Effects of a direct compressible co-processed novel excipient on the brittle fracture tendency of paracetamol tablets

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ABSTRACT

The objective of the study was to investigate the effects of a novel co-processed excipient on ameliorating the brittle fracture tendency of paracetamol tablets. A novel co-processed excipient was prepared using the suspension-agitation methods. The prepared excipient was mixed in varying proportions with paracetamol powder and used to produce three batches of tablets (M1-M3) by direct compression. Maize starch mucilage (10 %w/v) was used to prepare a batch of paracetamol granules (M4) by wet granulation and compressed into tablets. Pre- and post-compression parameters were evaluated for all batches. Brittle fracture indices (BFI) of the tablet formulations were determined and compared. Pre- and post-compression parameters of the batches met official compendial specifications and were comparable in their micromeritic properties, tablet weight uniformity, friability, crushing strengths, disintegration times and dissolution profiles. The brittle fracture indices of the tablets were not directly proportional to their tensile strengths and disintegration times. Tablets prepared with the co-processed novel excipient gave superior BFIs in the rank order of M4 > M1 > M2 > M3. The M3 batch of novel excipient tablets gave comparable tablet properties with those of maize starch mucilage. The tensile strengths and brittle fracture tendencies of the novel excipient tablets may suggest that the excipient can be used as an alternative to maize starch mucilage as binder in paracetamol tablet formulations.

Keywords: paracetamol, co-processed, novel excipients, direct compression, BFI

INTRODUCTION

The tendency of a tablet to cap or laminate during ejection from the tableting machine dies can be measured by the tablet's brittle fracture index (BFI). Tablet capping or lamination is a problem in the pharmaceutical industry leading to increased production cost as laminated or capped tablets will have to be reprocessed or rejected entirely. The tendency for a tablet to fracture may result from binder insufficiency, a high level of plastoelasticity of the tablets' excipients and a number of process factors which includes high compression pressures and over drying of granules/powders (Okor, 2005, Amidon *et al*., 2009). A relation of the elastic to the plastic compression property of pharmaceutical powders is described as plastoelasticity and it is directly correlated with the BFIs of tablets (Zhou and Qiu, 2010). Plastic materials are less prone to brittle fracture when compared with elastic materials because they deform readily under stress. This deformation helps to relief the stress that would have concentrated at the edge of a void and consequently, effectively ameliorating the brittle fracture of the material (Wang *et al*., 2012, Byrn *et al*., 2017).

Among the excipients used in tablet formulations, binders are usually used to ameliorate brittle fracture tendency with maize starch mucilage being frequently used in wet granulation. Mucilages of other starches used as binders have been studied and found to be comparable or even better in ameliorating this tendency (Uhumwangho *et al*., 2006, Eraga *et al*., 2015). Binders increase the inter-particulate bonding strength within a tablet and thus imparting plasticity. They also increase the degree of compaction or consolidation while reducing capping or lamination by promoting plastic deformation during tableting (Zhou and Qiu, 2010).

In direct compression or dry granulation without the use of a granulating fluid, the fracture tendency of tablets produced is multiplied. The use of directly compressible excipients that may be elastic or brittle under compression further compounds the problem. Co-processing these directly compressible excipients to achieve new compounds with superior functionalities can reduce brittle fracture tendency in tablets produced by direct compression to a large extent.

Co-processing has been defined as the mixing of two or more established excipients using an appropriate procedure (Gohel and Jogani, 2005). They physical admixtures of two or more already known excipients combined at the particle level (Bansal and Nachaegari, 2004). The formation of a new excipient with superior or multi-functional properties compared to the physical admixture of its various components can be achieved through co-processing.

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Co-processed products are being developed to address the problems of powder flowability and compressibility as well the disintegration potential of powder compacts. Excipients with filler-binder potentials are the most commonly evaluated materials of the co-processed products (Bansal and Nachaegari, 2004). Co-processing to produce filler-binder materials is usually carried out combining two excipients with one plastic and other brittle. For example, 75 % lactose (brittle material) has been co-processed with 25 % cellulose (plastic material) to yield the material Cellactose® (Maarschalk and Bolhius, 1999).

The main objective of this study was to compare the effects of a directly compressible co-processed novel excipient with maize starch mucilage binder in ameliorating the brittle fracture index of paracetamol tablets.

MATERIALS AND METHODS

Materials

Maize starch BP, microcrystalline cellulose (MCC), pre-gelatinized starch and sodium carboxymethyl cellulose were gifts from Edo Pharmaceuticals, Edo State, Nigeria, α-lactose monohydrate was obtained from Fluka Chemical Corp., USA), magnesium stearate and talc (International Co. Ltd, Anhui, China), paracetamol powder was purchased from Nomagbon Pharmaceuticals, Edo State, Nigeria. All other reagents used were of analytical grade and water was double distilled.

Methods

Preparation of binder mucilage

A 10 % mucilage of maize starch was prepared by dispersing 10.0 g of maize starch powder in 10 ml distilled water and stirred to from a homogenous mixture. Boiling water was immediately poured into the mixture to form a paste and stirred vigorously. The boiling water was used to make the mucilage up to 100 ml volume, (Odeku and Itiola, 2002)

Excipient preparation

The preparation of the excipient has been previously reported by Eraga *et al*. (2014). Six grams of maize starch BP was weighed and dispersed in distilled water at 32 °C, to make a 10 ml slurry in a 500 ml beaker. The slurry was well stirred to ensure that all the powder was properly wetted. Freshly boiled water at 100 °C was then added to the slurry to reach the 200 ml mark and stirred properly till a gel of uniform consistency was formed. Sodium carboxyl methylcellulose (2 g) powder was then dispersed in the gel, in little quantities at a time (to prevent lump formation) and stirred continuously until an even mixture was produced. Then, a mixture containing 2 g of microcrystalline cellulose in 5 ml of distilled water was added and stirred until a smooth suspension of all three substances was obtained. The suspension was then transferred into a transparent heat resistant plastic container, spread thinly and dried in the hot air oven at 60 °C for 48 h. The resulting flakes were pulverized using a dry kitchen blender (Phillips, Switzerland) and stored in an air tight container over silica gel until use. The excipient so prepared was termed "Novel" excipient.

Preparation of granules

Novel excipient granules

The novel excipient batches of paracetamol granules were prepared by dry granulation using the values in Table 1. Three batches (M1, M2 and M3) containing different novel excipient: drug ratios were prepared by dry mixing the weighed amounts of paracetamol powder, maize starch, lactose and the novel excipient in a mixer for 5 min. The powder mix was subjected to various analyses and thereafter the talc and magnesium stearate were weighed and mixed in a mortar and then added to the powder mix and mixed intimately in readiness for compression.

Conventional granules

Conventional paracetamol granules of batch M4 was prepared with the wet granulation method using the quantities shown in Table 1. Paracetamol powder and lactose (filler) were weighed and dry mixed for 5 min in a mixer. Half of the weighed amount of disintegrant (maize starch) was incorporated intragranularly to the powder mix in geometric proportions during the mixing.

The binder solution (10 %w/v) was added to the dry powder mix in sufficient quantities to form a wet mass. The wet mass was screened through a 710 µm sieve and the damp granules dried at 60 °C for 30 min in a hot air oven (Gallenkamp, UK). Various flow property analyses were carried out on the granules after rescreening with the same sieve and dried for another 30 min. The other half of the disintegrant, talc and magnesium stearate were weighed and mixed in a mortar and then added to the dry granules and mixed intimately in readiness for compression

Granule analysis

Bulk density: Thirty grams of the granules was poured into a 100ml graduated cylinder. The volume occupied by the granules was taken and then used to compute the bulk density.

Tapped density: The cylinder containing the 30 g of the granules was gently tapped on a wooden platform for a minute. The tapped volume of the granules was taken and then used to compute the tapped density.

Carr's index: The difference between the tapped and bulk density of the granules divided by the tapped density was calculated and the ratio expressed as percentage.

Hausner's ratio: The tapped density of the granules divided by the bulk density was calculated as the Hausner's ratio.

Flow rate: Fifty grams of the paracetamol granules was allowed to pass through the orifice of an Erweka flow tester (Model: GT, GmbH, Germany) and the time taken was recorded. The average time of three determinations was reported.

Angle of repose: Using the hollow cylinder method, a cylinder of 3 cm in diameter was fixed on a flat surface and filled with granules. The cylinder was slowly pulled up allowing the granules to form a cone-like heap on the flat surface. The height of the heap was measured and the angle of repose, θ, was calculated using Equation 1.

$$\theta = \tan^{-1}(h/r) \quad \ldots (1)$$

Where h is the height of the heap of granules and r is the radius of the heap base

Compression of granules

A single punch tableting machine (Manesty Machines, UK) was used in compressing the various batches of the paracetamol granules at a compression pressure of 32 kilonewton (KN). Uniform weight tablets were produced by adjusting the die volume to compress granules weighing 605 mg. One hundred and twenty tablets were produced per batch with twenty of them having centre holes by using special tableting adaptors. The tablets were kept in an air tight container until evaluation.

Tablet evaluations

The following tests (tablet dimensions and weight uniformity, tensile strength, friability, disintegration time and dissolution studies) were carried out on the compressed tablets.

Dimensions

The diameter and thickness of each of ten tablets per batch were measured using a micrometre screw gauge and their mean values recorded.

Weight uniformity

Twenty tablets from each batch were used for the test. The weight of each tablet was determined (Mettler Toledo, Switzerland) and the mean or average weight and standard deviation was computed.

Friability

Ten pre-weighed tablets were placed in the drum of a friabilator (Erweka GmbH, Germany) revolving at 25 rpm. After 4 min, the tablets were brought out, de-dusted and reweighed. The weight was then recorded and friability calculated as percentage loss in weight. Triplicate determination was carried out and the mean and standard deviation were reported.

Tensile strength

The tensile strength (T) of normal tablets and the apparent tensile strengths (T_o) of the compromised tablets with holes (ten tablets per batch) were determined by diametric compression using a hardness tester (Campbell Electronics, Model HT-30/50, India) and applying Equation 2 (Fell and Newton 1970).

$$T = 2F/\pi dh \quad \ldots (2)$$

Where T = Tensile strength in MN/m^2, F = Force in MN needed to cause diametral tensile failure or breaking force, d = Tablet diameter in m, h = Tablet thickness in m.

Determination of BFI

The BFI of the batches of tablets was obtained by comparing the tensile strengths of the tablets with a hole at their centre (which acts as a built-in stress concentration defect) with the tensile strengths of tablets without a hole. The brittle fracture index (BFI) was calculated using Equation 3.

$$BFI = 0.5\,[(T/T_o)-1] \quad \ldots (3)$$

Where T_o and T are the tensile strengths of tablets with and without a centre hole, respectively. The centre hole (≤ 0.6 mm) is a built-in model defect to simulate actual void formed in the tablet during compression.

Disintegration time

The time taken for six tablets per batch to disintegrate in distilled water at 37 ± 2 °C were determined using the BP disintegration tester (MK IV, Manesty Machines, UK). The mean or average time and standard deviation was calculated.

Dissolution studies

The dissolution analyses of the various batches of the paracetamol tablets were carried out using the BP basket method. A dissolution apparatus (Caleva ST7, UK) containing 900 ml of 0.1 M HCl solution thermostated at 37 ± 0.5 °C with a basket revolution of 50 rpm was used. Aliquot samples (5 ml) were withdrawn from the dissolution fluid at specific time intervals over a period of 60 min and replaced with an equivalent volume maintained at 37 ± 0.5 °C. The samples withdrawn were filtered and diluted appropriately with 0.1 M HCl solution. The resulting solutions were subjected to spectrophotometric analysis at λmax of 245 nm (T70, PG Instruments Ltd, USA). The concentration and percentage of drug release at various time interval was computed from the equation of the standard calibration plot of the pure paracetamol powder. Triplicate determinations was carried out and the results were reported as mean ± SD.

Statistical analysis

Statistical difference in the tablet parameters of the batches were subjected to student's t-test at 5 % level of significance using GraphPad InStat 3.10.

RESULTS

Granule properties

Bulk properties: The bulk and tapped density values of the granules are shown in Table 2. The granules of the novel excipient (M1, M2 and M3) exhibited a decrease in granule consolidation (increased loose packing) with increase in the

concentrations of the excipient. The M1 granules had the highest volume reduction followed by the M4 granules. Thus, the close packing of the granules followed the rank order: M1 > M4 > M2 > M3.

Flow properties: The Hausner's ratios, Carr's indices and angles of repose (Table 2) values indicated that the paracetamol granules had excellent flow properties. The values obtained for Carr's index ranged from 8.15 - 17.33 % while those of Hausner's ratio was from 1.09 - 1.21 and the angles of repose from 27 - 33°.

Table 1**:** Formula of prepared paracetamol granules and tablets

Ingredients	Quantities per tablet			
	Novel excipient			Conventional
	M1	M2	M3	M4
Paracetamol (mg)	100	100	100	500
Novel excipient (mg)	100	200	300	-
Maize starch (mg)	100	100	100	50
Lactose (mg)	300	200	100	50
Binder solution (10 %w/v)	-	-	-	qs
Magnesium stearate (%w/w)	0.5	0.5	0.5	0.5
Talc (%w/w)	0.5	0.5	0.5	0.5

qs= quantity sufficient

Table 2**:** Some physical properties of the paracetamol granules

Parameters	Batch			
	M1	M2	M3	M4
Bulk density (g/cm^3)	0.520	0.520	0.552	0.525
Tapped density (g/cm^3)	0.629	0.593	0.601	0.610
Flow rate (g/sec)	3.68	3.85	4.33	3.64
Angle of repose (^{o})	33	30	28	27
Hausner's ratio	1.21	1.14	1.09	1.16
Carr's index (%)	17.33	12.31	8.15	13.93

Table 3**:** Some physical properties of the paracetamol tablets.

Batch	Weight (g)	Friability (%)	Diameter (mm)	Thickness (mm)	Disintegration time (min)
M1	0.61 (0.01)	1.65 (0.03)	12.47 (0.06)	4.14 (0.09)	4.25 (1.26)
M2	0.66 (0.03)	0.97 (0.04)	12.55 (0.02)	4.32 (0.14)	5.20 (1.10)
M3	0.66 (0.02)	0.60 (0.02)	12.55 (0.01)	4.41 (0.09)	6.10 (1.05)
M4	0.60 (0.01)	0.65 (0.02)	12.49 (0.03)	4.50 (0.49)	4.66 (0.28)

SD values are listed in parentheses

Table 4**:** Brittle fracture indices of the paracetamol tablets

Batch	Crushing strength (N)		Tensile strength (MN/m^2)		BFI
	Tablets		Tablets		
	Blind	Hollow	Blind	Hollow	
M1	47.86 (0.57)	41.58 (0.71)	0.591 (0.02)	0.513 (0.10)	0.076
M2	40.80 (0.32)	34.42 (0.64)	0.479 (0.02)	0.404 (0.22)	0.092
M3	40.38 (1.40)	32.95 (0.82)	0.465 (0.22)	0.380 (0.23)	0.112
M4	105.90 (0.84)	85.32 (0.49)	1.194 (0.01)	0.961 (0.05)	0.121

SD values are listed in parentheses

Tablet properties

Dimensions

The diameter and thickness values of the tablets studied are shown in Table 3. The values were within the range for good tablets. Though tablet thickness is at the discretion of the tablet manufacturers, the British Pharmacopoeia (BP 2002) specifies a 5 % maximum deviation from the mean diameter value of a tablet. The standard deviations (SD) of the tablet diameter values ranged from 0.01 - 0.06.

Uniformity of weight

The weights of the tablets in all the batches (Table 3) met British Pharmacopoeia (BP 2009) specification that states that not more than two of the individual weights of the 20 tablets should deviate from the average weight by more than ± 5 % and none should deviate by more than ± 10 %. The variations in the tablet weights were not more than ± 3 % of the calculated mean weight.

Friability

A 1 % loss is considered as the acceptable upper limit for tablets formulated by wet granulation, but up to 2 % loss is permissible especially for large tablets prepared by direct compression (BP 2009). The friability values of the tablets (Table 3) were within acceptable limits ranging from 0.60 - 1.65 %.

Disintegration times

All the formulated tablets disintegrated within 15 min (Table 3) as specified in British Pharmacopoeia (BP 2009) for uncoated tablets, but the results showed an increase in the disintegration times with increasing concentration of the novel excipient. The disintegration time was of the rank order; M3 > M2 > M4 > M1.

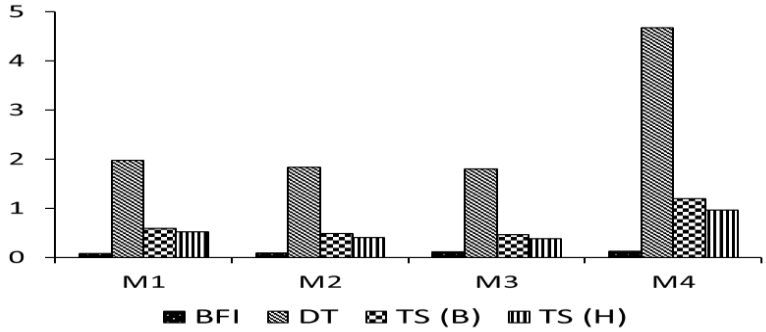

Figure 1*:* Comparisons of the brittle fracture indices (BFI), disintegration times (DT) and tensile strength of the blind (TS (B)) and hollow (TS (H)) tablets

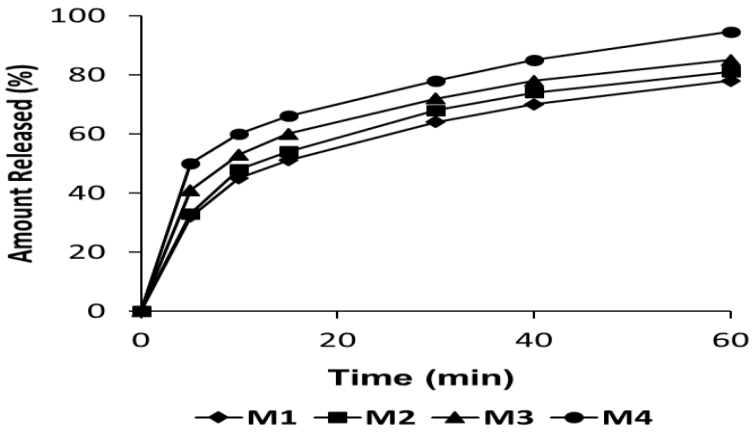

Figure 2**:** Dissolution profiles of the paracetamol tablets

Crushing strength and BFI

Hardness values greater than or equal to 4 kp (39.23 N) are considered optimal and acceptable (Rudnic and Schwartz, 2006). The hardness values of the formulated tablets ranged from 4.12 - 10.80 kp (40.38 - 105.90 N), i.e. within acceptable limits (Table 4). The conventional M4 tablets gave the highest value while the values of the novel excipient batches (M1-M3) decreased with increasing amounts of the excipients. Their calculated tensile strength values were also of this order.

The brittle fracture indices of the tablets were not directly proportional to their tensile strengths (Figure 1). BFI values have a range of 0 (no fracture tendency) to 1 (maximal fracture tendency) (Hiestand *et al*., 1977). The rank order of BFI of the paracetamol tablets was: M4 > M3 > M2 > M1.

Dissolution profiles

Figure 2 shows the dissolution profiles of the paracetamol tablets. All the tablets formulated did not pass the British Pharmacopoeia (BP 2003) dissolution test for tablets, which specifies that at least 70 % of the drug should be in solution after 30 min. Only the M3 and M4 batches of tablets met this specification. The dissolution pattern did not agree with the disintegration-dissolution theory, as the tablets disintegration times did not correlate with their drug release i.e. the faster disintegrating batches M1 and M2 did not release the highest amount of drug.

DISCUSSION

The brittle fracture ameliorating effect of a novel co-processed excipient for direct compression of tablets has been studied. Brittle fracture during tableting has been reported to be due to die wall pressure resulting in the concentration of stress at the edge of voids or low density pockets which are weak points in the tablet and from which cracks emanate during withdrawal of the upper punch pressure (i.e. decompression) (Uhumwangho and Okor, 2004, Okoye *et al*., 2010). Tablet excipient

particles able to undergo plastic deformation will relieve the stress and thus ameliorate brittle fracture. Tablet ingredients especially binders impact plasticity on tablet formulation and thereby ameliorate brittle fracture tendency (Zhou and Qiu, 2010). Although starches used as binders have been commonly used to alleviate tablet fracture, an attempt to use a novel co-processed excipient for the same purpose in directly compressible tablet formulations was undertaken.

The novel excipient in the different concentrations studied exhibited a superior capacity to ameliorate brittle fracture in paracetamol tablets. Their tablet BFI values (0.076, 0.092 and 0.112) when compared with that of maize starch mucilage tablets (0.121) imply that paracetamol tablets made with maize starch mucilage have a higher tendency to cap and laminate during ejection from the die than the tablets made with the co-processed excipient. Tablets made with the drug: excipient ratio of 1:1 had the lowest tendency to fracture than all the other tablets because of its lowest BFI value (0.076). This observation implies that the novel excipient compared with the maize starch mucilage promoted plastic deformation of the granule particles during compaction to a higher degree. Plastic deformation increases particle cohesion and particle-particle contact area leading to the formation of hard tablets (Byrn *et al*., 2017).

Surprisingly, the crushing strengths of the novel excipient tablets (40.38 - 47.86 N) were not as high as those of tablets formulated with maize starch mucilage (105.90 N), and their hardness decreased with increasing amounts of the excipient. Harder tablets are more likely to fracture due to resistance of their particles to deformation; it therefore implies that the novel excipient promotes plastic deformation of tablet particles without necessarily increasing the inter-particulate bonding strength which is responsible for increased hardness in tablets. Another inference from this observation could be that the co-processed excipient itself is plastic in nature and readily undergo deformation under compression.

While the choice of binder or other excipients must be taken into consideration by every manufacturer to produce tablets of low brittle fracture tendency, the tablet compression pressure should also be monitored as all these factors contribute to the hardness of a tablet. In an attempt to alleviate tablet fracture during manufacture, the tablet hardness should also not be compromised, but a careful selection of the tablet ingredients should be undertaken to produce a tablet of acceptable hardness. A soft tablet will easily crumble during transportation and handling while on the other hand, an overly hard tablet may not disintegrate and its drug content may eventually not be released and made available for dissolution and absorption.

CONCLUSION

Tablets prepared with the co-processed novel excipient gave superior BFI values in comparison with those of maize starch mucilage. Also, the M3 batch of tablets gave acceptable and comparable tablet properties with those of maize starch mucilage. This investigation may suggest that a change from maize starch mucilage as binder in wet granulation to the novel excipient using direct compression would lead to a decrease in the tensile strength and the brittle fracture tendencies of paracetamol tablets.

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