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Study of rheological and tableting properties of lubricated mixtures of co-processed dry binders for orally disintegrating tablets.

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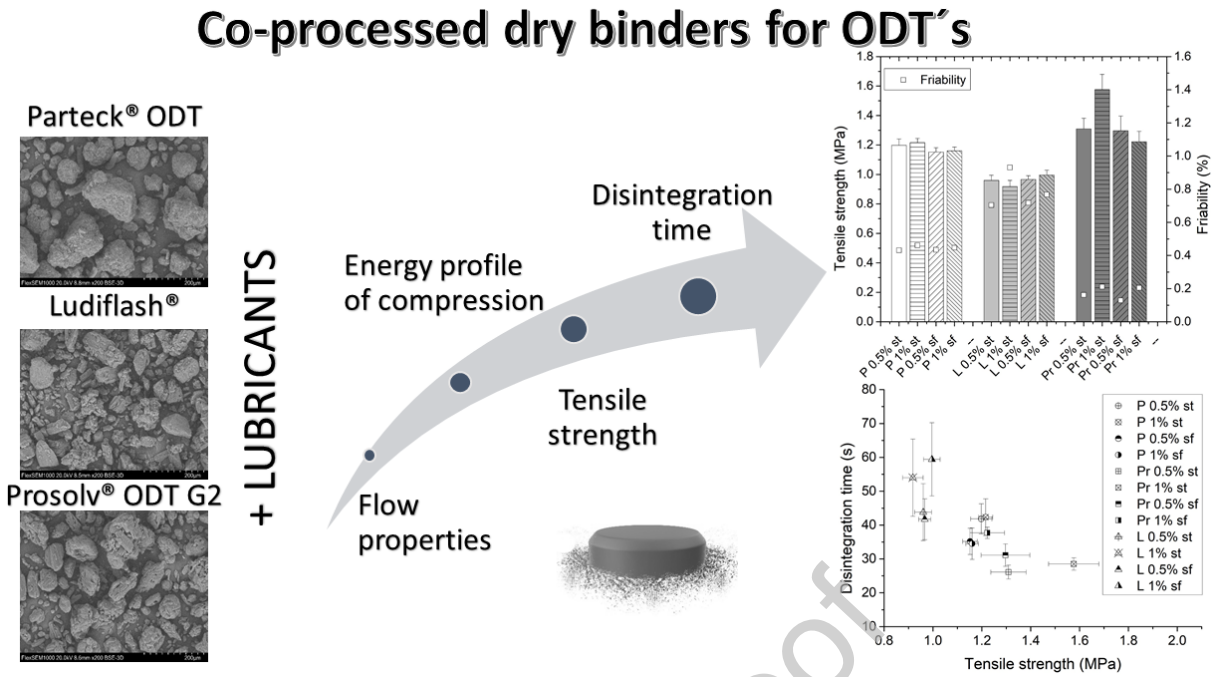
Graphical Abstract



Highlights

- Co-processed dry binders for ODT are multifunctional excipients
- The energy of pre-compression depends on the angle of internal friction
- Microcrystalline cellulose improves compression and tableting properties
- Composition of co-processed dry binders is more important than compression force
- Friability correlates with the tensile strength of tablets

- Disintegration time may not directly depend on wettability and porosity

Abstract

Co-processed dry binders for ODTs are important multifunctional excipients for tablet manufacturing by direct compression. Testing their binary mixtures with lubricants is an important aspect of their use in combination with drugs. The aim of this study was to evaluate the rheological and compression properties of lubricated mixtures of co-processed dry binders Parteck® ODT, Prosolv® ODT G2 and Ludiflash®, and subsequently also the compactability and disintegration time of the tablets made thereof. The lubricants employed were magnesium stearate and sodium stearyl fumarate in the concentrations of 0.5% and 1%. The best flowability was shown by Prosolv® ODT G2 combined with magnesium stearate in the concentration of 0.5%. Lubricated mixtures with Prosolv® ODT G2 showed a lower angle of internal friction as well as lower pre-compression energy values. The values of plastic deformation energy were the highest in the case of Prosolv® ODT G2, which was also reflected in the highest tablet strength. On the contrary, the ejection force values were the lowest for this co-processed dry binder. Magnesium stearate reduced the ejection force more effectively than sodium stearyl fumarate. Prosolv® ODT G2 tablets exhibited the highest tensile strength and shortest disintegration time.

Keywords:

orally disintegrating tablets

co-processed dry binders

flow properties

energy profile of compression

compactability

disintegration time

1. Introduction

Orodispersible tablets (ODTs) are described as solid dosage forms that disintegrate in the oral cavity within a few seconds without the need to chew or wash the tablet down. They represent a possible approach to improve patient compliance and simplify drug administration in geriatric patients, children, and patients with affected mucosa of the upper gastrointestinal tract (Kumar et al., 2011). A wide range of ODT medications, such as analgesics, antihypertensives, and antidepressants, are already commercially available (Comoglu and Dilek Ozyilmaz, 2019). In recent years there has also been a growing interest in the development of ODTs containing for example naloxone (Fischer et al., 2015), diphenhydramine (Wang et al., 2017), metformin (Petrovick et al., 2018) and probiotics (Hoffmann et al., 2020; Hoffmann and Daniels, 2019).

High demands are placed on ODTs, especially in terms of their disintegration time. According to the European Pharmacopoeia (Council of Europe - EDQM, 2020), it is important that the

disintegration time of ODTs does not exceed 3 minutes. However, the requirements of the USP (USP, 2015) and the FDA are stricter, demanding a disintegration time of up to 30 s. Therefore, the tablets must have sufficient porosity or contain a highly efficient superdisintegrant.

The simplest and economically most advantageous method of ODT preparation is direct compression. In this process, the API is simply mixed with excipients and subsequently compressed into tablets (Bowles et al., 2018). Despite the apparent simplicity of the process, the excipients must meet high requirements such as sufficient flowability, compressibility, compactability, and a high dilution potential (Drašković et al., 2018). Thus, the selection of fundamental excipients, especially dry binders, which often form a larger part of the tablet, is essential for direct compression technology.

In recent years, there has been considerable interest in the investigation of co-processed dry binders. They are a promising group of excipients that are formed by a combination of two or more excipients, produced by using the "co-processing" method, for example, spray drying, wet granulation or co-crystallization (Nadavadekar and Koliyote, 2014). Several studies have been performed to compare critical parameters of co-processed dry binders to the parameters of their physical mixtures. It has been shown that co-processed dry binders manifest improved dilution potential, flowability, compressibility, decreased lubricant sensitivity, and higher tensile strength of compacts (Apeji et al., 2018; Arida and Al-Tabakha, 2008; Drašković et al., 2018; Estrada Flores et al., 2000; Mužíková et al., 2017; Van Veen et al., 2005). The incorporation of a number of excipients into the monoparticle structure also eliminates problems caused by physical mixtures such as segregation, inhomogeneity of the mixture and tablet weight variability. Furthermore, fewer production steps are required to prepare the directly compressed mixtures resulting in a faster and more cost-effective procedure (Aljaberi et al., 2013).

Co-processed dry binders are used in the field of ODTs production especially because of their multifunctionality. Usually, co-processed dry binders for ODTs contain a superdisintegrant (Bowles et al., 2018). Moreover, the majority of co-processed dry binders are produced by spray drying, which results in more porous powders and faster disintegration time of compacts which is very important for ODTs (Benabbas et al., 2021; Daraghmeh et al., 2015; Mishra et al., 2006).

ODTs, compared to conventional tablets, are more prone to breaking during packaging or transportation due to their brittle structure. It has been proved that co-processed dry binders exhibit higher energy of plastic deformation with higher tablet tensile strength, and lower friability (Mužíková et al., 2019).

Co-processed dry binders investigated in this work are Ludiflash®, Parteck® ODT, and Prosolv® ODT G2. The main component of these co-processed dry binders is mannitol with an added superdisintegrant. Mannitol is a sugar alcohol, has a sweet taste, causes a cool mouthfeel, and is readily soluble, which are the main benefits of its use in ODTs (Stoltenberg and Breitkreutz, 2011).

A number of studies have been carried out to investigate Ludiflash®, Parteck® ODT, and Prosolv® ODT (Amelian et al., 2016; Gülbağ et al., 2018; Gulsun et al., 2018; Krupa et al., 2012; Moqbel et al., 2016; Petrovick et al., 2018; Tayel et al., 2017; Türkmen et al., 2018), however, their characterization was mostly influenced by the presence of an API.

The present paper aimed to describe the rheological properties of co-processed dry binders Ludiflash®, Parteck® ODT and Prosolv® ODT G2 in combination with lubricants by using the shear cell method, by measuring the flow time and by determining the Hausner ratio and compressibility index. Furthermore, the compressibility of powders was analyzed by using the energy profile of the compression process. The true density of the lubricated powders was measured, and the porosity of the tablets was calculated. The lubricant efficiency was

assessed by measuring the ejection force required to eject the tablet from the die. The compactability was examined by testing the tensile strength and friability of the tablets, and the effectiveness of superdisintegrants was tested by measuring the tablet wettability and disintegration time.

2. Materials and methods

2.1.Materials

The studied co-processed dry binders were Prosolv® ODT G2 (15-30 % microcrystalline cellulose, 1.5-2.5 % colloidal silicon dioxide, 60-70 % D-mannitol, 4-6 % fructose and 4-6 % crospovidone) (JRS Pharma, Germany), Ludiflash® (90% D-mannitol, 5% crospovidone and 5% polyvinyl acetate) (BASF, USA) and Parteck® ODT (90-95 % granulated D-mannitol and 3-7 % croscarmellose sodium) (Merck KGaA, Germany). As lubricants, magnesium stearate (Acros Organics, USA) and sodium stearyl fumarate (Lubripharm® SSF, SPI Pharma, France) were used.

2.2.Preparation of tableting powders

In total, 12 tableting mixtures containing Prosolv® ODT G2, Ludiflash® or Parteck® ODT with lubricants such as magnesium stearate or sodium stearyl fumarate in concentrations of 0.5% or 1% were prepared (**Tab 1**). Binary mixtures weighing 40 g each were mixed in a mixing cube (KB 15S, Fy Erweka, Germany) for 2.5 minutes. The revolutions velocity was set to 17 rpm.

Table 1 Composition of tableting powders containing Parteck® ODT (P), Ludiflash® (L), and Prosolv® ODT G2 (Pr) with magnesium stearate (st) or sodium stearyl fumarate (sf).

Sample	**Parteck® ODT (%)**	**Ludisflash® (%)**	**Prosolv® ODT G2 (%)**	**st (%)**	**sf (%)**
P 0.5 st	99.5			0.5	

P 1 st	99.0				1.0	
P 0.5 sf	99.5					0.5
P 1 sf	99.0					1.0
L 0.5 st		99.5			0.5	
L 1 st		99.0			1.0	
L 0.5 sf		99.5				0.5
L 1 sf		99.0				1.0
Pr 0.5 st			99.5		0.5	
Pr. 1 st			99.0		1.0	
Pr. 0.5 sf			99.5			0.5
Pr. 1 sf			99.0			1.0

2.3.Scanning electron microscopy (SEM)

The microstructure of the co-processed excipients was observed by a scanning electron microscope FlexSEM 1000 (Hitachi, Japan), the used accelerating voltages were 15 kV and 20 kV. Prior to the measurement, the samples were coated with a 7 nm-thick golden layer by a sputter coater EM ACE200 (Leica, Germany).

2.4.Determination of particle size and distribution by laser diffraction

In order to understand the properties of powders in more detail, the particle size and distribution were measured. The volume median diameters $d_{v0.1}$ (µm), $d_{v0.5}$ (µm), $d_{v0.9}$ (µm) and particle size distribution width (SPAN) of all three co-processed excipients were measured by laser light diffraction method using Malvern Mastersizer 3000 (Malvern Instruments, UK). SPAN values were calculated using the **Eq. (1)**.

$$SPAN = (d_{v0.9} - d_{v0.1}) / d_{v0.5} \quad (1)$$

where: $d_{v0.1}$, $d_{v0.5}$, $d_{v0.9}$ stand for volume median diameter of the particles (µm).

The powders were tested using a dry method with the employment of a dispersion unit (Aero S). Prior to the examination, all samples were carefully stirred to ensure homogeneity while sampling. Air pressure was set to 2 bars and feed rate to 50%. Refractive index (1.6) was chosen the same as for D-mannitol since it forms the most of all 3 powders. Absorption

indexes for Parteck® ODT, Prosolv® ODT G2 and Ludiflash® were set to 0.1; 0.01 and 0.01 respectively. All powders were measured in triplicates and the mean and standard deviation were calculated.

2.5.Evaluation of rheological properties of tableting materials

2.5.1. Shear tests by FT4

The most critical area to understand flowability is the effect of the compaction on bulk solids (Jan et al., 2017). The shear test method is most often used to analyze the flow of powders under consolidation stresses. In our study, the shear test was performed using an FT4 powder rheometer (Freeman Technology, UK) according to the ASTM D6773-16 standard. The powder bed was loosened by a spiral blade moving throughout the powder sample and thus any stress history or excess air occurring as a result of processing and handling the powder was removed (Tran et al., 2021). The shear test consisted of the following steps: 1. shear head reconsolidation, 2. preshear until steady state achieved, 3. shear test measurement (Freeman et al., 2009). The test consists of measuring five points for different shear stresses. The measuring apparatus consisted of two vessels (50 mm, 85 mL), blade, vented piston, and a shear head. The batch of material used for one experiment was 80 g. The test samples were preconsolidated at 1 kPa, 3 kPa and 6 kPa. The Mohr method of circles and linear yield locus were used for data analysis (Carson and Wilms, 2006). It is usually considered that the Mohr circle representing the state of stress during the material consolidation in the critical state shear closes the yield locus on the consolidation side (Macri et al., 2020). All measurements for individual consolidation stresses were repeated 3 times. The measurement results were interpreted as mean ± standard deviation. Cohesion (*C*), flow function parameter (*ff*), and Angle of internal friction (*AIF*) were derived from the measurement of shear properties.

2.5.2. Evaluation of flow time

In order to complete our understanding of flow properties of studied binary mixtures, flow time was tested by measuring the time required for flowing of a particular quantity of powder. The test was performed according to the European Pharmacopoeia (Council of Europe – EDQM, 2020) using an instrument for evaluation of flow properties (Erweka GTB, Germany).

40 g of mixture was freely poured into a 100 ml funnel with a 10 mm orifice. After opening the bottom of the funnel, flow time was measured. The test was performed five times and the mean and standard deviation were calculated from the results obtained.

2.5.3. Evaluation of bulk and tap density, Hausner ratio, and compressibility index

Bulk and tap density were measured according to the European Pharmacopoeia method (Council of Europe - EDQM, 2020), three times, and the means and standard deviation were calculated from the values obtained. 50 ml V_b of powder was freely poured into the weighed graduated cylinder. After determining the weight of powder m (g) the bulk density ρ_b (g/cm^3) was calculated using **Eq. (2)**.

$$\rho_b = m / V_b \quad (2)$$

Afterwards, the graduated cylinder was tapped 1250 times and the tap volume V_t (ml) was recorded. The tap density ρ_t (g/cm^3) was calculated according to the **Eq. (3)**.

$$\rho_t = m / V_t \quad (3)$$

Finally, Hausner ratio *HR* and compressibility index *CI* (%) were calculated from the values of both densities using the **Eq. (4)** and **Eq. (5),** respectively.

$$HP = \rho_t / \rho_b \quad (4)$$

$$CI = [(\rho_t - \rho_b) / \rho_t] \cdot 100 \quad (5)$$

2.6.Evaluation of energy profile of compression and ejection force

Tablets were compressed on a material testing device T1 – Fro 50 TH.A1K Zwick/Roell, which develops a tensile and compression force of up to 50 kN. 0.5000 ± 0.0010 g of

tableting powder was weighed for each tablet. The powder was quantitatively transferred to a special metal die with a diameter of 13 mm and fitted with circular flat-faced punches. Compression velocity was 40 mm/min, the preload 2 N, the preload velocity 2 mm/s and compression force 7 kN. The software testXpert V9.01 enabled complete visualization of the upper punch position and force in real time. For 10 tablets, the energy profile of compression process was evaluated using the software mentioned above and "force – displacement" record was graphically processed. The energy evaluation included quantification of pre-compression energy *E1* (J), energy of plastic deformation *E2* (J), energy of elastic deformation *E3* (J). Furthermore, the values of total energy of compression *Emax* (J) which is expressed by the sum of all three energies *(E1 + E2 + E3)* and energy of compression *Ecom* (J) which is the sum of *E2* and *E3* were obtained (Ragnarson, 1996). Plasticity *P1 (%)* was calculated according to the **Eq. (6)** (Stamm and Mathis, 1976).

$$Pl = [E2 / (E2 + E3)] \cdot 100 \quad (6)$$

For six tablets, the ejection force *Fe* (N) was evaluated using the testXpert V9.01 computer program, which was obtained after releasing the locking component of the lower punch and ejecting the tablet by the upper punch.

2.7.Evaluation of density and porosity of the tablets

The tablet porosity *P* (%) was calculated using the **Eq. (7).**

$$P = (1 - \rho_r) \cdot 100 \quad (7)$$

Relative density ρ_r was calculated using the **Eq. (8).**

$$\rho_r = m / (\pi r^2 h \rho_t) \quad (8)$$

where *m* means tablet mass (g), *r* - tablet radius (cm), *h* - tablet height (cm), ρ_t - true density (g/cm^3).

True density ρ_t values were obtained by measuring the powders using a helium pycnometer AccuPyc II 1340 (Micrometrics Inc., USA).

2.8.Evaluation of compactability and tablet friability

The compactability was evaluated using a test on the tablet tensile strength. Ten tablets from each formulation were tested at least 24 hours after compression. The Tablet Tester 8M (Dr. Schleuniger Pharmatron AG, Switzerland) was used for measuring destruction force together with the thickness and diameter of the tablets. The tensile strength was calculated according to the **Eq. (9)** (Fell and Newton, 1970).

$$TS = 2F / \pi dt \quad (9)$$

where: TS – tensile strength (MPa), F – destruction force (N), d – tablet diameter (mm), t – thickness of the tablet (mm).

Friability of 13 tablets from each formulation was measured using Sotax FT2 (Sotax Co., Switzerland) at 25 rpm for 4 minutes according to the Ph. Eur. (Council of Europe – EDQM, 2020). The friability was calculated in percentage as a ratio of weight loss and the initial weight.

2.9.Evaluation of wetting time, water absorption, and disintegration time of tablets

The tablets were evaluated 24 hours after compression. Four layers of filter paper were placed in a Petri dish with a diameter of 4 cm containing 4 mL of purified water and methylene blue. Prior to the measurement, the tablet was weighed on an analytical balance. Then the tablet was placed on the paper and the time of water uptake t (s) was measured. The wetted tablet was weighed again and water absorption ratio R (%) was calculated using Eq. (10) (Bi et al., 1996). The measurement was done in triplicate and mean and standard deviation were calculated.

$$R = (m_b - m_a) \cdot 100 / m_a \quad (10)$$

where m_a – mass of tablet before wetting (g), m_b – mass of tablet after wetting (g), R – water absorption ratio (%).

Six tablets of all formulations were tested for disintegration time using an Erweka ZT 301 (Erweka GmbH, Germany). The test was employed in accordance with requirements of European Pharmacopoeia 10 (Council of Europe – EDQM, 2020). The disintegration time test was performed without the use of discs in 750 ml of purified water tempered to 37 ± 1 ° C. The mean and standard deviation were calculated from the measured values.

2.10. Mathematical and statistical processing of results

The energy profile of the compression process was statistically evaluated directly by the program testXpert V 9.01 during the compression process. For statistical evaluation of results including flow properties, tensile strength, and disintegration time of tablets the program MS Excel was used. In the case of similar significance of values, an ANOVA test at the level of significance of 0.05 was employed. In the following text, "statistically significant" results are those for which the p-value is less than 0.05.

3. Results and discussion

The combination of dry binder and lubricant is a combination of two fundamental excipients in directly compressible tableting powders. For this reason, it is important to test the rheological, compression, and tableting properties of these mixtures. The aim of our work was to widen current knowledge of co-processed dry binders, which are suitable for orodispersible tablets, Prosolv® ODT G2 (**Fig. 1**), Ludiflash® (**Fig. 2**) and Parteck® ODT (**Fig. 3**). The studied co-processed dry binders were combined with lubricants magnesium stearate or sodium stearyl fumarate at 0.5% and 1% concentrations. The flow properties, the energy profile of the compression process, including the ejection force, and the properties of the tablets, namely the tensile strength, friability, wettability, porosity, and the disintegration time, were evaluated. The compression force of 7 kN was chosen so that the tensile strength of the tablets from all formulations was in the range of 1 – 1.2 MPa.

3.1.SEM imaging and particle size analysis

The SEM observations of the powders revealed several differences in their microstructure. The Prosolv® ODT G2 powder (**Fig. 1**) is similar to Ludiflash® (**Fig. 2**), with the difference that the Prosolv® ODT G2 particles have a smoother surface. The Parteck® ODT particles are quite blunt in shape, while Ludiflash® is composed of sharper plate-like particles and rough-surfaced aggregates of small fragments. Parteck® ODT particles (**Fig. 3)** are formed by agglomerated D-mannitol, whereas Ludiflash® and Prosolv® ODT G2 are comprised of non-agglomerated mannitol. Therefore, the surface of Parteck® ODT particles is smoother, and the shape is more regular. Parteck® ODT is also characterized by a bigger particle size compared to Ludiflash® and Prosolv® ODT G2. This fact is confirmed by the laser diffraction analysis, where volume median diameter d_{v50} of Parteck® ODT particles is 161.3 µm, whereas d_{v50} of Prosolv® ODT G2 and Ludiflash® is 64.4 µm and 81.4 µm, respectively (**Tab. 2**).

Ludiflash® powder shows less homogeneity. This is supported by the laser diffraction analysis as it reveals that SPAN value of Ludiflash® (3.030) is higher than for Parteck® ODT or Prosolv® ODT G2 (1.936 and 1.942). This indicates that Ludiflash® powder is more polydisperse which can lead to problems like segregation during the manufacturing of tablets. The SPAN values of commonly used co-processed excipients, including Ludiflash®, Parteck® ODT and Prosolv® ODT G2, were also investigated by (Hejduk et al., 2021). Although our results slightly differ (their SPAN of Ludiflash® was 6.23), they also came to the conclusion that further application of Ludiflash® should be carefully considered (Hejduk et al., 2021).

Table 2 Particle size distribution and SPAN of three studied co-processed dry binders; mean standard ± deviation.

Sample	d_{v10} ± STD (µm)	d_{v50} ± STD (µm)	d_{v90} ± STD (µm)	SPAN ± STD (-)
Parteck® ODT	52.2 ± 5.6	161.3 ± 5.3	364.0 ± 8.2	1.936 ± 0.048
Prosolv® ODT G2	20.3 ± 0.7	64.4 ± 1.3	145.3 ± 2.5	1.942 ± 0.032

Ludiflash®	16.3 ± 3.9	81.4 ± 2.8	266.3 ± 2.6	3.030 ± 0.077

3.2. Evaluation of rheological properties of tableting materials

3.2.1. Shear testing

Table 3 contains the values of parameters *C*, *ff* and *AIF* obtained from shear tests at consolidation stresses 1 kPa, 3 kPa, and 6 kPa. Cohesion is directly related to the physical properties of the material such as particle size and distribution and directly affects the mechanical and flow properties of the material (Saw et al., 2013). The analysis of Parteck® ODT samples (P) achieved the lowest value of cohesion I, in powder mixture with added 1% magnesium stearate (P 1% st), when at a consolidation stress of 6 kPa, the instrument was not able to analyze low values of cohesion by linear yield locus. Cohesion values at consolidation stress 1 kPa and 3 kPa, in the Parteck® ODT sample with sodium stearyl fumarate (sf) lubricant, increased with increasing lubricant content. In most experiments, higher cohesion values were found for Prosolv® ODT G2 (Pr) samples than for Parteck® ODT samples because Parteck® ODT has the biggest particles, and cohesion values increase with decreasing particle size. Samples with a lubricant concentration of 0.5% showed proportional growth of *C* with increasing consolidation stress. As with the Parteck® ODT samples, Prosolv® ODT G2 samples in most cases showed a decrease in *C* with increased lubricant content. The highest cohesion values for the Ludiflash® (L) material refer to the highest interparticle forces that caused the material not to sink through the orifices in the flow test. Ludiflash® also have a higher value of SPAN. Except for sample L 1% sf, all powder mixtures examined showed an increase in *C* associated with an increased lubricant content. The values of the flow function parameter (*ff*) reached, in most cases, values of more than 10, which characterize materials as free-flowing (Schulze et al., 2008). The values of the parameter *ff* had the opposite trend as in the work (Stoltenberg and Breitkreutz, 2011), which analyzed these co-processed dry binders in mixtures with Hydrochlorothiazide. The lowest *ff* values were observed for Ludiflash® samples. With increasing consolidation stress, the value of *ff* increased. For Prosolv® ODT G2 samples as well as for Ludiflash® with increasing consolidation stress, the *ff* value increased up to 57.81 for the sample Pr 1% sf. Prosolv® ODT G2 samples at a consolidation stress of 3

kPa had ff values similar to those in the work (Chen et al., 2018). Samples analyzed at a consolidation stress of 6 kPa had higher *ff* values for samples with a higher lubricant content; with lower stresses, the trend was mostly the opposite. Parteck® ODT analysis observed that at a lubricant content of 1%, the flow function parameter increased and decreased, with increasing consolidation stress using 0.5% lubricant. Although Parteck® ODT did not manage to determine high *ff* values at a consolidation stress of 6 kPa due to its excellent flow properties, the internal friction angle of the *AIF* was determined. Similar to *ff*, for samples containing 1% lubricant, its value increased. At consolidation stresses of 3 kPa and 6 kPa, the value of *AIF* increased with increasing lubricant content, at 1 kPa the trend was the opposite. All *AIF* values measured in Prosolv® ODT G2 samples increased with increasing consolidation stress as well as with lubricant content. The lowest *AIF* values were observed for Prosolv® ODT G2, the highest for Ludiflash®. For samples with 1% lubricant, *AIF* increased in proportion to consolidation stress. The higher the AIF value, the greater the interparticle forces in the powder material, which results in a deterioration of the flow properties of the material.

Table 3 Properties of experimental powder mixtures from shear cell tests.

Sample	C1kPa ± STD (kPa)	C3kPa ± STD (kPa)	C6kPa ± STD (kPa)	ff1kPa ± STD (-)	ff3kPa ± STD (-)	ff6kPa ± STD (-)	AIF1kPa ± STD (°)	AIF3kPa ± STD (°)	AIF6kPa ± STD (°)
P 0.5 st	0.027 ± 0.011	0.105 ± 0.031	0.065 ± 0.108	17.39 ± 6.35	13.43 ± 3.22	39.47 ± 0.00	33.98 ± 0.99	33.25 ± 0.87	35.25 ± 1.74
P 1 st	0.037 ± 0.024	0.037 ± 0.018	N/A	9.45 ± 1.93	48.82 ± 5.00	N/A	33.05 ± 1.84	34.25 ± 0.82	35.35 ± 0.13
P 0.5 sf	0.027 ± 0.016	0.059 ± 0.016	0.052 ± 0.033	23.38 ± 3.93	22.02 ± 5.41	60.09 ± 4.00	34.85 ± 1.16	33.17 ± 0.94	33.48 ± 0.24
P 1 sf	0.055 ± 0.005	0.073 ± 0.002	N/A	7.87 ± 0.64	17.67 ± 0.46	N/A	32.20 ± 1.16	33.86 ± 0.39	35.87 ± 0.10
Pr 0.5 st	0.039 ± 0.015	0.089 ± 0.043	0.108 ± 0.028	12.24 ± 3.58	16.49 ± 6.42	24.94 ± 7.26	29.85 ± 1.96	31.34 ± 0.66	32.18 ± 0.22
Pr 1 st	0.044 ± 0.011	0.107 ± 0.007	0.092 ± 0.002	10.65 ± 2.78	12.18 ± 0.91	27.77 ± 0.54	30.06 ± 1.57	32.28 ± 0.21	33.05 ± 0.10

Pr 0.5 sf	0.051 ± 0.025	0.114 ± 0.017	0.136 ± 0.030	10.95 ± 6.73	11.76 ± 1.77	19.43 ± 4.18	29.52 ± 2.49	30.52 ± 0.59	31.54 ± 0.18
Pr 1 sf	0.047 ± 0.012	0.095 ± 0.031	0.066 ± 0.037	9.97 ± 2.53	14.80 ± 5.33	57.81 ± 7.00	29.71 ± 1.32	31.37 ± 1.10	33.02 ± 0.42
L 0.5 st	0.060 ± 0.005	0.046 ± 0.041	0.077 ± 0.116	7.59 ± 0.74	19.04 ± 0.04	33.42 ± 3.00	36.61 ± 0.88	38.52 ± 0.97	37.92 ± 1.02
L 1 st	0.097 ± 0.010	0.150 ± 0.047	0.097 ± 0.139	5.02 ± 0.44	9.93 ± 3.41	16.77 ± 5.40	34.63 ± 0.25	35.80 ± 0.87	36.89 ± 1.72
L 0.5 sf	0.074 ± 0.035	0.088 ± 0.129	0.167 ± 0.066	7.22 ± 3.17	10.09 ± 4.78	13.11 ± 1.72	35.49 ± 1.69	36.69 ± 2.91	36.36 ± 0.70
L 1 sf	0.088 ± 0.013	0.155 ± 0.018	0.149 ± 0.087	5.49 ± 0.63	8.82 ± 0.94	26.67 ± 5.99	34.82 ± 1.34	36.13 ± 0.52	37.26 ± 0.80

The table shows mean values ± standard deviation (n = 3). *C* – cohesion, *ff* – flow function parameter, *AIF* – Angle of internal friction, P – Parteck® ODT, Pr – Prosolv® ODT G2, L – Ludiflash®, st – magnesium stearate, sf – sodium stearyl fumarate.

3.2.2. Evaluation of flow time, bulk and tap density, Hausner ratio, and compressibility index

The values of flow time, both densities and Hausner ratio are given in **Table 4**. The flowability was tested using a 10 mm orifice through which the powder mixtures with Ludiflash® did not flow. Therefore, its flowability was considered to be the worst, which corresponds to the results from shear testing. This may be due to the agglomerates of irregular, sharper plate-like particles with a rough surface (**Fig. 2**). In the case of the remaining co-processed dry binders, the magnesium stearate formulations always flowed better, and its increase in the concentration in Parteck® ODT led to a further improvement in the flowability. In the case of Prosolv® ODT G2, a 0.5% addition of magnesium stearate was more appropriate. Unlike Ludiflash® and Parteck® ODT, Prosolv® ODT G2 contains silicon dioxide, which certainly improves its flowability. Parteck® ODT also flows quite fast (flow time ranges from 7.5 s to 9 s) because its structure is based on granulated mannitol with a

more regular and smoother shape. Another reason for this is its bigger particle size (d_{v50} = 161.3 µm).

Prosolv® ODT G2 with 0.5% addition of magnesium stearate was the best of all formulations and, together with the formulations with Parteck® ODT, belonged to the formulations with the best flow with respect to Hausner's ratio and compressibility index. In terms of powder flow scale according to Ph. Eur. (Council of Europe – EDQM, 2020), it was possible to classify the tested formulations with a flow character *fair* except for the combination of Ludiflash® with 1% sodium stearyl fumarate, where the flow was *good* in terms of Hausner ratio and compressibility index, but the formulation did not flow. Another exception was the combination of Prosolv® ODT G2 with 1% sodium stearyl fumarate, which also did not flow under the given conditions and showed a *passable* flow in terms of Hausner ratio and compressibility index. Increasing the concentration of sodium stearyl fumarate always led to a deterioration in flowability.

Table 4
Flow time, densities, Hausner ratio, and compressibility index of powders (40 g; orifice 10 mm).

Sample	Flow time ± STD (s)	Bulk density ± STD (g/cm³)	Tap density ± STD (g/cm³)	True density ± STD (g/cm³)	Hausner ratio ± STD (-)	Compressibility index ± STD (%)
P 0.5 st	8.0 ± 0.2	0.58 ± 0.01	0.69 ± 0.01	1.4888 ± 0.0003	1.19 ± 0.01	15.67 ± 1.25
P 1 st	7.5 ± 0.4	0.57 ± 0.01	0.68 ± 0.02	1.4861 ± 0.0002	1.19 ± 0.02	15.67 ± 0.47
P 0.5 sf	8.3 ± 0.2	0.56 ± 0.00	0.68 ± 0.01	1.4930 ± 0.0001	1.21 ± 0.01	17.33 ± 0.47
P 1 sf	9.0 ± 0.4	0.57 ± 0.00	0.68 ± 0.00	1.4902 ± 0.0002	1.19 ± 0.00	16.51 ± 0.41
Pr 0.5 st	7.0 ± 0.2	0.65 ± 0.00	0.78 ± 0.01	1.4830 ± 0.0003	1.20 ± 0.01	16.47 ± 0.41
Pr. 1 st	8.8 ± 0.5	0.66 ± 0.02	0.80 ± 0.00	1.4807 ± 0.0001	1.23 ± 0.02	18.34 ± 1.70
Pr. 0.5 sf	8.8 ± 0.4	0.63 ± 0.01	0.77 ± 0.01	1.4860 ± 0.0002	1.22 ± 0.01	18.73 ± 1.18
Pr. 1 sf	N/A	0.61 ± 0.01	0.78 ± 0.00	1.4816 ± 0.0003	1.29 ± 0.01	22.20 ± 0.59
L 0.5 st	N/A	0.56 ± 0.00	0.68 ± 0.01	1.4599 ± 0.0001	1.21 ± 0.01	17.50 ± 1.08
L 1 st	N/A	0.55 ± 0.00	0.68 ± 0.01	1.4534 ± 0.0001	1.24 ± 0.01	18.67 ± 0.62
L 0.5 sf	N/A	0.56 ± 0.00	0.68 ± 0.01	1.4591 ± 0.0003	1.21 ± 0.01	17.00 ± 0.82

L 1 sf	N/A	0.57 ± 0.00	0.65 ± 0.01	1.4562 ± 0.0006	1.14 ± 0.01	12.20 ± 0.59

P – Parteck® ODT, Pr – Prosolv® ODT G2, L – Ludiflash®, st – magnesium stearate, sf – sodium stearyl fumarate.

3.3. Evaluation of energy profile of compression and ejection force

The values of individual energies and plasticity are given in **Table 5**. The values of precompression energy E1, which is consumed mainly for friction, are the lowest in the case of mixtures with Prosolv® ODT G2, which is associated with the fact that it contains silicified microcrystalline cellulose. MCC alone has a lubricating effect and together with colloidal silicon dioxide, one of the most efficient glidants, is a reason for decreased friction between particles (Majerová et al., 2016; Tran et al., 2019).

Table 5
Values of energy profile of compression, ejection force, and tablet porosity.

Sample	Emax ± STD (J)	E1 ± STD (J)	E2 ± STD (J)	E3 ± STD (J)	Ecom ± STD (J)	Pl ± STD (%)	Fe ± STD (N)	Porosity (%)
P 0.5 st	11.32 ± 0.22	6.12 ± 0.22	4.24 ± 0.03	0.95 ± 0.01	5.20 ± 0.03	81.68 ± 0.16	31.46 ± 1.53	27.44
P 1 st	10.21 ± 0.07	5.12 ± 0.06	4.14 ± 0.03	0.96 ± 0.01	5.09 ± 0.03	81.18 ± 0.15	21.88 ± 0.67	27.24
P 0.5 sf	10.40 ± 0.05	5.13 ± 0.04	4.33 ± 0.02	0.94 ± 0.00	5.27 ± 0.03	92.25 ± 0.09	52.09 ± 5.42	27.73
P 1 sf	10.52 ±0.09	5.35 ± 0.08	4.20 ± 0.02	0.96 ± 0.00	5.17 ± 0.02	81.34 ± 0.09	36.93 ± 1.17	27.13
Pr 0.5 st	8.68 ± 0.13	2.88 ± 0.10	4.88 ± 0.05	0.92 ± 0.02	5.80 ± 0.06	84.14 ± 0.21	21.76 ± 1.79	25.16
Pr. 1 st	9.36 ± 0.15	3.61 ± 0.13	4.81 ± 0.08	0.94 ± 0.01	5.75 ± 0.08	83.68 ± 0.31	19.43 ± 0.43	23.49
Pr. 0.5 sf	8.96 ± 0.07	3.13 ± 0.06	4.91 ± 0.06	0.91 ± 0.02	5.83 ± 0.07	84.32 ± 0.21	31.80 ± 3.75	26.14
Pr. 1 sf	8.53 ± 0.12	2.88 ± 0.09	4.72 ± 0.05	0.96 ± 0.01	5.64 ± 0.05	83.61 ± 0.17	27.74 ± 0.60	24.49
L 0.5 st	11.31 ± 0.12	6.03 ± 0.13	4.39 ± 0.04	0.90 ± 0.01	5.28 ± 0.04	83.01 ± 0.21	26.07 ± 3.56	23.93
L 1 st	10.71 ± 0.13	5.46 ± 0.13	4.33 ± 0.03	0.92± 0.01	5.25 ± 0.03	82.48 ± 0.22	28.15 ± 2.20	22.77
L 0.5 sf	11.12 ± 0.20	5.82 ± 0.16	4.37 ± 0.06	0.92 ± 0.01	5.29 ± 0.06	82.62 ± 0.18	41.26 ± 5.95	22.33
L 1 sf	10.56 ± 0.12	5.32 ± 0.11	4.32 ± 0.03	0.92 ± 0.01	5.24 ± 0.03	82.53 ± 0.17	32.04 ± 1.56	23.33

Emax – total energy of compression, E1 – energy of precompression, E2 – energy of plastic deformation, E3 – energy of elastic deformation, Ecom – energy of compression, Pl –

plasticity, Fe – ejection force, P – Parteck® ODT, Pr – Prosolv® ODT G2, L – Ludiflash®, st – magnesium stearate, sf – sodium stearyl fumarate.

The lower values of E1 also correspond to the results of the angle of internal friction measured by the shear test. The dependence of E1 on the *AIF* is shown in **Fig. 4**. The area of Prosolv® ODT G2 energies on the graph is significantly differentiated from others, where it also showed the lowest *AIF* values at a consolidation load of 1 kPa. The lowest precompression energy values were recorded for Prosolv® ODT G2 samples with 1% sodium stearyl fumarate and 0.5% magnesium stearate.

Precompression energy values (**Table 5**) are higher in the case of both other co-processed dry binders. A statistically insignificant difference between the values is in the case of the addition of 0.5% sodium stearyl fumarate and magnesium stearate, where the highest values of internal friction angle are recorded (**Fig. 4**). In the case of Ludiflash®, the pre-compression energy decreases with a higher concentration of lubricants.

The plastic deformation energy values are again highest in the case of mixtures with Prosolv® ODT G2, which is related to the presence of MCC in the product. Slightly higher values are also shown by Ludiflash® compared to Parteck® ODT. Higher concentrations of lubricants slightly reduce the values of this energy in the case of all co-processed dry binders. The values of elastic deformation energy E3 are slightly higher for mixtures with Parteck® ODT. The comparison of the values of the total energy of compression Emax, which is the sum of all three types of energy, is given mainly by the values of precompression energy where the biggest differences between the values are found. That is why the lowest values of the total energy of compression are shown by mixtures with Prosolv® ODT G2. Plasticity, i.e., the parameter calculated as the ratio of plastic deformation energy and compression energy **(Eq. 6)**, shows the highest values for mixtures with Prosolv® ODT G2, followed by mixtures

with Ludiflash®, and the lowest values, except for mixture with 0.5% sodium stearyl fumarate, are shown by Parteck® ODT. There are no statistically significant differences between the values within the type or concentration of lubricants, with the exception of the already mentioned mixture.

Another quantity tested to quantify the effectiveness of lubricants was ejection force. The lowest values for ejection forces were shown by mixtures with Prosolv® ODT G2 containing MCC, which itself has a lubricating effect, therefore it increases the efficiency of the added lubricant. Higher concentrations of lubricants increased their effectiveness and thus reduced the ejection force, with the exception of magnesium stearate in combination with Ludiflash®, where there was no statistically significant difference between the values. Otherwise, mixtures with Parteck® ODT showed the highest values of ejection force, except for the one with the addition of 1% magnesium stearate. The highest ejection force was recorded for a mixture of Parteck® ODT with 0.5% sodium stearyl fumarate. The effectiveness of magnesium stearate in reducing ejection force was more significant in all cases, and the ejection force values were lower than when sodium stearyl fumarate was used, which is probably given by the higher specific surface of magnesium stearate (Sheskey et al., 2020).

3.4.Evaluation of compactability and friability

Compactability was evaluated by measuring the tensile strength of tablets, the values of which are given and compared in **Fig. 5**. The test revealed that the highest values of tensile strength are shown by Prosolv® ODT G2. This can be a result of better interlocking of smaller Prosolv ODT G2 particles and higher bonding ability of MCC present inside.

In the case of a higher concentration of lubricant magnesium stearate, the tablet strength is higher; in the case of an increasing concentration of sodium stearyl fumarate, there is no statistically significant difference between the values. Mixtures with Ludiflash® show the lowest tablet tensile strength. This finding correlates with the true density of the powders

(**Tab. 4)**, since Ludiflash®-lubricated powders exhibit the lowest density out of all studied formulations (1.4534 g/cm^3 – 1.4599 g/cm^3). This co-processed dry binder together with Parteck® ODT does not show a statistically significant difference between the tablet strength values in the case of increased lubricant concentration.

The values of plastic deformation energy are also related to the values of tablet strength (**Fig. 6**). At the same compression force of 7 kN, the individual co-processed dry binders occupy separate areas on the graph. Parteck® ODT accumulates less energy of plastic deformation, but the tablets are harder, which may be due to the nature of Parteck® ODT particles. Parteck® ODT is the only one of the three tested co-processed dry binders that contains granulated mannitol with both fragmentation and plastic deformation compression mechanisms (Debord et al., 1987; Bolhuis and de Waard, 2011). During the compression, the agglomerates undergo fragmentation which leads to the creation of new interparticle surfaces and bonding formations, followed by plastic deformation of mannitol particles. This results in harder compacts in comparison to Ludiflash® that contains non-granulated mannitol which deforms only plastically. The lowest tensile strength of tablets was recorded at L 1% st (0.92 MPa). On the contrary, Prosolv® ODT G2 samples had the highest tensile strength, at Pr 1% st, up to 1.58 MPa. This effect was caused by higher energies of plastic deformations, caused by the presence of microcrystalline cellulose, which easily undergoes plastic deformations. The Prosolv® ODT G2 and Parteck® ODT samples had higher tablet tensile strength when magnesium stearate was used as a lubricant, while Ludiflash® had a higher strength when using sodium stearyl fumarate.

Values of friability, which are shown in **Fig. 5**, indicate that there is a correlation between friability and the tensile strength of the tablets. Prosolv® ODT tablets had the lowest friability which corresponds to their highest tensile strength, whereas tablets containing Ludiflash®

exhibited the highest friability and lowest tensile strength. Overall, all formulations met the pharmacopeial requirement < 1% (Council of Europe – EDQM, 2020).

3.5.Evaluation of wetting time, absorption ratio, and disintegration time

Wetting time is highly influenced by the inner structure and composition of the tablets and it also indicates the wicking effect of superdisintegrants (Brniak et al., 2013). Values of wetting times are given in **Fig. 7**. Ludiflash® tablets showed the shortest wetting time ranging from 16.0 s to 19.1 s, whereas Prosolv® ODT G2 and Parteck® ODT had slightly longer wetting times, 30.0 s – 36.3 s and 39.0 s – 57.0 s, respectively. Our results have several similarities with the findings of (Stoltenberg and Breitkreutz, 2011), whose results of placebo orally disintegrating mini-tablets containing these co-processed dry binders had the same increasing tendency of wetting times as follows, L < Pr < P. The possible explanation might be that crospovidone in Ludiflash® and Prosolv® ODT G2 had a better wicking effect than sodium croscarmellose which is present in Parteck® ODT. The higher efficiency of crospovidone is also proved by the fact that the tablet porosity of Ludiflash is the lowest (**Tab. 5**).

Regarding the water absorption ratio, we were able to obtain values just for Ludiflash® tablets, whereas Prosolv® ODT G2 and Parteck® ODT wet tablets were not possible to be weighed. The reason could be that the disintegration process of tablets of these two co-processed dry binders had started before the wetting of the whole tablet was finished. On the contrary, Ludiflash® contains polyvinyl acetate, an insoluble binder, which could hold the tablet structure still during the wetting.

According to our results, Ludiflash® with magnesium stearate absorbs more water than with sodium stearyl fumarate (L 0.5 st - 80.99% and L 0.5 sf 76.21%), which is surprising since sodium stearyl fumarate has more hydrophilic character whereas magnesium stearate is rather hydrophobic. Nevertheless, increasing the amount of lubricant led to decreased water absorption in both cases (L 1 st – 77.36% and L 1 sf – 72.25%).

Values of disintegration times of the formulations are also given in **Fig. 7**. The type and concentration of lubricant have different effects on the tablet disintegration times of co-processed dry binders. There is no statistically significant difference in the disintegration time of Parteck® ODT tablets containing different concentrations of lubricant, but tablets with more hydrophobic magnesium stearate take longer to disintegrate. A higher concentration of lubricant prolongs the disintegration time in the case of the other two co-processed dry binders, but in the case of Ludiflash® tablets there is no statistically significant difference between the values within the type of lubricant used. For Prosolv® ODT G2 tablets, there are statistically significant differences in disintegration time values within the lubricant type, since the same concentration of sodium stearyl fumarate provides tablets with a longer disintegration time than that observed with magnesium stearate tablets.

Overall, Prosolv® ODT G2 tablets provide the shortest disintegration time since they contain MCC, which promotes the disintegrating effect of crospovidone, a superdisintegrant present in the substance. The only exception is a mixture with 1% sodium stearyl fumarate that provides tablets with a disintegration time similar to the ones with Parteck® ODT and sodium stearyl fumarate. The second lowest disintegration time is observed in tablets with Parteck® ODT. This co-processed dry binder differs from the other two by the content of croscarmellose sodium instead of crospovidone. Due to its relatively long fibrous particles, croscarmellose acts even at greater distances within the tablet (Quodbach and Kleinebudde, 2016).

The Ludiflash® tablets showed the lowest porosity (**Tab. 5**), yet still had the shortest wetting time due to the crospovidone present inside. However, the tablets containing Ludiflash® provided the longest disintegration time, ranging from 41.7 s to 59.4 s. The wetting time of compacts did not correlate with the disintegration time probably because Ludiflash® also contains insoluble binder polyvinyl acetate.

We found slightly higher values of disintegration time of Ludiflash® with sodium stearyl fumarate with respect to those reported by (Brniak et al., 2013). The authors investigated different approaches for testing the disintegration time of tablets comprising of co-processed excipients including the test according to Ph. Eur. (Council of Europe - EDQM, 2020). Their placebo tablets (diameter 12 mm, weight 400 mg, compression force 10 kN) with Ludiflash® and 1% sodium stearyl fumarate disintegrated within 38 s, while our tablets (diameter 13 mm, weight 500 mg, compression force 7 kN) with the same composition disintegrated in 59.4 s. Although the parameters differ slightly, the results are a confirmation of a longer disintegration time of tablets with this formulation.

A comparison of dependency of disintegration time on tablet tensile strength, which is shown in **Fig. 8**, does not confirm the direct relationship between the tablet strength and the disintegration time in the sense that tablets with lower tensile strength disintegrate faster. In fact, the results prove the opposite since the tablets with the lower tensile strength containing Ludiflash® provide tablets with the longest disintegration time. Thus, the disintegration time is not related to the tensile strength of the tablets, but clearly to the composition of the co-processed dry binder. Prosolv® ODT G2 provides tablets with the highest tensile strength, but also with the shortest disintegration time, because of the presence of MCC. It not only increases compactability but at the same time acts as a disintegrant in this percentage and thus supports the function of crospovidone as it was discussed earlier.

We found that the tablet porosity does not influence disintegration time nor wetting time. As in the case of tensile strength, the disintegration time and wetting time are dependent more on the composition of the co-processed dry binders rather than on the porosity or internal structure of the tablets.

4. Conclusion

Testing binary mixtures of co-processed dry binders with lubricants is an important aspect of their use in combination with drugs. This study aimed to evaluate the rheological and compression properties of these mixtures, and subsequently also the compactability and disintegration time of the tablets. Three co-processed dry binders for ODT were studied in the mixtures, namely Parteck® ODT, Prosolv® ODT G2, and Ludiflash®.

The results proved that the composition of co-processed dry binders is an important parameter that determines the behaviour of their binary mixtures with lubricants. The positive effect of colloidal silicon dioxide on the flowability of Prosolv® ODT G2 in combination with 0.5% magnesium stearate was clearly demonstrated, as well as the effect of granulated mannitol in Parteck® ODT, which also flowed very well with the same lubricant in both concentrations. According to the values of the Hausner ratio and compressibility index, these mixtures showed a fair flow. Another important substance was MCC, which reduced the angle of internal friction and pre-compression energy values in mixtures with Prosolv® ODT G2. These lubricated mixtures therefore exhibit the lowest values of these parameters. MCC also significantly affected the values of plastic deformation energy, which were, on the contrary, the highest. This was also reflected in the highest strength values of the tablets made with this product. The higher concentration of lubricants slightly reduced the energy of plastic deformation in all the co-processed dry binders. The effectiveness of the magnesium stearate lubricant in reducing ejection force was in all cases more significant than the effectiveness of sodium stearyl fumarate. The lowest values of this parameter were exhibited by the mixtures with Prosolv® ODT G2, again due to the MCC that has both a lubricating effect and a disintegrating effect, which made it possible to obtain the strongest tablets with the lowest friability and shortest disintegration time. The multifunctionality of MCC significantly affected the compression and tableting properties of the co-processed dry binder Prosolv®

ODT G2. The high strength and low friability of the tablets in combination with their rapid disintegration are the optimal parameters of orodispersible tablets.

CRediT authorship contribution statement

Thao Tranová: Writing - review & editing, Methodology, Investigation, Visualisation

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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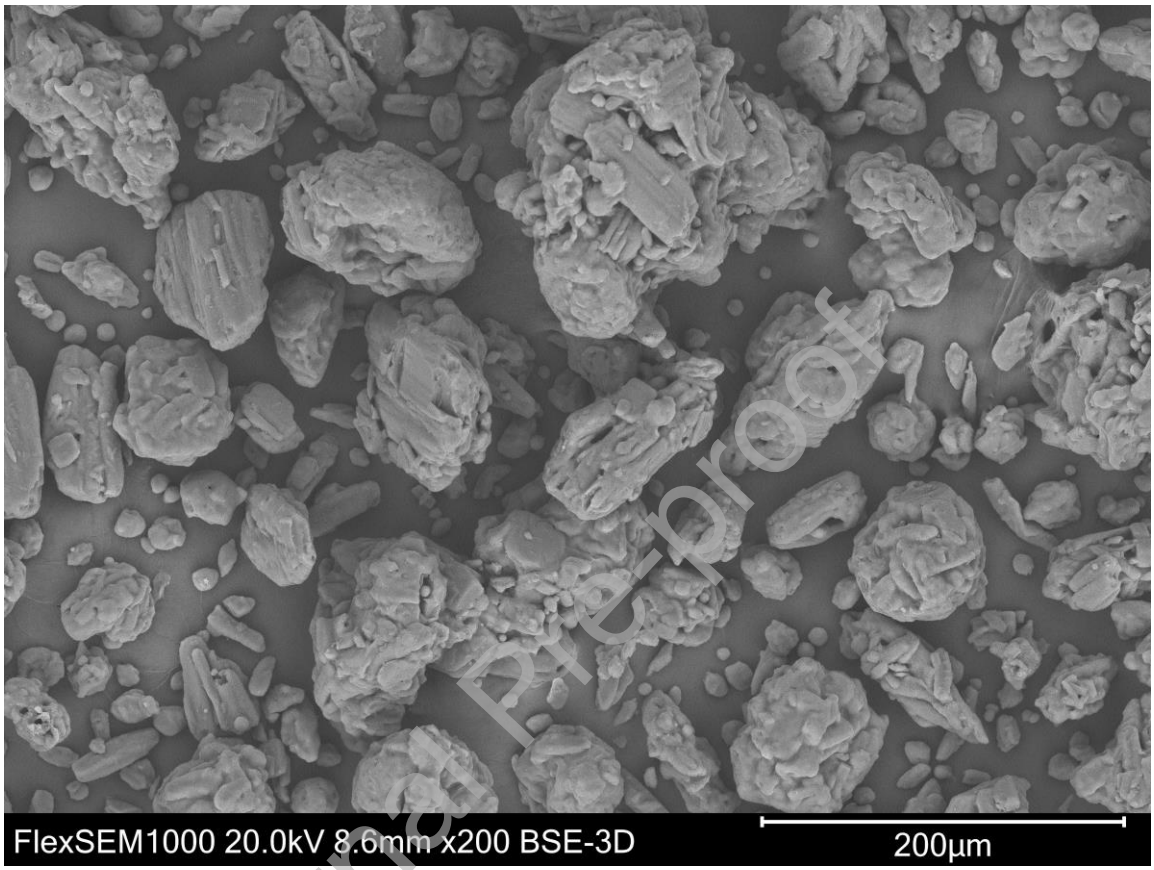
Fig. 1. SEM/BSE image of Prosolv® ODT G2 at 200x magnification.



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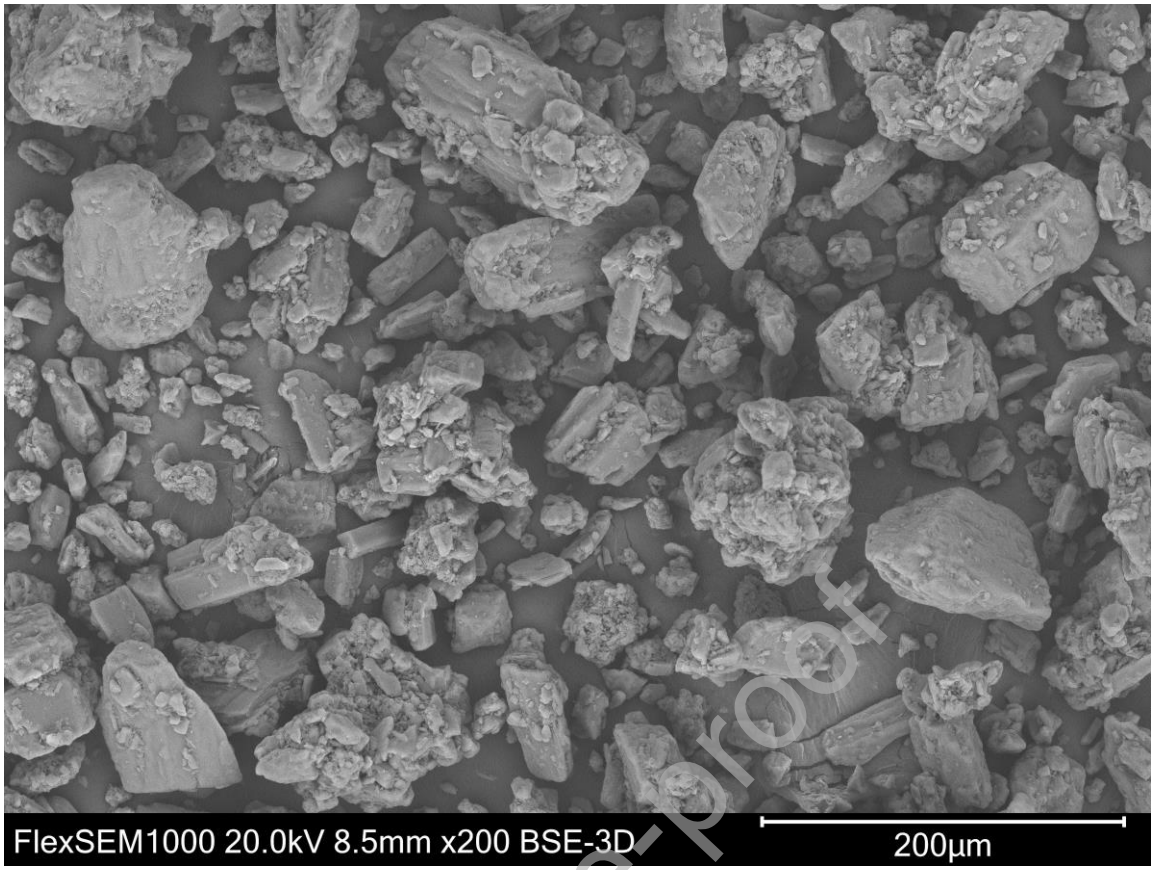

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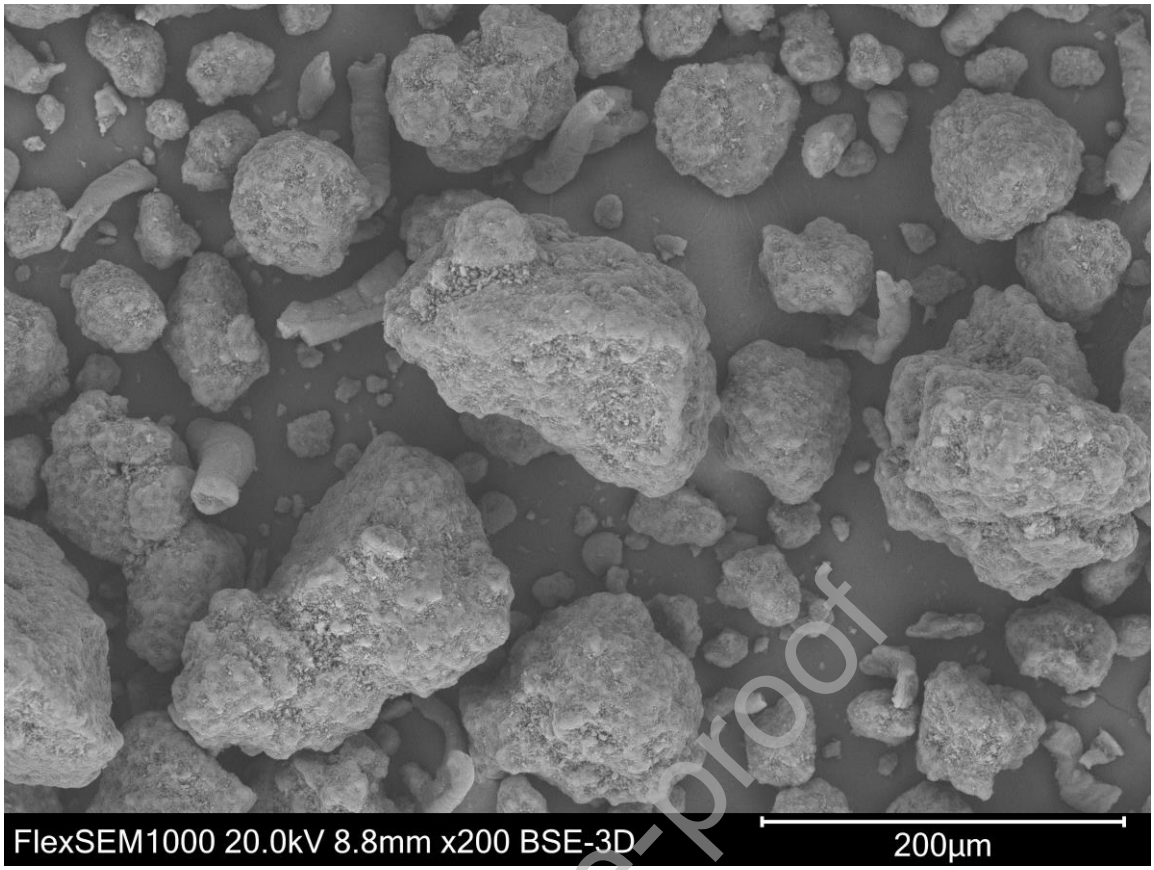

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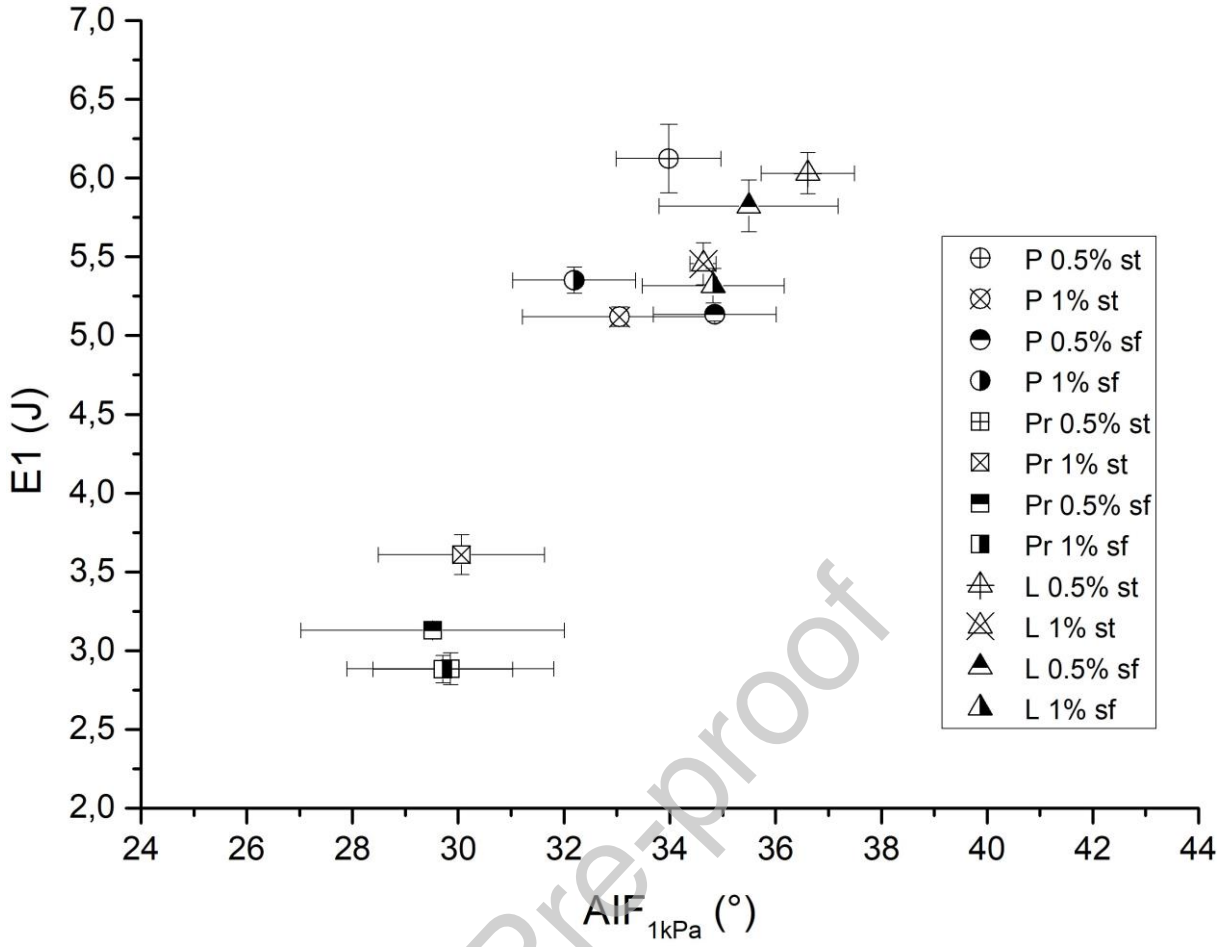

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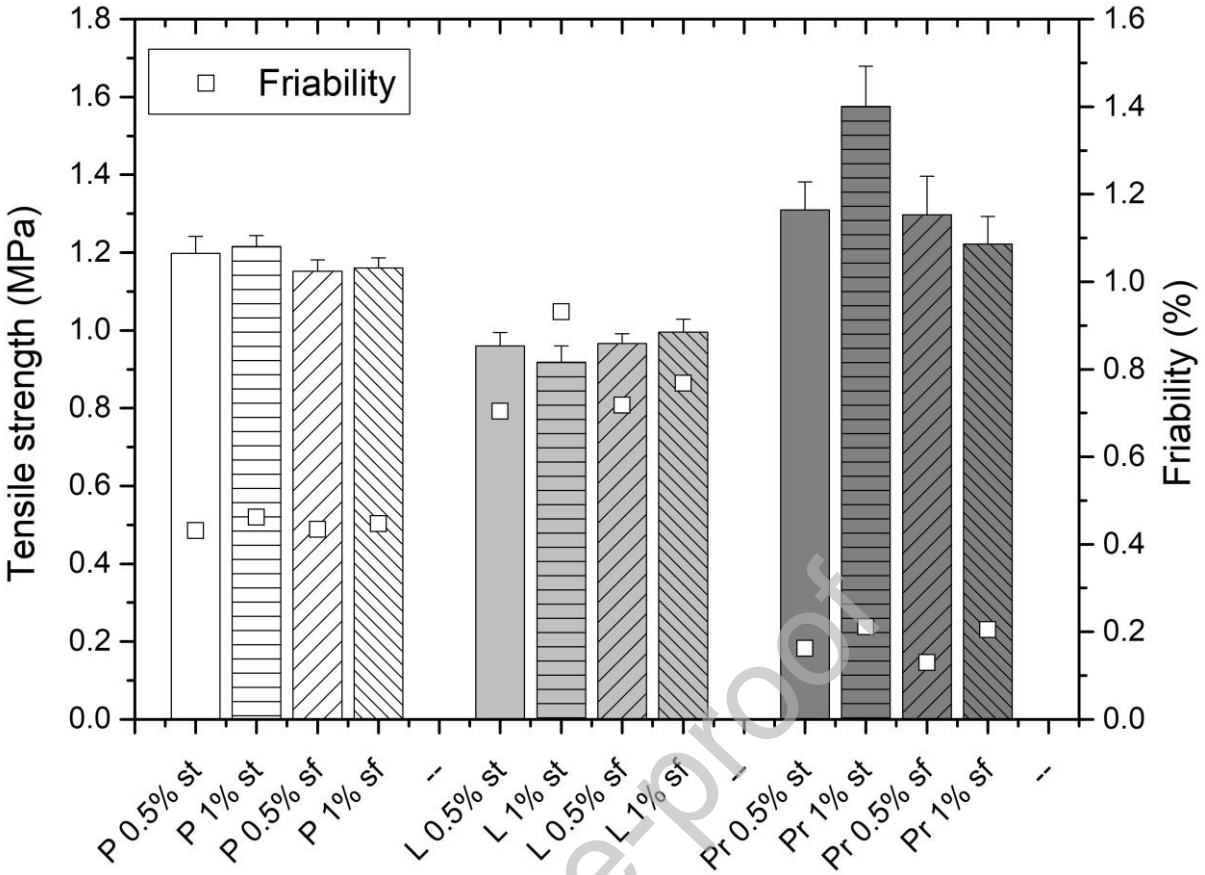

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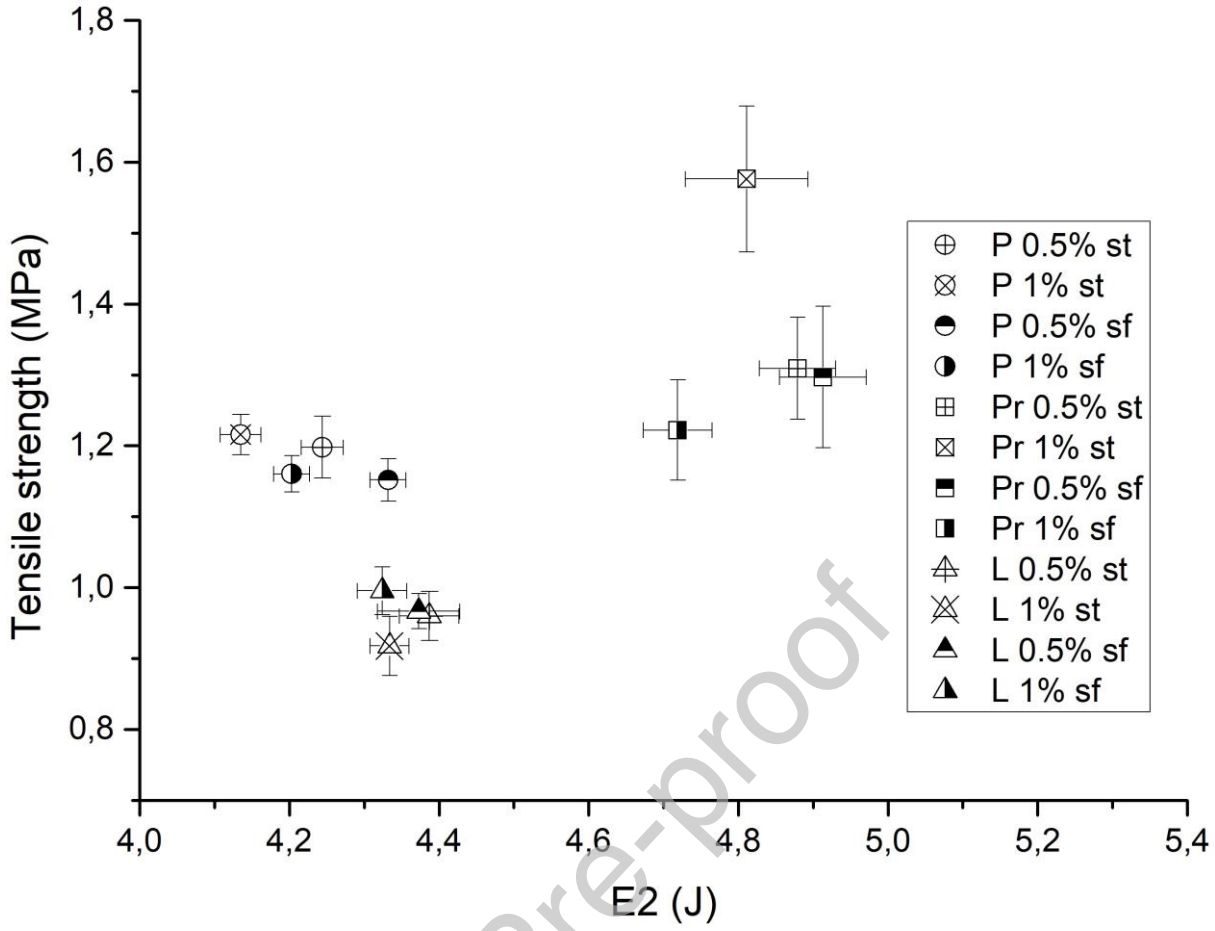

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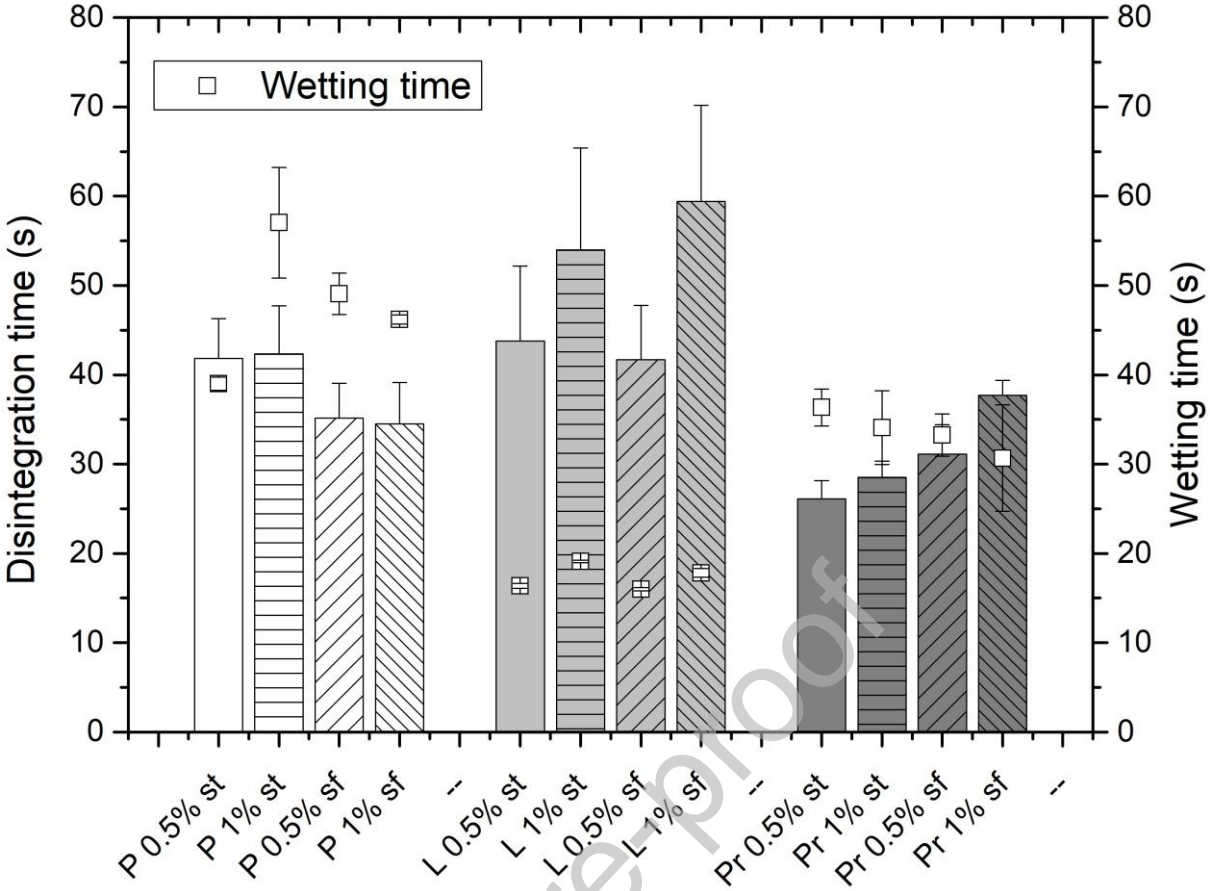

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