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The Effects of a Blend of Croscarmellose Sodium and Microcrystalline Cellulose on the Brittle Fracture Tendency of Paracetamol Tablets

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A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation; D – writing the article; E – critical revision of the article; F – final approval of article.

Abstract

Background: Capping and lamination are major problems encountered in tablet production and they are indicators of the brittle fracture tendency of a tablet formulation.

Objective: The study aimed at determining the effect of a blend of two super-disintegrants on the brittle fracture tendency of paracetamol tablet.

Methods: Batches of paracetamol granules and tablets (B1-B5) were prepared by wet granulation using a blend of croscarmellose sodium and microcrystalline cellulose (MCC) at different ratios. The formulated granules' pre- and post-compression parameters such as weight uniformity, dimensions, friability, crushing strength disintegration time, brittle fracture index (BFI) and dissolution studies were evaluated.

Results: Granules of the different batches of the formulations exhibited excellent flow properties. All of the formulated tablets met official compendial specifications for tablets except batch B4 tablets with tablet friability value of 1.35 %. The BFI of the paracetamol tablets with MCC alone (B5) had the lowest value (0.420), closely followed by the B3 tablets value (0.421) with 2 parts MCC and 1 part croscarmellose sodium. The highest BFI value of 0.582 was obtained from the B1 batch of tablets containing equal parts of the superdisintegrants.

Conclusion: The blend of superdisintegrants adversely affected the brittle fracture tendency of the paracetamol tablets by increasing the BFI of the tablets though to a lesser degree. The choice of two or more superdisintegrants in the formulation of fast disintegrating tablets should be undertaken with a careful study to avoid producing tablets that are prone to capping or lamination during tablet-die ejection.

Keywords: Superdisintegrants, Blend, Tablets properties, BFI

INTRODUCTION

Brittle fracture index (BFI) is a measure of the tendency of a tablet to cap or laminate during ejection from the tableting machine dies. It 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 be due to insufficient binder, a high plastoelasticity of the tableting base and process factors such as excessive compression pressures and over drying of granules/powders (Okor, 2005).

The brittle fracture tendency of a tablet formulation can be exacerbated or ameliorated by the excipients used in the formulation. Although binders are usually used to ameliorate brittle fracture tendency, studies involving other tablet excipients (bulking agents,

disintegrants, matrix forming agent, etc) and manufacturing parameters such as compression pressure, as to their role in exacerbating or ameliorating this tendency have been carried out (Uhumwangho and Okor, 2004; Eichie et al., 2005; Eraga et al., 2015).

A disintegrant is included in tablets to ensure that the tablet, when in contact with a liquid, breaks up into small fragments which promotes rapid drug dissolution. It is essential to choose a suitable disintegrant in an optimum concentration so as to ensure quick disintegration and high dissolution rate. Fast disintegrating or fast dissolving tablets (FDTs) containing one or more super-disintegrants that ensure quick or rapid break up of tablets for quick dissolution and increased bioavailability, are becoming the latest trend in tablet manufacturing (Shirsand et al., 2010; Sehgal et al., 2012; Eraga et al., 2014).

These tablets are gaining prominence as drug delivery systems and emerging as one of the popular and widely accepted dosage forms, especially for the paediatric and geriatric patients. As a result of its ability to solve the problems of dysphagia and to improve patient compliance, FDTs have gained considerable attention as preferred alternatives to conventional tablet and capsule formulations (Sehgal et al., 2012).

The main objective of this study was to determine the effect of a blend of two superdisintegrants - croscarmellose sodium with microcrystalline cellulose on the brittle fracture tendency of paracetamol tablets.

METHODOLOGY

Materials

Paracetamol powder and croscarmellose sodium (BDH Chemical, Poole, UK), microcrystalline cellulose (Avicel-PH 101) (FMC Biopolymer, Philadelphia, USA), α- lactose monohydrate (Fluka Chemical Corp., USA) polyvinylpyrrolidone (PVP) (ISP Technologies Incorporated, NJ, USA), magnesium stearate and talc (Kem Light Chemicals Ltd, Mumbai, India).

Methods

Preparation of granules

The paracetamol granules were prepared by wet granulation method of massing and screening using the quantities shown in Table 1. Five batches (B1-B5) containing different croscarmellose-microcrystalline cellulose ratios were prepared by dry-mixing the weighed amounts of paracetamol powder and lactose (filler) in a mixer for 5 min. Half of the weighed amount of croscarmellose and microcrystalline cellulose was incorporated intragranularly to the powder mix in geometric proportions during the mixing. Sufficient quantities of the polyvinylpyrrolidone solution (10 %w/v) required to form a wet mass was gradually added to the dry powder mix. The wet mass was passed through a 710 µm sieve mesh screen and the resulting granules dried at 60 °C for 30 min in a hot air oven (Gallenkamp, UK). The granules were rescreened through the same sieve and further dried for another 30 min. The other half of the croscarmellose and microcrystalline cellulose was added to the dry granules and mixed. The resulting mix was subjected to various analyses such as bulk and tapped densities, Carr's index, Hausner's ratio, flow rate and angle of repose and thereafter magnesium stearate and talc previously weighed and mixed in a mortar were added in three (3) portions of 200 mg per portion and thoroughly mixed each time a portion is added in readiness for compression.

Table 1: Formula of prepared paracetamol granules and tablets

Ingredients	Quantities per tablet				
	1:1	2:1	1:2	1:0	0:1
	B1	B2	B3	B4	B5
Paracetamol (mg)	500	500	500	500	500
Lactose (mg)	50	50	50	50	50
Croscarmellose sodium (mg)	15	20	10	30	0
Microcrystalline cellulose (mg)	15	10	20	0	30
Polyvinylpyrrolidone (10 %w/v)	q.s	q.s	q.s	q.s	q.s
Magnesium stearate (mg)	2.5	2.5	2.5	2.5	2.5
Talc (mg)	2.5	2.5	2.5	2.5	2.5

Granule analysis

Bulk and tapped densities: A 30 g quantity of the granules was poured gently into a 100 ml graduated measure. The volume of the granules was read and the bulk density calculated. The measure was tapped 100 times on a wooden platform. The volume was noted and used in calculating the tapped density.

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

Flow rate: The funnel method was employed. A glass funnel was clamped to a retort stand at a certain distance from a horizontal surface. Fifty grams of granules was poured into the funnel with its orifice blocked with a glass sheet. The glass sheet was withdrawn and the granules allowed to fall freely under the influence of gravity. The time taken for the entire granules to pass through the orifice was recorded. This was carried out in triplicate and the mean values recorded.

Angle of repose: The fixed funnel and free standing cone method was used. A transparent glass funnel was clamped at 2.7 cm above a flat horizontal surface. Granules were carefully poured through the funnel onto the horizontal surface until the apex of the cone made by the heap of granules touched the tip of the funnel. The height of the heap and the diameter of the cone base were measured. The angle of repose, θ, was calculated using Equation 1.

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

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

Compression of granules

Batches of the granules were compressed into tablets using a single punch tableting machine (Kilian and Co., Frankfurt, Germany) at a compression pressure of 32 kilonewton (KN). The die volume was adjusted to compress tablets of uniform weight by using granules weighing 585 mg. One hundred and twenty tablets were produced per batch with twenty of them having centre holes (diameter 0.60 mm) by using special tableting adaptors. The tablets were kept in air tight containers until evaluation.

Tablet evaluations

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

Dimensions

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

Weight uniformity

The weight of each of 20 tablets was determined from each batch using an electronic balance (College B154, Mettler Toledo, Switzerland) and the mean weight and standard deviation were computed.

Friability

Pre-weighed tablets (10) 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. Their percentage loss in weight value was calculated. Triplicate determination was carried out and the mean and standard deviation were reported.

Crushing and tensile strengths

Using a motorized tablet hardness tester (Campbell Electronics, Model HT-30/50, India), the crushing strength of ten individual tablets per batch was determined by diametric compression. The mean and standard deviation values were calculated.

The tensile strength (T) of the normal tablets and the apparent tensile strengths (To) of the compromised tablets with holes were determined by using their crushing strength values and applying Equation 2 (Fell and Newton, 1970).

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

Where T = Tensile strength in MN/m2, F = Force in MN needed to cause diametral tensile failure or breaking force (crushing strength), 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.

$$BFI = 0.5\left[\left(T/T_0\right) - 1\right]. \ldots . \ (3)$$

Where: T and To are the tensile strengths of tablets without and with 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 ± 0.5 °C were determined using the BP disintegration tester (MK IV, Manesty

Machines, UK). The mean or average time and standard deviation were calculated.

Dissolution studies

The dissolution profiles of the paracetamol tablets were determined using the BP basket method for the various batches of the tablets (Caleva ST7, UK). A dissolution medium of 900 ml of 0.1 N HCl solution maintained at 37 ± 0.5 ℃ with a basket revolution of 50 rpm was used. A 5 ml volume of dissolution medium was withdrawn at various intervals over a period of 60 min and replaced with an equivalent volume of fresh dissolution medium maintained at same temperature (37 ± 0.5℃). The samples withdrawn were filtered and suitably diluted with 0.1N HCl solution. The absorbances of the resulting solutions were measured at maximum wavelength of 245 nm (T70, PG Instruments Ltd, USA). The concentration and the percentage of drug released at each time interval was determined using the equation from the standard calibration plot obtained from the pure drug (British Pharmacopoeia, 2003).

Statistical analysis

Triplicate determinations was carried out for all experiments and the results were recorded as mean ± SD. Statistical difference in the tablet parameters of the batches were subjected to student's t-test at 5 % level of significance using GraphPad InStat 3.10.6.

RESULTS AND DISCUSSION

Pre-compression (granules) properties

The results of the flow properties of the granules are shown in Table 2. The bulk and tapped density values of the granules indicate loose packing of the granules in all the batches. The granules exhibited variable flow rate that were not significantly different from one another. Also, their angles of repose, Hausner ratios and Carr's indices indicated that the paracetamol granules had excellent flow properties (Mehta and Barker, 1994). The values obtained for the angles of repose ranged from 12.80 - 17.15° while those of Hausner's ratio were from 1.09 - 1.16 and the Carr's indices from 8.15 - 13.31 %.

Table 2: Some physical properties of the paracetamol granules

Parameters	Batch				
	B1	B2	B3	B4	B5
Bulk density (g/cm^3)	0.499 (0.004)	0.552 (0.001)	0.520 (0.002)	0.498 (0.004)	0.495 (0.005)
Tapped density (g/cm^3)	0.571 (0.005)	0.601 (0.003)	0.593 (0.001)	0.560 (0.002)	0.571 (0.004)
Flow rate (g/sec)	4.58 (0.02)	4.85 (0.03)	4.66 (0.01)	4.44 (0.05)	4.17 (0.03)
Angle of repose (^{o})	13.87 (0.01)	12.80 (0.02)	13.00 (0.05)	17.15 (0.03)	15.19 (0.05)
Hausner's ratio	1.12 (0.05)	1.09 (0.02)	1.14 (0.05)	1.16 (0.04)	1.15 (0.02)
Carr's index (%)	12.61 (0.03)	8.15 (0.05)	12.31 (0.03)	11.07 (0.05)	13.31 (0.02)

Post-compression (tablets) properties

Weight uniformity

The weights of the paracetamol tablets prepared are showed in Table 3. Their weights ranged from 580 - 588 mg, which is in compliance with the British Pharmacopoeia specification, which stipulates that not more than two of the individual weights should deviate from the average weight by more than ±5 % and none should deviate by more than ±10 % (British Pharmacopoeia, 2009). The variations in the tablet weights were not more than ±5 % of the calculated mean weight.

Table 3: Some physical properties of the paracetamol tablets

Batch	Weight (g)	Friability (%)	Diameter (mm)	Thickness (mm)	Disintegration time (sec)
B1	0.584 (0.05)	0.65 (0.03)	12.47 (0.06)	4.24 (0.09)	30.17 (2.04)
B2	0.582 (0.03)	0.97 (0.04)	12.55 (0.02)	4.32 (0.14)	25.20 (1.10)
B3	0.587 (0.02)	0.60 (0.02)	12.54 (0.01)	4.41 (0.09)	36.10 (2.05)
B4	0.588 (0.01)	1.35 (0.05)	12.52 (0.04)	4.44 (0.15)	37.83 (6.00)
B5	0.580 (0.04)	0.35 (0.02)	12.49 (0.03)	4.50 (0.49)	43.33 (5.16)

Friability

All the batches of tablets gave acceptable friability values below 1.0 % except batch B4 with a friability value of 1.35 %. The British Pharmacopoeia specifies a range of 0.8 - 1.0 % loss in weight of the tested tablets without capping, lamination or breaking up in the course of the test (British Pharmacopoeia, 2009). Although friability is a non-official test, it is related to the hardness of the tablet and it is the tendency of tablets to powder, chip or fragment during transportation and handling (WHO, 2012).

Dimensions

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

Disintegration times

All the tablets formulated disintegrated within 15 min (Table 3) as specified in the British Pharmacopeia for uncoated tablets (British Pharmacopoeia, 2009). As fast disintegrating tablets, they showed excellent disintegrating property by disintegrating in less than a minute (Alebiowu and Adeagbo, 2009).

Crushing strength and BFI

The crushing strength values of the formulated normal tablets ranged from 60.70 - 66.19 N while those of the compromised (hollow) tablets was from 28.05 - 35.99 N (Table 4). Crushing strength values greater than or equal to 39.23 N (4 kp) are considered optimal and acceptable (Rudnic and Schwartz, 2006), hence the crushing strength of all the normal tablets were within acceptable limits. The B5 batch of normal tablets containing only microcrystalline cellulose (MCC) gave the highest value, followed by the batch B3 tablets with croscarmellose sodium and MCC in a ratio of 1:2. The lowest value was obtained from B1 tablets containing 1:1 ratio of both disintegrants and followed by the B4 tablets prepared with croscarmellose sodium alone. The implication of this observation is that the hardness of the tablets is affected to a certain degree by the quantities of MCC and croscarmellose sodium combined in the formulation. It appears that the inherent binding effect of MCC that would have contributed to the hardening of the tablets was reduced to varying degree by the amount of croscarmellose sodium in the combination.

The calculated tensile strengths of the tablets did not follow the order of their crushing strengths (Table 4). The B2 batch of tablets gave the highest tensile strength value (0.751 MN/m^2) while the lowest value (0.702 MN/m^2) was obtained from the batch B4 tablets. This shows that the croscarmellose sodium while not contributing in increasing the tablet's hardness in increasing amounts, but in combination with the MCC may have resulted in a more elastic tablets as seen in the tensile strength of the B2 batch of tablets, since this was the batch with the highest amount of croscarmellose sodium in combination with MCC. This attribute of the B2 batch of tablets could be the result of the physicochemical properties of croscarmellose sodium.

The brittle fracture indices of the paracetamol tablets followed the order of B1 tablets greater than B2 tablets and then followed by B4, B3 and B5 tablets. BFI values have a range of 0 (no fracture tendency) to 1 (maximal fracture tendency) (Hiestand *et al*., 1977). A comparison of the tablet's BFI values with their disintegration times and crushing strengths (Figure 1) reveals that they are not directly proportional to each other. The import of the tablet's BFI values is that, the batch B5 tablets formulated with MCC alone is less likely to cap or laminate in the ejection of the tablet from the die during manufacture and followed by the B3 tablets with 2:1 ratio of MCC and croscarmellose sodium. Therefore, the 2:1 ratio in combining MCC and croscarmellose sodium in the formulation seems to be the optimum combination ratio in producing fast disintegrating tablets that are less prone to capping or lamination during tablet-die ejection.

Table 4: Crushing strength, tensile strength and brittle fracture indices of the paracetamol tablets

Batch	Crushing strength (N)		Tensile strength (MN/m^2)		BFI
	Tablets		Tablets		
	Normal	Hollow	Normal	Hollow	
B1	60.70 (4.57)	28.05 (6.68)	0.731 (0.020)	0.338 (0.010)	0.582
B2	63.80 (5.32)	32.42 (5.64)	0.751 (0.020)	0.381 (0.022)	0.484
B3	64.38 (4.40)	34.95 (6.82)	0.740 (0.021)	0.402 (0.023)	0.421
B4	61.39 (5.05)	32.36 (7.15)	0.702 (0.022)	0.370 (0.041)	0.449
B5	66.19 (4.84)	35.99 (5.49)	0.748 (0.010)	0.407 (0.050)	0.420

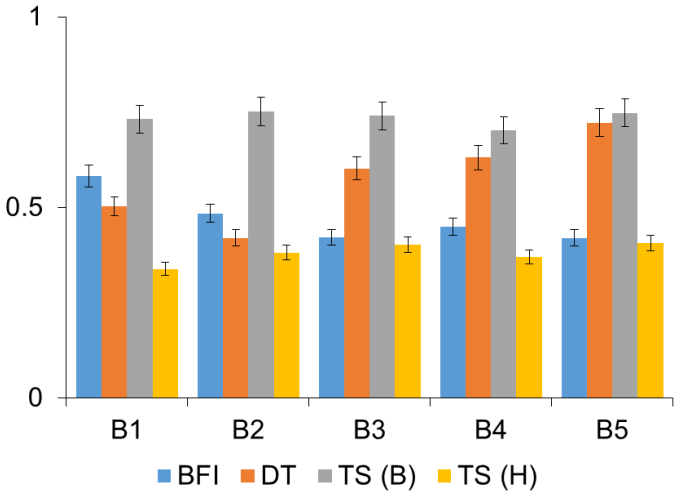

Figure 1: Comparisons of the brittle fracture indices (BFI), disintegration times (DT) and tensile strength of the normal (TS (B)) and hollow (TS (H)) tablets (n = 3)

Dissolution profiles

Figure 2 shows the dissolution profiles of the paracetamol tablets. All the tablets formulated passed the British Pharmacopeia dissolution test for tablets, which specifies that at least 70 % of the drug should be in solution after 30 min (British Pharmacopoeia, 2003). The dissolution pattern agreed with the disintegration-dissolution theory, as the tablets disintegration times correlated with their drug release i.e. the faster disintegrating batches B2 and B1 reached 100 % drug release in 30 min.

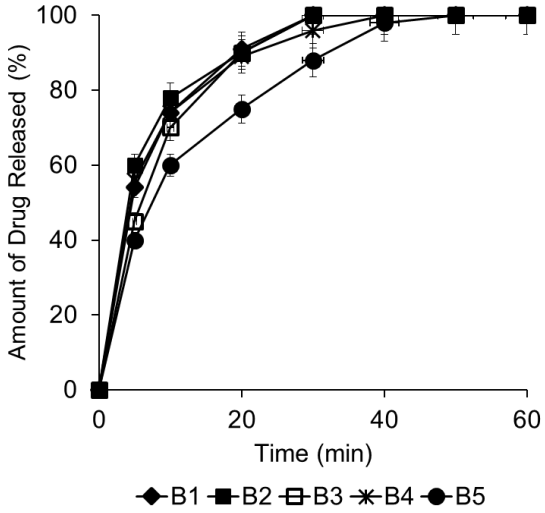

Figure 2: Dissolution profiles of the different batches of the paracetamol tablets formulated (n = 3)

CONCLUSION

The results of the study show that the blend of the superdisintegrants (MCC and croscarmellose sodium) adversely affected the brittle fracture tendency of the paracetamol tablets by increasing their BFI, though to a lesser degree. The B3 tablets with 2:1 ratio of MCC and croscarmellose sodium was the optimum combination ratio that produced tablets that were less prone to capping or lamination. It should be noted that the choice of superdisintegrants in the formulation of fast disintegrating tablets with two or more superdisintegrants should be undertaken with a careful study of their tendency to ameliorate or exacerbate brittle fracture in tablet formulations to avoid producing tablets that are prone to capping or lamination during tablet-die ejection.

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