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White Paper

How to Select the Optimal ODT Excipient System

Hans-Leonhard Ohrem, Adela Kasselkus

Orally disintegrating tablets (ODTs) are defined by the FDA as a solid dosage form containing medicinal substances, which disintegrate rapidly, usually within a matter of seconds, when placed upon the tongue.[1] Similarly, the European Pharmacopoeia defines orodispersible tablets as uncoated tablets intended to be placed in the mouth where they disperse rapidly before being swallowed.[2]

ODTs offer a clear advantage in terms of convenience when compared with conventional tablets; rapid disintegration in the mouth enables tablets to be taken without liquid and eliminates the need to chew or swallow a tablet whole. Originally developed for patients and indications where swallowing tablets led to poor compliance, particularly in children and geriatric patients, this mode of administration is also beneficial to active or travelling patient groups who prefer the convenience of a dosage form that doesn't require water for administration.

An ODT formulation may also offer the potential for enhanced bioavailability. Studies have shown that the rapid disintegration of tablets results in:

- Quick dissolution of the drug and fast absorption providing a rapid onset of action[3]
- Increased bioavailability of drugs absorbed in the mouth, pharynx, and esophagus which avoids hepatic metabolism, reducing the dose [4,5,6]

In addition to offering greater convenience to patients, this formulation and administration route can represent a product lifecycle extension – a strong economic driving force when competition is fierce. An orally dispersible form of a marketed drug may allow a manufacturer to prolong market exclusivity, create a value-added product line extension and continued patent protection.

There are numerous approaches available for ODT formulation such as lyophilization, direct compression, molding and spray-drying. Direct compression represents the most straight-forward and cost-effective approach as it relies on commonly available, conventional equipment.[7,8,9] This white paper explores a number of factors to be considered when evaluating and selecting an ODT excipient system suitable for direct compression. Available options differ in terms of dissolution, the number of components, compatibility with aqueous coatings, peroxide content and stability – all of which can impact success of the formulation.

ODT Excipient Systems: Comparison of Disintegration and Dissolution Times

ODTs are typically applied for medication which requires fast relief, with indications such as antihistamines, hypnotics, sedatives, antipsychotics, pain and anti-migraine. Possible indications may also include emergent medical conditions such as a heart attack.

When selecting an ODT excipient system, both disintegration and dissolution should be evaluated. Below, a recent study is summarized in which the disintegration and dissolution properties of tablet formulations made with a model API (ibuprofen) and five ready-to-use ODT excipient systems were evaluated.[10]

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Tables 1 and 2 provide an overview on the composition of the investigated sample formulation and used ODT excipient systems.

	Amount [mg/tablet]	Amount [% w/w]
Ibuprofen (38 µm)	200.0	40.0
ODT excipient system (A, B, C, D or E)	290.0	58.0
Silicon dioxide, highly dispersed	5.0	1.0
Parteck® LUB MST excipient (magnesium stearate)	5.0	1.0
Total	**500**	**100**

Table 1. Ibuprofen formulation using five different ODT excipient systems (tablet properties: 11 mm diameter, flat and faceted, tablet hardness 60–70 N).

ODT excipient system	Composition
A*	90–95% mannitol, 3–7% croscarmellose sodium
B	84–92% mannitol, 4–6% crospovidone, 3.5–6% polyvinyl acetate, 0.25–0.6% povidone
C	65% mannitol, xylitol, microcrystalline cellulose, crospovidone, magnesium aluminum silicate
D	80% mannitol, 20% starch
E	30–40% mannitol, 30–40% fructose, 15–30% microcrystalline cellulose, 4–6% crospovidone, 1.5–2.5% silicium dioxide

* Parteck® ODT excipient

Table 2. Excipient systems for ODT formulations and their composition used in this study. If the amount of the individual components is not specified, the precise composition was not available.

Disintegration was performed on six tablets of each excipient system according to USP/Ph. Eur. guidelines. Figure 1 shows how the hardness of ibuprofen tablets affects disintegration time for the ODT excipient systems tested. Most tablets disintegrated in 30 seconds or less, but only when tablet hardness was low (30 N or less), which would be considered rather weak for tablets produced on an industrial scale.

When hardness increased, disintegration times rose well beyond the 30 seconds. While compendial specifications vary, 30 seconds is the generally accepted performance of ODT, per FDA recommendations.[1] These results demonstrate the importance of evaluating disintegration behavior at the desired hardness during industrial production.

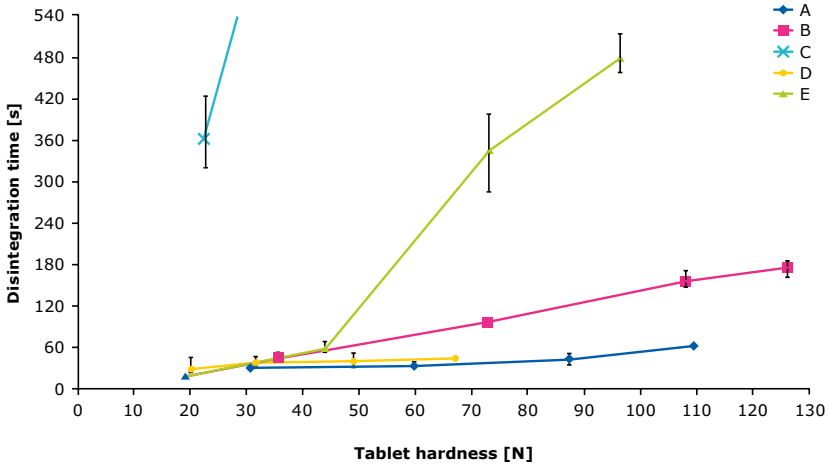

Figure 1. Effect of tablet hardness on disintegration time of ibuprofen tablets made with ODT excipient systems A – E.

Figure 2 shows the results of dissolution tests on ibuprofen tablets. A variation in the release of this poorly soluble API across the investigated ODT excipient systems was observed, clearly showing that most of the excipient systems do not provide immediate release of the API. In addition, the results appear to be dependent on the properties of the API – most likely hydrophobicity in this case – and on the excipient system. In this example, excipient system A shows the best release and the least sensitivity to the API in its release. The results were confirmed also with other APIs (data not shown).

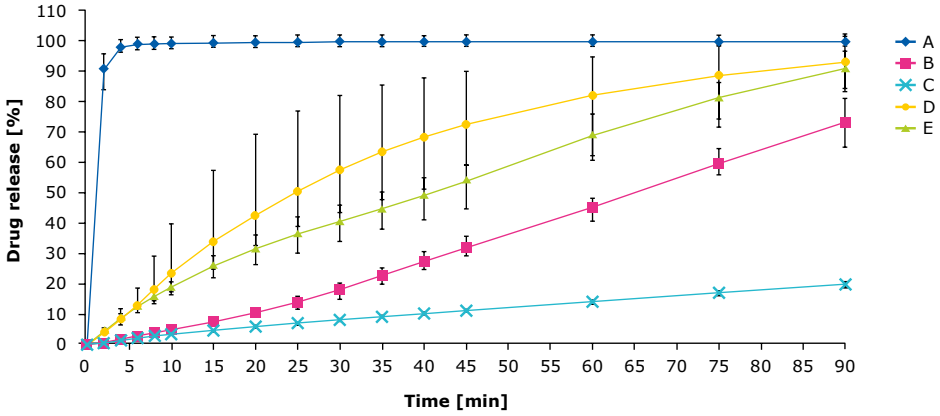

Figure 2. In vitro dissolution profiles of ibuprofen tablets made with ODT excipient systems A – E.

This study demonstrated that tablets made from the five ready-to-use ODT excipient systems showed significant differences in dissolution rates. The differences can be partly explained by the surface structures and porosities of the excipient combinations (Figure 3). These factors influence how well water penetrates the tablet, leading to different speeds of action of the superdisintegrants contained therein.

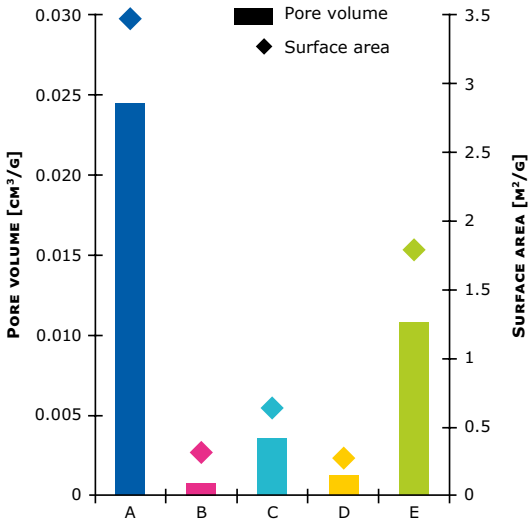

Figure 3. Surface area and pore volume of ODT excipient systems A – E.

Although the observed differences in particle structure of the excipients might result in a different galenic behavior, the major pharmacopeias do not account for this aspect in the excipient monographs, focusing instead on the chemical parameters of the individual components. Nonetheless, physical properties, especially particle morphology, play a major role in the performance of solid dosage forms. Yet because the measurements of porosity and dissolution do not correlate equally in all cases, other factors must also be at work. For example, some excipients contain polymers known to have retarding effects; swelling starch can have a similar effect.

No matter the factors contributing to the differences in physical properties, this study shows that formulators should evaluate ODT excipient systems on additional criteria beyond a simple disintegration test to find the best suitable excipient system for their respective API and desired final product performance.

Advantages of a Two Component ODT Excipient System

ODT excipient systems typically include a number of components. Most directly compressed ODTs rely on the inclusion of a sugar alcohol combined with a superdisintegrant to accelerate dissolution. Mannitol is often used as it exhibits a sweet taste and a pleasant mouth feeling and is stable, inert to virtually all APIs and not hygroscopic. If taste-masking of a bitter API is needed, a sweetener should be included in the formulation, such as aspartame or sucralose which do not exhibit the same unpleasant aftertaste as most other sweeteners and have a similar, pleasant taste as compared with sucrose.[11]

Most ODT excipient systems on the market contain several binders and a superdisintegrant. Thus, the amount of regulatory work required for registration increases due to the greater number of components added especially with regards to Quality by Design (QbD). This work could be significantly reduced if an ODTs only contained two components: one binder plus a superdisintegrant.

Parteck® ODT excipient is a combination of D-mannitol (a binder) and croscarmellose sodium (a superdisintegrant). Croscarmellose sodium is the sodium salt of a cross-linked, partly O-(carboxymethylated) cellulose. Both are well accepted by regulatory authorities, which may help to accelerate the registration procedure of a formulation.

The following data summarize disintegration and drug release tests for tablets including Parteck® ODT and different model APIs.[12]

To evaluate drug release kinetics in vitro, two Parteck® ODT drug formulations (Table 3) with paracetamol of different grades and sources as active substance were assessed.

Formulation 1	Amount [mg/tablet]	Amount [%/tablet]
Parteck® ODT excipient	700.0	70.0
Paracetamol (acetaminophen)	250.0	25.0
Trimyristin	40.0	4.0
Silicon dioxide, highly dispersed	10.0	1.0
Total	**1050.0**	**100.0**
Formulation 2	**Amount [mg/tablet]**	**Amount [%/tablet]**
Parteck® ODT excipient	222.3	44.5
Paracetamol (acetaminophen)	257.7	51.5
Sodium stearyl fumarate	15.0	3.0
Silicon dioxide, highly dispersed	5.0	1.0
Total	**500.0**	**100.0**

Table 3. Ingredients for formulations 1 and 2 used to test drug release kinetics.

Good Compression, Less Wear and Tear

Figure 4 shows that the morphology of the Parteck® ODT excipient system appears very rough and structured under a scanning electron microscope (SEM). This microstructure leads to good compression behavior which means that high tablet strength is achievable with low compression forces. This structure is also ideal for minimizing wear of the tableting equipment or to introduce high amounts of API; up to 50% API can be directly compressed with Parteck® ODT – usually the content of active in direct compression is limited to about 20–30% (Table 4).

Tablet properties	Formulation 1	Formulation 2
Compression force [kN]	20	10
Tablet thickness [mm]	5.0	4.7
Tablet weight [mg]	992.8	498.2
Weight variation [% RSD[a]]	0.49	0.16
Tablet strength [N]	162	172
Hardness variation [% RSD[a]]	15.33	8.66
Disintegration [s]	44–56	34–54
Friability[b] [%]	0.31	0.25

[a] Relative standard deviation | [b] Friability according to the Ph.Eur./USP test method

Table 4. Physical data for paracetamol tablets based on Parteck® ODT.

Experience with this type of polyol excipient usually shows a great deal of wear of the granulated particles upon mechanical stress. Thus, one would expect that the needle-like structure of the Parteck® ODT material, as seen on the SEM, would be crushed during compression. The morphology, however, surprisingly remains unchanged after mixing and compression and contributes to a very large specific surface area of the tablet matrix of up to 3.5 m²/g.[13,14]

Such an exceptionally large surface area can adsorb small API particles well and prevent de-mixing during the manufacturing process. In addition, this helps to enhance the water uptake and disintegration of the tablet matrix. Clearly, not only is it the superdisintegrant that is responsible for fast disintegration of the overall product; the unique surface structure of the binder contributes, too.

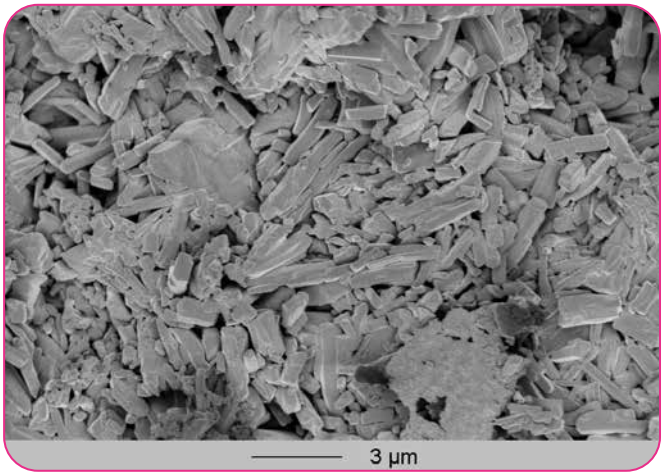

Figure 4. Morphology of Parteck® ODT excipient prior to compression.

Dissolution not Affected by API Content and Lubricant

Another key factor for any kind of formulation is the release time of the active. Experience shows that fast disintegration is not always concomitant with fast release. Some excipients retard the release of active. Our study showed that, after ten minutes, more than 95% of the API in the two formulations was released with Parteck® ODT as directly compressible excipient (Figure 5).

In addition, friability over a broad strength range is exceedingly low, as it is desirable for handling during production and application. Even at a very low compression force (e.g., 5 kN) – friability of < 0.4% can be achieved (data not shown). This characteristic of Parteck® ODT excipient allows the manufacture of extremely robust tablets.

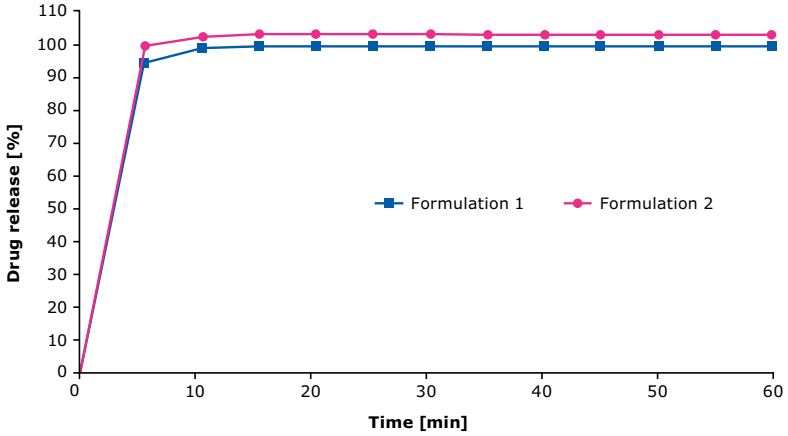

Figure 5. In vitro paracetamol release from Parteck® ODT-based tablets.

Rapid Disintegration

Disintegration is a key factor for the success of an ODT formulation and was tested using a formulation with sildenafil as active. The disintegration times for Parteck® ODT were shown to be well within the range expected for ODT applications. Even at low compression forces, good tablet hardnesses and low tablet friabilities are observed.

More importantly, however, producing hard and stable tablets does not cause the disintegration time to suffer. As Figure 6 shows, the disintegration time remains constant over a wide range of tablet strengths. This is a major difference from some ODT excipient systems on the market, which display fast disintegration only for rather soft tablets.

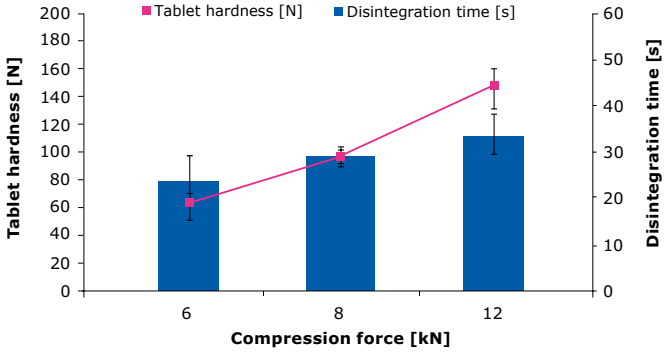

Figure 6. Disintegration time and tablet hardness of sildenafil-Parteck® ODT tablets manufactured using different compression forces (71.14 mg sildenafil citrate equivalent to 50 mg sildenafil, 107.86 mg Parteck® ODT excipient, 1 mg highly dispersed silicon dioxide, 15 mg microcrystalline cellulose, 2 mg magnesium stearate and 3 mg sucralose). Friability of 0.56, 0.24 and 0.23% for compression forces of 6, 8 and 12 kN, respectively.

Finally, the sensitivity of Parteck® ODT excipient added to a randomly chosen set of lubricants (2% sodium stearyl fumarate, 3% trimyristin, 1% Parteck® LUB MST magnesium stearate or 5% polyethylene glycol 6000) was tested using placebo formulations. No significant effect on disintegration behavior was observed, giving the formulator flexibility to resolve specific formulation problems.

The combination of two components in Parteck® ODT – one binder and a superdisintegrant – shows valuable characteristics for direct compression. Through its large surface area, the formulator can achieve high tablet strength at low friability while still achieving fast disintegration and a pleasant mouth feel. Tablets produced with Parteck® ODT exhibit rapid disintegration within the oral cavity, as well as fast release of the active. This excipient system can help to accelerate the regulatory registration process and is compatible with most actives, making it a good, economical option.

Compatibility of ODT Excipient Systems with Aqueous Coatings

Coating of a tablet can be required for a number of reasons including improvement of patient compliance, anti-counterfeiting, masking of unpleasant API colors and protection from light, oxygen or moisture.

However, coating is generally considered to be impossible for ODT formulations. This is because they are designed to disintegrate very fast upon the contact with very little moisture which is why most of the current ODT formulations are compressed to rather weak units. The low tablet hardness makes the formulations typically not suitable for coatings in general; Parteck® ODT, however, can be used with aqueous coatings.

The following study evaluated five ready-to-use ODT excipient systems in a coating process using a commercially available aqueous coating system based on polyvinyl alcohol.

All placebo formulations were compressed to a hardness of approximately 50 N to allow for a comparison of the disintegration times of the tablet cores. Due to the coating process, tablet hardness was observed to increase for all tested coating systems.[15]

Figure 7 shows that all but one of the excipient systems had an increase in the disintegration time. As a consequence, the prolonged disintegration times make these systems inappropriate for the intended ODT application. Similar results of increasing hardness and disintegration times were reproduced for tablets containing API (20% w/w ascorbic acid; data not shown) and also using a different commercially available aqueous coating system based on HPMC.[15]

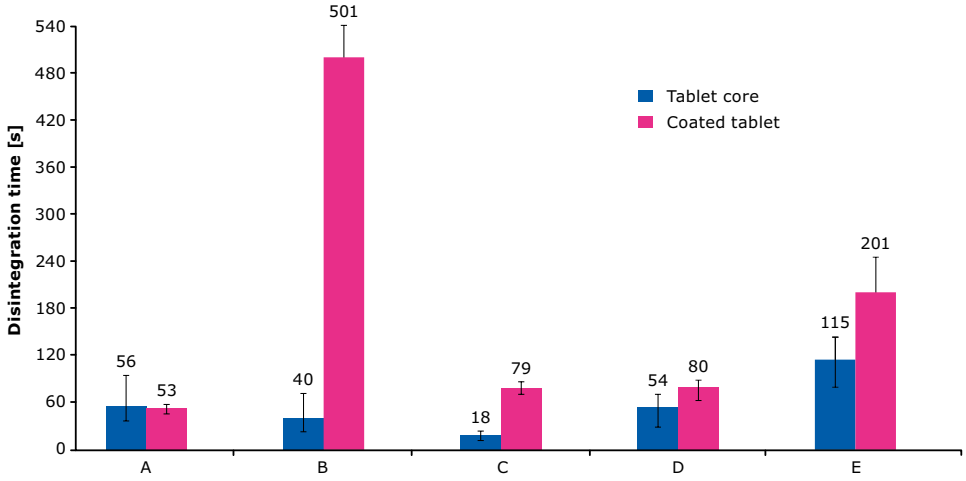

Figure 7. Tablet disintegration time before and after coating process for ODT excipient systems A – E.

The coating process was shown to have a strong impact on the mechanical integrity of the tablets as the tablet edges were observed to be chipped and eroded for several of the applied ODT excipient systems. This is due to the agitation in addition to the influence of moisture. For this reason, some of the excipient systems are not rendered suitable for an aqueous coating process.

As shown with this study, aqueous coating of ODT formulations is possible if the appropriate excipient system is used. All of the tablets studied showed a significant increase in hardness after the coating process. However, only the Parteck® ODT excipient system showed a constant disintegration time before and after the coating. For all others the disintegration time increased to an extent that made them inappropriate for use as ODT formulations.

Stability Issues Regarding the API

Stability of the API must be demonstrated in any pharmaceutical formulation. Impurities in the applied excipients may affect the stability. One of the commonly observed impurities in solid dose excipients are peroxides.

Since excipient systems for ODT formulations are usually a combination of two or more components, the composition is not always very transparent to the formulator. Additionally, the composition of some excipient systems is not disclosed, leaving no opportunity to evaluate the impact of the excipients on the formulation, thus making it difficult to foresee possible instabilities in the final formulation (see Table 1 for details on the composition of the applied ODT excipient systems).

Two methods for the analytical determination of peroxide content in pharmaceutical excipients were assessed.[16] The analytical method according to USP gives the peroxide concentration in parts per million.[17] However, it was observed that there is no linearity for low peroxide concentrations of 100 ppm and less. For this reason, this method is deemed too inaccurate as peroxide contents < 100 ppm may also affect the stability of a formulation.

The DAB method was assessed as an alternative. This method is based on iodometric titration and delivers the result as "peroxide count".[18] Unfortunately, this is not directly related to a concentration in terms of ppm. Also, the method itself relies on a very subjective parameter: the visible color change detected by eye. Despite these disadvantages, it was demonstrated that this method is very accurate even in concentrations below 100 ppm of hydrogen peroxide.[16] Due to the superior sensitivity, the DAB method for the quantification of peroxide impurities in pharmaceutical excipients was used.

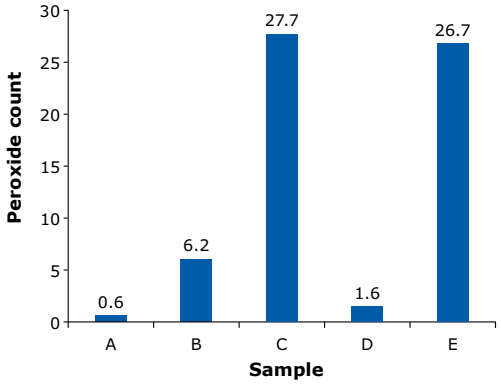

Figure 8. Comparison of the peroxide count of five different excipient systems which are commonly used for ODT formulations.

As shown in Figure 8, significant differences in peroxide content among the five excipient systems were determined. The peroxide content of the systems C and E was especially high in comparison to systems A and D with a peroxide count of 27.7 and 26.7 compared to 0.6 and 1.6, respectively. The lowest peroxide content was determined for system Parteck® ODT (0.6).

ODT excipient systems containing povidone and/or crospovidone had a significantly higher level of peroxides which may result in stability problems in the final formulation and should be avoided. Selection of the appropriate ODT excipient system is this crucial for a stable and successful final formulation.

Performance of Orally Disintegrating Tablets

When selecting the optimal excipient, it is crucial to consider its performance not just at time zero but also over its shelf life. This study characterized selected ODT excipients (Table 2) with respect to their compressibility and potential for quick disintegration. A tablet hardness of 100 N is the goal, as this ensures easy handling and enables use of conventional packaging. Stability of these ODT formulations was evaluated in terms of tablet hardness, disintegration time, and discoloration over a one year period under accelerated storage conditions.

Placebo formulations containing the ODT excipient mixed with 1% magnesium stearate were processed using a single punch press. Tablets weighing 300 mg with a diameter of 11 mm and a hardness of ~100 N were produced at compression forces between 13–30 kN. The tablets were stored in closed containers under accelerated conditions (40 °C, 75% r.H.) for 26 weeks and analyzed after 1 day, 1 week, 2, 4, 8, 12 and 26 weeks.

Compressibility

The desired tablet hardness of > 100 N was achieved for all the directly compressible excipients tested (Figure 9). However, compression forces between 13–30 kN were required. Parteck® ODT reaches its highest tablet hardness (132 N) at the lowest compression force (13 kN). These tablets also have the shortest disintegration time, just 21 seconds. Two of the other ODT excipients have disintegration times between 39–46 seconds, while two only disintegrate within 120 and 152 seconds respectively.

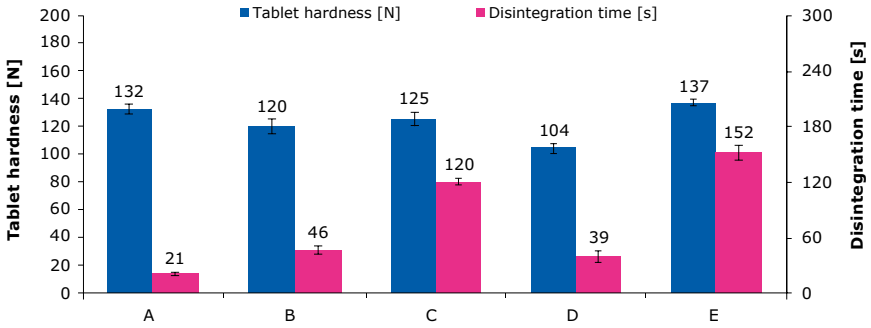

Figure 9. Tablet hardness and disintegration time of ODT tablets (n = 20).

Stability

The results of the stability study were different for the individual ODT excipients. Figure 10 demonstrates that there was a strong increase in disintegration time during storage for B and E; C did not show a significant increase, but the disintegration time was generally slightly higher. Parteck® ODT excipient and C and D showed good stability over 26 weeks under accelerated conditions.

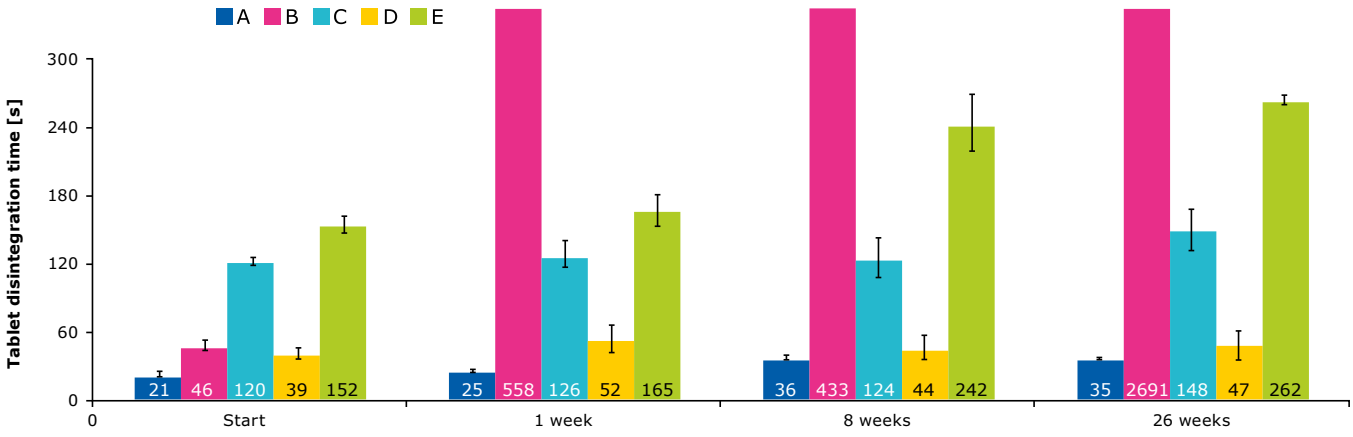

Figure 10. Disintegration time of tablets stored at 40 °C/75% r.H. over 26 weeks (n = 6).

Tablets manufactured using ODT excipient system E clearly showed discoloration during storage under accelerated conditions. The delta value (Figure 11) was significantly increased after just one week of storage. After 26 weeks, a strong discoloration was observed, which was visible to the naked eye and also confirmed by the delta value (Figure 12, right tablet). The other products showed acceptable stability and no visual changes were found.

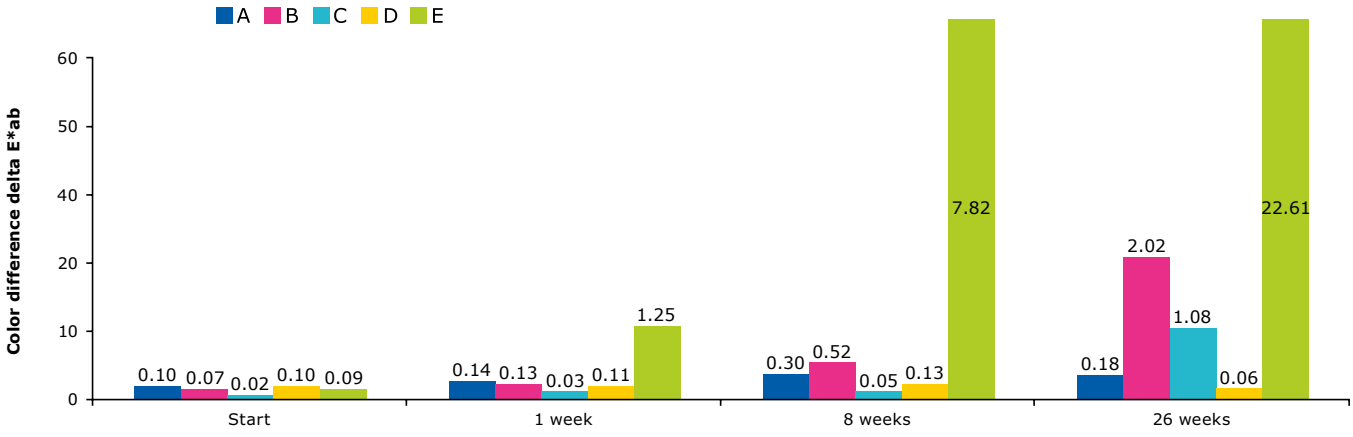

Figure 11. Color measurement of tablets stored at 40 °C/75% r.H. over 26 weeks (n = 5).

Figure 12. Color of tablets manufactured using ODT excipient system E (right tablet) vs. Parteck® ODT tablet (ODT excipient system A) after 26 weeks storage at 40 °C/75% r.H.

The Parteck® ODT Advantage

ODT formulations provide significant benefits including convenience, improved adherence, the potential for enhanced bioavailability and product lifecycle extension. While there are many choices of ODT excipient systems, they differ in key areas which should be considered prior to inclusion in a formulation.

As demonstrated by these studies, Parteck® ODT excipient allows the design of a robust dosage form with both fast disintegration and fast dissolution irrespective of the drug substance grade, tablet weight and tablet size. It was also shown to offer advantages in terms of tablet hardness, API stability, compatibility with aqueous coatings, low levels of peroxide and long-term stability.

ODT excipients differing in compressibility, hardness and storage stability are available for direct compression. This study clearly shows the importance of evaluating performance not only at time zero but after a certain period of storage. Parteck® ODT excipient combines excellent compressibility with a short disintegration time and stable performance under accelerated storage conditions.

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For further information, please contact:

hans-leonhard.ohrem@merckgroup.com

MerckMillipore.com

Merck KGaA, Darmstadt, Germany

Frankfurter Strasse 250
64293 Darmstadt
Germany

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