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Research Article

Synthesis of MCC–PEG Conjugate and Its Evaluation as a Superdisintegrant

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Abstract. PEGylated conjugate of microcrystalline cellulose (MCC) was synthesized by reacting MCC with polyethylene glycol (PEG) 200 in the presence of catalyst at elevated temperature. Conjugation between MCC and PEG was confirmed by FT-IR and ^{1}H NMR studies. The conjugate showed 61% PEG content increase in molecular weight determined by mass spectroscopy. PEGylation did not improve solubility of cellulose significantly. The physico-chemical properties of conjugate were compared against MCC. This conjugate was evaluated for water vapor uptake isotherms, maximum water saturation, water penetration rate, disintegration time, superdisintegration power, and dissolution study. After comparing its results with that of commercial superdisintegrants, it can be concluded that MCC–PEG conjugate can prove to be a good superdisintegrant.

KEY WORDS: disintegration; MCC–PEG conjugate; PEGylation; superdisintegrant.

INTRODUCTION

The importance of quick tablet disintegration and dissolution to ensure rapid availability of the active ingredient(s) for absorption is well recognized. A number of agents have been formerly used as tablet disintegrants, but only a few acceptable disintegrants are currently available to pharmaceutical purpose. Most compendial and industry standards for the disintegration time of a compressed tablet are considerably shorter than they were in the early 1970s. This shorter disintegration time requirement stimulated continuous efforts in the search for new more efficient disintegrating agents (1–3). The term superdisintegrant refers to substance which achieves disintegration substantially faster than the conventional disintegrants used. Wicking and swelling were found to be the primary mechanisms of action for tablet disintegrants, while other mechanisms, such as deformation recovery, particle repulsion theory, heat of wetting, and evolution of a gas *etc*., may play a role in particular cases of tablet disintegration (4). One of the most essential factors in disintegration processes of many formulations is the water uptake caused by capillary forces. The ability of particles to draw water into the porous network of a tablet is essential for efficient disintegration (5). As a general rule for most type of superdisintegrants, the higher the water uptake rate, the higher is the swelling capacity of the disintegrants (6).

Microcrystalline cellulose (MCC) is a purified partially depolymerized cellulose that occurs as a white, odorless, tasteless, crystalline powder composed of porous particles. It is commercially available in different particle sizes and moisture grades that have different properties and applications. MCC is used as disintegrant in most of the tablet dosage forms. Silicified MCC (SMCC) is manufactured by codrying a suspension of MCC particles and colloidal silicon dioxide such that the dried finished product contains 2% colloidal silicon dioxide (7). Tableting studies have suggested that SMCC has enhanced compactibility, even after wet granulation, and reduced disintegration time, compared to the regular grade of MCC.

The technique of attaching PEG to any drug, peptide, polymer, or any chemical moiety has been termed as "PEGylation." In recent studies, a hydrophobic polymer polylactide and rosin were copolymerized with PEG to increase the hydrophilic segments of the resulting moieties. (8,9). So considering the wide use of MCC as disintegrant and ability of PEG to improve the water uptake capacity, PEGylation of MCC was carried out.

MATERIAL AND METHODS

In the present study, PEGylated conjugate of MCC (hereafter mentioned as conjugate) was synthesized, and the physico-chemical properties of conjugate were compared against MCC. This conjugate was evaluated for water vapor uptake isotherms, maximum water saturation, water penetration rate, disintegration time, superdisintegration power, and dissolution study by comparing its results with the results of commercial superdisintegrants.

Materials

MCC PH 101 was kindly gifted by the Reliance Cellulose Products (Mumbai, India). Polyethylene glycol-200 (PEG) was procured from Merck Specialty Products. Cetirizine hydrochloride was a kind gift from Apex Drugs and Intermediates Ltd., Mumbai. All other materials were of pharmaceutical grade.

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Synthesis of Cellulose–PEG Conjugate

Step 1. Amount of PEG 200 (7.0 g) equal to half the weight of cellulose was placed in a glass reactor to which equivalent moles of concentrated hydrochloric acid were added along with a pinch of zinc chloride as a catalyst. The mixture was heated on a water bath at 70°C for 2 h (10).

Step 2. MCC (14.0 g) was separately placed into aqueous sodium hydroxide solution (30%) and allowed to swell to its maximum.

Step 3. Products of step 1 and step 2 were mixed slowly using magnetic stirrer assembly equipped with heater for 10 h with continuous heating at 70°C. The end product of step 3 was added to 100 ml of hot water (70°C) and was neutralized to pH 7 using glacial acetic acid. The neutralized product was filtered, and filtrate was collected in the separate vessel (for PEG content determination). Product was washed thoroughly with hot water (70°C) to remove any excess acid. Finally, product was dried in the oven at 80°C for 2 h.

Evaluation of Cellulose–PEG Conjugate

To confirm the incorporation of PEG molecules into MCC, same reaction as explained above was performed without addition of MCC to it. The final filtrate of both reactions was analyzed for a PEG content using periodate titration method (11). Charring temperature of a conjugate was determined by Herculus drop technique using thistle tube. Structural modifications were determined using FTIR (Jasco, 460, UK) and ^{1}H NMR (Bruker 400 MHz, UK, solvent was DMSO d6). Molecular weight was determined using mass spectrometer (API-2000 Applied Biosysytem, MDS Sciex, USA Solvent was Methanol).

Bulk, Tap, and Compressibility Index for MCC–PEG Conjugate

The bulk density was determined by pouring about 20 g of the powder into the glass cylinder (100 ml). Density was then calculated by dividing the mass of the powder by the measured volume. For tap density, the cylinder was tapped 20 times from the distance of 10 cm. The tap density was calculated in the same way as bulk density. Densities were determined as the mean of five measurements. The compressibility index was calculated according to the equation (12)

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

Angle of Repose

This technique is well illustrated in US Pharmacopeia (13). Approximately 10 g of conjugate was poured though a glass funnel with height of 1 in. from tip of funnel to level bench top. The angle made by conical heap with horizontal plane was recorded as the angle of repose. It was determined

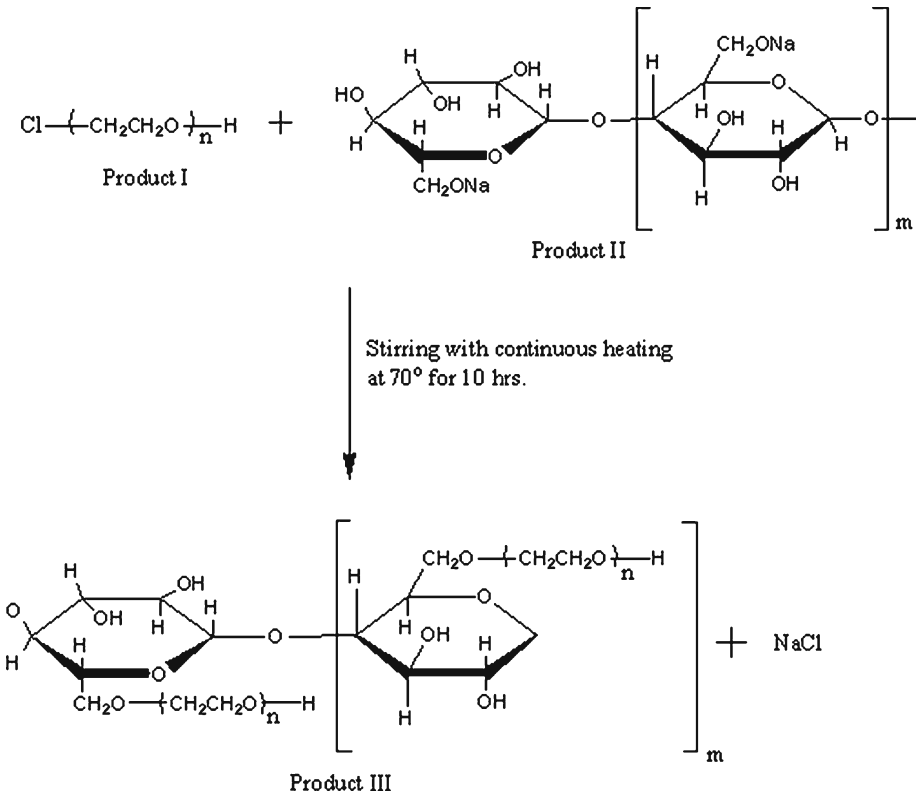

Fig. 1. Reaction scheme of MCC–PEG conjugate synthesis

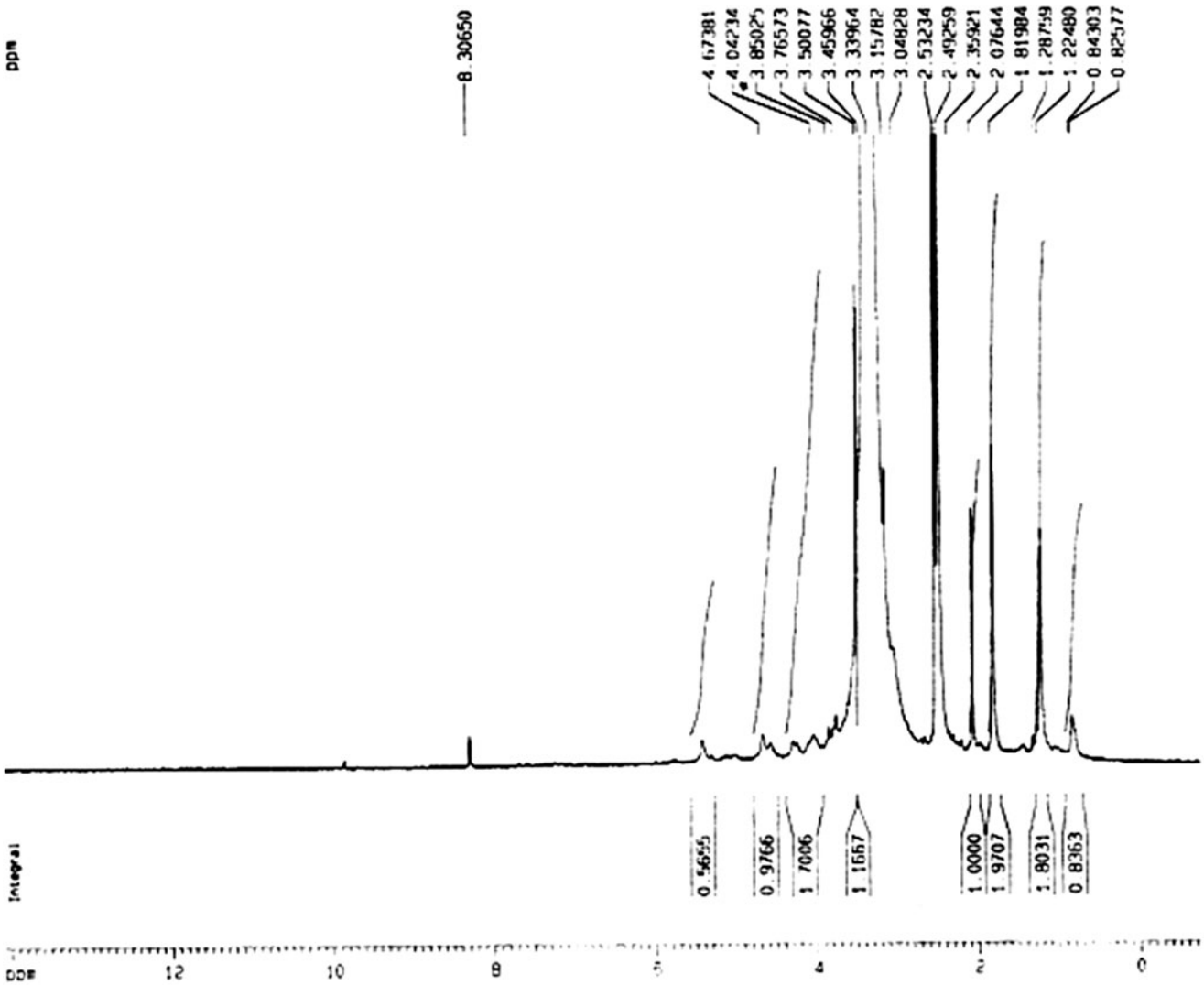

Fig. 2. ^{1}H NMR spectra of MCC and MCC–PEG conjugate

as the mean of five determinations. Values of angle of repose below 30 indicate better flow.

Tensile Strength *vs* Relative Density

Microcrystalline cellulose and MCC–PEG conjugate samples were compressed into tablet weighing 300 mg using 13-mm circular punch at compression forces from 14 to 126 kg/cm^2 using a single punch tableting machine (KBr Press, Karnavati Engineering, India). Relative density was calculated as the ratio of compact density to true density. Tablet hardness was measured using a Monsanto hardness tester. From this, tensile strength was calculated according to the equation (12)

$$\sigma_t = \frac{2F}{\pi Dh} \tag{2}$$

where F is tablet hardness, D is tablet diameter, and h is tablet thickness. The tensile strength *vs* relative densities were compared.

Heckel Plot Compressibility and Compactibility Study of MCC–PEG Conjugate

Tablets were prepared by the procedure given in the test above. Compact porosity was calculated according to the equation (12)

$$\varepsilon = 1 - \rho \tag{3}$$

where ε is porosity and ρ is relative density.

The graph of ln 1/*e vs* pressure was plotted to study the compressibility and compactibility of MCC–PEG conjugate.

Water Vapor Uptake Isotherms

The water sorption isotherms for conjugate along with the three other super disintegrants were generated by storing the materials (5 g of each) in programmable environmental test chamber (Remi, CHM-6S, India), which were previously dried in oven for 1 h at 105°C. Superdisintegrants were exposed to various %RH (10, 40, 60, 75, and 90) at 40°C in the chamber as per ICH

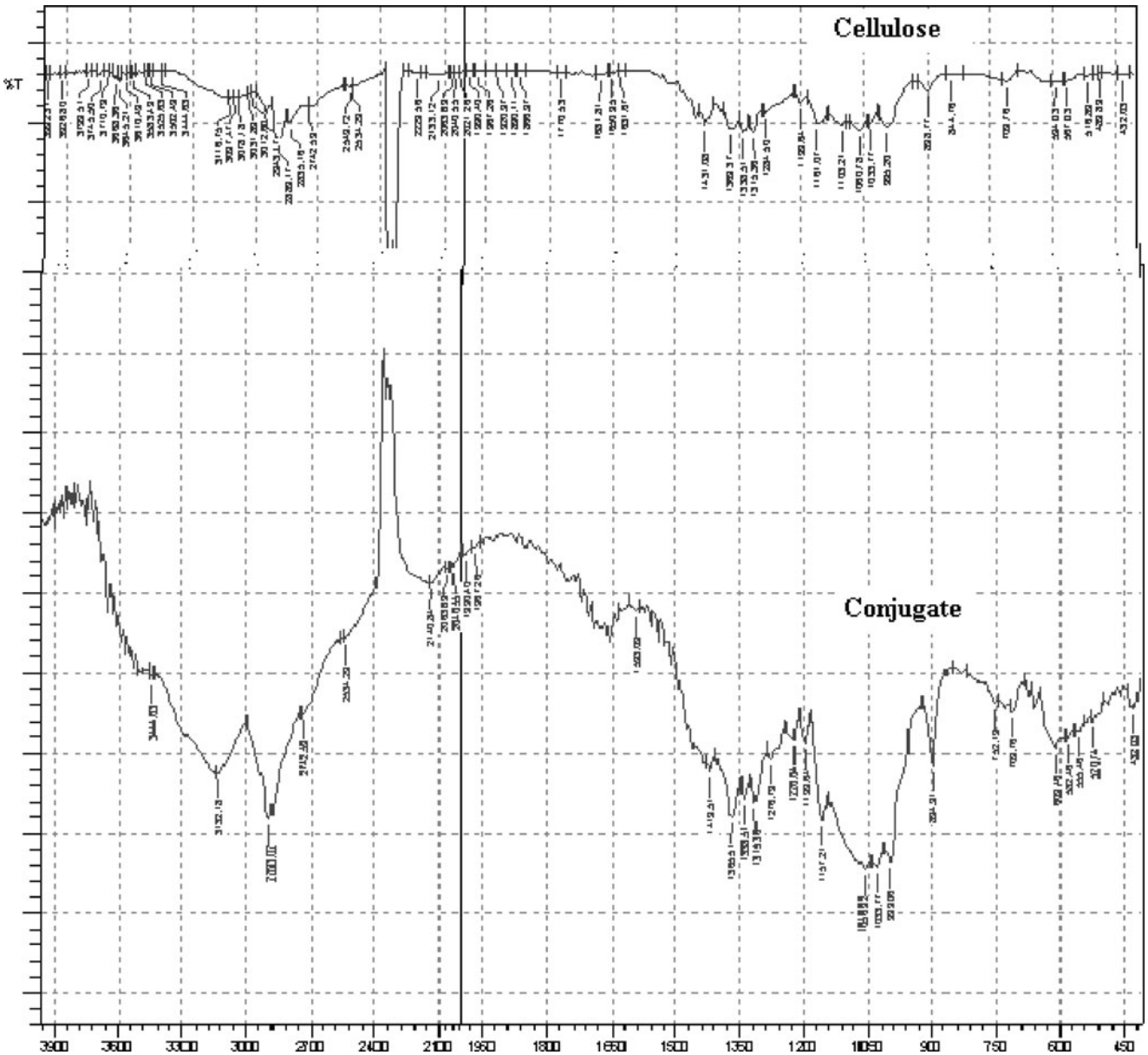

Fig. 3. FTIR spectra of MCC and MCC–PEG conjugate

guidelines. After equilibrium, the moisture content corresponding to individual isotherm points was measured by weighing the samples on Mettler analytical balance. Difference between the final and initial weight gives the water uptake of samples.

Maximum Water Saturation

This was performed by method described by El-Barghouthi *et al.* (14). Conjugate powder was added to 25 ml of water in stepwise manner at room temperature, under stirring using magnetic stirrer, until saturation end point was reached, indicated by formation of solid mass of powder and no further stirring required. The maximum saturation power of conjugate was calculated by dividing the mass of added powder by fixed volume of water. This test was further performed on sodium starch glycolate (SSG), croscarmellose sodium and crospovidone. Each set was performed thrice, and average was calculated.

Water Penetration Rate

Samples were prepared by mixing conjugate powder (0%, 5%, 20%, 35% *w*/*w*) with microcrystalline cellulose. MCC was selected because it does not hinder the water uptake due to gelling. The samples were poured individually into graduated cylinder to a fixed volume, 50 ml, without any applied pressure on the sample column. Of the sunset yellow solution, 25 ml was added to each of the prepared MCC conjugate powder mixture. The penetration rate was calculated by measuring the speed of water (milliliter per minute) penetrating the mixture columns. This test was further performed on SSG, croscarmellose sodium and crospovidone.

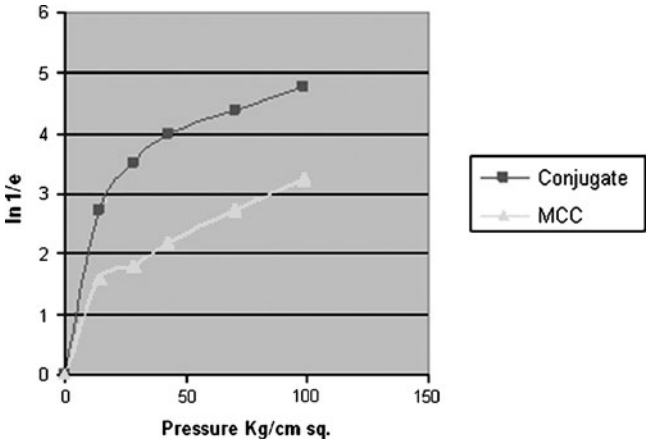

Fig. 4. Heckel's plot of MCC–PEG conjugate and MCC

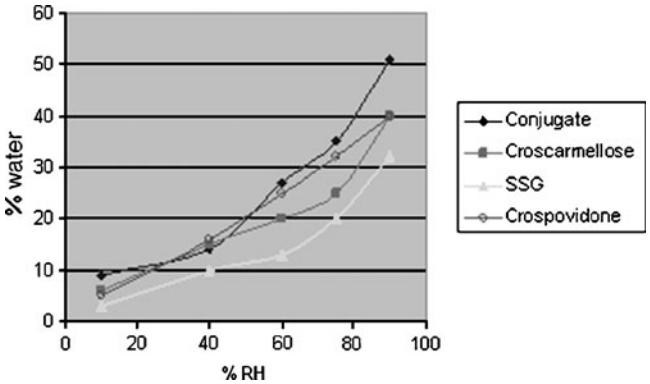

Fig. 6. Equilibrium water vapor uptake by crospovidone, SSG, croscarmellose, and conjugate as a function of RH

Disintegration Time

Tablets prepared from conjugate as described in tensile strength *vs* relative density test were exposed to disintegration test to determine the effect of compression forces on disintegration time.

Determination of Disintegration Efficacy of Conjugate Compared to Commercial Superdisintegrants

This was done by preparing tablets of MCC containing various proportions of superdisintegrants mixed thoroughly. Tablets with 300 mg weight, 4–5 kg/cm^2 hardness, and 10 mm diameter were prepared for this study. Various proportions of each superdisintegrants selected were 1%, 5%, 10%, 20%, and 35%.

Dissolution Study

Tablets containing model drug cetirizine hydrochloride were prepared. Each tablet (300 mg) consists of cetirizine HCl (50 mg), dibasic calcium phosphate (244 mg), disintegrant (3 mg), and magnesium stearate (3 mg). Isopropyl alcohol was used for wet granulation. All the components of given formulations except the lubricant were mixed in a mixer at 30 rpm for 5 min. The powder blend was screened through a 20-mesh screen, and the screened powder blend was lubricated with magnesium stearate at 30 rpm for 5 min in a powder mixer. The tablets were compressed using Rimek MINI PRESS-II MT single punch tablet machine (Karnawati Eng. Ltd., Mehsana, India) on standard concave punches at the tablet weight 300 mg, with 10 mm diameter and hardness of 5 kg/cm^2. The dissolution profiles were determined using the USP dissolution apparatus I. Distilled water (900 ml) was used as the dissolution medium, and a stirring speed of 100 rpm was maintained. Serial sampling of the medium at appropriate time intervals with subsequent UV analysis for drug content were performed at λmax of 231 nm to generate a cumulative percent released-time profile.

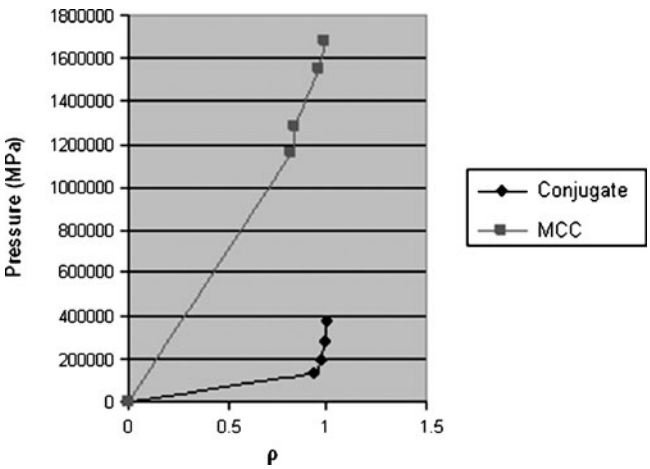

Fig. 5. The plot of tensile strength *vs* relative density for MCC–PEG conjugate and MCC

RESULT AND DISCUSSION

Synthesis and Characterization of Conjugate

In step 1, free PEG was converted to its chloride derivative (product I) by replacing terminal hydroxyl groups with chlorine. In step 2, treatment of cellulose with aqueous sodium hydroxide solution (30%) resulted into the swelling of MCC molecule which was necessary in order to accommodate the PEG-Cl into its cavity. This reaction

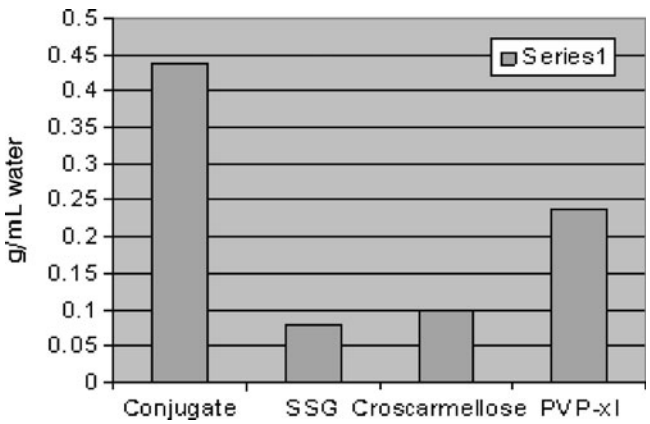

Fig. 7. Maximum amount of water various superdisintegrants needed to form a gel layer upon gradual addition of water

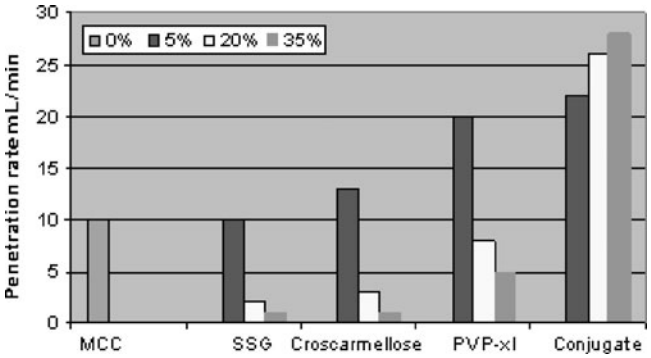

Fig. 8. Water penetration rates of conjugate and other commercial superdisintegrants mixed with MCC at superdisintegrants concentrations of 0, 5, 20, and 35

converted MCC to its sodium salt (product II) which has been reported to be more reactive compared to its precursor (15). In the last step, product I and II were reacted to form the MCC–PEG conjugate leaving sodium chloride as a side product (Fig. 1). The final reaction was continued till the constant amount of free PEG was detected in reaction mixture indicating completion of the reaction.

In the present study, % PEG attached was found to be 22% (SD ±2.64). Mass spectrum revealed an increase in the molecular weight of MCC, *i.e.*, from 367.3 to 437.4, and charring point showed decrease in charring temperature of MCC, *i.e.*, from 253°C to 204°C after PEGylation indicating attachment of PEG to the cellulose molecule. ^{1}H NMR (Fig. 2) and FTIR (Fig. 3) also evidenced the presence of PEG groups in the conjugate structure which were absent in the spectrums of MCC. These groups are as follows. ^{1}H NMR: δ3.76 (specific to CH_2CH_2O units of PEG), δ 3.5 (CH_2–O–CH_2), δ 1.82 (increase in number of C–H bonds by PEG).

FT-IR: 2,885 cm^{-1} (larger and sharper aliphatic stretching band of C–H, due to the increased number of C–H bonds by PEG), 1,230 cm^{-1}(CH_2CH_2O, aliphatic ether linkage).

Sharp crystalline peaks that were observed in MCC underwent broadening after PEGylation indicating the amorphous characteristics that MCC acquired after attachment of PEG.

Compressibility index and angle of repose

The powder compressibility index was calculated from measured bulk density 0.386 g/ml (SD ±0.00451) and tap density 0.423 g/ml (SD ±0.00366) according to equation 1. The resulting compressibility index found was 8.8% (SD ±0.35) which was categorized as an excellent flowable material according to United States Pharmacopeia (USP29-NF24). This was further confirmed by the angle of repose measured at the average value of 25° (SD ±0.58) for MCC–PEG conjugate powder (USP29-NF24).

Table I. Disintegration Time of Conjugate Tablets at different Compression Forces

Force (kg/cm^2)	Hardness (kg/cm^2)	Disintegration time (s)
14.05	3.2	7±0.57
28.12	4.6	9±0.66
42.18	6.9	10±1.1
70.30	7.5	12±0.44
98.42	7.9	13±0.39

Table II. Testing of Superdisintegrant Power of Conjugate Among Commercial Superdisintegrants

	DT at different disintegrant Proportions				
	1	5	10	20	35
SSG	<40 s	<30 s	<30 s	<50 s	>3 min
PVP-xl	<40 s	<30 s	<30 s	<20 s	>3 min
Croscarmellose	<40 s	<30 s	<40 s	<40 s	>5 min
Conjugate	<40 s	<30 s	<20 s	<15 s	<12 s

Heckel's Plot Compressibility and Compactibility Study of Cellulose–PEG Conjugate

The Heckel's plot for both MCC and conjugate showed no linearity at early stages of compression (Fig. 4). This was due to particle rearrangement and fragmentation of larger aggregates under lower compression pressure (16), but with increase in compression pressure, curve appeared to be linear because of plastic deformation. The slope of the Heckel's plot (k) is indicative of plastic behavior of material (16). Higher value of slope indicate higher amount of plasticity in the material. Both MCC and conjugate had almost the same slope (0.031 (SD ±0.0031) for MCC and 0.028 (SD ±0.0025) for conjugate) which indicated that like MCC, cellulose–PEG can also be evaluated as directly compressible material according to its compressibility and compactibility.

PEGylation of MCC resulted into the shift of curve to the more compactable form which could be due to the compact's narrow pore size compared to MCC. Narrow pore size favors faster disintegration (17), which could be the reason for the conjugates' superdisintegration activity.

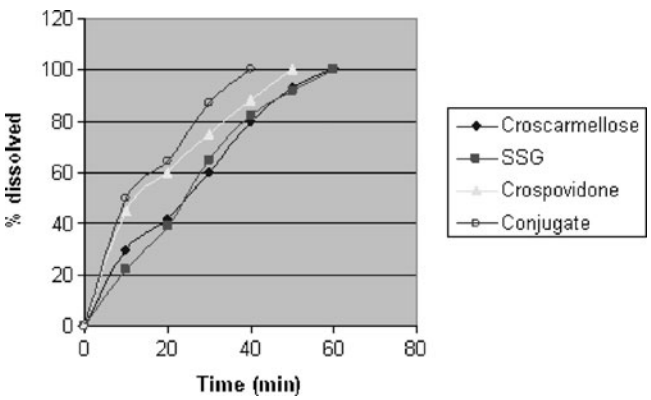

Fig. 9. Dissolution profiles for cetirizine hydrochloride tablets containing 1.0% disintegrant

Tensile Strength *vs* Relative Density

Theoretically, yield compact of less tensile strength favors shorter disintegration time (18). From Fig. 5, we can say that the PEGylation of MCC causes significant reduction in the tensile strength of the MCC. This could be attributed to the amorphous characteristics of conjugate. This favors the crystallanity–tensile strength relationship.

Water Vapor Uptake Isotherm

Disintegration power is dependent on water uptake. Figure 6 shows the moisture sorption isotherms for MCC–PEG conjugate and three super disintegrants. Conjugate sorbed significant amounts of moisture with increase in the % relative humidity. Moisture uptake was not significant at the values of humidity below 75% as is the case with other superdisintegrant. Such property makes the material superior as it averts any threat from humidity to the integrity of product. Conjugate, however, picked up more moisture than the other disintegrants at 75% and 90% RH. Conjugate was found to be capable of gaining moisture up to 51%. Under these equilibrium conditions, conjugate demonstrated its water uptake ability as a disintegrant.

Maximum Water Saturation

With increase in concentration of commercial superdisintegrants, entry of the water into tablet matrix get blocked which is attributed to the formation of gel-like layer that blocks the passage of water inside the deep layers. So it is necessary to determine maximum amount of superdisintegrant added to a fixed volume of water to form a gel layer.

Figure 7 indicated that larger amount of water was required before gelation of conjugate than other commercial superdisintegrants.

Water Penetration Rate

This test particularly highlights the mechanism of action of superdisintegrants.

From Fig. 8, we can say that SSG and croscarmellose showed good penetration within their limits of disintegration, but as the amount increases above that water penetration into the bulk of powder reduces indicating that disintegration action is dependent on amount of disintegrant into the dosage form. PVP-xl showed good water uptake at 5%, but with increase in the concentration, they also showed reduction in water uptake. MCC–PEG conjugate showed maximum water uptake which increased with increase in concentration of conjugate. Same kind of property was reported by El-Barghouthi *et al*. for chitosan silica complex (14).

Disintegration Testing

It was observed that disintegration time (DT) was not much affected by increase in the hardness as shown in Table I.

Tablets prepared using various proportions of disintegrants showed that conjugate was as effective as other commercial superdisintegrants at lower levels but was more effective at higher levels which were in conformity of water saturation and water penetration tests as reported in Table II. This states that tablet DT is also independent of conjugate concentration. Tablets with proportion of MCC–PEG conjugate less than 1% were also prepared, but their DT was not satisfactory in comparison with commercial superdisintergrants. So it can be inferred that utility of this conjugate is above 1% concentration.

Dissolution Study

Dissolution studies were conducted on tablets having calcium phosphate as diluent. Each disintegrant tablet showed the complete release of cetirizine in 60 min. Conjugate tablet showed faster release, *i.e.*, 100% release in 40 min followed by crospovidone and the release was much faster than other two superdisintegrants (Fig. 9)

CONCLUSION

PEGylated conjugate of MCC was synthesized, and the physico-chemical properties of conjugate were compared against MCC. Significant difference was observed in the properties of conjugate and MCC. All the evaluation parameters, *i.e,*. water vapor uptake isotherms, maximum water saturation, water penetration rate, disintegration time, superdisintegration power, and dissolution study shown promising results when conjugate was compared with commercial superdisintegrants. Utility of this conjugate as a disintegrant was found above 1% concentration. So it can be concluded that MCC–PEG conjugate can be evaluated as a superdisintegrant in pharmaceutical formulations.

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