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PHARMACEUTICAL TECHNOLOGY

EVALUATION OF COPROCESSED DISINTEGRANTS PRODUCED FROM TAPIOCA STARCH AND MANNITOL IN ORALLY DISINTEGRATING PARACETAMOL TABLET

OLUWATOMIDE ADEOYE and GBENGA ALEBIOWU*

Department of Pharmaceutics, Faculty of Pharmacy, Obafemi Awolowo University, Ile-Ife, Nigeria

Abstract: The study evaluated two novel coprocessed excipients (with two methods) as disintegrants in an orally disintegrating paracetamol tablet formulation. The tablets produced were assessed for mechanical properties with the use of friability and tensile strength while the release properties were assessed with wetting time, water absorption ratio, disintegration time and dissolution profile. The results obtained showed that the methods of coprocessing and disintegrant incorporation influenced the activities of the disintegrants. The novel disintegrant enhanced the mechanical properties of the tablets containing them as shown by lower friability and higher tensile strength of the tablets. The result further showed that the rate and amount of water absorbed, type of disintegrant and the method of disintegrant incorporation influenced the total amount of paracetamol released. The study concluded that the novel disintegrants will be effective in the formulation of orally disintegrating paracetamol tablets.

Keywords: co-fusion, co-grinding, dissolution, tensile strength, friability, disintegration time, water absorption ratio, wetting time

Tablets are the most preferred oral dosage forms due to their numerous advantages, which includes: ease of manufacture and administration, high physical and chemical stability, high patient compliance, convenient packaging/storage and the ability to provide accurately measured dose of the drug (1–3). However, its use in therapy is still associated with some challenges most especially among the geriatric and pediatric populations. Over the past two decades, orally disintegrating tablets (ODTs), a patient friendly dosage form, which disintegrates rapidly in the mouth upon contact with saliva, have gained increased importance, focus and patient acceptance because of their ability to addresses some of the challenges facing conventional tablets (4–6). These ODTs obviate the need to swallow tablets thereby making drug usage more convenient for pediatric and geriatric patients who usually have compromised swallowing ability due to various physiological/psychological factors (7). The convenience of administration without water also enables "dosing on the go", which facilitates patient adherence to the dosing regimen or administration (8).

Various methods such as lyophilization, molding, cotton candy, direct compression or tableting after granulation have been used in the manufacture of ODTs (6). Coprocessed multifunctional excipients based on polyols, disintegrants and binders with improved physico-mechanical properties (e.g., pleasant mouth-feel, low hygroscopicity, better flow and compactability) have been used to conveniently manufacture ODTs with excellent disintegration properties without compromising the mechanical properties (8).

The objectives of this study were to coprocess native tapioca starch (an excipient with binding, disintegrating and diluent properties) (9) with mannitol (an excipient that aids dissolution; has diluent and sweetening properties; and has the ability to impart cooling and pleasant mouth feel into ODTs) (10); and to evaluate the novel excipients produced as disintegrants in an orally disintegrating paracetamol tablet formulation.

EXPERIMENTAL

Materials

The materials used were: paracetamol B.P. and corn starch B.P. (BDH Chemicals Ltd., Poole, UK), lactose B.P. (A.B. Knight and Co., London, UK),

* Corresponding author: e-mail: gbengaalaba@gmail.com; phone: +234 80 938 4107

tapioca starch (prepared in our laboratory from tubers of *Mannihot utilisima* L.*)*, mannitol (BDH Chemicals Ltd., Poole, UK) and acetone (Sigma-Aldrich Laborchemikalien GmbH, Seelze, Germany).

Extraction of tapioca starch

The tapioca starch was extracted from the root tubers of cassava (*Manihot utilisima* L.) using established procedures (11). The cassava tubers were peeled, washed and cut into small pieces, which were soaked in distilled water for 48 h for softening. The softened tubers were milled to a pulp, and distilled water was added to dilute the slurry, which was then sieved using a 100 µm mesh. The procedure was repeated three times until starch was fully extracted from the tubers as confirmed by iodine test on the remaining chaff, which was negative. The extracted starch was dried at 50°C in hot air oven (Gallenkamp, Model OV-335, Vindon Scientific Ltd., Oldham, UK) for 72 h. The dried mass was powdered in a laboratory mill (Christy and Norris Ltd., Chelmsford, UK) and stored in a screw capped bottle until needed.

Coprocessing by co-fusion

Fifty grams each of dried mannitol (MNT) and tapioca starch (TPS) were fused together by dispersing the TPS in distilled water. The dispersion was then stirred for 5 min at 50°C to form a paste. The dry MNT powder was then added to the TPS paste and mixed together for 10 min. The resulting paste (fused MNT and TPS) was dried at 50°C in a hot air oven for 24 h before it was milled and sieved using a 250 µm sieve. The coprocessed product (FTM) was stored in a screw capped bottle until needed

Coprocessing by co-grinding

Fifty grams each of mannitol (MNT) and tapioca starch (TPS) was used. The MNT and dry TPS were triturated together using a porcelain mortar and pestle for 10 min to ensure uniform size reduction and mixing of the two powders (12). The resulting product (GTM) was then sieved using a 250 µm sieve and stored in a screw capped bottle until needed.

Swelling capacity test

The swelling capacity (SC) test was carried out according to the method described by Bowen and Vadino (13).

Preparation of binder mucilage

Corn starch mucilage was prepared by weighing the amount required (Table 1). The starch powder was suspended in the required amount of distilled water in a beaker and heated with continuous stirring until mucilage was formed. The mucilage was then used while hot to facilitate an effective binding of the powder mass.

Table 1. Basic formulation table.

	Formula				
Ingredients	I	II	III	IV	V
Paracetamol	90%	90%	90%	90%	90%
Corn starch (Binder)	3%	3%	3%	3%	3%
Lactose (Diluent)	6%	5%	4%	3%	2%
Disintegrant	1%	2%	3%	4%	5%

Table 2. Physicochemical properties of excipients.

Excipients	Particle density (g/cm^{-3})	Bulk density (g/cm^{-3})	Swelling index	Moisture content (%)
MNT	1.517 ± 0.011	0.349 ± 0.007	0.00 ± 0.00	1.62 ± 0.08
TPS	1.455 ± 0.004	0.546 ± 0.008	1.04 ± 0.06	13.43 ± 0.11
FTM	1.389 ± 0.018	0.500 ± 0.012	1.57 ± 0.20	8.51 ± 0.09
GTM	1.431 ± 0.026	0.512 ± 0.018	0.34 ± 0.04	8.76 ± 0.07

Table 3. Physical properties of tablets compressed at 121.38 MNm^{-2}.

Disintegrants	Disintegrant concentration (% $^{w}/_{w}$)	Tensile strength (MNm^{-2})		Friability (%)		Disintegration time (min)	
		Intragranular	Extragranular	Intragranular	Extragranular	Intragranular	Extragranular
TPS	1	0.54 ± 0.010	0.33 ± 0.040	6.40 ± 0.020	10.09 ± 0.010	3.12 ± 0.026	3.14 ± 0.061
	2	0.56 ± 0.012	0.42 ± 0.021	5.54 ± 0.015	7.13 ± 0.041	2.24 ± 0.091	2.34 ± 0.007
	3	0.56 ± 0.031	0.52 ± 0.013	4.19 ± 0.014	3.87 ± 0.031	2.20 ± 0.014	2.20 ± 0.042
	4	0.57 ± 0.009	0.60 ± 0.031	3.15 ± 0.010	2.24 ± 0.051	1.58 ± 0.031	2.12 ± 0.050
	5	0.62 ± 0.011	0.63 ± 0.079	1.89 ± 0.012	1.06 ± 0.017	1.01 ± 0.022	1.00 ± 0.001
FTM	1	0.63 ± 0.021	0.78 ± 0.029	0.94 ± 0.019	0.68 ± 0.012	16.31 ± 0.045	6.53 ± 0.044
	2	0.64 ± 0.007	0.79 ± 0.017	1.76 ± 0.011	0.49 ± 0.030	6.56 ± 0.026	4.32 ± 0.041FTMFTM
	3	0.76 ± 0.031	0.81 ± 0.045	0.79 ± 0.031	0.38 ± 0.051	4.22 ± 0.016	3.51 ± 0.033
	4	0.76 ± 0.042	0.87 ± 0.016	0.54 ± 0.051	0.36 ± 0.020	2.45 ± 0.021	1.52 ± 0.011
	5	0.81 ± 0.008	0.89 ± 0.003	0.47 ± 0.010	0.31 ± 0.010	2.37 ± 0.015	1.34 ± 0.020
GTM	1	0.46 ± 0.014	0.74 ± 0.004	7.20 ± 0.021	0.83 ± 0.010	9.40 ± 0.018	4.36 ± 0.022
	2	0.52 ± 0.002	0.86 ± 0.013	5.18 ± 0.005	0.90 ± 0.041	4.45 ± 0.032	4.12 ± 0.021
	3	0.55 ± 0.014	0.92 ± 0.046	3.87 ± 0.010	0.65 ± 0.012	2.55 ± 0.026	2.35 ± 0.012
	4	0.59 ± 0.019	0.93 ± 0.020	1.25 ± 0.016	0.58 ± 0.001	2.23 ± 0.021	1.20 ± 0.032
	5	0.71 ± 0.007	0.94 ± 0.043	1.08 ± 0.022	0.44 ± 0.020	1.30 ± 0.013	0.59 ± 0.014

*The mean ± SD, n = 3.

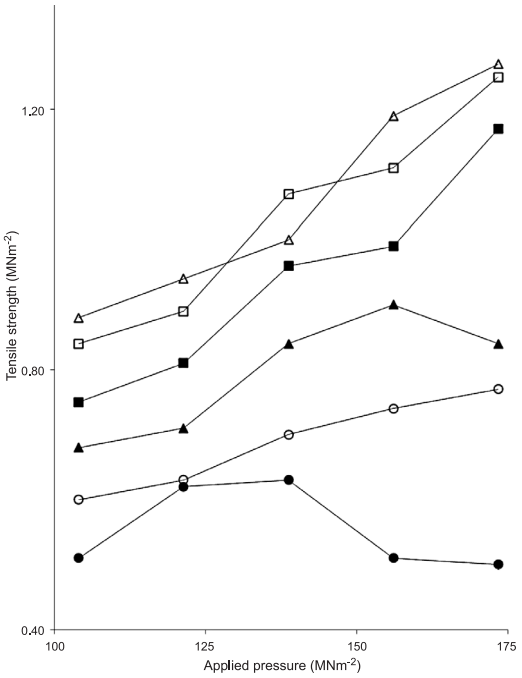

Figure 1. Plots of tensile strength against applied pressure for paracetamol formulations containing 5% w/w disintegrant. TPS (●), FTM (■), GTM (▲) for intragranular disintegrant and TPS (○), FTM (□), GTM (△) for extragranular disintegrant

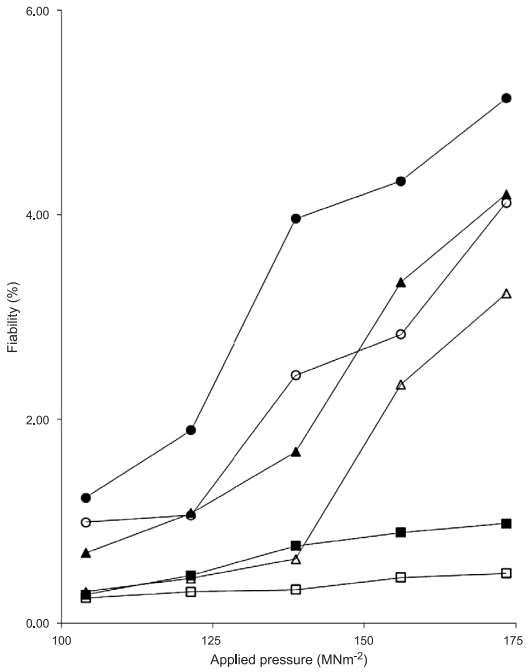

Figure 2. Plots of friability against applied pressure for paracetamol formulations containing 5% $^{w}/_{w}$ disintegrant. TPS (●), FTM (■), GTM (▲) for intragranular disintegrant and TPS (○), FTM (□), GTM (△) for extragranular disintegrant

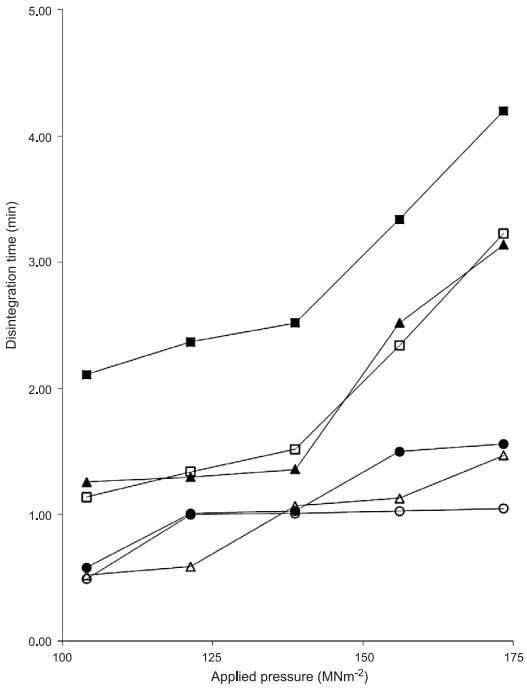

Figure 3. Plots of disintegration time againts applied pressure for paracetamol formulations containing 5% $^{w}/_{w}$ disintegrant. TPS (●), FTM (■), GTM (▲) for intragranular disintegrant and TPS (○), FTM (□), GTM (△) for extragranular disintegrant

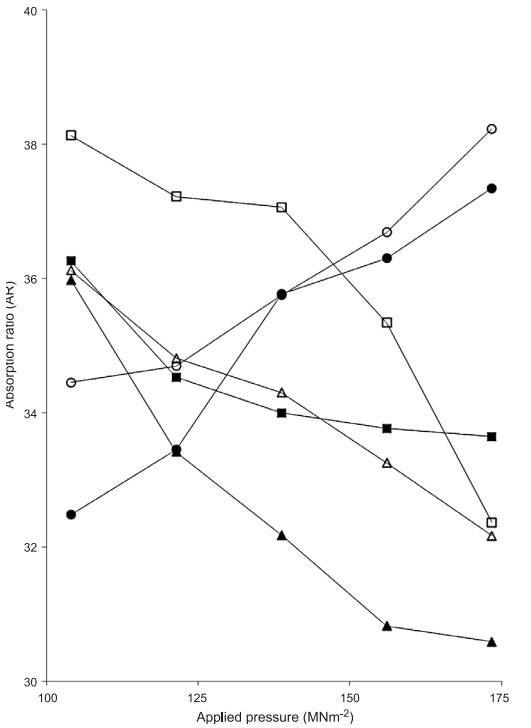

Figure 4. Plots of absorption ratio against applied pressure for paracetamol formulations containing 5% $^{w}/_{w}$ disintegrant. TPS (●), FTM (■), GTM (▲) for intragranular disintegrant and TPS (○), FTM (□), GTM (△) for extragranular disintegrant

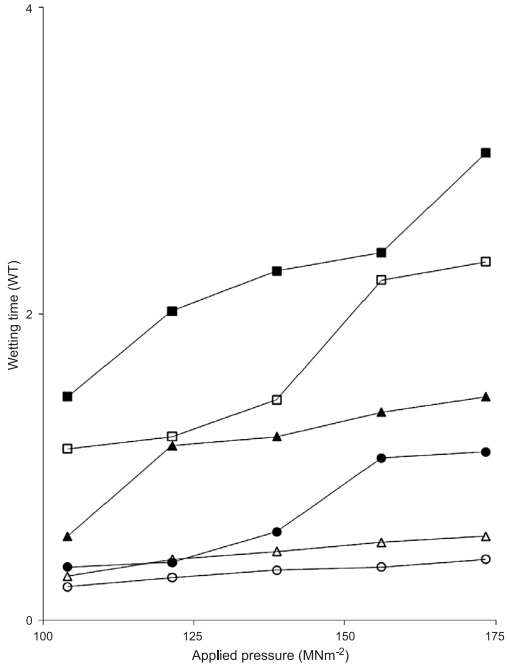

Figure 5. Plots of wetting time against applied pressure for paracetamol formulations containing 5% $^{W}/_{W}$ disintegrant. TPS (●), FTM (■), GTM (▲) for intragranular disintegrant and TPS (○), FTM (□), GTM (△) for extragranular disintegrant

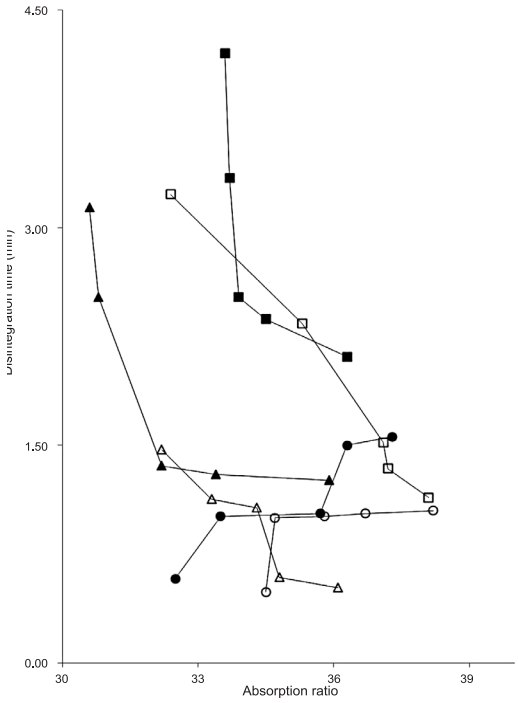

Figure 6. Plots of absorption ratio against disintegration time for paracetamol formulations containing 5% $^{W}/_{W}$ disintegrant. TPS (●), FTM (■), GTM (▲) for intragranular disintegrant and TPS (○), FTM (□), GTM (△) for extragranular disintegrant

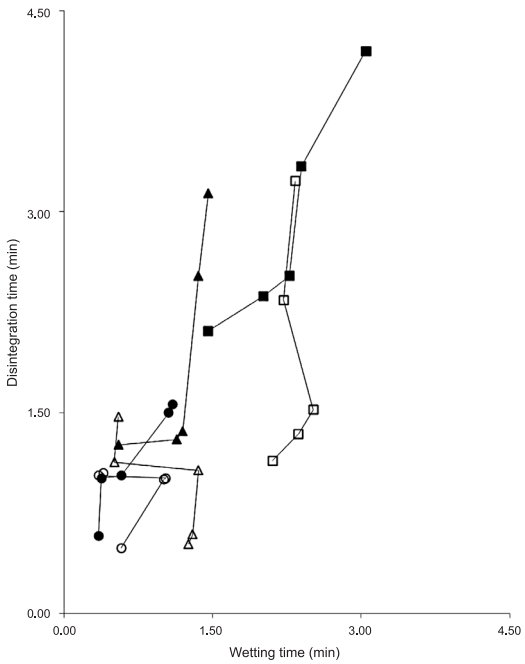

Figure 7. Plots of wetting time against disintegration time for paracetamol formulations containing 5% w/w disintegrant. TPS (●), FTM (■), GTM (▲) for intragranular disintegrant and TPS (○), FTM (□), GTM (△) for extragranular disintegrant

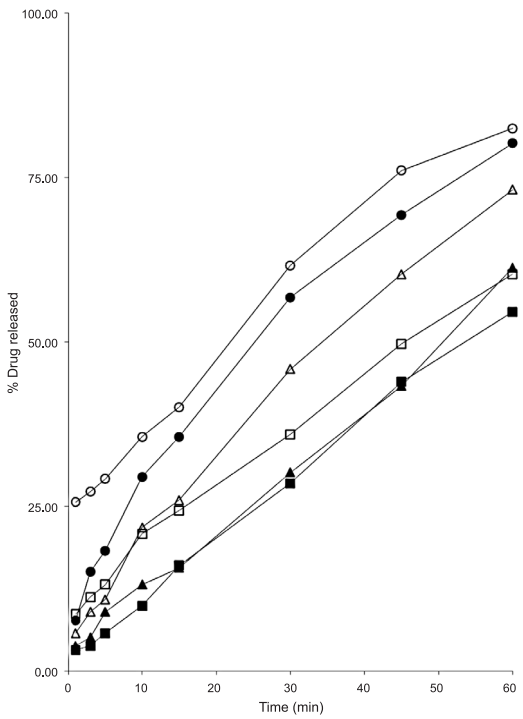

Figure 8. Plots of % drug released against time for paracetamol formulations containing 3% $^{W}/_{W}$ disintegrant. TPS (●), FTM (■), GTM (▲) for intragranular disintegrant and TPS (○), FTM (□), GTM (△) for extragranular disintegrant

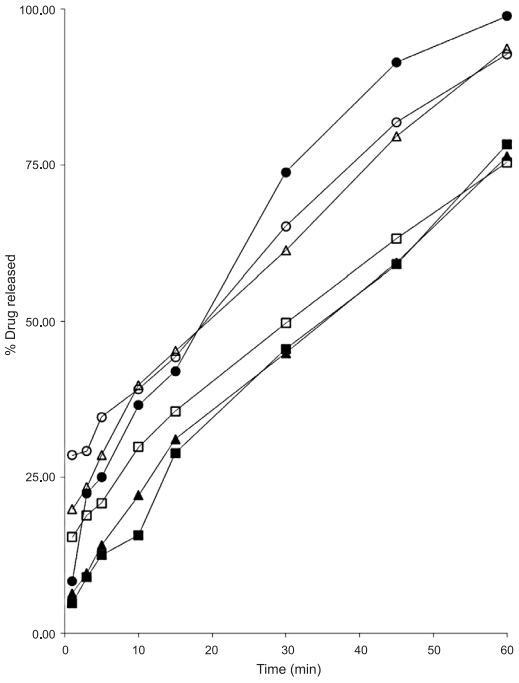

Figure 9. Plots of % drug released against time for paracetamol formulations containing 5% $^{w}/_{w}$ disintegrant. TPS (●), FTM (■), GTM (▲) for intragranular disintegrant and TPS (○), FTM (□), GTM (△) for extragranular disintegrant

Preparation of granules

Three hundred grams batches of paracetamol granules containing different concentrations of the disintegrants added as intragranular or extragranular disintegrants were prepared by the wet granulation method of massing and screening. The granules containing intragranular disintegrant were prepared by dry mixing the required quantities of paracetamol, lactose and the disintegrant for each batch for 5 min in a Hobart planetary mixer (Hobart Canada Inc., Don Mill, ON, Canada) and then moistening them with the corn starch binder mucilage. Wet massing continued for 5 min before the resulting wet masses were granulated by passing them through a sieve size 1400 µm, dried at 60°C for 2 h in a hot air oven. The dried granules were then re-sieved through a sieve size 1000 µm after which they were stored in airtight containers (14).

Granules containing extragranular disintegrants were prepared by dry mixing the required quantities of paracetamol and lactose for each batch for 5 min in a Hobart planetary mixer. The blend was then moistened with the corn starch binder mucilage. Wet massing was carried out for 5 min, after which the wet masses were granulated by passing them through a sieve size 1400 µm, dried at 60°C for 2 h in a hot air oven and then re-sieved through a sieve size 1000 µm. The required amount of disintegrant was added and adequately mixed with the granules before storage in an airtight container (14).

Preparation of tablets

Quantities (555 mg) of granules from each batch were compressed for 30 s into tablets with predetermined loads (104.04, 121.38, 138.72, 156.06 and 173. 40 MNm^{-2}) on a Carver hydraulic hand press (Carver, USA) using a 12 mm die and flat-faced punches lubricated with a 2% w/v dispersion of magnesium stearate and talc (1 : 1) in acetone before each compression. After ejection, the tablets were stored over silica gel for 24 h to allow for elastic recovery and hardening and to prevent falsely low yield values during analysis.

Determination of tablet crushing strength and friability

The tablet crushing strength was determined using the Erweka digital hardness tester (G.B. CALEVA, Dorset, England). The percent friability (FR) of the tablets was determined using the Roche friabilator (Erweka Apparatebau, Germany) operated at 25 rpm for 4 min.

Measurement of water absorption ratio and wetting time

The water absorption ratio was determined according to the method described by Battu et al. (15), while the wetting time (WT) was determined according to the method described by Bi et al. (16). All determinations were done in triplicate and the mean values were taken.

Disintegration test

Tablet disintegration time (DT) was determined in distilled water at 37 ± 0.5°C in a B.P. Manesty (Manesty Machines Ltd., Liverpool, UK) disintegration test unit. Six tablets at each compressional force were placed on the wire mesh just above the surface of the distilled water in the tube. The time taken for each tablet to disintegrate and all the granules to go through the wire mesh was recorded. Results were expressed as an average of three determinations.

Dissolution test

The dissolution rate of the relevant tablets was determined at 37 ± 0.5°C in 1 L of distilled water

using a Veego dissolution testing station (Veego Instruments Co., Mumbai, India) and a stirring speed of 100 rpm according to USP XXIII. The tablet was placed in the rotating basket and 5 mL of the medium was sampled with a pipette and filtered. The same quantity of the medium was added at the same temperature immediately after each sampling to keep the volume of the dissolution medium constant. The concentration of dissolved paracetamol in the medium was determined spectrophotometrically at 249 nm with a Unicam 8620 UV/Vis spectrophotometer (Pye Unicam, UK). All determinations were made in triplicate and the results are given as the mean values.

RESULTS AND DISCUSSION

Table 3 and Figures 1–3 show the mechanical and disintegration properties of formulations containing the native and novel disintegrants. A concentration and applied pressure dependent behavior was observed for all the parameters. An increase in disintegrant concentration in the formulations resulted in tablets with higher tensile strength, suggesting a positive disintegrant influence on the mechanical strength of the tablets. An increase in the tensile strength was also observed when the applied pressure was increased except for formulations containing intragranular TPS and GTM, where a decrease in tensile strength was observed after an initial period of increase. This decrease could be due to overcompaction at high compressional forces (17). A rank order of FTM > GTM > TPS and GTM > FTM > TPS were obtained for tensile strength for formulations containing intragranular and extragranular disintegrants, respectively. This suggests that the method of disintegrant incorporation into the formulation influenced the disintegrant's effect on mechanical strength of the tablets. The friability of the tablets was also observed to reduce with an increase in disintegrant (Table 3) with a rank order of FTM < GTM < TPS with formulations containing intragranular disintegrants being more friable that those with extragranular disintegrants. However, an increase in friability was observed with an increase in the applied pressure (Fig. 2) due to excessive expansion of the tablets after ejection from the die.
The disintegration time decreased as the concentration of the disintegrant in the formulation increased while it increased with increasing compressional force. The ability of the disintegrants to facilitate a disintegration time less than 1 min was observed

Table 4. Absorption ratio and wetting time values of tablets compressed at 121.38 MNm^{-2}.

Disintegrants	Disintegrant concentration (% w/w)	Absorption ratio (R)		Wetting time (min)	
		Intragranular	Extragranular	Intragranular	Extragranular
TPS	1	27.03 ± 0.132*	28.45 ± 0.310	1.52 ± 0.002	1.23 ± 0.001
	2	28.38 ± 0.072	31.42 ± 0.052	1.22 ± 0.006	1.08 ± 0.004
	3	31.85 ± 0.092	33.25 ± 0.112	1.08 ± 0.003	1.02 ± 0.002
	4	33.21 ± 0.102	34.19 ± 0.014	0.48 ± 0.002	0.39 ± 0.002
	5	33.45 ± 0.212	34.70 ± 0.116	0.38 ± 0.004	0.28 ± 0.003
FTM	1	22.68 ± 0.124	27.27 ± 0.011	4.12 ± 0.003	2.52 ± 0.004
	2	24.15 ± 0.047	29.20 ± 0.002	2.46 ± 0.005	2.30 ± 0.002
	3	32.16 ± 0.099	32.65 ± 0.010	2.34 ± 0.001	1.57 ± 0.003
	4	33.01 ± 0.082	34.75 ± 0.102	2.34 ± 0.001	1.44 ± 0.001
	5	34.53 ± 0.216	37.22 ± 0.073	2.02 ± 0.002	1.20 ± 0.003
GTM	1	25.33 ± 0.108	28.26 ± 0.427	2.58 ± 0.002	2.27 ± 0.001
	2	27.30 ± 0.106	28.99 ± 0.052	2.31 ± 0.001	1.53 ± 0.010
	3	29.50 ± 0.065	29.94 ± 0.061	1.47 ± 0.004	1.23 ± 0.007
	4	32.14 ± 0.081	34.28 ± 0.072	1.29 ± 0.003	0.57 ± 0.004
	5	33.42 ± 0.018	34.81 ± 0.013	1.14 ± 0.005	0.40 ± 0.002

*The mean ± SD, n = 3.

(Fig. 3) in formulations containing 5% w/w intragranular and extragranular TPS and extragranular GTM at applied compression force of = 121.38 MNm^{-2}. This suggests that the pressure applied in compressing the tablets would affect the activity of a disintegrant in an orally disintegrating tablet formulation. It is important to note that while the US FDA's (18) requirement for ODT is a disintegration time less than 30 s, scientific literature generally categorizes tablets with disintegration times of less than 1 min as ODT (10, 19–21). Furthermore, disintegration time less than 3 min in the mouth as observed in all formulations containing 5% w/w disintegrants except FTM at applied pressure = 156.06 MNm^{-2} and intragranular GTM at applied pressure = 173.40 MNm^{-2}, meets the requirements of the European Pharmacopoeia (22) for fast disintegrating tablets, which requires that fast disintegrating tablets should disintegrate in the mouth in less than three minutes. It was also observed that formulations containing extragranular disintegrants produced tablets with lower disintegration times (Table 3) when compared with their intragranular counterparts. This could be as a result of faster access to the disintegrating fluid, which would lead to a quicker wetting time and a subsequent faster initiation of the disintegration process in these formulations.

The absorption ratio (AR) and wetting time (WT) of the tablets containing the test disintegrants are shown in Table 4 and Figures 4 and 5. It was observed that the wetting time and absorption ratio were dependent on the type and concentration of the disintegrant used and the applied pressure. Generally, AR values increased with an increase in disintegrant concentration for native and novel disintegrants with formulations containing extragranular disintegrants absorbing more water that those containing intragranular disintegrants. This could be due the general ability of the disintegrant to facilitate water uptake into the tablet. The lower AR values of intragranular disintegrant could also be due to the presence of the disintegrant in the inner matrix of the tablets. A reduction in AR values with an increase in applied pressure (Fig. 4) was observed for formulations containing the novel disintegrants FTM and GTM, while the AR values of formulations containing TPS increased with applied pressure. The presence of water soluble mannitol in the novel disintegrants might have resulted in a reduced water requirement to overcome the stronger bonds formed at higher pressures. The rank order for water absorption is FTM > TPS > GTM. The tablet wetting time increased with increasing applied compression pressure. This could be due to a reduction in tablet porosity as the applied pressure increased. Formulations containing extragranular disintegrants had lower wetting times compared to their intragranular counterparts; probably due to a faster access of the disintegrant to the disintegrating fluid. A reduction in wetting time was also observed with an increase in disintegrant concentration with extragranular disintegrants facilitating faster wetting time. This could be due to the general ability of the disintegrant to facilitate a higher water absorption and the easy access of extragranular disintegrant to the disintegrating fluid.

Representative plots of disintegration time (at 5% w/w disintegrant concentration) against absorption ratio and wetting time are shown in Figures 6 and 7, respectively. It was observed that disintegration time reduced with increased water absorption for formulations containing FTM and GTM disintegrants while it increased in formulations containing TPS disintegrants. This suggests a different mechanism of disintegration in coprocessed disintegrants whereby the water soluble mannitol allows for a faster water absorption and subsequent swelling of the tapioca starch component. Thus, ODTs containing GTM and FTM disintegrants would have a reduced disintegrating fluid requirement and the ability to optimize the low volume of saliva (normal flow of about 0.1 to 0.2 mL/min, reaching 7 mL/min on stimulation) present in the oral cavity to facilitate their oral disintegration (22). On the other hand, formulations containing TPS, whose mechanism of disintegration was only by water uptake and swelling, will require a higher amount of water to facilitate disintegration since the dissolution effect of mannitol will be absent. It was also observed that an increase in wetting time increased the disintegration time for all formulations containing intragranular disintegrants while it had no influence on formulations containing extragranular disintegrant at applied compressional pressure greater than 138.72 MNm^{-2}.

Figures 8 and 9 show the dissolution behavior of the formulations (3 and 5% w/w, respectively) as percent drug release against time for 60 min. It was observed that tablets containing extra-granular disintegrants produced an initial burst effect, which resulted in the availability of a higher amount of the drug in the dissolution medium within 5 min. This could be as a result of the faster disintegration time of the tablets prepared with extra-granular disintegrants and the reduced access to water expected with intra-granular disintegrants located within the matrix of the tablets, which would result in reduced disintegration and drug release. It was also observed at disintegrant concentration of 5% w/w that the extra-granular addition of TPS and FTM disintegrants facilitated a faster

availability of the drug, while the total amount of drug released after 60 min was higher in tablets containing intragranular disintegrants. This could be due to the continued ability of the disintegrant present within the inner matrix of the tablet prepared with intragranular disintegrant to facilitate drug release from granules after the initial disintegration of the tablets into granules. The fact that this effect occurred at higher concentration of disintegrants with higher swelling index (i.e., FTM > TPS > GTM as presented in Table 2), implies the strong influence of the swelling ability of the disintegrant on the drug release pattern. It also suggests that there could be a change in the mechanism of drug release at high concentrations, when different methods of disintegrant inclusion into formulations are employed.

The type of disintegrants (i.e., co-ground, co-fused or native) also affected the dissolution profiles of the formulations. It was observed that tablets prepared with TPS facilitated the release of the highest amount of the drug from the tablets, followed by GTM and FTM, respectively. This ranking further supports that of the disintegration time obtained and suggests the strong influence of a fast disintegration time on drug release from the tablet matrix.

CONCLUSION

From the results obtained from the study, it can be concluded that:

The method employed in coprocessing excipients would affect the properties of the excipients and the effect they have on the formulations in which they are used.

The coprocessed disintegrants consisting of native tapioca starch and mannitol, when used in the formulation tablets would enhance the mechanical properties of the resulting tablets.

The rate/amount of water ingress into the tablets and disintegration time would be limiting factors in early onset of drug dissolution and bioavailability.

Coprocessed disintegrants consisting of native tapioca starch and mannitol would be effective disintegrants in the formulation of orally disintegrating tablets with disintegration times of less than 1 min without compromising the mechanical properties of the tablets.

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