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Full Length Research Paper

Brittle fracture index (BFI) as a tool in the classification, grouping and ranking of some binders used in tablet formulation: Lactose tablets

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This work aims at classifying, grouping and ranking binders based on their abilities to ameliorate capping and lamination in lactose tablets using BFI as a tool. Binders from different "families" (for example, starches, celluloses, natural gums, and synthetic gums) were employed via the wet granulation process at concentrations ranging from 1.0 - 12.5% w/w to formulate tablets with and without centre holes at a compression pressure of 7.5 arbitrary units. The tablets dimensions were determined in triplicates, with the resulting values used to calculate their tensile strengths. The means of the tensile strengths were then used to calculate BFI. Analyses of the results were done using Friedman's test and regression analysis. The analyses revealed that BFI was a useful tool in grouping binders based on their abilities to ameliorate capping and lamination in lactose tablets. It was also useful in ranking the binders based on their levels of effectiveness in solving the problem; however, it was not useful in classifying the binders based on nature or origin since no particular "family" occupied a unique range of BFI values in the task of ameliorating capping and lamination in lactose tablets. The findings from this work will be very helpful to pharmaceutical formulators since the selection of the best and most economic alternative binder(s) from an array of available binders to produce tablets with little or no incidence of capping and lamination will be greatly enabled by them.

Key words: BFI, grouping, ranking of binders, lactose tablets, capping, lamination.

INTRODUCTION

Tablets are solid dosage preparations each containing a single dose of one or more active substances and are usually obtained by compressing uniform volumes of particles (BP 2003). Tablets have remained the most common dosage form by which medicaments are usually administered to patients because of their advantages over the other dosage forms (Mattsson, 2000; Armstrong, 2002; Nachaegari and Bansal, 2004). Among the major essential properties required of a well formulated tablet is its robustness in order to withstand post compaction handling and transportation (Rubinstein, 1990).

In the production of tablets, some problems are usually encountered. The most common ones include: binding, sticking, picking, filming, chipping, cracking, capping and lamination (Bandelin, 1989). A tablet is said to have capped when the upper or lower segment of the tablet separates horizontally, either partially or completely from the main body of the tablet and comes off as a cap during ejection from the tablet press or during subsequent handling. Capping is usually caused by air entrapment in a tablet during compaction and subsequent expansion of the tablet on ejection from the die. Its other causes include presence of large amount of fines in the

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granulation, use of granules that are too dry or have very low moisture content, insufficient amount or improper binder, high plastoelasticity of the tableting base, excessive compression force, and lack of sufficient clearance between the punch and the die wall (Okor, 2005). Lamination on the other hand means the separation of a tablet into two or more distinct horizontal layers. Its causes are similar to those of capping.

Different methods of ameliorating capping and lamination have been reported (Odeku, 2006). One method that has been extensively studied is the use of binders (Odeku and Itiola, 2002; Olufunke et al., 2005; Eichie and Amalime, 2007). Binders act to ameliorate capping and lamination by decreasing the plastoelasticity of pharmaceutical powders. Materials used as binders predominantly display plastic compaction characteristics. Hence, when incorporated into elastic or fragmenting natured powders, they impart plasticity to them, thereby reducing their plastoelasticity. Plastoelasticity refers to the relative elastic to the plastic compression property of the pharmaceutical powder (Uhumwangho and Okor, 2004). Brittle fracture index (BFI) has been used as a measure of plastoelasticity of pharmaceutical powders (Ejiofor et al., 1986; Esezobo and Pilpel, 1987; Okor et al., 1998; Eichie and Okor, 2002; Onyekweli et al., 2004) and also to estimate the tendency of a tablet to cap or laminate under a diametral stress (Hiestand et al., 1977; Hiestand, 1996; Alebiowu and Itiola, 2002; Iwuagwu and Onyekweli, 2003; Eichie et al., 2005). BFI is measured by comparing the tensile strength (T_o) of a tablet with centre hole with the tensile strength (T) of a similar tablet without a centre hole. The centre hole is a built-in model defect, which simulates the actual voids formed in the tablets (due to air entrapment) during manufacture. The voids or low density regions in the tablet are weak points from which cracks propagate when stress (due to die wall pressure) is applied on the tablet during decompression (Uhumwangho, 2004). The ability of a material to relieve stress around the voids by plastic deformation is the property estimated with BFI (Williams III and McGinity, 1988). BFI is calculated with the equation (Hiestand et al., 1977):

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

and T or T_o is computed using the equation (Fell and Newton, 1970):

$$T \text{ or } T_o = 2F/ \pi Dh \quad (2)$$

where, T or T_o = tensile strength (MN/m^2) of tablet without or with centre hole respectively; F = diametral compression load (MN) needed to cause tensile failure of the tablet; D = tablet diameter (m); h = tablet thickness (m).

BFI values range from 0 to 1. A high value (tending to 1) implies high fracture tendency, while a low value (tending to 0) implies low fracture tendency. Tablet formulations with BFI values ≥ 0.5 are prone to high fracture tendencies (Hiestand et al., 1977). Incorporation of binders to pharmaceutical powders reduces the BFI values of their compacts. Materials used as binders in tablet production have been classified based on nature or origin (BPC 1994; Ofuer III and Klech-Gelotte, 2002). This work however, aims at utilizing BFI as a tool to classify, group and rank some binders used in the formulation of lactose (a fragmenting pharmaceutical powder) into tablets with low tendencies to cap or laminate.

MATERIALS AND METHODS

Model pharmaceutical powder

-D (+) – Lactose monohydrate (Fluka Netherlands): Model fragmenting powder was used as supplied by Zayo-Sigma Jos, Nigeria.

Binder materials

The gums used were extracted from acacia exudates (*Acacia senegal*), cashew exudates (*Anacardium occidentale*), they were all supplied by the plant collector in National Institute for Pharmaceutical Research and Development (NIPRD) Abuja; and okra pods (*Abelmoschus esculentus*) were purchased from a local market in Suleja, Niger State.

The starches used were extracted from maize (*Zea mays*), sweet potato (*Ipomoea batatas*), cassava (*Manihot utilissima*), and wheat (*Triticum aestivum*), all purchased from a local market in Suleja. Corn starch BP (Sigma – Aldrich USA), was supplied by Zayo-Sigma Jos, Nigeria, and pregelatinized starch, prepared from corn starch BP according to BP 1993 method.

The cellulose derivatives: carboxymethylcellulose sodium (Fluka Netherlands), hydroxypropylmethylcellulose (Fluka USA); and other binders-gelatin [gel strength (Bloom): 160] (Fluka Germany) and povidone (Polyvinylpyrrolidone) K15 (Fluka USA), were all used as supplied by Zayo-Sigma Jos, Nigeria.

The gums were extracted as reported by Nasipuri et al., 1996. Briefly, whereas clean acacia and cashew gum tears were pulverized and screened through a 600 µm sieved and not autoclaved, the okra pods were washed several times, thinly sliced and autoclaved at 121°C for 10 min. Thereafter, each material was separately soaked in 0.1% of sodium metabisulphite solution for 24 h, and then strained through a filter cloth. The resulting dispersion was again strained through a muslin bag before undergoing centrifugation at 18000 rpm for 90 min. The supernatant was carefully decanted and gum precipitation effected by treating it with twice its volume of acetone. The resulting precipitate was redissolved in distilled water and the solution reprecipitated with twice its volume of acetone. Finally, the precipitate was dried at 40°C for 5 h in a hot air oven. The dried gum was pulverized and sieved through 600 µm screen before storing in air tight containers.

Extraction of starches was executed as reported by Nasipuri (1979) with little modification (the maize and wheat grains were separately soaked in 0.1% sodium metabisulphite solution for 24 h before milling in order to enhance the separation of starch from the grains).

Preparation of granules

100 g batches of a basic formulation of lactose powder, representing a fragmenting/brittle natured drug powder (82% w/w), lactose

Table 1. Amount of binder solution used in the granulation process.

Starches and CMC		Gums, povidone, gelatin and HPMC	
Stock: 25% w/v	**Stock: 50% w/v**	**Stock: 10% w/v**	**Stock: 20% w/v**
2.5% w/w = 10.2 ml	7.5% w/w = 16.2 ml	1.0% w/w =10.1 ml	3.0% w/w = 15.5 ml
5.0% w/w = 21.0 ml	10.0% w/w = 22.2 ml	2.0% w/w = 20.4 ml	4.0% w/w = 20.9 ml
	12.5% w/w = 28.6 ml		5.0% w/w = 26.3 ml

as filler (8% w/w) and corn starch BP as disintegrant (10% w/w) were dried and mixed for 10 min in a planetary mixer (Model A 120, Hobart Manufacturing CO, UK). The powder mixture was moistened with the appropriate amount of binder solution (Table 1) equivalent to 1.0, 2.0, 3.0, 4.0 and 5.0% w/w (for gums, povidone, HPMC and gelatin) and 2.5, 5.0, 7.5, 10.0 and 12.5% w/w (for starches and CMC) in the final granules and granulated by wet massing with mortar and pestle. The homogeneous wet mass was then screened through a 1400 µm sieve and the wet granules dried in a hot air oven (Unitemp LTE Scientific Ltd Great Britain) at 50°C for 18 h. Thereafter, the dried granules were screened through a 600 µm sieve and stored in air tight containers over silica gel before tableting.

Determination of granule density

Granule density of each formulation was determined using the fluid displacement method (Reich et al., 2002; Eichie et al., 2005) and applying the equation (Ohwoavworhua et al., 2007):

$$\rho_g = W/[(a + w) - b]\,SG \quad \ldots\ldots\ldots\ldots\ldots\ldots \quad (3)$$

where, ρ_g = granule density in grams per cubic centimeter; W = granule weight in grams; SG = liquid paraffin specific gravity = 0.802; a = Pycnometer + liquid Paraffin weight in grams; b = Pycnometer + Liquid paraffin + granule weight in grams.

Preparation of tablets

Immediately before tableting, each batch of granules was mixed with 0.5% w/w of talc. Tableting was done with a single punch tableting machine (Kilian Frankfurt Germany) having a flat punch surface of diameter 12.55 mm. Tablets were made by weighing accurately 500 mg of granules and carefully transferring them into the die and then compressing manually at a pre-determined pressure of 7.50 arbitrary units. The pressure held on the granules for 30 s before releasing to allow consolidation to occur. The tableting procedure was repeated for tablets with center hole, 1.5 mm in diameter (made with the upper and lower adapters having a hole and a pin at their centres respectively) (Uhumwangho et al., 2006). All the tablets were compressed to the same relative density (0.80). Prelubrication of the die and punches in each stage was done by compressing a powder of pure talc before the granules were compressed (Sinka et al., 2004). The tablets were stored in air tight containers over silica gel for 72 h before the relevant tests were conducted.

Tests carried out on tablets

Weight and dimension measurements

Tablet weights were determined using electronic balance (Mettler Toledo B154, Switzerland) while the dimensions were measured with Mitutoyo gauge (Model 10C – 1012 EB Japan), to within ±1 mg and ± 0.01 mm, respectively. All the measurements were made in triplicates and the means utilized in relevant calculations.

Crushing strength

Crushing strengths of tablets were determined at room temperature by diametral compression (Odeku and Itiola, 1998), using a hardness tester (Kal Kolb, Erweka Germany). Results were taken from tablets that split cleanly into two halves without any sign of lamination. All measurements were made in triplicates and their means reported. Tablets tensile strengths and BFI were then evaluated using Equations (2) and (1), respectively.

Statistical analyses

Friedman's Test (Jones, 2002)

Friedman's test was employed to test the null hypotheses (H_o) that:

i) There were no significant differences between the BFI values of Lactose tablets formulated with different binders at fixed concentrations within the range 2.5 - 12.5% w/w.
ii) There were no significant differences between the BFI values of Lactose tablets formulated with different binders at fixed concentrations within the range 1.0%w/w - 5.0%w/w.

Alternate hypothesis (H_A): there are considerable differences between the tablets' BFI values.
Level of Significance (α): 0.05. The Friedman Test is executed with the formula:

$$X^2_R = \frac{12}{N_{rows}\,N_{columns}\,(N_{columns}+1)} \lesseqgtr R^2 - 3N_{rows}\,(N_{columns}+1)$$

where : N_{rows} = number of rows in table; $N_{columns}$ = Number of columns in table; R = Sum of ranks in each column; X^2_R = calculated Friedman's Statistic

Regression analysis

This was carried out using Microsoft excel 2003 regression analysis tool pack.

RESULTS AND DISCUSSION

Tables 2 and 3 reveal that BFI values for all the tablets

Table 2. Friedman's test for lactose tablets formulated with binders at fixed concentrations within the range 2.5% w/w – 12.5% w/w.

	Brittle fracture index (BFI)						
Binder concentration (% w/w)/ rank	**LCOS**	**LCAS**	**LMAS**	**LPOS**	**LWES**	**LPGS**	**LCMC**
2.5	0.4270	0.3908	0.4563	0.3021	0.3279	0.3803	0.3137
(R')	(6)	(5)	(7)	(1)	(3)	(4)	(2)
5.0	0.3206	0.3334	0.3066	0.2650	0.2970	0.2797	0.3067
(R')	(6)	(7)	(4)	(1)	(3)	(2)	(5)
7.5	0.2269	0.1909	0.3015	0.2416	0.2839	0.1991	0.2212
(R')	(4)	(1)	(7)	(5)	(6)	(2)	(3)
10.0	0.1850	0.1555	0.2323	0.2004	0.2009	0.1559	0.1493
(R')	(4)	(2)	(7)	(5)	(6)	(3)	(1)
12.5	0.1369	0.1391	0.2006	0.1673	0.1332	0.1450	0.1180
(R')	(3)	(4)	(7)	(6)	(2)	(5)	(1)
R	23	19	32	18	20	16	12

LCOS – Lactose tablets formulated with corn starch B.P. as binder.
LCAS – Lactose tablets formulated with cassava starch as binder.
LMAS – Lactose tablets formulated with maize starch as binder.
LPOS – Lactose tablets formulated with potato starch as binder.
LWES –Lactose tablets formulated with wheat starch as binder.
LPGS – Lactose tablets formulated with pregelatinized starch as binder.
LCMC –Lactose tablets formulated with carboxymethylcellulose sodium as binder.
R - Sum of Ranks (R') in each column calculated Friedman's statistic = 10.1999; Tabular Value = 12.592.

Table 3. Friedman's test for lactose tablets formulated with binders at fixed concentrations within the range 1.0 – 5.0% w/w.

	Brittle fracture index (BFI)					
Binder concentration (% w/w)/ rank	**LACG**	**LCAG**	**LOKG**	**LGEL**	**LPVP**	**LHPMC**
1.0	0.4672	0.3764	0.4245	0.3815	0.6853	0.4465
(R')	(5)	(1)	(3)	(2)	(6)	(4)
2.0	0.4157	0.3365	0.3338	0.3105	0.5073	0.3054
(R')	(5)	(4)	(3)	(2)	(6)	(1)
3.0	0.2957	0.2016	0.2815	0.3011	0.3891	0.2959
(R')	(3)	(1)	(2)	(5)	(6)	(4)
4.0	0.2322	0.1933	0.2073	0.2536	0.2463	0.2298
(R')	(4)	(1)	(2)	(6)	(5)	(3)
5.0	0.2055	0.1677	0.1831	0.1927	0.2221	0.1932
(R')	(5)	(1)	(2)	(3)	(6)	(4)
R	22	8	12	18	29	16

LACG – Lactose tablets formulated with acacia gum as binder.
LCAG – Lactose tablets formulated with cashew gum as binder.
LOKG – Lactose tablets formulated with okra gum as binder.
LGEL – Lactose tablets formulated with gelatin as binder.
LPVP – Lactose tablets formulated with povidone as binder.
LHPMC–Lactose tablets formulated with hydroxypropylmethylcellulose as binder.
R- Sum of ranks (R') in each column.
Calculated Friedman's Statistic = 15.5857; Tabular Value = 10.490.

decreased with increase in binder concentration. This effect resulted from decrease in the ratio of elastic to plastic compliance of the lactose granules as more binder (plastic material) was incorporated into the powder mix. The starches apparently displayed differences in their abilities to reduce BFI of the tablets. This is in line with earlier findings (Alebiowu and Itiola, 2002; 2003; Odeku et al., 2005), however, Friedman's test revealed that the differences were not statistically significant ($p > 0.05$). The insignificant difference may not be unconnected with

Table 4. Summary of regression analyses of BFI on binder concentration for lactose tablets formulated with binders at fixed concentrations within the range 2.5 – 12.5% w/w.

Tablet type	r	R^2	F	Sign. F	Slope
LCOS	0.9808	0.9619	75.8316	0.0032	-0.0286
LCAS	0.9524	0.9070	29.2527	0.0124	-0.0273
LMAS	0.9386	0.8810	22.2120	0.0181	-0.0234
LPOS	0.9953	0.9905	314.000	0.0004	-0.0142
LWES	0.9620	0.9255	37.2456	0.0088	-0.0194
LPGS	0.9554	0.9127	31.3621	0.0112	-0.0238
LCMC	0.9750	0.9506	57.6783	0.0047	-00220

the fact that the binders tested, except CMC, were from the same "family" (starches). On the other hand, differences in the compaction properties of the pharmaceutical powders utilized in the previous studies, and the non application of any statistical analysis in the interpretation of the results reported by those researchers may be responsible for the present observation. Plant gums, povidone, gelatin and HPMC exhibited obvious differences in their abilities to reduce BFI of the tablets (Table 3). Previous researches (Odeku and Itiola, 2002; Eichie and Amalime, 2007) also revealed similar findings, but the researchers did not state whether such differences were statistically significant or not. The application of Friedman's test to the results of the present study has shown that the observed differences between the BFI of lactose tablets formulated with these binders are statistically significant ($p > 0.05$). The significant difference being reported in this work may or may not be revealed if such statistical test is employed to BFI values of tablets formulated with the same binders within similar concentration range, but with a pharmaceutical powder of dissimilar compaction properties. In this work however, it is evident that binders from different "families" possess different abilities in their effectiveness in reducing BFI, and these differences are statistically significant. Furthermore, since reduction in BFI values invariably implies reduction in the incidence of capping and lamination in tablets (Okor, 2005), BFI may be a useful tool in the grouping and ranking of these binders based on their abilities to ameliorate capping and lamination in lactose tablets. By inspection, it is evident from Table 3 that cashew gum consistently imparted the lowest BFI values to lactose tablets. When placed side by side with acacia gum or povidone, its superiority to these two binders in reducing BFI in a fragmenting material which lactose exemplifies is very obvious. Albeit, cashew gum belongs to the same "family" as acacia gum, the difference between their rank sums is higher than that between cashew gum and okra gum, cashew gum and gelatin, cashew gum and HPMC (Table 3), thereby suggesting the usefulness of BFI in the identification of very effective binders, thus grouping and ranking them based on their abilities to ameliorate capping and lamination in lactose tablets.

The regression analyses (Tables 4 and 5) reveal that there is a strong correlation between binder concentration and BFI (all the correlation coefficient values, $r, > 0.9$). The slope values show that starches and CMC employed at the range of 2.5 - 12.5% w/w with increment of 2.5% w/w each time reduced the BFI of lactose tablets to values between 0.01 - 0.03; while gums, povidone, gelatin and HPMC employed at the range of 1.0 - 5.0% w/w with increment of 1.0% w/w each time caused BFI reductions to values between 0.04 - 0.12, equivalent to four times the reductions imparted by starches or CMC at the concentrations used. This implies that although plant gums, povidone, gelatin and HPMC, consistently used at lower concentrations than starches and CMC, they exhibited greater ability to reduce BFI. This further confirms that binders may be grouped based on their ability to reduce BFI (amelioration of capping and lamination) (Itiola and Pilpel, 1986; Odeku and Itiola, 1998) and ranked based on their levels of effectiveness.

It is evident from Table 6 that no particular "family" of binders occupied a unique range of BFI values. Rather, binders from various "families" appeared at different concentrations to achieve a range of BFI reduction in lactose tablets. This implies that BFI cannot be a useful tool in the classification of binders based on their abilities to solve the problem of capping and lamination in tablets. However, binders from different families can be grouped together based on the range of reduction in BFI they can achieve at fixed concentrations. They can also be ranked based on their levels of effectiveness in reducing the incidence of capping and lamination in tablets using BFI as a tool. This grouping emphasizes that one is at liberty to choose binder(s) from any of the "families" of binders used in this study to achieve a certain range of BFI values depending on the compaction properties of the drug and/or filler(s). Where the drug, irrespective of its nature(plastic, fragmenting, or elastic), is of very low dose and the diluent forms the major part of the powder mix, this grouping remains very relevant to a pharmaceutical formulator since lactose usually is the commonest diluent used in tablet formulation. It is also useful in taking decisions based on performance of the binders

Table 5. Summary of regression analyses of BFI on binder concentration for lactose tablets formulated with binders at fixed concentrations within the range 1.0 – 5.0%w/w.

Tablet Type	r	R^2	F	Sign F	Slope
LACG	0.9786	0.9576	67.7719	0.0038	-0.0707
LCAG	0.9388	0.8813	22.2748	0.0180	-0.0561
LOKG	0.9849	0.9701	97.2883	0.0022	-0.0609
LGEL	0.9793	0.9590	70.2290	0.0036	-0.0435
LPVP	0.9767	0.9539	62.1437	0.0043	-0.1187
LHPMC	0.9819	0.9624	80.7113	0.0029	-0.0616

Table 6. Grouping of binders using BFI as a tool within fixed concentrations.

	Binder concentration (% w/w)								
BFI	**1.0**	**2.0**	**2.5**	**3.0**	**4.0**	**5.0**	**7.5**	**10.0**	**12.5**
0.05 – 0.10									
0.10 – 0.15								CMC	COS CAS WES PGS CMC
0.15 – 0.20					CAG	CAG OKG GEL HPMC	CAS PGS	COS CAS PGS	
0.20 – 0.25				CAG	ACG OKG PVP HPMC	ACG PVP	COS POS CMC	MAS POS	MAS
0.25 – 0.30			CAG	ACG OKG HPMC	GEL	POS WES PGS	WES		
0.30 – 0.35		CAG OKG GEL HPMC	POS WES CMC	GEL		COS CAS MAS CMC	MAS		

and their economy since some binders are more expensive than others (Eichie and Amalime, 2007).

Furthermore, Table 6 also reveals that more than one type of binder at fixed concentration may impart a chosen range of BFI value on tablets. There is therefore, need to rank these binders based on performance or effectiveness. For example, a target BFI range of 0.10 - 0.15 will be achieved by COS, CAS, WES, PGS and CMC at concentration of 12.5% w/w. When ranked based on performance, the following order was observed (Table 2): CMC > WES > COS > CAS > PGS. In addition, at 4.0% w/w concentration, ACG, OKG, PVP, and HPMC imparted a BFI range of 0.20 - 0.25 on lactose tablets in the order (Table 3):OKG > HPMC > ACG > PVP. These rankings show that from an array of binders that can impart the same range of BFI value at the same concentration, choice may still be made based on the level of effectiveness of each binder. However, it must be stressed that this choice should also be guided by the dissolution profile desired from the formulation. For example, CMC ranked better than starches while HPMC ranked better than acacia gum and povidone, but these two cellulosic binders are unsuitable for the formulation of conventional tablets due to delayed release drug from them.

Non-excipient factors that influence the BFI values under normal conditions are the compression pressure, tableting speed, machine tooling and environmental factors.

All these must be well controlled to achieve good outcome.

Conclusion

This work has shown that Brittle fracture index could be a useful tool in grouping binders based on their abilities to ameliorate capping and lamination in tablets. Its usefulness also extends to the ranking of binders based on their levels of effectiveness in solving the problem of capping and lamination. However, “families” of binders based on nature or origin could not be classified using BFI as no “family” occupied a unique range of BFI values within the concentration ranges used in the present study.

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