which is present in an excessive amount in the mixture [14]. In the case of LSR values for the mixtures containing the active ingredient, the highest value was again found in the mixture 3:1 with 1% of Pruv, i.e., that with the highest share of starch and lubricant.

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# ZPRÁVY

**VYBRANÉ KURZY, SEMINÁŘE A STÁŽE IPVZ V ZÁŘÍ, V ŘÍJNU A V LISTOPADU 2007**

## Subkatedra klinické farmacie

*IPVZ, Ruská 85, 100 05 Praha 10*
*Vedoucí: doc. RNDr. Jiří Portych, CSc.*
*tel. 271 019 259, 271 019 270*
*e-mail: portych@ipvz.cz*

**213101 Dispenzační seminář – Řešení rizik farmakoterapie I.**
Určeno pro lékárníky provádějící dispenzační činnost.
Program: Léková rizika – nežádoucí účinky a lékové chyby. Přístup k identifikaci a řešení lékových rizik, nežádoucích účinků a interakcí léčiv formou SAZE, řešení kazuistik modelových nebo z vlastní praxe. Seminář probíhá za účasti lékaře a klinického farmaceuta. Je vítána i vlastní zkušenost s lékovými problémy, které ohrožovaly vaše pacienty.
*Vedoucí:* doc. RNDr. J. Vlček, CSc.
*Místo konání:* Hradec Králové, Heyrovského 1203, Farmaceutická fakulta UK
Předpokládaná cena: 600 Kč
**8. 10. 2007**

**213105 Odborná stáž se zaměřením na problematiku polyfarmakoterapie**
Určeno pro zájemce z řad lékárníků nemocničních i veřejných lékáren.
Program: Specifika léčby ve stáří z pohledu nevhodných lékových interakcí, rizika kombinované léčby, polypragmazie, problematika bioaktivace léčiv, toxikologické důsledky přeměny léčiv, problematika polymorfismu, řešení kazuistik důležitých pro každodenní praxi lékárníka.
*Školitel:* prof. RNDr. L. Kameníková, DrSc.
*Místo konání:* Praha 2, Londýnská 15, Geriatrická klinika 1. LF UK
Předpokládaná cena: 1500 Kč
**30. 10. – 1. 11. 2007**

**213106 Odborná stáž – Biologická léčba a cílená terapie**
Určeno pro farmaceuty se zájmem o danou problematiku.
Program: Mechanismy účinku biologické léčby, experimentální možnosti, strategie a klinická aplikace látek (monoklonální protilátky, cytokiny, směřovaná léčiva), imunomodulátory, klasifikace a klinické využití v alergické a onkologické léčbě.
*Školitel:* prof. RNDr. L. Kameníková, DrSc.
*Místo konání:* Praha 2, Albertov 4, Farmakologický ústav 1. LF UK, ÚEM ČAV, Praha 4 – Krč
Předpokládaná cena: 1500 Kč
**19.–21. 11. 2007**