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Effect of a superdisintegrant on disintegration of orally disintegrating tablets determined by simulated wetting test and *in vitro* disintegration test

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The disintegration time is critical for characterizing orally disintegrating tablets (ODTs), according to regulatory standards. The current study aimed to assess the effect of superdisintegrants such as sodium starch glycolate, croscarmellose sodium, and crospovidone on the disintegration of ODTs using simulated wetting and *in vitro* disintegration tests. The results showed that the wetting time of ODTs containing sodium starch glycolate and croscarmellose sodium was 17 – 21 s, but the wetting time of ODTs containing crospovidone was 9 – 12 s. In contrast, there was no significant difference in *in vitro* disintegration time among ODTs using different disintegrants (ca. 14 to 18 s) The quick wetting time of ODTs with crospovidone may be attributed to strong capillary characteristics of crospovidone. It is suggested that determining the disintegration time of ODTs just through simulated wetting test is insufficient and may lead to biases. As a result of the findings, it is recommended that an additional disintegration test, imitating saliva fluid absorption and tablet breaking, to provide a more precise evaluation of ODTs.

1. Introduction

Several types of dosage forms have been developed in recent years to fulfill a variety of patient demands, especially to improve compliance. Orally disintegrating tablets (ODTs) are one of these items that are specially designed for patients who have swallowing difficulties with conventional dosage forms. ODTs may be made using a variety of technologies. Molding, lyophilization, and direct compression are the most often used preparation processes. Direct compression is a typical tablet production procedure for ODTs. It is frequently preferred over alternative ODT production procedures because it leverages current high-speed tablet press equipment and common excipients (Trisopon et al. 2021). A direct-compression formulation offers better physical qualities than conventional approaches, which may reduce the requirement for specific packaging such as blister containers. Direct-compression ODT formulations often contain high amounts of a superdisintegrant, including sodium starch glycolate, croscarmellose sodium, and crospovidone, to induce fast disintegration (Ahmad 2018; Desai et al. 2016). Thus, selecting the proper superdisintegrant is crucial when designing an ODT formulation for direct compression.

The disintegration time of a product is the most important criteria in classifying it as an ODT. According to the US FDA recommendation, an ODT should dissolve quickly, with an *in vitro* disintegration time of 30 s or less using the United States Pharmacopeia (USP) disintegration technique or an alternative (Food and Drug Administration, 2008). The disintegration test recommended by the USP requires 900 mL of water. Recent study on ODTs indicated that this volume did not accurately mimic the oral environment and that a smaller volume of water that closely represented the oral environment was necessary (Hooper et al. 2016). Several alternative disintegration tests have been proposed (Abay and Ugurlu 2015; Hooper et al. 2016; Chinwala 2020; Ghourichay et al. 2021). Among these methods, the wetting test has received a lot of interest in characterization of ODTs due to its convenience and simplicity. However, it takes some time for the dye solution to diffuse and cover the entire surface of the tablet. In addition to the wetting test, other alternative methods for determining *in vitro* disintegration time have been proposed in recent years, including modified USP dissolution apparatus II (Bi et al. 1996), charge coupled device camera (Morita et al. 2002), shaking bath (Fu et al. 2006), rotary shaft (Narazaki et al. 2004), *in vitro* disintegration test by medium dripping (Hoashi et al. 2013), and texture analyzer (Scheuerle et al. 2015), among others.

The purpose of this study was to investigate the effect of several superdisintegrants, i.e., sodium starch glycolate, croscarmellose sodium, and crospovidone on the disintegration of ODTs using two approaches, namely simulated wetting and *in vitro* disintegration tests. The simulated wetting test was slightly modified from the method proposed by Park and colleagues (Park et al. 2008). The concept behind this technique is to place a tablet on a colored, wet filter paper and then record the color diffusion on the tablet until it is completely covered. The *in vitro* disintegration test described by Hoashi et al. (2013) was adopted in this investigation with minor modifications since it requires a simple equipment setup and can simulate the physiological conditions in the mouth. The *in vitro* disintegration test method involves dripping water on top of the mesh-encased tablet. The time required for the upper mesh to completely touch the lower mesh is then recorded. The relationship between simulated wetting time and *in vitro* disintegration time of these ODTs was also examined.

2. Investigations, results and discussion

2.1. Physical properties of ODTs

All formulations were off-white in color, round, and smooth flat-face ODTs. The amount of superdisintegrants, such as sodium starch glycolate, croscarmellose sodium, and crospovidone, was varied at 2%, 4% and 6% to investigate their effect on wetting time and *in vitro* disintegration time of ODTs. All ODT formulations had a friability of less than 1% (data not shown), which was

within an acceptable range. Table 1 reveals that the diameter and thickness of ODTs were in the same range of roughly 9.7 mm and 2.1 mm, respectively. The hardness of the prepared ODTs ranged from 34.0 to 48.1 N (Table 1), which was within the acceptable range (30-40 N). According to an ANOVA analysis, the hardness of the ODTs was unaffected by increasing concentration of superdisintegrant ($p>0.05$), but the type of superdisintegrant had a significant ($p<0.05$) effect on the hardness of the prepared ODTs. The results showed that the hardness of ODTs containing crospovidone was the highest with the mean hardness values ranging from 46.2 to 48.1 N, followed by those containing sodium starch glycolate (40.3 – 42.0 N) and croscarmellose sodium (34.0 – 38.4 N). The findings were consistent with the findings of Mehta et al. (2012), who discovered that the hardness of multiparticulate tablets containing crospovidone was greater than that of sodium starch glycolate and croscarmellose sodium. The binding properties of crospovidone, which promote the adhesive force within the tablets, might explain this. As a result, ODTs made with crospovidone were harder than others (Mehta et al. 2012).

Table 1: Physical properties of ODTs

Formulation	ODTs properties				
	Diameter (mm±SD) n=10	Thickness (mm±SD) n=10	Hardness (N±SD) n=10	Wetting time (s±SD) n=3	*In vitro* disintegration time (s±SD) n=3
SSG2	9.72±0.02	2.10±0.02	41.2±2.5	17±2	16±1
SSG4	9.67±0.03	2.11±0.01	40.3±2.9	20±1	14±1
SSG6	9.69±0.02	2.09±0.02	42.0±0.5	20±1	15±2
CCS2	9.69±0.01	2.09±0.00	37.1±1.2	21±1	14±1
CCS4	9.68±0.00	2.10±0.01	38.4±2.5	20±0	15±1
CCS6	9.68±0.00	2.11±0.01	34.0±3.6	21±1	17±1
CP2	9.71±0.04	2.14±0.01	46.2±2.1	12±1	18±1
CP4	9.68±0.02	2.15±0.01	46.3±0.9	10±1	14±2
CP6	9.69±0.00	2.16±0.01	48.1±0.8	9±1	16±1

2.2. Wetting time of ODTs

When a tablet is exposed to an aqueous solution *in vitro* or *in vivo*, water seeps into the tablet, causing the superdisintegrants to expand in volume, facilitating disintegration. As a result, moisture is required for a tablet to disintegrate and dissolve. A simulated wetting test may be used to determine the wetting time of ODTs. This wetting time can therefore be used instead of the USP disintegration technique to determine if the tablet fits the FDA guideline for ODTs. Many variations of the simulated wetting test are now in use (Park et al. 2008; Pabari and Ramtoola 2012; Hooper et al. 2016). However, no defined approach exists at this time. A typical wetting test includes putting an ODT on a colored, wet filter paper and then record the color diffusion on the tablet until it is completely covered. All of the ODTs in this investigation showed complete wetting within 30 s. Figure 1 shows the stages of wetting of all ODT formulations. The change in appearance of tablets observed during the wetting test confirmed the disintegration mechanism of the disintegrants used. According to Fig. 1, all of the ODT using different disintegrants drew water into the tablet, causing it to slightly swell and disintegrate. This action was similar with a previous work revealing that sodium starch glycolate, crospovidone, and croscarmellose sodium disintegrate by analogous wicking and swelling processes. Because of the porous particle morphology, they draw water into the tablet by capillary action, resulting in secondary swelling, interparticle bond breakage, and tablet disintegration (Bele and Derle 2012).

Table 1 also shows the average wetting time of each formulation. At each concentration level (2%, 4%, or 6%), the wetting time of ODTs containing various superdisintegrants was in the following order: crospovidone < sodium starch glycolate ≈ croscarmellose sodium. At all concentration levels, crospovidone wetted the tablets

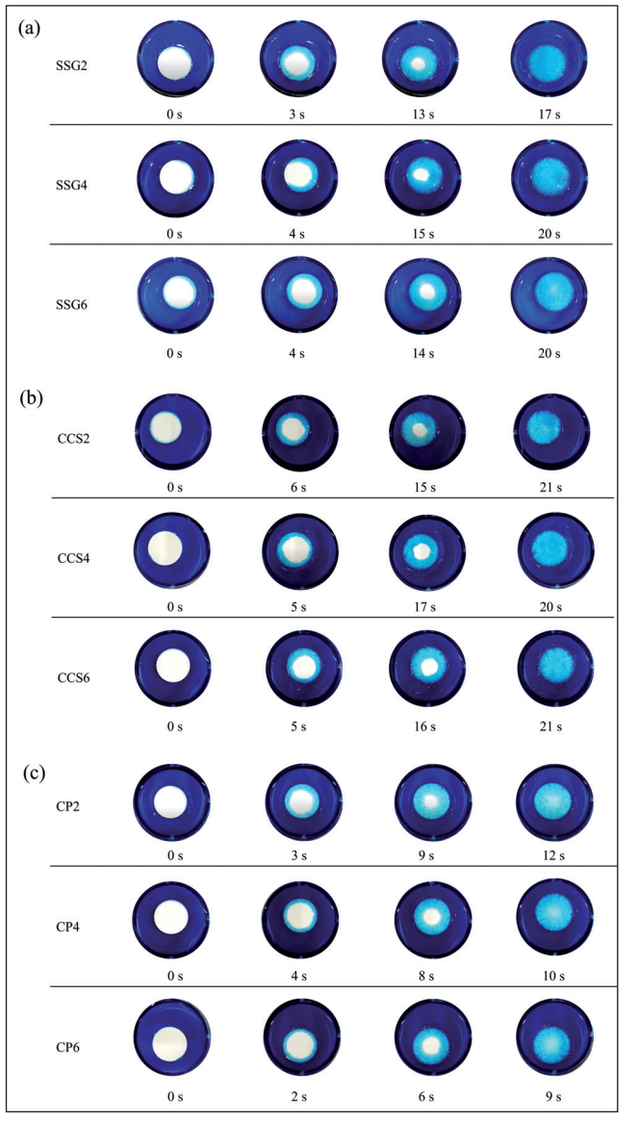

Fig. 1: Stages of wetting test of (a) SSG2, SSG4, SSG6 (with 2, 4, 6% sodium starch glycolate, respectively), (b) CCS2, CCS4, CCS6 (with 2, 4, 6% croscarmellose sodium, respectively), and (c) CP2, CP4, CP6 (with 2, 4, 6% crospovidone, respectively)

faster than sodium starch glycolate and croscarmellose sodium. The ODTs containing crospovidone outperformed ODTs containing other superdisintegrants, in terms of wetting time; they had a shorter wetting time of 9 to 1 s (Table 1). Crospovidone rapidly swells and disperses in water (Rowe et al. 2009b). When compared to sodium starch glycolate and croscarmellose sodium, it had the greatest degree of swelling (Desai et al. 2016; Mehta et al. 2012; Rowe et al. 2009b). As a result, after being placed on wet filter paper, the ODTs containing crospovidone rapidly absorbed dye solution. The shortest wetting time may be explained by a wicking mechanism that draws water into the tablet by capillary action, as well as crospovidone's superior hydration capacity over other superdisintegrants (Desai et al. 2016; Mehta et al. 2012; Rowe et al. 2009b). The wetting time decreased as the crospovidone concentration increased from 2% to 6%. The fastest wetting of the ODTs containing crospovidone occurred at a concentration of 6% (CP6)

Because sodium starch glycolate has a high water absorption rate and a swelling capacity of 6% (Desai et al. 2016; Rowe et al. 2009a), swelled tablets with a wetting time of roughly 17-20 s were observed. There was no significant difference in wetting time when the concentration of sodium starch glycolate was increased from 2% (SSG2) to 4% (SSG4) and 6% (SSG6). The ODTs prepared with croscarmellose sodium exhibited modest

swelling and a wetting time ranging from 17 to 21 (Table 1). In fact, croscarmellose sodium has limited water solubility but higher degree of swelling up to 4-8 times of its initial volume. When the concentration of croscarmellose sodium was increased from 2% to 6%, there was no significant difference in wetting time.

2.3. In vitro disintegration time of ODTs

In this study, the *in vitro* disintegration time of all ODTs was also determined. Table 1 also shows the average disintegration time of all ODT samples, which was in the same range of 14 to 18 s. In the case of sodium starch glycolate and croscarmellose sodium, the *in vitro* disintegration times were consistently shorter than the wetting times for all ODTs in this study, regardless of concentration levels. However, in the case of the ODTs containing crospovidone, the results showed a different trend when compared to the simulated wetting test; the *in vitro* disintegration times were longer than the wetting times at all concentration studied. This is most likely owing to a greater hardness of the ODTs containing crospovidone. The effect of disintegrant concentration on disintegration time was insignificant. This might be due to the main diluents, mannitol and spray-dried lactose monohydrate, used in the formulation. Because these diluents are easily soluble, the swelling mechanism of the disintegrant used in this study is hardly effective on this system (Paul et al. 2019). As a result, a significant amount of the disintegrant can trigger tablet disintegration by pulling water into the tablet. In terms of physiological circumstances, the breakdown of ODTs in the mouth occurs in two phases. The first phase is saliva absorption, which begins when the tablet is placed on the tongue and is followed by tablet breakdown into minute particles in the second phase, which is connected to the pressure between the tongue and the upper hard palate. Because that pressure was overlooked, calculating wetting time alone may not be sufficient to define the ODT and may result in biases in result evaluation.

2.4. Relationship between wetting time and in vitro disintegration time of ODTs

A linear regression analysis of simulated wetting time and *in vitro* disintegration time of ODTs using different concentration levels of superdisintegrants revealed no good correlation with a coefficient of determination (R^2) value less than 0.5 (data not shown). The ODTs containing 4% and 6% disintegrants also had a low R^2 value. Only the ODTs containing 2% disintegrants showed a high inverse correlation with a R^2 value of 0.9887. The faster the wetting time, the longer the disintegration time. It is likely that as soon as the water penetrated the tablet, it swelled, delaying the disintegration of tablet. Govedarica et al. (2011) also showed that sodium starch glycolate and croscarmellose sodium absorb a large amount of water and swell, which may delay tablet disintegration. Because sodium starch glycolate swelling is known to be followed by gelling, this might potentially occlude the pores in the tablet, limiting additional water entry into the tablet matrix, thus causing a delay in the disintegration time of these tablets. The findings are also consistent with those of Remya et al. (2010), who found a disintegration time of 60 s for tablet formulations containing 3% sodium starch glycolate and a disintegration time of 45 s for tablets containing croscarmellose sodium.

2.5. Conclusion

The fast disintegration time is important for identifying the tablets as ODTs, according to regulation recommendations. As a result, superdisintegrants are critical in shortening the time required for ODT formulation disintegration. Furthermore, appropriate testing to imitate oral circumstances are required for formulation development tools. The modified wetting test and *in vitro* disintegration test were found to be useful tools for evaluating and studying the tablet behavior of ODT formulations in this study. Furthermore, due to its strong water absorption characteristics, the wetting time of ODTs made with wicking disintegrant crospovidone was shorter than that of other substances. However, all samples showed the *in vitro* disintegration at the same pace. This study concludes that each superdisintegrant provides a distinct mechanism for disintegration; hence, selecting the optimal disintegrant for the ODT formulations is critical.

3. Experimental

3.1. Materials

Mannitol (lot number 302004308) was obtained from Shandong Tianli Pharmaceutical Co., Ltd., China. Spray dried lactose monohydrate (Supertab®11SD, lot number 23034009) and sodium starch glycolate (Primojel®, lot number 10519TW) were purchased from DMV-Fonterra Excipients GmbH & Co., Germany. Microcrystalline cellulose (Comprecel® M101D+, lot number C2006037) and croscarmellose sodium (Disolcel®, lot number D02003103) were obtained from Mingtai Chemical Co., Ltd., China. Crospovidone (Polyplasdone XL®, lot number 0002434812) and polyvinyl pyrrolidone K-30 (PVP K-30, lot number 002377911) were received from Ashland Chemical Inc., USA. Magnesium stearate (Kemilub EM-F-V®) was obtained from Italmatch Chemicals, Spain.

3.2. Preparation of ODTs

The 200-mg ODTs were prepared by direct compression technique and their formulations are shown in Table 2. The superdisintegrants and other excipients were passed through a 425-µm sieve before use. Mannitol, spray-dried lactose monohydrate, microcrystalline cellulose, and superdisintegrant were blended in a plastic bottle (10 g per batch) using the geometric blending technique, and the obtained mixture was then blended for another 5 min. Finally, each of the remaining components (PVP K-30 and magnesium stearate) was added and blended for 1 min. The mixture was compressed by a hydraulic press machine (SPECAC15011, Specac Ltd., UK) using flat-face 9.65-mm punch and die set, at a compression force of 1 ton and dwelling time of 10 s. The resulting ODTs were kept in air-tight container and stored in desiccator for further characterization.

3.3. Physical characterization of ODTs

The diameter, thickness, and hardness of ODTs were measured using hardness tester (TBH225TD, Erweka GmbH, Germany). The friability of 32 to 33 ODTs (with a total weight of about 6.5 g) was evaluated using a friability tester (TA120, Erweka GmbH, Germany). The samples were dedusted and weighed before placing in the drum. The testing operated at a constant speed of 25 rpm for 4 min. Then, the ODTs were taken out, any loose dust was removed, and weighed. The friability of ODTs can be calculated using Eq. (1):

$$\text{Friability (\%)} = \frac{\text{Initial weight (g)} - \text{Final weight (g)}}{\text{Initial weight (g)}} \times 100 \quad (1)$$

Table 2: Formulation of ODTs with total weight of 200 mg

Ingredients	Quantity (mg/tablet)								
	SSG2	SSG4	SSG6	CCS2	CCS4	CCS6	CP2	CP4	CP6
Mannitol	90	90	90	90	90	90	90	90	90
Spray-dried lactose monohydrate	81	77	73	81	77	73	81	77	73
Microcrystalline cellulose	21	21	21	21	21	21	21	21	21
Sodium starch glycolate	4	8	12	-	-	-	-	-	-
Croscarmellose sodium	-	-	-	4	8	12	-	-	-
Crospovidone	-	-	-	-	-	-	4	8	12
PVP K-30	2	2	2	2	2	2	2	2	2
Magnesium stearate	2	2	2	2	2	2	2	2	2

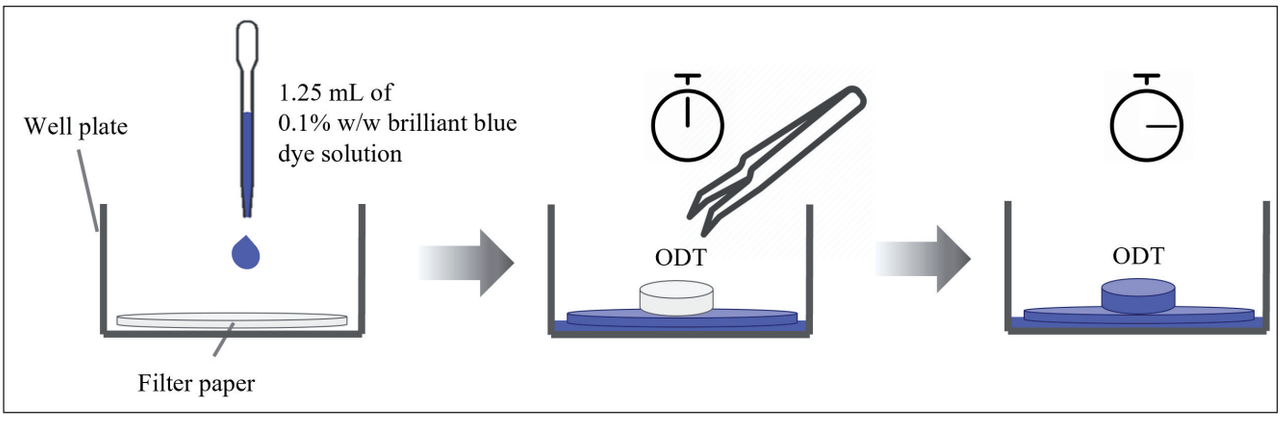

Fig. 2: Schematic diagram showing the setup for simulated wetting test

3.4. Simulated wetting test

In this work, the wetting behavior of ODTs was evaluated using the method proposed by Park et al. (2008), as shown in Fig. 2. A 21-mm diameter filter paper was placed on the bottom of each well (Corning® polystyrene, 12-well plate with a well diameter of 22 mm) Then, 1.25 mL of 0.1% w/w brilliant blue dye solution was added into each well. The ODT sample was placed on a wet filter paper using a pair of forceps. Each formulation was tested in triplicate. Video recording was utilized to determine the wetting time, which is the time necessary for the dye solution to diffuse and completely cover the tablet surface.

3.5. In vitro disintegration test

The *in vitro* disintegration test was carried out according to the method provided by Hoashi et al. (2013), with minor changes, to determine disintegration time of ODTs. The apparatus was assembled following the diagram in Fig. 3. An ODT was initially put on the center point of lower mesh and then covered with upper mesh. Then, a 20-g ring weight was carefully put on top of that pile. The video recorder was turned on while the simulated saliva fluid (flow rate of 4 mL/min, 37±0.5 °C) was dropped onto the ODT. The time required for the upper mesh to fully contact the lower mesh, determined from video recording, was considered as the *in vitro* disintegration time. Each formulation was tested in triplicate.

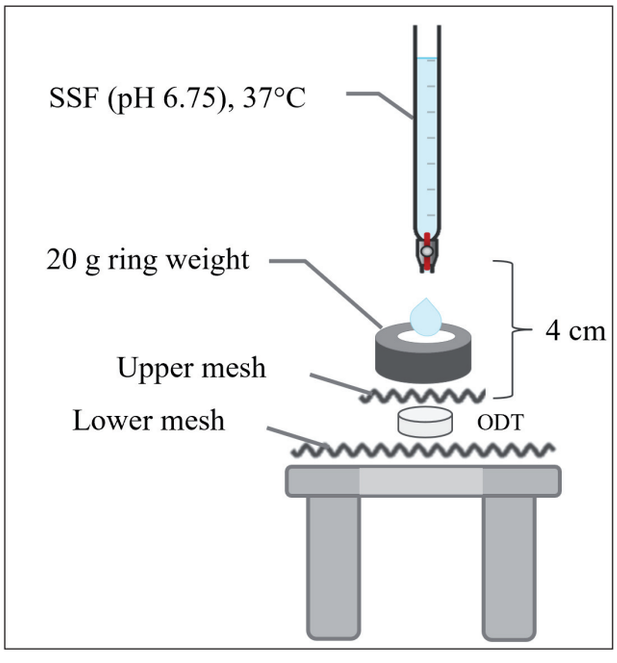

Fig. 3: Schematic diagram showing the assembly of *in vitro* disintegration test

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