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INFLUENCE OF CONCENTRATION OF MODIFIED MAIZE STARCH ON COMPACTION CHARACTERISTICS AND MECHANICAL PROPERTIES OF PARACETAMOL TABLET FORMULATIONS

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SUMMARY: Compact -forming ability of a multi-component paracetamol tablet formulations with varying amounts of modified Maize Starch incorporated as external disintegrant was studied with a view to know the influence of the increase on compaction characteristics and the quality of resulting tablets. Three formulations coded B-1, B-2 and B-3 with similar constituents but varying amount of modified Maize starch were designed and prepared by wet granulation process to yield granules that were compacted into tablets. Data and information were collected from out-of-die method; using hand operated tablet press at 5 predetermined pressures and fitted into Heckel plots. Compaction behaviours and mechanical properties of the tablets were evaluated.

The three formulations showed consolidation by deformation but at different levels. Sample B-3 which has highest concentration of modified Maize starch seemed to perform on the average better than B-2 and B-1. Mean yield pressure vindicated the ease of compression of granules to be B-3 > B-1 > B-2. It is inferred that modified Maize starch could be used to moderate the compaction characteristics of pharmaceutical agglomerates and mechanical properties of resulting tablets. Lower values of yield pressure, constant A, and relative density of B-3 justified the increase in concentration to be beneficial to the formulation. B-3 had highest concentration of modified Maize starch and showed less resistance to consolidation, decrease in granules fragmentation and fast onset of deformation.

Keywords: Packing fraction, Heckel plot, Mean yield pressure, Tensile strength, Dosage forms.

INTRODUCTION

Pharmaceutical dosage forms design; development and delivery are essential components of industrial pharmaceutical manufacturing practice. The development and manufacture of solid dosage forms are more critical as many variable parameters at both formulation and processing stages must be properly gauged if the final product must deliver as required (1, 2). Tablet which

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was reported to be the most popular of all dosage forms (2), is composed of active ingredient(s) and several other excipients each of which performs distinct functions that enable the design of quality into the product right from the onset. These excipients are however not without demerits either alone or in combination. One of such excipients is Starch of various sources and modifications; all of which were widely reported in literature (1). Of particular reference is the use of Starch and its modified forms as disintegrant in tablet formulation where it is incorporated intra- or inter-granularly. Modified Maize Starch was quoted to have additional properties of fluidity, compressibility and compactibility which engendered better processing performance and improved tablet characteristics (1). These additional qualities prompted this current study to explore the concentration dimensions of MMS on compaction phenomena unlike the previous work that compared MMS with other disintegrants.

Wet granulation which was reported to be the most widely adopted method for production of granules for various purposes including manufacture of tablets, allowed incorporation of active ingredient(s) with as many excipients as may be required. In the process, mixture of powders with poor cohesion is converted to granules that possess essential properties of fluidity and compressibility which allow for uniform die-fill, tablet content and weight uniformity during compaction operations (3,4).

In literature, a large number of compaction equations were reported, but no single one is found to be capable of fulfilling all the requirements needed for proper articulation of satisfactory and valid material constant such as yield strength. However, compaction models proposed by Heckel and Kawakita were commonly deployed especially by pharmaceutical scientists as useful information could be derived that relate to physical properties of materials under compaction process (5, 6, 7). Powder compaction displays the ability of powder particles to yield a compact of good strength, and plays important roles in manufacturing of solid products of metallic, ceramic and especially pharmaceutical powders and granules. As a process, compaction of powder is reported to take place in several stages some of which may occur simultaneously in an overlapping manner. Such stages as powder particle sliding, rearrangement, fragmentation, loose and dense packing, and reduction in powder bed porosity were mentioned in literature. On application of load, a reduction in space and increase in interparticles friction prevent particle movement and lead to changes in particles dimensions which culminate in deformation and fragmentation. The particle fragments occupy the voids between particles and lead to further reduction in volume. Further increase in pressure makes the fragments to undergo deformation (5, 6).

Comoglu 2007, Sonnergaard 1999, observed that none of the powder compaction equations was found to satisfy comprehensive analysis of compaction mechanisms, but agreed that they provided useful information that help to determine phases of compaction and predominant mechanisms that took place. They opined that more than one compaction equation may be needed to validate the results of any study if such results will be of any practical value. They also showed that the two most common models of Heckel and Kawakita are mathematically identical especially at pressures lower than yield strength and that the experimental data obtained at the initial or final stages of consolidation process should be fitted into the equation (5, 6).

The assumption that the consolidation of powder bed follows first order kinetics, and that the extent of consolidation is correlated to powder porosity is reported in literature (8). The need for robust characterization of compaction behaviour is evident and such must achieve the goal of predicting the strength of resulting compact from force – density curves and other derived parameters. Such robust process will diffuse the confused picture shown by a review of values of yield pressure of a particular material from different authors. The variations are too large to give satisfactory and valid material constant (6).

In Heckel model which is represented by equation 1, the process of densification is a proportionality between change in density arising from application of pressure and pore fraction (5). Thus, a plot of ln [1/ (1-D)] versus P is linear especially at the initial stage of consolidation. (1-D) is the pore fraction and D the density of compact; (1-D) reduces and D increases as applied pressure P is

increased. K is a constant derived from the slope of linear

$$\ln [1 / (1 - D)] = KP + A \quad \text{---------- 1}$$

portion of the plot. It is inversely proportional to the mean yield pressure of the material in question (i.e P_y=1/K). The higher the value, the smaller the yield pressure and the easier it is to compress such material into compact. A, is also a constant derived from the intercept of extrapolated linear portion of the plot. It is the relative density when no pressure has been applied to the powder bed (zero pressure). It represents original compact volume and the two stages of consolidation due to initial relative density of powder and the densification due to the particle rearrangement (8, 9).

In this research work, the compaction behaviours of a multi-component paracetamol tablet formulations with varying concentrations of modified Maize Starch used as external distintegrant were studied. The composition of the three formulations is similar except that concentrations of 3, 6 and 9% modified Maize starch were inter-granularly incorporated respectively. The mechanical properties of resulting tablets were equally investigated. Experimental data derived from "out-of-die" method was fitted into Heckel equation so as to derive information and data that could be used to justify the characteristics of the formulations and the relevance of increase in concentration of modified Maize starch.

MATERIALS AND METHODS

Modified Maize Starch (MSS) was prepared from Maize Starch BP as previously reported (1). Other materials used include paracetamol powder (Wenzhou Pharma, China), microcrystalline cellulose (J. Rotten Maier and Sohnne, Germany), polyvinyl pyrrolidone (PVP), (BASF, Germany), and magnesium stearate (Vigenesh, India). The items were sourced courtesy Roche (Nigeria) Ltd, Lagos.

Each formulation batch is composed of paracetamol 83.33%, microcrystalline cellulose (PH-102) 10.33%, PVP 2.5%, magnesium stearate 0.5% and MMS 3, 6, and 9%. Quantity of microcrystalline cellulose was adjusted to accommodate 6% and 9% respectively. Each of the materials was separately weighed for each batch coded B-1, B-2 and B-3 using Mettler PM-140 balance (Mettler Switzerland). Paracetamol and microcrystalline cellulose were dry-mixed for 3 min at 200 rpm using Erweka AR mixer (Erweka, Germany). Binder solution of PVP was prepared by dissolving in 160 ml hot distilled water and allowed to cool to 40°C. The binder was added to the powder mixture and kneaded for 2 min at 200 rpm. The mixer was opened, scraped, closed back and kneaded for another 1 min. Wet granules were carefully discharged, manually pressed through sieve #10 (2mm size) and dried at 60°C (Ehret dryer) until moisture content (Ohaus moisture balance) was about 1.2%. Dried granules were manually pressed through sieve #20 (1.4mm). 3, 6 and 9% of MMS, and 0.5% of magnesium stearate were weighed, mixed and added into granules of each of batches B-1, B-2 and B-3 in a litre plastic container respectively. Each of the containers was rotated for 5 min to achieve blending. With hand operated tablet press (Carver), fitted with 12.5mm flat face punch and die, the granules were compressed to tablets with weight of between 500mg and 600mg at 5 different predetermined compression forces. 20 tablets from each batch were stored properly in airtight container for about 24h after which the tablets were reweighed; thickness and diameter measured with micrometer (Mituoyo). Multiple readings were taken; average and standard deviation calculated. Tablets hardness was determined by diametral compression using Schleuniger tester; average and standard deviation determined, and tablet density (D), tensile strength (Ts) and Porosity (Po) calculated using equations 2, 3 and 4 respectively.

$$\text{Tablet density } (D) = W/\pi r^2 h \quad \text{---------- 2}$$

$$\text{Tensile Strength } (T_s) = 2H/\pi dh \quad \text{---------- 3}$$

$$\text{Tablet Porosity } (P_o) = 1 - [4W/(\pi d^2 hD)] \quad \text{----------4}$$

W is weight (g), r is radius (cm), h is thickness (cm), d is diameter (cm) and D is density of the tablet. The values of ln [1/(1-D)] at different compression pressures; P were extrapolated from information and data on tablets characteristics (eqn. 2), and Heckel plots drawn. Other compaction parameters such as K which is slope derived from linear portion of Heckel plot, A; an intercept and represents relative density at zero pressure were determined. From value of A, relative density of tablet, DA was estimated from equation 5 as shown below (8, 9).

$$D_B = D_A - D_o \quad \text{---------- 5}$$

$$\text{Packing fraction } (P_f) = W/\pi r^2 h\rho \quad \text{---------- 6}$$

The mean yield pressure; P_y, was extrapolated from slope of the plots and used in the analysis of the compaction characteristics. Equation 6 was used to estimate the packing fraction of resulting tablets. Powder density is represented by ρ. Using equation 7; the pore fraction (1-D) is estimated while D is tablet density (5).

$$\text{Pore Fraction} = (1-D) \quad \text{----------7}$$

Table 1: Properties of tablets at different compression pressures.

Parameters	Batches	Compression Pressure (MN/m^2)				
		18.42	36.84	55.26	73.68	88.42
Weight (g),	B-1	0.5867 ± 0.0082	0.560 ± 0.0075	0.5601 ± 0.008	0.590 ± 0.007	0.5933 ± 0.009
n=10,	B-2	0.6038 ± 0.0055	0.5659 ± 0.0057	0.605 ± 0.0051	0.6009 ± 0.0072	0.5980 ± 0.0078
±SD	B-3	0.5005 ± 0.0059	0.5039 ± 0.0061	0.5170 ± 0.0055	0.500 ± 0.0065	0.5041 ± 0.0065
Thickness	B-1	0.5097 ± 0.0021	0.4763 ± 0.0027	0.4736 ± 0.0018	0.4954 ± 0.0024	0.4980 ± 0.0017
(cm), n=10,	B-2	0.5077 ± 0.0013	0.4720 ± 0.0017	0.5025 ± 0.0015	0.4977 ± 0.0015	0.4952 ± 0.0019
±SD	B-3	0.5177 ± 0.0014	0.4863 ± 0.0010	0.4647 ± 0.0015	0.4500 ± 0.0014	0.4300 ± 0.0014
Density	B-1	0.9380	0.9582	0.9637	0.9704	0.9708
(D)	B-2	0.9692	0.9770	0.9811	0.9838	0.9840
(g/cm^3)	B-3	0.7878	0.8443	0.8956	0.9056	0.9093
Hardness	B-1	19.5 ± 0.31	52.5 ± 0.82	88.5 ± 1.52	109.5 ± 1.81	123.5 ± 1.63
(N), n=10,	B-2	19 ± 0.23	36 ± 0.39	71 ± 0.95	90.5 ± 1.17	106 ± 1.4
±SD	B-3	16 ± 0.13	36 ± 0.36	77.5 ± 0.74	88 ± 0.70	111 ± 0.83
Packing	B-1	1.59	1.63	1.64	1.64	1.65
Fraction	B-2	1.82	1.83	1.84	1.85	1.85
(P_f)	B-3	1.47	1.57	1.67	1.69	1.78
Tensile	B-1	0.20	0.56	0.95	1.13	1.26
Strength, Ts	B-2	0.19	0.39	0.72	0.93	1.09
(MN/m^2)	B-3	0.16	0.38	0.85	0.99	1.31
Pore	B-1	0.0620	0.0418	0.0363	0.0296	0.0292
Fraction	B-2	0.0308	0.0230	0.0189	0.0162	0.0160
(1-D)	B-3	0.2122	0.1557	0.1044	0.0946	0.0907

RESULTS

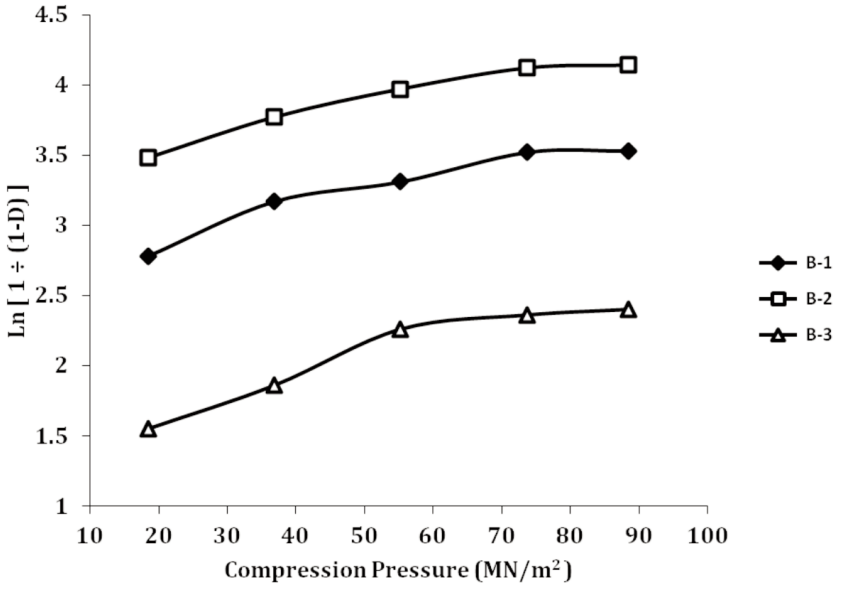
The results as presented in Table 1 indicate different attributes of tablets of batches B-1, B-2 and B-3 at various compression pressures. Tablets characteristics such as mean weight, thickness and density are in the table. Other tablets properties such as hardness, packing fraction, tensile strength and pore fraction are also contained therein.

There was a progressive reduction of tablets thickness in all the three batches as compression pressure increased but was much more pronounced in B-3 with about 16.94%, and is similar in B-1 (7.08%) and B-2 (7.03%). On the other hand, tablet density increased as applied pressure is increased. The increase was noticed across the formulation batches in the order B-3 (15.42%)> B-1 (3.5%) > B-2 (1.53%). The results indicated that B-3 which has higher concentration of 9% MMS was more sensitive to increase in compression force. The values of hardness of tablets from the three formulations indicated an increase as compression force was increased from minimum to maximum and followed similar trend of higher increase in the order B-3 (593.75%) > B-1 (533%) > B-2 (457.9%).

The packing fraction which is a measure of degree of consolidation of tablet upon compaction showed an increase in value as compression force was increased across the formulations. The increase of 21.69% in B-3, 4.4% in B-1 and 1.51% in B-2, were indications that B-3 consolidated more easily than B-1 which in turn densified readily than B-2. The tensile strength estimated increased across the formulations. The increase is amplified in B-3 in which the value changed from 0.16 at compression pressure of 18.42 MN/m^2 to 1.31 at applied pressure of 88.42 MN/m^2. Similarly, tensile strength of B-1 changed from 0.20 to 1.26 while that of B-2 amplified from 0.19 to 1.09; all at the same range of compression pressures.

Juxtaposing the results of packing fraction with that of tensile strength, it could be understood that the interparticles voids at the highest pressure are highly reduced in B-3 which has packing fraction of 1.78 and tensile strength of 1.31 MN/m^2, followed by B-1 with packing fraction of 1.65 and tensile strength of 1.26 MN/m^2 while B-2 being the least with values of 1.85 and 1.09 MN/m^2 respectively. These results were further corroborated by the outcome of estimation of pore

Figure 1: Heckel plots of multicomponent formulations of paracetamol tablets.



fraction and tablet porosity. Reduction in pore fraction of B-1 from 0.062 at pressure of 18.42 MN/m^2 to 0.0292 at pressure of 88.42 MN/m^2 and decrease from 0.0308 to 0.016 in similar pressures in B-2 and decline from 0.2122 to 0.0907 in B-3 at same pressure ranges were indications of decrease in volume of compact as a result of pressure application. The porosity values of 0.65 (B-1), 0.85 (B-2) and 0.78 (B-3) supported the assertion that the extent of volume reduction is a measure of compressibility of the material in question. This has made for good cohesion and strength in the resulting tablets as the number of pores was greatly reduced.

The summary of parameters extrapolated from Heckel plots in Figure 1 and density measurements are shown in Table 2. All the parameters were derived from the linear portion of the plots where the correlation coefficient is greater than 0.970 in all the three formulations. All the batches showed consolidation by deformation but in different degrees. Data from density measurements also portrayed the characters of each of the batches. K values were derived from slopes while A values were extrapolated from the intercepts of all the plots using Microsoft Office Excel 2007 (10).

DISCUSSION

It is recognized that the yield pressure; Py which is derived from inverse of K is related to the ability of materials to deform plastically thus higher K value means that the material will yield to low compression

Table 2: Parameters derived from Heckel plots and Density measurements.

Parameters	B-1	B-2	B-3
K	0.0128	0.0133	0.0193
Mean yield pressure; Py, (MN/m^2)	78.06	75.19	51.89
A	2.605	3.250	1.180
Correlation coefficient (R)	0.977	0.994	0.997
D_o	0.514	0.487	0.474
D_A	0.9574	1.1786	0.1655
D_B	0.4434	0.6916	0.3085

pressure and be made into compacts at low pressure. The opposite is the case with low value of K. The values of Py as shown in Table 2 and Figure 1 were indications that formulation B-3 will easily and rapidly attain onset of deformation compared to others. With Py value of 51.89 MN/m^2 for B-3 being the least, it is instructive that the formulation started consolidation by deformation faster than formulations B-2 which in turn set for deformation earlier (Py of 75.19 MN/m^2) than B-1 with the highest Py value of 78.06 MN/m^2. On the basis of these observations it is opined that the materials in B-1 are harder than those in B-2 which in turn are harder than those in B-3. It was noted also that the crushing strength (hardness) of tablets was uniformly spread in B-3 probably because of its lower Py value as reported by other researchers (11), but may not necessarily lead to strongest compacts at the highest compression pressure. The same low value of Py in B-3 could also be said to be responsible for its high tensile strength (1.31) compared to other batches as shown in Tables 1 and 2. Other researchers (9) attributed low Py values to creation of more contacts within the powder bed that culminated in strong interparticles bonding thus corroborating the observation in this study.

The constant A; which represents initial consolidation due to granules rearrangement, initial relative density and original compact volume (8, 9), gave values that corroborated the observations about yield pressure. The values showed that granules of B-3 were hard, B-1 harder while B-2 were the hardest. Comparison of values of A and K indicated that, as one increases the other decreases. This characteristic has been observed by other researchers, to be typical of most multi-component formulations with identical composition (12). High value of Do exhibited by B-1 as compared to other batches was an indication of high dense packing especially at zero pressure. The values of DA which were extrapolated from constant A were 0.1655 in B-3 < 0.9574 in B-1 < 1.1786 in B-2. Low value of DA is an indication of less resistance by the granules to consolidation and the fact that this occurred in B-3 with highest concentration of 9% MMS could mean that the granular nature may have provided few contact points that are responsible for less opposition. However, other researchers were of the opinion that other variables such as particle size and distribution, particle shape and specific surface area interplay to affect contact areas in a powder bed and may be difficult to distinguish (11). The values of DB as reflected in Table 2 indicated that B-2 with highest value has granules with best free-flowing attributes followed by B-1 and then B-3. This implied that swift movement of granules into die cavities during tablets compression will follow similar pattern. But this fluidity in B-2 did not translate into faster onset of deformation as a result of its higher resistance to consolidation and high Py value as shown in Table 2. Although B-3 had the least value of DB which implied resistance to movement by its granules especially after the initial rearrangement, its least resistance to densification has more than compensated for this to the extent that its Py value is the smallest of the three batches. Although researchers opined that the compaction bahaviour of mixture of powders appeared to be dependent on the deformation properties of the constituent materials and the processing techniques (13), it seemed from this work that MMS could be used to moderate the behaviours. Thus adding another dimension to the qualities of MMS as elucidated in the previous research work wherein it was shown that MMS is fluid, free-flowing, directly compressible and comparable to other disintegrant at some concentrations (1).

CONCLUSION

It could be established that the behaviours of the 3 formulations during compaction process were not the same, and these dissimilarities arose partly from different concentrations of MMS incorporated as every other components are identical and made the effects that may arise from different constituents inconsequential. Increase in quantity of MMS as reflected in B-3 resulted in better mechanical properties of resulting tablets as evidenced by tensile strength, hardness, packing fraction and pore fraction. It could also be inferred from the outcome of this research work that increase in concentration of MMS when used as external disintegrant led to decrease in value of mean yield pressure Py, thus facilitating easy and rapid onset of deformation which could be elastic, plastic or both, during compaction process. The low value of DA observed at the highest concentration of MMS in B-3, could also be explained to mean that there will be less resistance to consolidation and reduction in granules fragmentation during compaction as previously observed by other researchers (9).

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