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Development of Directly Compressible Excipients from Phoenix dactylifera (Date) Mucilage and Microcrystalline Cellulose using Co-Processing Techniques

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ABSTRACT

The objective of this study was to harness the excipient potential of date mucilage by co-grinding and co-fusing with avicel for enhanced performance in the direct-compression of metronidazole.

Co-grinding and co-fusing of parent polymers were done using established methods and excipients were used in the direct-compression of metronidazole tablets.

The shape and surface morphology of the particles of date mucilage (DAM) and co-processed excipients were generally granular, rough and irregular. There was a significant improvement in the disintegration of tablets prepared using the co-processed excipients in comparison to that prepared using DAM alone. The disintegration time for tablets prepared using co-fused excipients was lower than that of co-grinded additives although the differences were not significant ($p > 0.05$).

Generally, the co-processed excipients improved the mechanical and disintegration properties of the tablets produced compared to tablets prepared using DAM alone and could be further developed as direct-compression excipients.

Keywords: Date mucilage, avicel, co-processing, metronidazole tablets.

INTRODUCTION

Excipient functionality has been expanded by direct compression process and the need to use high-speed equipment in tablet manufacturing. The increase in the speed of tableting machinery requires the use of excipients that can offer high weight consistency and good compressibility[1]. In addition, new drug moieties with unpredictable physicochemical and stability properties are constantly being introduced and existing adjuvants like microcrystalline cellulose loses compaction

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upon wet granulation and demonstrates poor die filling as a result of agglomeration[2]. There is therefore a need to search for newer excipients or prepare novel ones from existing forms. Furthermore, direct compression is the preferred method for the preparation of tablets due to reduced processing steps, faster processing, usefulness for substances having high moisture sensitivity and cost[3].

One of the methods of obtaining functional excipients having direct-compression properties with inherent ability to demonstrate the properties of two or more excipients is co-processing. IPEC[4] has described a co-processed additive as any excipient obtained by combining two or more materials together using physical methods to modify their properties without any chemical alteration. The starting materials may be compendia or non-compendia excipients. Co-processed excipients are prepared by incorporating one excipient into the particle structure of another, using processes such as co-drying, co-grinding and co-fusion. Co-processing is involved with particle manipulation of two or more existing excipients in which the interaction occurs at sub-particulate level yielding simple physical mixtures and no chemical changes are expected to occur[5]. A synergy is obtained between the particles of the participant excipients with ultimate functionality improvements, concealing undesirable properties[5]. Co-processing has been found to be easy, cost-effective and has also been used to improve stability, wettability, solubility and gelling properties of food and pharmaceutical excipients[6]. For example, Cellactose® is a co-processed product from the combination of cellulose (25 %) and lactose monohydrate (75 %); it has good flowability and good compactibility. The compactibility has been attributed to a synergistic effect of consolidation by fragmentation of lactose and plastic deformation of cellulose[7]. It has been pointed out that cellactose® exhibits dual consolidation behaviour since it contains a fragmenting component (lactose) and a substance (cellulose) that consolidates mainly by plastic deformation[8]. Furthermore, co-processed excipients find application in drug delivery systems by enhancing the pharmaceutical properties of the dosage forms such as accurate dosing hence improving therapeutic efficacy and further patient compliance[9].

Phoenix dactylifera popularly known as date (also called Nakhla and 'tree of life' by the Arabs, Nigerian local name in Hausa-Dabino) is a member of the palm family Arecaceae or Palmae[10]. It has been reported that date palm has its origin in countries with a coastline on the Persian Gulf such as Kuwait, Omar, Qatar, Bahrain, Iraq, Saudi Arabia and UAE[11].

The date palm *(Phoenix dactylifera L.)* is one of the oldest cultivated fruit trees and has been used as staple food in the Middle East for over 6000 years[12]. Dates and their constituents show a role in the prevention of diseases through anti-oxidant[13], anti-inflammatory and anti-bacterial activity[14]. Rahmani et al., also reported the therapeutic effects of date fruits in the prevention of cancer via modulation of anti-tumour activity[15]. Dates can be classified as foods with low glycaemic index most likely due to the high amount of fructose[16]. This has made date fruit a useful aid in diabetic management and its use has been reported to reduce HbA1c[16]. *Phoenix dactylifera* is known to contain high concentration of polysaccharides, proteins, fats and edible fibre[17].

The presence of polysaccharides, safety, availability and usefulness as food has made dates to be of interest in excipient development for pharmaceuticals. Ngwuluka et al., studied the binding potentials of the dried and milled pulp of the fruit[18] but the excipient potentials of date fruit mucilage have remained largely unharnessed. Mucilage is the polymeric slimy material which is a normal product of cell wall and is readily available in certain fruits. Ajala et al., studied the binding potentials of *Chrysophylum albidum* fruit mucilage and reported that it induces faster onset of plastic deformation and higher amount of total plastic deformation but produced tablets with lower tensile strength and faster drug release properties than methylcellulose[19]. In this study, the mucilage of date fruit was extracted and purified by established methods[20] and preliminary studies on the tableted mucilage showed very hard tablets with disintegration times greater than 1 h. Co-processing of this novel mucilage with microcrystalline cellulose was explored using co-grinding and co-fusion methods in order to improve the disintegration properties. The products of the co-processing techniques were then used for direct compression of metronidazole tablets.

METHODOLOGY

Materials

Metronidazole powder was obtained from Suixian Hengtai Biotechnology Co., Ltd. China Mainland; Microcrystalline cellulose (Avicel® PH-101) was obtained from FPC Bio polymer, USA; all other reagents were of analytical grade.

Extraction and purification of mucilage from dried date fruits

The method of *Ajala et al*, was used with modification[19]. Dried fruits of *Phoenix dactylifera* were deseeded, cut into pieces and soaked in chloroform-water Double Strength for 36 h. This was then sieved with a muslin cloth to remove the extraneous matter. Ethanol (90 $\%^{v}/_{v}$) was then used to precipitate the mucilage and further purification was done using di-ethyl ether. The mucilage was then dried at 40 °C in a hot air oven and coded DAM i.e. date mucilage.

Co-processing of excipients

The co-excipients were prepared using two methods (co-grinding and co-fusion) as described below: Date mucilage (DAM) and avicel® (AV) were weighed according

to the proportional quantities (25:75, 33:67 and 50:50) in the respective batch. The weighed quantities of the DAM and AV were triturated together using a porcelain mortar and pestle for 10 min to ensure uniform size reduction and powder mixing. The resulting product was further screened using a sieve of mesh size 0.25 mm to reduce the particle size. The method was repeated for each batch to obtain the co-grinded excipients and coded DAMAV. For the co-fused excipients, a weighed amount of DAM according to the proportions (25 %) calculated was made into a paste using distilled water. Appropriate quantity (75 %) of AV was also premixed with distilled water and added to the dispersed DAM in aliquots. The mixture was stirred occasionally on a water bath until a homogenous mixture was observed. This process was repeated for the remaining batches (33:67 and 50:50). The paste obtained was spread evenly on a slab and dried in a hot air oven (Model 77-9083, Techmel & Techmel, China) at 50 °C. It was later pulverized with mortar and pestle and the particle size was further reduced by using a sieve of mesh size 0.25 mm.

Swelling capacity

Co-processed excipients (5 g) were transferred into a 50 mL measuring cylinder and the volume occupied was noted. Distilled water was then added gradually making up to 50 mL with thorough agitation for 5 min. The dispersion was allowed to stand for 24 h. The sedimentation volume was measured and swelling capacity was calculated using equation 1.

$$\text{Swelling capacity} = \frac{V2 - V1}{V1} * 100$$

(V_1: initial volume, V_2: final volume) (1)

Determination of particle density

The particle density of the excipients was determined by the liquid-pycnometer method using xylene as the displacement liquid[21]. An empty 50 mL pycnometer bottle with its lid was weighed empty (W), it was then overfilled with xylene and covered with the lid, wiped off the excess and weighed (W1). The sample of excipient (2 g) was weighed (W3) and transferred into the pycnometer bottle, covered with the lid and excess xylene wiped off the surface of the bottle. This was weighed again (W4). The particle density was then calculated using equation 2.

$$\text{Particle density} = \frac{W2 * W3}{50\{(W3 - W4) + (W2 - W)\}} \quad (2)$$

Determination of bulk and tapped densities

The bulk density of the excipients was determined by weighing 10 g of the sample and transferring it at an angle of 45° through a funnel into a 100 mL glass measuring cylinder with a diameter of 3.0 cm The height reached by the powder was recorded and the volume and density were then calculated[22].

$$\text{Bulk density} = \frac{m}{\pi r2h} \quad (3)$$

where:

m = weight of the sample in the cylinder,

r = radius of the cylinder,

h = height of the sample in the cylinder.

The method of Reus-Medina[23] was used in evaluating the tapped volume and density using a weighed quantity (10 g) of the excipients. Tapping rate was standardized with 38 taps per minute and a total of 250 taps was applied to the material in a graduated glass cylinder. The height, h (cm) of the powder bed and the internal radius, r (cm) of the measuring cylinder were utilized in the computation of the volumes obtained.

The Carr's index[24] and Hausner's ratio[25] were computed from the bulk and tapped densities using the formula below in equations below:

$$\text{Carr's index} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} * 100 \quad (4)$$

$$\text{Hausner's ratio} = \frac{\text{Tapped volume}}{\text{Bulk volume}} \quad (5)$$

Determination of angle of repose

Weighed quantities of each excipient (5 g) were poured slowly through a funnel under the force of gravity to form a conical heap[26]. The angle of repose was then calculated as:

$$\text{Angle of repose } (\tan\theta) = \frac{h}{r} \quad (6)$$

Where

h= height of powder heap

r = radius of the cylinder used.

Preparation of powder mix and tablets

Powder mixtures for tablet compression were prepared using drug-excipient ratio of 1:1. The weighed quantities of excipient and metronidazole were mixed for 5 min in a porcelain mortar. It was then transferred into screw-capped bottles and placed in the rotomixer (VSF3843C Forster equipment Co. Ltd, Whetstone, Leicester, England) for 10 min to ensure efficient mixing.

The powder mixtures produced above were compressed into tablets using a single punch Carver hydraulic hand press (Model C, Carver Inc., Menomonee Falls, Wis-

consin, USA) at different pressures. Tablets of 400 mg were compressed for 30 secs at varying pressures using a die of 10.5 mm in diameter. Magnesium stearate dispersion (1 $\%^{w}/_{v}$) in acetone was used to lubricate the die and punch surfaces before compressing the tablets. Compressed tablets were stored in a dessicator containing silica gel for 24 h before conducting tablet evaluation.

Mechanical Properties

The crushing strength-friability ratios (Cs/Fr) of the tablets were calculated from the values of crushing strength and friability.

The crushing strength (Cs) test was carried out using a hardness tester (MHT-100, Model P&M 01, Pharma Alliance Group, Indonesia). Five tablets were selected at random from each batch. Each tablet was placed between the anvil and the spindle of the hardness tester. The force at which the tablet cracked into two halves was then recorded, and the mean from each batch was calculated.

The friability (Fr) test for tablets was carried out using a friabilator (DBK instruments, Mumbai-6, model 40FTA01, India). Ten tablets (10) were selected at random from each batch, weighed with the aid of a weighing balance and then transferred into the drum of a friabilator. The device was operated at a speed of 25 rpm for 4 min. The tablets were removed, dusted, reweighed and the percentage loss calculated.

Disintegration time

The disintegration test was carried out using the DBK disintegration testing apparatus (Type 40TDA01, India). Six tablets were selected at random from each batch and placed on the mesh of the disintegrating apparatus, the disintegration time (Dt) of the tablets was determined in distilled water at 37 ± 0.5 °C. The time taken for tablet to disintegrate and pass through the mesh was recorded.

Disintegration efficiency ratio

The disintegration efficiency ratio (DER)[27] for the tablets was calculated as a ratio of Cs, Fr and Dt as shown in the equation the equation below:

$$DER = \frac{Cs/Fr}{Dt} \quad (7)$$

where

Cs: crushing strength

Fr: friability

Dt: disintegration time.

Compression behavior of the excipients

The compression behavior of the excipients was evaluated using Heckel equation and the plots of LN{1/(1-D)} versus applied pressure for co-grinded and co-fused excipients and the parent polymers are expressed in Figures 8 & 9 while parameters derived from the plots are presented in Table 5.

Statistical analysis

Most of the tests were done in triplicate but crushing strength, friability and disintegration time tests had n=5, 10 and 6 respectively. The results were reported as mean ± SD except where values were derived by calculation like Cs/Fr and DER. Comparison of means were done using the students't-test and significance levels determined at $p < 0.05$.

RESULTS AND DISCUSSION

Co-processing of date mucilage and Avicel® produced co-excipients which were used for direct compression of metronidazole tablets. The material properties of the parent polymers (date mucilage and Avicel®) and co-excipients are presented in Tables 1 and 2 respectively. The densities for DAM were greater than that of AV. Both materials had poor flow as shown from the Carr's index and angle of repose; although the Hausner's ratio for DAM seemed to show that its flow improved compared to that of AV but other parameters did not confirm this. The particle density of co-grinded excipients reduced with increased amount of DAM while tapped density generally increased, however, bulk density showed no trend. The co-fused excipients showed increased pattern for bulk and tapped densities with increasing quantities of DAM while the particle density showed no particular trend. The Carr's index and Hausner's ratio for both co-grinded and co-fused excipients also showed no particular order. In addition, DAM had significantly higher ($p < 0.01$) swelling index compared to AV.

Table 1. Material properties of date mucilage and Avicel® used to prepare co-processed excipients

Parameter	DAM	AV
Particle density	1.307 ± 0.023	1.136 ± 0.034
Bulk density	0.571 ± 0.001	0.357 ± 0.004
Tapped density	0.634 ± 0.031	0.534 ± 0.042
Carr's index	25.034 ± 1.203	33.180 ± 2.034
Hausner's ratio	1.109 ± 0.233	1.496 ± 0.745
Angle of repose	69.650 ± 2.045	54.210 ± 3.002
Swelling index	92.170 ± 1.356	13.001 ± 2.114

The scanning electron micrographs (SEM) of Avicel® is not shown being a standard material which is well known and has been reported to be irregular in shape[28]. The SEM of DAM is shown in Figure 1, while that of co-grinded and co-fused excipients is shown in Figures 2 and 3 respectively. The shape and surface morphology of the particles were generally granular and rough and DAM showed irregularly shaped particles with rough surfaces. Adetunji et al.,[29] co-processed *Cedrela odorata* gum with plantain starch and microcrystalline cellulose in order to enhance the material, flow and compressional properties. The study reported that the co-processed excipients produced varying degrees of sphericity identified as oval, cylindrical or irregular.

In this study, the particle shape of the parent polymers was irregular and the co-processed excipients generally exhibited irregular shapes. However, the co-fused excipients offered some degree of sphericity which reduced as the concentration of DAM increased. This agrees with the study of Rahmati et al.,[30] which reported that the methods employed in particle processing affects the morphological outcome of the resulting excipients.

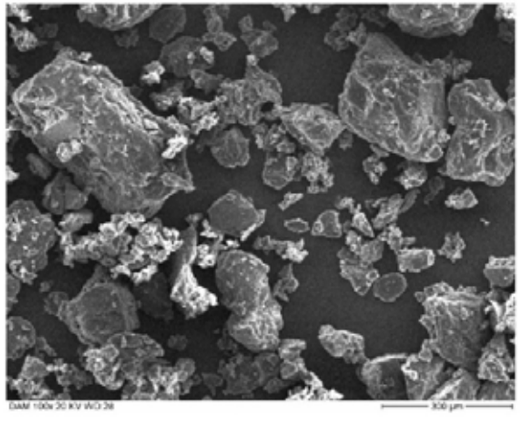

Figure 1. SEM of Date mucilage (DAM) X100.

Figure 2. SEM of co-processed excipients prepared using co-grinding method (A-25% DAM, B-33% DAM, C-50% DAM) X150

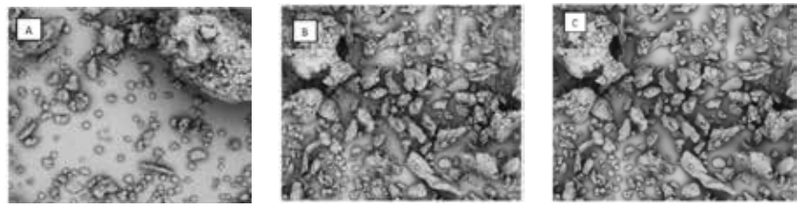

Figure 3. SEM of co-processed excipients prepared using co-fusion method (A-25% DAM, B-33% DAM, C-50% DAM) X200

Table 2. Material properties of co-processed excipients

Parameter	Amount of DAM ($\%^{w}/_{w}$)	Amount of AV ($\%^{w}/_{w}$)	Method of co-processing	
			Co-grinding	Co-fusion
Particle density	25.0	75.0	1.663 ± 0.018	1.562 ± 0.006
	33.0	67.0	1.504 ± 0.030	1.733 ± 0.001
	50.0	50.0	1.408 ± 0.009	1.541 ± 0.001
Bulk density	25.0	75.0	0.297 ± 0.001	0.349 ± 0.004
	33.0	67.0	0.276 ± 0.003	0.411 ± 0.007
	50.0	50.0	0.399 ± 0.001	0.481 ± 0.008
Tapped density	25.0	75.0	0.361 ± 0.002	0.478 ± 0.006
	33.0	67.0	0.360 ± 0.005	0.524 ± 0.013
	50.0	50.0	0.506 ± 0.007	0.649 ± 0.006
Carr's index	25.0	75.0	11.81 ± 0.042	26.881 ± 0.071
	33.0	67.0	23.28 ± 0.021	27.36 ± 0.219
	50.0	50.0	21.14 ± 0.071	25.822 ± 0.078
Hausner's ratio	25.0	75.0	0.812 ± 0.005	0.731 ± 0.023
	33.0	67.0	0.761 ± 0.008	0.785 ± 0.006
	50.0	50.0	0.789 ± 0.002	0.741 ± 0.009
Angle of repose	25.0	75.0	59.62 ± 0.011	66.381± 0.113
	33.0	67.0	59.870 ± 0.042	57.322 ± 0.071
	50.0	50.0	60.500 ± 0.092	56.102 ± 0.069
Swelling index	25.0	75.0	162.600 ± 0.177	134.403 ± 0.048
	33.0	67.0	86.670 ± 0.042	150.003 ± 0.227
	50.0	50.0	82.700 ± 0.007	275.001 ± 0.527

The mechanical and disintegration properties of metronidazole tablets prepared using co-grinded and co-fused excipients are presented in Tables 3 and 4 respectively while Figures 4 and 5 showed the effect of relative density on crushing strength of tablets made from co-grinded and co-fused excipients; and Figures 6 and 7 showed the effect of relative density on the friability of tablets prepared from co-grinded and co-fused excipients respectively. The crushing strength of tablets produced using co-grinded and co-fused excipients increased with relative density. Generally, the Cs of tablets produced using co-grinded (CG) excipient was higher than that of co-fused (CF) while Avicel® produced tablets with higher Cs in comparison with that of the co-grinded excipient (AV > CG > CF). It was observed that the relative density of tablets prepared using 100 % DAM were higher than that for other excipients. This could be because as seen in Table 1, the density of DAM is greater than that of AV and its presence within the tablet could confer higher density to them. It also implies that using DAM alone as a direct-compression excipient will require higher compaction forces to produce tablets with appreciable crushing strength compared to Avicel® which requires low compression pressure to impact higher hardness on tablets. The lowest values of Cs were obtained with excipient containing 50 % DAM irrespective of co-processing method while those containing 25 and 33 % DAM had higher crushing strength. This indicates that when stronger tablets are required, lower concentrations (< 50 %) of DAM in the co-excipient will be more valuable. Tablets produced with 100 % DAM and 100 % AV generally had acceptable friability which were significantly ($p<0.05$) lower compared to the co-processed excipients. The friability values in all cases reduced with increase in relative density. The ranking of friability among co-grinded excipients was 25 % DAM < 50 % DAM < 33 % DAM while for co-fused excipients, the order was 33 % DAM < 25 % DAM < 50 % DAM. The strength and weakness of the tablets were influenced by the concentration of DAM and the method of co-processing adopted.

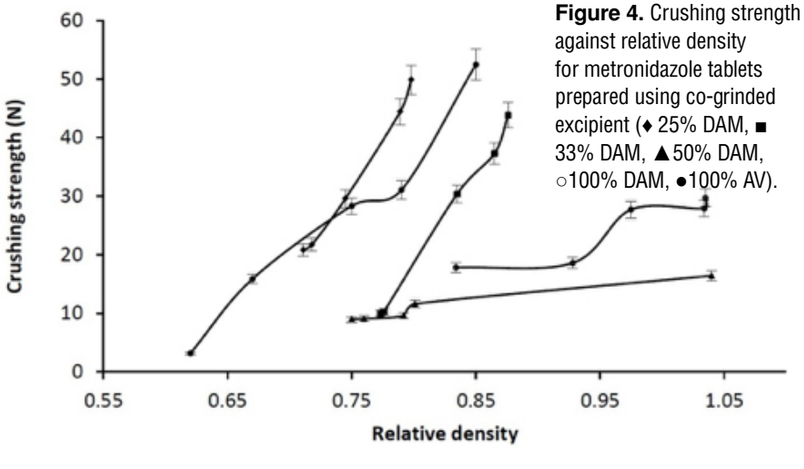

Figure 4. Crushing strength against relative density for metronidazole tablets prepared using co-grinded excipient (♦ 25% DAM, ■ 33% DAM, ▲50% DAM, ○100% DAM, ●100% AV).

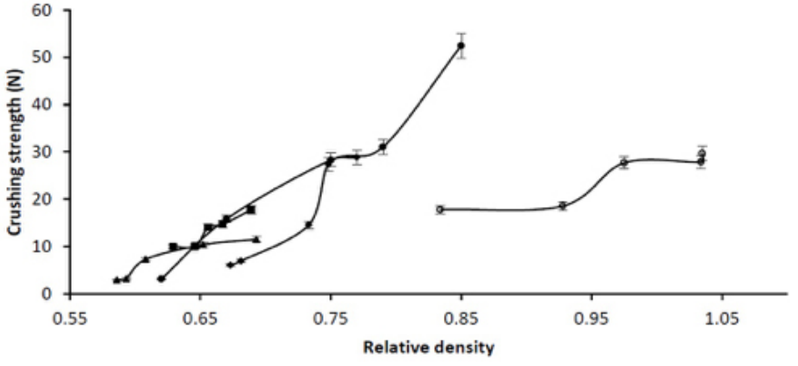

Figure 5. Crushing strength against relative density for metronidazole tablets prepared using co-fused excipient (♦ 25% DAM, ■ 33% DAM, ▲50% DAM, ○100% DAM, ●100% AV).

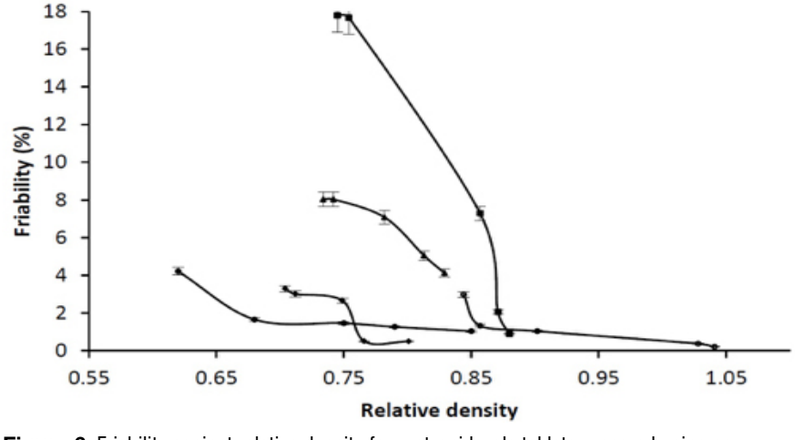

Figure 6. Friability against relative density for metronidazole tablets prepared using co-grinded excipient (♦ 25% DAM, ■ 33% DAM, ▲50% DAM, ○100% DAM, ●100% AV).

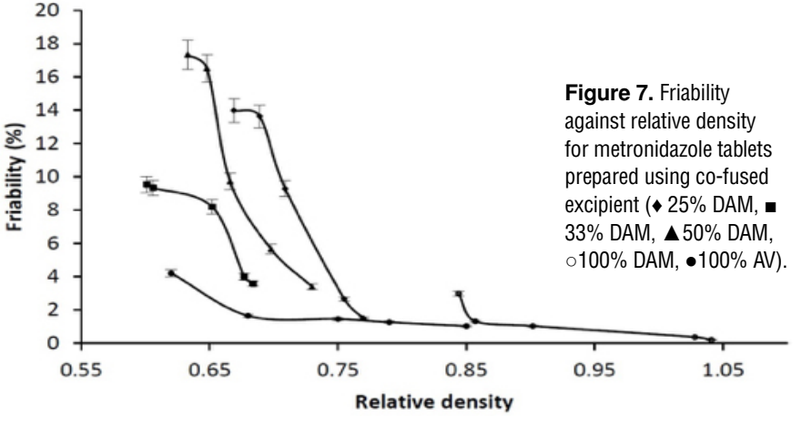

Figure 7. Friability against relative density for metronidazole tablets prepared using co-fused excipient (♦ 25% DAM, ■ 33% DAM, ▲50% DAM, ○100% DAM, ●100% AV).

Table 3. Mechanical and disintegration properties of metronidazole tablets prepared using co-grinded excipient

Applied pressure	Amount of DAM (%$^{w}/_{w}$)	Amount of AV (%$^{w}/_{w}$)	Cs/Fr	Dt (min)	DER
56.62	0.0	100.0	9.606	0.210 ± 0.010	45.743
84.92			19.397	1.120 ± 0.004	17.319
99.08			24.659	1.220 ± 0.006	20.212
113.23			50.951	1.540 ± 0.010	33.085
56.62	25.0	75.0	16.699	0.211 ± 0.003	79.142
84.92			23.307	0.262 ± 0.001	88.958
99.08			34.707	0.267 ± 0.001	129.989
113.23			45.762	0.300 ± 0.001	152.540
56.62	33.0	67.0	5.189	0.367 ± 0.001	14.139
84.92			17.572	0.383 ± 0.001	45.880
99.08			30.806	0.392 ± 0.002	78.587
113.23			49.801	0.500 ± 0.033	99.602
56.62	50.0	50.0	2.135	0.288 ± 0.004	7.413
84.92			3.542	0.393 ± 0.002	9.013
99.08			10.642	0.417 ± 0.001	25.520
113.23			26.934	0.419 ± 0.016	64.282
56.62	100.0	0.0	8.990	17.560 ± 0.015	0.512
84.92			14.091	25.340 ± 0.056	0.556
99.08			26.893	25.670 ± 0.059	1.048
113.23			75.405	39.410 ± 0.065	1.913

Table 4. Mechanical and disintegration properties of metronidazole tablets prepared using co-fused excipient

Applied pressure	Amount of DAM (%$^{w}/_{w}$)	Amount of AV (%$^{w}/_{w}$)	Cs/Fr	Dt	DER
56.62	0.0	100.0	9.606	0.210 ± 0.010	45.743
84.92			19.397	1.120 ± 0.004	17.319
99.08			24.659	1.220 ± 0.006	20.212
113.23			50.951	1.540 ± 0.010	33.085
56.62	25.0	75.0	1.915	0.200 ± 0.002	9.575
84.92			7.565	0.200 ± 0.001	37.825
99.08			35.621	0.222 ± 0.008	160.455
113.23			41.286	0.227 ± 0.007	181.877
56.62	33.0	67.0	12.287	0.201 ± 0.002	61.129
84.92			15.161	0.300 ± 0.030	50.537
99.08			36.75	0.318 ± 0.001	115.566
113.23			49.444	0.330 ± 0.002	149.830
56.62	50.0	50.0	0.388	0.233 ± 0.023	1.665
84.92			3.712	0.300 ± 0.015	12.373
99.08			9.204	0.320 ± 0.004	28.763
113.23			33.906	0.330 ± 0.001	102.745
56.62	100.0	0.0	8.990	17.560 ± 0.015	0.512
84.92			14.091	25.340 ± 0.056	0.556
99.08			26.893	25.670 ± 0.059	1.048
113.23			75.405	39.410 ± 0.065	1.913

Generally, the mechanical properties depicted by Cs/Fr increased with increase in applied pressure and tablets prepared with co-grinded excipient containing 33 % DAM had the highest values at the highest pressure, while 50 % showed the least at all pressures. For the Cs/Fr, the concentration of DAM in the co-processed product increased the tablet mechanical property up to a point and a further increase to 50 % reduced it. An increase from zero percent date mucilage to 25 % caused a significant increase in tablet strength except at the highest pressure. Tablets prepared with 100 % DAM all failed the disintegration time test but co-processing with AV yielded disintegration times less than 1 min showing a significant improvement on the disintegration profile of the tablets. Disintegration efficiency ratio is a measure of the balance between mechanical and disintegration properties of tablets[27]. The DER of tablets prepared using 0 % DAM reduced with compression pressure except for the highest pressure while other concentrations increased with increase in applied pressure. Co-grinded excipient containing 25 % DAM showed optimal DER while 50 % showed least. Generally, tablets containing 100 % DAM showed significantly lower ($p < 0.01$) values of DER compared to the other concentrations.

The mechanical and disintegration properties of metronidazole tablets prepared using co-fused excipients are presented in Table 4. Generally, the mechanical properties of tablets prepared using co-fused excipients as expressed by Cs/Fr increased with increase in applied pressure. At the highest pressure, the ranking of Cs/Fr was 100 % DAM > 100 % AV > 33 % DAM >25 % DAM > 50 % DAM. At all pressures, co-fused excipients containing 50 % DAM showed the least mechanical property which was significantly lower ($p<0.05$) in comparison with that of the parent excipients. There was a significant improvement in the disintegration of tablets prepared using the co-processed excipients in comparison to that prepared using DAM 100 %. The disintegration time for tablets prepared using co-fused excipients was lower than that of co-grinded additives although the differences were not significant ($p > 0.05$). Generally, the disintegration time increased with an increase in applied pressure. Ramya and Chowdary[31] prepared coprocessed excipients of pregelatinised starch-polyethylene glycol 1500-Aerosil and evaluated its application as directly compressible vehicle in tablet formulations. The authors reported that all the tablets disintegrated rapidly within 15-30 sec. The results of this current study agree with that of Ramya and Chowdary[31] by yielding fast disintegration times of 12.66 to 30 sec for cogrinded and 12.00 to 19.8 sec for cofused excipients. Generally, co-processing impacted this property as DAM alone failed the disintegration time test while avicel alone produced 12.60 – 92.40 secs as disintegration times.

The DER for tablets compressed at lowest and highest pressures had least DER when 50 % DAM was present in the co-fused excipient. Among the tablets, those produced with co-fused excipients containing 25 % DAM showed the strongest DER while those produced with 100 % DAM had extremely low DER showing a poor balance of mechanical and release properties. Generally, the co-processed excipients improved the mechanical and disintegration properties of the tablets produced compared to tablets prepared using DAM alone.

Furthermore, the compressional characteristics of the co-processed excipients as shown in Figures 8 and 9 revealed linearity at two segments. The initial segment indicates rearrangement and fragmentation of the component particles. The second segment shows deformation by plasticity. It has been pointed out that cellactose® exhibits dual consolidation behaviour since it contains a fragmenting component (lactose) and a substance (cellulose) that consolidates mainly by plastic deformation[8]. The co-processed excipients therefore showed similarity to previously reported cellactose® in compression properties[8]. However, the parent polymers showed plots typical of single component systems.

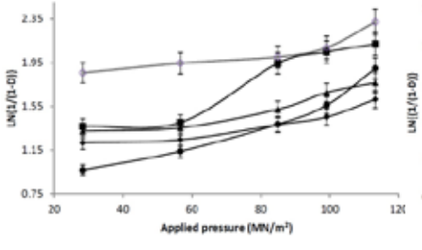

Figure 8. Heckel plots for metronidazole tablets prepared using co-grinded excipient (♦ 25% DAM, ■ 33% DAM, ▲50% DAM, ○100% DAM, ●100% AV).

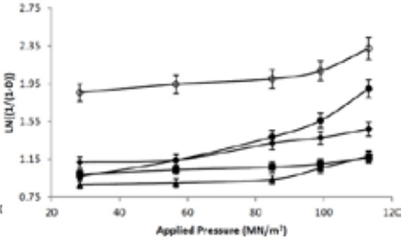

Figure 9. Heckel plots for metronidazole tablets prepared using co-fused excipient (♦ 25% DAM, ■ 33% DAM, ▲50% DAM, ○100% DAM, ●100% AV).

The parameters derived from the Heckel plots are shown in Table 5. The values of the relative density at zero pressure, D_o, which represents the degree of packing in the die as a result of die filling, increased generally with increase in the concentration of DAM in the co-excipients irrespective of production method. Co-fused excipients showed higher D_o than the co-grinded implying a higher degree of packing for formulations containing the co-excipients prepared by co-fusion.

Table 5. Parameters derived from Heckel plots for metronidazole tablets prepared using the co-excipients

Co-processing method	Amount of DAM (%$^{w}/_{w}$)	Amount of AV (%$^{w}/_{w}$)	D_o	P_y (MN/m^2)	D_a	D_b
Co-grinding	0.0	100.0	0.357	103.093	0.620	0.263
	25.0	75.0	0.297	204.082	0.673	0.376
	33.0	67.0	0.276	769.231	0.617	0.341
	50.0	50.0	0.399	909.091	0.593	0.194
	100.0	0.0	0.571	384.615	0.834	0.263
Co-fusion	0.0	100.0	0.357	103.093	0.620	0.263
	25.0	75.0	0.349	175.439	0.681	0.332
	33.0	67.0	0.411	769.231	0.646	0.235
	50.0	50.0	0.481	116.279	0.593	0.112
	100.0	0.0	0.571	384.615	0.834	0.263

The mean yield pressure (Py) for the metronidazole tablet formulations were calculated from the slope of the linear region of the Heckel plots having correlation coefficient > 0.990, and the intercept, A, was determined from its extrapolation[32]. The mean yield pressure, Py, is inversely related to the ability of the metronidazole formulations to deform plastically when pressure is applied. Among the cogrinded excipients, P_y reduced as the concentration of DAM in the co-excipients reduced giving a ranking of 50 % >33% > 25%. However, the Py for 33 % was significantly higher than when 100 % DAM was used. Generally, cofused excipients offered significantly lower ($p<0.05$) values of P_y. Lower values of P_y implies faster onset of plastic deformation and the cofused excipients in this case would deform more readily under pressure on a high-speed tablet machine[33], compared to the cogrinded types. Avicel (0 % DAM) showed the least P_y and this is not surprising since it's a direct-compresion excipient. In addition, 33 % cofused and co-grinded excipients has same P_y indicating same deformation pattern irrespective of production method.

The total degree of packing achieved at zero and low pressures is referred to as total relative precompression density, D_a. The values increased with reduced concentrations of DAM without significant differences ($p > 0.05$) between excipients prepared using both methods of co-processing. DAM however had the highest D_a, suggesting a display of higher total degree of packing.

The phase of particle rearrangement in the early stages of tablet compression is called the relative density at low pressure, D_b and indicates the degree of fragmentation of particles[33]. Akin- Ajani et al[32]., has reported that fragmentation of particles can occur concurrently with plastic and elastic deformation during compression. The D_b of the excipients generally reduced with increase in the concentration of DAM using both methods of co-processing. Interestingly, the parent polymers both had equal D_b values probably implying same level of rearrangement of particles. Higher values of Db indicate improved particle re-arrangement showing that 25 % co-grinded and 33% co-fused excipients would offer optimal re-arrangements of particles or granules during compression. The compaction results obtained here agrees with the study of Odeku and Patani[34] on dika nut mucilage extracted and used as an excipient in metronidazole tablet formulations.

CONCLUSION

The excipients developed in this study using co-grinding and co-fusion methods of co-processing enabled the direct compression of metronidazole which is a poorly compressible drug. The co-processed excipients also improved the disintegration time and disintegration efficiency ratio of metronidazole tablets compared to date mucilage alone. Co-excipients prepared by co-fusion method showed faster disintegration and onset of plasticity compared to the ones from co-grinded method. For both methods, co-excipients containing 25 % DAM showed optimal disintegration properties while 33 % showed optimal mechanical properties. The co-excipients may therefore be further developed as direct-compression excipients for poorly compressible active agents especially when tablets requiring fast disintegration are needed.

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