PŮVODNÍ PRÁCE

Prosolv® Easytab as a new multifunctional co-processed dry binder: a study of the properties of tablets and energy evaluation of the compaction process

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SUMMARY

Prosolv® Easytab as a new multifunctional co-processed dry binder: a study of the properties of tablets and energy evaluation of the compaction process

The paper studies the tensile strength and disintegration time of tablets made from the new co-processed dry binder Prosolv® Easytab. The results are compared with Prosolv® SMCC 90 and the physical mixtures of Prosolv SMCC 90 with Explotab (1% or 1.5%) and Pruv (0.5% or 1%). It also evaluates the mixtures with the active ingredients ascorbic acid and acetylsalicylic acid. The process of compaction of the new excipient is studied also from the energetic aspect. The tablets made from the substance Prosolv Easytab possessed a lower strength than those from Prosolv SMCC 90 and the physical mixtures of Prosolv SMCC 90 with Explotab and Pruv. The disintegration time of tablets was markedly shorter in the case of the substance Prosolv Easytab than in Prosolv SMCC 90, the shortest being in the tablets made from the physical mixtures of substances. From the energetic aspect, Prosolv Easytab was the best compressible one, because under the given compression force the value of the maximal energy was the lowest one of the all tableting compositions under study, primarily due to a lower energy for friction and the energy accumulated by the tablet.

Key words: Prosolv Easytab – Prosolv SMCC 90 – tensile strength of tablets – disintegration time – force-displacement profile

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SOUHRN

Prosolv Easytab jako nové multifunkční směsné suché pojivo: studium vlastností tablet a energetické hodnocení lisovacího procesu

V práci je studována pevnost a doba rozpadu tablet z nového směsného suchého pojiva Prosolv® Easytab. Výsledky jsou srovnány s Prosolvem® SMCC 90 a s fyzikálními směsmi Prosolvu SMCC 90 s Explotabem (1% nebo 1,5%) a Pruvem (0,5% nebo 1%). Jsou hodnoceny i směsi s léčivými látkami kyselinou askorbovou a kyselinou acetylsalicylovou. Proces lisování nové pomocné látky je studován i z energetického hlediska. Tablety z látky Prosolv Easytab měly nižší pevnost než z Prosolvu SMCC 90 a z fyzikálních směsí Prosolvu SMCC 90 s Explotabem a Pruvem. Doba rozpadu tablet byla výrazně kratší v případě látky Prosolv Easytab než Prosolv SMCC 90, nejkratší

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byla u tablet z fyzikálních směsí látek. Z energetického hlediska byl Prosolv Easytab nejlépe lisovatelný, neboť hodnota maximální energie byla při dané lisovací síle nejnižší ze všech sledovaných tabletovin, a to především díky nižší energii na tření a energii akumulované tabletou při lisování.
Klíčová slova: Prosolv Easytab – Prosolv SMCC 90 – pevnost tablet v tahu – doba rozpadu tablet – záznam „síla – dráha“

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Introduction

Microcrystalline cellulose (MCC) is even after nearly 50 years since the origin of its first proprietary product Avicel® a very widely used dry binder in the manufacture of tablets by direct compression. Within this space of time it has been introduced to the market in many types differing in their particle size, humidity content, and bulk and tapped densities. MCC yields solid tablets with the use of low compression pressures, it is compressible even without the use of lubricants, and tablets rapidly disintegrate[1)]. An important step in its improvement was its silicification, when a co-processed dry binder was prepared containing 98% of MCC and 2% of colloidal silicon dioxide, which improved flowability and compressibility and decreased also the lubricant sensitivity[2–7)]. This substance is known under the proprietary name Prosolv® SMCC and also underwent further innovation. This gave rise to Prosolv HD®, which is Prosolv of a high-density degree. Directly compressible Prosolv HD® 90 was prepared by silicification of Avicel PH-302. The strength of the compacts from this substance is significantly higher than that of the input microcrystalline cellulose, the substance has better flowability and lower sensitivity to the rate of tableting, a disadvantage being higher lubricant sensitivity[8)]. Tablets made from Prosolv HD 90 are less strong than those from Prosolv SMCC 90 and possess a shorter disintegration time[9)]. The latest product of the Prosolv® series for classic oral tablets is the substance Prosolv® Easytab. It is the first lubricant-coated highly functional excipient effectively combining four individual ingredients: the dry binder microcrystalline cellulose (95–98%), the superdisintegrant sodium starch glycolate (0.5–2%), the glidant colloidal silicon dioxide (1.5–2.5%), and the lubricant sodium stearyl fumarate (0.3–1%). The IR spectrum demonstrates that there is a synergistic arrangement of the ingredients without chemical changes, so no new covalent bonds develop[10)]. The literature of the manufacturing firm lists considerable advantages in the manufacture of tablets, e.g. economical production and thus decreased production costs, high flowability, possibility of high velocity of tableting, dust-free manufacturing, decreased possibility of capping and breaking of tablets, lower friability, perfect balance between flowability, compression, lubrication, disintegration and content uniformity of tablets[10)].

The aim of the paper was to study the properties of tablets, in particular the strength and disintegration time, which were made from this new co-processed dry binder. The substance was in these parameters compared with the already sufficiently known Prosolv® SMCC 90 and the physical mixtures of Prosolv® SMCC 90 with double concentration of sodium starch glycolate and sodium stearyl fumarate. The energetic course of compression was also evaluated.

EXPERIMENTAL PART

Materials

Prosolv® Easytab – co-processed dry binder with microcrystalline cellulose (95–98%), colloidal silicon dioxide (1.5–2.5%), sodium starch glycolate (0.5–2%) and sodium stearyl fumarate (0.3–1%) (JRS PHARMA Gmbh + Co.KG, Germany);

Prosolv® SMCC 90 – co-processed dry binder with microcrystalline cellulose (98%) and colloidal silicon dioxide (2%) (JRS PHARMA Gmbh + Co.KG, Germany);

Explotab® – sodium starch glycolate (JRS PHARMA Gmbh+Co.KG, Germany);

Pruv® – sodium stearyl fumarate (JRS PHARMA Gmbh + Co.KG, Germany);

ascorbic acid (Northeast General Pharmaceutical Factory, China);

acetylsalicylic acid (Merck KgaA, Darmstadt, Germany).

Preparation of tableting compositions

The experiment employed pure Prosolv SMCC 90, Prosolv Easytab, and the mixtures of Prosolv SMCC 90 with 1% of Explotab and 0.5 and 1% of Pruv, the mixtures of Prosolv SMCC 90 with 1.5% of Explotab and 0.5 and 1% of Pruv. The active ingredients ascorbic acid and acetylsalicylic acid in the ratio 1 : 1 with regard to the dry binder were then added to each of these tableting compositions. The tests further included the tableting compositions from Prosolv SMCC 90 with 1 and 1.5% of Explotab, further with 0.5% and 1% of Pruv. Tableting compositions were prepared by graded mixing in a stainless steel cube KB 15S (Erweka GmbH,

Hausenstamm, Germany), and after the addition of each of the other added substances the material was mixed for 5 minutes at the rate of 17 revolutions per minute. The lubricant was always added in the final stage of mixing, and in the case of the preparation of tableting compositions with active ingredients, the active ingredient was first mixed with the dry binder. The amount of prepared tableting compositions was 30 g.

Preparation of tablets and energy evaluation of the process of compaction

All tableting compositions were used to produce 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). Proper compaction took place by applying the pressure on the upper punch. The tablets were of a cylindrical shape without facets with a diameter of 13 mm and weight of 500 ± 1 mg. Compression velocity was 40 mm/min and compression forces 3, 3.5 and 4 kN, in the case of Prosolv SMCC 90 with Explotab or with Pruv 3 kN and in the case of tableting compositions with active ingredients 4 kN. Each compression force was used to compact 16 tablets. In the case of tableting compositions compressed with 3.5 kN in 10 tablets the force-displacement plot was drawn by means of a computer programme testXpert V 9.01 and the compression process was evaluated as far as energy was concerned, i.e. the energies E1, E2 and E3 were expressed numerically. Energy E1 is the energy consumed by friction, energy E2 is the energy accumulated by the tablet in the course of compression, and energy E3 is the energy released during decompression[11].

Measurement of tensile strength of tablets

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 crushing force in N. Tensile strength of tablets was calculated according to Eq. [1][12]:

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

where P is the tensile strength of tablets (MPa), F is the crushing force (N), d is the tablet diameter (mm), and h is the thickness of the tablet (mm).

Measurement of 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 of tablets Erweka ZT 301 (Erweka GmbH, Hausenstamm, Germany) following the method described in the chapter *Pharmaceutical Technical Procedures* in the European Pharmacopoeia, 6th Edition. The test was carried out without discs 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.

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 aimed to evaluate the properties of the tablets made from the substance Prosolv® Easytab, the strength and disintegration time of tablets in dependence on compression force. For the sake of comparison, these properties were examined in the tablets made from Prosolv SMCC® 90 and the physical mixtures of Prosolv SMCC 90 with different shares of sodium starch glycolate (Explotab) and sodium stearyl fumarate (Pruv). They were the mixtures containing 1 or 1.5 % of Explotab and 0.5 or 1% of Pruv, because these are the concentration ranges in which these substances are found in the co-processed dry binder Prosolv Easytab. Their absolutely accurate concentrations are not stated, only the concentration ranges are listed, 0.3–1% for Pruv and 0.5–2% for sodium starch glycolate. The strength and disintegration time were evaluated in tablets compressed by 3, 3.5 and 4 kN. This range of compression forces was selected in such a way as to make the tablets oscillate in the optimal range of strength as much as possible, which is 0.56–1.11 MPa[13]. At the compression force of 3.5 kN the compression process was evaluated in these tableting materials also from the energetic aspect. Prosolv SMCC 90 was further examined in order to reveal the effect of Explotab alone in the concentrations of 1 and 1.5% and Pruv alone in the concentrations of 0.5 and 1% on the strength and disintegration time of tablets under one compression force, i.e. 3 kN. The tests included also mixtures with active ingredients, which were compacted by the compression force of 4 kN. The selected model active ingredients were acetylsalicylic acid and ascorbic acid, due to different mechanisms of compaction of these substances and also different solubilities in water. Acetylsalicylic acid is compressed mainly by plastic deformation, and is insoluble in water; ascorbic acid is compressed mainly by fragmentation of particles which are watersoluble[14].

Figure 1 shows the dependence of the tensile strength of tablets on compression force for Prosolv SMCC 90, Prosolv Easytab and for the mixtures of Prosolv SMCC 90 with Explotab and Pruv in various concentrations. The dependences increase, the highest strength is achieved in

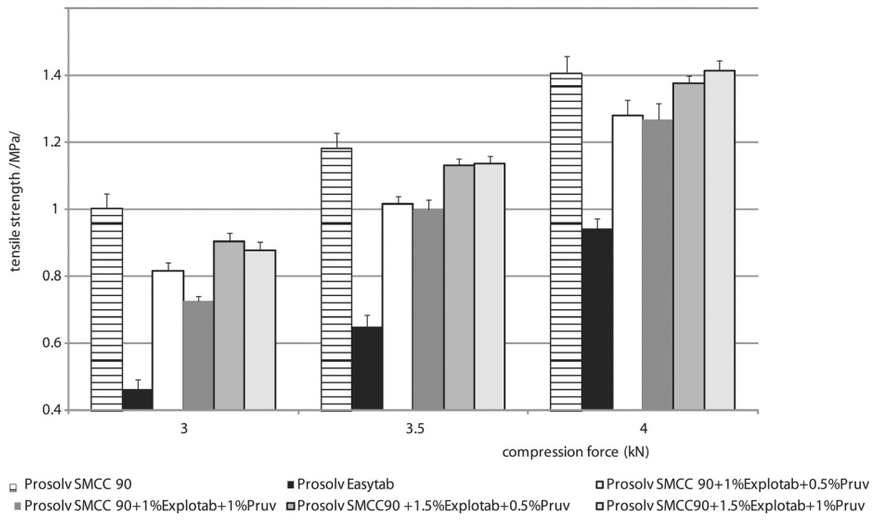

Fig. 1. Tensile strength of tablets in function of compression force

Table 1. Values of energies of compression and the value of plasticity at the compression force of 3.5 kN

Tableting material	E_{max} /J/(s_d /J/)	E1 /J/ (s_d /J/)	E_2 /J/ (s_d /J/)	E_3 /J/ (s_d /J/)	Pl /%/ (s_d /%/)
Prosolv SMCC 90	9.38 (0.28)	4.169 (0.260)	4.802 (0.024)	0.407 (0.009)	92.20 (0,14)
Prosolv Easytab	8.65 (0.19)	3.706 (0.180)	4.526 (0.025)	0.414 (0.005)	91.61 (0.12)
P + 1% E + 0,5% Pr	9.19 (0.16)	4.045 (0.144)	4.725 (0.019)	0.418 (0.004)	91.88 (0.07)
P + 1% E + 1% Pr	9.24 (0.22)	4.145 (0.189)	4.681 (0.033)	0.412 (0.005)	91.92 (0.08)
P + 1.5% E + 0.5% Pr	9.06 (0.17)	3.96 (0.159)	4.692 (0.017)	0.412 (0.006)	91.92 (0.11)
P + 1.5% E + 1% Pr	9.41 (0.12)	4.306 (0.099)	4.700 (0.023)	0.409 (0.004)	91.99 (0.08)

E_{max} – total energy (E_1+E_2+E_3), E_1 – energy of friction, E_2 – energy accumulated by the tablet, E_3 – energy of decompression, Pl – plasticity, s_d – standard deviation, P – Prosolv SMCC 90, E – Explotab, Pr – Pruv

tablets made from Prosolv SMCC 90 alone; on the other hand, the least strength was found in tablets made from the substance Prosolv Easytab, the compression forces of 3 kN being the values below the lower limit of the optimal strength of tablets (0.56 MPa)[13]. The difference in the strength with respect to the tablets made from pure Prosolv SMCC 90 is about 0.5 MPa, so from this aspect the substance is worse compressible. An increase in the compression force by 1 kN nevertheless increases the strength approximately twice. In the mixtures from Prosolv SMCC 90 it is evident that stronger tablets are provided by the mixture with a higher share of Explotab. The influence of Pruv on the strength varies within the range of the individual compression forces; at the compression force of 3 kN a higher share of Pruv decreases tablet strength, with 4 kN it is the reverse in the case of the mixture with 1.5% of Explotab, and with the compression force 3.5 kN there is no statistically significant difference within different Pruv concentrations.

The results of the energetic evaluation of compaction of these tableting compositions by the compression force of 3.5 kN are shown in Table 1. This compression force was selected for this evaluation on the basis of evaluated strength, which in the compression force ranges already in the case of all tableting compositions in the optimal range or at the upper limit of this range (0.56–1.12 MPa)[13]. The result shows the lowest value of the maximal energy in the substance Prosolv Easytab, which is due to the lowest value of energy for friction (E_1) and the energy accumulated by the tablet during compression (E_2). There are no marked differences between the tableting compositions in the values of energy of decompression and plasticity, the highest value of plasticity being recorded in Prosolv SMCC 90 alone. It means that in the case of the substance Prosolv Easytab less energy is consumed with the same compression force than in Prosolv SMCC 90 alone or its mixtures with Explotab and Pruv, but the compacts are less strong due to the presence of other ingredients. Nevertheless, this is not a significant problem because an increase in the compression force by 0.5 kN increases the strength by about 0.2–0.3 MPa.

Figure 2 represents the dependence of disintegration time of tablets on compression force. Tablets made from pure Prosolv SMCC 90 show the longest disintegration time, and the dependence on compression force increases. Tablets made from Prosolv Easytab show a markedly shorter disintegration time due to the presence of the disintegrant Explotab and it is of interest that the dependence on compression force slightly decreases. Tablets made from the physical mixtures of Prosolv SMCC 90, Explotab and Pruv show even a shorter disintegration time, but there is no principal

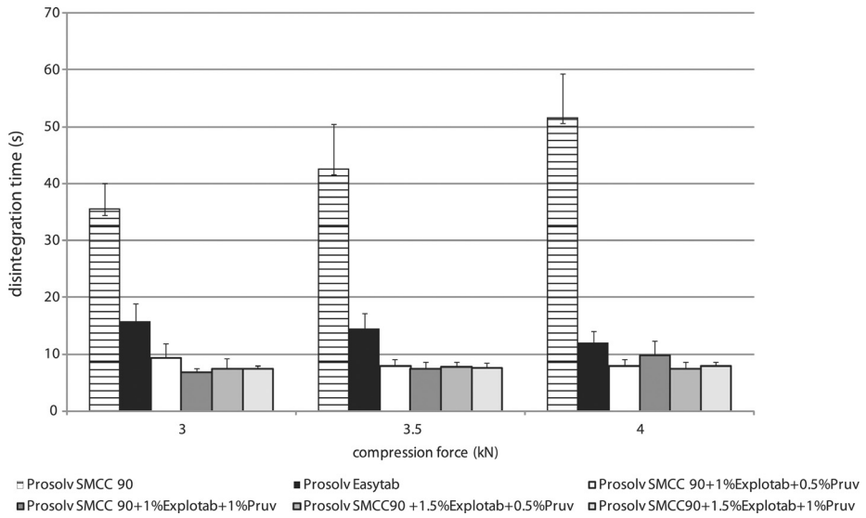

Fig. 2. Disintegration time in function of compression force

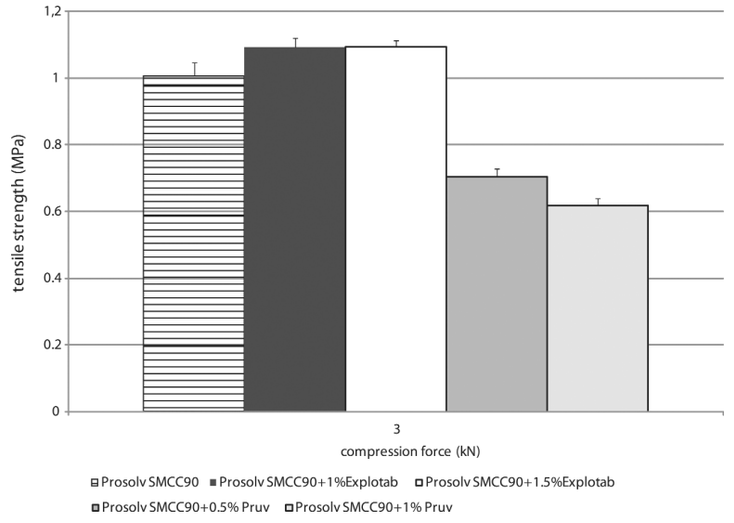

Fig. 3. Tensile strength of tablets at the compression force of 3 kN

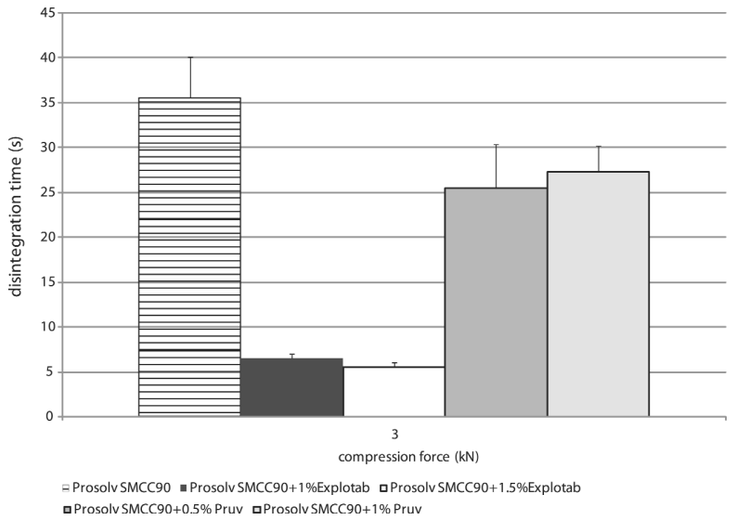

Fig. 4. Disintegration time at the compression force of 3 kN

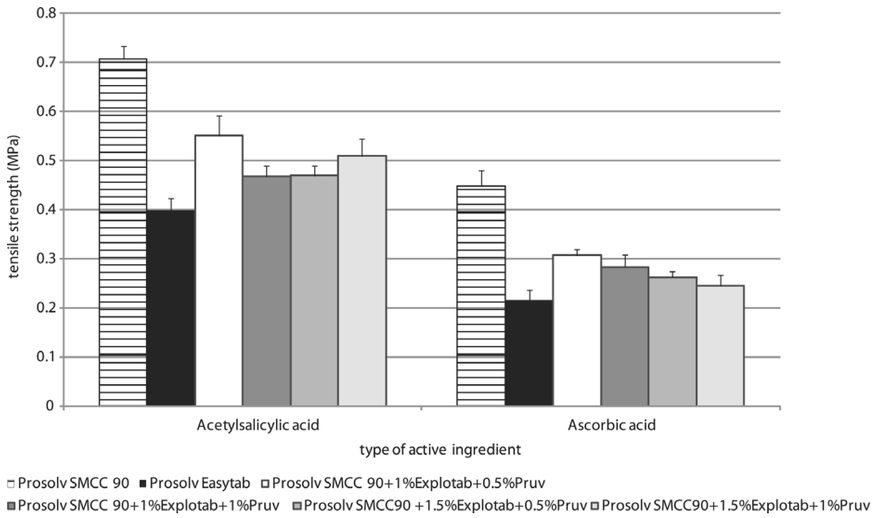

Fig. 5. Tensile strength of tablets at the compression force of 4 kN: mixtures with active ingredients

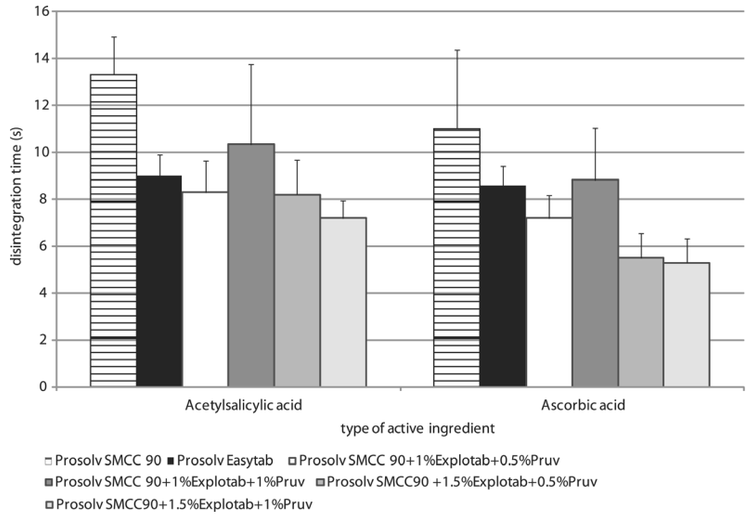

Fig. 6. Disintegration time at the compression force of 4 kN: mixtures with active ingredients

difference within the individual mixtures. However, it could be theoretically assumed that the longest disintegration time will be found in the tablets containing 1% of Explotab and 1% of Pruv, due to a lower concentration of the disintegrant, and on the other hand, a higher concentration of the hydrophobic lubricant. Nevertheless, the experiment confirmed it only at the compression force of 4 kN. At the compression force of 3.5 kN there is no statistically significant difference in the values of disintegration time of tablets from the individual physical mixtures, at the compression force of 3 kN there is only a higher value for a mixture containing 1% of Explotab and 0.5% of Pruv.

Figure 3 represents individually the effect of Explotab and the effect of Pruv in two concentrations on the tensile strength of tablets made from Prosolv SMCC 90 at the compression force of 3 kN. This compression force was selected because it seemed to be optimal from the aspect of tensile strength of tablets made from pure Prosolv SMCC 90. The above facts clearly show that an addition of Explotab increases the strength of tablets and there is no statistically significant difference within the range of the employed concentrations of 1 and 1.5%. An addition of Pruv decreases the tensile strength, more in the case of the concentration of 1%.

Figure 4 records the same for the disintegration time of tablets. The longest disintegration time is found in the tablets made from pure Prosolv SMCC 90. An addition of Pruv shortens disintegration time, because in spite of its hydrophobicity it decreases the strength of bonds of the dry binder. Within the range of its concentrations employed, there is no statistically significant difference between the values. The most marked shortening of disintegration time of tablets is produced by an addition of the preparation Explotab, more in the concentration of 1.5%. It is logical, because Explotab acts as a disintegrant.

Figure 5 represents the values of tensile strength of tablets made from tableting compositions containing active ingredients at the compression force of 4 kN. The strongest tablets in the case of both active ingredients are those with pure Prosolv SMCC 90; those containing acetylsalicylic acid are the only ones to achieve the optimal strength with this compression force. Within the framework of the comparison of active ingredients, the tablets containing acetylsalicylic acid are stronger, which is due to its plastic deformation[14]. On the other hand, the least strong tablets are those made from the substance Prosolv Easy tab, i.e. their strength is lower than the strength of the tablets made from the physical mixtures of Prosolv SMCC 90, Explotab and Pruv. Of these mixtures, the strongest tablets are always those containing 1% of Explotab and 0.5% of Pruv.

Disintegration times of tablets containing active ingredients were very short, in the units of seconds (Fig. 6). Greater standard deviations blur more significant differences within the comparison of tableting compositions and active ingredients. The longest disintegration time was observed in the case of acetylsalicylic acid in the tablets with pure Prosolv SMCC 90 and in those made from the mixture of Prosolv SMCC 90 with 1% Explotab and 1% Pruv. It is also the case of ascorbic acid, where there is no statistically significant difference in the case of the above-mentioned mixture with the tablets made from the substance Prosolv Easytab. The shortest disintegration time was found in the tablets with 1.5% of Explotab, a slightly shorter period was in the case of ascorbic acid, because it is, in addition, well soluble in water.

It can be concluded that the substance Prosolv Easytab is well compressible from the energetic aspect, because the total energy of compression is decreased due to decreased energy consumed by friction and the energy accumulated by the tablet after compaction. Compacts possess a lower strength in comparison with Prosolv SMCC 90 and the physical mixtures of Prosolv SMCC 90 with Explotab and Pruv. However, their strength can be easily increased even by a small increase in compression force; with an increase in compression force from 3 to 4 kN their strength is increased already about twice. Tablets disintegrate due to the contained disintegrant much more quickly than those with pure Prosolv SMCC 90. The results of this paper and above all the facts that the high functionality excipient Prosolv Easytab ensures altogether the functions of the dry binder, lubricant, glidant, and disintegrant, which eliminates multiple mixing of individual excipients and markedly decreases productions costs, demonstrate the suitability of the use of this co-processed dry binder.

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