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Full Length Research Paper

Effect of the type of disintegrant on the characteristics of orally disintegrating tablets manufactured using new ready-to-use excipients (Ludiflash® or Parteck®) by direct compression method

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The challenge in orally disintegrating tablets (ODTs) production encompasses the compromise between instantaneous disintegration and sufficient physico-mechanical properties, therefore the aim of this study was to evaluate the influence of selected disintegrants on the characteristics of ODTs manufactured using novel ready-to-use excipients (Ludiflash® or Parteck®) by direct compression method. Effect of selected disintegrants (croscarmellose sodium, microcrystalline cellulose and four types of crospovidone) on hardness, friability, wetting time, *in vitro* and *in vivo* disintegration time, roughness and stability parameters has been studied. The prepared tablets were also evaluated for surface morphology and pore structure. 3% w/w addition of all examined disintegrants enabled obtaining tablets showing physico-mechanical properties that are suitable for ODTs, but disintegration times < 30 s were observed only in formulations with crospovidones. The surface of Ludiflash® and Parteck® ODTs was relatively homogenous dispersion with pores, cracks and fissures. Formulations with Ludiflash® showed both less porous textures with low specific surface area (BET values up to 0.77 m^2/g) and shorter wetting and disintegration times. The optimized formulation containing superfine crospovidone and Ludiflash® (L2) or Parteck® (P2) was found to be stable, had a pleasant mouth feel and disintegrated in the oral cavity within only 10 and 26 s, respectively.

Key words: Orodispersible tablet, Ludiflash®, Parteck®, direct compression, disintegrant.

INTRODUCTION

Recently, there has been the increasing interest in development of orally disintegrating tablets (ODTs), which are a convenient solid oral dosage form for patients who have difficulty with swallowing conventional tablets or capsules. ODTs are a new generation of formulations which combine the advantages of both liquid and traditional tablet formulations. Several technologies are available to manufacture this type of tablets (Shukla et al., 2009a). The most common preparation methods are moulding, lyophilisation, direct compression, sublimation, mass extrusion and spray drying. Direct compression is the simplest and the most cost effective technique for manufacturing ODTs, as conventional tablet machines and conventional packaging machinery can be used (Shukla et al., 2009a).

Excipients for ODTs have to be selected based on material characteristics and desired functionalities like defined particle size distribution, good flowability, enhanced compactability or fast disintegration. Mannitol is often used as the excipient for ODTs. However, when it is used as untreated powder, it is characterized by poor flowability, insufficient binding properties and compactability; therefore co-processed excipients with mannitol are used (Stoltenberg and Breitkreutz, 2011). Co-processing means the interacting of two or more excipients at the subparticle level, due to co-spray-drying, co-spray-agglomerating or co-granulating, which led to an improved functionality (Nachaegari and Bansal, 2004; Gohel and Jogani, 2005; Saha and Shahiwala, 2009).

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Co-processed mannitol could be useful because of its sweet taste, good disintegration properties and low hygroscopicity, which enables stability comparable with conventional tablets without the need of sophisticated packaging (Stoltenberg and Breitkreutz, 2011). Ludiflash® and Parteck® are new commercially available ready-to-use tableting excipients based on co-processed mannitol. Ludiflash® is a combination of D-mannitol, crospovidone and polyvinyl acetate, whereas Parteck® contains two components: D-mannitol and croscarmellose sodium (Ludiflash® Technical Information- BASF, 2011; Parteck® Technical Information- Merck Chemicals, 2011).

The challenge in ODTs manufacturing encompasses the compromise between instantaneous disintegration and sufficient hardness. Direct compression is one of the techniques that requires the incorporation of disintegrants into the formulation, which mainly affects the rate of disintegration (Shukla et al., 2009a). To our knowledge, little experimental data on the preparation of ODTs using Ludiflash® and Parteck® have been reported thus far. Therefore, the aim of this study was to compare the disintegrants' efficiency of six disintegrants (croscarmellose sodium, microcrystalline cellulose and four types of polyvinylpyrrolidone) in ODTs manufactured using Ludiflash® or Parteck® by direct compression method. The influence of selected disintegrants on physico-mechanical properties of prepared ODTs was also examined. Tablets were evaluated for weight variation, hardness, friability, thickness, wetting time, disintegration time, stability, surface morphology and pore structure. To demonstrate the basic properties of the excipients, and because of consideration of the ethical aspects involved in testing ODTs in humans (Mimura et al., 2011), only placebo formulations that lacked inclusion of drugs were manufactured and examined.

MATERIALS AND METHODS

The ready-to-use tableting excipient Ludiflash®, Kollidon® CL (crosslinked PVP), Kollidon® CL-F (standard fine), Kollidon® CL-SF (superfine), Kollidon® CL-M (micronized), were obtained from BASF, Ludwigshafen, Germany. Parteck® ODT was purchased from Merck, Darmstadt, Germany. Magnesium stearate was a product of POCH, Piekary Slaskie, Poland. Avicel® PH-102 and Ac-Di-Sol® were purchased from FMC Biopolymer, Brussels, Belgium.

Characteristics of the powder flowability

Bulk density (Db) is the ratio of total mass of powder to the bulk volume of powder. The weighed powder was poured into a measuring cylinder and initial weight was noted. This initial volume was called the bulk volume. The bulk density was calculated according to the formula:

$$Db = M / Vb$$

where M and Vb are mass of powder and bulk volume of the powder, respectively (EP, 2008).

Tapped density (Dt) is the ratio of total mass of the powder to the tapped volume of the powder.

Volume was measured using a tapping density analyzer (Electrolab ETD-1020, Mumbai, India) by tapping the powder for 750 times, and the tapped volume was noted if the difference between these two volumes is less than 2%. If it is more than 2%, tapping is continued for 1,250 times and tapped volume was noted (EP, 2008). It is expressed in g/ml and is given by:

$$Dt = M / Vt$$

where M and Vt are mass of the powder and tapped volume of the powder, respectively.

For determination of angle of repose (θ), the blend were poured through the walls of a funnel, which was fixed at a position such that its lower tip was at a height of exactly 2.0 cm above hard surface. The blends were poured till the time when the upper tip of the pile surface touched the lower tip of the funnel. Angle of repose was calculated using following equation:

$$\tan \theta = h / r,$$

where h is height and r is radius of pile.

Carr's index (or % compressibility) is expressed in percentage and is given by:

$I = Dt - Db / Dt \times 100$, where Dt and Db are tapped and bulk density, respectively.

Hausner ratio is an indirect index of ease of powder flow and is calculated by the following formula:

Hausner ratio = Dt / Db, where Dt and Db are tapped and bulk density, respectively (EP, 2008).

All the procedures was repeated three times per batch.

Preparation of ODTs

ODTs were prepared by direct compression method according to the formulae given in Table 1. Ludiflash® or Parteck® and various disintegrants were mixed for 20 min in porcelain mortar and passed through a 0.8 mm sieve. This blend was mixed with magnesium stearate for 5 min and processed for direct compression by using 8 mm round flat-faced single punch tablet press (EP1 Erweka, Heusenstamm, Germany). Different adjustments of the machine settings were tried. The adjustment giving the highest possible hardness value with the highest accepted disintegration time was selected and applied to all tablet formulations.

Evaluation of tablets

Weight variation and thickness

Twenty tablets were selected randomly to determine the tablets weight variation and thickness. Tablets were weighed individually using an electronic balance and compared with an average weight. Thickness of the tablets was assessed using digital calliper (Beta 1651 DGT, Sovico, Italy).

Hardness

The tablet crushing load, which is the force required to break a tablet by compression in the radial direction, was measured using a tablet hardness tester (5Y, Pharmatron AG, Thun, Switzerland). The test was performed in 10 runs, and the average was calculated.

A piece of tissue paper folded twice was placed

Table 1. Composition of manufactured ODTs formulations.

Ingredient (mg/tablet)	L0	L1	L2	L3	L4	L5	L6	P0	P1	P2	P3	P4	P5	P6
Ludiflash®	178.2	172.8	172.8	172.8	172.8	172.8	172.8	-	-	-	-	-	-	-
Parteck®	-	-	-	-	-	-	-	178.2	172.8	172.8	172.8	172.8	172.8	172.8
Kollidon® CL	-	5.4	-	-	-	-	-	-	5.4	-	-	-	-	-
Kollidon® CL-SF	-	-	5.4	-	-	-	-	-	-	5.4	-	-	-	-
Kollidon® CL-M	-	-	-	5.4	-	-	-	-	-	-	5.4	-	-	-
Kollidon® CL-F	-	-	-	-	5.4	-	-	-	-	-	-	5.4	-	-
Avicel® PH 102	-	-	-	-	-	5.4	-	-	-	-	-	-	5.4	-
AcDiSol®	-	-	-	-	-	-	5.4	-	-	-	-	-	-	5.4
Magnesium stearate	1.8	1.8	1.8	1.8	1.8	1.8	1.8	1.8	1.8	1.8	1.8	1.8	1.8	1.8

in a Petri dish Ø 7 cm containing 7 ml of water. A tablet was put on the paper and the time for complete wetting was measured. The wetted tablet was again weighed. The water absorption ratio (R) was calculated using the formula: $R = 100 (W_a - W_b) / W_b$, where W_a and W_b are the weight before and after water absorption (Shukla et al., 2009b; Bi et al., 1999). The results were the average of six measurements.

Measurement of disintegration time

Disintegration test in conventional disintegration apparatus

Disintegration time was determined using tablet disintegration test apparatus (Erweka ED-2L, Heusenstamm, Germany). The tablet was placed in 900 ml distilled water maintained at 37°C and agitation speed of 30 shakes per min. Only one tablet at a time was tested. The tablet was considered disintegrated completely when all the particles passed through the screen (EP, 2008). The disintegration time of 6 individual tablets were recorded, and the average was reported.

Disintegration test on wire cloth

Disintegration time was determined according to Motohiro et al. (2001) by placing ODT on a wire cloth (Ø 2 mm) and water was dropped on it at a rate of 4 ml/min. The time required by the tablet to completely pass through the wire cloth was noted as disintegration time.

Disintegration test on a Petri dish

Disintegration time was measured using a modified disintegration test method (Gohel et al., 2004; Giri and Sa, 2009). Water (10 ml) was placed in a Petri dish Ø 7 cm and a tablet was carefully placed in the centre and agitated mildly. Time required for complete disintegration of the tablet into fine particles was noted.

Disintegration time in the mouth

Measurements of disintegration time in the mouth were carried out in 6 volunteers. After the mouth was rinsed with purified water, one tablet was held in the mouth until the tablet disintegrated without chewing and then spat out, and the mouth was rinsed again. The time required for complete disintegration of the tablet was measured.

Moisture uptake studies

The test was performed by keeping ten tablets in a desiccator (containing calcium chloride) for 24 h at 37°C to assure complete drying. The tablets were then weighed and stored for 2 weeks at 75% humidity. Tablets were re-weighed and the percentage increase in the weight was recorded (Shukla et al., 2009b).

Sensory evaluation of roughness of tablets

Sensory test of roughness of tablets was carried out in 6 volunteers. After the mouth was rinsed with purified water, one tablet was held in the mouth for 60 s and then spat out, and the mouth was rinsed again. The roughness level was recorded. A numerical scale was used with the following values: 0, no roughness; 1, slight roughness; and 2, roughness.

Determination of the specific surface area

The specific surface area of the co-processed excipients was measured by nitrogen adsorption (EP, 2008) using nitrogen porosimeter Gemini VII (Micromeritrics, Norcross, USA). About 2 g of each excipient was weighed in a sample tube, and was then degassed for 24 h at a temperature of 80°C using helium as purge gas. Evaluation of the specific surface was made in an adsorbing device (Tristar 3000, Micromeritrics, Norcross, USA), where a mixture of nitrogen and helium flowed over the powder. The adsorbed amount of nitrogen was calculated using the equation according to Brunauer, Emmet and Teller, to determine the specific surface (BET). The average pore radius and cumulative volume of pores were calculated

using Micromeritrics Gemini VII software (Micromeritrics, Norcross, USA). The measurements were performed in triplicate per batch.

Surface morphology

Powders and ODTs were studied for surface morphology by scanning electron microscope (Hitachi S-3000N, Ibaraki, Japan). Prior to examination, samples were mounted on an aluminium stub using a double sided adhesive tape and thereafter making it electrically conductive by coating with a thin layer of gold (approximately 20 nm) in vacuum. The scanning electron microscope was operated at an acceleration voltage of 15 kV.

Stability studies

The obtained tablets were stored in desiccators at 40, 60 and 80% relative humidity (RH) for a period of six months at 25°C. After 1, 3 and 6 months, samples were withdrawn and evaluated for appearance, weight variation, thickness, hardness, friability, water absorption, wetting and disintegration times.

Statistical analysis

The differences in average of data were compared by simple analysis of variance (one-way ANOVA) at $p < 0.05$ level using the software SPSS (SPSS Inc., Chicago, USA). The significance of the difference was determined at 95% confidence limit.

RESULTS AND DISCUSSION

In the present study ODTs were prepared by direct compression method. For direct compression, the flowability of the powder blends is very important. Flow properties of the powder can be judged from the angle of repose. This measurement gives qualitive and quantitative assessment of internal cohesive and frictional force. The angle of repose < 30° indicates free flowing material and > 40° with poor flow properties (Lachman et al., 1991). Values for angle of repose for Ludiflash® or Parteck® was 29° and 30° (Table 2) showing that the base was free flowing. The spray dried excipients showed lower angle of repose (better flow properties) than the excipients alone (Table 2), which is probably due to increased sphericity of spray dried excipients base. The Hausner ratio and the Carr's index refer to the packing characteristics of the materials, and are also used as indicators for flowability of the powders. The values for Ludiflash® or Parteck® indicate a passable flowability (Table 2), whereas the flow properties of different disintegrants according to European Pharmacopoeia (EP, 2008) were fair (Kollidon® CL), poor (Kollidon® CL-F, Avicel® PH-102, Ac-Di-Sol®) or very poor (Kollidon® CL-SF, Kollidon® CL-M). Poor fluidity of excipients is improved by the use of lubricants. However, lubricants may reduce the tablet strength and has a negative effect on the wettability of the tablet, which could prolong the disintegration time. Preliminary experiments with powder blends containing Ludiflash® or Parteck® were performed to determine a suitable amount of lubricant. The comparative study between ODTs containing various concentrations (between 0.5 to 5%) of magnesium stearate was performed. Hence, a concentration 1% w/w was used as lubricant for the investigated formulations to balance lubrication and disintegration properties.

ODTs were prepared using either Ludiflash® or Parteck® by direct compression method using single punch tablet press type EP1 Erweka, Heusenstamm, Germany. All the tablets were prepared under similar conditions. To examine the influence of different types of disintegrants, formulations L0 to L6 and P0 to P6 were prepared (Table 1). Disintegrants are the class of compounds which primarily aid the rapid disintegration of ODTs in the oral cavity. This class of disintegrants have been shown to be effective at excipients concentrations as low as 2 to 10% when compared to traditional disintegrant starches, which may need concentrations as high as 20% (Augsburger et al., 2007; Zhao and Augsburger, 2006). Croscarmellose sodium and crospovidone are well known disintegrants used in ODTs. They have very strong disintegrating ability. Croscarmellose sodium swells to a large extent when it comes in contact with water. Also, it has a fibrous nature that allows intraparticulate as well as extraparticulate wicking of water even at a low concentration (Augsburger et al., 2007; Zhao and Augsburger, 2005). Crospovidone has an excellent wicking nature though it swells only minimally (Augsburger et al., 2007; Thibert and Hancock, 1996). Microcrystalline cellulose is widely used in oral pharmaceutical formulations as a binder, diluent, antiadherent and disintegrant (Watanabe et al., 1995). It has a good compressibility, compactibility and lubricity, and is generally regarded as relatively nontoxic and nonirritant (Rowe et al., 2009; Rojas et al., 2011). To examine the most suitable ratio of disintegrants, various formulation of ODTs were prepared. The disintegration time of tablets were decreased significantly with respect to increase in the concentration of disintegrants from 1 to 3 and 5%. However, formulations containing 5% of disintegrant did not meet the hardness and friability requirements. Therefore, the concentration of disintegrants was estimated as 3%, because using disintegrants in lower or higher concentration did not enable obtaining ODTs with satisfactory disintegration time and physico-mechanical properties (data not shown).

The manufactured formulations L0 to L6 and P0 to P6 exhibited white colour, odourless, flat in shape, with smooth surface, and were evaluated for physical parameters such as weight and thickness variation, hardness and friability. The average weight and thickness of tablets for all the formulations was found to be in the range of 180.6 to 181.8 mg and 4.01 to 4.07 mm, respectively (Table 3). All the formulations exhibited low weight variation which lies within the pharmacopoeial limits of ± 7.5% of the average weight (EP, 2008; USP 35: United States Pharmacopeial Convention, 2012). The

Table 2. Flow properties of the powders used for ODTs formulations.

Formulation	Density (g/ml)		Flow property			
	Bulk	Tapped	Hausner ratio	Carr's index	Angle of repose (°)	According to EP
Ludiflash®	0.51±0.01	0.65±0.00	1.28±0.01	22.0±0.30	29.0±0.90	Passable
Parteck®	0.54±0.01	0.67±0.01	1.25±0.02	20.0±0.20	30.0±0.60	Fair
K*_CL	0.43±0.01	0.52±0.01	1.21±0.02	17.0±0.95	32.0±0.60	Fair
K*_CL-SF	0.28±0.01	0.44±0.01	1.57±0.02	36.6±0.56	-	Very poor
K*_CL-M	0.19±0.00	0.28±0.00	1.48±0.01	32.4±0.32	-	Very poor
K*_CL-F	0.28±0.01	0.39±0.00	1.39±0.01	28.0±0.93	-	Poor
Avicel®	0.43±0.01	0.60±0.01	1.40±0.01	29.0±0.97	31.0±0.60	Poor
AcDiSol®	0.61±0.01	0.85±0.01	1.41±0.01	28.0±0.92	-	Poor

*K_ - Kollidon®; – not determinable. All values are expressed as mean ± SD.

Table 3. Physical parameters of prepared ODTs.

Formulation	Weight (mg)	Thickness (mm)	Hardness (N)	Friability (%)	Wetting time (s)
L0	181.8±1.16	4.07±0.09	60±2.02	0.70	18±0.57
L1	181.3±1.21	4.06±0.08	77±1.92	0.60	15±0.57
L2	180.8±0.98	4.04±0.06	56±1.85	0.82	14±1.15
L3	181.3±0.89	4.05±0.07	74±1.89	0.81	23±0.00
L4	180.8±0.75	4.01±0.03	72±1.20	0.72	21±2.00
L5	181.3±1.51	4.03±0.05	75±2.51	0.75	29±1.15
L6	180.6±0.81	4.02±0.04	73±1.79	0.73	26±0.57
P0	181.1±1.16	4.01±0.03	59±2.04	0.70	35±0.00
P1	180.9±0.98	4.04±0.06	70±2.07	0.51	38±1.15
P2	181.2±0.87	4.01±0.05	45±2.13	0.85	22±0.00
P3	180.9±1.14	4.01±0.05	45±2.13	0.85	22±0.00
P4	181.6±1.51	4.04±0.07	72±1.74	0.78	48±0.00
P5	181.8±1.15	4.01±0.04	75±1.56	0.60	45±1.15
P6	181.8±1.15	4.03±0.05	75±2.44	0.57	45±0.00

All values are expressed as mean ± SD.

pharmacopoeial limit of friability using tablet friability apparatus, carried out at 25 rpm for 4 min, is not more than 1%. However, it becomes a great challenge to achieve friability within this limit, keeping hardness at its lowest possible level in order to achieve a minimum possible determination time. The hardness of the obtained tablets was maintained in the range of 45 to 77 N and the friability results were found to be < 1%, which suggest that all the manufactured formulations posses the sufficient mechanical integrity (Table 3) and are able to withstand abrasion in handling, packaging and shipment.

Wetting time is related to the inner structure of the tablets and hydrophobicity of the components. The results of wetting time are shown in Table 3. It was observed that formulations L2 and P2 (containing crospovidone Kollidon® CL-SF) had the shortest wetting time. The most important parameter that needs to be optimized in the development of ODTs is the disintegration time. Focusing on a tri-regional Pharmacopeia, that is the Japanese Pharmacopeia (JP), United States Pharmacopeia (USP) and European Pharmacopeia (EP), the EP has categorized ODTs as tablets which disintegrate in less than 3 min, using a conventional test (EP, 2008). More recently, in Food and Drugs Administration (FDA) Guidance for Industry, ODTs are considered as solid oral preparations that disintegrate rapidly in the oral cavity, with *in vitro* disintegration time of approximately 30 s or less, when based on the USP disintegration test method for conventional tablets (Food and Drug Administration, 2008). However, no special apparatus is mentioned in the pharmacopoeias for disintegration test of ODTs, and the conventional method available seems to be inappropriate for this type of tablets. The conventional test employs a relative huge volume of test solution (900 ml) compared to the volume of saliva in human buccal cavity, which is less than 6 ml. Therefore, the results obtained from the conventional disintegration test do not reflect the actual disintegration time in the human mouth. In this study, disintegration times of manufactured ODTs were measured using four

Table 4. Disintegration times of manufactured ODTs evaluated by four independent methods.

Formulation	Disintegration time (s)			
	In vivo	Conventional apparatus	Petri dish	Metal mesh
L0	35±0.57	37±0.57	34±0.57	37±0.62
L1	37±0.64	59±0.57	45±0.74	30±0.57
L2	10±0.97	23±0.57	15±1.15	18±0.57
L3	33±0.42	32±1.00	28±1.47	33±0.57
L4	27±0.57	36±0.57	30±0.57	33±1.15
L5	63±0.57	98±1.15	80±0.57	80±1.15
L6	46±0.61	38±1.15	34±0.57	35±1.00
P0	56±1.15	57±0.57	56±0.00	52±0.57
P1	59±1.00	76±0.57	70±0.57	64±0.57
P2	26±1.15	21±1.15	23±1.15	25±0.57
P3	39±0.00	35±0.00	37±1.15	35±1.00
P4	41±0.57	29±1.15	28±1.15	30±1.15
P5	120±0.57	120±0.57	90±1.52	90±0.57
P6	42±0.57	30±1.00	30±1.15	33±1.15

All values are expressed as mean ± SD.

independent methods, both *in vitro* and *in vivo* (Table 4). Although the different types of disintegrants used in the examined formulations enabled obtaining acceptable hardness and friability of ODTs (Table 3), they significantly influenced the disintegration time of the tablets. The results shown in Table 4 indicate that crospovidone is the strongest among other disintegrants, which results in the fastest *in vitro* and *in vivo* disintegration times, followed by croscarmellose sodium, then microcrystalline cellulose. Disintegration times < 30 s measured by four independent methods was observed only in formulations with Kollidon® CL-SF (L2 and P2). The faster disintegration of ODTs with crospovidone may be attributed to the strong wicking action of this disintegrant, its rapid capillary activity and hydration with little tendency to gel formation (Rowe et al., 2009). Based on these results, superfine crospovidone seems to be the most suitable disintegrant for ODTs manufactured both with Ludiflash® and Parteck®.

The relationship between tablet hardness and disintegration time is shown in Figure 1. Generally, disintegration time increases with increased hardness. Our results have demonstrated that an increase in tablet hardness has a different extent of impacts on disintegration time, depending on the type of disintegrant used. Hardness of tablets containing Avicel® PH 102 as a disintegrant (formulation L5 and P5) was the most responsive to increases in disintegration time, while that of tablets containing Kollidon® CL-SF (formulation L2 and P2) was the least responsive. It was shown, that Kollidon® CL-SF can be suitable disintegrant for the production of ODTs because it enables it to obtain tables with relatively high hardness and short disintegration time. Tablets containing Avicel® PH 102 are the most difficult and slowest to disintegrate.

Using a scanning electron microscope (SEM), Ludiflash® and Parteck® particles before and after compression were analyzed for surface morphology. It has been shown that Parteck® particles have more porous and filamentous structure, which remains unchanged after mixing and compression (Figure 2D and F). The surface of Ludiflash® and Parteck® ODTs was relatively homogenous dispersion with pores, cracks and fissures (Figure 2). The porous and filamentous Parteck® structure is a measure of its large specific surface area and contributes to nitrogen adsorption (BET) of the tablet matrix of up to 4.00 m^2/g (Table 5), which enhances the water uptake and disintegration time of the matrix. However, the differences in the wetting time and disintegration time values between Ludiflash® and Parteck® formulations (L0 to L6 and P0 to P6) cannot be easily justified by the scanning electron microscope images and pore structure examinations. Formulations with Ludiflash® showed both less porous textures, with low specific surface area (BET values up to 0.77 m^2/g) (Table 5) and shorter wetting and disintegration times (Tables 3 and 4). Although pores form channels, which are assumed to facilitate water ingress and support rapid tablet disintegration, the main role in disintegration time is played by the presence of disintegrants.

Due to high content of hydrophilic excipients, ODTs have increased chance of moisture uptake which greatly affects stability of products, so there is a need for special attention towards storage and packaging. Therefore, moisture uptake studies are strongly recommended for ODTs (Shukla et al., 2009b). The moisture uptake study indicates no significant uptake of moisture by the prepared batches during the 14 days test period (data not shown). Obtained formulations of ODTs exhibited low hygroscopicity, mainly driven by the specific character of

Table 5. Parameters of the pore structure of manufactured ODTs.

Formulation	Total surface area (m^2/g)	Pore radius (Å)	Cumulative volume of pores (cm^3/g)
L0	0.38±0.02	16.80±0.1	0.001
L1	0.66±0.04	43.01±0.2	0.001
L2	0.38±0.01	46.02±0.2	0.001
L3	0.77±0.02	40.00±0.3	0.001
L4	0.56±0.04	74.02±0.8	0.001
L5	0.59±0.05	47.00±0.4	0.001
L6	0.66±0.03	48.04±0.8	0.001
P0	3.60±0.04	109.00±0.6	0.021
P1	3.98±0.07	137.01±0.5	0.013
P2	3.20±0.04	94.05±0.9	0.014
P3	3.70±0.08	122.00±0.9	0.022
P4	3.00±0.06	79.05±0.7	0.012
P5	3.12±0.04	12.00±0.8	0.017
P6	4.00±0.05	84.02±0.8	0.021

All values are expressed as mean ± SD.

Table 6. Sensory evaluation of manufactured ODTs.

Volunteer	Score[a]													
	L0	L1	L2	L3	L4	L5	L6	P0	P1	P2	P3	P4	P5	P6
A	0	0	0	0	0	1	1	0	1	0	0	0	0	1
B	0	0	0	0	0	1	1	0	0	0	0	0	1	1
C	0	0	0	0	0	0	1	1	0	0	0	0	1	0
D	1	0	0	0	0	0	0	0	0	0	1	0	1	0
E	0	0	0	0	0	0	0	0	0	1	1	0	0	0
F	0	0	0	0	1	0	0	0	0	0	0	1	0	1
G	0	0	1	0	0	0	0	0	0	0	0	1	0	1

[a]Scored as follows: 0 = not rough; 1 = slightly rough; 2 = markedly rough.

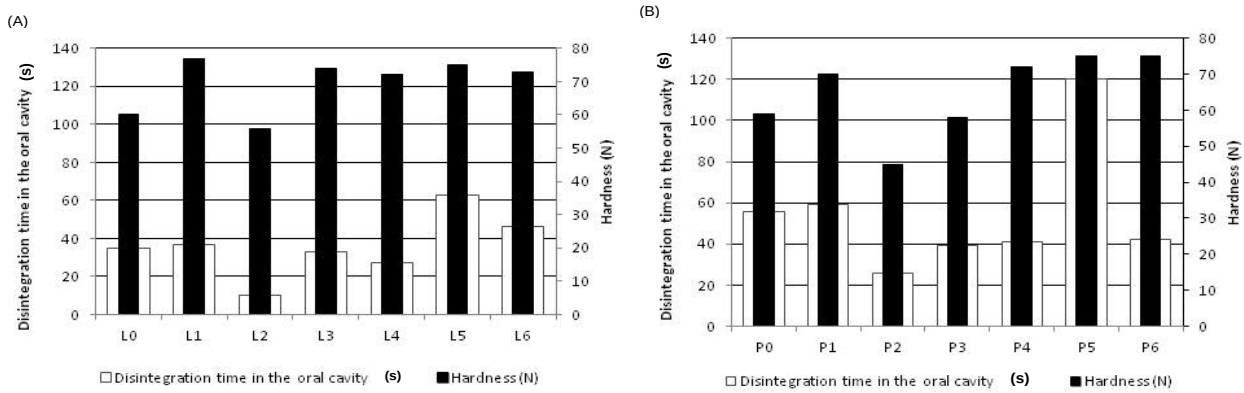

Figure 1. Effect of hardness on disintegration time in: (A) formulations L0 to L6 and (B) P0 to P6.

D-mannitol as the main component.

Another important feature of ODTs is taste and roughness. In general, polyols are known to exhibit a sweet taste and a pleasant mouth feeling, with mannitol being one of the most commonly used of this class (Rowe et al., 2009). In this study, microcrystalline cellulose, crospovidones and croscarmellose sodium were used as disintegrants.These water-insoluble excipients have a very rough texture. Watanabe et al. (1995) reported that tablets pre-pared with

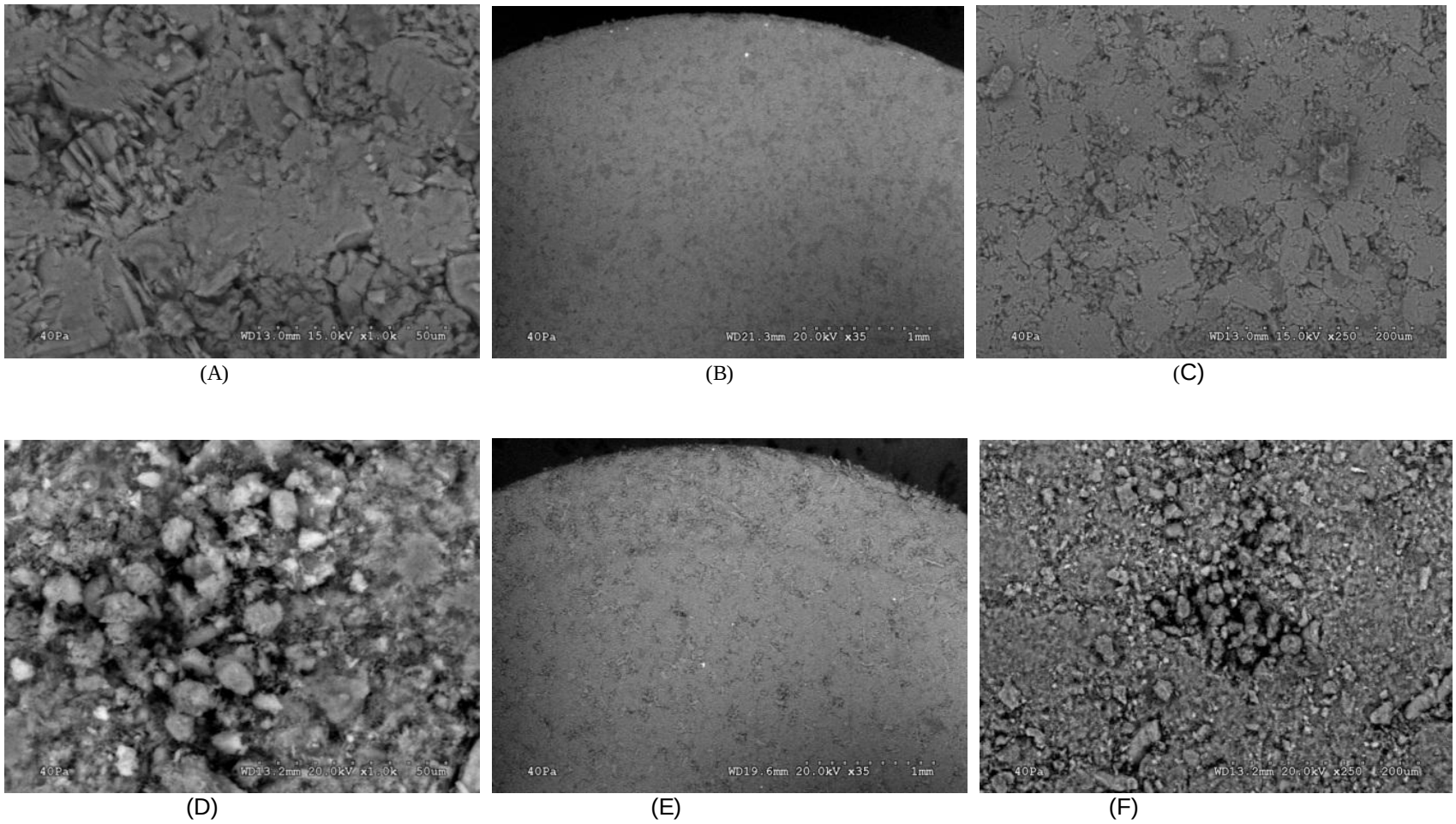

Figure 2. Scanning electron micrographs of: (A) Ludiflash® particle before compression (original magnification ×1000); (B), (C) ODT formulation L0 (original magnification ×35 and ×250); (D) Parteck® particle before compression (original magnification ×1000); (E), (F) ODT formulation P0 (original magnification ×35 and ×250).

microcrystalline cellulose rapidly disintegrated with saliva, but it was indicated that patients sometimes sensed roughness in the mouth due to the incomplete solubili-zation (Ishikawa et al., 2001). However, water- insolubleexcipients with small particle size are smoother. To elucidate the effect of disintegrant type on the feeling of roughness when prepared, tablets were taken orally, and a sensory evaluation of ODTs

containing different disintegrants was performed. The results of evaluation by volunteers are presented in Table 6. The rough texture was evaluated as more unpleasant in the order: ODTs with croscarmellose sodium > ODTs withmicrocrystalline cellulose > ODTs with crospovidones. Short-term stability studies (40, 60 and 80% relative humidity for a period of three months at 25°C) indicated that there were no significant changes in appearance of ODTs, weight variation, thickness, hardness, friability, wetting and disintegration times of the prepared formulations (data not shown). After six months of storage, all obtained ODTs were characterized by slightly more hardness and friability (but still within pharmacopoeial limits), whereas disintegration times were without significant changes.

Conclusion

It has been provided that selecting an appropriate disintegrant is extremely important in designing ODTs. The results from this study suggest that disintegration of ODTs is dependent on the nature of disintegrant, and the most effective disintegrant in ODTs manufactured using new ready-to-use excipient Ludiflash® or Parteck® is superfine crospovidone, which enables obtaining pleasant-tasting and pleasant feeling in the mouth tablets that disintegrate rapidly and posses satisfactory physico-mechanical properties.

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