



Evaluating superdisintegrants for their performance in orally disintegrating tablets containing lysozyme enzyme



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ABSTRACT

Orally disintegrating tablets (ODTs) are gaining importance and popularity due to their numerous advantages. Lysozyme, an enzyme with antibacterial properties, is currently only available as a conventional tablet and syrup. The main aims of this study were to formulate ODTs containing lysozyme using a variety of excipients and evaluate how formulation technology and excipient selection affected enzyme activity. Three different superdisintegrants in two concentrations, two different types of fillers, and three types of modern, ready-to-use co-processed excipients were investigated. The effect of the quality of the materials and the applied compression force were also studied. The investigated Critical Quality Attributes were disintegration time, dissolution profile and activity of lysozyme enzyme. A higher enzyme activity was found for ODTs with a higher hardness and density, containing the stabilizing agent in a smaller particle size. The structure of the superdisintegrant crystals had a greater impact on the disintegration time and dissolution profile of ODTs than the amount of superdisintegrants used. The results also revealed that despite the general advantages and effectiveness of ready-to-use excipients, the use of tailored formulations is more advantageous for sensitive drugs like enzymes.

1. Introduction

Lysozyme is a natural enzyme that can be found in human mucus, saliva, and tears and also in hen egg white. Lysozyme exhibits a strong antibacterial activity against Gram-positive bacteria and a weaker activity against Gram-negative bacteria [1]. Lysozyme is widely used in dietary supplements, and it is highly valued to treat headaches, cold and throat infections, for example, in Malaysia, and lysozyme is also used as an antimicrobial preservative in foods [2]. Furthermore, a recent study suggests [3] that lysozyme may be effective in the treatment of certain chronic gastrointestinal inflammations, such as ulcerative colitis, Crohn's colitis, and Barrett's oesophagitis. Lysozyme can also be used during COPD treatment as a mucolytic enzyme [4].

Lysozyme is available on the global market only as a conventional tablet and syrup [2] and, despite the numerous advantages of this dosage form, it has not yet been incorporated into orally disintegrating tablets (ODTs). ODT as a solid dosage form can be administered with or without water and disintegrates rapidly, usually within a matter of seconds (30 s or less according to the United States Pharmacopoeia (USP) disintegration test) when placed upon the tongue [5]. ODTs are

gaining importance and popularity among novel oral drug delivery systems, as they are convenient to administer, and can offer improved patient adherence, especially in the case of the elderly and the pediatric populations, which may have difficulty swallowing conventional tablets or capsules [6–8]. Furthermore, ODTs may provide improved bioavailability, since the drug starts to absorb in the mouth, which means reduced first pass effect and greater stability for drugs that are sensitive for the lower GI conditions (e.g., proteins).

ODTs can be produced by a variety of manufacturing techniques, including lyophilization, molding, sublimation, and sugar-floss system [9], but direct compression is still the simplest and most cost-effective process from the perspective of industrial manufacturing. Direct compression allows for the use of conventional tablet manufacturing equipment and inexpensive, readily available pharmaceutical excipients to produce ODTs [10]. Among the various excipients are several groups that play a crucial role in ODT formulations: superdisintegrants, which ensure the rapid dissolution; and multifunctional filler-binders, which may ensure acceptable mouthfeel in order to ensure patient compliance [11,12]. Based on the disintegrating method, including swelling, wicking, deformation and disintegrating particle/

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particle repulsive forces, four types of superdisintegrants are available on the market today [13]. Among them, sodium starch glycolate, crospovidone, and croscarmellose sodium are the most commonly used. As filler-binders, saccharides such as mannitol, trehalose, xylitol, sorbitol and dextrin may be used. These widely used bulking agents provide a smooth and pleasant mouthfeel, along with a sweet taste. Additionally, they dissolve rapidly in the saliva; thus, their use is also preferred for the characteristic of rapid disintegration [14]. In the present study, applicability of mannitol and trehalose was tested since these materials are widely used protectants against thermal stress in protein processing [15]. High temperatures may occur for milliseconds during direct compression, which may affect the structure of proteins and, therefore, their activity [16].

Besides the traditional excipients, more and more excipient manufacturers offer special co-processed compounds for different purposes, such as for direct compression of ODTs. The benefits of these ready-to-use components include multifunctionality, simplified formulation development, and a cost-effective direct compression process. When using such ingredients, their potential influence on tablet properties, such as crushing strength, dissolution, and friability should be taken into account [17–19]. ODTs are the focus of recent pharmaceutical developments, but despite of their advantages in this field, information on protein-containing ODTs is limited. Therefore, the main goal of the present study was the investigation of how the quality of generally used excipients and processing parameters influence the critical quality attributes, including tablet hardness, disintegration time, dissolution rate and enzyme activity, of lysozyme-containing ODT formulations.

2. Materials and methods

2.1. Materials

Lysoch™, a lysozyme, was used as the model active ingredient in this study; it was provided by Handary SA (Brussels, Belgium). The ready-to-use tableting excipients in this study were received as gifts from suppliers; they included Prosolv® ODT G2 (a mixture of a filler, binder, superdisintegrant and glidant, JRS Pharma LP, USA), Prosolv® EASYtab (a mixture of a filler, glidant, superdisintegrant and lubricant, JRS Pharma LP, USA), and Ludiflash® (a mixture of a filler, binder, and disintegrant, BASF Corporation, USA). Two different types of crospovidone, namely Kollidon® CL-SF (BASF, Germany) and Polyplasdone® XL 10 (GAF Chemicals Corporation, USA), as well as sodium starch glycolate (Primojel®, DFE Pharma, Germany) were used as superdisintegrants; all were received as gifts. Concentrations of superdisintegrants used in this study (i.e., 5% and 10%) were based on the manufacturers' general recommendations. Spray-dried mannitol (Pearlitol® SD 200, Roquette Pharma, France) and trehalose (Cargill, USA) were employed as fillers and were received as gifts. Prosolv® SMCC HD 90 was used as a binder and PRUV® as a lubricant; both ingredients were received as gifts from JRS Pharma LP, USA. The composition of each type of tablet is shown in Table 1. *Micrococcus lysodeikticus* (Sigma Aldrich Co. LLC, USA) was used for the enzyme activity tests.

2.2. Methods

2.2.1. Preformulation studies

The individual particles of each excipient were examined to study the surface morphology with an FEI Quanta 3D FEG Dual Beam (FEI, Hillsboro, OR, USA) scanning electron microscope in Toledo, Ohio, operated at 5 kV. Samples from each excipient were mounted onto a double-sided copper conductive tape (NEM Nisshin EM Co. Ltd.) fixed on aluminum stubs. They were then sputter-coated with a thin layer of gold in a vacuum for 45 s at 20 mA, using a coating unit (Cressington 108 auto sputter coater, UK) to make them electrically conductive.

Scanning electron micrographs of the prepared tablets were taken

and analyzed in Szeged with a Hitachi S-400 (Hitachi Ltd., Tokyo, Japan) scanning electron microscope. Tablets were fixed on a double-sided carbon adhesive tape. A SEM sputter coating unit (Polaron E5100, VG Microtech, UK) was used to charge the surfaces for the SEM measurements. The air pressure was 1.3–13 mPa. The SEM was operated at 10 kV. The scanning electron micrographs were used for particle size evaluation, the particle size was determined by ImageJ software (Image J 1.51n; National Institute of Health, Bethesda, USA).

The flowing properties of the powder mixtures were examined according to USP35 [20].

2.2.2. Preparation of powder mixtures for ODTs

The powders for the 300 mg ODTs were mixed using a Turbula mixer (Clifton, NJ, USA). All ingredients except for the lubricant were blended for 8 min. Then, sodium stearyl fumarate lubricant was added to the mixture, and it was blended for 2 additional min.

2.2.2.1. Preparation of ODTs. ODTs of 300 mg were prepared using a Korsch EK0 eccentric tablet press (Korsch GmbH, Berlin, Germany) and standard concave punches and die 0.375 inches (9.525 mm) in diameter. Fifteen different ODTs were made using different powder mixtures, as shown in Table 1. Series A, B and C were made of conventional physical powder mixtures, while series D was prepared using special ODT ready-to-use excipient composites. The compression force was adjusted to produce tablets with three different theoretical hardness values: 30 N, 50 N and 70 N. The real hardness values were deviated around the theoretical within a ± 5 N range. The reason for this was to compare the disintegration of tablets with similar mechanical parameters. In total, 45 different batches of tablets were made. The tableting process, as well as the final storage of the ODTs, took place in a conditioned room at 21 ± 0.5 °C and $30 \pm 5\%$ RH.

2.2.2.2. Physical evaluation of ODTs. Physical tablet parameters evaluated included weight uniformity, diameter, thickness, hardness and friability. The weight of ten tablets was measured in grams. Thickness, diameter and hardness of ten tablets were measured with a Sotax Hardness Tester Model HT1 (Sotax GmbH, Allschwil, Switzerland) in mm and Newtons (N), respectively.

Friability was evaluated according to USP 34, using an Erweka Friability Apparatus Model TAP 23644 (Erweka GmbH, Heusenstamm, Germany). Measurements were performed in triplicate. Tablets were brushed to remove excess powder, both prior to their initial weight determination and after 100 revolutions (4 min at 25 rpm). The percentage of weight loss for 6.5 g of total tablet weight was calculated with Equation 1. According to USP 34, less than 1% loss and no tablet breakage is acceptable for 100 revolutions in 4 min [21].

$$\text{Friability} = \frac{(\text{initial weight} - \text{final weight})}{\text{initial weight}} \times 100\%$$

Equation 1. Calculation of friability.

2.2.2.3. Performance evaluation of ODTs. For the disintegration studies, six tablets were tested according to the USP 34 standard method, using an Erweka model ZT2 apparatus (Erweka GmbH, Heusenstamm, Germany). The time necessary for each tablet to disintegrate at 37 ± 0.5 °C in DI water to the point where it was small enough to pass through the mesh at the bottom of the basket was recorded using a stopwatch. According to the FDA guideline, a time of less than 30 s is recommended for a product to be considered an ODT [5].

Dissolution studies were performed according to the USP 34 standard method (Apparatus 2), using a Sotax AT (Sotax, Westborough MA, USA) dissolution tester. 900 mL of DI water with a pH of 6.7–6.9 (at 37 ± 0.5 °C) was used as the dissolution medium. Aliquots of 4.5 mL were taken manually from the dissolution medium at regular time intervals (10, 20, 30, 40, and 50 s, and then 1, 1.5, 2, 2.5, 3, 4, 5, 7.5, 10,

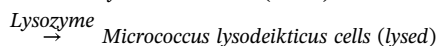
Table 1
Composition of ODTs.

Series	Ingredients used (%)										
	Lysozyme	Kollidon CL-SF	Polyplasdone XL 10	Primojel	Pearlitol SD200	Trehalose	Prosolv SMCC	PRUV	Prosolv EASYtab	Prosolv ODT G2	Ludiflash
A1	10.0	5.0	–	–	54.0	–	30.0	1.0	–	–	–
A2	10.0	5.0	–	–	–	54.0	30.0	1.0	–	–	–
A3	10.0	10.0	–	–	49.0	–	30.0	1.0	–	–	–
A4	10.0	10.0	–	–	–	49.0	30.0	1.0	–	–	–
B1	10.0	–	5.0	–	54.0	–	30.0	1.0	–	–	–
B2	10.0	–	5.0	–	–	54.0	30.0	1.0	–	–	–
B3	10.0	–	10.0	–	49.0	–	30.0	1.0	–	–	–
B4	10.0	–	10.0	–	–	49.0	30.0	1.0	–	–	–
C1	10.0	–	–	4.0	55.0	–	30.0	1.0	–	–	–
C2	10.0	–	–	4.0	–	55.0	30.0	1.0	–	–	–
C3	10.0	–	–	8.0	51.0	–	30.0	1.0	–	–	–
C4	10.0	–	–	8.0	–	51.0	30.0	1.0	–	–	–
D1	10.0	–	–	–	10.0	–	–	1.0	79.0	–	–
D2	10.0	–	–	–	–	–	–	1.0	–	89.0	–
D3	10.0	–	–	–	–	–	–	1.0	–	–	89.0

12.5 and 15 min) for all samples, without replacing the medium. Medium loss was taken into account during the calculations. The absorbance of lysozyme was analyzed at 281 nm, using an Agilent 8453 UV-Vis spectrophotometer (Santa Clara, CA, USA) and Graphpad Prism (GraphPad Software, Inc., CA, USA).

One of the main aims of this study was to incorporate lysozyme with mannitol or trehalose into ODTs. The enzyme activity of lysozyme was evaluated to ensure that the tablet manufacturing process did not affect negatively the active ingredient's main function. The enzyme activity was examined directly via measuring the degradation kinetic of *Micrococcus lysodeikticus*. The enzymatic rate determination is based on the following reaction [22]:

Micrococcus lysodeikticus cells (intact)



A Genesys 10S UV-Vis Spectrometer (Thermo Fisher Scientific Inc, Waltham, MA, USA) was used for the detection. For sample preparation, one tablet of each mixture was dissolved in 75.0 mL, pH = 6.25 phosphate buffer, after being filtered through a Chromafil Xtra 0.45-micron filter (Macherey-Nagel GmbH & Co. KG, Düren, Germany). The 100 µL sample was added to 2.5 mL of 0.2 mg/mL bacterial suspension (0.0100 g bacteria were suspended in 50 mL, pH = 6.25 phosphate buffer for 20 tests); it was then homogenized, and absorbance was measured at 450 nm every 5 s between 20 s and 5 min 20 s. The kinetic was compared to a 0.4 mg/mL lysozyme solution's kinetics.

The results were analyzed by Statistica for Windows v12 software (Statsoft Inc., Tulsa, OK, USA) using factorial ANOVA method; the level of significance was $p < 0.05$.

3. Results and discussion

3.1. Physical evaluation of the ODTs

The morphological characteristics (spherical agglomerates of dried droplets) of lysozyme (Fig. 1a) suggest that it was crystallized with the spray drying method. The good sphericity and relatively big particle size are intended to provide good powder rheological properties. Prosoolv SMCC (Fig. 1c) had anisometric particles, with an average particle size of 90 µm. Amongst the stabilizers, the spray-dried particles of Pearlitol SD 200 (Fig. 1b) were spherical with a 100 µm average particle size, while trehalose (Fig. 1b) had bigger columnar-isometric, smooth surfaced crystals with a particle size of 300–500 µm. This suggests that Pearlitol may be distributed more uniformly in the tablets. The investigated disintegrants had different structures, which may explain the differences in their effectiveness. Primojel (Fig. 1g) had considerably

large, spherical and smooth-surfaced particles with an average particle size of 50 µm. By contrast, Kollidon CL-SF (Fig. 1e) and Polyplasdone XL-10 (Fig. 1f) were both agglomerates of smaller, platelet-like crystals with an approximate particle size of 3–5 µm. Nevertheless, there are considerable differences of their structures. The agglomerates of Kollidon CL-SF were fluffy with a rough surface, while Polyplasdone XL-10 formed more densified, spherical and smooth-surfaced particle agglomerates.

Table 2 presents the results of the powder mixtures' flow test. As it was expected based on the morphological studies, all the results fell into the USP's excellent category (i.e., 25–30°). Thus, it was concluded that the powder mixtures were suitable for direct compression.

The compressed ODTs were analyzed for weight uniformity, diameter, thickness, friability, and hardness (Tables S1–3), and apparent density of tablets was calculated. All ODTs passed the friability test and exhibited appropriate mechanical strength. However, the edges of tablets with 30 N hardness were chipped, indicating 30 N as a minimum level of suitable tablet hardness. There were no visual defects on tablets with 50 N and 70 N hardness values.

The setting of hardness was appropriate. There was no significant difference between the theoretical and actual hardness values of samples; only the hardness of the 70 N mannitol- and trehalose-containing tablets of series A differed significantly from one another.

The statistical results (see supplementary material) revealed that the apparent density of tablets showed significant differences according to all studied factors. There was no significant difference between the densities of series A and B, both containing crospovidone. However, series C, containing sodium starch glycolate, exhibited a significantly higher density (Fig. 2). The increase of the disintegrant content significantly decreased the measured densities. Samples with trehalose exhibited a significantly higher density than samples with mannitol. Furthermore, it was revealed that there was a significant interaction between the disintegrants and fillers from the aspect of tablet texture. ODTs with Polyplasdone exhibited less difference than other compositions, especially at 50 N theoretical hardness (Fig. 2), which also influenced the disintegration performance of the ODTs.

3.2. Performance evaluation of the ODTs

The results of the disintegration tests are shown in Table 3. It can be concluded that ODTs containing Polyplasdone® XL-10 as a super-disintegrant (series B) had the shortest disintegration times. With the exception of one, all ODTs disintegrated in less than 30 s (the one exception was still under 50 s). Furthermore, series B tablets exhibited the least sensitivity to tablet hardness and the applied filler (Fig. 3). The various ODTs containing Kollidon CL-SF (series A) exhibited similar

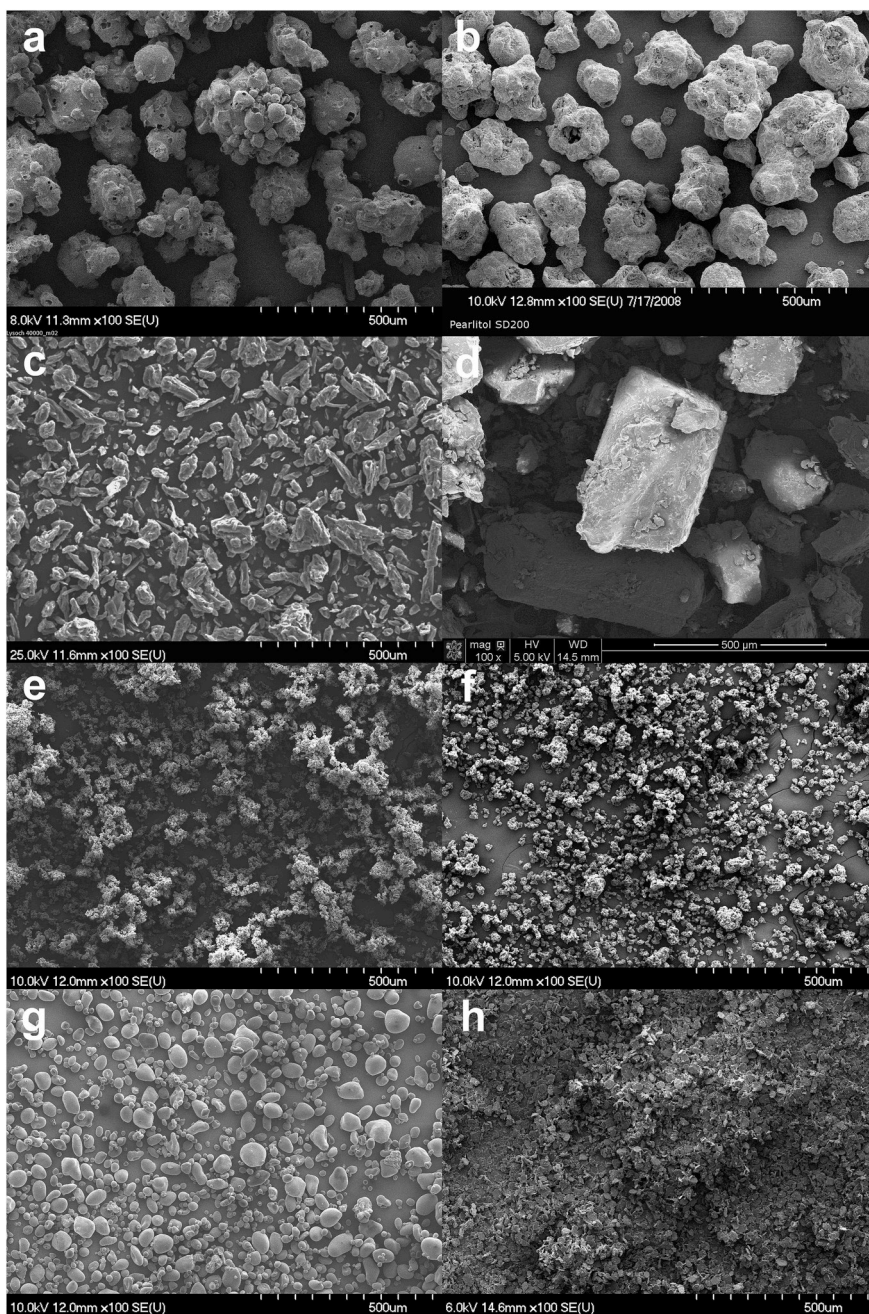


Fig. 1. Scanning Electron Micrographs of lysozyme (a), Pearlitol SD200 (b), Prosolv SMCC 90 (c), trehalose (d), Kollidon CL-SF (e), Polyplasdone XL-10 (f), Primojel (g) and Pruv (h) in 100x magnification.

disintegration times at low compression forces. The disintegration times were significantly longer at 70 N hardness, especially for ODTs prepared with trehalose. Primojel-containing tablets (series C) exhibited shorter disintegration times than the Kollidon-containing samples at 30 N and similar disintegration times as the Kollidon-containing samples at 50 N hardness, with the exception of C4, which was much longer than A4. A jelling effect was observed for the Primojel-containing

samples when placed in the disintegrating medium; which resulted in significantly longer disintegration times at higher hardness than other compositions. This effect was especially strong for trehalose-containing samples where the higher density and slower dissolution of the filler provided enough time for gel formation. This gel slowed down the disintegration process. Primojel-containing ODTs also exhibited the highest sensitivity to both hardness and filler type from the aspect of

Table 2
Average angle of repose of the mixtures (n = 3, results are displayed as mean ± SD).

Series	A1	A2	A3	A4	B1	B2	B3	B4
Average (°) ± SD	17.3 ± 1.9	13.7 ± 0.7	15.0 ± 1.4	17.2 ± 1.4	17.6 ± 1.1	19.3 ± 2.0	19.8 ± 2.2	22.4 ± 6.1
Series	C1	C2	C3	C4	D1	D2	D3	
Average (°) ± SD	21.7 ± 1.7	22.0 ± 2.0	21.7 ± 3.0	19.0 ± 0.6	24.2 ± 3.1	19.1 ± 2.5	23.8 ± 2.8	

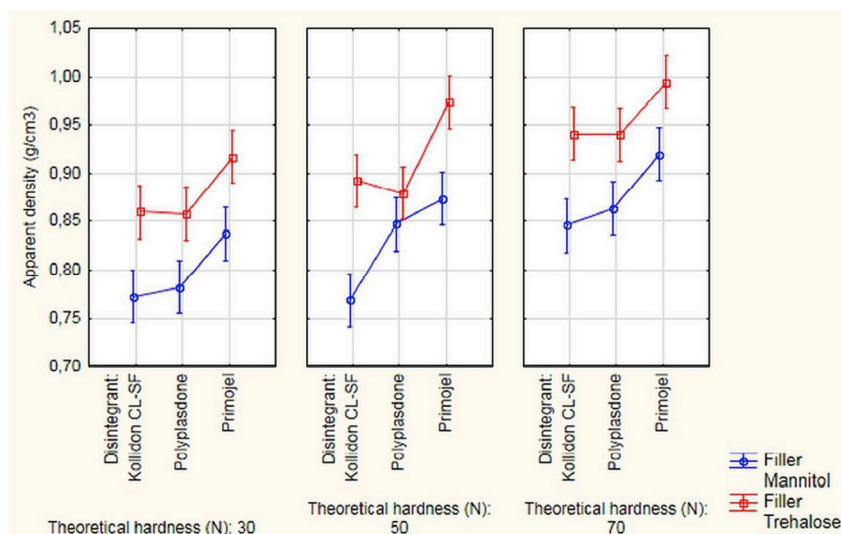


Fig. 2. The change of the tablet apparent density.

disintegration. It is notable that increasing the disintegrant content had a negative effect on the disintegration time in all cases, which could be explained by the elastic nature of the polymers. An increased amount of the disintegrant decreased the compressibility of the powder mixtures. The lower tablet density decreased the swelling efficacy, since the disintegrant swelled into the primary and secondary pores and less energy remained for the rupture of the tablet texture.

The difference seen in the performance of series A and B may be explained with their different textures (Fig. 4). The loosely agglomerated particles of Kollidon CL-SF (Fig. 1e) underwent a strong fragmentation and only the primary particles of the disintegrant may be identified (see white arrows on Fig. 4a, c, and e), which decreased their swelling efficacy. This was especially true for tablets with trehalose (Fig. 4e and f), which contained numerous secondary pores. By contrast, the agglomerates of Polyplasdone XL-10 (Fig. 1f) remained intact during compression; therefore, the presence of smaller pores did not affect their ability to disintegrate. The lubricant-covered spherical Polyplasdone XL-10 agglomerates can be clearly identified on the scanning electron micrographs (see white arrows on Fig. 4b, d, and f).

As discussed above, the 30 N ODTs showed signs of minor edge attrition in friability tests. There was no considerable difference in the disintegration times of the 30 N and 50 N tablets, while 70 N resulted in significantly longer disintegration times. Therefore, the 50 N ODTs were selected to be tested for dissolution.

Based on the dissolution results (Fig. 5), it can be concluded that the dissolution rates exhibited an exponential decay with an increase in disintegration time. Series B ODTs exhibited the fastest dissolution,

followed by series A and then series C. Certain irregularities were noted as well, which can be related to the composition of the tablets. The dissolution rates of ODTs with trehalose were lower, as expected, based on the exponential model. This may be explained by the fast dissolution and uneven distribution of trehalose crystals (Fig. 4e, and f). Dissolution of the excipient may help the disintegration of the whole tablet; however, the active ingredient could also remain entrapped in the smaller fragments, resulting in a lower dissolution rate.

Beside the fast disintegration and drug liberation, the appropriate enzymatic activity is still a key question of tablet performance. The results revealed no significant difference in enzyme activity between the two types of crospovidone used in this study, but ODTs with sodium starch glycolate exhibited significantly better results (Fig. 6). It is notable that from the aspect of enzyme activity crospovidone-containing samples exhibited considerable high sensitivity to the filler type, which was not observed for the sodium starch glycolate-containing samples. Additionally, the crospovidone-containing samples also exhibited significantly lower enzyme activity values when trehalose was used as filler. It is an interesting phenomenon that ODTs formulated with mannitol and a higher hardness value had a higher enzyme activity, despite the higher mechanical stress during tablet compression. A possible explanation may be that the stronger contact between particles of the active ingredient and mannitol provided better stabilization against friction and thermal effects that can be experienced during ejection and handling of the high-density tablets. ODTs with trehalose, in which the scanning electron micrographs (Fig. 4e, and f) confirmed the presence of secondary pores and uneven distribution of the

Table 3
Disintegration time of ODTs displayed in seconds as average (n = 6).

Hardness	Series							
	A1	A2	A3	A4	B1	B2	B3	B4
30 N	31.7	25.5	39.3	67.3	9.3	6.3	10.0	8.3
50 N	36.9	28.6	41.4	86.5	13.4	21.9	14.0	18.9
70 N	29.1	166.4	104.9	107.1	21.4	18.6	13.8	49.0

Hardness	Series						
	C1	C2	C3	C4	D1	D2	D3
30 N	20.5	14.0	12.9	16.1	9.6	25.5	29.7
50 N	38.6	26.6	27.0	357.6	12.4	78.0	47.7
70 N	70.4	409.4	206.1	783.8	59.1	234.5	161.0

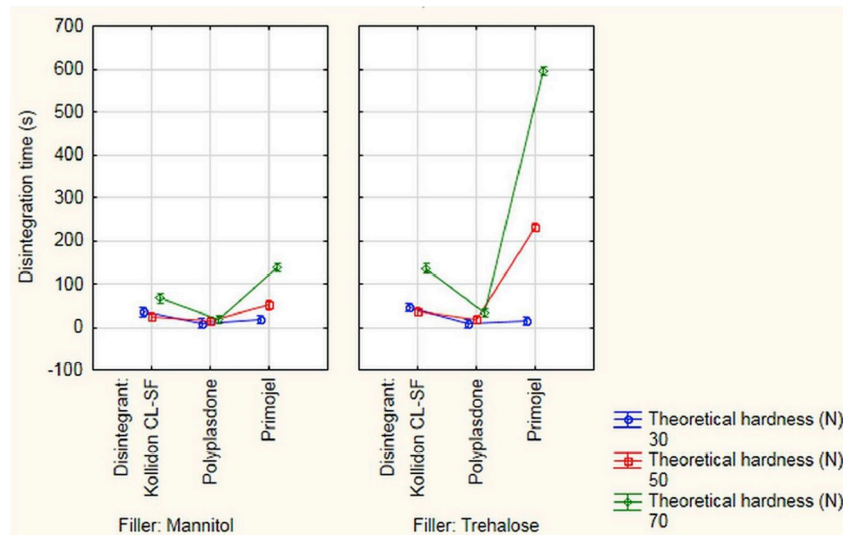


Fig. 3. The change of disintegration times.

stabilizing agent, did not show the same phenomenon due to a lack of strong contact between the particles. This effect may also be responsible for the slight decrease in enzyme activity at high disintegrant contents, meanwhile, the higher density values and stronger contact may explain the extraordinary activity results of the sodium starch glycolate ODTs.

If all critical quality attributes, including disintegration time, dissolution speed and enzyme activity, are considered, the best performance was provided by the B1. The B series with Polyplasdone XL-10 provided the shortest disintegration times and fastest dissolution speed, regardless of filler type and tablet hardness. Furthermore, the enzyme

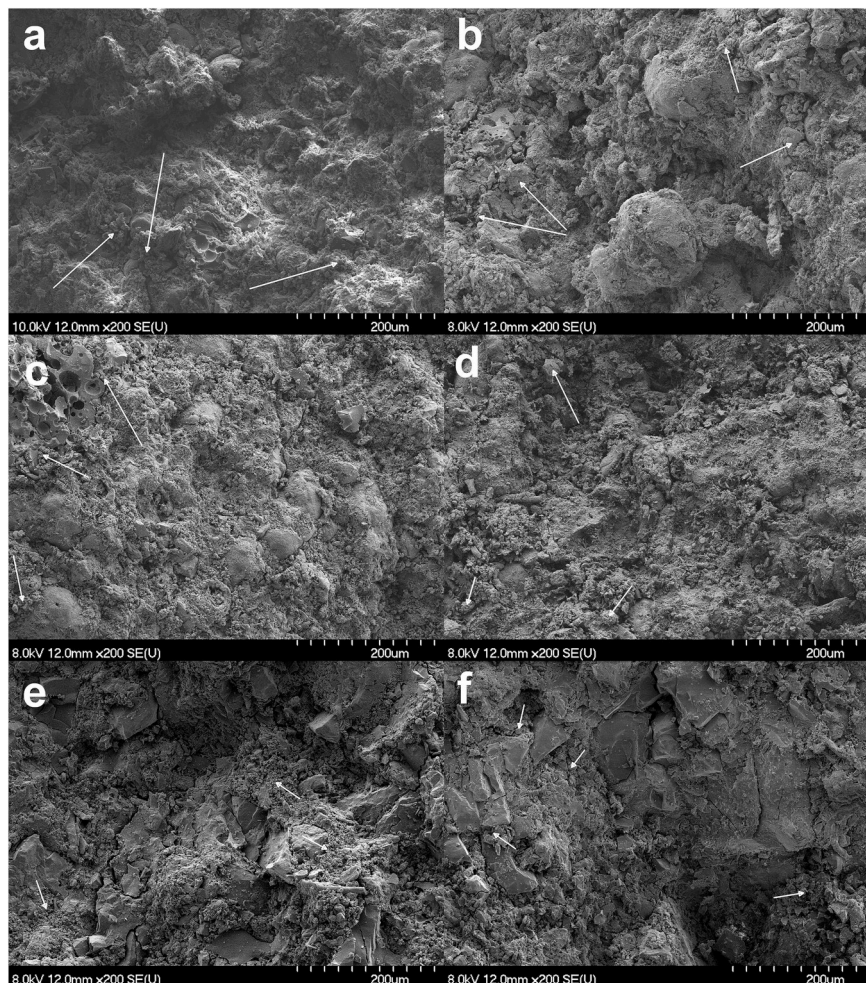


Fig. 4. Scanning electron micrographs of the breaking surfaces of A3 30N (a), B3 30N (b), A3 70N (c), B3 70N (d), A4 70N (e), B4 70N (f) tablets (white arrows indicating disintegrant particles).

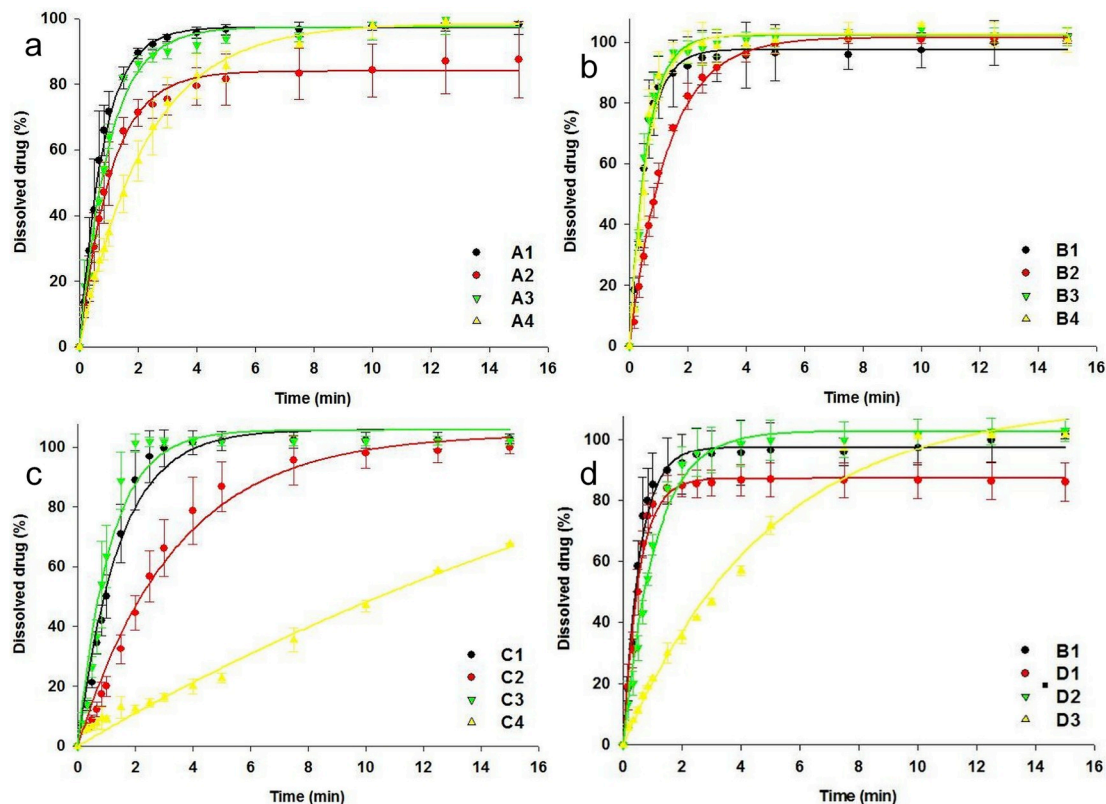


Fig. 5. Drug dissolution from ODTs with a 50 N hardness value, (a) series A, Kollidon CL-SF tablets. (A1: 5% superdisintegrant + mannitol; A2: 5% superdisintegrant + trehalose; A3: 10% superdisintegrant + mannitol; A4: 10% superdisintegrant + trehalose), (b) series B, Polyplasdone XL 10 tablets (B1: 5% superdisintegrant + mannitol; B2: 5% superdisintegrant + trehalose; B3: 10% superdisintegrant + mannitol; B4: 10% superdisintegrant + trehalose), (c) series C, Primojel tablets (C1: 4% superdisintegrant + mannitol; C2: 4% superdisintegrant + trehalose; C3: 8% superdisintegrant + mannitol; C4: 8% superdisintegrant + trehalose) (d) series D, tablets made from ready-to-use excipient composites (D1: Prosolv EASYtab; D2: Prosolv ODT G2; D3: Ludiflash).

activity may be maintained above 90% when using low amount of disintegrant and mannitol as a filler and using 70 N for hardness. Therefore, in the second part of this study, the performance of this composition was compared to various ready-to-use excipients.

When comparing the disintegration times, it was found that B1 exhibited superior disintegration properties over the different ready-to-use excipients (Fig. 7a). Only D1, containing a mixture of the directly compressible Prosolv Easytab and the filler/stabilizer mannitol showed a similar performance at 30 N and 50 N hardness values. However,

ODTs formulated at 70 N exhibited significantly longer disintegration times than B1. Prosolv ODT G2 and Ludiflash, excipients recommended for the formulation of ODTs, showed significantly worse results at each of the three hardness values. It should be noted, however, that the disintegration times provided by these formulations were still under 30 s at 30 N. A possible explanation for this phenomenon may be the difference in apparent densities of the compositions (Fig. 7b). It is notable that D1 exhibits significantly lower densities than all other compositions. These low-density values may also explain the low enzymatic

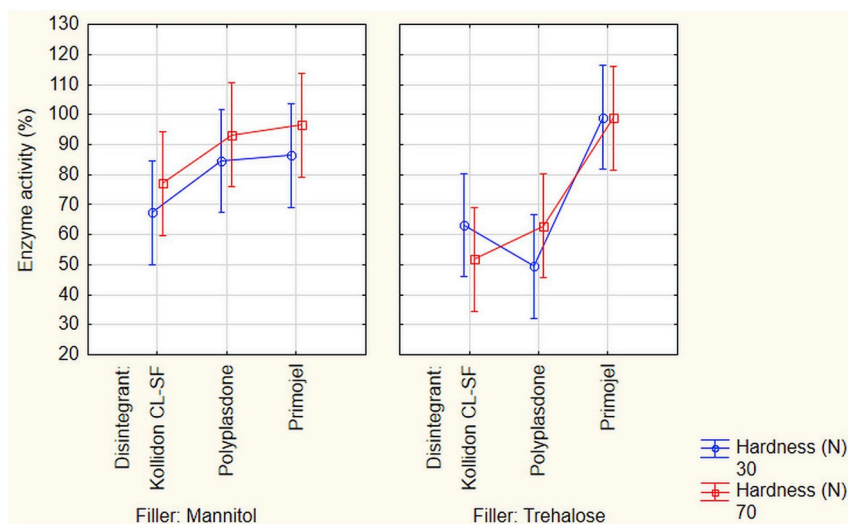


Fig. 6. Results of the statistical analysis on the enzymatic activity.

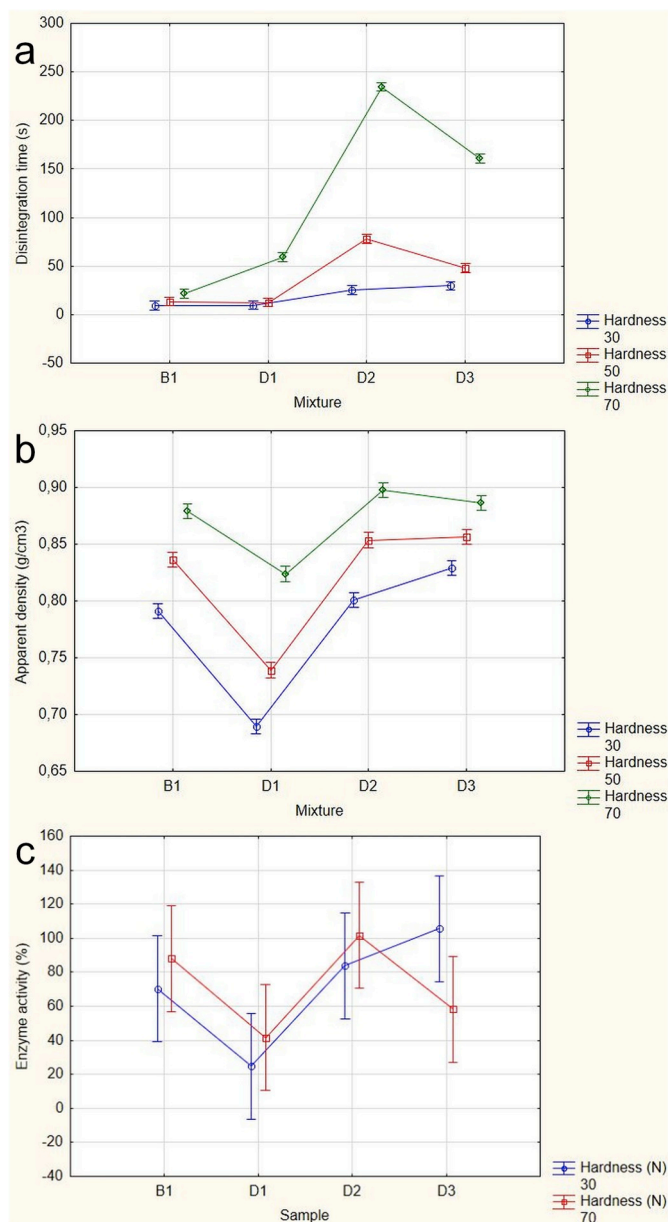


Fig. 7. Comparison of the performance of ready-to-use excipients.

activity measured in the case of this composition (Fig. 7c). The bond between the particles of lysozyme and mannitol was not strong enough for an appropriate stabilizing effect. In the case of D2 and D3, the enzyme activity was excellent, probably due to the high density and the higher mannitol content of these excipients. Nevertheless, it is noteworthy that D3 was the only composition in which greater hardness and density resulted in a decreased enzymatic activity. A possible explanation is that D3 did not contain microcrystalline cellulose and may have been less capable of “absorbing” the mechanical energy, which in turn affected the enzyme activity negatively.

When looking at the drug dissolution results (Fig. 5d), B1 and D2 exhibited a similar, superior performance. In the case of D1, the dissolution speed was fast as expected based on the disintegration time; however, the amount of dissolved drug was lower. A possible explanation for this decrease may be that the first quick phase of the disintegration process was provided by the fast dissolution of mannitol. However, the agglomerates of Prosolv Easytab disintegrated at a lower speed. Since part of the active ingredient particles was stuck in these agglomerates, they could not dissolve as quickly as mannitol. D3

exhibited a slower, but complete, drug dissolution. The lower rate of dissolution can be related to the lower disintegration time.

4. Conclusion

The main goals of this study were to incorporate an enzyme into ODTs formulated by direct compression and to study how excipient selection and manufacturing technology affected the physical properties and performance of the tablets. Results revealed that despite the higher mechanical load experienced during compression, ODTs with higher hardness values provided better stability for the enzyme against post-compressional stress. This may be related to the higher tablet density and stronger contact between the enzyme and stabilizing agents. Using a well deformable stabilizer with a smaller particle size is essential to ensure appropriate distribution of the particles and appropriate contact among the particles, and to avoid the formation of secondary pores, which could have a negative effect on enzyme activity.

Series B tablets - containing Polyplasdone® XL-10 - had the shortest disintegration times (11 of 12 samples under 30 s), and they exhibited the least sensitivity to tablet hardness and the applied filler. Series A tablets - containing Kollidon CL-SF - had longer disintegration times than series B, but more than half of the disintegration times were still under 60 s. Series C tablets - containing Primojel - exhibited shorter or similar disintegration times than series A at lower hardness. A jelling effect was observed for series C samples when placed in the disintegrating medium; which resulted in significantly longer disintegration times at higher hardness than other compositions. This effect was especially strong for trehalose-containing samples. The dissolution rates exhibited an exponential decay with an increase in disintegration time. Series B ODTs exhibited the fastest dissolution, followed by series A and then series C. Formulation B1 provided the shortest disintegration time and fastest dissolution speed, regardless of tablet hardness.

The application of co-processed, ready-to-use excipient composites may provide an easy solution for formulating ODTs, but their composition and physical performance (including particle size, compressibility, and disintegration mechanism) should be critically evaluated before selection. In this study, B1 formulated with individual excipients exhibited superior disintegration properties over the different ready-to-use excipients. B1 and D2 exhibited a similar, superior performance in the dissolution studies. However, the amount of dissolved drug was lower in the case of the ready-to-use excipient. This study demonstrated that in certain cases, developing an individually customized formulation may be more beneficial, especially if requirements of multiple critical quality attributes are to be met. Our results also showed that instead of increasing the amount of the disintegrant, selecting a differently structured type of even the chemically same disintegrant may provide a better solution for issues experienced during disintegration.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jddst.2018.12.012>.

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