

orally disintegrating tablets

DIRECTLY COMPRESSIBLE ODT PLATFORMS: A COMPARATIVE STUDY

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This article describes the benefits of orally disintegrating tablets for pediatric and geriatric patients and presents the results of a study comparing several commercially available directly compressible ODT platforms with an ODT blend that the researchers prepared.

Orally disintegrating tablets (ODTs) are not just another fancy dosage form; they address a very important component of treatment success: compliance. This is especially true for pediatric and geriatric patients. Children and the elderly are not easily persuaded to take medicines and can have difficulty swallowing tablets or capsules whole, making therapeutic compliance a significant challenge.

Figure 1

Key DC ODT platform performance attributes and formulation challenges

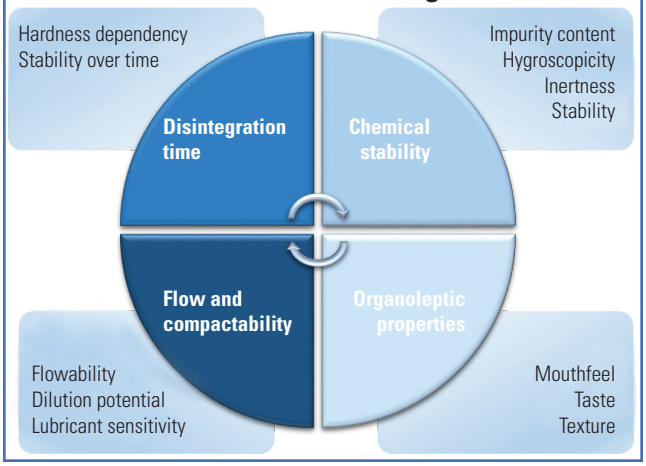
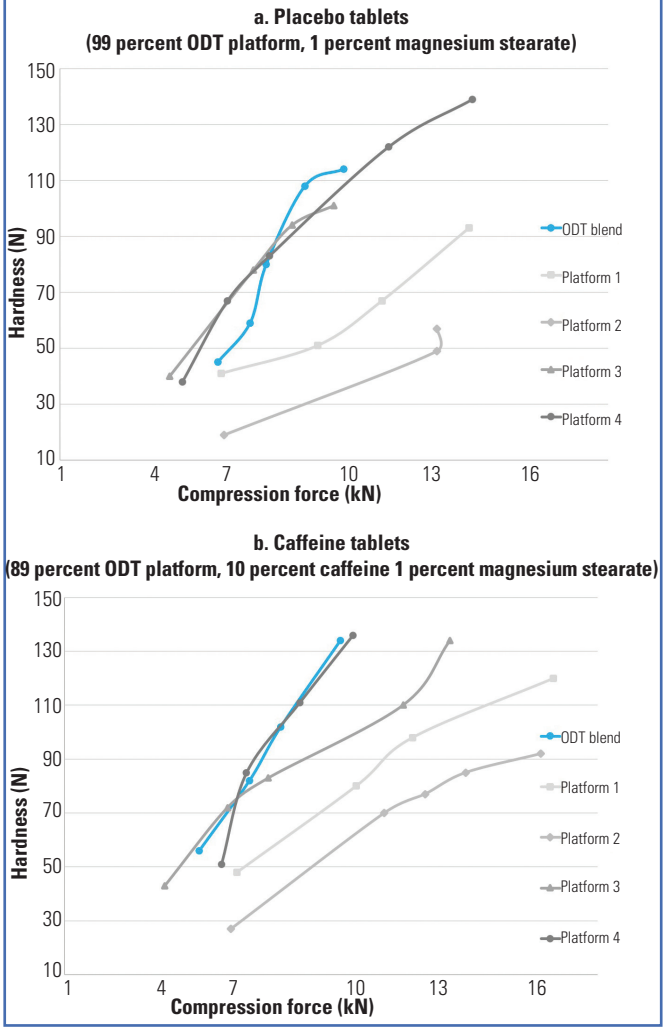


Figure 2

Compression force versus tablet hardness



The world's aging population has increased the demand for geriatric drug products, and this trend is expected to continue. Also, evidence shows that children are not just small-sized adults when it comes to medication. For example, a child's metabolism differs significantly from that of an adult, so pediatric medicines may require not only different dosages but also different API release profiles than adult medicines. In fact, since 2007 the European Medicines Agency has required pharmaceutical companies to submit a pediatric investigation plan to the agency's pediatrics committee at the end of the first phase of testing a new drug in adults [1].

The need to develop age-appropriate formulations targeting pediatric and elderly patients is clear. ODTs can help improve compliance for these two populations because ODT tablets are usually smaller than traditional tablets and capsules; they disintegrate rapidly in the patient's mouth; and they have a pleasant mouthfeel and flavor.

In the combined regions of the US, the European Union, and Japan, the ODT market has doubled in the last four years. A 2017 study by Persistence Market Research predicted that the global ODT market will grow at a significant pace in coming years, with annual revenue anticipated to rise from an estimated $11.4 billion in 2017 to about $27 billion in 2025 [2]. Table 1 lists some examples of the more than 450 over-the-counter

Table 1

Examples of currently marketed ODTs [4]

Active ingredient	Brand name	Category	Technology
Loratadine	Claritin	Antihistaminic	Lyophilization
Mirtazapine	Remeron	Antidepressant	Compressed tablets
Olanzapine	Zyprexa	Antipsychotic; serotonin-dopamine antagonist	Lyophilization
Ondansetron	Zofran ODT	Nootropic; antiemetic; serotonin receptor antagonist	Lyophilization
Risperidone	Risperdal	Antipsychotic; dopamine receptor antagonist; serotonin-dopamine antagonist	Lyophilization
Rizatriptan	Maxalt	Antimigraine; serotonin receptor agonist	Lyophilization
Tramadol	Ultram	Analgesic (non-narcotic)	Cotton candy process
Zolmitriptan	Zomig	Antimigraine; serotonin receptor agonist	Compressed tablets
Zolpidem	Ambien	Sedative/hypnotic	Cotton candy process

Figure 3

Friability versus tablet hardness

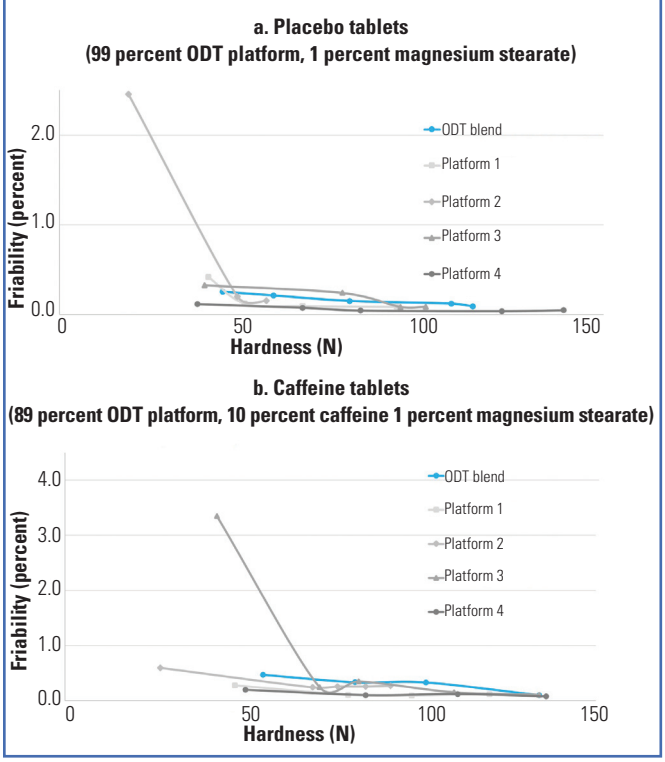
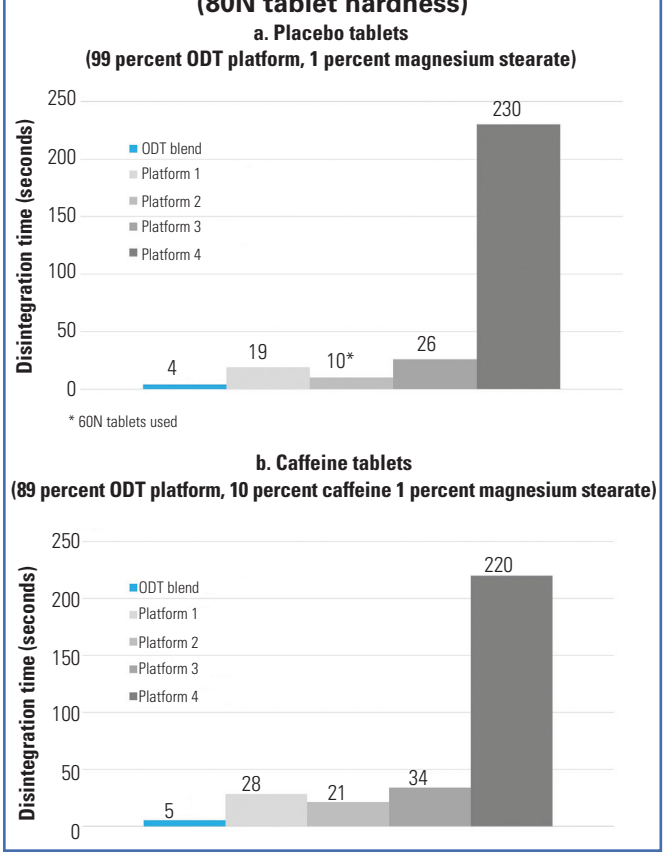


Figure 4

Disintegration time (80N tablet hardness)



(OTC) and prescription ODT products currently available on the market.

ODT formulation technologies

In addition to fast disintegration, an ODT platform must also be stable, have a good level of inertness, have good flowability and compactability, and contribute to the pleasant mouthfeel of the final formulation. Formulators produce ODTs using several different technologies, including direct compression (DC), lyophilization (freeze drying), molding, mass extrusion, and spray drying [3]. Each of these technologies has disadvantages such as relatively slow disintegration, poor mouthfeel or taste masking, high manufacturing costs, special packaging requirements due to hygroscopicity, or low chemical and/or mechanical stability. However, DC ODT platforms have a clear advantage over other technologies in terms of cost-effectiveness and ease of manufacturing. Figure 1 shows the key performance attributes expected in a DC ODT platform and the associated formulation challenges, and Table 2 lists some currently marketed DC ODT platforms.

Table 2

Some currently marketed DC ODT platforms

ODT platform	Manufacturer	Composition
Prosolv ODT G2	JRS Pharma	Microcrystalline cellulose, colloidal silicon dioxide, mannitol, fructose, crospovidone
F-Melt	Fuji Chemicals	Mannitol, xylitol, calcium sulphate,crospovidone, magnesium aluminometasilicate
Pearlitol Flash	Roquette	Mannitol, starch
Parteck ODT	Merck	Mannitol, croscarmellose sodium
Ludiflash	BASF	D-mannitol, crospovidone, polyvinyl acetate
StarLac	Meggle/Roquette	Lactose, starch
Granfiller-D	Daicel	Mannitol, crospovidone, carmellose and microcrystalline cellulose
Pharmaburst	SPI Pharma	Mannitol, starch, crospovidone, croscarmellose sodium, colloidal silica, silica
PanExcea ODT	Avantor	Mannitol, silicate salt

FIGURE 5

Disintegration time versus tablet hardness for placebo tablets

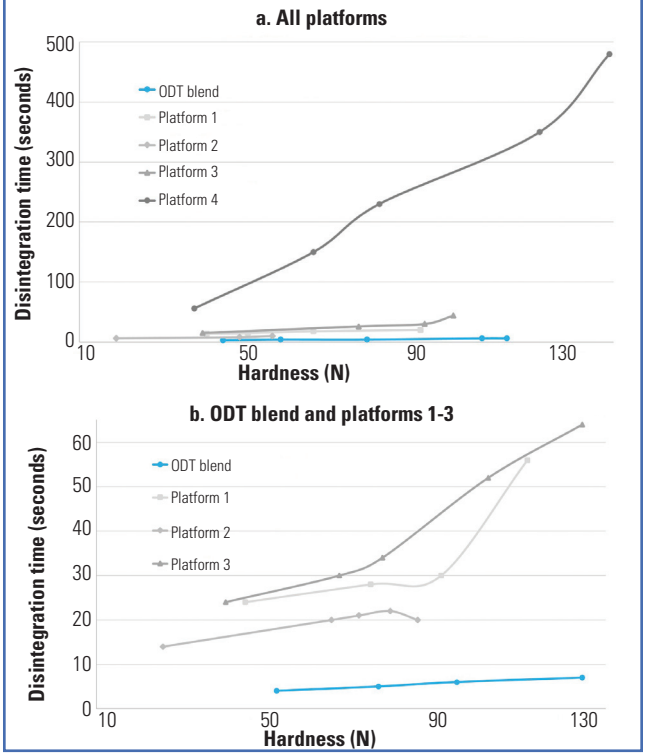
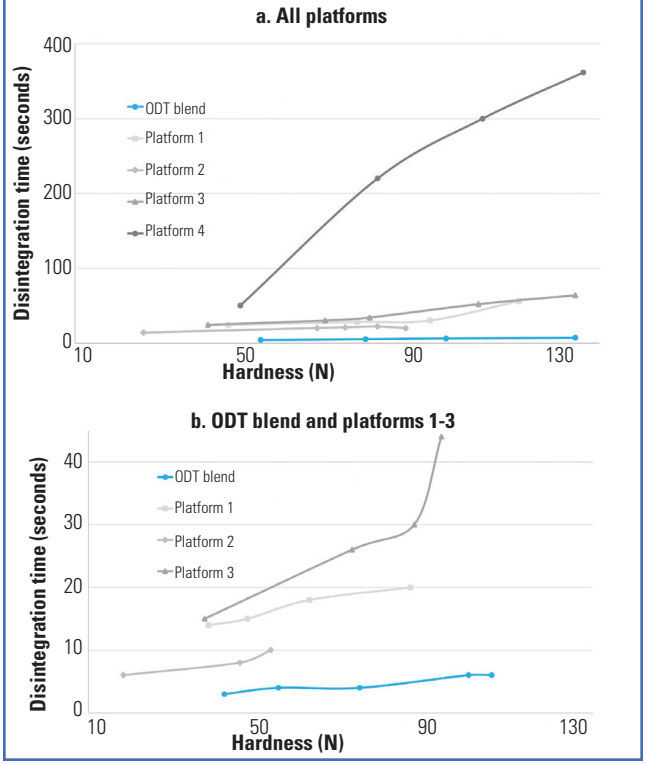


FIGURE 6

Disintegration time versus tablet hardness for caffeine tablets



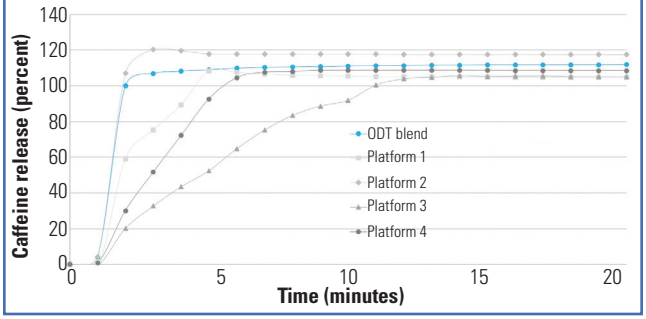
Comparing DC ODT platforms

The study presented here compared the key performance attributes of several commercially available DC ODT platforms with those of a dry granulated ODT blend that the researchers prepared. The ODT blend was composed of Omyapharm 500-OG and croscarmellose sodium. Omyapharm 500-OG is a novel co-processed multifunctional mineral excipient comprising calcium carbonate and tribasic calcium phosphate. The product's particles have an external lamellar structure that encloses a core of interconnected pores, giving it several desirable properties, including high compactability, the ability to be used in dry granulation without requiring a binder, and dilution potential.

To compare the ODT blend with the commercially available ODT platforms, both placebo tablets and caffeine-containing tablets were manufactured. The placebo tablets consisted of 99 percent ODT platform or blend ingredient and 1 percent lubricant (magnesium stearate), while the caffeine tablets consisted of 10 percent caffeine, 89 percent ODT platform or blend ingredient, and 1 percent lubricant. It is worth mentioning that tablets consisting of 0.3 percent lubricant were initially tested, but the commercially available ODT platforms showed very poor compactability at that lubricant concentration, so 1 percent lubricant was selected to allow the manufacturing of tablets from all of the available excipients.

FIGURE 7

Caffeine dissolution versus time (Average of 3 tablets for each ODT platform)



Flow and compactability

Compactability is the most important functional consideration when producing a tablet [5]. To characterize the compactability of the ODT platforms and the ODT blend, the study tested the flowability of each as well as tablet hardness and friability versus compression force. Table 3 describes the flow properties of the ODT platforms and blend. Each showed good or at least fair flow properties. Figure 2 shows the tablet hardness achieved at different compression forces for each. The tableting machine settings were defined to reach, whenever possible, tablet hardness values between 30 and 140 newtons (N). The study used a Fette 1200i rotary tablet press operating at a speed of 10,000 tablets per hour.

The results showed that, for the placebo tablets, ODT platform 2 did not achieve hardness above 60N, regardless of the compression force used. To reach a tablet hardness above 40N, ODT platform 1 required significantly higher compression force than the ODT blend or platforms 3 or 4. Platforms 3 and 4 showed a linear cor-

relation between compression force and hardness in the studied range (R^2=0.9862 and R^2=0.9686, respectively). Moreover, ODT platform 4 was able to reach hardness above 130N at compression forces lower than 14 kilonewtons (kN). In the placebo tablets, the ODT blend reached hardness above 110N at lower compression forces than any of the ODT platforms tested.

All of the tablets containing 10 percent caffeine were able to achieve hardness above 80N but at different compression forces. In general, platforms 1 and 2 required a higher compression force than the ODT blend and platforms 3 and 4 to achieve equal hardness. All the tablets showed a linear correlation between compression force and hardness, but the ODT blend had the highest linear correlation coefficient (R^2=0.9912). In addition, in the range of hardness studied, the ODT blend required lower compression forces than most of the studied platforms to achieve caffeine tablets of equal hardness.

Friability was measured according to the European Pharmacopoeia and compared among the different platforms, as Figure 3 shows. For the placebo tablets, ODT platform 4 showed the lowest friability, but friability was relatively low (1 percent or less) for all platforms—at least for tablets with hardness above 40N. For the caffeine-containing tablets, the friability was also below 1 percent in most cases. The ODT blend achieved friability lower than 1 percent on placebo tablets with a hardness higher than 45N, and caffeine-containing tablets, with hardness higher than 50N.

Disintegration time

An ODT should disintegrate in less than 30 seconds, according to the US Pharmacopeia (USP), and less than 180 seconds, according to the European Pharmacopoeia. This study compared the disintegration time of the ODT platforms according to the European Pharmacopoeia for tablets with equal hardness (80N), as Figure 4 shows. The disintegration times varied significantly between ODT platforms.

ODT platforms 1, 2, and 3 showed disintegration times ranging from 19 to 34 seconds, with longer disintegration times for the caffeine tablets than for the placebo tablets. Note that, while the placebo tablet for ODT platform 2 had a disintegration time of 10 seconds, this test was run with 60N tablets because platform 2 could not achieve the 80N hardness value.

While ODT platform 4 showed better compactability than other ODT platforms, its disintegration time was significantly higher, at around 230 seconds for the placebo and 220 seconds for the caffeine tablets. ODTs manufactured with the ODT blend had significantly lower disintegration times than the commercially available platforms, at 4 seconds for the placebo and 5 seconds for the caffeine-containing samples.

To study the effect of tablet hardness on disintegration time, the disintegration time was also measured at increasing ODT hardness values, as Figures 5 and 6 show. For both placebo and caffeine-containing ODTs, the disintegration time increased most significantly for platform 4 as the hardness increased. Of the remaining ODT platforms, platform 3 showed the highest gradient, followed by platform 1, platform 2, and finally, the ODT blend, which had a slope close to zero, indicating that the disintegration time was only slightly affected by increasing tablet hardness. In fact, the 114N placebo ODTs and 134N caffeine ODTs manufactured with the ODT blend disintegrated in 6 seconds and 7 seconds, respectively.

To determine whether the disintegration time affected the API release, the caffeine release profile of the ODTs was compared according to USP Apparatus 2 for 80N ODTs in a Sotax AT7 Smart tester (n=3). The four ODT platforms and the blend completely released the caffeine, as Figure 7 shows, but the release profiles varied. The ODT blend and platform 2 had the fastest caffeine release, at less than 3 minutes. Platforms 1 and 4 completed caffeine release shortly before or after 5 minutes, respectively, while platform 3 completed caffeine release only after more than 10 minutes.

Stability and organoleptic perception

This study primarily focused on compactability and disintegration time as key performance attributes. Organoleptic perception is a highly subjective attribute and also depends on several factors unrelated to the ODT platform, such as the amount of API needed in the formulation and the target population. On the other hand, stability is an attribute that can clearly be measured. Stability trials were run as part of this comparison but are not covered in this article.

Table 3

Flow properties of different ODT platforms

	ODT blend	Platform 1	Platform 2	Platform 3	Platform 4
Loose bulk density (g/ml)	0.78	0.61	0.50	0.54	0.62
Tapped bulk density (g/ml)	0.90	0.70	0.60	0.71	0.76
Angle of repose (°)	39.60	34.70	34.60	38.50	35.00
Hausner factor	1.15	1.15	1.20	1.31	1.23
Compressibility index	13.33	12.86	16.67	23.94	18.42

Conclusions

A successful DC ODT platform should simultaneously address several key performance attributes such as poor compactability, slow disintegration, lack of stability, and inferior organoleptic properties. The ODT blend prepared by the researchers and the commercially available ODT platforms in this study each demonstrated advantages and disadvantages, but the ODT blend combined good compactability with the fastest disintegration time of the platforms studied, overcoming several challenges to ODT formulation.

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