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EVALUATION OF SORGHUM AND ANDROPOGON MCC AS FILLER-BINDERS IN ACETAMINOPHEN, ASCORBIC ACID OR METRONIDAZOLE TABLETS

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ABSTRACT

Dilution capacity of Sorghum or Andropogon MCC was evaluated for acetaminophen, ascorbic acid and metronidazole compacts. Empirical study involved binary blends of powder of any of these drugs with either of the new MCC in ratios between 10:90 and 50:50 at incremental and decreasing unit of 10%. Compacts of the blends were made with hydraulic tablet press at pressures of 32.2 – 124.8 mPa. Assessment parameters included bonding capacity, tablet density, friability and tensile strength. All formulations containing less than 20% of either polymeric filler -binder exhibited bonding capacities lower than 500 Kgf/m with capping and low compact densities. However, at concentrations of 30% w/w and above, the derived MCC produced compacts with BC of 1000 – 2210 Kgf/m at compression pressure of 62.4 mPa for acetaminophen and ascorbic acid formulations. Compacts of metronidazole powder blended with the dry binders at concentrations of the later ≥30% w/w exhibited tensile strength above 1.0 MN/m^3 at compression pressures of 93.6 -124.8 mPa. Tablet density increased with concentration of the binders at 30% w/w and above with good friability profiles of less than 2 % and tensile strength above 1.5MN/m^3. The new filler-binders derived from Sorghum and Andropogon at 30% w/w and above modulated the deformation profile of acetaminophen, ascorbic acid or metronidazole; from partially plastic /non-plastic to plastic behaviours, with

good compact characteristics. It can be inferred that Sorghum and Andropogon stalk could serve as non-woody source of MCC for pharma, food, cosmetic and allied industries.

KEYWORDS: Sorghum, Andropogon, MCC, Filler-binder, non-woody.

INTRODUCTION

Direct Compression (DC) is the simplest and most economic technique of oral dosage production but requires high level of skill to achieve the desired process speed and efficiency.[1,2,3] Excipients most preferred are those whose particles have been engineered for good flow and compressibility characteristics. Most often used DC excipients include spray-dried (anhydrous and granulated) Lactose, Microcrystalline Cellulose (MCC) and modified starch.

MCC has relatively low bulk density and broad particle size distribution such that small amounts of the polymer are able to efficiently bind other materials, especially active pharmaceutical ingredients with poor flow and compressible qualities. MCC exhibits a high dilution potential; the broad particle size range provides optimum packing density and coverage of other materials.[1, 2, 3] Doelker et al[4] compared sixteen MCCs from seven manufacturers and noted that differences in packing and flow properties were due to variations in moisture content, particle shape and particle size distribution. Other tableting quality differences were attributed partly to dissimilarities in moisture content and internal structure of the particles caused by processing conditions specific to each manufacturer. In another paper Doelker concluded that large differences exist among various MCCs, even if all of them comply with compendial specifications.[5] Therefore, substitution of one product for another must be validated.

Acetaminophen is a popular analgesic with bitter taste and poor flow characteristics.[6] Researchers and manufacturers are continually innovating on value addition in the production and packaging of this commonly used medicine. Pure paracetamol particles are partly elastic but behavior under compressive load can be changed to a more plastic deformation when granulated with binding agents.[7, 8, and 9] Rowe[10] noted that addition of polymeric binders increases the crushing strength of paracetamol tablets.

Capping and lamination are problems which frequently occur during tablet production. Malamataris et al[11] noted that the incidence of capping and lamination during production of

pharmaceutical tablets, followed by ejection from the die, depends on the plastic and elastic behavior of the material used and they proposed that the ratio of elastic recovery to the plastic compression (ER/PC) was a useful parameter to measure capping tendency. As alternative to granulation technique, Yu et al[12] suggested that in order to produce acceptable Avicel/ paracetamol tablets the percentage energy ratio should be lower than 10%. They also showed that the optimal mixture of the two powders with respect to tensile strength, friability and absence of capping was 50:50 MCC/PCM mixture.

Garr and Rubinstein[13], Wells and Langridge[14] reported that using microcrystalline cellulose/dicalcium phosphate dihydrate in paracetamol formulations resulted in resistance to capping and produced tablets with much greater tensile strength compared to compacts containing MCC alone. MCC predominantly undergo plastic deformation and the mechanical strength is largely due to hydrogen bonding which is related to the proximity of adjacent particles.[15] The number and area of the contact points will increase with compaction pressure leading to an increase in tensile strength. Dicalcium phosphate dihydrate on the other hand increases the TS of the tablets by improving flow and the initial filling of the die. The material fills the void spaces during compression as a result of extensive fragmentation. This leads to optimum force utilization, improved consolidation and better binding of MCC.[13, 14]

Ascorbic acid is a white, or colorless crystalline compound structurally related to the monosaccharides.[16,17] It is stable in the solid state but easily oxidized on exposure to moisture or air. Oxidation is accelerated by heat, light, alkaline, oxidative enzymes and traces of copper and iron. The ease with which ascorbic acid oxidizes in presence of air and moisture renders it unsuitable a candidate in wet granulation technique involving the use of aqueous dispersion as binder. It is therefore a material of prime consideration in direct compression formulation. Nystrom and Glayer[18] reported that ascorbic acid particles show intermediate fragmentation during compaction. The relatively low tablet strength obtained indicates that the attractive forces in plain vitamin C tablets are relatively weak as in paracetamol and therefore not resistant to stress relaxation and elastic recovery.

When a dry binder adequately coats such powders, the tablet strength increases with the binder concentration. The indication is that relatively high proportion of dry binders will be required to compress powders such as paracetamol and ascorbic acid.

Metronidazole is widely used in the treatment of trichomonal infections of the genito-urinary tract, intestinal amoebiasis and giardiasis.[17] Oduyebo et al. reported that metronidazole is among the top 10 most prescribed antibiotics for therapeutic (2nd only to ceftriaxone) and prophylactic (1st) purposes in Nigeria.[19] It is therefore amongst the very vital molecules in the Nation's essential medicines list. Robust and elegant production of the tablets is of critical importance to the nation's health care delivery.

Itiola and Pilpel[20] studied metronidazole tablet formulations containing different binders. They found that incorporation of these excipients altered the tensile strength, disintegration and dissolution times. Also in 1991, Itiola and Pilpel[21] evaluated formulation effects on the mechanical properties of metronidazole tablets. They found that changing binder concentration from 'low' to high levels increased the tensile strength of the tablets. Methylcellulose binding effect had greater ability to reduce lamination tendency of the tablets than polyvinyl pyrolidone. Plain metronidazole crystals appear to exhibit some high elastic recovery with low plastic compression effect and high capping tendency similar to paracetamol and ascorbic acid. Incorporation of MCC or other suitable dry filler-binder may improve compressibility of this amoebicidal agent and render such blend suitable for direct compression tableting.

Direct compression formulations require careful and systematic determination of parameters that would result in optimum compact properties. Materials have different characteristics depending on their sources and mode of production.[4,15, 22] Determination of physical equivalent is therefore very important in direct compression tableting. New MCC products must be evaluated in order to validate their effects on fluidity, compressibility and /or lubricity. Wells and Langridge[14] stated that the capacity or compressibility potential of a compression aid is the proportion of a non-compressible drug which can be incorporated into the vehicle to produce satisfactory tablets. In previous investigations[23, 24], the extraction, physicotechnical, compression and compatibility characteristics or behaviours of microcrystalline cellulose derived from Sorghum and Andropogon plants were elucidated. SOMCC or AMCC exhibited potentials as DC diluent. The current study is aimed at determining dilution capacity of these polymers as modulating agents for non-compressible drugs; acetaminophen, ascorbic acid and metronidazole particles in DC tableting.

MATERIALS AND METHODS

Ascorbic acid, acetaminophen and metronidazole (Vision Pharm. Co. Ltd China) were used as obtained from the supplier. The grades of microcrystalline cellulose SOMCC and AMCC were derived from de-lignified α-cellulose following hydrolysis with a mineral acid HCl as previously processed.[23 and 24] The resulting slurry was neutratrilized with dilute ammonia solution, washed, air dried, pulverized, screened and stored in a desiccator. The powder was micronized with Kenwood Blender model BL 350 (Kenwood Ltd, UK) while the Carver hydraulic press was used for tableting.

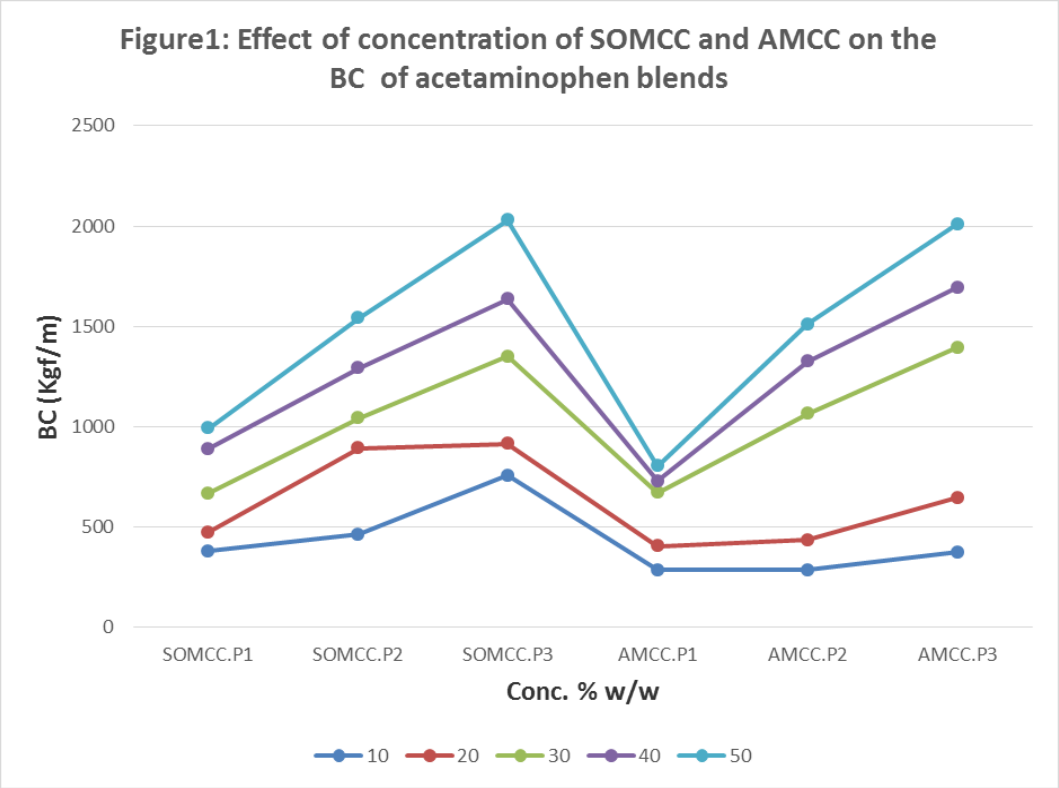
The effect of concentration of SOMCC or AMCC on the compressibility of acetaminophen, ascorbic acid and metronidazole was determined. This is to enable determination of optimal drug carrying capacity of the new polymers with no capping tendency at specified compression conditions. Tablet density, friability, bonding capacity (BC), and tensile strength were used as basis for comparing the bonding properties as has been applied previously for different direct compression excipients.[14]

Batches of Blend of the new filler-binder and drugs were made in ratios, which ranged from 0:100 increasing concentration of 10 %. In each case, appropriate quantity of the polymer and the drug was weighed and blended at constant time interval. Compacts of the binary matrix were made, total weight per tablet being average of 400mg. Six different pressure levels of 31.2, 62.4, 93.6, 124.8, 156.0 and 187.2 MPa were employed. Tablet dimensions: thickness (t) and diameter (D) were taken 24h after compression, crushing strength as applied load (P) was measured with Erweka hardness tester and the tensile strength (Ts) was calculated using equation $Ts = 2P / \pi Dt$.. The ratio of crushing strength to tablet thickness ((BC) described as bonding capacity[14] was applied in accessing formulation characteristics of the compacts

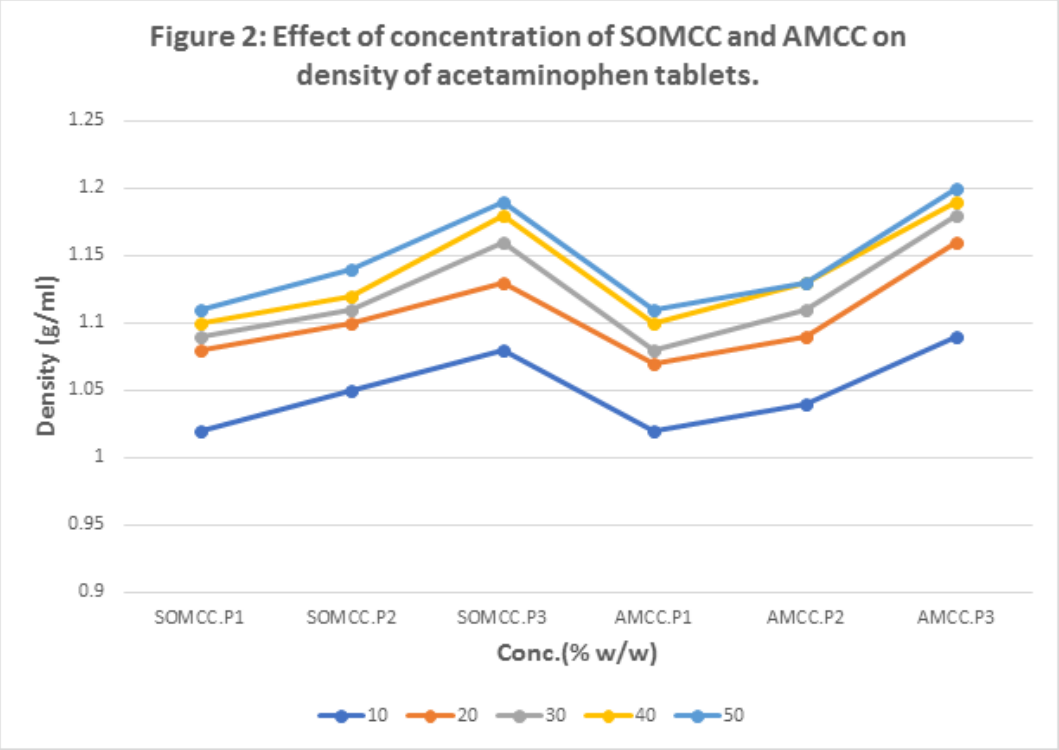
RESULTS AND DISCUSSION

Acetaminophen compacts

Figures 1 and 2 shows the effect of BC and tablet densities (D) of SOMCC- Acetaminophen (S-P) and AMCC – Acetaminophen (A-P) compacts at different compression pressure. Both BC and D increased with concentration of either cellulose product at all the compression pressures used. Plasticity of the blends increased with increasing concentration of the polymers. This implies that as the concentration increases, creation of larger bonding areas occurs and therefore



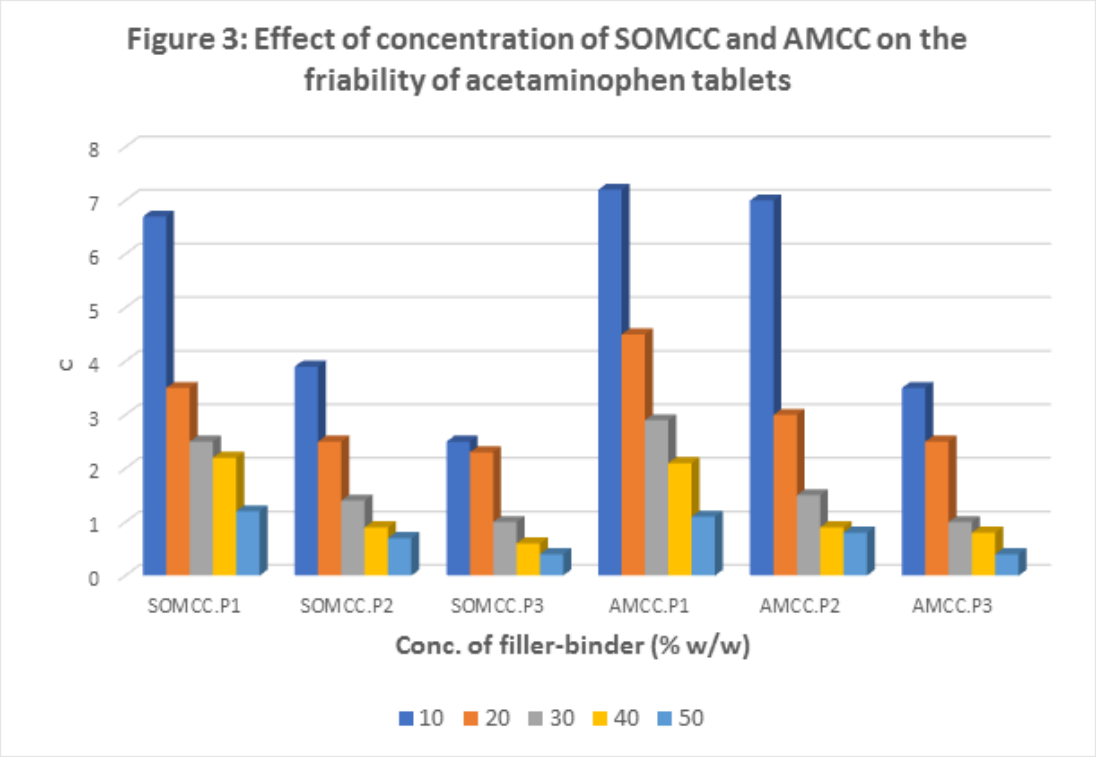
P1=62.4MPa P2=93.6MPa P3=124.8MPa



P1=62.4MPa P2=93.6MPa P3=124.8MPa

higher BC. As the compression pressure is also raised, the bonding chance is also enhanced as the particles are brought closer, resulting in increasing BC. The same reasoning is

responsible for the pattern observed with the compact densities i.e. creation of larger bonding surfaces and densification due to increasing concentration and pressures. This behaviour is consistent with Heckel analysis[18, 25] for plastically deforming materials such as MCC. At concentrations below 20% w/w of the excipients, the tablet densities were found to be relatively low in both set of formulations, BC values were lower than 500 kgf/ m and capping was observed in either of the cases, using SOMCC or AMCC. This indicates a probable lack of sufficient bonding between the particles of the blends. However, at concentrations above 20% w/w, the elastic behaviour of acetaminophen[26] was considerably modified into a more plastic flow characteristics, resulting in higher density values with negligible capping tendencies. A 50% w/w concentration of the excipients exhibited the highest BC of 2130 or 2010 kgf/m corresponding to D of 1.19 or 1.2 g/ml for SOMCC or AMCC respectively. All the blends produced compacts of less than 1000 kgf/m BC at 31.2 MPa and this may be considered sub-optimal pressure. The Compacts containing 30 % w/w of either polymer had BC of not less than 1000kgf/m with corresponding density above 1.1g/ml at compression pressure of 62.4MPa. Figures 3 shows the relationship between BC and friability (F) of S-P or A-P blends. The friability (F) value is noted to be inversely related to the.

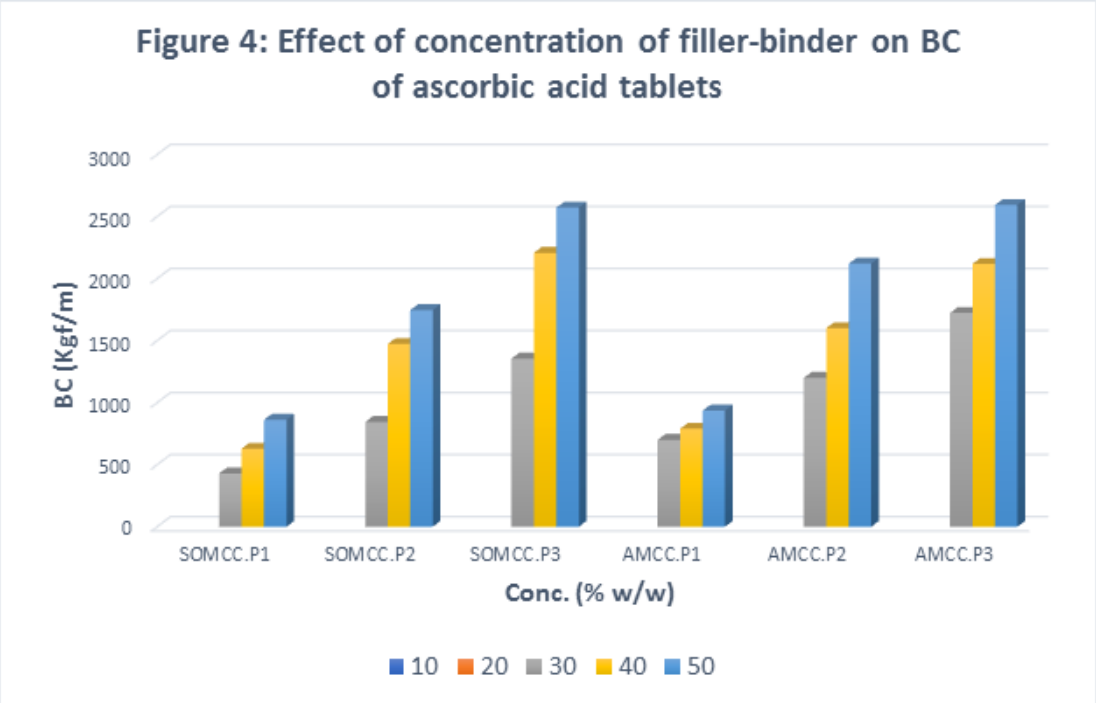


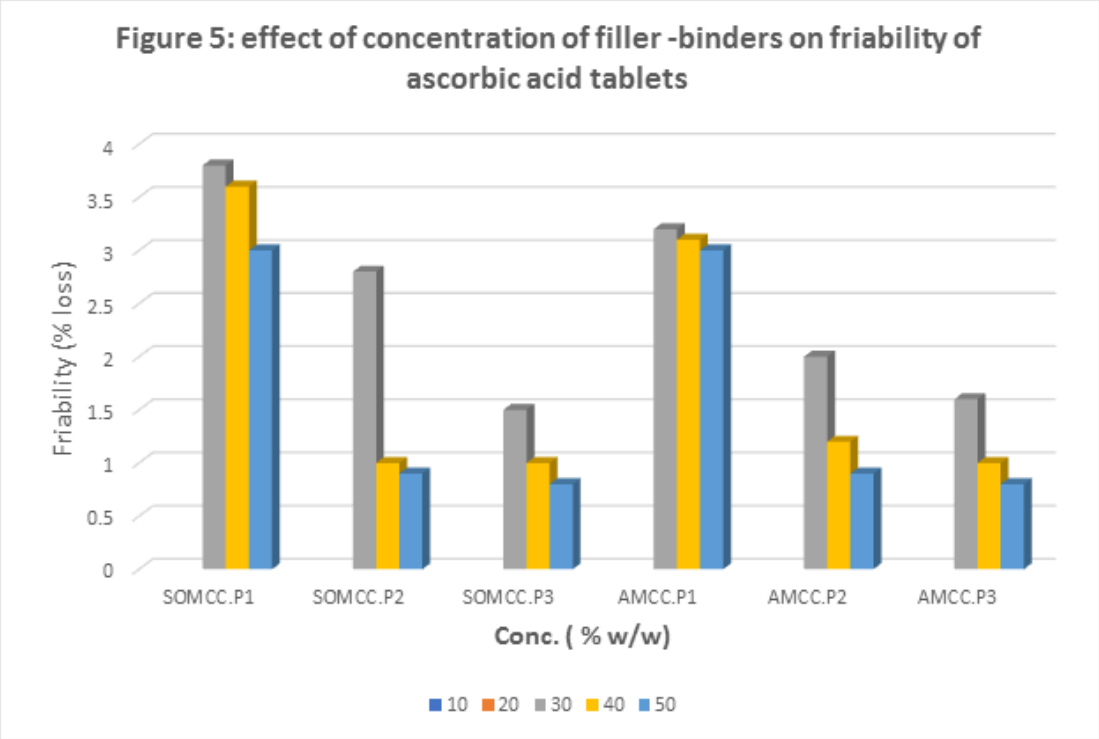
bonding capacity. At polymer concentration of 50% w/w, compact exhibited friability lower than 2% at all compression pressures above 31.2 MPa.

Ascorbic acid compacts

The bonding capacity and density profiles of SOMCC- Ascorbic acid (S-C) and AMCC-Ascorbic acid (A-C) blends are shown in figures 4 and 5. At compression pressure of 31.2 MPa, tablet failure occurred with blends containing less than 30% excipient as there was no significant interaction between the particles. At 30% w/w and above BC increased with concentration as well as compression pressure. The density was also found to increase with compression pressure similar to the trend in acetaminophen tablets. Ascorbic acid particles has been reported to exhibit some fragmentation propensity during compaction.[18] The binding forces in the plain material are however relatively weak and therefore not resistant to stress relaxation and elastic recovery. It may be deduced that sufficient attractive forces are not generated at excipient concentration of 20% w/w and below.

As the concentration of the polymers increases, plasticity also increased due to infiltration of the fragmented particles[14] of ascorbic acid into the void spaces resulting in closer rearrangement, higher density and greater bonding. The relationship between BC and friability profiles of S-C and A-C blends. At concentrations above 20 % w/w of the polymers, compacts made at 93.6 MPa



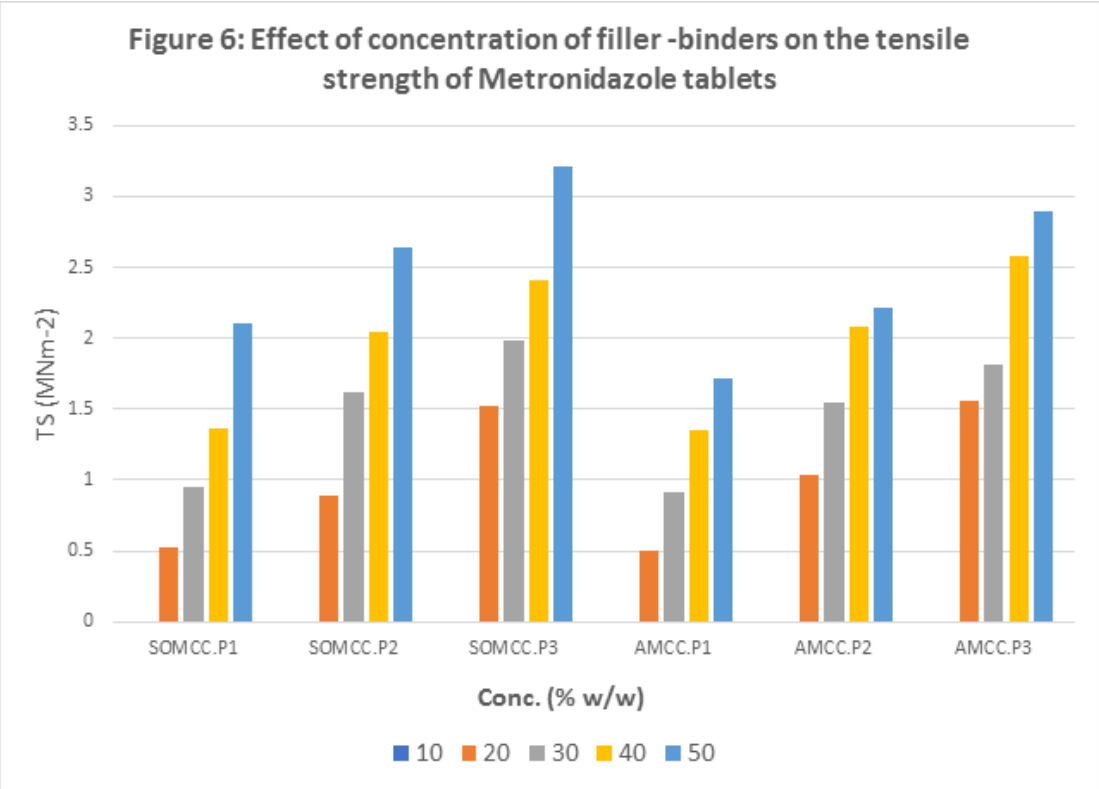


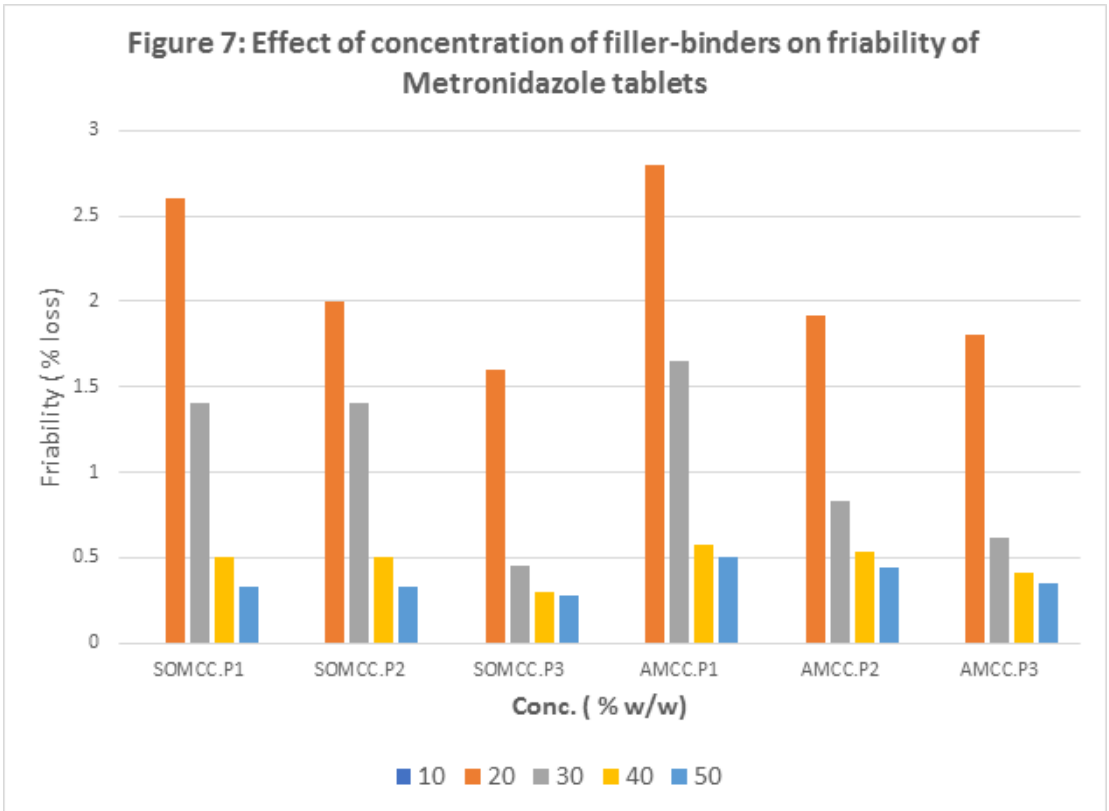
exhibited friability values less than 2%. In these instances, BC's are well over 1000 kgf/m. Interpolation from the graph shows that at 25% w/w of SOMCC or AMCC, BC is more than 900 kgf / m and friability less than 2% for tablet batch made at 93.6MPa. Therefore, a 25-40% w/w composition of these new grades of MCC may be considered optimal for producing acceptable ascorbic acid tablets at compression pressure of between 62.4-93.6 MPa.

Metronidazole Compacts

The effect of concentration on the tensile strength and friability of compacts of metronidazole – polymer blends are shown in figures 6 and 7. The tensile strength increases with concentration of either grade of cellulose at all compression pressures. Blends containing less than 20% of the cellulose were not evaluated because of capping and other unsuitable tablet qualities at all the compression pressures applied. Compression of metronidazole alone yielded no compact even at compression pressure of 186.2 MNm^{-2}. At compression pressure of 124.8 MPa, all the mixtures containing 20% cellulose and above formed good compacts with tensile strength of not less than 1.5 MNm^{-2}. At 62.4 MPa compression pressure, sufficiently hard compacts were produced only at concentration of 50% w/w of either SOMCC or AMCC. The hardest compact was obtained with this level of the new excipients at 124.8 MPa. At 25% w/w of either polymer, compacts having tensile strength above 1 MNm^{-2} could be produced at compression pressures of 93.6 to 124.8MPa. The friability

profile of SOMCC-Metronidazole or AMCC-Metronidazole blends is shown respectively in figures 7. Resistance to abrasion is important in





maintaining the integrity of a tablet during handling including transportation.[14] A friability value less than 1% is normally acceptable and not more than 2% with directly compressed tablets or that made with flat-faced punches.[14] The friability is inversely related to the tensile strength in either batches of SOMCC or AMCC formulations. Friability of less than 2% was obtained for all the blends at compression pressure of 124.8 MPa. Abrasion of not more than 2% was also achieved at all the compression pressures at excipient level of 30% w/w and above. At 25% w/w composition of the new cellulose filler-binder, TS above 1MNm-^{2} could be obtained at compression pressures of 93.6-124.8 MPa having friability values of below 1.5%. It is therefore reasoned that optimum tablet qualities could be obtained by formulating metronidazole tablets with 30 to 50 % SOMCC or AMCC at compression pressures between 93.6 to 124.8 MPa using the type of compaction machine employed in this study.

Tensile strength of microcrystalline starch (MCS) co-processed starch and microcrystalline cellulose (MCC) increased with concentration of the filler-binders in ascorbic acid or metronidazole binary blend formulations[27], the latter excipient, (MCC) being better in enhancing compact strength of the binary mix. Similar trend was observed in the current investigation. Dilution capacity of 30% is considered as threshold for achieving good compact qualities in acetaminophen, ascorbic, and metronidazole formulations using the new polymeric filler -binders.

CONCLUSION

MCC derived from Sorghum and Andropogon plants altered the compaction characteristics of acetaminophen, ascorbic acid and metronidazole powders. In all cases tensile strength and bonding capacity increased with concentration of the polymers while friability decreased. Tablets with bonding capacities above 1000kg/m exhibited high tensile strength and good friability profiles. These qualities were achieved at dilution levels of 30 - 50 %w/w. These plant residues, predominantly fibrous and non – woody, are potential sources of cellulose and callose derivatives. The next phase of study involved determination of compatibility and characteristics of drug formulations containing the new filler-binders including dissolution profiles on storage. This will constitute a separate report.

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