International Journal of Pharmaceutics 388 (2010) 159–167

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

Pharmaceutical Nanotechnology

Novel multifunctional pharmaceutical excipients derived from microcrystalline cellulose–starch microparticulate composites prepared by compatibilized reactive polymer blending

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ARTICLE INFO

Article history:
Received 15 October 2009
Received in revised form
22 December 2009
Accepted 24 December 2009
Available online 8 January 2010

Keywords:
Microcrystalline cellulose
Maize starch
Microcrystalline cellulose–maize starch composites
Direct compression

ABSTRACT

The choice of excipients remains a critical factor in pharmaceutical formulations. Microcrystalline cellulose–maize starch composites (MCC–Mst) have been prepared by mixing colloidal dispersions of microcrystalline cellulose (MCC) with 10% (w/w) of chemically gelatinized maize starch (Mst) at controlled temperature conditions for use as multifunctional excipients with direct compression and enhanced disintegration abilities. The novel excipient was evaluated for its direct compression and enhanced disintegrant properties and the result compared with the properties of the individual components. Some of its physicochemical and thermal properties were also determined together with effects of freeze–thaw cycles of processing on the functional and physicochemical properties. The scanning electron micrograph (SEM) shows that the particles of the MCC–Mst were irregular in shape and multiparticulate with a marked degree of asperity. The indirect assessment of the powder flow properties as determined by Carr's compressibility index and angle of repose showed that the MCC–Mst possesses better flow compared with MCC and Mst. MCC–Mst is moderately hygroscopic and shows a Type III moisture sorption isotherm. The FT-IR spectra and DSC thermograms of the composite were different from those of MCC and Mst. The hardness of aspirin tablets was enhanced by incorporating MCC–Mst and MCC, but was reduced by Mst. While the tablets prepared with MCC–Mst and Mst disintegrated within 7 min, aspirin compacts devoid of any excipient and those prepared with MCC did not disintegrate even after 2 h. Acetaminophen compacts prepared with MCC and MCC–Mst showed similar compact hardness characteristics and loading properties. The loading capacity of the different samples of the composite decreased with increase in the freeze–thaw cycles. The loading capacity of the different materials as assessed by their compact hardness efficiency can be represented as follows (MCC > T0 > T1 > T4 > T3 > T2 > Mst). Generally, the different samples of MCC–Mst are characterized by physicochemical and functional properties that are similar at different degrees to MCC and Mst.

1. Introduction

Numerous medical conditions abound which requires the drug to be swallowed whole and the medicament released rapidly in the gastrointestinal tract (GIT) (Newman et al., 2008). In the development of such important delivery system, one shortcut is the use of high-performing excipients (Deorkar and Baker, 2008). The choice of excipients becomes critical in terms of its functionality as regards direct compression and rapid disintegration abilities (Zhao and Augsburger, 2005; Chang and Chang, 2007). Only few polymers posses multiple functionalities especially in terms of good flow, direct compression and enhanced disintegration abilities. Thus, novel polymer biomaterials with effective multifunctional properties are continually being sought for drug delivery purposes (York, 1992; Watering et al., 2005). The importance of good powder flow and simplicity of direct compression technology as well as the benefits of efficient disintegrants in the formulation of rapid release tablets cannot be over emphasized. Many pharmaceutical scientists have focused their attention on the production of multifunctional excipients with enhanced performance to meet the needs of formulation experts in terms of costs of production, enhanced excipient functionality and quality of tablets (Chang and Chang, 2007).

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doi:10.1016/j.ijpharm.2009.12.056

The task of developing quality rapid release tablets for oral delivery of active pharmaceutical ingredient (API) to the GIT is easily accomplished by the availability and use of suitable excipients especially diluents and disintegrants. Excipients with multiple functional properties confer many advantages such as reduction of cost of production and the number of steps used during production (Nachaegari and Bansal, 2004; Sherwood, 2003). Materials with high loading capacity/dilution potential and enhanced disintegration ability will be superior excipients as they will meet such important formulation requirements as direct compression and rapid disintegration of tablets. The high disintegration efficiency of such novel excipients will enhance the rapid release of the APIs from the tablets (Massimo et al., 2002; Caramella et al., 1986).

Microcrystalline cellulose is a purified, partially depolymerized cellulose prepared by treating alpha cellulose which is obtained as a pulp from fibrous plant material with mineral acids. Because of its excellent compaction property it is used as an efficient dry binder in direct compression technology. It is, however, not a good tablet disintegrant (Gohel et al., 2007). Dry starch is one of the most commonly used tablets disintegrant. Its important drawbacks, which include poor flow and compaction as well as production of friable tablets has limited its use. The demand for robust tablets with high mechanical strength and faster dissolution properties has resulted in the search for more efficient excipients especially those with multifunctional properties (Bolhuis et al., 1996; Labella and McDougal, 2006). Rapid tablet disintegration is necessary for quick release and bioavailability of the APIs and direct compression apart from its benefit in the production of moisture sensitive APIs also offers significant savings in energy, equipment and materials handling costs.

The widely used superdisintegrants are sodium starch glycolate, crospovidone, and croscarmellose sodium (Gohel et al., 2007). These do not have the direct compression ability of MCC. Thus, they are combined when both functionalities are required (Massimo et al., 2002; Caramella et al., 1986).

Many novel excipients have successfully been produced by modification of naturally occurring ones (Gohel and Jogani, 2005; Jacob et al., 2007). Formulations of polymer composites are popular methods by which new polymers and pharmaceutical excipients are produced for purpose of drug delivery (Wu et al., 2004; Builders et al., 2009). An important attribute of such hybrid polymers is that the new species either combine the qualities of the components in terms of functional and physicochemical properties or new functional properties different from the primary materials result. This may result in superior functional and physicochemical properties when compared with the primary materials.

The objective of this work is to prepare and evaluate MCC–maize starch composite (MCC–Mst), generated by mixing colloidal dispersions of microcrystalline cellulose (MCC) and chemically gelatinized maize starch (Mst) at controlled temperature conditions. This process of polymer composite formation is termed compatibilized reactive polymer blending. The direct compression efficiency of the novel polymer was also evaluated together with the disintegrant property.

2. Materials and methods

2.1. Materials

The materials used were microcrystalline cellulose (Fluka Biochemica, Ireland), maize starch, sodium chloride, magnesium chloride and acetaminophen (Sigma–Aldrich Chemie, Germany); potassium dihydrogen phosphate (May & Baker, Dagenham, England); sodium hydroxide (NaOH), potassium thiocyanate, potassium chloride and calcium chloride (BDH Chemicals, UK). Acetyl salicylic acid was kindly supplied by Juhel Pharmaceuticals Nig. Limited (Enugu, Nigeria).

2.2. Preparation of microparticulate microcrystalline cellulose–starch complex

MCC was solubilised by using a modified method of Kuo and Hong (2005). A 10% (w/v) dispersion of MCC was prepared by using a 10% (w/v) sodium hydroxide solution. A 10% (w/v) dispersion of maize starch in distilled water was prepared. The pH of the dispersion of MCC in deionised water was determined and used as the reference point for the end pH of the final product. The starch dispersion was then added to the solubilised MCC such that the Mst constitutes 10% of the mix (T0). The mixture was 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 1 M HCl. Another mix was prepared, such that the MCC dispersion was stored at −30 °C for 24 h before the starch dispersion was incorporated. This was thawed at 30 °C (T1). Three other samples (T2, T3 and T4) were also prepared and the freezing and thawing carried out for two, three and four cycles, respectively. In each sample the dispersion mixture was gradually introduced into a 2 L beaker containing three parts by volume of acetone maintained at −30 °C with continuous stirring at 400 rpm. The coarcervate was recovered by filtration, using a standard sieve having a mesh size of 150 μm. More portions of acetone were used to rinse the generated microparticles to remove residual water. The harvested hybrid polymer microparticles were then spray dried at (40 °C) with an automatic air blower machine (Lion Brand, Germany) fitted with a closed calico bag. The particles were screened through a 250 μm mesh sieve (US Standard sieve, USA) using a sieve shaker (Retsch, D 42781 Haan, Germany) and then stored in a desiccator for 48 h before storing in an airtight container.

2.3. Scanning electron microscopy

The scanning electron micrographs (SEMs) of MCC, Mst and the various samples of the novel excipient were obtained. The samples were prepared by gold-plating, while imaging was carried out on a scanning electron microscope (FEI Quanta 400, FEI Company, Oregun, USA).

2.4. Particle properties

The bulk and tapped densities were measured in a 50 ml graduated measuring cylinder as a measure of densification of the powders. The measuring cylinder and its content were 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 porosity and compressibility were determined using the values obtained for the bulk and tapped densities using Eqs. (1) and (2), respectively (Well, 2003):

$$\%\,\text{Porosity} = \left(\frac{1 - \text{true volume}}{\text{bulk volume}}\right) \times 100 \quad (1)$$

$$\%\,\text{Compressibility} = \frac{\text{tapped density} - \text{bulk density}}{\text{tapped density}} \times 100 \quad (2)$$

The packing properties of the powders were determined by the tapping method described by Kawakita's equation (Eq. (3)) (Iida et al., 2001; Paronen, 2006).

$$\frac{1}{\varepsilon_n - \varepsilon_f} = Kn + \frac{1}{\varepsilon_o - \varepsilon_f} \quad (3)$$

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

2.5. Equilibrium moisture sorption (EMS)

Quantities of MCC, Mst and MCC–Mst composites were placed in Petri dishes and stored in an activated desiccating chamber at 25 °C for 1 week to remove residual moisture from the materials. The moisture sorption isotherms were determined by the gravimetric method (Beristain et al., 2006). In each case, a 1 g quantity of the dry sample 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 thiocynate (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 Eq. (4):

$$\text{EMS} = \frac{M_e}{M_d} \times 100\% \quad (4)$$

where M_e is the amount of moisture sorped at equilibrium and M_d is the dry weight of the material (Lin and Chen, 2005). The moisture sorption profile represented by the plot of percentage weight gain vs. relative humidity was then evaluated.

2.6. Differential scanning calorimetry (DSC)

DSC studies were carried out using a DSC machine (DSC 204 F1-Phoenix NETZSCH, Germany) equipped with a thermal analysis system. Indium (156.8 °C) was used as the internal standard. Samples of MCC, Mst and the various samples of the MCC–Mst samples (approximately 1 mg each) were individually 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 25 to 500 °C at a rate of 10 °C min^{-1}. The relevant thermodynamic parameters were evaluated with Proteus analysis software (Builders et al., 2009).

2.7. Fourier transform infrared spectroscopy (FT-IR)

FT-IR spectra were acquired on a NICOLET IR 100 (Themo 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 the powder samples per 400 mg of KBr). Spectra scan for MCC, Mst and the various MCC–Mst samples were determined.

2.8. Loading capacity

Compacts containing different ratios of binary mixtures of acetaminophen and each of the powders of the novel excipients (MCC–Mst composites), MCC and Mst were prepared. The binary mixtures were such that each of the 400 mg tablets contained acetaminophen (Apn) and the excipients in ratios (400:0, 380:20, 320:80, 200:200, 80:320, 20:380, 0:400). The tablets were prepared by compressing the powder mixtures at a compression pressure of 22.5 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. The compacts were stored in an airtight container for 24 h before evaluation. The tablets were tested for hardness (Erweka ZT2, Germany) and friability (Erweka TA, Germany). The punch and die were lubricated with a 10% (w/v) dispersion of magnesium stearate in ethanol.

2.9. Disintegration efficiency

Compacts containing 300 mg of aspirin crystals and 10% (w/w) of either MCC, Mst or the different samples of the novel excipients (MCC–Mst) were prepared by mixing the aspirin crystals and the excipient in a tumbler mixer (JEL, KARL KOLB, Germany) and compressed with a compression load of 20 kg F using a single press compression machine (Shanghai Tiaxiang & Chenta, Pharmaceutical Machinery Co. Ltd.) fitted with an 11.5 mm flat faced punch and die (Bi et al., 1999). The aspirin tablets were stored in a desiccator for 24 h before evaluation of the hardness with a hardness tester (Erweka HT, Germany) and friability with a friabilator (Erweka TAR 20, Germany). The disintegration time for the various aspirin compacts in 0.1 N HCl were determined using a disintegration apparatus (Erweka ZT4, Germany).

2.10. Data and statistical analysis

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

3. Results and discussion

Preparation of polymer composites is one of the successful methods used for the preparation of novel polymers with improved functional properties (Builders et al., 2009; Wu et al., 2004). Evaluation of the physicochemical and functional properties of the composite showed the formation of a new polymer type. The resultant hybrid polymer exhibited physicochemical and functional properties different from the individual components.

3.1. Preparation of MCC–maize starch composite

The dispersion of MCC and Mst in the strong NaOH solution resulted in the formation of colloidal dispersion of MCC and Mst. The formation of the colloidal dispersions in the strong alkali was effected by the dislocation or breaking of the numerous rigid glucosidic bonds in the glucopyronysyl linkages of the partially depolymerized cellulose and the amylose and amylopectin chains of the MCC and Mst respectively (Kuo and Hong, 2005; Builders et al., 2009). During the solubilisation process, the glucopyronysyl chain network of MCC was dislocated due to the breaking of numerous β-(1–4) bonds of the polymer. This process resulted in the destabilization of the hydrophobic and hydrogen bonds in both the MCC and Mst. The exposure of the numerous –OH and –COOH groups in the strong alkali resulted in the interaction of the different moieties due to protonation and deprotonation of various –OH and –COOH groups. A solid composite was regenerated by a pH induced coacervation process which occurred when the pH of the colloidal polymer composite shifted from alkaline to acidic pH. The stabilization of the coarcervate and removal of water molecules from the microparticles was achieved by washing with chilled (−20 °C) acetone. Dispersion of MCC and dry Mst in 10% NaOH solution resulted in the solubilisation of the polymers. The regenerated composites of the two homo-polysaccharide polymers indicated a new polymer moiety with physicochemical properties different from those of Mst and MCC probably due to the reorientation of their oligosaccharide chains and functional groups.

3.2. Polymer morphology

Scanning electron micrographs of Mst, MCC and the generated composite polymer microparticles are shown in Fig. 1. The mor-

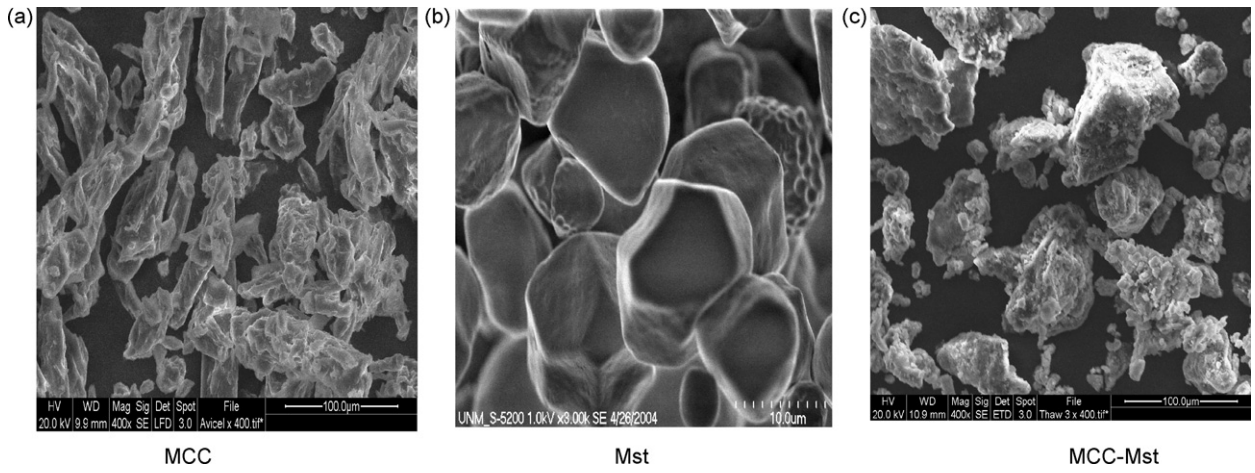

Fig. 1. SEM micrograph of (a) MCC, (b) Mst and (c) MCC–Mst. MCC = microcrystalline cellulose; Mst = maize starch; MCC–Mst = microcrystalline cellulose and maize starch complex.

phology as characterized by the particle shape and size can be used as an important feature for the identification and distinction of different polymers (Builders et al., 2009). The characteristics of the morphology may also give an indication of the processing parameters. Mst is characterized by granules, which are round to oval with no asperity while MCC occurs as long thin rectangular strands with rough porous surfaces (Builders et al., 2009). The composite generated from mixture of the colloidal dispersions of Mst and MCC has a peculiar morphology different from those of either the maize starch granules or the MCC particles. The MCC–Mst particles are irregular in shape and multiparticulate with a marked degree of asperity.

The differences in the morphology of the hybrid and the primary component polymers indicate the formation of a new polymer type. The chemically induced gelation of maize starch and the dissolution of the MCC in the strong alkali solution due to the breaking of numerous glucosidic bonds and the reorientation of the glucopyranosyl chain network are responsible for the formation of a new moiety.

3.3. Particle physical properties

The particle properties of any material for use as an excipient especially in direct compression formulations are of critical importance. This is because important processes such as mixing, bulk particle movement and compaction are procedures that are critically dependent on the powder particle properties (Gustafsson et al., 1999). There are many industrial processes that require powders to be moved from one location to another, thus the need for the material to have good flow properties. The efficiency of the flowability of a direct compression excipient in automated technology employing rotary compression system is essential for production of tablets with uniform weight (Bolhuis et al., 1996). The flow characteristics of MCC, Mst and the various samples of their modified composite were indirectly assessed by determining their angle of repose and Carr's compressibility indices. The flowability of the particles as assessed by the angle of repose is based on the cohesion between the particles. As a general guide an angle of repose less than 25° is considered to have very-good flow whereas 50° is poor (Well, 2003). Using the 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 angle of repose and Carr's compressibility indices are presented in Table 1. The flow qualities of the three polymer types obtained by angle of repose were similar to that obtained by evaluating the Carr's compressibility index. The flowability of the various polymer samples as assessed by the angle of repose and Carr's compressibility index show that this parameter increased with the number of freeze–thaw cycles for the composites and were generally higher than that of either MCC or dry Mst powder.

Evaluation of angle of repose and Carr's compressibility index of MCC, Mst in comparison with the different samples of the composites shows that all the regenerated samples had better flowability than both dry Mst and MCC (Table 1). However, by comparing with acceptable standards, dry Mst has a comparatively poor flow when compared with MCC and the composites (Marshall, 1987).

One of the essential attributes of MCC is its excellent compactibility at low pressure (Tebyn et al., 1998). The tapping method is an indirect but simple technique that could be used to assess the packing characteristics of powders and granules by using the Kawakita equation (Eq. (3)) (Iida et al., 2001). The packing characteristics of MCC–Mst in comparison with MCC and Mst were assessed using the Kawakita equation. The plot of $1/(\varepsilon_n - \varepsilon_f)$ vs. n is presented in Fig. 2. This showed a linear relationship between $1/(\varepsilon_n - \varepsilon_f)$ and n. The K value for MCC, Mst and the various samples of MCC–Mst composite are presented in Table 1. A high K value corresponds to a high compactibility (Iida et al., 2001). Though, the K values for the various MCC–Mst samples produced by the variation of the number freeze–thaw cycles were similarly lower than that of MCC they were however higher than that of Mst. The differences observed in the K values for these polymers relates to their compaction ability as determined by their respective particle densities, size and shape (Marshall, 1987).

Table 1
Some physicochemical properties of Mst, MCC and Mst–MCC.

Parameter	MCC	Mst	T0	T1	T2	T3	T4
Bulk density	0.30 ± 0.01	0.51 ± 0.00	0.41 ± 0.02	0.38 ± 0.03	0.40 ± 0.05	0.36 ± 0.00	0.41 ± 0.05
Tapped density	0.42 ± 0.01	0.62 ± 0.02	0.54 ± 0.01	0.46 ± 0.02	0.44 ± 0.07	0.43 ± 0.06	0.54 ± 0.07
Carr's index	21.03 ± 0.45	8.08 ± 0.50	25.61 ± 0.02	19.78 ± 0.05	20.79 ± 0.04	19.79 ± 0.95	5.54 ± 0.65
Angle of repose	23.8 ± 0.65	20.46 ± 0.87	18.96 ± 0.98	14.63 ± 0.65	15.38 ± 0.95	14.65 ± 0.90	11.10 ± 0.97
K	0.0098	0.0048	0.0055	0.0076	0.0082	0.0087	0.0068

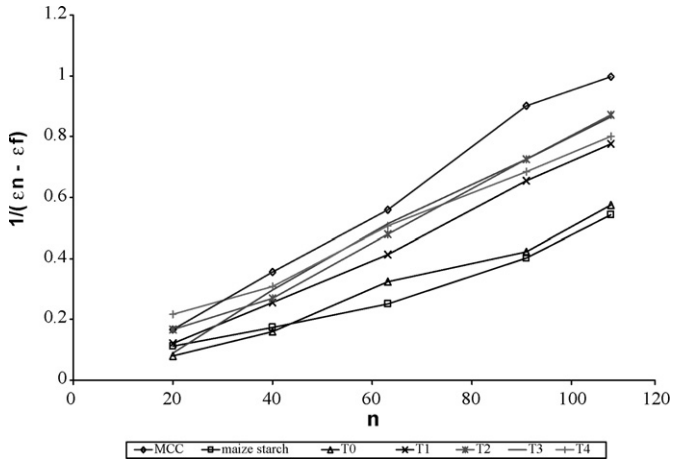

Fig. 2. Relationship between $1/(\varepsilon_n - \varepsilon_f)$ and n in Kawakita equation for MCC, maize starch and their composites.

3.4. Equilibrium moisture sorption

The interaction of moisture with pharmaceutical solids is highly crucial to an understanding of water-based processes especially as it relates to their physicochemical and functional properties (Hancock and Zografi, 1997; Mangel, 2000). Moisture in polymeric excipients may induce unpredicted phase transitions. In addition, the moisture characteristic of a polymer can be used as a simple method for assessing the comparative amorphous or crystalline nature of the polymers (Mackin et al., 2002).

The isothermal moisture sorption of Mst, MCC and the different samples of the MCC–Mst composites are presented in Fig. 3. The moisture sorption profiles of MCC and MCC–Mst composites correspond with Type III isotherm according to the IUPAC classification (Sing et al., 1985). Type III moisture sorption isotherm is characterized by a low uptake at low RH and a high uptake at high vapour concentration (Sing et al., 1985; Rouquerol et al., 1999). The Type III isotherm appears when all the sorption occurs according to a multilayer mechanism throughout the range of RH. This mode of sorption is typical of polymers with high crystalline domain (Sing et al., 1985).

The moisture sorption profile of Mst showed a sigmoidal shape that corresponds to Type II isotherms. This shows that moisture sorption by Mst is associated with the monolayer–multilayer sorption on macroporous surface of the powder. The resultant curve is caused by the combination of the colligative effects, capillary effects and surface–water interactions (Bell and Labuza, 2000).

Although, the moisture sorption isotherms of MCC and MCC–Mst composites were similar, the extent of moisture uptake by the composites was different and comparatively similar to that of maize starch (Fig. 1). Evaluation of the moisture sorption profiles of the polymers based on the classification of Callahan et al. (1982) shows that MCC is slightly hygroscopic, while Mst and MCC–Mst composites are moderately hygroscopic. The implication of this finding is that MCC–Mst composites may not be good as direct compression excipient for drugs that are highly moisture labile. The adsorption of moisture unto polymer materials occurs by the formation of hydrogen bonds with the hydrophilic sites on the surface of the solid (Beristain et al., 2006). Water molecules first adsorb onto the surfaces of dry material to form a monomolecular layer (adsorption), which is subjected to both surface binding and diffusional forces. The diffusional forces eventually exceed the binding forces as more water molecules adhere to the surfaces and moisture is transferred into the material by absorption (York, 1981) and hydrophilic drag.

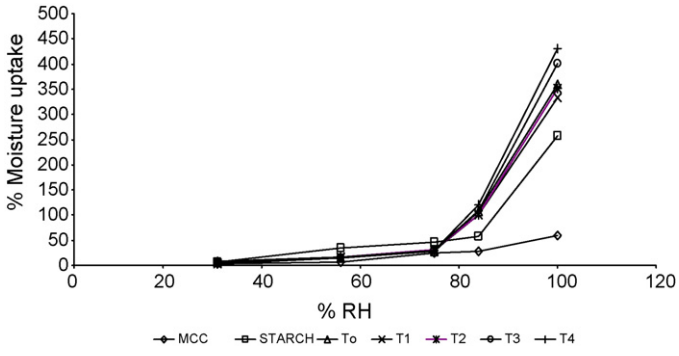

Fig. 3. Moisture sorption profile for avicel and starch and avicel–starch composite.

Moisture sorption characteristic has been reported to be one of the most sensitive techniques for predicting some physicochemical and functional properties of polymers (Bravo-Osuna et al., 2004; Lin and Chen, 2005). The amount of water adsorbed is dependent on the affinity between the surface and water molecules, temperature and the relative humidity as well as the surface area exposed (Airaksinen et al., 2005). The difference in the moisture sorption characteristics between the polymers could be due to the differences in the polar groups available for inter-molecular interaction with water molecules. The glycan chain network of MCC shows numerous OH groups, which are however, not available for hydrophilic interaction with water molecules due to its strong intra- and inter-chain hydrogen bonds that confer it a high degree of hydrophobicity. The moisture sorption by Mst has been attributed to the interaction between the hydroxyl groups of the hexose moiety and water molecules. Apart from water molecules forming hydrogen bonds with both amylose and amylopectin which are the primary components of starch, the amylopectin structures are known to physically trap water molecules. The comparatively high moisture uptake of MCC–Mst composites could be due to the formation a new polymer type. During the formation of the composite, the chain network of MCC and the starch polymers were dislocated by the breaking of numerous β-(1–4) bonds of MCC and α-(1-4) and α-(1-6) of amylose and amylopectin of starch. This process resulted in the destabilization of the bonds hence, the exposure of many OH groups, making them available for interaction with water molecules. Thus, the hybridization caused reorientation of the glucosidic bonds, which resulted in modified oligosaccharide chains with the chain network containing numerous free OH groups that formed series of hydrophilic hydrogen bonds with the water molecules.

Generally, there was a gradual increase in moisture sorption between 31 and 84% RH by the three polymers followed by a sharp increase reaching a maximum at 100%RH. This may be due to the gradual saturation of the monomolecular layer of the polymer powder beds at these RH. The sharp increase in moisture uptake occurred between 84 and 100% RH. This corresponds to the saturation of monomolecular layer and subsequent diffusion of excess moisture (absorption) into bulk powder bed (York, 1981).

For similar polymeric materials, the moisture uptake profile for the amorphous form exhibits a higher shift when compared to the more ordered crystalline form (Mackin et al., 2002; Burnett et al., 2006). The amount of moisture taken up by a hydrophilic polymer depends on its amorphous or crystalline composition. Generally the various samples of the MCC–Mst composite prepared at different freeze–thaw cycles show that the moisture uptake increased with increasing freeze–thaw cycles (Fig. 3). Thus, the amorphicity of the hybrid increased with increasing freeze–thaw cycles of the colloidal dispersions of the Mst and MCC mixtures.

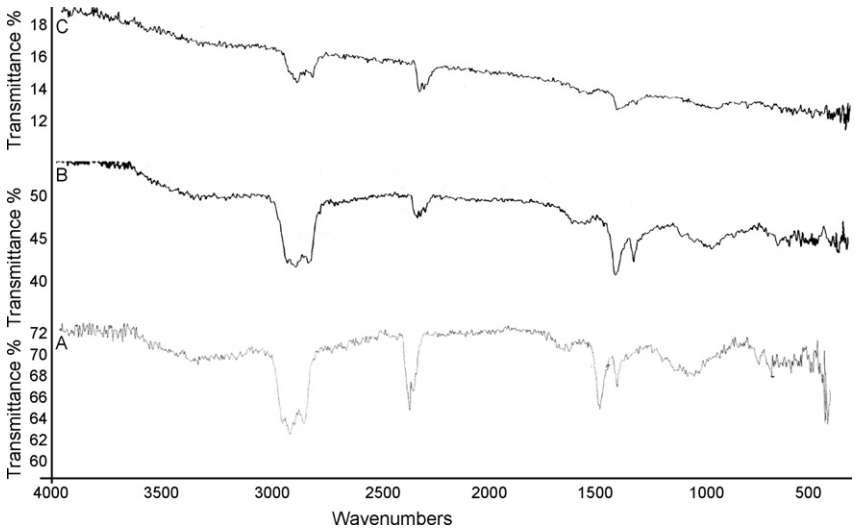

Fig. 4. FT-IR spectra for MCC, starch, and starch–MCC. (a) MCC; (b) starch; (c) starch–MCC.

3.5. Fourier transform infrared spectroscopy (FT-IR)

FT-IR spectroscopy is a quick and simple technique for identifying compounds (Sherman, 1997). The IR spectrum of a given compound is unique and characteristic. This is because IR spectrum distinguishes between the different kinds of bonds in a molecule.

The IR spectra of MCC, Mst and MCC–Mst composites are presented in Fig. 4. The IR spectra of MCC, Mst and MCC–Mst were carried out as finger prints to identify MCC–Mst relative to MCC and maize starch. The IR spectra of the composite polymers were different from those of MCC and Mst (Fig. 4). The spectra of MCC and starch are characterized by five strong peaks, which were identified at 2926.89, 2357.85, 1457.85, 1376.45 and 1031.65 cm^{-1}, and 2935.71, 2342.98, 1469.39, 1376.66 and 1022.82 cm^{-1}, respectively, while the MCC–Mst composites showed only three strong peaks which were identified at 1457.39, 1016.76 and 722.64 cm^{-1}. The peaks at 1031.65, 1022.82 and 1016.76 cm^{-1} for MCC, starch and the MCC–Mst composites, respectively, reflect comparable vibrational frequencies and corresponds to absorption in the finger print region. The presence of similar absorption frequencies within fingerprint region of absorption reflects the similarities of the polymers; the three are primary monomers of glucose. The presence of another prominent peak in the finger print region in the composite at 722.64 cm^{-1} could arise due to the exposure of a new functional group due to dislocation and reorientation of the monomers of the polymer chain. Apart from these prominent peaks identified, other peaks were present in the spectrum. The non-identification of these peaks could be due to either intra- or inter-molecular shielding of functional groups represented by these peaks that prevented the detection of their vibrations. The characteristic differences between the spectrum of MCC–Mst composites and those of Mst and MCC show consumption of some functional groups and indicate that a new polymer type was formed.

3.6. Differential scanning calorimetry (DSC)

Polymer DSC is a useful method of characterizing polymers based on their exothermic and endothermic thermal transitions (Calandrelli et al., 2000). The DSC thermograms of MCC, Mst and the regenerated MCC–Mst composite are shown in Fig. 5. The thermal characteristics of a hybrid polymer are based on the differential separation and identification of various transitions in relation to the component materials. The thermograms of the hybrid samples indicate that all the samples are characterized by glass transition (T_g) temperatures and cold crystallization peaks as compared to those of Mst and MCC, which are characterized by T_g and melting peaks.

Fig. 4a shows the relationship between the thermograms of Mst, MCC and the representative MCC–Mst composite. Table 2 shows the thermal properties of the polymers as evaluated from their thermograms. Two prominent transitions characterize the thermograms of MCC and Mst. An initial endothermic transition peak which corresponds to the T_g and an endothermic peak that corresponds to their melting. The thermogram of the composite also has two transitions: an initial endothermic peak which corresponds to the T_g and an exothermic transition, which corresponds to the polymer cold crystallization.

Evaluation of the thermograms of the Mst, MCC and the composite indicates that a new polymer type resulted from the temperature and pH-controlled precipitation of colloidal mixtures of Mst and MCC. The T_g of the composites generated at the different temperature-controlled conditions was generally higher than that of any of the component polymers (Table 2). This is an indication of the formation of a new polymer type with relatively lower chain flexibility due to the inclusion of pendant groups within the polymer network due to molecular reorientation thereby impeding chain mobility (Macrogalleria Directory, Copyright, 2005).

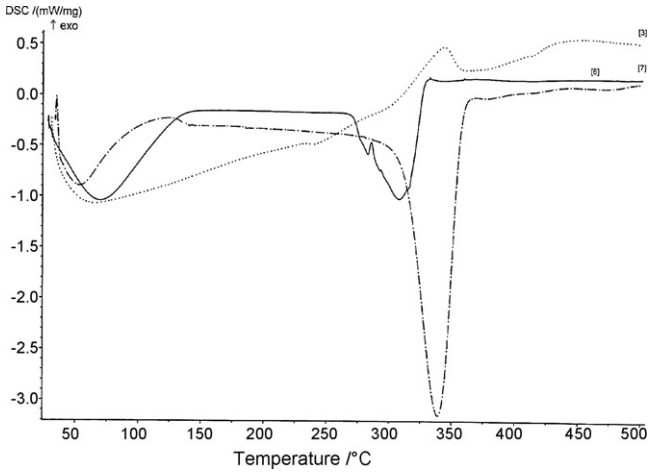

Fig. 5. DSC thermogram for MCC, maize starch and MCC–maize starch composite. (—) MCC, (. . .) maize starch and (·–) MCC-maize starch composite.

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

Parameters	MCC	Mst	T0	T1	T2	T3	T4
T_g (°C)	30.4	29.9	35.9	35.3	35.6	35.8	42.2
ΔH (J/(g K))	4.073	3.505	6.397	7.861	11.706	1.582	3.473
T_m (°C)							
Onset	315.6	297.3	–	–	–	–	–
End	346.2	325	–	–	–	–	–
T_{cr}							
Onset			332.9	332.7	310.5	274.4	307.6
End			356.9	355.6	353.3	348.8	334.9

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

The thermograms of the Mst and MCC are characterized by the presence of melting peaks which are absent in those of the composite. The melting peaks are characteristic and indicative of the polymer crystalline domain. The absence of a melting peak in the thermogram of the composite shows that the novel material has no obvious crystalline domain. The exothermic shift in the thermogram of the composite represents the crystallization of the pseudo-amorphous portion of the polymer, i.e. cold crystallization. Further increase in temperature resulted in the decomposition of the novel polymer.

Generally, all the MCC–Mst composites showed similar thermograms. Empirical values of their T_g were similar, while onset and end of their cold crystallization temperatures decreased with increase in the freeze–thaw cycles. Similarity in their T_g was possibly due to the similarity in their polymer chain network, while their cold crystallization characteristics could be due to the polymer chain arrangement.

3.7. Compact hardness

Tablet hardness relates to the ability of a tablet to withstand abrasion especially due to mechanical handling and transport. The hardness of the different tablets is shown in Fig. 6. All the tablets had different hardness values. Tablets prepared with MCC had the highest hardness value, while tablets prepared with Mst had the least hardness value. MCC is an efficient dry binder used for direct compression formulations. At concentration above 5% (w/w) starch reduces tablet compactibility especially when used in direct compression formulation. Aspirin forms hard tablets when compacted alone. This is due to its good compaction characteristics (Bolhuis et al., 1996). While Mst decreased the hardness of the aspirin compacts, MCC and the various MCC–Mst composites enhanced the hardness of the aspirin tablets (Fig. 6).

3.8. Disintegration property

The most common tablets are those intended to be swallowed whole and to disintegrate and release their medicaments rapidly in the gastrointestinal tract. The proper choice and efficiency of the disintegrant are of critical importance to the formulation of such tablets since disintegration is the first step and may be the limiting one in the release of the API from the tablet especially when the API has limited solubility (Carmella, 1991). The comparative disintegration time of aspirin tablets prepared with MCC, Mst and MCC–Mst composites as the disintegrants are presented in Fig. 7. Aspirin was chosen as the drug for this study because of its good compactibility and low solubility in water (Zhao and Augsburger, 2005). The compact of aspirin without excipient and that prepared with MCC showed similar disintegration characteristics as both did not disintegrate even after 2 h. However, tablets prepared with Mst and the MCC–Mst composite generated at different freeze–thaw cycles showed varied disintegration times. The tablets prepared with MCC–Mst generated at the fourth freeze–thaw cycle had the least disintegration time (6.28 ± 0.6 min) while that prepared with maize starch had a slightly higher disintegration time (8.00 ± 0.55 min). Generally, the disintegration time of the aspirin tablets prepared with the composites generated at the different freeze–thaw cycles decreased with increasing freeze–thaw cycle (Fig. 7). Apart from the aspirin tablets prepared with the sample generated at the fourth freeze–thaw cycle all the tablets prepared with MCC-Mst composites of other freeze–thaw cycles had longer disintegration times when compared with those prepared with Mst ($p < 0.05$). Different mechanisms have been proffered for the action of disintegrants. These include water wicking, deformation recovery, swelling among others. Mst is a classical disintegrant and its disintegrating ability has been partially supported by a combination of different mechanisms of disintegration, but most strongly by swelling, water wicking and deformation recovery theories.

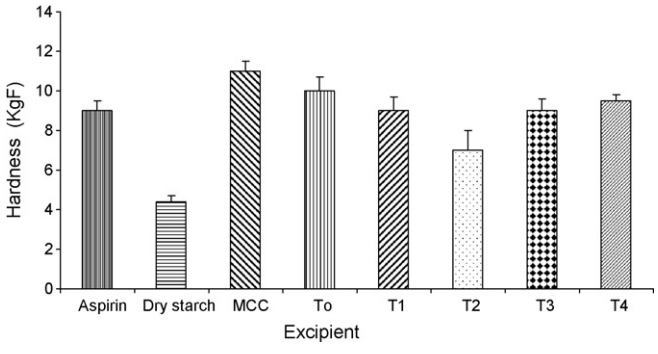

Fig. 6. Hardness of compacts prepared with ratios of aspirin, dry starch, MCC and MCC–starch composite.

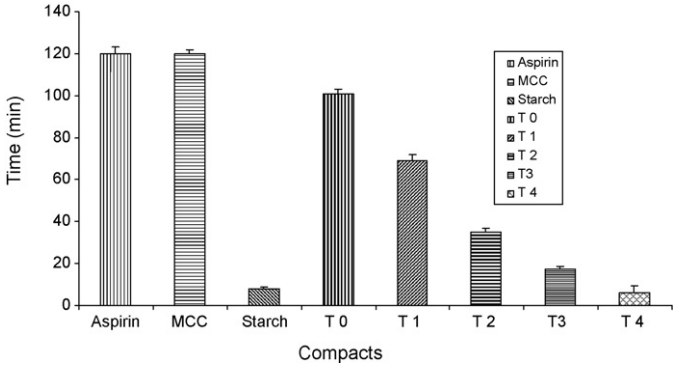

Fig. 7. Disintegration time for pure aspirin and aspirin–excipient compacts.

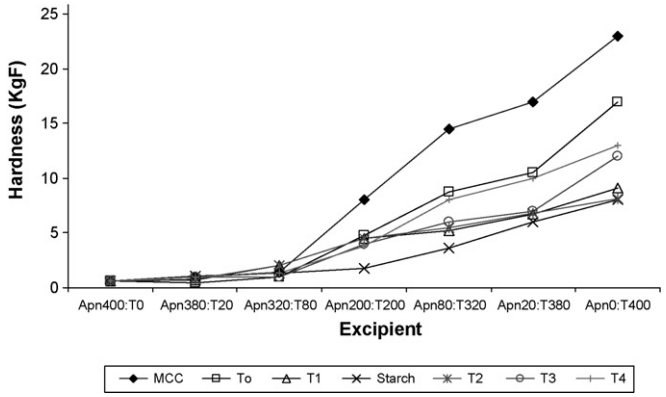

Fig. 8. Loading capacity of MCC, maize starch and MCC-modified starch composite.

Though MCC has been used as a disintegrant in some formulations, it is, however, not as efficient as Mst on gram per gram basis (Augsburger et al., 2002). Its disintegrant ability has been attributed mostly to water wicking and swelling. Combination of the disintegration and hardness properties of the aspirin tablets show that tablets formulated with MCC–Mst composites have superior quality for peroral tablets relative to those formulated with MCC and Mst. While aspirin tablets prepared with MCC showed poor disintegration property those prepared with Mst exhibited poor hardness.

3.9. Loading capacity

An important property of direct compression materials is their high carrying or loading capacity (Alderborn and Nyström, 1984). The loading capacities of the MCC–Mst in comparison with those of MCC and Mst were determined by assessing the hardness of compacts prepared with the different ratios of the excipient and acetaminophen mix. Acetaminophen (Apn) was used for assessing the loading capacity because of its poor compaction property resulting from its ability to undergo considerable elastic recovery after withdrawal of the compaction pressure (Alderborn and Nyström, 1984). Carrying capacity measures the amount of a drug substance in the tablet, usually a poorly compressible API that can be added to the excipient, while still maintaining satisfactory physical strength with respect to hardness and/or friability. Generally the more API that can be added to the excipients the higher its carrying capacity. The hardness of the compacts prepared with MCC, Mst and MCC–Mst increased as their ratio relative to that of Apn in the compacts increased. Compacts prepared with MCC and T0 showed similar compact hardness characteristic as their hardness increased significantly after the Apn and excipient (T) ratio of Apn320:T80 (Fig. 8). Compacts prepared with MCC had the highest hardness at the various ratio mixtures after Apn 320:T80. The loading capacity of the different samples of the composite decreased with increase in the freeze–thaw cycle.

The functional properties of directly compressible polymers are controlled not only by their intrinsic properties but also by their physical properties which are dependent on the material's processing technique. Excipient's bulk and tapped densities which is controlled primarily by processing techniques relates inversely with the powder's loading capacity (Bolhuis et al., 1996). The bulk and tapped densities of the MCC, Mst and MCC–Mst are presented in Table 1, and correlates well with their loading capacities as characterized by the hardness of their compacts (Fig. 8).

The loading capacity of the different materials as assessed by their compact hardness efficiency at equal excipient and acetomenophen mixture can be represented as follows (MCC > T0 > T1 > T2 > T3 > T4 > starch) (Fig. 8). The decrease in the hardness of the compacts prepared with the regenerated MCC–Mst composites could be due to the reprocessing of MCC. Reprocessing of MCC by procedures involving wetting are known to lower the hardness of its compacts (Bolhuis et al., 1996). The general reorientation of the polymer molecular structure due to the solubilisation and regeneration may also contribute to the changes in the hardness of the compacts as compared to those of the neat unprocessed MCC. The lower hardness of the acetomenophen compacts prepared with Mst is primarily due to the poor intrinsic compactibility of both acetomenophen and Mst (Bolhuis et al., 1996).

4. Conclusions

The results obtained from the FT-IR spectra, DSC thermograms and other physicochemical characterization, showed that a new polymer type was generated from the pH and temperature-controlled hybridization effected by mixing colloidal dispersions of Mst and MCC. The composite also showed functional properties that partly resemble the component polymers in terms of flow, direct compression ability and disintegration efficiency. The MCC–Mst composites were similar to MCC and Mst in terms of direct compression ability and disintegration efficiency, respectively. The physicochemical and functional properties of the composites varied with changes in the freeze–thaw cycles. The desirable functional properties; direct compression ability and enhanced disintegrant efficiency were exhibited to different degrees by the various samples of the composite prepared at the different conditions. However, T4 showed more efficient multifunctional excipient characteristics in terms of disintegration efficiency and loading capacity for the formulation of oral tablets for rapid release of APIs by direct compression process.

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