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Impact of Co-Processing on Some Fundamental Physicochemical and Functional Properties of Microcrystalline Cellulose

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ABSTRACT: *The aim of this study was to evaluate the effect of co-processing of microcrystalline cellulose (MCC) with Eudragit L100$^{(R)}$, cellulose acetate phthalate and ethyl cellulose respectively on the compaction, flow and disintegration properties of MCC. Co-processing MCC with the different polymers enhanced the flow and disintegration properties of MCC as a direct compression excipient for tablets production. When evaluated with the Heckle model, there was no remarkable change in the packing characteristics of the modified motifs in relation to the unmodified; however there was a slight but variable decrease in dilution capacity. This study shows the potential attribute of co-processing MCC with other polymers.*
Keywords: *Microcrystalline cellulose, Eudragit L100, cellulose acetate phthalate, ethyl cellulose, co-processing*

I. INTRODUCTION

The rapidly evolving competitive pharmaceutical market is promoting the production of innovative, high quality but cheap products. These have contributed to the pressure to develop new excipients especially those with multifunctional properties to reduce final cost of production and also meet the increasing need for emerging new drug delivery technology [1-3]. In modern drug production technology the availability of excipients with innovative physicochemical and functional properties is as critical as the invention of new formulation techniques. Several innovative polymers such as those with multifunctional properties and application have been produced to meet these needs [4, 5]. Many of the available polymers used as multifunctional excipients in pharmaceutical manufacture are produced by modification of existing ones by altering certain properties of the native material by innovative physical and/or chemical techniques [6-10].

Microcrystalline cellulose (MCC) has an excellent compaction property and is used as an efficient dry binder in direct compression technology [11-13]. However certain limitations due to its intrinsic functional properties such as poor flow and disintegration efficiency have limited its use as a multifunctional excipient [14, 15]. Enhanced flow-ability, loading capacity as well as rapid tablet disintegration represent improvements on the functional properties of MCC [6]. In attempt to improve its multifunctional efficiency, MCC has been co-processed with colloidal silicon dioxide, however silicified MCC is expensive.

MCC has demonstrated effective interface for both film formation and uniformity of coating [16, 17]. Thus, coating of MCC microparticles with certain polymers may impart new properties that may improve its functional properties. The basic process of film coating involves the application of a film forming polymer unto the surface of particles or substrate material. Ethyl cellulose (Etyl-cel), Eudragit L100® (Eud) and Cellulose acetate phthalate (CAP) apart from being generally regarded as safe are also efficient film forming polymers which have desirable properties that have been used to impact specialized properties to tablets and particles [18]

In oral pharmaceutical manufacture Ethyl-cel is commonly used as a hydrophobic coating agent for tablets and granules [19]. CAP and Eud are used as enteric coating and matrix excipients for oral tablets and granules. They have also been explored as binders in tablets and capsules [20]. This study seeks to co-process MCC with CAP, Etyl-cel and Eud respectively by particulate film coating and also evaluate certain physicochemical and functional properties of the products as potential multifunctional excipient for tablet production.

II. MATERIALS AND METHODS

2.1 Materials

The materials used were microcrystalline cellulose (Fluka Biochemica, Ireland), Eudragit L100, cellulose acetate phtalate (Evonik GmbH, Darmstadt, Germany), ethyl cellulose, sodium chloride, magnesium

chloride and acetaminophen (Sigma–Aldrich Chemie, Germany); potassium dihydrogen phosphate (May & Baker, Dagenham, England); Toluene, sodium hydroxide (NaOH), potassium thiocyanate, potassium chloride and calcium chloride (BDH Chemicals, UK). Acetyl salicylic acid was kindly supplied by Juhel Pharmaceuticals Nigeria. Limited (Enugu, Nigeria).

2.2.0 Methods

2.2.1 Film coating of microcrystalline cellulose (Co-processing)

Eud, Etyl-cel and CAP coated MCC were prepared by solubilizing Eud, Etyl-cel and CAP appropriately in ethanol, toluene and acetone respectively. Quantities of the coating polymers corresponding to 5 $\%^{w}/_{w}$ of MCC were dispersed in 100 ml of the solubilizing solvent. The coating polymers were impregnated on the MCC particles by continuous stirring at 200 rpm with a magnetic stirrer and maintaining at 70 ^{o}C for the system containing acetone and ethanol and 90 ^{o}C for toluene. On complete evaporation the dry powder was screened through a sieve of 250 µm mesh size (WVR Scientific, USA) using a sieve shaker (Retsch, D 42781 Haan, Germany) before storing in an airtight container.

2.2.2 Particle properties

The bulk and tapped densities of MCC, MCC-Eud, MCC-Etyl-cel, and MCC-CAP powders were each evaluated in a 50 ml graduated measuring cylinder as a measure of densification of a predetermined weight of the powders. The measuring cylinder with its content was tapped mechanically with a Stampfvolumeter (STAV 2003 JEF, Germany). The bulk volume corresponds to the volume before tapping while the tapped volume corresponds to the stable final volume with unchanging particle arrangement. The powders' compressibility indices were determined using equation 1 [21].

$$\text{Compressibility (\%)} = \frac{\text{tapped density} - \text{bulk density}}{\text{tapped density}} \times 100 \quad \ldots\ldots 1$$

The angles of repose of the powders were determined by measuring the internal angle between the surface of the heap of powders obtained when 50 g of each of the powders was allowed to flow through a glass funnel (orifice diameter 2 cm) and clamped 10 cm above a flat surface. The angle of repose was calculated using equation 2 [21, 22].

$$\text{Angle of repose} = \text{Tan } \square = \frac{\text{Height of cone}}{\text{Radius of cone (r)}} \quad \ldots\ldots 2$$

2.2.3.0 Packing properties

2.2.3.1 Kawakita model

The packing characteristic of MCC, MCC-Eud, MCC-Etyl-cel, MCC-CAP powders were determined using the Kawakita model [23]. Fifty gramme quantities of MCC and the film coated MCC powders were placed in a 200 ml measuring cylinder to determine the initial volume (V_o) occupied by the powder, the volumes occupied after series of numbers of mechanical tapings (N) until total powder consolidation was determined. The compressibility of the powders were then evaluated using the Kawakita equation 3.

$$C = (V_o - V)/V_o = abP/(1+bP) \quad \ldots\ldots 3$$

Where C is the degree of volume reduction, V_o initial volume reduction, V is volume of powder column under applied pressure and ab is constant characteristic to powder being compressed. When the volume reduction is described in terms tapping, Equation 3, can thus be represented by equation 4.

$$N/C = N/a + 1/ab \quad \ldots\ldots 4$$

The intercept of the linear portion of the plot of N/C vs N gives a value representative of 1/ab while the slope represents the reciprocal of the constant "a". "a" is known as the compressibility and gives an indication of the maximum volume reduction available and is characteristic for a powder, while b describes an inclination towards volume reduction [23].

2.2.3.2 Heckle model

The bulk and true densities [24] of MCC and the motifs (MCC-Eud, MCC-CAP and MCC-Etyl-cel) were determined. The relative densities D_0 of each material were determined by evaluating the ratio of the bulk to its particle true densities. Compacts equivalent to 250 mg of MCC and the coated motifs were produced by compressing the powder for 1 min at compression pressures range of 13.75-20 KN using a single press

compression machine (Shanghai Tiaxiang & Chenta, Pharmaceutical Machinery Co. Ltd, China) fitted with an 11.5 mm flat faced punch and die. Before each compression, the die and the punches were lubricated with a 2% (w/v) dispersion of magnesium stearate in ethanol. After ejection, the compacts were stored in a desiccator for 24 h to allow for elastic recovery and hardening preventing false low yield values. Their weights (W) and dimensions were then determined to within ± 1mg and 0.01 mm respectively, and their relative densities (D) were calculated using the equation 5 [25].

$$D = W / V_t . \rho s \quad \ldots 5.$$

Where V_t is the volume (cm^3) of the tablet and ρs is the particle density (g/cm^3) of the solid material. A plot ln (1/1-D) versus applied pressure (P) which corresponds to the Heckle plots were then made for MCC and the different MCC motifs.

2.2.4 Scanning electron microscopy

The scanning electron micrographs (SEMs) of MCC, MCC-Eud, MCC-Etyl-cel and MCC-CAP were determined using a FEI Quanta 400 scanning electron microscope (FEI QUANTA 400, FEI Company, USA).

2.2.5 Moisture sorption characteristics

MCC, MCC-Eud, MCC-Etyl-cel and MCC-CAP were respectively placed in Petri dishes and stored in desiccators containing activated silica gel as the desiccant for one week at 25°C to remove residual moisture. The moisture sorption isotherms were then determined by the gravimetric method [26, 27]. A 1 g quantity of the polymer powders were each placed in an aluminum foil and put in a sealed glass chamber with a gauze holding tray containing water or saturated solution of different salts to provide the required relative humidity (RH) (water 100%, potassium chloride 84%, sodium chloride 75%, potassium thiocynate 47 % and calcium chloride 31 %) [27]. The powders were then weighed at 12 h intervals until there was no further increase in weight. The percentage equilibrium moisture uptake was determined using equation 6.

$$\text{Equilibrium moisture uptake} = M_e/M_d \times 100\% \quad \ldots . 6$$

Where M_e is the amount of moisture absorbed at equilibrium and M_d is the dry weight of the material [28]. The moisture sorption profile of percentage weight gain vs RH was then evaluated.

2.2.5 Differential scanning calorimetry

Differential scanning calorimetry (DSC) studies were carried out on a differential scanning calorimeter (DSC 204 F1, Phoenix NETZSCH, Germany) equipped with a thermal analysis system. Indium (156.8°C) was used as the internal standard. Samples of approximately 5 mg of MCC and MCC-Eud, MCC-Etyl-cel, MCC-CAP powders were placed in an aluminum pan (25 µl) and covered with a perforated lid. Dry nitrogen was used as the purge gas (purge 20 ml min^{-1}). The probes were heated from a start temperature of 25 °C to 500 °C at a rate of 10 °C min^{-1}. The glass transition (T_g), melting point (T_m), and cold crystallization (T_c) temperatures were evaluated with the Proteus analysis software [29].

2.2.6 X-ray powder diffraction

Structural characterization was carried out using a Siemens D5000 X-ray diffractometer (Siemens, Munich, Germany). MCC, MCC-CAP, MCC-Eud and MCC-Etyl-cel were each packed in rectangular aluminum cells, were illuminated using CuKα radiation (λ=1.54056 Å) at 45 kV and 40 mA. Samples were scanned between diffraction angles of 57 to 407 2y, which was sufficient to cover all significant diffraction peaks of MCC crystallites. Scan steps of 0.1^o were used and the dwell time was 15 s. A nickel filter was used to reduce the Kβ contribution to the X-ray signal. The'd' spacing were computed according to Bragg's law of diffraction, using equation 7. Measurements were made at ambient temperature [30].

$$n\lambda = 2d \sin\theta \quad \ldots . 7$$

Where: λ is the wavelength of the X-ray beam, d is spacing between unit cell edge of the powder and θ is angle of diffraction and *n* is the order of interference.

2.2.7 Dilution capacity

Compacts containing different ratios of binary mixtures of acetaminophen and each of MCC and coated motifs (MCC-Eud, MCC-Etyl-cel, MCC-CAP) were prepared. The binary mixtures were such that each of the 400 mg tablets contained acetaminophen (Apn) and the test excipients at different ratios: 400:0, 380:20, 320:80, 200:200, 80:320, 20:380, 0:400. The compacts were prepared by compressing with a predetermined load of 22.5 KgF using a single press compression machine (Shanghai Tiaxiang & Chenta, Pharmaceutical Machinery Co. Ltd.) fitted with an 11.5 mm flat faced punch and die [31]. The punch and die were lubricated with a dispersion

of magnesium stearate in ethanol before each compression. The diameter and thickness of the tablets were determined with a Vernier caliper (Mitutoyo, Japan) as well as their hardness using hardness tester (Erweka ZT2, Germany). Their radial tensile strengths were evaluated using equation 8 [32].

$$T = 2\,F/\pi dt \qquad \ldots . 8$$

Where T is the radial tensile strength, F is the load needed to break the tablet, and d and t are the diameter and thickness respectively.

2.2.8 Disintegration efficiency

Compacts containing 300 mg of aspirin and 10% $^{w}/_{w}$ of MCC or the coated motifs as disintegrant, were prepared by mixing the aspirin and the disintegrants in a tumbler mixer (JEL, KARL KOLB, Germany) and compressed with a predetermined load of 20 KgF using a single press compression machine (Shanghai Tiaxiang & Chenta, Pharmaceutical Machinery Co. Ltd.) fitted with an 11.5 mm flat faced punch and die [31]. Tablets disintegration time were determined in 0.1N HCl at 37 ±0.5 ^{o}C in a BP disintegration test unit (Erweka ZT4, Germany). Tablets were considered to have disintegrated when all particles had passed through the wire mesh.

2.3 Data and statistical analysis

All experiments were performed in replicates for validity of statistical analysis. Results were expressed as mean ± standard error of mean. ANOVA and Student t-tests were performed on the data sets generated using SPSS software. Differences were considered significant for p values <0.05.

III. RESULTS

3.1 Film coating of microcrystalline cellulose (Co-processing)

The dispersion of the MCC particles in the solutions of the coating polymers as well as the evaporation and screening through a sieve produced discrete free flowing particles. Passing the powders through the 250 µm mesh sieve ensured the breakdown of agglomerates.

3.2 Particle properties

The bulk and tap densities of MCC showed higher values as to those of the coated motifs produced by the co-processing of MCC with Eud, CAP and Etyl-cel respectively and are presented in Table 1. These showed the relative higher volume to weight of the motifs.

The flow parameters of the powders as determined by the indirect methods: angle of repose and Carr's compressibility index are presented in Table 1. The Carr's compressibility indices and angles of repose of MCC and co-processing motifs show corresponding values. MCC particles coated with Eud, Etyl-cel and CAP commonly showed enhanced flow.

3.3 Packing properties

3.3.1 Kawakita model

The Kawakita plots for the MCC and the coated MCC motifs are presented in Fig. 1. The values obtained for the constants a and 1/b which corresponds to compressibility (or amount of densification) and cohesiveness respectively are presented in Table 1.

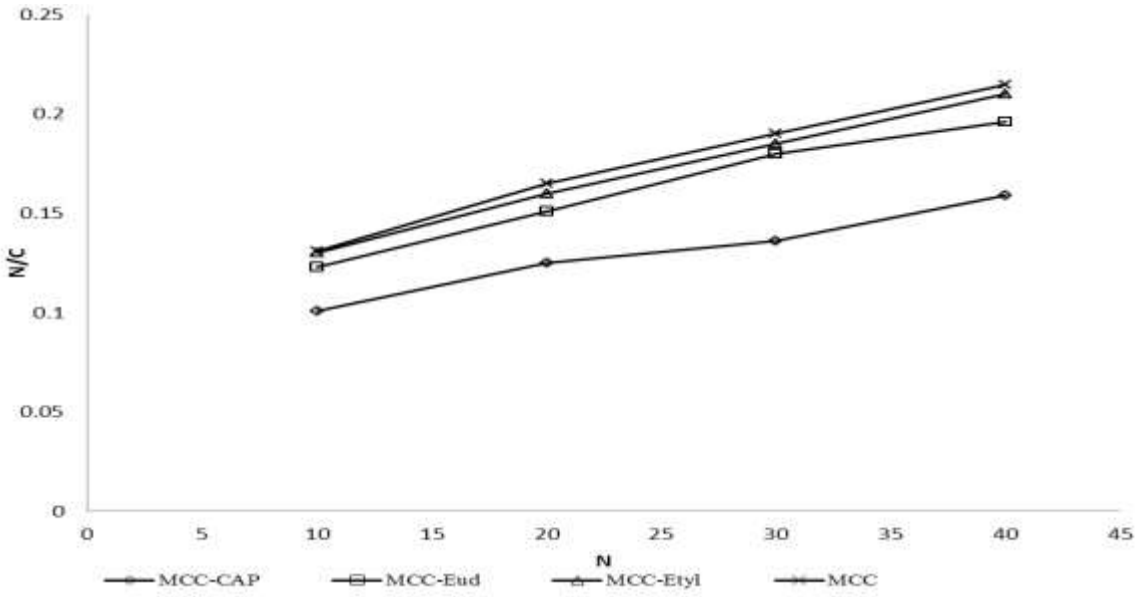

Fig. 1: Kawakita plot for MCC and MCC co-processed with Eud, Etyl-cel and CAP.

MCC=Microcrystalline cellulose; Eud=eudragit; CAP=cellulose acetate phthalate; Etycel=ethyl cellulose

3.3.2 Heckle compaction model

The Heckle plot for MCC and the coated motifs are presented in Fig. 2. The relevant compaction parameters: D_o, D_a, D_b and P_y which corresponds to the relative densities of the powder bed at the point when the applied pressure equals zero, at zero and low pressures, at the rearrangement phase and the mean yield pressure of the compacts respectively are presented in Table 1.

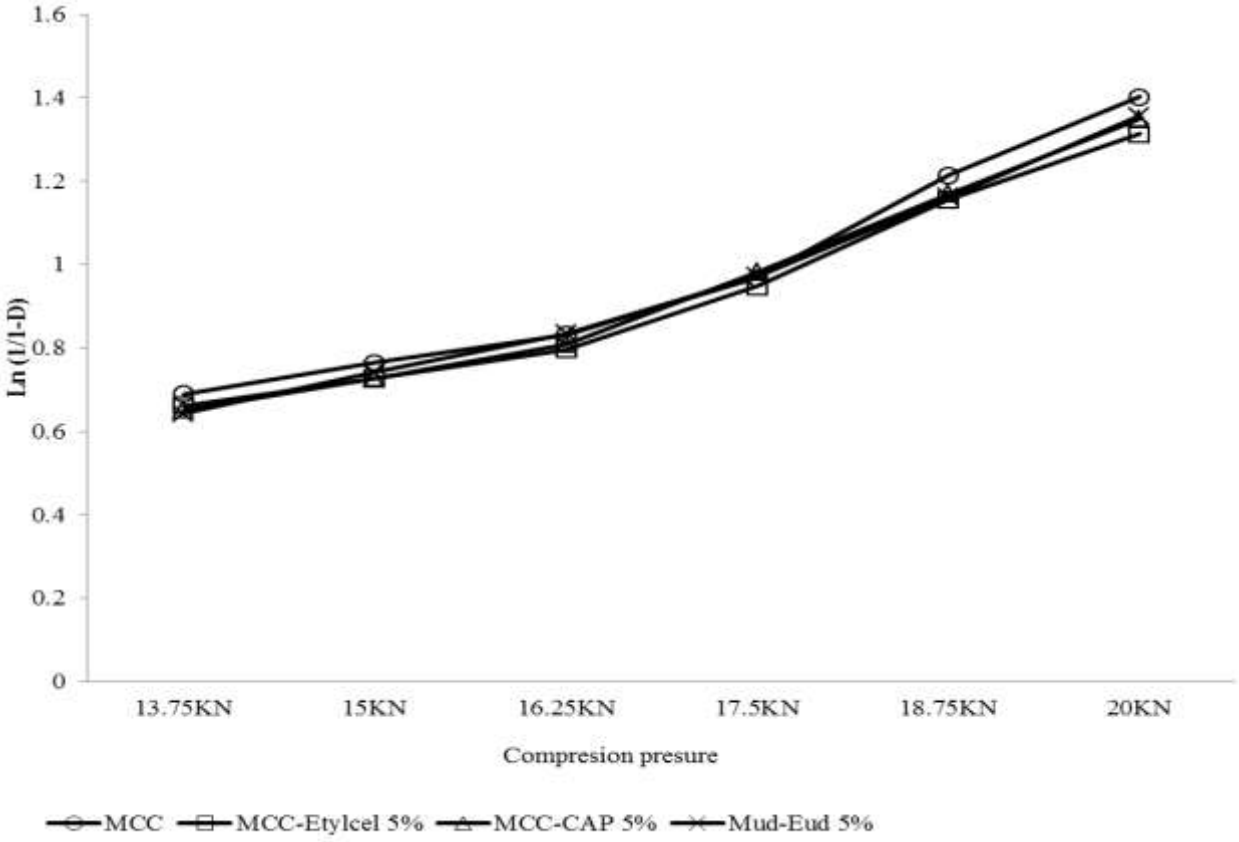

Fig. 2: Heckle plot for MCC and MCC particles coated with 5% Eud, Etyl-cel and CAP.

MCC=Microcrystalline cellulose; Eud=eudragit; CAP=cellulose acetate phthalate; Etycel=ethyl cellulose

3.4 Scanning electron microscopy

Scanning electron micrographs of MCC particles and the coated motifs are presented in Fig. 3. The photomicrographs show the characteristics long thin rectangular strands and rough porous surface of MCC. The coated particles however, showed increased densification and surface roughness.

3.5 Moisture sorption characteristics

The moisture sorption characteristics of the native MCC and the coated motifs are presented in Fig. 4. The native MCC and the different coated motifs all showed significant differences in moisture uptake at the different RH. The average moisture uptake of the different motifs of the MCC in low humidity through moderate to high RH conditions can be presented thus, in hierarchy of increasing moisture uptake: Eud>CAP>MCC>Etyl-cel.

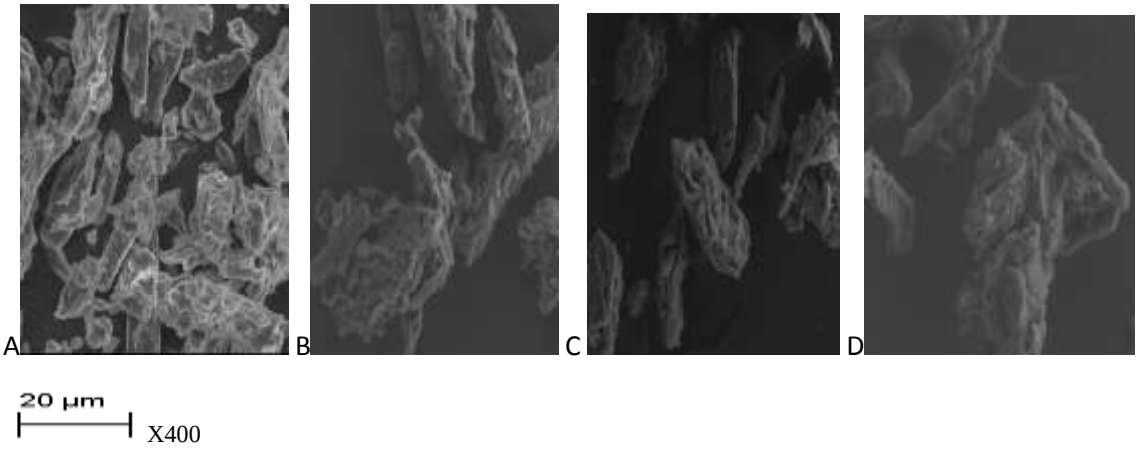

Fig. 3: SEM photomicrograph of MCC and MCC coated with Eud, CAP and Etyl-cel.

A=MCC; B= Eud-MCC; C=MCC-CAP; D=MCC-Etylcel
MCC=Microcrystalline cellulose; Eud=eudragit; CAP=cellulose acetate phthalate; Etycel=ethyl cellulose

3.6 Differential scanning calorimetry

The DSC thermographs of MCC and changes imparted by the coating with the polymers are presented in Fig. 5. The thermographs of MCC and that of the coated motifs show basic similarities in terms of their glass transitions and melting peaks. The thermographs of the native MCC and the coated motifs show two characteristic transitions peaks. An initial endothermic transition peak which corresponds to the glass transition temperature (T_g) and an endothermic peak that corresponds to their melting temperature (T_m). The coated MCC motifs retained the T_g and T_m of the native proprietary MCC. There were, however, shifts in the T_g and T_m for the modified MCC motifs that can be related to the coating polymers. The changes in the thermal transitions of native proprietary MCC by coating with the polymers are presented in Table 2.

Table 2: Thermal properties of MCC and MCC Co-processed with Eud, CAP and Etyl-cel

Parameter	MCC	MCC-Eud	MCC-CAP	MCC-Etyl-cel
T_g (^oC)	75.4	58.6	48.6	51.6
ΔH J/(gK	1.511	5.075	2.890	2.890
T_m (^oC) Peak	335.8	320.5	328.7	339.0

T_g Glass transition temperature
T_m Melting temperature
MCC=Microcrystalline cellulose; Eud=eudragit; CAP=cellulose acetate phthalate; Etyl-cel=ethyl cellulose

3.7 X-Ray Diffraction

The powder X-ray diffraction pattern of MCC and the coated motifs are shown in Fig. 6. The reflection angle, 2θ, along with the interplanar spacing, d, and the relative intensity of the peaks are presented in Table 3. Though the diffraction pattern of the modified MCC motifs did not show obvious differences relative to the native proprietary material, there were however, shifts in both the strong and minor peaks (Table 3).

The X-ray diffraction patterns of MCC particles coated with Eud, Etyl-cel and CAP are shown in Fig. 6. The properties of the of the difractogram as shown by the reflection angle, 2θ, along with the interplanar spacing d, and the relative intensity of the peaks showed obvious changes (Table 3). The coated MCC motifs showed patterns similar to that of the native proprietary MCC powder (Fig. 6). The peak intensity showed variable shifts that are characteristic of the coating polymer as shown in Table 3. The position and intensities of the prominent peaks varied with the different coating polymers.

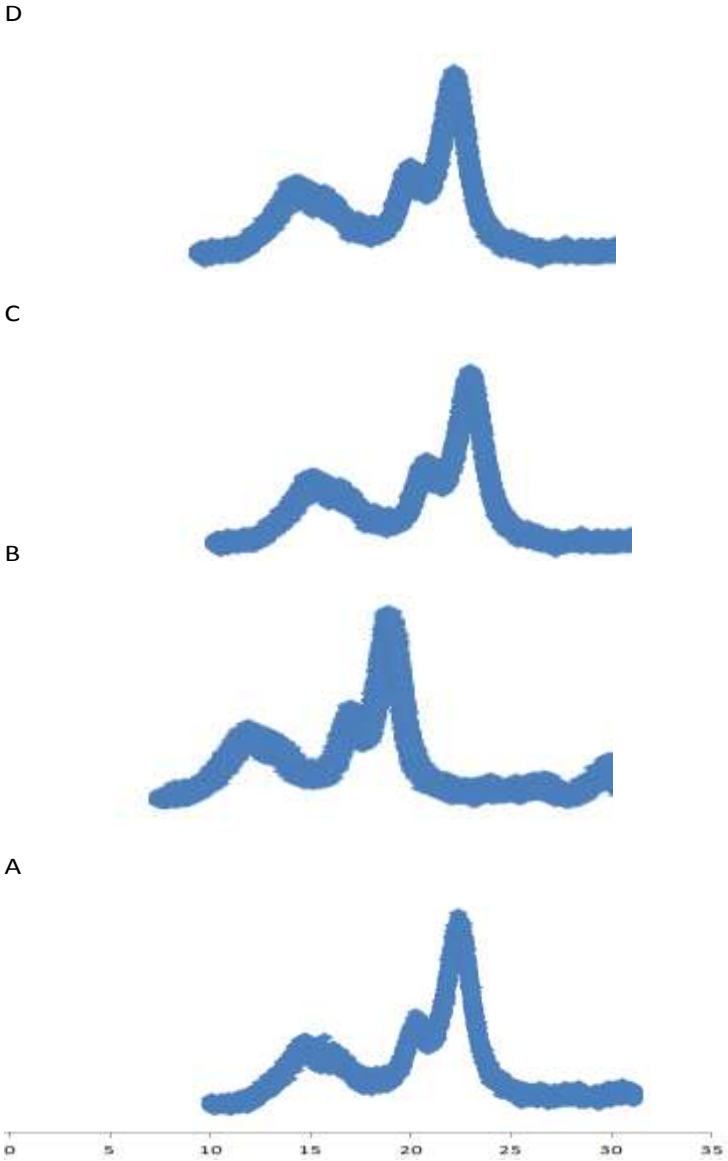

Fig. 6: X-ray difractogram of MCC and motifs coated with Eud, CAP and Etyl.

A=MCC; B=MCC-Eug; C=MCC-Cap; MCC-Etylcel

MCC=Microcrystalline cellulose; Eud=eudragit; CAP=cellulose acetate phthalate; Etycel=ethyl cellulose

Table 3: X-ray powder diffraction data for MCC, MCC-CAP, MCC-Eud and MCC-Etylcel

MCC

Diffraction angle (2□)	d-spacing [Å]	Relative Intensity(%)
16.2019	5.47083	54.29
20.1882	4.39869	100.00
27.7551	3.21428	7.57
30.9494	2.88943	9.78
34.3192	2.61304	42.28
44.8321	2.02171	8.29

MCC-CAP

Diffraction angle (2□)	d-spacing [Å]	Relative Intensity(%)
14.6273	6.05602	30.99
16.5072	5.37032	20.72
20.3249	4.36940	40.60
22.5321	3.94614	100.00
22.7204	3.91386	94.27
28.0303	3.18334	1.48
30.9683	2.88771	4.14
34.4867	2.60073	16.30
41.2566	2.18827	2.73
44.9743	2.01565	2.97

MCC-Etylcel

Diffraction angle (2□)	d-spacing Å]	Relative Intensity(%)
14.5775	6.07659	30.65
16.7451	5.29456	18.57
20.4656	4.33969	42.80
22.3781	3.97295	100.00
28.0064	3.18601	0.57
31.0025	2.88460	3.33
34.4884	2.60060	14.28
44.8516	2.02088	2.57

MCC-Eud

Diffraction angle (2□)	d-spacing [Å]	Relative Intensity(%)
14.3300	6.18097	73.79
20.2629	4.38263	100.00
28.0126	3.18532	3.44
30.8662	2.89703	11.04
34.3989	2.60717	49.30
41.4601	2.17800	7.91
44.6722	2.02857	5.72

MCC= Microcrystalline cellulose; CAP =Cellulose acetate phthalate; Eud=Eudragit L100; Etylcel= Ethyl cellulose

3.8 Dilution capacity

The dilution capacities of the native MCC and the coated motifs were determined by assessing the tensile strength of the acetomenophen loaded compacts. The effect of coating of MCC particles with CAP, Eud, and Etyl-cel respectively on the dilution properties of MCC are shown in Fig. 7. The tensile strength of the acetaminophen loaded compacts prepared with the coated motifs showed variable tensile strengths at the different ratio mix of the drug and excipient as well as with the different coating polymers. At high Apn concentrations, the various MCC coated motifs showed similar tensile strength (Fig. 7), however the compacts mixtures containing higher excipient concentrations showed variable tensile strength corresponding to the dilution capacity which has been related to the compaction efficiency of the excipient. Considering the relationship of the dilution potential tensile strength of the compacts the comparative dilution potential of the co-processed MCC motifs can represented thus: MCC> Eud >CAP> Etyl-cel.

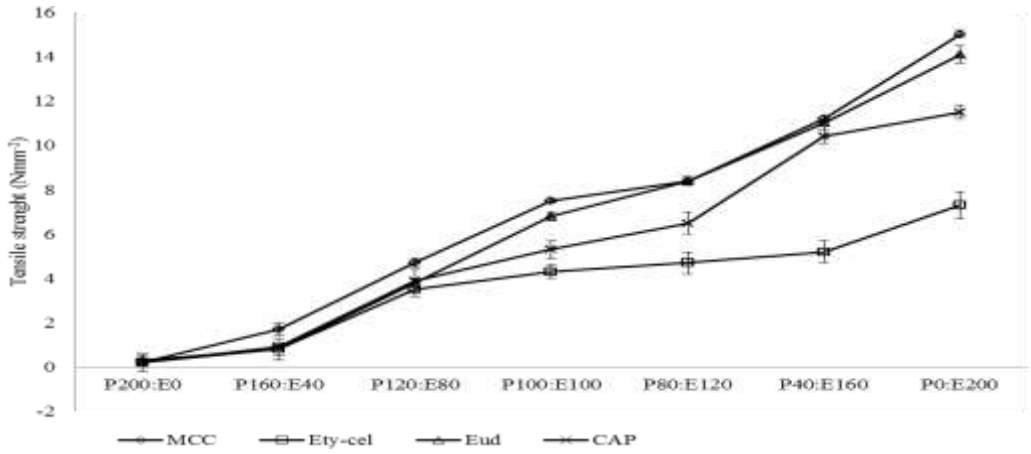

Fig. 7: Effect of co-processing with Eud, CAP and Etyl-cel on the dilution capacity of MCC.

P=Acetomenophen; E= Excipient

3.9.1 Disintegration efficiency

The disintegration characteristics of the compacts prepared with ASA, the native MCC and its coated motifs are presented in Fig. 8. The coated MCC motifs generally modified the disintegration time of the ASA compacts in both the SGF and SIF. The disintegration of the compacts generally showed a higher shift in disintegration time in SGF as compared to SIF. The comparative disintegration time of the plain ASA compacts and compacts containing MCC and its coated motifs, incorporated as disintegrant can generally be ranked as follows: ASA>Eud>CAP>Eud>MCC>Etylcel in SGF and ASA>MCC>Etyl-cel>Eud>CAP in SIF. In SGF all the compacts disintegrated after 1 h while in SIF all the compacts prepared with the film coated MCC particles disintegrated in less than 15 min.

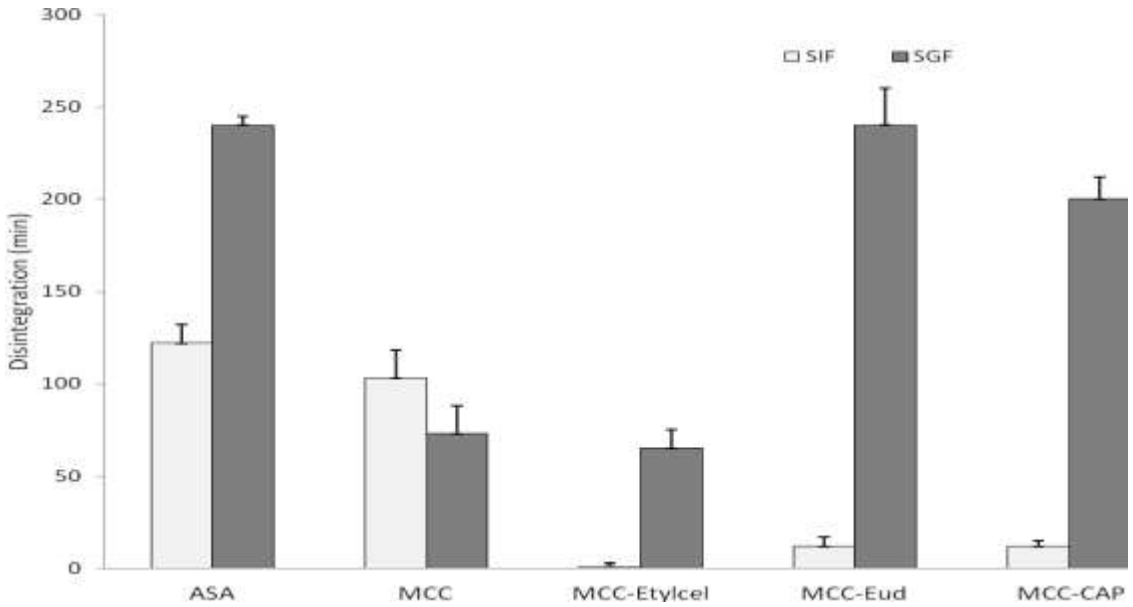

Fig. 8: Effect of co-processing with Eud, CAP and Etyl-cel respectively on disintegration time of ASA compacts in SGF and SIF.

Etyl-cel= ethyl cellulose; Eud= eudragit L100; CAP= cellulose acetate phthalate

IV. DISCUSSIONS

4.1 Preparation of co-processed MCC

The dispersion of MCC in the solutions of the coating polymers produced colloidal slurries that resulted in the even exposure of the particles to the polymer coat. The stirring was to ensure even coating and rapid removal of the organic solvents. The screening process ensured loosening of clumps due to agglomeration. The co-processed MCC, Eud, CAP and Etyl-cel excipients were derived as discrete, fine powders that are free-flowing.

4.2 Particle properties

The evaluation of the bulk and tap densities of powdered excipients especially those to be used for direct compression formulation is important as important formulation processes such as mixing, bulk particle movement, storage and compaction are among processes that are either directly or in directly controlled by the bulk and tapped densities [33]. Also critical parameters that affect bulk and tapped densities include material composition, particle size, shape and distribution, moisture content, specific density and applied pressure [35]. In comparison to the native MCC there were marked reduction in the bulk and tapped densities of the co-processed MCC motifs (Table 1) which could be related to the enhanced flow properties of the motifs.

4.3.0 Compaction characteristics

4.3.1 Kawakita model

Kawakita is one of the simple models commonly used for assessing the compaction as well as the flow characteristics of powdered pharmaceutical excipients intended for direct compression applications. This compaction model considers the bulk and tap densities state of the powders as it relates to the densification behavior of the powders, and works best for only a range of materials [22, 23].The curves of the plain MCC as well as that of the coated motifs showed a near perfect straight line curves with the correlation ranging from 0.9937 to 0.9819. Plain MCC showed the highest correlation and MCC-CAP the least (Fig. 1). Although some Kawakita plots gave good straight lines throughout the whole range of tapping: from low to high, over which they were plotted, many however showed curvatures especially at low pressure [22]. The linear relationship indicates the tendency of the powders to increased densification with increase in pressure. The smaller values of a shown for the motifs reflects the enhanced compressibility which corresponds to enhanced flow (Table 1) while a higher values for higher cohesiveness was indicated for the plain MCC relative to the motifs.

4.3.2 Heckle compaction model

The curves generated from the Heckle compaction model for MCC and the coated motifs gave a linear relationship at all the pressures levels (Fig. 2), this corresponded to type A compaction characteristic according to the basic Heckle compaction model [22, 25]. This thus, indicates that the polymeric coating with Eud, CAP and Etyl-cel did not change the deformation characteristic of MCC as compared to the significant differences observed for that of the coating polymers: Eud (which did not form stable compacts at the compression pressures), CAP and Etyl-cel (data not shown) in which there were initial linear relationship at the lower compaction pressures followed by a curvature at higher pressures which corresponds to type B.

4.4 Scanning electron microscopy (SEM)

The SEM images of the native MCC and the coated motifs present the morphology of the particles (Fig. 3). SEM images can be used as a quality control parameter for monitoring and characterization of the material during production. Information such as surface texture and roughness parameters as well as particle shape and size which are important features for identification and distinction of pharmaceutical excipients are parameters that can be evaluated from the SEM images [29]. Though the native MCC and the coated motifs showed some basic similarities obvious distinguishing features that were common to all the co-processed motifs were their larger and less rectangular particles that were more compact with smoother surfaces. The denser feature and surface roughness of the different co-processed motifs could be as a result of the minute inter-particulate agglomeration due to the aggregation of the very small particle of the native MCC during the coating process.

4.5 Moisture sorption

The moisture sorption characteristic of the native MCC and its co-processed motifs (Fig. 4) showed a slightly hygroscopic profile according to Callahan classification [35]. The classification is based on their equilibrium moisture uptake being less than 40% after storing at 100% RH for seven days. Generally, the moisture content especially of powders is controlled by the equilibrium RH of the environment [36]. Generally, the moisture sorption characteristics of most pharmaceutical excipients have been related to their moisture content [11]. Thus, the evaluation of the moisture sorption characteristics of MCC and its co-processed motifs becomes imperative as many of their physicochemical, stability and functional properties are affected by their moisture content. The moisture uptake characteristics of the co-processed motifs showed sensitivity that was characteristic and related to the coating polymers. Motifs produced by co-processing MCC with Etyl-cel showed the least moisture uptake as compared to those of CAP and Eud. The variation in moisture content of the co-processed MCC motifs can be used to impact new functional properties on powder mix for encapsulation and compressed tablets [26].

4.6 Differential scanning calorimetry (DSC)

DSC remains a useful tool for characterizing polymers based on their exothermic and endothermic thermal transitions [37]. The thermal transitions of polymers are characteristics and relates to the polymer crystalinity. The thermographs of the processed motifs of MCC show prominent transitions similar to that of the native MCC in terms of their glass and melting transitions. The thermographs of the plain MCC and the co-processed motifs are characterized by two endothermic transition peaks; the first corresponds to the glass transition (T_g) and the second to the melting (Fig. 5). The effect of the polymer film coating is reflected by the slight shifts in the relative transition temperatures of the glass transition and melting temperatures which can be related to the coating polymers.

4.7 X-Ray Diffraction

The classical way of determining the degree of order (crystallinity) in polymeric materials like cellulose is by using powder X-ray diffraction technique. X-ray diffraction provides strong signals with which the cellulose crystallinity can be characterized. These signals can be used to determine crystallographic parameters, like measuring the distances in the crystalline unit cell [38]. The non-crystalline part of the cellulose structure is represented by broader and less clearly refined features in the diffraction pattern which may lead to challenges in the evaluation of the signals for a quantitative crystallinity measure. MCC, the native cellulose allomorph is a pure form of cellulose1. The X-ray diffraction patterns of the native MCC and the co-processed motifs showed patterns that are similar and characteristic of MCC (Fig. 6)[39, 40]. Although the patterns of the native MCC showed no obvious differences between it and the co-processed motifs, however, all the motifs showed shifts in the prominent peaks at 2( ) relative to the native MCC. The primary intensive peaks for the native MCC appeared at 16, 20 and 34, while the various MCC motifs modified by surface film coating with CAP, Etyl-cel and Eud showed variable shifts occurring predominantly at 14, 16, 20, 22 and 34. There were also differences in the minor peaks in the coated motifs a variation that can be related to differences in the crystalline lattice of the MCC chain network.

4.8 Dilution capacity

An important attribute of an excipient intended for direct compression application is high dilution potential which impact minimum possible weight on the tablets. The dilution capacity of a potential direct compression excipient may also be influenced by the compressibility of the active pharmaceutical ingredient (API) [41]. Apn was used for assessing the comparative dilution potential of the coated MCC motifs because of its poor compaction property resulting from its ability to undergo considerable elastic recovery after withdrawal of the compression pressure [42]. The loading capacities of the native MCC and the coated motifs were determined by assessing the tensile strength of the Apn loaded compacts. The effect of the film coating of the MCC particles with Eud, CAP and Etyl-cel respectively as shown in Fig. 7 indicated that the tensile strength of the acetaminophen loaded compacts prepared with MCC caused a remarkable reduction in the tensile strength of the native MCC. The higher tensile strength shown by compacts prepared with the native MCC is related to the hydrogen bonds on adjacent cellulose molecules such that when MCC particles are compressed they deform plastically to yield an extremely large number of clean surfaces which when brought in contact during this deformation form a strong compact even under low compression forces [43]. The reduction in the tensile strength of the compacts formed with the co-processed motifs could be related the shielding of the hydrostatic forces that hamper hydrogen bonding and surface interactions responsible for compaction in MCC [44].

4.9 Disintegration

Disintegration is the first step and may be the limiting one in the release of active pharmaceutical ingredients (APIs) from the tablet especially when the API has limited solubility [45]. Thus, rapid disintegration is remains an important attribute of oral solid dosage formulations especially those intended for rapid release. Aspirin was chosen as the drug for this study because of its efficient compactibility, low solubility and non-disintegration properties [46]. The ASA tablets prepared with MCC and the co-processed motifs incorporated as disintegrant showed different disintegration time. The compacts also showed sensitivity to fluid type. The ASA compacts were none disintegrating in both SGF and SIF, disintegration of the pure ASA crystals were over 2h in both fluids (Fig. 8). MCC and its co-processed motifs reduced the disintegration time of ASA. Though SIF is not a conventional fluid for assessing disintegration time of tablets the use of SIF for assessing the disintegration potential of the coated motifs of MCC was intended to evaluate the activity of the enteric coating polymers (Eud and CAP) on the disintegration of the ASA compacts. The MCC motifs produced by coating with Eud and CAP showed longer disintegration time in SGF as compared to the disintegration in SIF (Fig. 8). This thus, reflects the enteric activity of the MCC coated with Eud and CAP. MCC coated with Etyl-cel showed the least disintegration time of the three coating polymers in both SGF and SIF (Fig 9). MCC is known to induce disintegration by its fast water wicking activity, however the tendency of the powder to develop static charges due to high moisture content may extend the disintegration time.

III. CONCLUSION

This study has established the effect of co-processing of MCC with some film coating polymers. Some fundamental properties of MCC were modified by coating the discrete particles of MCC with the polymers. Functional properties such as powder flow and disintegration capacity were enhanced while the dilution capacity was reduced to varying degrees with the different coating polymers. This study thus, portends a potential value in the production of new multifunctional MCC motifs with new physicochemical properties, comparable dilution capacity and, superior flow and disintegration capacity relative to the native MCC.

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