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Carboxymethyl gum kondagogu: Synthesis, characterization and evaluation as mucoadhesive polymer

Ashok Kumar, Munish Ahuja*

Drug Delivery Research Laboratory, Department of Pharmaceutical Sciences, Guru Jambheshwar University of Science and Technology, Hisar 125 001, India

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ABSTRACT

The objective of the study was to modify gum kondagogu by carboxymethylation and to evaluate it for potential pharmaceutical applications. Carboxymethylation of gum kondagogu was carried out by reacting gum kondagogu with monochloroacetic acid under alkaline conditions. The results of characterization studies revealed that carboxymethylation of gum kondagogu increases its degree of crystallinity and surface roughness, reduces its viscosity and improves its mucoadhesive properties. Further, carboxymethyl gum kondagogu was explored for pharmaceutical applications by formulating ionotropically gelled beads using metformin as the model drug and calcium chloride as cross-linking agent. *Ex vivo* bioadhesion study conducted using isolated chick-ileum by wash-off test revealed bioadhesion of >80% over a period of 24 h. It was observed that increasing the concentration of cross-linking agent increases the % drug entrapment and reduces the release rate. The beads were found to release the drug by Fickian-diffusion mechanism and following zero-order release kinetics.

1. Introduction

Natural gums have been used extensively in food and pharmaceutical applications because of their easy availability, low cost, biocompatibility and biodegradability (Bhardwaj, Kanwar, Lal, & Gupta, 2000), but their applications are limited due to uncontrolled hydration, microbial contamination, pH dependent solubility and changes in viscosity during storage. Chemical modifications of natural gums have been employed to improve their properties as biopolymer (Rana et al., 2011). Carboxymethylation is among one of the various strategies used for functionalization of natural polymers (Biswal & Singh, 2004). It is widely employed modification approach because of its ease of processing, lower cost of chemicals and versatility of the product. Carboxymethyl derivatives are usually polyelectrolyte with better aqueous solubility. During earlier studies this approach has been employed to synthesize high performance macromolecular materials (Boppana, Kulkarni, Setty, & Kalyane, 2010; Miyamoto, Tsuji, Nakamura, Tokita, & Komai, 1996). Carboxymethylation of polysaccharides is based on the William synthesis (Silva et al., 2004), in which the polysaccharide alkoxide is reacted with monochloroacetic acid and the primary and secondary alcohol groups are substituted by carboxymethyl group.

Gum kondagogu (GK) is an important forest produce of Andhra Pradesh, India, which is collected by tribals by tapping from the tree of *Cochlospermum gossypium* DC (Family: *Bixaceae*) (Janaki & Sashidhar, 1998). GK is an anionic polysaccharide belonging to the class of substituted rhamnogalacturonans. It comprises of rhamnose, galacturonic acid, glucuronic acid, β-D-galactopyranose, α-D-glucose, β-D-glucose, galactose, arabinose, mannose and fructose with sugar linkage of (1 → 2) β-D-Gal p, (1 → 6) β-D-Gal p, (1 → 4) β-D-Glc p, 4-O-Me-α-D-Glc p, (1 → 2) α-L-Rha (Vinod et al., 2008). It absorbs large amount of water forming thixotropic gels and during earlier studies it has been explored as sustained release matrix (Naidu et al., 2009), template matrix for synthesizing silver nanoparticles (Kora, Sashidhar, & Arunachalam, 2010), as emulsifying agent (Vegi et al., 2009) and also for the preparation of mucoadhesive microspheres in combination with sodium alginate (Mankala, Nagamalli, Raprla, & Kommula, 2011). Modification of release behavior of GK matrix has been carried out by graft copolymerization of acrylamide on GK backbone (Malik & Ahuja, 2011).

In the present study, the chemical modification of GK has been carried out by carboxymethylation. Carboxymethyl gum kondagogu (CMGK) was characterized by Fourier-transform infrared spectroscopy (FT-IR), differential scanning calorimetry (DSC), X-ray diffraction (XRD) and scanning electron microscopy (SEM). The degree of carboxymethyl substitution was determined by classical wet chemistry method. Rheological behavior of CMGK was studied using Brookfield viscometer. The mucoadhesive performance of CMGK was assessed using texture profile analysis. CMGK was evaluated for pharmaceutical applications by formulating mucoadhesive beads.

Metformin an oral biguanide hypoglycemic agent which is therapeutically indicated for the management of type-2 diabetes was

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* Corresponding author. Tel.: +91 1662 263515; fax: +91 1662 276240.
E-mail address: munishahuja17@yahoo.co.in (M. Ahuja).

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used as the model drug in the present study. It shows a dose dependent, saturable transport with absorption window in the upper part of intestine (Marathe et al., 2000). Its bioavailability is improved by gastric retention (Gusler et al., 2001). During earlier studies bioadhesive systems have been formulated for improving the oral delivery of metformin (Adikwu, Yoshikawa, & Takada, 2003; Ige & Gattani, 2012).

2. Experimental

2.1. Materials

Gum kondagogu (GK) (grade I) and metformin were obtained as gift samples from Girijan Co-operative Corporation (Hyderabad, India), and GMH Laboratories Pvt. Ltd. (Baddi, India), respectively. Monochloroacetic acid was purchased from Hi-Media Lab. Pvt. Ltd. (Mumbai, India). Sodium hydroxide, methanol and glacial acetic acid were procured from Sisco Research Laboratory, (Mumbai, India). All other chemicals used were of reagent grade, and were used as received. Isolated chicken ileum was obtained from the local butcher shop (Hisar, India).

2.2. Preparation of carboxymethyl gum kondagogu (CMGK)

Carboxymethylation of GK was carried out employing monochloroacetic acid as reported earlier (Narayana, 1992). GK (1 g) was dispersed in 80 ml of ice cold sodium hydroxide solution (45%, w/w) with the aid of stirring for 30 min, followed by addition of 10 ml of monochloroacetic acid solution (75%, w/v) under constant stirring. The reaction mixture was then heated to 70 °C under constant stirring for 30 min, cooled and suspended into an 80% (v/v) methanol. The precipitate so obtained was then filtered and washed with glacial acetic acid till washings were neutral. The product so obtained, was washed three times with 60 ml portions of 80% (v/v) methanol, filtered and dried in an oven at 40 °C.

2.3. Characterization of CMGK

2.3.1. FT-IR spectroscopy

The samples of GK and CMGK were subjected to FT-IR spectroscopy in a Fourier-transform infrared spectrophotometer (IR Affinity, Shimadzu) in range of ($4000\,\mathrm{cm}^{-1}$ to $400\,\mathrm{cm}^{-1}$) as KBr pellet.

2.3.2. Differential scanning calorimetry

Differential scanning calorimetric thermograms of GK and CMGK were recorded using differential scanning calorimeter (Q10, TA Systems, USA) in the temperature range of (40–300 °C) at a heating rate of 10 °C per minute in nitrogen atmosphere.

2.3.3. X-ray diffractometry

X-ray diffractogram of GK and CMGK samples were recorded employing X-ray diffractometer (Bruker Focus D8). The sample powders were scanned from 0° to 70° diffraction angle (2θ) range under the following measurement conditions: source, nickel filtered Cu-Kα radiation; voltage 35 kV; current 25 mA; scan speed $0.05\,\mathrm{min}^{-1}$.

2.3.4. Scanning electron microscopy

Scanning electron micrographs of GK and CMGK were taken using a SEM (JEOL, JSM-6100). These were coated with gold and mounted in a sample holder. The photomicrographs of sample were taken at an accelerating voltage of 10 kV at different magnifications.

2.3.5. Viscosity

Viscosity of 2% (w/v) dispersions of GK and CMGK was determined using Brookfield viscometer (Model RVDVE 230, Brookfield Engineering Laboratories, Middleboro, USA) using spindle number 63 at different shear rates.

2.3.6. Degree of substitution

The degree of substitution was determined by classical acid-wash method (Eyler, Klug, & Diephuis, 1947). Briefly, 5 g of freshly precipitated CMGK was dispersed in 50 ml of hydrochloric acid reagent, in 250 ml Erlenmeyer flask for 3–4 h, followed by filtration and washing with 70% methanol till the washings were neutral to methyl red followed by drying to constant weight in an oven at 80 °C.

An accurately weighed 500 mg of dried CMGK was dispersed in 10 ml of 70% methanol in Erlenmeyer flask and stirred for 30 min. To this an aliquot of 50 ml of distilled water and 15 ml of 0.5 N sodium hydroxide was added and stirred for 3 h to dissolve the sample completely. The excess of sodium hydroxide was back titrated with 0.5 N hydrochloric acid using phenolphthalein as an indicator. The degree of substitution (DS) of CMGK was calculated using the following equation:

$$\mathrm{DS} = \frac{0.162A}{1\text{–}0.058A} \tag{1}$$

where, A is the miliequivalents of sodium hydroxide required per gram of the sample.

2.4. Evaluation of CMGK as mucoadhesive polymer

The mucoadhesive property of CMGK was comparatively evaluated with GK by conducting tensile test of polymer compact using texture analyzer (Tamburic & Craig, 1997). Polymer compacts of GK and CMGK were prepared by compressing 150 mg of polymer in IR hydraulic press (KP795, Kimaya Engineers, Thane, India) using 13 mm diameter die at a pressure of 5 tonne for 60 s. The mucoadhesive performance was measured using texture analyzer (TAX_2 Stable Microsystem, UK). The texture analyzer was equipped with the 5 kg load cell. The polymer compacts were attached to the upper probe, a cellophane membrane hydrated with dispersion of mucin (0.3%, w/v) and attached to the lower probe was used as the model membrane. The upper probe was lowered at a rate of 0.1 mm/s until the contact with the membrane and constant force of 0.25 N was applied for 300 s and upper probe was withdrawn at a rate of 0.1 mm/s. The force of detachment of the polymer compact with membrane was taken as the indicator of mucoadhesive performance.

2.4.1. Preparation of beads of CMGK

Mucoadhesive applications of CMGK were explored by formulating ionotropically gelled beads using calcium chloride as ionic cross-linker and metformin as the model drug (Ahuja, Yadav, & Kumar, 2010). Briefly, an aqueous solution of CMGK (2.5%, w/v) containing metformin (1.25%, w/v) was extruded through #18G needle into aqueous solution of calcium chloride (5–20%, w/v) at room temperature. The gelled beads were allowed to harden for 5 min followed by filtration and washing with distilled water. The beads so obtained were freezed at −80 °C for 4 h followed by lyophilization in laboratory model freeze dryer (Alpha 2-4 LD Plus, Martin Christ, Germany) for 24 h at −90 °C, at 0.0010 mbar.

2.4.2. Evaluation of CMGK beads

Metformin loaded CMGK beads were characterized for *ex vivo* bioadhesion, drug entrapment efficiency and *in vitro* release behavior.

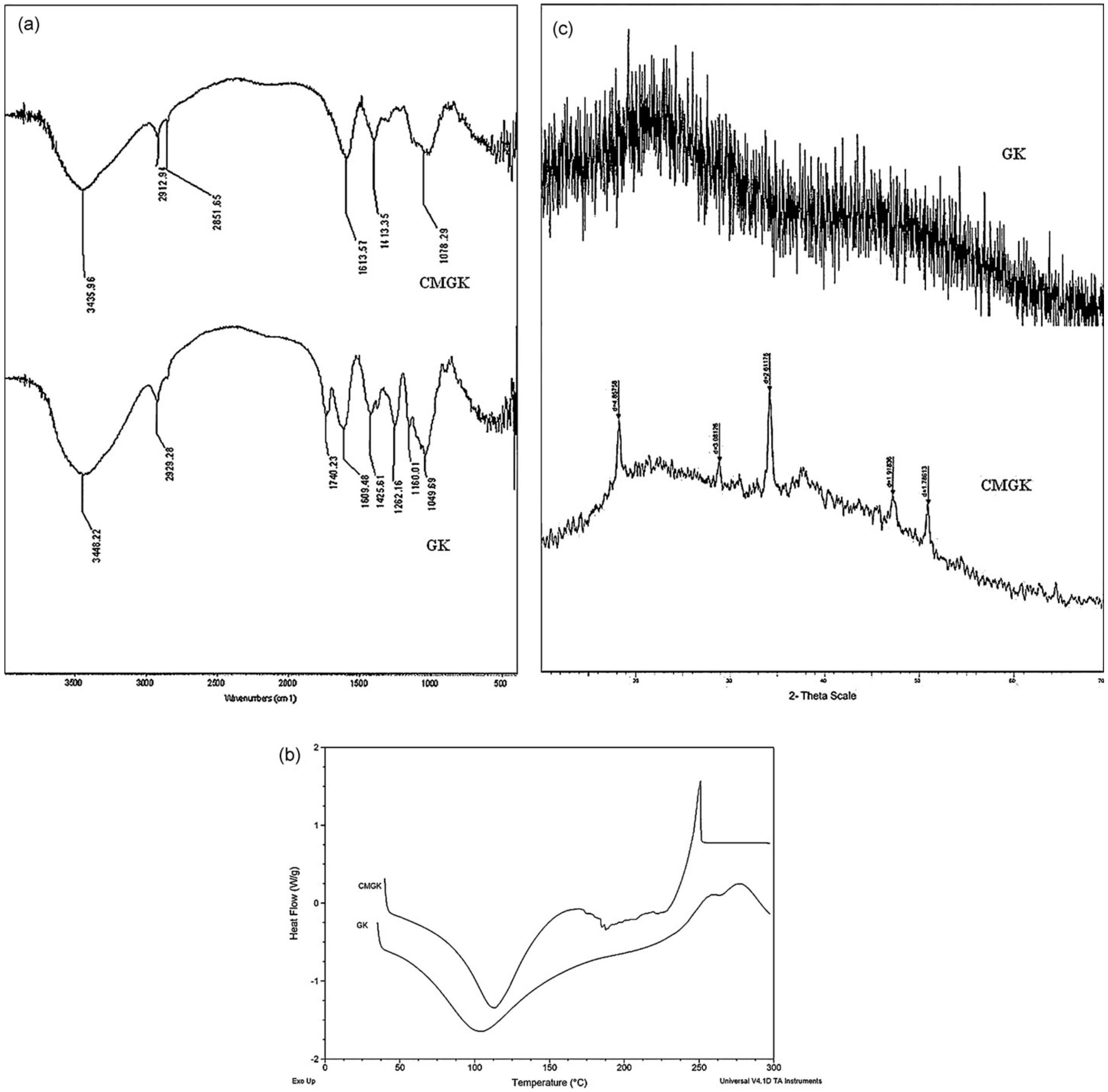

Fig. 1. FTIR spectra (a), DSC thermograms (b) and X-ray diffractograms (c) of GK and CMGK powders.

2.4.2.1. Ex vivo bioadhesion study. The *ex vivo* bioadhesion of CMGK beads was determined by wash-off test (Lehr, Bowstra, Tukker, & Junginer, 1990). A freshly excised chick intestine was obtained from a local butcher house (Hisar, India) within an hour of slaughter and transported to laboratory in cold (4 °C) isotonic saline. Intestinal tissue was excised and cleaned by washing with isotonic saline and was pasted on glass slide using cyanoacrylate glue with mucosal surface facing out. About 50 CMGK beads were adhered to intestinal mucosal tissue by applying light force with fingertip for 30 s. The glass slide was hung on to arm of USP tablet disintegrating machine, which was suspended in 900 ml of phosphate buffer (pH 6.8) at 37 ± 0.5 °C. The tissue specimen was given slow, regular up and down movement by operating the USP tablet disintegrating test machine. The numbers of beads adhering to tissue were counted at regular intervals up to 24 h.

2.5. Entrapment efficiency

Entrapment efficiency is the percentage of actual mass of drug encapsulated in the polymeric matrix, related to initial amount of loaded drug.

$$\%\,\text{entrapment efficiency} = \frac{\text{actual drug loading}}{\text{theoretical drug loading}} \times 100. \qquad (2)$$

For the theoretical drug loading it was assumed that entire drug gets encapsulated in beads. For actual drug loading an accurately

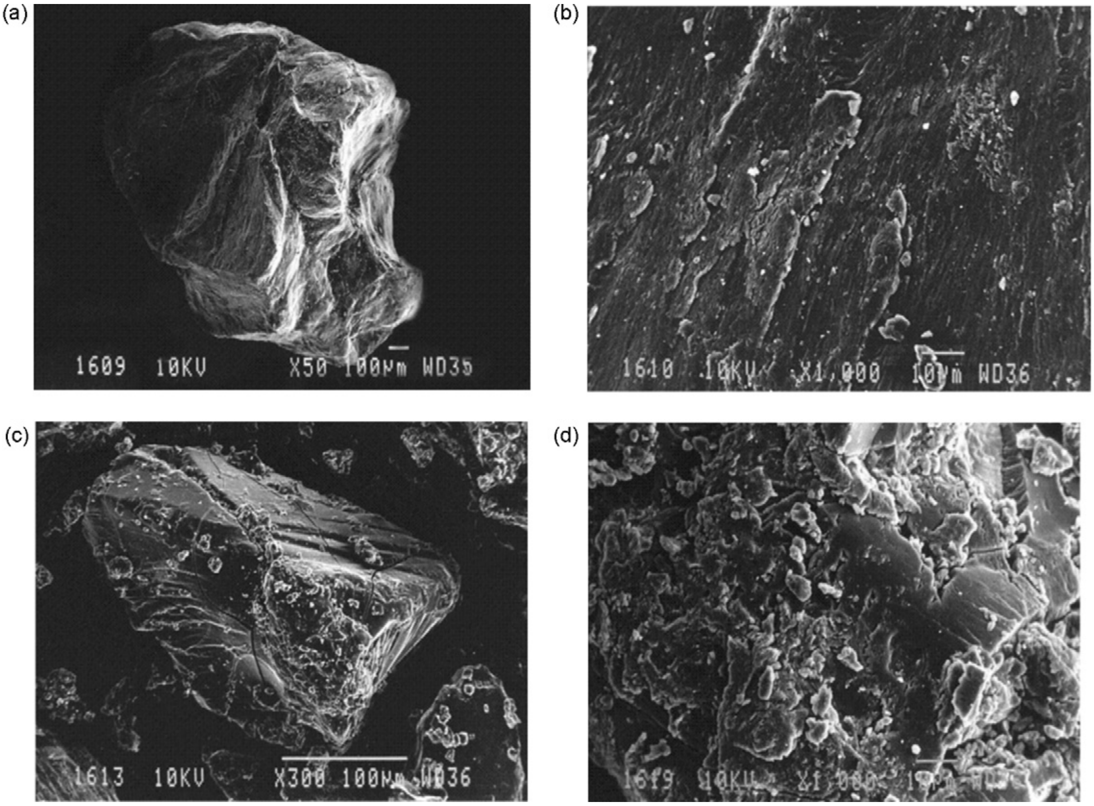

Fig. 2. Scanning electron micrograph showing (a) shape, (b) surface of GK and (c) shape (d) surface of CMGK powders.

weighed 25 mg of beads were taken, grounded and sonicated in 100 ml of phosphate buffer (pH 6.8) for 30 min, filtered through 0.45 µ-syringe filter and diluted appropriately. The contents of metformin in the beads were determined spectrophotometrically by measuring the absorbance at 233 nm.

2.6. In vitro drug release

The *in vitro* release of metformin from beads was determined using USP type II dissolution apparatus (TDT-08L, Electrolab, India), employing 250 ml of phosphate buffer (pH 6.8) as release media maintained at 37 ± 0.5 °C and rotated at the speed of 100 rpm. An accurately weighed beads containing equivalent of 25 mg of drug were enclosed in the muslin cloth and the cloth was tied with the paddle (Sharma & Ahuja, 2011). Sample aliquots of 5 ml were withdrawn at regular intervals and replaced with fresh release media. The contents of metformin in withdrawn samples were estimated spectrophotometrically by measuring absorbance at 233 nm.

3. Results and discussion

The CMGK so synthesized from GK was characterized by FTIR, DSC and XRD study. Fig. 1(a) shows the FTIR spectra of GK and CMGK. The spectra of GK shows a broad absorption band at 3448 cm^{-1} attributed to O—H stretching band of hydroxyl group, a peak at 2929 cm^{-1} due to C—H stretching of alkane, a peak at 1740 cm^{-1}due to —C═O stretching of acetyl. The peaks appearing at 1609 and 1425 cm^{-1} can be ascribed to C═O stretching of carboxylic acid of glucuronic acid. The peaks at 1160 and 1049 cm^{-1} can be attributed to C—O stretching of —C—O—C— and primary alcohol (—C—O—H—), respectively.

The spectra of CMGK shows a broad absorption band at 3435 cm^{-1} due to O—H stretching of alcohols, a peak at 2912 cm^{-1} due to C—H stretching of alkane. The peaks appearing at 1613, 1413 and 1078 cm^{-1} can be ascribed to C═O stretching, —COO⁻ of carboxylate anion and C—O stretching of primary alcohols respectively. Due to deacetylation of GK, the peak at1740 cm^{-1} disappeared in CMGK (Vinod & Sashidhar, 2010).

Fig. 1(b) represents the DSC curve of GK and CMGK. Thermogram of GK shows a broad endotherm at 108.9 °C with a heat of fusion of 392.1 J/g. The thermal curve of CMGK shows an endothermic peak at 113.65 °C with a heat of fusion 347.3 J/g followed by an exotherm at 251.0 °C with heat of fusion of 8.257 J/g.

Fig. 1(c) displays the XRD spectra of GK and CMGK. The X-ray diffraction curve of GK is typical of amorphous material with no sharp peak while the diffractogram of CMGK is also typical of amorphous material but with its characteristic peaks appearing at 17.0, 28.9, 34.2, 47.2, 51.0 (2θ). Thus carboxymethylation of CMGK results in slight increase in crystalinity.

Fig. 2(a)–(d) displays the scanning electron micrographs of GK and CMGK particles showing their shape and surface morphology. It can be observed from the photomicrographs that the GK and CMGK particles are polyhedral in shape but surface of CMGK is rougher than GK. The degree of substitution of carboxymethyl groups in CMGK was determined to be 0.2.

Fig. 3 shows the effect of shear rate on the viscosity of dispersions of GK and CMGK. It can be observed that apparent viscosity changes significantly with applied shear stress, with fall in viscosity with increase in the shear stress. The viscosity of CMGK was less than that of GK. The viscosity of GK may be attributed to the entanglement of the random polymer chain and on shearing the aggregation of GK chains is reduced resulting in fall in viscosity. The fall in viscosity of GK on carboxymethylation may be attributed to the increased anionic character of the GK chain, imparted by carboxymethylation, which results in greater extent of ionization. The columbic repulsion between the backbone chains prevents their aggregation thereby reducing viscosity (Maiti, Ray, Mandal, Sarkar, & SA, 2007).

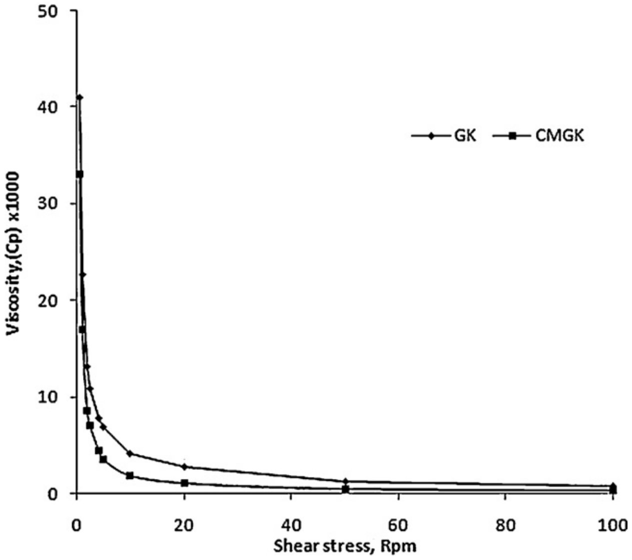

Fig. 3. Rheological behavior of aqueous solutions of GK and CMGK.

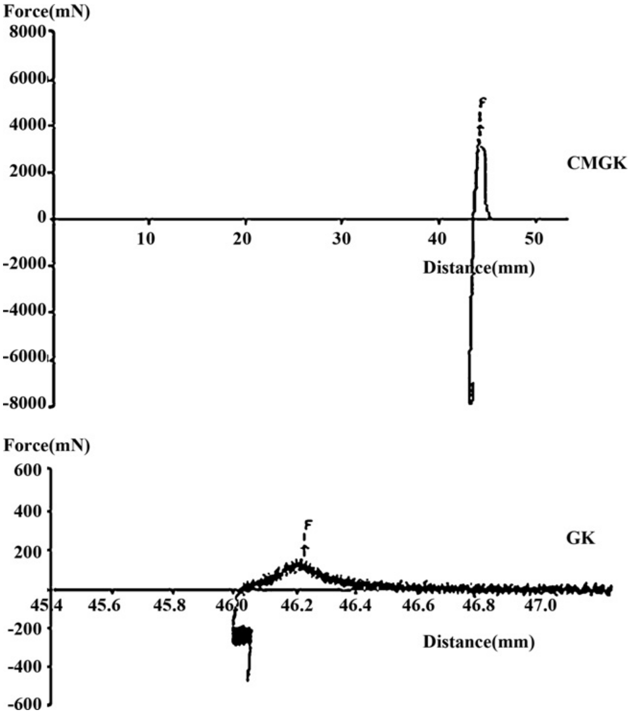

Fig. 4. Tensile test profiles of GK and CMGK polymer compacts.

Fig. 4 shows the tensile test profiles of GK and CMGK pellets. The maximum force of detachment for GK and CMGK polymer compacts was found to be 157.132 and 3503.4 mN respectively, indicating the greater adhesion of CMGK to mucin than GK. The greater adhesion of CMGK prompted us to explore its use in formulating the mucoadhesive formulation.

GK has earlier been used for formulation of mucoadhesive microcapsule of gliclazide in combination with sodium alginate (Mankala et al., 2011). During preliminary trials in our laboratory it was observed that the GK itself did not form microspheres or spherical beads on cross linking using ionic cross linkers such as calcium chloride. On the other hand CMGK was observed to form spherical beads. Gum kondagogu shows anionic character due to the presence of carboxylic groups of the uronic acid residue on the GK backbone chain. The interaction between the calcium ions and the uronic acid residue of GK resulted in gelation of gum kondagogu but this interaction was not too strong to allow the formation of microsphere. However, carboxymethylation of GK increases its anionic character. The interaction between the calcium ions (Ca^{2+}) and carboxylate anion (COO^-) provided by the uronic acid and carboxymethyl moiety on the GK backbone chain was found to be adequate enough to allow the formation of spherical beads or microsphere. Thus, mucoadhesive applications of CMGK were explored by preparing ionically cross-linked beads using metformin as the model drug.

Table 1 shows the results of evaluation of metformin-loaded CMGK beads. It was observed that on increasing the concentration of cross-linking agent from 5% to 20%, there was a corresponding increase in drug entrapment which can be attributed to higher degree of cross-linking with increasing cross-linker. However, no difference was observed in the *ex vivo* bioadhesion time of CMGK beads prepared using different concentration of cross-linker, and all the batches of bead showed *ex vivo* bioadhesion of more than 80% up to 24 h of the study period.

Fig. 5(a) and (b) shows the shape and surface morphology of metformin loaded-CMGK beads. The scanning electron micrograph of CMGK beads show that the metformin loaded bead are spherical in shape and have rough porous surface.

Fig. 6 compares the *in vitro* release profile of metformin from different batches of CMGK beads; it can be observed that there was an initial burst release of the drug from all the batches of CMGK beads. The burst release of the drug from the beads may be attributed to the porous matrix and to the greater quantity of drug entrapped on the surface of the CMGK matrix during the process of bead formation (Huang & Brazel, 2001). The initial burst release of drug will provide the higher initial response required for immediate effect followed by the slow release of the drug over a prolonged period of time for longer duration of action. Further, it can be observed that as the concentration of cross linking agent was increased from 5 or 10% to 20% there was a corresponding decrease in the initial burst release.

The higher degree of drug entrapment and decrease in burst release with increase in concentration of cross-linking agent may be explained by gelling interaction between the CMGK and calcium chloride. The gelling interface formed during interaction between the calcium ion and CMGK is more viscous when 20% calcium chloride solution is used compared with 5 or 10% calcium chloride solution. As a result the migration of the drug from within the matrix to the bulk of the solution as well as to the surface of the bead is reduced, resulting in higher entrapment and smaller burst

Table 1
Ex vivo bioadhesion, entrapment efficiency and release kinetics of different batches of metformin-loaded CMGK beads.

Formulation code	Entrapment efficiency	*Ex vivo* bioadhesion (%)				Release kinetics				
		Time (h)				Zero order	First order	Higuchi square root	Korsemeyer-Peppas	
		0	8	16	24	R^2	R^2	R^2	R^2	*n*
CMGK5	33	100	93	86	80	0.987	0.952	0.939	0.771	0.067
CMGK10	38	100	90	83	83	0.987	0.904	0.948	0.986	0.057
CMGK20	60	100	96	90	88	0.992	0.980	0.964	0.926	0.217

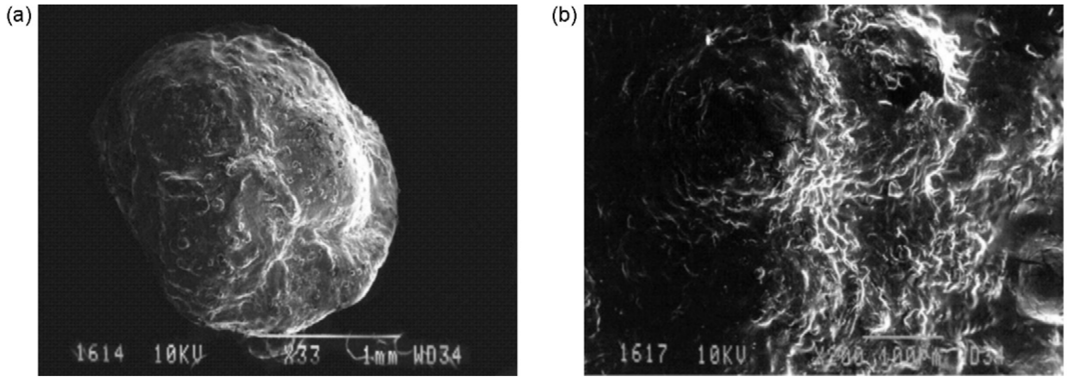

Fig. 5. Scanning electron micrograph showing the shape (a) and surface (b) of metformin-loaded CMGK beads.

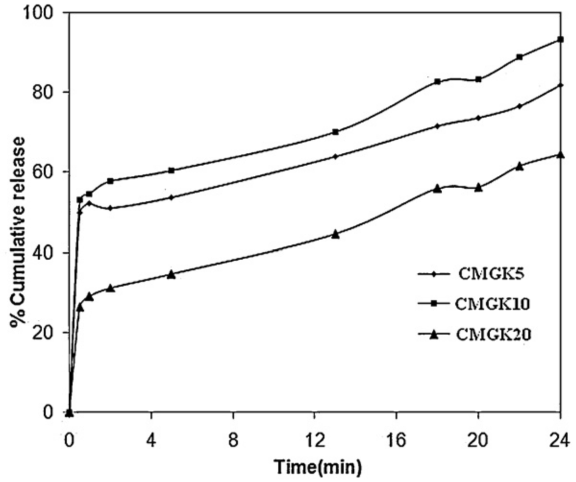

Fig. 6. Comparative *in vitro* release profile of metformin from different batches of CMGK beads.

release of drug from beads formulated using 20% calcium chloride. Further, it can be observed that a decrease in the release rate was observed on increasing the concentration of cross-linking agent.

To determine the release kinetics and mechanism of release, the release data was fitted in to various kinetic models, and it was observed to fit best into zero-order release kinetics (Costa & Loba, 2001). As the value of '*n*' the release exponent of Korsmeyer-Peppas is less than 0.43, the drug release from the matrix follows Fickian diffusion mechanism (Siepmann & Peppas, 2001). Further, to compare the release profile, the release data was treated for calculation of similarity factor f_2, and dissimilarity factor f_1. The values of $f_1 < 15$ and $f_2 > 50$ indicate similarity of the dissolution profiles. On comparing the release of metformin from the CMGK5 with CMGK10, the value of f_1 and f_2 were found to be 12.18 and 53.57, respectively indicating the similarity of the two release profiles. The corresponding values of f_1 and f_2 for comparison between CMGK5 and CMGK 20 (f_1-29.56, f_2-35.96), and between CMGK10 and CMGK20 (f_1-28.71, f_2-37.21) indicate dissimilarity of release profiles. By modulating the concentrations of CMGK, Ca^{2+} ions, and the drug polymer ratio, one can easily design the formulation of bead having minimum or no burst release and sustained-release over a desired period of time. Thus, CMGK is a promising mucoadhesive polymer.

4. Conclusion

In the present study, carboxymethylation of GK was carried out. Carboxymethylation of GK was found to reduce its viscosity, improve mucoadhesive property and its ionic gelling behavior.

The results of present study show that the carboxymethylation of GK provided means of preparing mucoadhesive, sustained-release bead formulation of metformin, releasing the drug by zero-order release kinetics. However, further studies *in vivo* are needed to comment more on its bioadhesive performance.

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