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Research paper

Preparation and characterization of mucinated cellulose microparticles for therapeutic and drug delivery purposes

Philip F. Builders [a,*], Nneka Ibekwe [b], Larry C. Okpako [c], Anthony A. Attama [d], Olobayo O. Kunle [a]

[a] Department of Pharmaceutical Technology and Raw Materials Development, National Institute for Pharmaceutical Research and Development, Abuja, Nigeria
[b] Department of Medicinal Chemistry and Quality Control, National Institute for Pharmaceutical Research and Development, Abuja, Nigeria
[c] School of Pharmacy, University of Bradford, United Kingdom
[d] Department of Pharmaceutics, University of Nigeria Nsukka, Nigeria

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ABSTRACT

Mucinated cellulose microparticles were generated by mixing equal concentrations of colloidal dispersions of porcine mucin (Mc) and microcrystalline cellulose (MCC). The hybrid polymer was recovered by precipitating at controlled temperature and pH conditions using acetone. Some physicochemical, functional and thermal properties of the hybrid polymer were determined and compared with those of Mc and MCC. The new polymer Mc-MCC had swelling and moisture sorption profiles that were different from those of Mc and MCC in buffer solutions with different pH values and relative humidity, respectively. The mucoadhesive property of the new polymer was similar to that of Mc. The scanning electron micrographs (SEMs) showed that the microparticles generated from the hybridization were similar to those of MCC, but with larger and denser particles. The Fourier Transform Infrared (FT-IR) spectrum and Differential Scanning Calorimeter (DSC) thermogram of the hybrid polymer were characteristically different from those of Mc and MCC. The presence of new peaks in the FT-IR spectrum and distinct cold crystallization exotherm, which were absent in both Mc and MCC, confirms the formation of a new polymer type with synergistic physicochemical and functional properties.

1. Introduction

There is a constant pressure to develop new polymers for use as excipients with the desired set of functionalities to meet the increasing need for newer delivery technology [1]. Several techniques have been explored to meet this need. These include direct synthesis [2,3] and preparation of new polymer types from the composites of the existing ones [1,4]. Such new polymers are often tailored to meet specific needs [5]. Many commercially available polymers employed as excipients are produced by chemical modification of the naturally occurring ones [6]. Both chemical crosslinking and physical crosslinking are popular methods by which new polymer types are produced [7]. Hybrid polymers with superior functional and physicochemical properties have been produced by physical and chemical crosslinking of polymers with different but desirable properties [8]. An important attribute of polymer hybridization is that the new species combine the qualities of the components in terms of functional and physicochemical properties [9]. Other important attributes in developing such novel excipients are non-toxicity, biocompatibility and biodegradability which are acquired from the component polymers.

Mucins are high-molecular weight glycoproteins found on the surface of epithelial tissues where they act as lubricants and protectants [10]. In the gastrointestinal tract, mucin protects the mucus membrane against the harsh conditions of the gastric environment due to hydrochloric acid. It also controls the diffusion of molecules across the mucus membrane. These functions are mainly due to its intrinsic viscoelastic consistency [11]. The functional properties of mucin (Mc) as a protective coat make it a potential pharmaceutical excipient for new drug delivery concepts. Such excipients may contribute in drug therapeutics, such as safe delivery of aspirin and other non-steroidal anti-inflammatory drugs to ulcer patients. Microcrystalline cellulose (MCC) is purified partially depolymerized cellulose. It is nonirritant and nontoxic, and is widely used in oral pharmaceutical formulations and food products. In many conventional pharmaceutical formulations, it is primarily used as binder and diluents in oral tablets and capsules in both wet granulation and direct compression processes. It is also used as a lubricant and disintegrant in tablets. Because of its desirable physicochemical and functional properties, MCC has been co-processed with other excipients [6]. By hybridizing Mc and MCC, a novel polymer with a combination of the physicochemical and functional properties characteristic of the two component poly-

* Corresponding author. Department of Pharmaceutical Technology and Raw Material Development, National Institute for Pharmaceutical Research and Development, 234 Abuja, Nigeria. Tel.: +234 8035874698.
E-mail address: philsonsky@yahoo.com (P.F. Builders).

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mers is expected. The new polymer will be directly compressible as well as acting as a mucus membrane protectant.

Thus, to produce a novel excipient with membrane-protective, mucoadhesive and direct compression properties for therapeutics and drug delivery purposes, a Mc and MCC hybrid (Mc-MCC) will be prepared by regenerating colloidal mixtures of Mc and MCC at controlled pH and temperature conditions. The novel excipient in comparison with the starting materials will be characterized by evaluating their FT-IR spectra and DSC thermograms, mucoadhesive properties, swelling as well as their moisture sorption profiles to determine relevant physicochemical and functional properties.

2. Materials and methods

2.1. Materials

The materials used were microcrystalline cellulose (MCC) (Fluka Biochemica, Ireland); porcine mucin (Mc), sodium chloride, and magnesium chloride (Sigma–Aldrich Chemie, Germany); potassium dihydrogen phosphate (May & Baker, Dagenham, England); and sodium hydroxide, potassium thiocyanate, potassium chloride and calcium chloride (BDH Chemicals, UK).

2.2. Preparation of mucin-microcrystalline cellulose hybrid

MCC was solubilised by using the method of Kuo and Hong [12]. A 10% w/v dispersion of MCC was made using 9% w/v sodium hydroxide solution in distilled water. The dispersion was stored at −30 °C for 24 h and then thawed at 30 °C. The freezing and thawing cycle was repeated thrice. The pH of 10% w/v dispersion of Mc in distilled water was determined and used as the reference point for the end pH of the final product. Equal volumes of Mc and MCC colloidal dispersions were mixed and homogenized for 30 min with a Kenwood mixer (Kenwood Ltd., USA) at a mixing speed of 200 rpm. The pH of the mixture was then adjusted to 6.5 using 2 M HCl. The dispersion mixture was gradually introduced into a 1 L beaker containing three parts by volume of acetone maintained at −30 °C with continuous stirring at 400 rpm. The coacervate formed was recovered by filtration with a filter paper (Whatman, USA), with more portions of acetone used to rinse the generated microparticles to remove any residual water. The hybrid polymer microparticles were then dried with a flush of cold air (10 °C). The dry sample was screened with a 250-μm sieve (US Standard sieve, USA) using a sieve shaker (Retsch, D 42781 Haan, Germany). The powder was then stored in a desiccator for 48 h before storing in an airtight container.

2.3. Particle properties

The packing properties of the powdered polymer samples were determined with the tapping method using the Kawakita equation [13,14] as represented by

$$1/(\varepsilon_n - \varepsilon_f) = K \cdot n + 1/(\varepsilon_o - \varepsilon_f) \quad (1)$$

where ε_o, ε_n and ε_f are the porosities of the powder bed at initial, nth and final tappings, respectively, and n is the number of taps. The packing rate constant K is determined as the slope of the plot of $1/(\varepsilon_n - \varepsilon_f)$ vs the number of taps, n.

The flow properties were determined by two empirical methods; Angle of repose (Φ), determined using Eq. (2), and Carr's compressibility index (CI), determined using Eq. (3) [15]

$$\tan \Phi = \frac{2h}{D} \quad (2)$$

where h is the powder bed height and D is the powder bed diameter

$$CI = (V_o - V_t)/V_o \times 100 \quad (3)$$

where V_o is the inverse of the bulk density and V_t is the inverse of the tapped density.

2.4. Photomicrograph

The scanning electron micrographs (SEMs) of the various polymer microparticles were obtained. The samples were prepared by gold-plating the particles, while imaging of the formulations was carried out on a scanning electron microscope (FEI Quanta 400, FEI Company, OR, USA) at a magnification of 250×.

2.5. Mucoadhesive properties

Compacts of Mc, MCC and Mc-MCC were prepared by compressing 500 mg powder with a compression machine (Shanghai Tiaxiang & Chenta. Pharmaceutical Machinery Co. Ltd.) fitted with a 12-mm flat faced punch and die set at a pressure of 20 KN. The mucoadhesive characteristics of Mc, MCC and Mc-MCC were studied by evaluating the force required to detach the hydrated compacts from the surface of freshly excised porcine small intestinal tissue, using a Du Nouy tensiometer adapted for this purpose [11].

2.6. Swelling properties

Compacts of Mc, MCC or MCC-Mc microparticles each weighing 250 mg (W_d) were placed in a desiccator for 48 h. Each disc was placed on a mini glass plate (2 × 4 cm) of known weight, which was then transferred into a Petri dish containing 60 ml of a buffer solution (the buffers had pHs of 2, 4, 7 and 9, respectively) at 25 °C. At 10 min intervals, the glass plates with the hydrated discs were removed, dried by blotting with tissue paper and weighed (W_t). The degree of swelling, (Q) was determined using Eq. (4). When the hydrated discs reached a constant weight (W_e), the percentage swelling at this point was considered to be the percentage equilibrium swelling (Q_e) and was determined according to Eq. (5) [16]

$$Q = [W_t - W_d/W_d] \times 100 \quad (4)$$

$$Q_e = [W_e - W_d/W_d] \times 100 \quad (5)$$

2.7. Moisture sorption characteristics

Quantities of Mc, MCC and MCC-Mc microparticles were placed in a Petri dish and stored in an activated desiccating chamber at 10 °C for one week to remove residual moisture from the materials. The moisture sorption isotherms of the microparticles were determined by the gravimetric method [17]. One gram of each dry polymer powder was placed in an aluminum foil and put in a desiccator with a gauze holding tray containing either distilled water or saturated solution of different salts to provide the required relative humidity (RH) (water 100%, potassium chloride 84%, sodium chloride 75%, potassium thiocyanate 47% and calcium chloride 31%). The powders were weighed at 12 h intervals until equilibrium was attained. The equilibrium moisture sorption (EMS) was determined using

$$EMS = M_e/M_d \times 100 \quad (6)$$

where M_e is the amount of moisture sorped at equilibrium and M_d is the dry weight of the material [18]. The profile of percentage weight gain vs RH was then evaluated for each material.

2.8. Fourier Transform Infrared (FT-IR) spectroscopy

The FT-IR-spectra were acquired on a NICOLET IR 100 (Thermo Electro Corporation, USA). Spectra over a range of 4000–400 cm^{-1}

with threshold of 1.303, sensitivity of 50 and resolution of 2 cm^{-1} range were recorded on KBr tablets (1 mg of polymer powder per 400 mg of KBr). Spectra scan for each of the polymers (Mc, MCC and Mc-MCC) was determined.

2.9. Differential Scanning Calorimetry (DSC)

DSC studies were carried out on a DSC 204 F1 (Phoenix NETZSCH) machine equipped with a thermal analysis system. Indium (156.8 °C) was used as the internal standard. Approximately 1 mg of Mc, MCC or MCC-Mc was 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 relevant thermodynamic parameters were evaluated with the Proteus analysis software.

3. Results and discussion

Porcine mucin is the mucin extracted from the pig gastric mucosa. Mucin is a protein that contains oligosaccharide chains covalently attached to the polypeptide side chains via N- and O-glycosidic bonds. Mucin is capable of interacting via its glycopeptide subunits by means of non-covalent interactions [19,20]. MCC comprises glucose units connected by a 1-4-β-glycosidic bond [21], solubilising it by the dislocation of the rigid bonds exposed the carboxylic and hydroxyl groups to interactions with the functional groups of the mucin peptide chains and to the cleaved oligosaccharide subunits. Thus, the mixture of colloidal dispersions of Mc and MCC in sodium hydroxide provides a veritable atmosphere for a number of intimate interactions between the various functional groups in Mc and MCC.

A new polymer type (Mc-MCC) resulted from the precipitation of the dilute colloidal dispersion of a mixture of Mc and MCC under pH- and temperature-controlled conditions. The resultant hybrid polymer exhibited superior physicochemical and functional properties characteristic of the individual components [4,22]. The dispersion of MCC in strong sodium hydroxide solution as well as the freezing and thawing was carried out to solubilise MCC, which was achieved by dislocating or breaking the strong β-(1-4) glucosidic bonds of the glucopyranosyl linkages of the partially depolymerized cellulose [11]. Working at a low temperature (−30 °C) will be expected to stabilize Mc by minimizing any possible denaturation of the glycoprotein during processing [23]. The pH of the dispersion mixture was reverted to that of Mc dispersion in distilled water to maintain its (Mc) viscoelastic consistency in the hybrid [11]. Recovery of the regenerated hybrid polymer was also achieved by precipitating with chilled acetone (−30 °C). Apart from preventing the denaturation of Mc, working at a low temperature will also increase the formation of crystallite points that will enhance physical crosslinking by acting as crosslinking sites through the formation of hydrogen bonds among amine, amide, carboxylic and the hydroxyl groups that are present in the hybrid dispersion [24].

3.1. Polymer morphology

The micrographs of MCC (Fig. lA), Mc (Fig. lB) and Mc-MCC (Fig. lC) obtained by scanning electron microscopy are shown in Fig. l. The micrographs show that Mc occurs as broad thin smooth sheets with serrated edges, and that MCC occurs as long thin rectangular strands with rough porous surfaces, while the particles of the hybrid, Mc-MCC, though similar in shape to MCC are characterized by larger and less rectangular particles with denser and rougher surfaces. The denser feature of the hybrid could be as a result of Mc filling and interconnecting with the micro-pores of the MCC particles. The morphology of the hybrid indicates intimate interconnectivity, resulting from the interplay of different inter- and intra-molecular polymer chain interactions that could have resulted from hydrogen and ionic bonding as well as from physical entanglement between the different polymer chain networks.

3.2. Particle physical properties

The consideration of the particle properties of a material for use as a direct compression excipient in oral pharmaceutical dosage forms is of critical importance. This is because important processes such as mixing, flow and compression are procedures that are dependent on particle properties [27]. The flow characteristics of Mc, MCC and Mc-MCC were indirectly assessed by determining their angle of repose and Carr's compressibility indices. Flowability of the particles assessed by angle of repose is based on inter-particulate cohesion. As a general guide, angle of repose less than 25° is considered to have very good flow, whereas 50° is poor [15]. The flow characteristics of the various polymer powders as assessed by the angle of repose are presented in Table 1. By assessing with Carr's compressibility indices, values below 15% represent good flow, while values above 25% indicate poor flowability. The results of the flow properties assessed by the Carr's compressibility index are also presented in Table 1. The flow quality of the three polymer types obtained by Carr's compressibility index was similar to that obtained by evaluating the angle of repose. The polymer powder

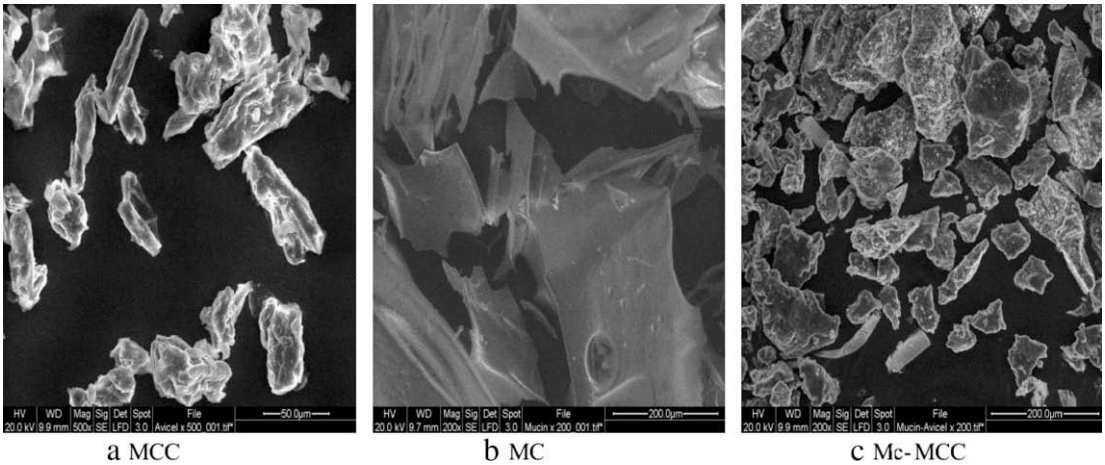

Fig. 1. SEM micrographs of MCC, Mc and Mc-MCC.

Table 1
Some particle properties of Mc, MCC and Mc-MCC.

Parameter	MCC	Mc	MCC-Mc
Angle of repose	24.5 ± 0.5°	53 ± 1.3°	17 ± 0.8°
Compressibility index (%)	20.93	78.13	14.24
K	0. 566	0. 435	0. 368

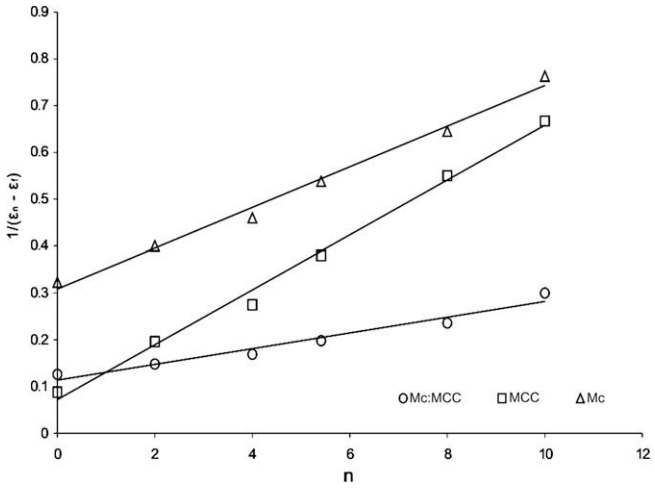

Fig. 2. Relationship between $1/(\varepsilon_n - \varepsilon_f)$ and n in Kawakita's equation. ○, Mc-MCC; □, MCC; △, Mc.

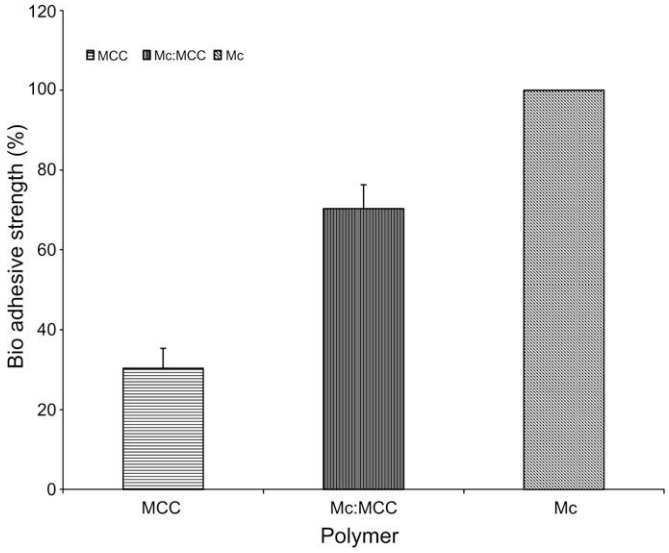

Fig. 3. Mucoadhesive strength of MCC, Mc, and Mc-MCC. —◇—, MCC; —□—, Mc:MCC; —△—, Mc.

flowability can be represented in the order Mc-MCC > MCC > Mc. Based on acceptable standards, MCC and Mc-MCC can be said to have good flow, with Mc-MCC having the better flow [28].

One of the essential attributes of MCC is its excellent compactibility at low pressure [29]. The tapping method is a simple way of assessing the packing characteristics of the hybrid polymer in comparison with MCC and Mc using Eq. (1) [13]. The plot of n vs $1/(\varepsilon_n - \varepsilon_f)$ is presented in Fig. 2. This shows a linear relationship between n and $1/(\varepsilon_n - \varepsilon_f)$. The K values for Mc, MCC and Mc-MCC are 0.435, 0.566 and 0.368, respectively. A high K value corresponds to a high compactibility [13]. Thus, Mc-MCC has lower compactibility relative to Mc and MCC. The difference observed in the K values for the different polymer types is related to their true density, size and shape of the particles [28].

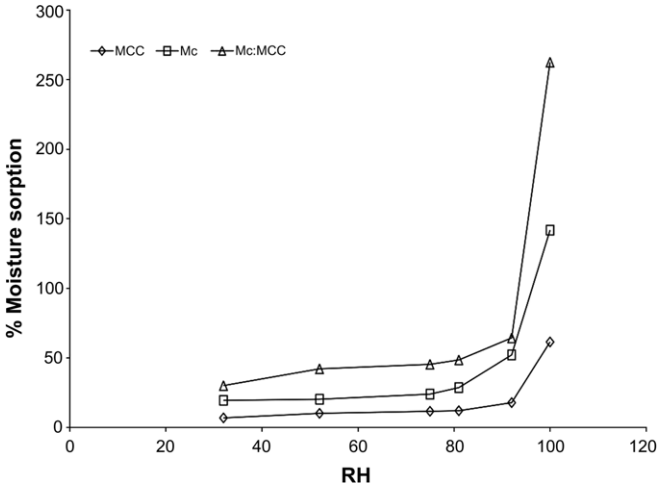

Fig. 4. Moisture sorption profile for MCC, Mc, and Mc-MCC at different RH. —◇—, MCC; —□—, Mc; —△—, Mc-MCC.

3.3. Mucoadhesive properties

The mucoadhesive strength of the discs made from the polymers was assessed to determine the mucoadhesive effectiveness of Mc-MCC in comparison with its component polymers. The mucoadhesive strength of Mc, which was the highest, was used as the reference standard with a value of 100% and the others measured relative to it (Fig. 3). The order of mucoadhesive strength was Mc > Mc-MCC > MCC. The adhesion of the polymer discs to the mucus membrane is due to the reduction of the surface energy (interfacial tension) between the membrane and the polymer [25].

High hydration capacity is one of the fundamental properties of a mucoadhesive polymer. Hydration results in the relaxation of stretched, entangled or twisted molecules in the polymer chain leading to the release of adhesive sites necessary for mucoadhesive interaction [26]. Thus, the low mucoadhesiveness of MCC is due to its low hydration capacity resulting from its high hydrophobicity. The hydrophobicity of MCC is predominantly due to the presence of numerous intra- and inter-chain hydrogen bonds in the bulk polymer. Mc has a high wetting and water holding capacity [11], apart from this, the high mucoadhesiveness of Mc may be contributed more by the interpenetration of the mucus gel layer formed by the hydrated Mc disc and the mucus gel layer of the intestinal tissue, thus resulting in a stronger adhesive interaction.

The mucoadhesive strength of Mc-MCC was higher than the average of its components (Fig. 3), thus, the hybridization process resulted in a new polymer type with mucoadhesiveness similar to that of Mc than to that of MCC.

3.4. Moisture sorption characteristic

Moisture sorption is a general term used to describe adsorption and absorption as well as desorption and resorption of moisture [30]. The adsorption of moisture onto polymer materials occurs by the formation of hydrogen bonds with the hydrophilic sites on the surface of the solid [17]. Water molecules first adsorb onto the surfaces of dry materials to form a monomolecular layer (adsorption), which is subjected to both surface binding and diffusional forces as shown in Fig. 4. The diffusional forces eventually

exceed the binding forces as more water molecules adhere to the surfaces and moisture is transferred into the material (absorption) [31].

The moisture uptake experiment was aimed at assessing the comparative amorphicity or crystallinity of Mc, MCC and Mc-MCC, to provide evidence of crosslinking between Mc and MCC in Mc-MCC produced from colloidal mixture of MCC and Mc by the temperature-controlled regeneration of the mucinated cellulosic micro-fibers. The isothermic moisture sorption profiles of Mc, MCC and Mc-MCC are shown in Fig. 4. MCC is slightly hygroscopic, while Mc and Mc-MCC are moderately hygroscopic [32]. Moisture sorption characterization has been reported to be the most sensitive technique for assessing variation in the amorphous content of polymers as well as for predicting some physicochemical and functional properties of polymers [18,33,34]. The amount of water adsorbed is dependent on the affinity between the surface and water molecules, temperature and the relative humidity as well as on the amount of surface area exposed [30]. The adsorption occurs when the water molecules form hydrogen bonds with the hydrophilic sites on the surface of the polymer [17].

The difference in the moisture sorption characteristics between the polymers could be due to the difference in the polar groups available for intermolecular interaction with water molecules. The glycan chain network of MCC contains numerous OH groups, which are, however, not available for hydrophilic interaction with water molecules due to the high degree of hydrophobicity conferred by the presence of strong intra- and inter-chain hydrogen bonds. Mc showed intermediate moisture uptake because of the presence of oligosaccharide chains. Mc-MCC showed the highest moisture uptake (Fig. 4). During the solubilisation process, the chain network of MCC was dislocated due to the breaking of numerous β-(1-4) bonds. This process resulted in the destabilization of the hydrophobic hydrogen bonds hence, in the exposure of many OH groups, making them available for interaction with water molecules. Thus, the hybridization of mucin with the modified oligosaccharide chains of MCC resulted in a novel moiety, probably a graft polymer chain with its chain network containing numerous free OH groups resulting in the formation of hydrophilic hydrogen bonds with the water molecules.

There was a gradual increase in moisture sorption by the three polymers between 31% and 92% RH, after which there was a sharp increase. This may be due to the gradual saturation of the monomolecular layer of the polymer powder beds between 31 and 92 RH. The sharp increase in moisture uptake between 92% and 100% RH corresponds to the total saturation of monomolecular layer and subsequent diffusion of excess moisture into the bulk powder bed or the formation of a multimolecular layer [31].

The amount of moisture taken up by a hydrophilic polymer depends on its amorphous or crystalline composition. For similar polymeric materials, the moisture uptake profile for the amorphous form exhibits a higher shift when compared to that for the more ordered crystalline form [33,35]. Thus, the hybrid material Mc-MCC is more amorphous than either Mc or MCC (Fig. 4). The higher amorphous domain in Mc-MCC relative to that of Mc and MCC is evidence of crosslinking between Mc and MCC. Due to its characteristic high crystalline domain, MCC absorbed the least amount of moisture. Mc and Mc-MCC showed similar amorphous characteristics, however, Mc has an apparently lower amorphous domain when compared to Mc-MCC. The amorphous domain of Mc and Mc-MCC is due largely to the presence of numerous branching and crosslinking oligosaccharides on the peptide backbone [11].

3.5. Swelling characteristics

Evaluation of the swelling characteristics of any material for use in drug delivery is important because swelling is one of the primary mechanisms by which active agents are released from delivery systems [36]. The compacts of Mc, MCC and Mc-MCC in buffer solutions of different pHs showed different swelling profiles (Figs. 5 and 6). Mc showed a steady and prolonged swelling in the various buffer solutions as compared to MCC and Mc-MCC (Fig. 5). This is due to the ability of the Mc compacts to maintain their structural integrity by forming a stable gel network due to its high viscoelastic consistency. The equilibrium swelling for all the compacts made with MCC and Mc-MCC was attained within a short time with their maximum equilibrium swelling time obtained in buffer solutions of pH 4 and pH 9, respectively (Fig. 5). The time taken to attain stable equilibrium swelling with stable disc structure integrity was 20 min for MCC and 10 min for Mc-MCC, after which the compact started to disintegrate. While MCC did not exhibit pH responsiveness to swelling, the reverse was true for Mc and Mc-MCC (Figs. 5 and 6). Mc and Mc-MCC showed similar pH responsiveness to swelling, both attaining maximum swelling at pH 9. For Mc-MCC, the least equilibrium swelling was attained at pH 7, swelling for MCC generally increased with decrease in pH (Fig. 6) while for Mc, the equilibrium swelling in buffer solutions below pH 9 (pH 7 and pH 4) was quantitatively similar (Fig. 6).

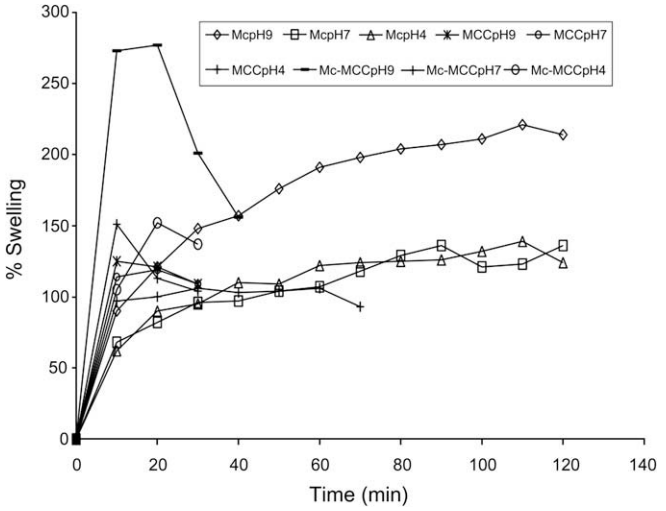

Fig. 5. Swelling characteristics of Mc, MCC, and Mc-MCC in different pH buffer solutions.

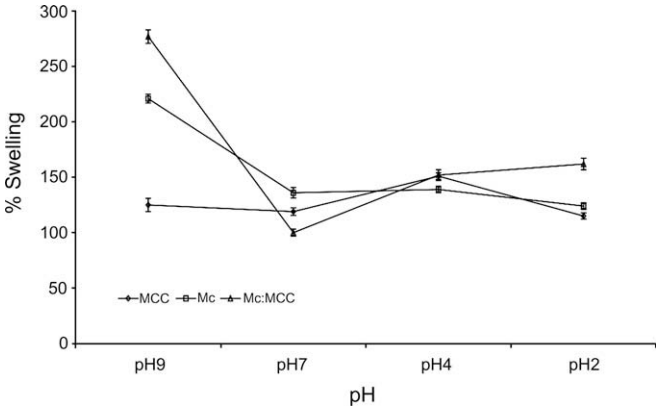

Fig. 6. Effect of pH on the swelling of Mc, MCC, and Mc-MCC. —◆—, MCC; —□—, Mc; —△—, Mc-MCC.

The comparatively low equilibrium swelling obtained for MCC could be due to its largely crystalline nature which would result in increased hydrophobicity. Its rigid β-(1-4) glucosidic bonds, reinforced by the strong intra-molecular hydrogen bonds, are responsible for the minimal interaction between the polar groups of the cellulose glycan chains with water molecules [37]. The high swelling capacity of Mc is due to oligosaccharide side chains attached to its protein backbone [10]. Its equilibrium swelling was less than that of Mc-MCC. The Mc and MCC hybrid is probably a graft polymer of peptide and oligosaccharide chains with numerous ionisable carboxylic acid and hydroxyl groups; these are probably responsible for the pH responsiveness of Mc-MCC. The degree of ionization in a particular pH medium is responsible for the extent of chain repulsion that results in change in free volume required for water uptake.

Generally, the differences in the swelling characteristics of Mc-MCC compared with those of Mc and MCC in the different buffer solutions are an indication of the formation of a new polymer.

3.6. Fourier Transform Infrared (FT-IR) spectroscopy

The IR spectrum of a given compound is always unique and characteristic. Thus, IR spectroscopy is a quick and relatively cheap technique for identifying compounds [38]. The IR spectra of Mc, MCC and Mc-MCC are presented in Fig. 7. IR spectra of Mc, MCC and Mc-MCC were carried out as finger prints to identify Mc-MCC relative to MCC and Mc. The IR spectrum of Mc-MCC was different from those of Mc and MCC (Fig. 7). Spectrum of MCC is characterized by five strong peaks, which were identified at 3365.51, 2904.05, 1373.44, 1166.47 and 1058.84 cm^{-1}. Mc and Mc-MCC showed only one strong peak each at 1654.67 and 1060.97 cm^{-1}, respectively. The peak at 1654.67 cm^{-1} obtained for Mc corresponds to absorption by a carbonyl group attached to an amide group, while the peak at 1060.97 cm^{-1} corresponds to absorption in the finger print region. Apart from these prominent peaks identified by the equipment, there were several other peaks present in the spectrum. The non-identification of these peaks could be due to either intra- or intermolecular shielding of the functional groups represented by these peaks, which prevented the detection of their vibrations. The characteristic differences between the spectrum of Mc-MCC and those of Mc and MCC further indicate that a new polymer type was formed.

3.7. DSC thermal analysis

The thermal characteristics of a hybrid polymer are based on the differential separation and identification of various transitions in relation to its components materials. Fig. 8 shows the thermographs of the Mc-MCC in relation to Mc and MCC. Two prominent transition peaks characterize the thermographs of MCC, Mc and

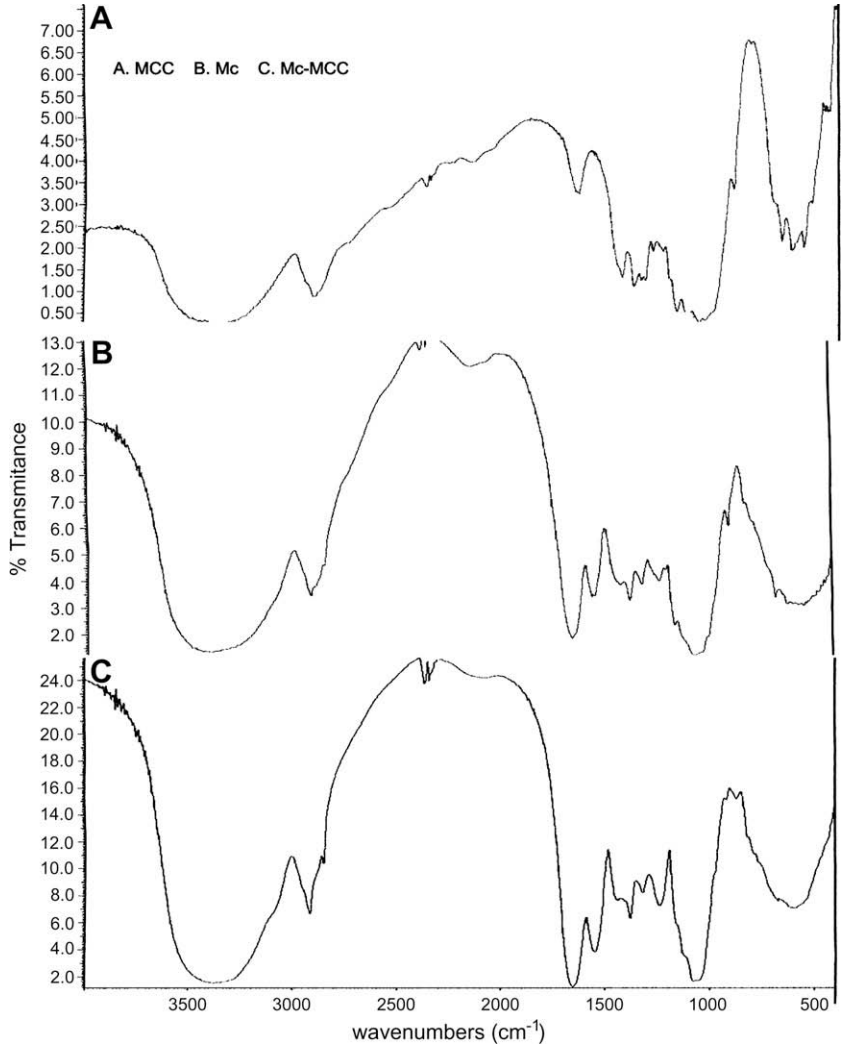

Fig. 7. FTIR spectra for MCC, Mc, and Mc-MCC. (A) MCC; (B) Mc; (C) Mc-MCC.

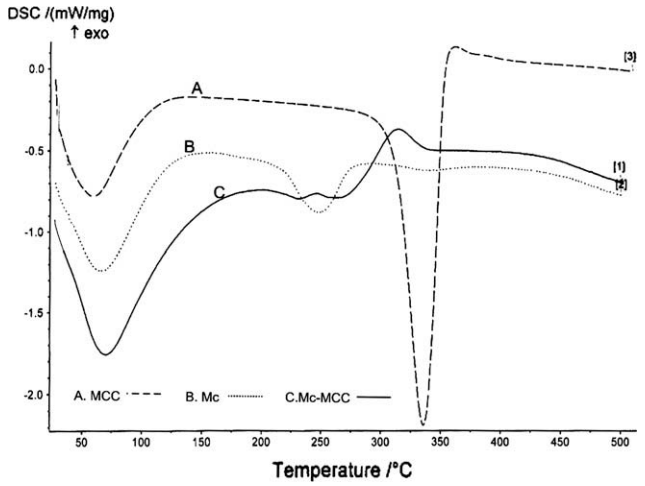

Fig. 8. DSC thermogram for MCC, Mc, and Mc-MCC. (A) MCC, ----; (B) Mc, ·····; (C) Mc-MCC, ——.

Table 2
Thermal properties of MCC, Mc and Mc-MCC.

Parameters	MCC	Mc	MCC-Mc
T_g (°C)	30.4	35.6	35.9
ΔH J/(gK)	4.073	5.291	8.860
T_m (°C) onset	315.6		210.9
End	346.2	269.6	245.2
T_{cr} onset			274.4
End			334.9

T_g, glass transition temperature; T_m, melting temperature; T_{cr}, crystallisation temperature.

Mc-MCC. The thermographs of MCC are characterized by an initial endothermic peak at 30.4 °C, this peak corresponds to the glass transition temperature, while the second transition peak is an endothermic peak that corresponds to the melting of the crystalline domain which occurred at 319 °C. The thermograph of Mc also has two transition peaks at 35.6 and 248 °C corresponding to the glass transition and crystalline domain melting transition, respectively. The thermograph of Mc-MCC is characterized by three distinct peaks: An initial second-order transition endothermic peak at 50.6 °C, which corresponds to the glass transition, this is followed by an apparently weak first-order transition endothermic peak at 230.1 °C representing a melting transition, and finally a prominent exothermic transition peak at 245.2 °C corresponding to cold crystallization.

Evaluation of the thermographs of Mc, MCC and Mc-MCC indicates that a new polymer type resulted from the pH- and temperature-controlled precipitation of the colloidal mixtures of Mc and MCC. The glass transition temperature of Mc-MCC (Table 2) was higher than that of any of the component polymers. This is an indication of the formation of a new polymer type by crosslinking [39]. The presence of a weak melting peak at 230 °C in the Mc-MCC thermogram may represent the melting of residual mucin, which may indicate the existence of a possible optimum molecular ratio necessary for interaction between Mc and MCC. The thermogram indicates that Mc-MCC is largely in the pseudo-amorphous form, which on heating reverted to its crystalline form and before finally decomposing.

4. Conclusion

The results obtained from the various physicochemical and functional characterizations show that a new polymer type was formed by the temperature- and pH-controlled hybridization of Mc and MCC. The new polymer showed synergistic physicochemical and functional properties between Mc and MCC in terms of particle morphology, flow and compaction properties, as well as mucoadhesiveness. Its inherent similarity to Mc in terms of mucoadhesiveness indicates its potential gastric mucus membrane-protecting ability. Generally, the mucoadhesive and compaction characteristics together with its moisture sorption and swelling properties make the Mc-MCC hybrid a potential excipient for the safe delivery of especially moisture-sensitive active pharmaceutical ingredients (APIs) with gastric irritation properties.

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