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Varying efficacy of superdisintegrants in orally disintegrating tablets among different manufacturers

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Purpose: The main objective of the present study was to develop an orally disintegrating tablet formulation of domperidone and to study the functionality differences of superdisintegrants each obtained from two different sources on the tablet properties. *Methods*: Domperidone tablets were formulated with different superdisintegrants by direct compression. The effect of the type of superdisintegrant, its concentration and source was studied by measuring the *in-vitro* disintegration time, wetting time, water absorption ratios, drug release by dissolution and *in-vivo* oral disintegration time. *Results*: Tablets prepared with crospovidone had lower disintegration times than tablets prepared from sodium starchglycolate and croscarmellose sodium. Formulations prepared with Polyplasdone XL, Ac-Di-Sol, and Explotab (D series) were better than formulations prepared with superdisintegrants obtained from other sources (DL series) which had longer disintegration times and lower water uptake ratios. The *in-vivo* disintegration time of formulation D-106 containing polyplasdone XL was significantly lower than that of the marketed formulation Domel-MT. *Conclusions*: The results from this study suggest that disintegration of orally disintegrating tablets is dependent on the nature of superdisintegrant, concentration in the formulation and its source. Even though a superdisintegrant meets USP standards there can be a variance among manufacturers in terms of performance. This is not only limited to *in-vitro* studies but carries over to disintegration times in the human population.

1. Introduction

Recently, there has been increasing interest in development of orally disintegrating tablets (ODTs). These novel formulations can be administered without water, anywhere, anytime and have been shown to increase patient compliance (Sallam et al. 1998; Bi et al. 1999; Fu et al. 2004; Bandari et al. 2008). For example, ODTs can be administered with relative ease to geriatric populations who have dysphagia (Lindgren and Janzon 1991) and to patients suffering from nausea, vomiting, or motion sickness (Sastry et al. 2000). From the patient perspective, in order to achieve a successful ODT formulation, emphasis should be placed on both taste and dissolution time to increase palatability. From the industrial side ODT formulations have benefits beyond the typical solid oral dosage form, including; a rapid onset of action, increased or at a minimum equivalent bioavailability, and relatively good stability (Bi et al. 1996).

Superdisintegrants (SDTs) are the class of compounds which primarily aid in the rapid disintegration of ODT in the oral cavity. This class of disintegrants have been shown to be effective at excipient 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). To date there have been three primary classes of modified starch used as SDTs in the formulation of ODT's; sodium starch glycolate (SSG), croscarmellose sodium (CCS), and synthesized polymer crospovidone (CP) (Zhao and Augsburger 2006). The efficacy or performance of a SDT can be characterized before formulation by; the size of starch particles, water uptake and bulk swelling, and to a certain degree the extent of cross-linking of the starches. However, it has been shown that the same SDT (CCS) can vary widely (up to 10 fold) in terms of purity, size, and water uptake rates depending on the manufacturer of the starch even though they meet USP requirements (Zhao and Augsburger 2006). Considering that the SDT's are used in such small concentrations it is the hypothesis of this work that subtle differences in starch behaviors from different manufacturers will lead to differences in disintegration time both *in-vitro* and *in-vivo*. Moreover, little is known about whether these variances in starches can ultimately influence disintegration time and potential efficacy in human patients.

In the present study, domperidone, a D2 receptor antagonist, was chosen as a model drug in an ODT. This drug was chosen since it acts as an antiemetic and a prokinetic agent through its action on chemoreceptor trigger zone and motor function of stomach and small intestine (Brogden et al. 1982; Barone 1999; Reddymasu et al. 2007). This drug was then formulated into an ODT in separate tablets using the three primary SDTs found in manufacturing (SSG, CCS and CP). Each SDT was obtained from two different manufacturing sources. End points of measurement

Table 1: Formulation characteristics of domperidone orally disintegrating tablets

Superdisintegrant (Source)	Formulation	Mean Weight (mg) ± SD	Mean Thickness (mm) ± SD	Drug content (% ± SD)	RSD*
Crospovidone	DL 104	103.2 ± 1.51	3.89 ± 0.012	96.16 ± 0.83	0.87
(Span Pharma Ltd)	DL 106	103.1 ± 2.35	3.93 ± 0.007	96.12 ± 4.05	2.53
	DL 108	98.8 ± 3.04	4.03 ± 0.088	99.27 ± 4.06	1.42
Polyplasdone XL	D 104	103.8 ± 2.12	4.21 ± 0.015	96.47 ± 0.95	0.98
(ISP technologies)	D 106	103.5 ± 2.98	4.23 ± 0.030	95.80 ± 2.13	2.21
	D 108	98.0 ± 1.81	4.14 ± 0.052	99.21 ± 0.53	0.54
Croscarmellose sodium	DL 114	100.8 ± 2.31	3.88 ± 0.026	95.83 ± 0.99	1.04
(Perific Onufluinus)	DL 116	99.1 ± 2.45	3.86 ± 0.047	99.04 ± 1.94	1.96
	DL 118	98.8 ± 3.04	3.80 ± 0.026	97.38 ± 1.24	1.23
Ac-Di-Sol	D 114	100.9 ± 1.64	3.97 ± 0.048	96.71 ± 2.38	2.47
(FMC Biopolymers)	D 116	100.4 ± 2.85	3.98 ± 0.012	100.93 ± 4.34	4.35
	D 118	100.2 ± 2.23	3.92 ± 0.075	102.75 ± 1.31	1.28
Sodium starchglycolate	DL 124	101.3 ± 1.80	3.80 ± 0.026	101.17 ± 3.69	3.65
(Aditya chemicals)	DL 126	97.5 ± 2.54	3.81 ± 0.029	99.11 ± 4.54	4.56
	DL 128	98.2 ± 2.40	3.72 ± 0.016	98.32 ± 2.45	2.51
Explotab	D 124	99.6 ± 1.31	3.89 ± 0.058	96.1 ± 0.64	0.64
(JRS Pharma)	D 126	105.1 ± 2.73	3.97 ± 0.059	107.2 ± 1.92	1.79
	D 128	104.2 ± 4.12	4.01 ± 0.025	97.02 ± 0.54	0.56

* RSD = Relative Standard deviation

included water absorption, *in-vitro* dissolution-drug release and *in-vivo* disintegration time in human volunteers. Uniformity of the tablets was determined in terms of tablet weight, thickness, hardness, and friability.

2. Investigations and results

2.1. Tablet properties

For all formulations, tablet weight and thickness were within mean ± 10% and mean ± 5%, respectively. Tablet hardness was maintained at 2.5 ± 0.5 kg and friability values were less than 1% in all cases (data not shown). Domperidone formulations demonstrated content uniformity, with a mean drug content of >95.0% and relative standard deviation of <5.0% (Table 1).

2.2. In-vitro disintegration time

Increasing the SDT concentration from 4 to 8% resulted in a general decrease in disintegration time (Fig. 1). Formulations developed with Polyplasdone XL, Ac-Di-Sol, and Explotab (D series) showed the fastest disintegration times which were significantly (p<0.001) lower than the disintegration times of the DL series. An increase in the SDT concentration from 4-6% had a significant decrease in disintegration time of all tablets an effect not seen when the concentration increased from 6-8%, with the only exception being the ODT containing CCS. While the aims of this study did not directly compare the SDT in terms of efficacy and disintegration, it should be noted that the disintegration times of formulations containing CP were lowest of all the superdisintegrants used in the study.

2.3. Wetting time

Although wetting test is not a standard USP test, it is useful for quality control and provides a correlative evaluation to water uptake rates. Unlike the disintegration test, the wetting test uses minimal water, which may be more representative of the quantity of moisture available in oral cavity. Wetting time was determined for all of the formulations. A correlation between wetting time and SDT concentrations was not evident. Similar to disintegration time, wetting time of formulations containing CP was less compared to formulations containing CCS or SSG at equivalent concentrations (data not presented).

2.4. Water absorption ratio

Water absorption ratio values increased concurrently with increases in the SDT concentrations from 4–8% (Fig. 2). Of the three SDTs used CP had the lowest water absorption ratio (147–170%) whereas SSG had the highest (210–269%). The difference between the water absorption ratio of tablets (D vs DL series) prepared from SSG was statistically significant ($p < 0.001$). However, water absorption ratio values of tablets prepared with CP and CCS showed a marginal difference (D vs DL series, $p > 0.05$). An inverse correlation ($r > 90\%$) between water absorption ratio and disintegration time was noticed for all superdisintegrants (Fig. 3).

2.5. In-vitro release studies

In all 18 formulations, with an increase in the concentration of superdisintegrant the cumulative percent drug release increased with time and ∼90% of drug was released in the first 8 min (data not shown). The formulation which has the shortest release time was D106, where ∼72% drug was released in the first 2 min. However, the corresponding formulation DL106 released only ∼64% drug in same time. In comparison, the marketed product Domel-MT released ∼62% drug in same time (Fig. 4).

2.6. In-vivo oral disintegration test

In-vitro disintegration time was measured for the optimized formulation D106 and was compared with DL106 and marketed formulation (Domel-MT). The disintegration time of D106 was significantly lower ($p < 0.001$) than the other two formulations. Formulation D106 was further studied for *in-vivo* disintegration along with the marketed formulation.

The disintegration time of the optimized formulation D106 along with the marketed formulation (Domel-MT) was measured in six healthy male human volunteers as per the protocol (Ethics permit # 14EC/pharm/ku/2006). The same formulation

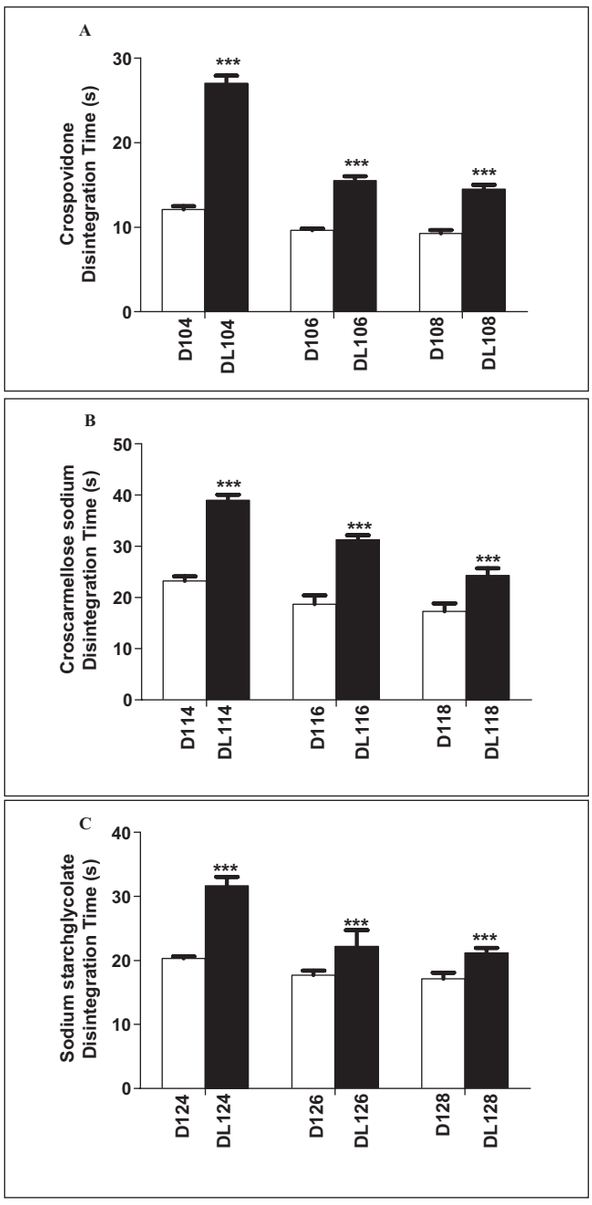

Fig. 1: Comparison of disintegration time of the three superdisintegrants (open bar represents the superdisintegrants of known purity (D series), filled bars represents superdisintegrants for which purity is not readily available (DL series)) each obtained from two different manufacturers for all 18 formulations. Data represent mean ± SD; n = 6 for all data points. An (***) indicates $p < 0.001$

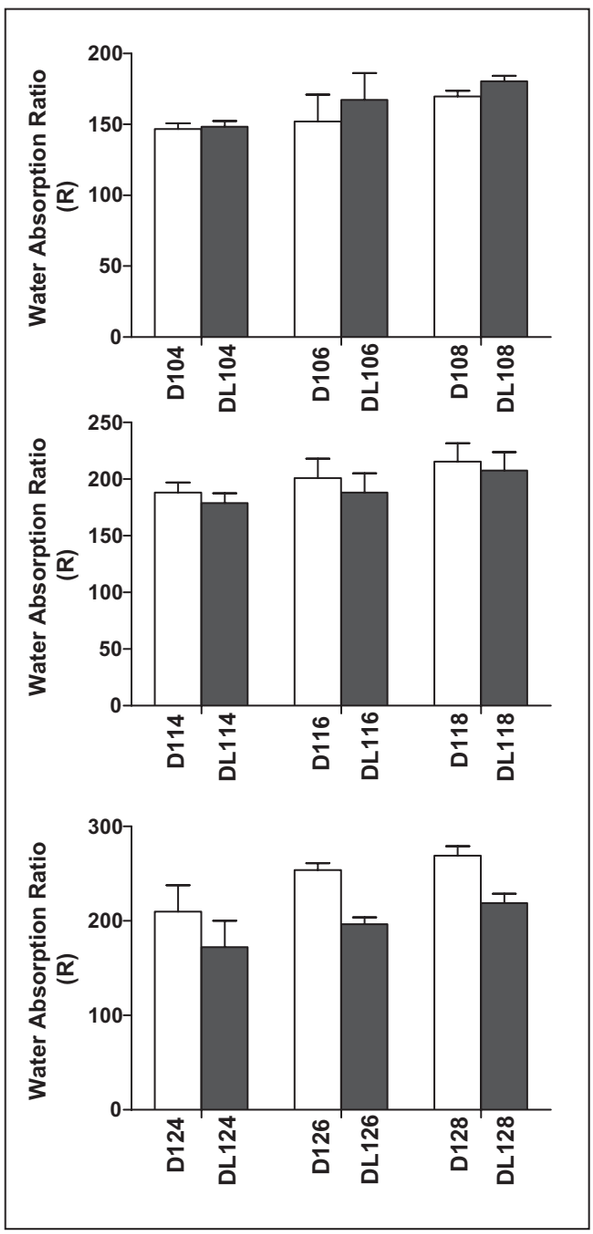

Fig. 2: Water absorption ratio (R) for the superdisintegrants (crospovidone **Fig. 2A**; croscarmellose sodium **Fig. 2B**; sodium starchglycolate **Fig. 2C**) at three different concentrations obtained from two different manufacturers. Data are mean ± SD; n = 6 for all data points

was administered three times to each individual and the average of the measurements represents an individual oral disintegration time. Complete disintegration was achieved at 18.9 ± 1.4 s which was significantly faster ($p < 0.001$) than that of the marketed formulation (29.0 ± 2.3 s) (Fig. 5B).

3. Discussion

The results presented herein confirm previous reports that both concentration and purity of SDT's influence both the *in-vivo* and *in-vitro* disintegration time of an ODT. The importance of this report is two-fold. First, we document that even though a SDT meets USP standards there can be a variance among manufacturers in terms of performance (e.g., water uptake rates, disintegration time, etc. . .). Second, the variance in SDT performance in an ODT is not only limited to *in-vitro* studies but carries over to disintegration times in the human population. This data is significant considering ODT disintegration time has been correlated with both patient satisfaction and compliance in medication administration and may influence how manufacturers procure SDTs.

The mechanisms of SDTs to produce a rapidly disintegrating ODT are initially started by "water wicking" which is defined as the ability of the starch to draw water into the tablet matrix through a channel of hydrophilic pores that are created between the SDT particles during compression manufacturing. Once this wicking process occurs, the starch swells on contact with water. The SDT particles are then rapidly deformed which leads to the breakdown of the tablet. In addition, water inside the hydrophilic

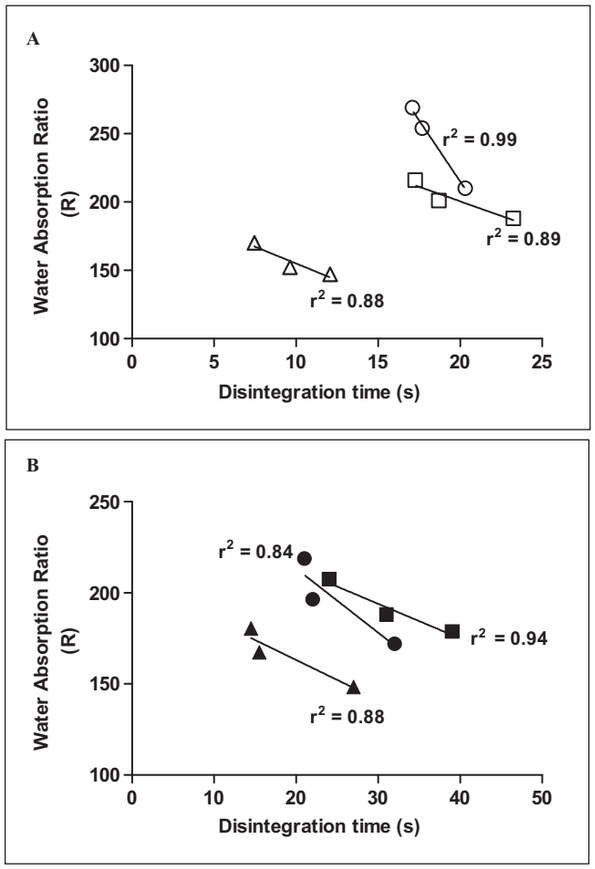

Fig. 3: Correlation between disintegration time and water absorption ratio for D series (**Fig. 3A**), and DL series (**Fig. 3B**). (△ - crospovidone; (□ - croscarmellose sodium; ○ - sodium starchglycolate; open symbols represent formulations from D series, filled symbols represent formulations form DL series)

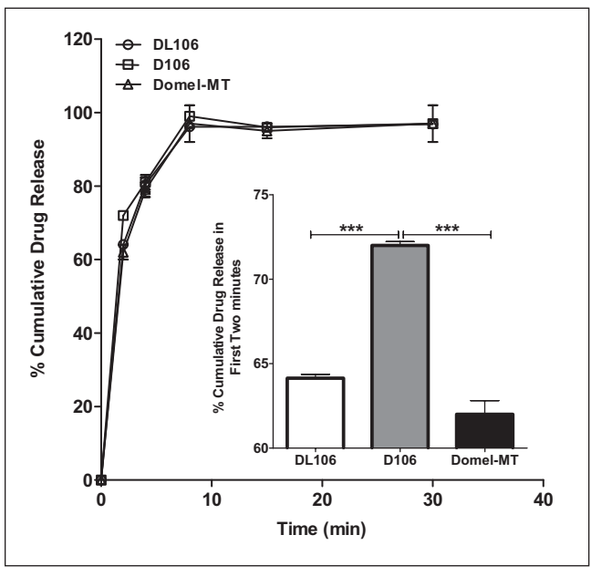

Fig. 4: Comparison of dissolution profiles of domperidone rapidly disintegrating tablets of D106, DL 106, and Domel-MT (a commercially available domperidone orally disintegrating tablet). The inserted bargraph indicates the % of drug release in the first two minutes. Values represent mean ± SD (n = 6)

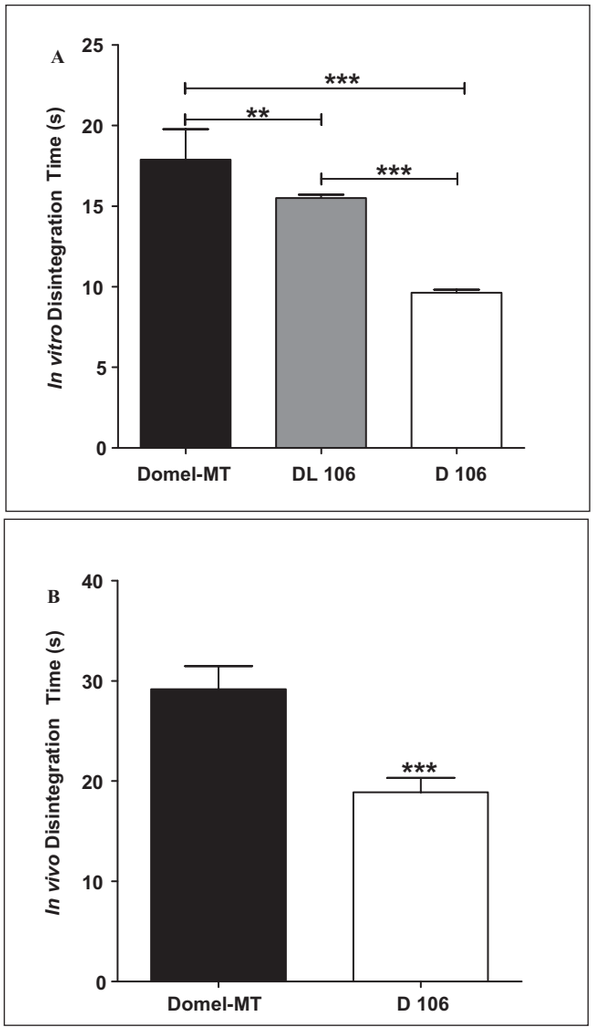

Fig. 5: *In-vitro* disintegration time (**Fig. 5A)** and *in-vivo* disintegration time (**Fig. 5B)** for the optimized formulations (D106, DL 106) and commercially available domperidone rapid disintegrant tablets. Values represent mean ± SD (n = 6) for all the data points. An (**and ***) indicates a p value of <0.05 and <0.001 respectively

pores may also help to break hydrogen bonds present between starch grains (repulsion theory) and produce heat, both of which may aid in disintegration (Augsburger et al. 2007).

The measurement of SDT efficacy is typically completed by observing overall disintegration times, with the hope that the data will be generally consistent in the human population. However, additional *in-vitro* experiments can also shed light on *in-vivo* efficacy. Specifically, wetting times and total water absorption will provide insight into how fast the hydrophilic pores allow water to penetrate the tablet and the total amount of water that is accumulated by tablet which may be influenced by gel formation.

Each SDT starch has different molecular weights and polar surface areas and therefore exhibit slightly different properties in terms of wicking and disintegration. For example, CP is a cross-linked homo-polymer of *N*-vinyl-2-pyrollidone which has good water wicking characteristics and smaller disintegration times due to the hydrophilic pores created in compression (Kornblum and Stoopak 1973). In contrast, SSG at high concentrations has a tendency to coagulate and swell in the presence of water which can create a wicking barrier and reduce disintegration times

Table 2: Excipient / drug composition of orally disintegration tablets

Ingredients	Super disintegrant concentration		
	4%	6%	8%
Domperidone	10	10	10
Pearlitol	24.45	23.85	23.25
Avicel pH 101	57.05	55.65	54.25
Super disintegrants	4	6	8
Aspartame (2%)	2	2	2
Orange flavour (1%)	1	1	1
Aerosil (1%)	1	1	1
Sodium stearyl fumarate (0.5%)	0.5	0.5	0.5

* All the amounts given in above table are in milligrams

Table 3: Formulation codes

Super Disintegrant (Source)	Conc. (%)	Formulation code
Crospovidone (Span Pharm Ltd)*	4	DL 104
	6	DL 106
	8	DL 108
Polyplasdone XL (ISP technologies)	4	DL 104
	6	DL 106
	8	DL 108
Croscarmellose sodium (Perific Onufluinus)*	4	DL 114
	6	DL 116
	8	DL 118
Ac-Di-Sol (FMC Biopolymers)	4	DL 114
	6	DL 116
	8	DL 118
Sodium starch glycolate (Aditya Chemicals)*	4	DL 124
	6	DL 126
	8	DL 128
Explotab (JRS Pharma)	4	DL 124
	6	DL 126
	8	DL 128

* were purchased form Span Pharma Ltd, Hyderabad, India

(Rudnic EM et al. 1983; Bolhuis et al. 1997; Bolhuis et al. 2009). Our data agrees with these general principles of starch behavior. Specifically, we observed that the use of CP as the SDT at all concentrations, regardless of manufacturer had faster wetting times, needed less water to disintegrate the tablet (Fig. 2) and overall had faster tablet disintegration times (Fig. 1) than the corresponding SSG formulations. In addition, CCS, which is a cross linked sodium carboxy methyl cellulose, had water uptake values intermediate to CP and SSG, which is consistent with previous reports (Battu et al. 2007). Our data also confirm that disintegration times and water absorption values are inversely related (Fig. 3), where an increase in water absorption ratio was associated with a lower disintegration time. This was observed across all SDTs, at all concentrations, regardless of the manufacturer. It should be noted that overall *in-vitro* drug release characteristics were not substantially different across the various formulations, suggesting potential bio-equivalence (Fig. 4).

Of major significance, the data in this report which demonstrate the variances in SDT efficacy amongst the different manufacturers highlights an understudied problem in tablet manufacturing. We observed that *in-vitro* disintegration times varied as much as three fold using the same SDT, at the same concentration in a similar tablet formulation (e.g., CP at 4%; Fig. 1; Table 2). These variances were noted among all of the starches, independent of concentration utilized. We suggest that even though all starches met USP requirements, issues such as uniformity of particle size and purity may be contributing to the longer disintegration times of DL series formulations which did not readily provide the starches characteristics (Zhao and Augsburger 2006).

Next, we asked the question to what extent the *in-vitro* data can be translated into *in-vivo* oral disintegration time. To accomplish this we tested the D106 formulation in 6 healthy human volunteers compared to the marketed product, Domel-MT. The D106 formulation D106 was used since CP demonstrated significantly better characteristics of wetting time, water absorption ratio, and *in-vitro* disintegration time compared to the other starches. In addition, 6% CP was used in the formulation since it had faster disintegration times compared to 4% but was not substantially different than 8% (Fig. 1). DL106 was not evaluated in humans given that the purity of the starch was not readily available and to minimize the number of experiments. In our initial *in-vitro* tests D106 had a significantly faster disintegration time (∼33%) compared to the marketed formulation Domel-MT (Fig. 5A). When we carried out parallel experiments in the human volunteers a similar proportional rate of disintegration was observed (Fig. 5B). This data suggests that *in-vitro* disintegration data may be predictive of ODT properties in the patient population.

In summary, this research confirms previous literature suggesting that various SDTs can differ significantly in tablet disintegration times, yet extends the literature by demonstrating that SDTs from different manufactures can also be variable in disintegration efficacy. In addition, this data supports the suggestion that *in-vitro* observations of disintegration will carry over to human *in-vivo* disintegration times.

4. Experimental

4.1. Materials

Domperidone, Polyplasdone® XL (ISP Technolgies), Ac-Di-Sol® (FMC biopolymers), Explotab® (JRS pharma) and sodium stearyl fumarate were kind gift samples from Zydus Cadila (Ahmedabad, India). Colloidal silicon dioxide, talc, orange flavor, peppermint flavor, aspartame were gifted by Euro Drug Laboratories. Pearlitol® SD 200 was obtained as a gift sample from signet chemical corporation (Mumbai, India). Superdisintegrants purchased from Span Pharma limited (Hyderabad, India) were used as such with no further modification in formulation of tablets (DL series). Nigrosine® RM 247 (a water soluble dye) was purchased from Hi Media Laboratories Pvt. Ltd (Mumbai, India). All other chemicals used were of analytical grade and purchased from Merck Ltd (Mumbai, India).

4.2. Assignment of formulation codes

There are three SDTs (CP, CCS, SSG) that were obtained from two different sources for a total of 6 different SDT formulation. Each SDT, was studied at 3 different concentrations for a total of 18 formulations. These are assigned with formulation codes in order to distinguish from each other (Table 3). The DL series formulations are from manufacturers that did not readily provide starches purity and characteristics whereas the D series did. It should be noted though, all starches met USP requirements.

4.3. Blending and tabletting

Tablets containing 10 mg of domperidone were prepared by direct compression method as described in our previous work (Battu et al. 2007). Briefly, formulation components were accurately weighed, passed through a 40-mesh sieve and mixed in a V-blender for 15 min. Directly compressed, biconvex tablets of 100 mg in weight and 6 mm in diameter were prepared on a 16-station single rotary tabletting machine (STD model RDD3, Riddhi, Ahmedabad, India). Tablet thickness and hardness were maintained at 4.0 ± 0.1 mm and 2.5 ± 0.5 kg, respectively for all of the formulations. Table 2 outlines the compositions of various ODT formulations studied.

4.4. ODT Evaluation

The prepared tablets were evaluated for weight variation, thickness variation, hardness, friability, disintegration time and wetting time according to USP

(2004). In weight variation test, 20 tablets were randomly selected from each formulation and their average weight was determined. Tablets were weighed individually and compared with the average weight. The thickness of the tablet was determined using a digital screw gauge (Digimatic outside micrometer, Mitutoyo, Japan). The Monsanto hardness tester and the Roche friabilator (Pharmalab, Ahmedabad) were used to test hardness and friability respectively as described in the USP.

4.5. Drug content of the tablets

The formulated ODTs were assayed for the drug content. Twenty tablets from each formulation were crushed in a mortar, samples containing amount of powder equivalent to one dose of drug were taken in triplicate and assayed for content of drug using a UV-VIS spectrophotometer (Model SL-150, Elico Pvt. Ltd., Hyderabad, India) at a wavelength of 281 nm.

4.6. In-vitro disintegration time

In-vitro disintegration time of the ODTs was determined using the procedure described by Gohel et. al. (2004). Briefly, water at 25 °C (10 mL) was placed in a petri dish of 10 cm diameter. The tablet was then positioned in the center of the petri dish and the time required for the tablet to completely disintegrate into fine particles was documented. Measurements were carried out in replicates (n = 6) and mean ± SD values were recorded.

4.7. Wetting time and water absorption ratio (R)

Five circular tissue papers were placed in a petri dish with a 10-cm diameter. Ten mL of water containing nigorsine, a water-soluble dye, was added to the petri dish. The dye solution is used to identify the complete wetting of the tablet surface. A tablet was placed on the surface of tissue paper in the petridish at room temperature. The time required for water to reach the upper surface of the tablets and completely wet them was defined as wetting time (Gohel et al. 2004). To check for reproducibility, the measurements were carried out in replicates (n = 6). The wetting time was recorded using a stopwatch.

The weight of the tablet before placing in the petri dish was noted (W_b) using a Shimadzu digital balance. The wetted tablet from the petri dish was taken and reweighed (W_a) using the same. The Water absorption ratio, R, was determined according to the following equation:

$$R = 100(W_a - W_b)/W_b$$

where W_b and W_a are the weight before and after water absorption respectively (Bi et al. 1996).

4.8. Dissolution study

In-vitro release of domperidone from tablets was performed in an USP apparatus 2, paddle method utilizing a dissolution system (Disso 2000, Lab India, Thane, India) equipped with an auto sampler and fraction collector. Paddle speed was maintained at 50 rpm and 900 mL of 0.1N HCl was used as the dissolution medium. Samples (5 mL) were collected at predetermined time intervals (2, 4, 8, 15 and 30 min) and replaced with equal volume of fresh medium. The collected samples were filtered through a 0.22 μm filter and analyzed with a UV-VIS spectrophotometer (λ = 281 nm). Drug concentration was calculated from a calibration plot and expressed as cumulative percent drug dissolved at the stated time intervals. The release studies were performed in replicates of six.

4.9. In-vivo oral disintegration time

Oral disintegration time was assessed in 6 healthy male human volunteers (as per protocol, Ethics permit # 14EC/pharm/ku/2006) for a series of different test tablets, following randomized administration (Abdelbary et al. 2005). Prior to the test, all volunteers were asked to rinse their mouth with distilled water. Tablets were placed on the tongue and immediately a stopwatch was started. Volunteers were allowed to move the tablet against the upper palate of the mouth with their tongue and to cause a gentle tumbling action on the tablet without biting it. Immediately after the last noticeable granule had disintegrated, the stopwatch was stopped and the time was recorded. Swallowing of saliva was prohibited during the test, and volunteers were asked to rinse their mouth after each measurement (Bi et al. 1996). The average of triplicate measurements represented an individual oral disintegration time. For each ODT examined, the mean oral disintegration time and the standard deviation (S.D., $n = 6$) as well as relative standard deviation (RSD) was calculated.

4.10. Statistics

Two-way ANOVA analysis followed by a Bonferroni's multiple comparison test was used for the comparison of disintegration times, water absorption ratios of prepared ODT formulation. Linear regression analysis was performed to check the correlation between water absorption ratio and disintegration time. For all data, errors are reported as standard deviation unless otherwise indicated. Differences were considered statistically significant at the $p < 0.05$ level. (Graph Pad Prism version 5.00 for Windows, Graph Pad Software, San Diego, CA USA).

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