Functionality assessment of microcrystalline cellulose derived from rice husk as a pharmaceutical excipient

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ABSTRACT

Herein, microcrystalline cellulose obtained from rice husk (RH-MCC) has been evaluated for its role as a diluent in ascorbic acid tablet formulation, as well as disintegrant in dicalcium phosphate (DCP) compacts. Critical material attributes of the MCC including morphology (SEM), thermal behavior (DSC), micromeritic, flow, swelling and sorption properties correlated well to its roles, and are comparable to the well-known commercial brand, Avicel PH 101. Consequently, RH-MCC could function as a potential pharmaceutical excipient.

Keywords: Microcrystalline cellulose, Functionality assessment, Tablet, Rice husk

1. INTRODUCTION

The goal of research and development in pharmaceutical excipients utilization from non-traditional sources is to establish their functionality in relevant drug product, and that entails delivering to the patient the required amount of drugs, at the required rate, and with equal potency over their shelf-life period. Excipient functionalities relate to their roles in drug products where they may be used for improving process, enhancing aesthetics, optimizing product performance, and /or facilitating patient compliance (Dave et al., 2014).

Commercial MCCs, which are obtained from wood and cotton sources have functioned as a stabilizer, flow-aid, disintegrant, and as direct compression fillers/binder in various industries including pharmaceutical, cosmetics and food. However, with non-wood, biomass-based sources, like rice husk, for it to be use as alternative to commercial grade MCCs their potentials as tablet excipient must be

adequately assessed, particularly when even unintentional variability from the same excipient is unavoidable. For instance, variability could arise from batch-to-batch, source-to-source, and from supplier-to-supplier, and it could be both at molecular and macroscopic levels. Many researchers agree that the critical material attributes (CMA) of excipient correlate closely to the functionality of that excipient and it determines the consistent performance of product during its shelf-life (Haware et al., 2014; Chamarthy et al., 2009; Zhao and Augsburger, 2006; Zhao and Augsburger, 2005; Shah and Augsburger, 2001). Material properties such as morphology, thermal, micromeritics, mechanical, compaction, rheological, and chemical consist the CMA (Dave et al., 2014).

In this study, pharmaceutical-grade MCC obtained from rice husk as described previously (Ohwoavworhua et al., 2019) was used for this assessment. It should be noted that rice husks (otherwise called rice hulls) as part of chaff from rice production exist as huge residue with a total annual yield of 1.72 x10^8 tons globally (Liu et al., 2013).

2. MATERIALS AND METHODS

Pharmaceutical grade MCC obtained previously was used (Ohwoavworhua et al., 2019). To assess the structural properties of the RH-MCC, the scanning electron microscopy (Joel 6310 Instrument, Tokyo, Japan) was used, with the system running at 10 KeV. The sample was fixed unto one side of a two-sided carbon adhesive tape and sputtered with platinum for 25 s using Agar sputter device (Agar Scientific Ltd., Stansted, UK) and thereafter the photomicrograph was taken, which was used for morphological characterization.

To assess the thermal characteristics of the RH-MCC, the differential scanning calorimetry, DSC, (model DSC 204 F1 NetzschGeratebau, GmbH, Selb, Germany, a heat-influx DSC equipped with Netzsch Thermokinetic Analysis Software) was used. Thermograms for RH-MCC and Avicel 101 powder samples were obtained by heating from 26 to 500 °C at a heating rate of 10 °C in a sealed aluminum pan with the lid perforated, with an empty pan as the reference. Nitrogen gas flow at 70 ml/min was used to provide inert dynamic atmosphere. The parameters determined include: temperatures of MCC water loss (T_d), and melting temperature (T_M).

Micromeritics Properties

Particle size and size distribution assessment was carried out using the sieve-shaker (Endicott's Ltd UK). The set of sieves were arranged in a descending order from 1,180 to 75 μm. RH-MCC sample (50 g) was weighed unto the top sieve and the sieve-set was vibrated for 5 min. The fraction retained on each sieve was weighed and the average particle diameter computed using the equation:

Average particle diameter = Σ(% retained) x (mean aperture)/100...(1)

The true density, D_t, estimation of the sample was determined by the liquid displacement method, with xylene as the immersion fluid (Ohwoavworhua et al, 2004) and computed according to Eq. 2:

$D_t = w/[(a + w)-b] \times SG$ ..... (2)

where *w* is the weight of sample, SG is the specific gravity of xylene, *a*is the weight of bottle + solvent and *b* is the weight of bottle + solvent + sample.

We next assessed the bulk and tapped densities of the MCC samples using a 250 mL measuring cylinder and Stampf volumeter apparatus (Model STAV 2003 JEF, Germany). Sample (40 g) was weighed into the measuring cylinder and the volumes (V_0 and V_{500}) occupied after 2 and 500 taps were noted. Using Eq. 3 the bulk and tapped densities were computed.

Density = Weight/ Volume..... (3)

To estimate the porosity of the MCC samples, the true and bulk densities data were fitted into the equation:
$e = 1- B_b/D_t \times 100$..... (4)

where B_b is the bulk density, D_t is the true density and *e* is the porosity.

We also determined the flow properties of the samples using these three tests: compressibility, Hausner ratio and angle of repose. The compressibility and Hausner ratio were computed using bulk and tapped densities data obtained as described above.

(i) Compressibility: This was computed as in Eq 5:

% Compressibility = [Tap density – bulk density)/Tap density] x 100 %].... (6)

(ii) Hausner ratio: This was computed using the formula in Eq. 7:
Hausner ratio =Tap density/ bulk density..... (7)

(iii) Angle of repose: The Train (1958) fixed funnel and freestanding cone method was used. A funnel was clamped with its tip 2 cm above a graph paper placed on a flat horizontal surface. The MCC samples were carefully poured through the funnel until the apex of the cone thus formed just reached the tip of the funnel. The mean diameter of the base of the powder cones was recorded and the tangent of the angle of repose computed using Eq. 8:

Tan a = 2h/D..... (8)

Where h is the height of the heap of powder and D is the diameter of the base of the heap of powder.

Lastly in the series of determinations to evaluate the critical material attributes, we assessed the hydration, swelling and moisture sorption capacities, which are predictive of the ability of the excipient to take up and hold water.

Hydration and swelling capacities were determined using the method of Okhamafe and Azubuike (1994). The moisture sorption capacity was determined in tarred *Petri* dish and desiccator simulated to be at relative humidity of 100% using distilled water and at room temperature. The Petri dish containing samples (2.0 g), evenly spread, were placed in the desiccator. The weights gained at the end of a five-day period were recorded. The amount of water taken up was computed from the weight difference (Ohwoavworhua et al., 2004).

Tablet Preparation and Properties

In pharmaceutical tableting, microcrystalline cellulose is used both as diluent and disintegrant. To investigate the RH-MCC for its diluent properties, tablets composing of Ascorbic acid (33.3 % w/w), as a model water-soluble drug, and MCC (66.7 % w/w) of either, Avicel PH 101 or RH-MCC were compressed using a single punch tablet machine (Model STC THP, TianxiangChentai Pharm. Machinery Co. Ltd., Shanghai, China). Proper mixing of the drug and MCC was carried out in a bottle rotated as figure eight for 10 minutes. Using a pre-determined fixed compression force of 31.25 KN, 300 mg of the powder mixture was filled into the die and compressed. The flat-faced punch was pre-lubricated with 2 % dispersion of magnesium stearate in ethanol-ether (1:1). The compacts were evaluated for tablet properties after being stored in a silica gel desiccator for one week.

To assess the disintegrant properties of the MCC samples, plain compacts of dicalcium phosphate dihydrate, DCP, (a practically insoluble hydrophilic direct compression excipient), as well as those of DCP/microcrystalline cellulose (MCC) types were prepared using a single punch tablet machine at the same compression force as above. The compositions of these formulations are shown in Table 1.

Table 1: Formula for DCP/microcrystalline cellulose (MCC) powder compacts

Ingredient (wt %)	Formulation		
	A	B	C
DCP	300 mg	300 mg	300 mg
Avicel PH 101	-	60 mg	-
RH-MCC	-	-	60 mg

Evaluation of tablet properties

The compressed tablets were evaluated for their dimensions, friability, crushing strength, disintegration time, and dissolution rate of the medicament.

For tablet dimensions

Twenty tablets were selected randomly from each batch. Tablet thickness and diameter were measured with thickness gauge (ID type, Mitutoyo, Japan).

For friability measurement

Sample size of twenty tablets was selected from each batch and freed of dust, weighed, and placed in the drum of a Roche fribilator programmed to revolve for 4 min at 25 rpm, after which the tablets were freed of fine dust and weighed again. The weight, before and after the test, were used to calculate friability as in Eq. 9:

$$\text{Friability} = W_L/W_O \times 100 \quad (9)$$

where W_L is weight loss and W_O is original weight.

For crushing strength measurement

Six tablets were used in a tablet crushing strength tester (Karl Kolb, West Germany). The mean crushing strength was determined for both the RH-MCC and Avicel PH101 containing tablets.

For Disintegration time

The USP., (2014) method was adopted and a disintegration apparatus (DT 2, Ereweka) was used. The disintegration medium of 0.1N hydrochloric acid was maintained at 37°C. A tablet was placed in each of the six glass tubes carrying a 10 mesh-sieve, and the time it took for each tablet to disintegrate was determined using a stopwatch. Six replicate determinations were made and the mean and standard deviation calculated for each batch.

For dissolution time

The test was performed in a dissolution test unit (Erweka Dissolution Rate Testing Unit, Type DT). The paddle method was used; and the dissolution medium of 0.05 M acetate buffer (pH 4.5), 900 mL was used. The temperature of the bath for all determination was kept constant at 37 ± 0.5°C, with the paddle rotation speed maintained at 50 rpm. Dissolution medium samples of 5 mL were withdrawn at regular intervals with the aid of a syringe. To maintain sink conditions, the sample withdrawn was replaced with equal a volume of the medium in each case. The concentrations of drug in the withdrawn samples were determined spectrophotometrically (model MillonSpectronic 1001) using an aliquot suitably diluted (1:1) with 0.05 M acetate buffer and the measurement wavelength was 263 nm. Using the calibration curve prepared from the active drug reference standard, the concentration of drug in each sample was calculated. Drug dissolution was plotted against time and the result is shown in Fig 4.

Statistical analysis

The data obtained were expressed as means of five determinations, except otherwise stated. Standard deviations, expressed as ±, were computed using Microsoft Excel.

3. RESULTS AND DISCUSSION

Structural characteristics

Fig. 1 shows the SE photomicrographs of the MCCs. As can be seen, the MCCs showed different morphological presentations. Rice husk MCC appears to consist of short fibers and tended largely to aggregation or agglomeration of primary particles, while the Avicel PH 101 consisted of highly fibrous primary particles with no aggregations, but with long fibers.

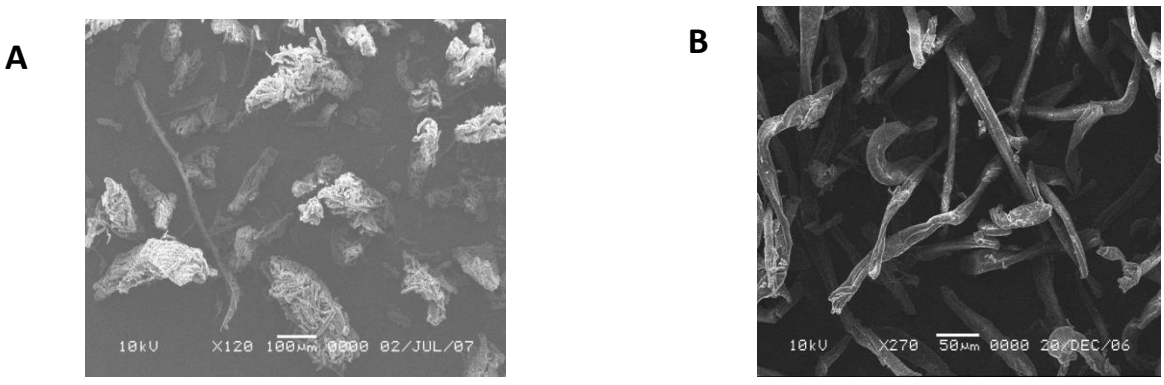

Fig.1 Scanning electron photomicrographs of (A) derived (Rice husk MCC) and (B) reference (Avicel® PH 101) microcrystalline

cellulose

The DSC thermograms for the tested RH-MCC and Avicel PH 101 are presented in Figure 2. The thermograms indicate that the RH-MCC and the reference, Avicel PH 101 have similar thermal properties. Viera et al., (2007) stated that the first endotherm peaks indicate de-sorption of water from the cellulose materials, with desorption temperatures (T_d) of 53.5 and 58.7 ˚C, for RH-MCC and Avicel PH 101, respectively. The second peaks, which represents the melting endotherms are also similar for both the MCCs and had melting temperatures (T_m) of 339.2 and 349.5 ˚C.

Viera et al., explained that the first endotherm was due to the interaction of the water with the hydroxyl groups of the cellulosevia the formation of hydrogen bonds, and the breaking of the bonds by heat causes the loss of water. The melting endotherm is characteristics of crystalline portion of the polymer and is a first order transition (Ohwoavworhua FO and Okhamafe AO, 2020).

Thermal analysis as a technique is convenient and reproducible, and is considered a useful method for characterizing heterogeneous organic material. In particular, it is a valuable analytical method to investigate the physico-chemical properties of macromolecules such as cellulose (Sun et al., 2005).

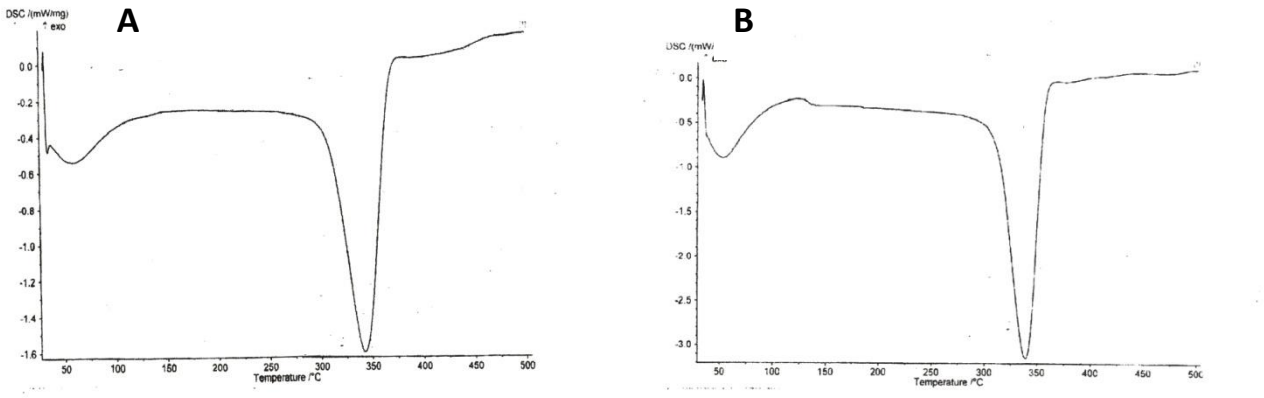

Fig. 2 Diffraction scanning calorimetry thermograms of microcrystalline cellulose prepared from (A) rice husk, and (B) Avicel PH 101.

Micromeritic properties:

The result of the particle size distribution is shown in Figure 3. As evidence in the figure, the size distribution for RH-MCC does not reflect a normal distribution curve, which is characteristic of the population of powder particles obtained from a single batch. In sharp contrast, it exhibited multi-modal distribution curve, which suggest that its population of powder particles is drawn from a pool of several batches – a common feature with laboratory extractive processes. The computed average particle size for RH-MCC is 375 μm, compared to < 150 μm for Avicel PH 101.

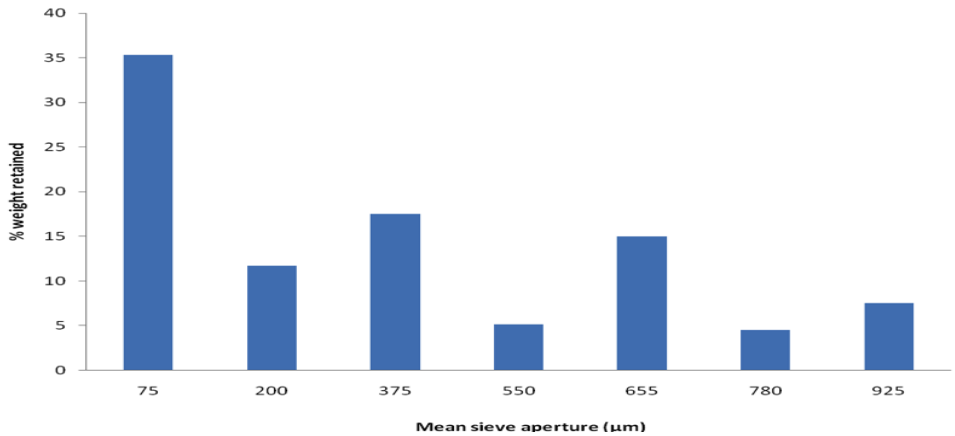

Fig. 3 Particle size distribution of microcrystalline cellulose obtained from rice husk (RH-MCC)

Table 2 shows the results of micromeritic measurements for both MCCs. Density measurements have been correlated to a number of physical properties. The crystallinity and purity of powders have been investigated using a variety of density measurements. Particle shape has been shown to influence bulk and tap densities (Newman, 1993). The flow properties of powders have been correlated to bulk density measurements. It was reported that increase in bulk density would increase flow properties (Newman, 1995).

Both MCC types exhibited low bulk and tapped densities and this is in accordance with literature report (Bhimte and Tayade, 2007; Doelker et al., 1987; McKenna and McCaffery, 1982; Czeisler and Perlman, 1991). Avicel PH 101and prepared RH- MCC from rice husk have comparable bulk and tap densities.

Porosity: The porosity data showed considerable difference between the cellulose types (see Table 2). This could be due to the particle shape. The RH-MCC, which tended to aggregates and largely oval-like had the low porosity. The high porosity value for Avicel PH 101 could be due to its longer fibers that preclude close packing.

Table 2: Micromeritic properties of microcrystalline cellulose powders

MCC type	Bulk density(g/cm^3)	Tapped density(g/cm^3)	True density(g/cm^3)	Porosity (%)	Mean particle size(µm)
Avicel	0.31 ± 0.04	0.42 ± 0.12	1.40 ± 0.38	78	< 150
RH-MCC	0.31 ± 0.09	0.45 ± 0.03	1.37 ± 0.22	57.5	375

Flow properties

Table 3 shows the flow properties of the MCCs. Flow characteristics of the pharmaceutical excipients are of major concern with respect to the handling and compaction of powder materials, especially for directly compressible excipients. The angle of repose gives a qualitative assessment of internal and cohesive friction. An angle of up to 40˚ indicates reasonable flow potential and those with an angle greater than 40˚ exhibit poor flow or absent flow. Angle of repose measurement is sensitive to moisture content and may provide a means of monitoring batch-to-batch differences (Ohwoavworhua et al., 2004). Thus, Avicel PH 101 and RH-MCC with angle of repose < 40˚ are expected to have some flow potential.

Table 3: Flow properties of microcrystalline celluloses powders

MCC type	Angle of repose	Compressibility (%)	Hausner ratio
Avicel PH 101	30.0 ± 2.0	26.2	1.35
RH-MCC	39.9 ± 0.7	31.2	1.45

Compressibility is calculated from bulk density and tapped density. Compressibility value of 20% and above is characteristics of a powder that is not free flowing and has a tendency to create bridges in the hopper. Materials with compressibility of 40% to 50% are particularly difficult to discharge from hopper (Sandel, 1983). Consequently, the MCCs investigated with compressibility in the range of 26 to 34˚ would not flow through hopper easily as such flow aid (glidant) may be blended with them. It should be noted that the compressibility or Carr's index indicates the aptitude of a material to diminish in volume, while the Hausner ratio is indicatives of inter-particle friction. With respect to the Hausner index, both the RH-MCC and Avicel PH 101 exhibited poor flow, as value above 1.25 is considered to have poor powder flowability (Rubinstein, 1996). Overall, taking into account the three flow indices, Avicel PH 101 was adjudged 'good', while RH-MCC, with somewhat irregularly shaped particles and a tendency to aggregate, was 'fair'. The difference in the flow properties could be attributed to particle shape, and particle size distribution (Doelker et al., 1987a).

Hydration, swelling and moisture sorption capacities

Caramella (1991) noted that swelling is generally accepted as an indication of tablet disintegration ability, and could be predicted by the determination of hydration capacity, swelling capacity and moisture sorption profile. Hydration capacity values are listed in Table 4. Both values indicate that the MCCs are capable of absorbing more than twice its own weight of water.

Swellability, which reflects increase in the volume of cellulose following water uptake is in the order: Avicel PH 101 > RH-MCC. The low values suggest that only a small fraction of absorbed water actually penetrated the individual cellulose particles causing them to swell. And that implies that if the celluloses were to be incorporated in a tablet formulation as a disintegrant, it would probably produce tablet disintegration by two mechanisms: capillary or wicking due to interparticulate water and swelling.

Moisture sorption capacity is used to assess the moisture sensitivity of materials and its values for both MCCs are comparable. Tamm (1964) noted that the crystalline portion of cellulose does not adsorb water and the extent of water adsorption by cellulose should therefore be proportional to the amount of amorphous cellulose present. Hence, the results obtained here suggest that Avicel

PH 101 has a higher proportion of amorphous cellulose than the RH-MCC. It should be noted also that water sorption measurement is of importance because it could indicates the relative physical stability of tablets made from cellulose when stored under humid conditions. By and large, the data obtained showed that cellulose powders are sensitive to atmospheric moisture and should therefore be stored in air-tight containers.

Table 4: Hydration capacity, swelling index and moisture sorption capacity of microcrystalline cellulose powders

Samples	Hydration capacity	Swelling index (%)	Moisture sorption capacity (%)
Avicel 101	2.2 ± 0.2	21.4 ± 2.2	16.6 ± 1.3
RH-MCC	2.6 ± 0.2	15.0 ± 2.1	13.5 ± 1.1

Filler-diluents properties of MCCs in ascorbic acid tablet formulations

Table 5 shows some physical properties of ascorbic acid tablet formulation with MCCs as filler-diluents. The data showed that tablets prepared with Avicel PH 101 are relatively stronger. This superiority in strength could be attributed to stronger bonding due to the smaller particle size of Avicel PH 101 and hence larger contact area of particles for bond formation during compression.

Both batches of ascorbic acid tablet (AST) formulations disintegrated within the upper limit of 15 minutes official values (USP, 2014). However, the tablets made from RH-MCC had relatively high disintegration time of 13.48 min, when compared to the 8.76 min for Avicel PH 101. This data mirror their hydration and swelling indices (see Table 5).

Table 5: Some physical properties of ascorbic acid tablet formulations containing microcrystalline cellulose powders as filler-diluents

Formulation	Crushing strength (kgf)	Friability (%)	Disintegration time (min)
Ascorbic/Avicel	11.26 ± 1.82	1.4	8.76 ±2.34
Ascorbic/RH-MCC	5.88 ± 0.96	2.5	13.48 ± 2.12

The dissolution-time release profile for ascorbic acid tablets formulated with the prepared RH-MCC and Avicel PH 101 are shown in Figure 4. Their release profiles are somewhat different, however they both appear to peakat 90% release rate after 30 min. The difference in the release profiles could be due to differences in their particle sizes (< 150 μm for Avicel PH 101 and averaged 375 μm for RH-MCC), as well as in their mean disintegration time.

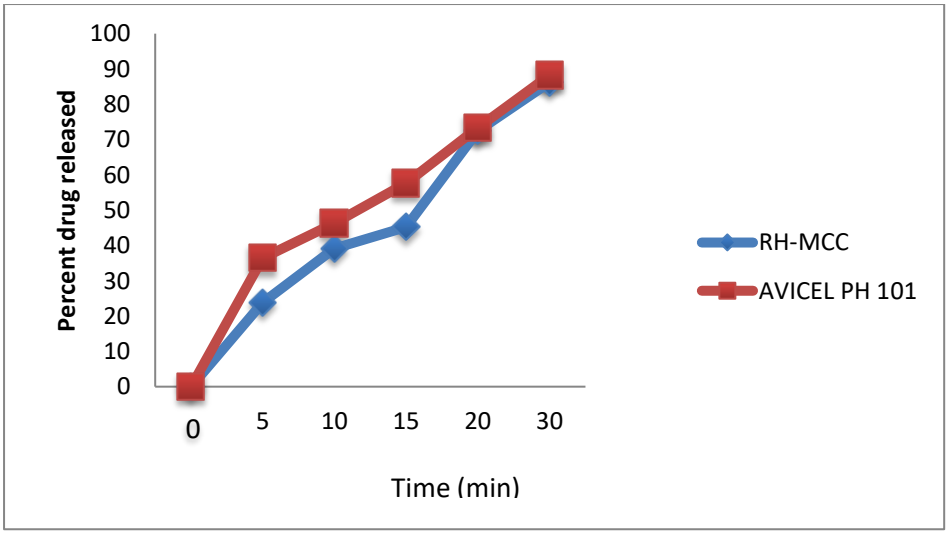

Fig. 4 Dissolution time-release profiles of ascorbic acid tablets with microcrystalline cellulose powders as filler-diluents

Disintegrant properties of the MCCs in directly compressed dicalciumphosphate dihydrate compacts

The effect of MCC type on DCP compact characteristics is shown in Table 5. Generally, incorporation of as low as 60 mg (approximately 20% w/w) of disintegrant in the DCP compact affected the compact properties and the extent was dependent on the

MCC type. The crushing strength of the compacts fell following the incorporation of the MCC. The rank order of reduction in crushing strength is as follows: RH-MCC >Avicel PH 101. The crushing strength of DCP compact without disintegrant was 17.22 kgf, while the values for DCP containing MCC ranged from ~ 12 to 14 kgf.

Table 6: Characteristics of dicalcium phosphate (DCP) compact with microcrystalline cellulose powders as the disintegrant

Formulation	Crushing strength (kgf)	Friability (%)	Disintegration time (min)
DCP alone	17.22 ± 2.14	0	>120
DCP/Avicel	13.85 ± 1.47	0.32	11.17
DCP/RH-MCC	11.96 ± 2.56	1.2	14.46

Thus, it seems that the cohesive force between DCP particles is stronger than adhesive forces between DCP and MCC particles. Alternatively, the disintegrant could be functioning as a surface 'contaminant' of DCP particles and hence the overall reduction in bonding strength of the compacts. Bowden and Tabor (1950) noted that the strongest bonds are formed between clean surface, so that incorporation of MCC as disintegrant to DCP could have weaken the cohesive bonds between the particles of DCP due to the presence of a physical barrier (or 'contaminant') of disintegrant between the particles.

The friability of all DCP compacts was adjudged satisfactory as all compacts approximated to 1% limit (Sandel, 1983). Friability correlates with crushing strength. The lower the crushing strength, the more friable was the compacts.

The disintegration time data indicated the disintegration power of the MCCs. MCCs at 20% w/w concentration exerted profound disintegrant effect on DCP compacts. Sheth et al., (1980) reported that MCC at a concentration of 20% or higher is an effective disintegrant in tablet preparations. However, the disintegrant power of the MCCs varied with the type. The low disintegration time exhibited by Avicel PH 101, relative to RH-MCC, could be correlated with its high moisture sorption capacity and swelling index (see Table 4), as well as its particle size of < 150 m.

4. CONCLUSION

The critical material attributes (CMA) of the derived microcrystalline cellulose (RH-MCC), such as morphology (SEM), thermal behavior (DSC), micromeritic, flow, swelling and sorption properties compared favorably with the well-known commercial brand, Avicel PH 101. RH-MCC roles both as diluent and disintegrant could be related its CMA. RH-MCC could be used as a potential pharmaceutical excipient.

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This study has not received any external funding.

Conflict of Interest

The authors declare that there are no conflicts of interests.

Data and materials availability

All data associated with this study are present in the paper.

Peer-review

External peer-review was done through double-blind method.

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