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Effect of a Disintegration Mechanism on Wetting, Water Absorption, and Disintegration Time of Orodispersible Tablets

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ABSTRACT

The aim of this study was to evaluate the influence of disintegration mechanism of various types of disintegrants on the absorption ratio (AR), wetting time (WT), and disintegration time (DT) of orodispersible tablets (ODTs). ODTs were prepared by direct compression using mannitol as filler and disintegrants selected from a range of swellable, osmotic, and porous disintegrants. Tablets formed were characterized for their water AR, WT, and DT. The porosity and mechanical strength of the tablets were also measured. Results show that the DT of formulated ODTs was directly related to the WT and was a function of the disintegration mechanism of the disintegrant used. The lowest WT and DT were observed for tablets formulated using the osmotic disintegrant sodium citrate and these tablets also showed the lowest AR and porosity. The wetting and disintegration of tablets containing the highly swellable disintegrant, sodium starch glycollate, was slowest despite their high water AR and high tablet porosity. Rapid wetting and disintegration of ODTs were therefore not necessarily related to the porosity of the tablets.

Key words: Absorption ratio, disintegration time, orodispersible tablets, porosity, wetting time

INTRODUCTION

Orodispersible tablets (ODTs) are patient friendly oral solid dosage forms offering enhanced patient compliance and convenience of dosing and have become increasingly popular among the wider patient population.[1-3] As ODTs are designed to disintegrate and/or dissolve in the patient's mouth in a very small volume of saliva, their disintegration and/or dissolution time is critical to their in vivo performance. ODT technologies used range from lyophilization to tablet compression resulting in ODTs with differing characteristics.[2-4] Lyophilized tablets and ODTs formulated by moulding at low pressure disintegrate rapidly due to their porous structure. This high porosity contributes to their weak mechanical strength, an undesirable quality requiring special packaging.[4-8] The ideal property of ODTs is rapid buccal disintegration with sufficient mechanical strength to allow for handling and shipment without recourse to specialized packaging.

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Conventional granulation and compression methods have been adapted to formulate ODTs with higher mechanical strength; however, these show a longer DT. To decrease the DT, a number of strategies have been investigated. These range from low compression force, use of fast dissolving sugars, and the addition of effervescent

excipients.[2,3] Wehling *et al*.[9] studied the formulation of ODTs by direct compression using low compression force to formulate highly porous ODTs resulting in rapid disintegration of the tablets. Others examined the use of superdisintegrants and/or effervescent excipients to promote rapid disintegration times (DTs).[10-14] The addition of effervescent excipients adds an extra complexity to the formulations of ODTs as the resultant tablets are moisture sensitive and therefore require controlled conditions of humidity during processing and storage.

Superdisintegrants such as sodium starch glycollate (SSG), cross-linked polyvinylpyrrolidone (crospovidone) and calcium silicate (CS) are reported to have porous structure facilitating water uptake into the tablet,[15,16] a pre-requisite for disintegration to occur. Both crospovidone and SSG have also been reported to result in rapid volume expansion and hydrostatic pressures allowing tablet disintegration.[11] Various disintegrants at increasing concentrations have been examined for enhancing the disintegration rate of ODTs.[15-19] Khinchi *et al*.[17] showed that tablets formulated with crospovidone and SSG exhibited quicker disintegration of tablets than tablets containing croscarmellose sodium as disintegrant. Bi *et al*.[18,19] investigated ODT formulations containing croscarmellose sodium and reported a small increasing effect of disintegrant concentration on tablet porosity; however, the effect on wetting time (WT) and disintegration time (DT) was larger. While the swellable disintegrants have been extensively investigated and compared in many studies, evaluation of the effect of non-swellable disintegrants on WT and DT of tablets have not been studied.

In this study, the effect of disintegrant mechanism on the absorption ratio (AR), WT and DT of ODTs was investigated. The relationship between WT, DT, and tablet porosity were also examined. Disintegrants evaluated ranged from the porous and swellable disintegrants SSG and crospovidone to the osmotic disintegrants sodium citrate and citric acid.

MATERIALS AND METHODS

Materials

Mannitol 200 was a gift from Parteck® Merck KGaA (Norman Lauder, Dublin). Cross-linked polyvinylpyrrolidone; crospovidone (Kollidon® CL-SF) and potassium polyacrylate (Luquasorb® 1280) were a gift from BASF, Cheshire, UK. Sodium starch glycollate (Explotab®) was a gift from JRS Pharma, Germany. Calcium silicate (RxCIPIENTS™ FM1000) was a gift from Huber Engineered, Finland. Citric acid (anhydrous) and sodium citrate (anhydrous) were purchased from Leochem, China. Magnesium stearate was a gift from JMB, UK. Rhodamine B was obtained from Sigma-Aldrich, Ireland.

Methods

Formulation of tablets

Mannitol 200 and the disintegrant(s) were weighed and blended together for 5 min in a resealable plastic bag. The disintegrant was added at 10% w/w except for potassium polyacrylate (PPA), crospovidone, and CS, which was added at concentrations of 2, 5, and 18% w/w, respectively, as recommended by respective suppliers [Table 1]. Magnesium stearate at 0.5% w/w was added to the sugar and disintegrant blend and blended gently for 1–2 min. Tablets were compressed at a high compression force of 10 kN and a speed of 7 rpm using an 8 Station rotary tablet press (Riva Piccola, Hampshire, UK) fitted with flat-faced bevelled edge (FBE) tools of a diameter 15 mm.[20] Tablets were compressed to a target weight of 500 mg ± 10% with final weights ranging from 487 to 550 mg depending on the density of the powder blend.

Characterization of tablets

Uniformity of weight and tablet thickness. Uniformity of tablet weight was carried on n = 5 tablets, taken randomly and weighed individually on a Sartorius balance, Model CP225D, Bradford, MA, USA. The average weight of the tablets ± standard deviation was calculated. The thickness of each ODT (n = 5 tablets) was measured using a pair of calibrated digital Vernier callipers (Digital Caliper Workzone, UK).

Mechanical strength and friability of tablets. Hardness or crushing strength of the tablets was carried out individually on n = 5 tablets using a pre-calibrated PTB 411E Tablet hardness tester (PharmaTest, Germany). The average hardness ± standard deviation was calculated. The tensile strength ($\sigma_{tensile}$) which takes into account dimensions of the compact was calculated from the measured hardness/crushing strength ($\omega_{failure}$), using Eq. 1:[21]

Table 1: Formulation composition of F01–-F07 tablet batches Magnesium stearate was added at 0.5% w/w in all batches

Ingredients (%w/w)	F01	F02	F03	F04	F05	F06	F07
Mannitol 200	81.5	89.5	94.5	89.5	89.5	96.9	79.5
Potassium polyacrylate (PPA)	2	–	–	–	–	–	–
Sodium starch glycollate (SSG)	–	10	–	–	–	–	10
Crospovidone	–	–	5	–	–	–	–
Calcium silicate (CS)	–	–	–	18	–	–	10
Citric acid	–	–	–	–	10	–	–
Sodium citrate	–	–	–	–	–	10	–

$$\sigma_{\text{tensile}} = \frac{2.F_{\text{failure}}}{\pi.A_{\text{cross-sectioned area}}} \quad (1)$$

$A_{\text{cross-sectional area}} = 2 \times (\text{cup area}) + 2\pi rh$

where

r is the radius of the tablet, h is the height of the tablet edge, and cup area is provided by Natoli Engineering Company, Inc., Missouri, USA.

Friability test

The friability test on tablets was performed on n = 10 tablets using a pre-calibrated PTFE Friability tester (PharmaTest, Germany). If tablets cracked, cleaved, or broke after testing, the sample was recorded as 'Failed' for failed friability test.

Wetting time and water absorption ratio

The WT of the tablets was evaluated (n = 6). This experiment mimics the action of saliva in contact with tablet. A Whatman filter paper disk folded once diametrically was placed in a petri dish of 8.5 cm in diameter. A small volume (8 ml) of water containing the water soluble dye, Rhodamine B (0.1 g) was added to the filter paper on the petri dish. The tablet was carefully placed on the filter paper at t = 0 and the time for complete wetting was measured.[10,22] The appearance of the dye on the surface of the tablet was taken as a sign for complete wetting. The wetted tablet was then weighed and water AR was determined according to Eq. 2:[10,22]

$$\text{AR} = (W_a - W_b)/W_b \quad (2)$$

where W_a and W_b are the tablet weights after and before wetting.

Disintegration test

The disintegration test was performed using deionized water maintained at a temperature between 37 °C ± 2 °C, using a pre-calibrated Pharmatest PTZ Auto, PTFE Disintegration tester (PharmaTest, Germany). The pH of the deionized water was at 6.1 similar to the pH of the saliva of 6.8. Only one ODT at a time was placed into the disintegration apparatus and the time taken (seconds) for the tablet to fully disintegrate was recorded. The test was repeated with four additional ODTs, and the average DT ± standard deviation was calculated.

Porosity of tablets

The porosity of the tablets (e) was calculated using Eq. 3:[23]

$$\varepsilon = \left(1 - \frac{m}{\rho_{true^{\nu}}}\right) \times 100 \quad (3)$$

where ρ_{true} is the true density of the tableting mixture, ν is the weight of the tablet, and n is the volume of the tablet and is given by:

$$\nu = 2 \times (\text{cup volume}) + \pi r^2 h \quad (4)$$

where r is the radius of the tablet, h is the height of the tablet edge, and the cup volume as provided by Natoli Engineering Company, Inc., Missouri, USA.

The true density of each excipient was determined using a helium pycnometer (Accupyc 1330, V3.03, Micrometrics, Norcross, USA).

Statistical analysis

The results obtained are expressed as a mean ± standard deviation calculated using Microsoft excel (Redmond, WA, USA) software. Statistical analysis was performed using SPSS version 15.0 for windows (SPSS, Inc., Chicago, IL, USA). One-way ANOVA followed by the Tukey HSD multiple comparisons were used to compare the results. A *P* value of less than 0.05 was considered as statistically significant.

RESULTS AND DISCUSSION

Characteristics of tablets

Uniformity of weight and thickness

The tablets showed a low weight variation, irrespective of the type of the disintegrants used. The thickness of the tablets ranged from 2.55 to 2.91 mm and was in general related to the weight of the tablets [Table 2].

Disintegration mechanism and water absorption ratio

The disintegration mechanism of the disintegrants used was demonstrated by the change in appearance of tablets observed during the wetting test [Figure 1a–i]. Tablets containing the swellable disintegrants; PPA, SSG with or without CS and crospovidone showed a significant swelling [Figure 1c–e and g]. The degree of swelling as measured by the water AR was significantly higher for tablets containing PPA or SSG with/without CS (ANOVA, post hoc, $P < 0.0001$). The AR for PPA and SSG was 2.1 and 2.8, respectively [Figure 2]. A similar swelling capacity in terms of increase in diameter of 251% was reported for SSG[24] while a swelling capacity of 58.92% is reported for PPA (MSDS; btc-europe.com) lower than the value we

observed. Interestingly, crospovidone, also known for its disintegration action by swelling, had a lower AR of 0.88 although this was significantly higher than the AR of ≤0.62 observed for the non-swelling or osmotic disintegrants; CS, citric acid or sodium citrate (ANOVA; post hoc, $P < 0.0001$). Crospovidone disintegrants are reported to act by a wicking mechanism; drawing water into the tablet through capillary action due to its porous particle morphology, resulting in secondary swelling and rupture of interparticulate bonds and in tablet disintegration.[25] Our data show that this wicking action of crospovidone is effective at wetting the tablet matrix despite its low water absorption as shown in Figure 1e.

CS and the osmotic agents, citric acid, and sodium citrate showed the lowest AR of ≤0.62 and showed little or no loss of original tablet shape [Figures 1f, h, i and 2]. The water absorption potential of CS is related to its characteristic porous structure which facilitates water uptake into the tablet by capillary action facilitating tablet disintegration,[15] while the disintegration mechanism of citric acid and sodium citrate is related to their high water solubility and affinity for the aqueous medium.

Wetting time, disintegration time, and water absorption ratio

The WT of the ODTs was found to be directly related to the water AR of the tablets except for PPA containing tablets [Figure 3]. Linear regression analysis of WT (WT) and water AR of all tablets formulated showed a coefficient of determination (R^2) value of 0.9339 when the value for PPA was excluded [Figure 3]. Similarly, the DT and water AR showed a linear correlation, R^2 value of 0.9711, when the value for PPA was excluded. The DT of the tablets was therefore a direct correlation of the WT observed for each disintegrant or combination of disintegrants; linear regression analysis of DT vs. WT showed an R^2 value of 0.9095 [Figure 4].

SSG containing ODTs which showed the highest AR value of 2.8 also had the longest WT and DT values of 93 and 36.7 s, respectively. The WT and DTs of tablets containing sodium citrate was most rapid at <12 and 8.2 s, respectively [Figures 2–4]. The AR of these tablets was lowest at 0.51. Interestingly, while the AR of tablets containing PPA was high at 2.08, its WT and DT were fast at 25 and 12.2 s, respectively. PPA appears to have both a high water uptake potential and a rapid rate of water uptake. PPA was used at only 2% w/w, at least 5-fold less than other disintegrants and appears therefore to be a very effective disintegrant.

ODTs formulated with a combination of CS and SSG showed a significant decrease in WT to 70 s in comparison to tablets containing SSG alone ($P < 0.0001$) although the AR and DT of these tablets was similar to that of tablets

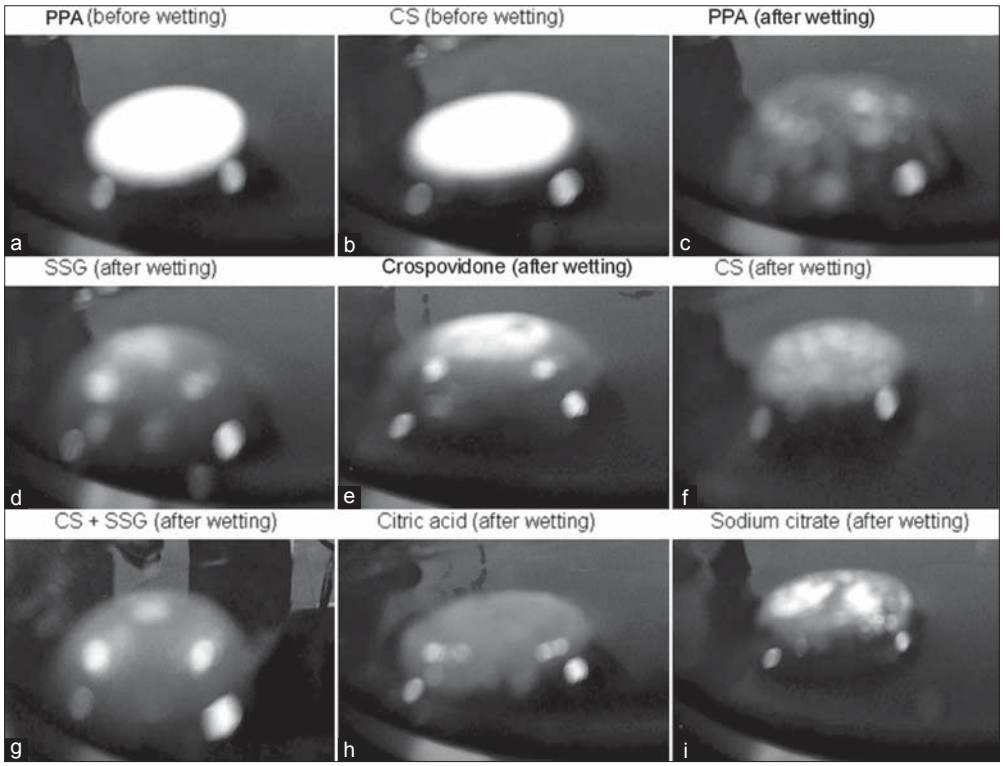

Figure 1: Appearance of FDTs formulated using various disintegrants (a and b) before wetting and (c–i) after wetting in water-containing rhodamine B.

containing SSG alone [Table 2 and Figures 2–4]. The addition of CS to SSG containing tablets enhanced the wetting of the tablets as a result of its porous structure; however, this did not result in a decrease in DT of the tablets.

Remya *et al.*[26] reported a high DT of 60 s for tablet formulation containing SSG at 3% and a DT of 45 s for tablets containing the swellable disintegrant croscarmellose. The significantly longer WT and DT and high AR observed for the SSG containing tablets was related to the disintegration mechanism of SSG which acts by swelling on contact with aqueous medium. As the swelling of SSG is reported to be accompanied by gelling this could possibly occlude the pores in the tablet preventing further penetration of water into the tablet matrix hence the delay observed in the DT of these tablets.[15,24] A similar phenomenon was observed for the swellable disintegrant croscarmellose sodium (Ac-di-Sol®) by Bi *et al.*[18] The addition of CS to SSG containing ODT formulations while enhancing the rate of water uptake did not result in a decrease in DT of these tablets. It is possible that the gelling action of SSG contributes to binding of the tablet matrix and hence limiting tablet disintegration. Figure 1(c–i) show that while SSG containing tablets demonstrate higher swelling effect, this swelling is contained and is not accompanied by a visible 'breakdown' of the tablet matrix as were observed for ODTs containing other disintegrants including disintegrants which are non-swellable.

Tablets containing the osmotic disintegrants; citric acid and sodium citrate showed rapid wetting and disintegration [Figure 2 and Table 2]. The water AR of these tablets was low at <0.61. Citric acid and sodium citrate are anhydrous and highly water soluble and act by facilitating uptake of aqueous medium into the tablets which acts to dissolve water soluble excipients and breaking.

Porosity, DT, and mechanical strength of tablets

The porosity of the ODTs was found to be in the range of 23.5% and 35%. Generally, high tablet porosity is associated with rapid tablet disintegration and achieving high tablet porosity is a key objective of most ODT technologies. Our data show that tablets with the highest porosity did not necessarily show a faster disintegration. While the tablets containing crospovidone or CS show a higher porosity of 29.5% and 34.5%, respectively, and a rapid disintegration of ≤12 s, the DT of tablets containing SSG or SSG and CS was significantly higher at 37.3 and 36.7 s, respectively (ANOVA; post hoc; $P < 0.0001$) despite a high porosity of >30% for these tablets. The lowest porosity of ≤26.5% was observed for tablets containing PPA, citric acid or sodium citrate, yet these tablets disintegrated rapidly within 15 s. The rapid disintegration was related to the hydrophilic properties of these disintegrants enabling rapid wetting of the tablets and facilitating tablet disintegration. Fukami *et al.*[12] reported that the fast disintegration property of tablets

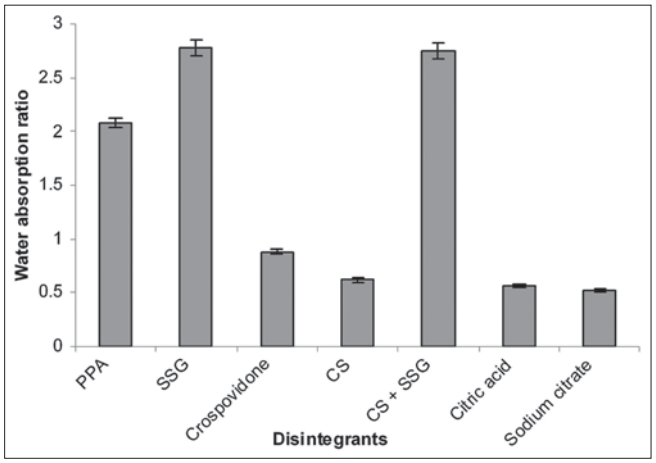

Figure 2: Water absorption ratio of FDTs formulated using various disintegrants. Data expressed as mean ± SD (n = 6)

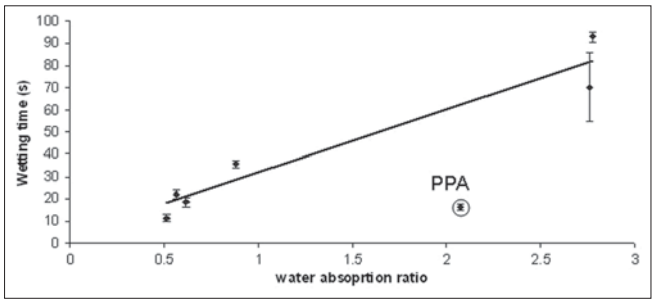

Figure 3: Correlation between water absorption ratio and wetting time of FDTs formulated using various types of disintegrants

Table 2: Characteristics of tablets prepared using various disintegrants

Disintegrant	Weight (mg)	Thick (mm)	Hardness (N)	TS[a] (N/ cm²)	Friab[b]	DT (s)	Porosity (%)
PPA	497.6 ± 2.7	2.55 ± 0.05	36.5 ± 2.6	4.2	0.60	12.2 ± 1.5	23.5
SSG	549.1 ± 7.4	2.91 ± 0.02	49.8 ± 2.1	5.6	0.91	36.7 ± 4.9	32.1
Crospovidone	487.4 ± 0.4	2.73 ± 0.02	45.7 ± 2.2	5.2	0.81	12.3 ± 0.6	29.5
CS	511.8 ± 5.4	2.67 ± 0.02	33.6 ± 6.1	4.2	Failed[c]	11.0 ± 4.2	35.0
Citric acid	521.6± 4.7	2.76 ± 0.03	55.5 ± 3.0	6.3	0.61	14.8 ± 1.8	26.5
Sodium citrate	510.9± 6.7	2.69 ± 0.01	47.1 ± 3.0	5.4	0.61	8.2 ± 0.8	24.3
CS + SSG	551.1 ± 4.8	2.78 ± 0.03	37.5 ± 1.2	4.3	0.00	37.3 ± 3.8	30.0

[a]Tensile strength, [b]Friability (% weight loss), [c]Nine tablets broke, Data expressed as mean ± SD (n = 5)

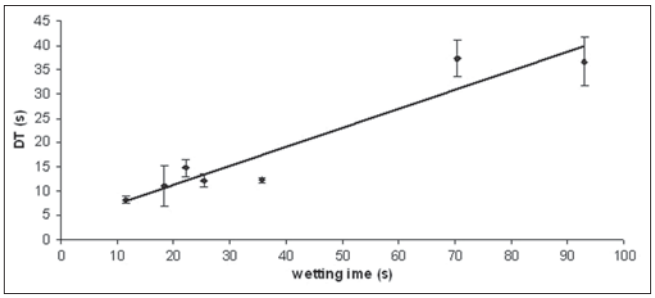

Figure 4: Correlation between wetting and disintegration times of FDTs formulated using various types of disintegrants.

containing croscarmellose was due to its fine wetting property as opposed to the tablet porosity. The authors reported a low porosity of the tablets at 15%, a WT of less than 10 s and a DT of 25 s.

A high porosity while used for the enhancing disintegration rate of ODTs is undesirable for tablet mechanical strength. Tablet hardness is generally inversely related to tablet porosity.[12] High tablet porosity is associated with low mechanical strength. The hardness and tensile strength of the tablets formulated in this study was found to be a function of the type of disintegrant used. Tablet hardness was found to be inversely related to the porosity of the tablets in the case of tablets containing the osmotic disintegrants [Table 2], which showed a high hardness of >45 N and tensile strength of >5 N/cm^2 and low porosity of 24.3–26.5%. Similarly tablets containing CS had a high porosity of 35% and a low hardness value of 33.6 N and tensile strength of 4.2 N/ cm^2. For ODTs containing the swellable disintegrants; SSG, crospovidone or PPA, no relationship was observed between porosity and hardness. The lower hardness values observed for tablets containing PPA or CS as disintegrant [Table 2] was related to the low binding capacity of PPA and CS and in the case of tablets containing CS additionally to the high porosity of these tablets.[27,28]

Friability of the tablets was observed to be related to the porosity of the tablets as expected. Tablets formulated using CS or SSG showed the highest porosity and highest friability while tablets with low porosity of 24–26% showed a lower friability of less than 0.61%. To investigate the effect of changing tablet porosity on hardness and friability of these porous disintegrants, tablets were subsequently prepared using a combination of CS and SSG as disintegrants at ~50% of each component. CS has a $D_{50\%}$ value of 4.0 μm while SSG has a $D_{50\%}$ value of 42.7 μm. Combining the two disintegrants should result in the smaller particles of CS packing in the voids between SSG and mannitol particles, and hence in a decrease in tablet porosity and in a higher mechanical strength. The resultant tablets showed an improvement in friability with no broken tablets or loss in tablet weight observed on friability testing. The hardness value was intermediate to the hardness of the tablets containing CS or SSG alone.

CONCLUSIONS

The data in this study show that the DT of tablets was related to the WT and disintegrant mechanism and was not necessarily a function of tablet porosity. Generally, the formation of a porous matrix or tablet is a key goal of many ODT technologies in order to enhance the water absorption into the tablet matrix and facilitating rapid disintegration of the ODTs. Tablets containing the highly swellable SSG disintegrant had a high porosity of 32.1% and showed the highest water AR of 2.8. However, these tablets showed the highest WT and DT. In contrast the osmotic disintegrants, citric acid and sodium citrate showed lowest water AR of <0.6, and were associated with effective wetting and disintegration despite their low tablet porosity of 24–26%. Only tablets formulated with the porous disintegrants crospovidone and CS had high porosity of 32–35% and showed rapid wetting and disintegration. Tablets with high porosity are in general shown to have lower mechanical strength requiring specialized packaging. Our data show that by selection of the appropriate type of disintegrant, it is possible to formulate ODTs with low porosities to give ODTs of high mechanical strength and rapid disintegration properties.

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