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Effect of ionic crosslink on the release of metronidazole from partially carboxymethylated guar gum tablet

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ABSTRACT

Partially carboxymethylated guar gum (PCMGG) was crosslinked in situ by Ca^{2+} ions during wet massing step of tablet preparation. The resulting tablets were evaluated for the effect of the extent of crosslinking on drug release and matrix swelling. Increase in the concentration of Ca^{2+} ions increased the viscosity of gel layer and reduced the water penetration velocity into the matrix with subsequent decrease in swelling of the tablets and drug release. Beyond a certain concentration of Ca^{2+} ions, the viscosity of the gel layer decreased and the drug release rate increased primarily due to erosion of the matrix. The mechanism of drug release appeared to be non-Fickian or anomalous transport. The release data also best fitted in zero order equation. The model drug, metronidazole, was compatible with the matrix materials as evident from instrumental analyses. Such formulation may provide flexibility in achieving the desired drug release rate from crosslinked matrix tablets.

1. Introduction

More than 90% of the dry weight of all biomass consists of carbohydrate and more than 90% of the carbohydrate is available in the form of polysaccharide (Zohuriaan-Mehr & Pourjavadi, 2003). Guar gum (GG) is a naturally occurring galactomannan polysaccharide and is derived from the seeds of *Cyamopsis tetragonolobus* (Family Leguminosae). In recent times, GG has emerged as a versatile polymer because of its multifunctional role in pharmaceutical product development.

Being a biopolymer it is non toxic and falls under the category "generally regarded as safe" (GRAS) (Sinha & Kumria, 2004). This has led to its extensive use in various food products as stabilizer and thickener (Mudgil, Barak, & Khatkar, 2011). For the same reasons, it has been used as thickening, suspending and stabilizing agents in liquid pharmaceutical dosage form and as binder and disintegrant in tablet dosage form (Krishnaiah, Satyanarayan, & Rama Prasad, 1999). As it hydrates quickly in contact with water and produces viscous pseudoplastic solution that have greater low shear viscosity (Prabaharan, 2011), it has been examined as drug release retarding material either alone (Al-Saidan, Krishnaiah, Patro, & Satyanaryana, 2005; Krishnaiah, Karthikeyan, Gouri Sankar, & Satyanarayana, 2002a) or in combination with other hydrocolloids (Mughal, Iqbal, & Neau, 2011) in formulation of sustained release tablets. Further, the knowledge of carbohydrate chemistry and human physiology has established that GG remains undigested in the stomach and small intestine and undergoes degradation by the vast anaerobic microflora of the colon e.g. *bacteroides*, *bifidobacteria*, *eubacteria, clostridia* to smaller polysaccharides (Sinha & Kumria, 2004). As a result, GG has emerged as a prospective polymer for the development of colon-specific drug delivery system. It has been used as either matrix material (Rama Prasad, Krishnaiah, & Satyanarayana, 1998) or compression coating material (Krishnaiah, Bhaskar Reddy, Satyanarayana, & Karthikeyan, 2002; Krishnaiah, Satyanarayana, Dinesh Kumar, & Karthikeyan, 2002) for the design of colon targeted tablets.

Natural polymers are amenable to various chemical modifications (Vyas & Khar, 2002) and thus many important functional properties can be imparted to these materials (Tapia et al., 2002). GG has been grafted with acrylamide to introduce hydrophobicity and steric bulkiness for protecting the matrix against rapid dissolution and erosion and thus to provide extended release of drugs (Toti & Aminabhavi, 2004). GG has also been crosslinked with various chemicals such as trisodium trimetaphosphate (Gliko-Kabir, Yagen, Baluom, & Rubinstein, 2000), glutaraldehyde (Chaurasia et al., 2006) to reduce the high swelling characteristics of the matrices and provide better control on drug release from various dosage forms e.g. disc and beads. Further development in the area of modification involved insertion of carboxymethyl group to GG and subsequent crosslinking with metal ions to reduce the

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high hydrophilicity and solubility of the resultant carboxymethyl guar gum in comparison to the parent gum. Ca^{2+} and Ba^{2+} ions crosslinked carboxymethyl guar gum beads have been developed to prevent release of acid sensitive drugs in gastric fluid (Reddy & Tammishetti, 2002; Thimma & Tammishetti, 2001).

Drug release from a hydrophilic matrix is a complex interaction between swelling, diffusion and erosion of the polymer (Munday & Cox, 2000). Crosslinking of some of the functional groups of hydrophilic polymers may further alter the above characteristics and subsequently the drug release behavior. To the best of our knowledge, there is no report on the impact of crosslinking on drug release from partially carboxymethylated guar gum (PCMGG) matrix tablet. Hence, the objective of this work was to develop PCMGG matrix tablet by in situ crosslinking with Ca^{2+} ion using wet granulation method and to evaluate the effect of crosslinking on the swelling of the matrix and the drug release behavior. It was also intended to assess whether such crosslinked matrix could prevent premature drug release in the upper gastrointestinal tract. The release and swelling kinetics were characterized and the drug-excipient compatibility was examined. Such kind of work may be useful to interpret the behavior of crosslinked polymer required for optimization of modified release tablet dosage form. Metronidazole has been used as a model drug because its delivery in colon may provide better therapeutic efficacy (Krishnaiah, Bhaskar Reddy et al., 2002; Mundargi, Patil, Agnihotri, & Aminabhavi, 2007).

2. Materials and methods

2.1. Materials

Guar gum (GG), monochloro acetic acid, and calcium gluconate (CG) were purchased from Merck Specialities Pvt. Ltd., Mumbai, India. Metronidazole (MNZ) was obtained as gift sample from Caplet India Pvt. Ltd., Kolkata, India. All other chemicals of analytical grade were obtained commercially.

2.2. Preparation of PCMGG

Modification of GG to PCMGG and determination of the degree of substitution were performed following the procedure of carboxymethylation of xanthan gum (Sa & Setty, 2008). GG was sprinkled slowly in water containing NaOH with vigorous stirring at 0–8 °C. After 30 min, the temperature was increased to 15–18 °C and monochloro acetic acid solution was added slowly with stirring. The temperature of the reaction mixture was elevated to 75 °C and maintained for 1 h. The resulting mass, after cooling, was washed repeatedly with 80% methanol and during the last washing the pH of the suspension was adjusted to neutrality with glacial acetic acid. Finally, the mass was washed with methanol and dried at 45–50 °C to constant weight.

2.3. Preparation of tablets

Required amount PCMGG, CG and MNZ (passed through # 60 mesh BS screen) were manually blended. Appropriate amount of water was added to get a cohesive mass which was passed through # 18 mesh BS screen. The granules were dried in a tray drier at 60 °C till the moisture content of the granules reached 2–4%. The dried granules were passed through # 22 mesh BS screen, mixed with magnesium stearate and compressed into tablet using a flat face 10 mm punch in a 10 station rotary minipress tablet machine (RIMEK, Karnavati Engineering Ltd., Gujarat, India). The tablets were prepared using different PCMGG/CG ratio. 50 tablets of each formulation were prepared in duplicate. The composition of the tablets is shown in Table 1. The resulting tablets were evaluated for weight variation, hardness, friability and thickness by standard methods. Each test was conducted using 6 tablets.

2.4. MNZ content in tablet

A tablet was powdered in a glass mortar and transferred quantitatively in 500 ml stoppered conical flask. 250 ml of pH 1.2 HCl solution was added and stirred for 4 h. The mixture was filtered and an aliquot, following suitable dilution, was analyzed at 278 nm using Microplate Spectrophotometer (MULTISKANGO, Thermo Scientific, US). The drug content was determined using a calibration curve constructed in acid solution. Average drug content of 6 tablets were reported.

2.5. Fourier transform infrared (FT-IR) analysis

FTIR spectra of GG, PCMGG, MNZ and powdered tablet were recorded in a FTIR spectrophotometer (Perkin Elmer, RX-1, UK). The samples were mixed with KBr and converted into pellets at 5.5 ton pressure using a hydraulic press. The spectra were taken in the wave number region of 4000–400 cm^{-1}.

2.6. Differential scanning calorimetry (DSC) study

DSC thermograms of MNZ and powdered tablet were obtained in the following way: weighed amounts (6.8–8.2 mg) of samples were kept in hermetically sealed aluminium pan and heated at a scan speed of 10 °C/min over a temperature range of 30–500 °C under nitrogen atmosphere in a differential scanning calorimeter (DSC Q2000 V24.2 Build 107, Universal V4 TA Instruments, UK). The instrument was calibrated against indium.

2.7. X-ray diffraction (XRD) study

The qualitative X-ray diffraction studies of MNZ and powdered tablet were performed using an X-ray diffractometer (X'Pert PRO, PANanalytical, Holland). The powdered samples were scanned from 0 to 100° diffraction angle (2θ) range under the following measurement conditions: source, Ni filtered Cu-$K\alpha$ radiation; voltage 45 kv; current 30 mA; scan speed 1°/min.

2.8. In vitro drug release study

In vitro drug release studies were carried out in USP II tablet dissolution rate test apparatus (TDP-06P, Electro Lab, Mumbai, India) at 37 ± 0.5 °C and 75 rpm following the method described in Indian Pharmacopoeia (2010) for modified release tablet with slight modification. Considering the transit time and pH values prevailing in different segments of gastrointestinal tract, in vitro drug release study was performed in the following way. The tablets of each formulation were immersed in 700 ml HCl solution of pH 1.2 (gastric pH), and dissolution was carried out for 2 h. Thereafter, the pH of dissolution medium was brought to pH 7.4 (small intestinal pH) by adding 200 ml of 0.2(M) tri-sodium orthophosphate dodecahydrate and the dissolution study was carried out for 3 h in 900 ml solution of pH-7.4. After 5 h, the pH of the dissolution medium was adjusted to pH 6.8 (colonic pH) by adding 5 ml 2(M) HCl and drug release study was continued upto 12 h in 905 ml of dissolution medium. During the dissolution study, 5 ml aliquot was withdrawn from the dissolution medium at predetermined time and replaced with 5 ml of the respective fresh fluids. The absorbance was measured at 278 nm for acid solution and 319 nm for buffer solutions of pH 7.4 and 6.8. The amount of drug released from the tablet was calculated using calibration curves drawn in the respective medium.

Table 1
Composition of matrix tablets.

Formulation code	Amount of drug (mg)	PCMGG (mg)	CG (mg)	PCMGG:CG ratio	Magnesium stearate (mg)	Hardness (kg/cm^2)
F1	100	400	–	10:0	5	3
F2	100	363.6	36.4	10:1	5	3
F3	100	352.94	47.058	7.5:1	5	3
F4	100	333.5	66.5	5:1	5	3
F5	100	200	200	1:1	5	3
F6	100	100	300	1:3	5	3
F7	100	66.5	333.5	1:5	5	3

2.9. Swelling study

Swelling study of the tablets was conducted in the USP II dissolution rate test apparatus simulating the condition of drug release study. Tablets prepared using different PCMGG/CG ratios were weighed and placed in wire baskets and immersed in liquid. At predetermined time intervals (dissolution sampling points), the tablets were removed from the liquid and weighed in an electronic balance (Precisa XB600M/C, Switzerland) after removing the excess surface water. Percentage swelling of the tablets was determined from the following relationship:

$$\%\ \text{Swelling} = \frac{(W_w - D_t) - (W_i - D_0)}{(W_i - D_0)} \times 100$$

where W_i = initial weight of matrix tablet at time 0, D_0 = amount of drug in matrix tablet at time 0. W_w = weight of matrix tablet at time t after immersion in the dissolution medium, D_t = amount of drug in matrix tablet at time t.

After determining the weight, the hydrated tablets were dried to constant weight at 70 °C in a vacuum oven for 2 days before reweighing to determine the remaining dry weight. The percent erosion was calculated as:

$$\%\ \text{Erosion} = \frac{(W_i - D_0) - (W_d - D_t)}{(W_d - D_0)} \times 100$$

where W_d = dry weight of the matrix tablet at time t after immersion in the dissolution medium.

2.10. Viscosity determination

Various amounts of CG (0–1.53%, w/v) was added in 1.53% w/v PCMGG solution, mixed, and kept for 48 h. The viscosity of the resulting solution was measured at 25 °C in a Rheometer (Anton Parr MCR102, Austria, Europe) using cone and plate apparatus (D-CP/3, diameter 40 mm, gap between cone and plate 0.08 mm).

2.11. Data treatment

2.11.1. Diffusion coefficient of drug

For the determination of diffusion coefficient (D_C) of MTZ from the tablets, equivalent spherical diameter (cm) of the tablets were calculated from the relationship: $d = (6r_c h)^{1/3}$, where d, r_c and h represent equivalent spherical diameter, radius and height of the tablets respectively. The diffusion coefficients (cm^2/s) were determined using Eq. (1) which was used to calculate the diffusion coefficient of drug from spherical matrices (Agnihotri & Aminabhavi, 2006):

$$D_C = \pi \left(\frac{r\theta}{6M_\alpha} \right)^2 \quad (1)$$

where r is the equivalent spherical radius of tablets, θ is the slope of linear portion of M_t/M_α versus $t^{1/2}$ plot, M_t is the amount of drug released at time t and M_α is the total amount of drug loaded.

2.11.2. Swelling and drug release mechanism

The swelling data upto 5 h during which the swelling of the matrix appeared to predominate and the drug release data upto 60% were fitted to Eq. (2) (Korsmeyer, Gurney, Doelker, Buri, & Peppas, 1983).

$$\frac{M_t}{M_\alpha} = Kt^n \quad (2)$$

where M_t/M_α represents the fractional solvent absorbed or drug released at time t, K is a constant incorporating the structural and geometric characteristics of the matrix tablets and n denotes the diffusion exponent indicative of transport mechanism. In case of tablet, $n = 0.45$ indicates Fickian diffusion, $0.45 < n < 0.89$ indicates non-Fickian transport, and $n > 0.89$ is for Case II transport.

2.11.3. Water penetration velocity

The penetration velocity of water in tablet matrix was determined from the % swelling (weight gain) data using Eq. (3) (Katime, Novoa, Dı′az de Apodaca, Mendizábal, & Puig, 1999):

$$V = \frac{1}{2\rho A} \times \frac{dw}{dt} \quad (3)$$

where V denotes penetration velocity, dw/dt represents the slope of % swelling versus time (upto 5 h) curve, ρ is the density of water at 310 K and A denotes surface area of a tablet.

3. Results and discussion

GG which consists of linear chain of (1-4)-β-D-mannopyranosal unit with α-D-galactopyranosal unit attached by (1–6) linkages (Goldstein, Alter, & Seaman, 1973) possesses numerous hydroxyl groups in its structure. The hydroxyl groups can be substituted with carboxymethyl groups by reacting in alkaline medium with chloroacetic acid (Dodi, Hritcu, & Popa, 2011). Since, there is an average of 3 —OH groups per sugar unit (Sullad, Manjeshwar, & Aminabhavi, 2011), the degree of substitution should theoretically be 3. In the present study, however, the degree of substitution was found to be 0.643 ± 0.08. From the work of various researchers, it appears that the degree of carboxymethyl substitution in guar gum, derivatized in either aqueous or non-aqueous medium rarely exceeds 1 (Dodi et al., 2011; Gong et al., 2012; Parvathy, Susheelamma, Tharanathan, & Gaonkar, 2005; Thimma & Tammishetti, 2001). Although, there are a number of —OH groups in GG, carboxymethylation occurs primarily at free CH_2OH groups (i.e. the C_6 position of units) due to steric resistance. The steric hindrance by —OH groups present in the gum is probably responsible for low degree of substitution (Rana et al., 2011). Hence, the resulting carboxymethyl guar gum is designated as partially carboxymethylated guar gum (PCMGG).

The derivatization of GG to PCMGG was ascertained by FTIR study. The FTIR spectra of guar gum and PCMGG are shown in Fig. 1. The FTIR spectrum of GG exhibited a broad absorption band at 3399.03 cm^{-1} due to —OH stretching vibration. A sharp absorption band at 2924 cm^{-1} was assigned to —CH_2 symmetrical stretching vibration. The absorption band appearing at 1651 cm^{-1} was due to

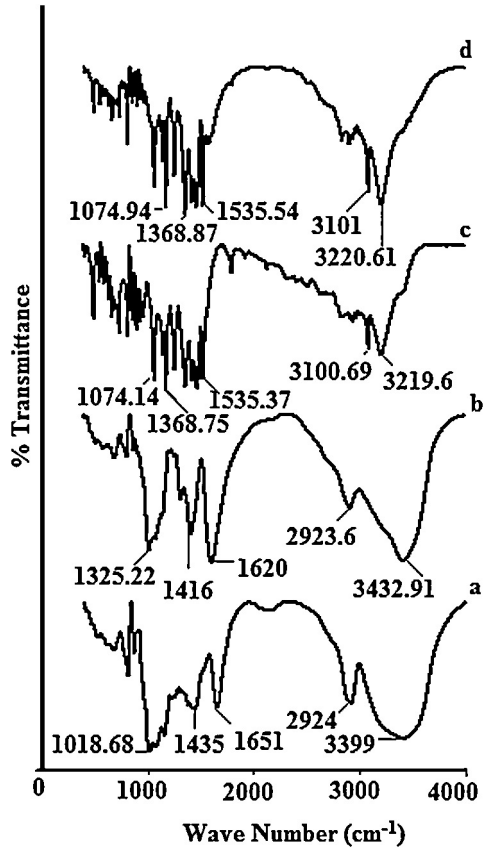

Fig. 1. FTIR spectra of (a) GG, (b) PCMGG, (c) MNZ, and (d) MNZ loaded matrix tablet.

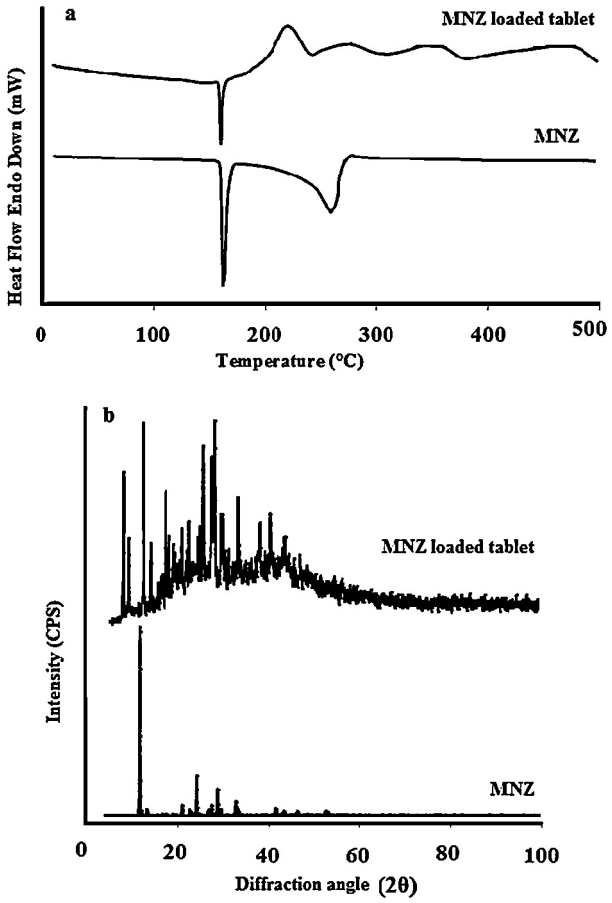

Fig. 2. DSC thermograms (a) and XRD patterns (b) of MNZ and MNZ loaded matrix tablet.

OH bond belonging to water molecules. The CH_2 bending in GG was assigned to an absorption at 1435 cm^{-1} and the bending of C—O—C appeared at 1018.68 cm^{-1} frequency region. The absorption band due to —OH stretching vibration in PCMGG shifted to 3432 cm^{-1} and its intensity appeared to be reduced. This means that some of the —OH groups of GG were involved in carboxymethylation. The band assigned to water (bending of water) which appeared at 1651 cm^{-1} in GG was absent in PCMGG. In addition, three new peaks due to carboxymethyl moiety emerged in the spectrum of PCMGG. A peak at 1620 cm^{-1} was due to asymmetric stretching vibration and peaks at 1416 and 1325.22 cm^{-1} were concerned with the symmetrical stretching vibration of carboxylate ion in PCMGG.

Physical characteristics of the tablets were well within the acceptable limits. The variation in weight and drug content of the tablets was confined within ±5% of the average values. The friability varied from 0.11 to 0.48 with maximum standard deviation (MSD) 0.12. The thickness of the tablets varied within 5.11–5.71 mm with MSD 0.14. Although, preformulation studies revealed an increase in hardness of the tablets with decrease in PCMGG/CG ratios, the hardness of the tablets was kept constant at 3 kg/cm^2 to eliminate the effect of hardness and porosity on drug release.

The compatibility of the drug in matrix tablet was assessed through FTIR, DSC and XRD analyses.

Absorption bands at 3223, 3100, 1535, 1370 and 1076 cm^{-1} have been assigned as the fingerprint of MNZ (Ramukutty & Ramachandran, 2012). FTIR spectrum of MNZ showed characteristic bands for stretching of OH, CH and C=CH, NO, NO_2 (symmetrical) and C—O respectively at 3219.6, 3100.6, 1535.37, 1368.75 and 1074.74 cm^{-1}. The spectrum obtained from the powdered tablet showed the presence of all the characteristic bands of the drug almost at the same wave numbers (Fig. 1). The DSC curve of MNZ showed a sharp endothermic peak at 160 °C for its melting. A broad peak extending from about 180° to 260 °C indicates complete evaporation/decomposition of the drug (Kiss, Zelkó, Novák, & Éhen, 2006). The endothermic peak for melting of the drug in the tablet was also found at 160 °C (Fig. 2). However, the broad endothermic peak (180–260 °C) was not visible. Probably due to the presence of excipients (PCMGG and CG), the surface area available for evaporation/decomposition of MNZ increased and the endotherm broadened significantly and shifted to lower temperature (Kiss et al., 2006). In addition, an exothermic peak at about 205 °C due to mass loss of CG was noticed in the DSC curve of drug loaded tablet. Similar observation was found in case of diltiazem-loaded alginate-CG matrix tablet (Mandal, Basu, & Sa, 2009). XRD trace of MNZ showed reflection at 12°, 21°, 24°, 27°, 29°, 33°, 43° and 53° 2θ. Drug-loaded tablet showed reflection at 8°, 12°, 21°, 24°, 27°, 29°, 33°, 43° and 53° 2θ (Fig. 2). The results demonstrated that the characteristic peaks of the drug appeared at the same 2θ values in the XRD chart of drug-loaded tablet, although the intensity of the peaks was considerably less due to dilution of the drug with the tablet excipients. It indicates that no solid state transformation of the drug took place in the tablet. The results confirmed the physical stability of the drug in the matrix.

The results of MNZ release from matrix tablets prepared with only PCMGG or PCMGG/CG in different ratios are shown in Fig. 3. The release of the drug from tablet F1, which was prepared with only PCMGG, was slow liberating 26.56% of the loaded drug in acid solution in 2 h. Change of pH of the dissolution medium to 7.4 and thereafter to 6.8 did not produce any abrupt increase in drug release. Instead, F1 tablet released 40.53% and 85.75% drug respectively in 5 h and 12 h in a gradual manner.

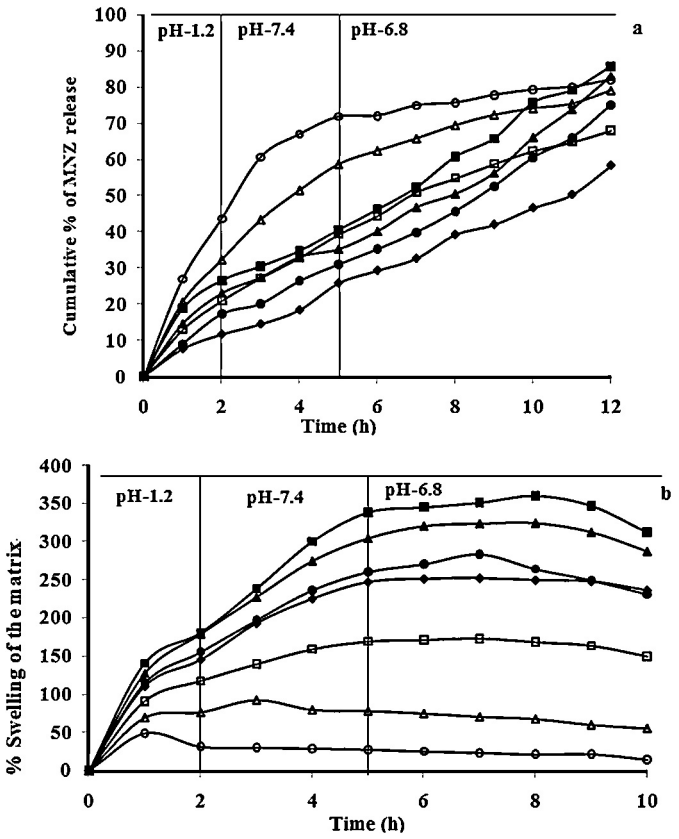

Fig. 3. Release of MNZ from various matrix tablets (a) and dynamic swelling profiles of different matrix tablets (b) in acid solution at pH 1.2 for 2 h followed by in buffer solution (pH 7.4 and pH 6.8). Key: PCMGG/CG: 10:0 (F1, ■), 10:1 (F2, ▲), 7.5:1 (F3, ●), 5:1 (F4, ♦), 1:1 (F5, □), 1:3 (F6, △), 1:5 (F7, ○). Maximum SD = ±6.07, $n = 4$.

Table 2
Area under the curve (AUC) calculated from release profiles and diffusion coefficient of drug from various tablets.

Formulation code	AUC (% h^{-1})	Diffusion coefficient (cm^2/s)
F1	82.48	2.24×10^{-07}
F2	78.53	1.97×10^{-07}
F3	70.69	1.71×10^{-07}
F4	54.37	1.24×10^{-07}
F5	66.45	2.05×10^{-07}
F6	77.20	3.23×10^{-07}
F7	81.18	3.74×10^{-07}

Addition of CG in the tablet matrix altered the drug release rate considerably in different ways. Increase in the amount of CG as in tablets F2 (PCMGG:CG = 10:1), F3 (PCMGG:CG = 7.5:1), and F4 (PCMGG:CG = 5:1) decreased the drug release rate. Tablet F4 exhibited the slowest release profile liberating 11.69%, 25.86% and 58.39% drug respectively in 2 h, 5 h and 12 h. However, further increase in the amount of CG as in tablets F5 (PCMGG:CG = 1:1), F6 (PCMGG:CG = 1:3) and F7 (PCMGG:CG = 1:5) increased the drug release rate. Tablet F7 produced the fastest release liberating 43.65%, 71.92% and 82.20% drug in 2 h, 5 h and 12 h respectively. Comparison of the area under the curves (AUCs) of the cumulative % drug release versus time profiles, calculated using trapezoidal rule, showed that AUC decreased from tablets F1–F4 and then increased from tablets F5–F7 (Table 2).

In contact with water, a hydrophilic polymer matrix swells due to stress induced by the ingressed water and forms a viscous aqueous layer (weak mechanical gel) of the polymer around its surface due to simple entanglement of the polymer chains. The viscous

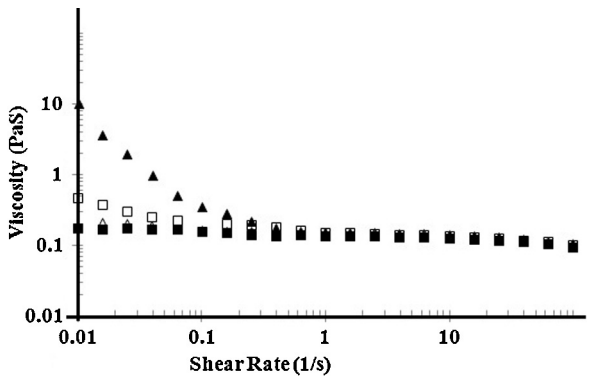

Fig. 4. Viscosity profiles of PCMGG containing different amount of CG. Key: PCMGG/CG: 10:0, (■); PCMGG/CG: 10:1, (□); PCMGG/CG: 2.5:1, (▲); PCMGG/CG: 1:1, (△).

layer becomes diluted with time and the polymer dissolves away or erodes from the surface promoting further penetration of water to hydrate the preceding layer of tablet surface. Simultaneously, the drug molecules present in the swollen matrix dissolve and diffuse out into the surrounding aqueous environment (Collett & Moreton, 2002). The diffusion of drug depends on the viscosity of the swollen region that in turn depends on the amount of polymer in the matrix (Mughal et al., 2011). Since, F1 tablet was made up of around 80% PCMGG, a highly viscous layer of polymer solution having considerable mechanical strength was formed around the tablet surface that acted as a barrier to diffusion of drug. Incorporation of CG in the tablet matrices (F2–F7) resulted in the formation of Ca^{2+} ions due to dissolution of CG in water during the wet massing step of tablet preparation and dissolution study. The liberated Ca^{2+} ions reacted with the carboxyl groups of PCMGG and crosslinked the polymer chains. Crosslink restrict the mobility of the polymer chains and result in the formation of a true gel layer in contact with water around the tablet surface (Collett & Moreton, 2002). Increase in the amount of crosslinking agent increases the crosslink density inducing higher gel strength (Maestrelli, Cirri, Corti, Mennini, & Mura, 2008) and lower macromolecular mesh size (Kim & Lee, 1992). As a result diffusion and hence, release of the drug through the gel layer decreased. The diffusion coefficient of the drug from various tablet matrices through the viscous polymer solution or gel layer was determined based on Fickian diffusion model using Eq. (1). The results (Table 2) demonstrated that an increase in the amount of CG upto a certain level decreased the diffusion coefficient of the drug and further increase in the amount of CG increased the diffusion coefficient. Since diffusion coefficient of drug is inversely related to viscosity, it appeared that addition of CG might have altered the viscosity of gel layer. Determination of viscosity of PCMGG solution containing various amounts of CG simulating the composition of tablets revealed that viscosity gradually increased with the addition of CG and at higher level of CG, the viscosity of PCMGG solution decreased (Fig. 4). Thus, addition of Ca^{2+} ion as crosslinking agent increased the mechanical strength of the gel layer by increasing its viscosity and reduced the diffusion and release of the drug. However, at higher content of Ca^{2+} ion, the mechanical strength of the gel layer weakened due to fall in viscosity and this produced faster diffusion and release of the drug. It has been reported that increase in calcium content decreased the drug release from Ca^{2+} ions crosslinked pectin and alginate matrix tablets and beyond a critical concentration of Ca^{2+} ions, drug release increased due to either weakening of the gel strength of the polymer caused by excessive crosslinking by Ca^{2+} ions resulting in a non-homogenous pectin matrix (Ashford, Fell, Attwood, Sharma, & Woodhead, 1994; Sungthongjeen, Sriamornsak, Pitaksuteepong, Somsiri, & Puttipipatkhachorn, 2004) or channeling effect of Ca^{2+}

Table 3
Swelling parameters (exponent n_s and kinetic constant k_s), swelling rate (obtained from dynamic swelling study) and water penetration velocity in tablet matrix.

Formulation code	Swelling exponent (n_s)	Swelling kinetic constant (k_s) (h^{-1})	Correlation coefficient (r)	Swelling rate (%/$\sqrt{h}$)	Correlation coefficient (r)	Water penetration velocity (cm/s)
F1	0.560	2.124	0.974	165.70	0.977	0.0023
F2	0.549	2.099	0.997	146.40	0.996	0.0020
F3	0.519	2.051	0.994	121.10	0.994	0.0017
F4	0.516	2.032	0.998	114.90	0.990	0.0016
F5	0.391	1.958	0.997	64.66	0.996	0.0009

Table 4
Swelling rates of tablets in acid solution and buffer solution.

Formulation code	Swelling rate in acid solution (%/$\sqrt{h}$)	Correlation coefficient (r)	Swelling rate in buffer solution (%/$\sqrt{h}$)	Correlation coefficient (r)
F1	152.20	0.961	227.90	0.994
F4	111.70	0.997	186.10	0.998
F5	67.67	0.990	128.80	0.985
F7	27.35	0.506	93.81	0.998

ions present in excess to that required for crosslinking of alginate (Mandal et al., 2009).

The dynamic swelling profiles of various tablets are shown in Fig. 3. F1 tablet swelled 172% in acid solution in 2 h. Subsequent increase in pH to 7.4 increased swelling to 300% in 5 h. Equilibrium swelling reached within 6–7 h after which mass loss of the tablet was evident. Since 63.43% mass loss of tablet F1 was recorded after 10 h, it is reasonable to assume that swelling was accompanied with erosion due to relaxation of the polymer at the gel surface.

Swelling of tablets containing CG was less than that of the uncrosslinked PCMGG tablet. Increase in the amount of CG decreased the swelling and erosion of the tablets. Tablet F4 containing PCMGG/CG in a ratio of 5:1 showed the lowest erosion of 52.25% at 10 h. It has been stated that Ca^{2+} ions may restrict the erosion of calcium–pectin matrix tablet (Wei, Sun, Wu, Yin, & Wu, 2006). However, at higher level of CG, erosion tended to increase and the swelling of the matrix decreased considerably. While tablet F6 swelled a maximum of 92.84% and started eroding after 3 h, tablet F7 swelled a maximum of only 48.87% and began to erode after 1 h. At the end of 10 h of swelling study, the % of erosion changed in the following order: F1 (63.40%) > F2 (62.78%) > F3 (60.01%) > F4 (53.25%) < F5 (65.13%) < F6 (75.32%) < F7 (79.24%). The swelling profiles indicated that swelling dominated over erosion during the initial period; after 5 h, a synchronization phase between swelling and erosion was evident; and finally perceptible erosion started.

Swelling of hydrophilic polymer matrices generally follows Fickian diffusion. Since the swelling of the tablets F6 and F7 was exceedingly low, the dynamic swelling data of tablets F1–F5 upto 5 h, during which swelling predominated over erosion, were fitted in Eq. (2). The values of n_s indicated that swelling almost followed Fickian diffusion. The values of n_s and slope of the % swelling versus $t^{1/2}$ plots tended to decrease as the amount of CG in the tablets was increased (Table 3). Decrease in swelling of the tablets was the result of decrease in the penetration rate of water into the matrices through the viscous polymeric layer or gel layer. Water penetration rate into the matrices was determined using Eq. (3). It was found that increase in the amount of CG in the tablets decreased the rate of penetration of water (Table 3).

Scrutiny of the release profiles indicated that the amount of MNZ released in acid solution was more than the actual amount released in dissolution medium of higher pH. The COOH groups of PCMGG or the COOH groups of the crosslinked polymer, formed by decrosslinking through extraction of Ca^{2+} ion by the Cl^- ions of acid solution, remain unionized in acid solution and do not induce charge repulsion to increase the gel porosity and swelling of matrix. On the other hand, considerable charge repulsion between the ionized COO^- groups formed in solution of higher pH increases gel porosity and swelling (Bajpai, Saxena, & Sharma, 2006). Hence, the release of a drug from ionically crosslinked matrix should be expected to be less in a solution of low pH. The swelling study of the tablets was also performed separately in acid solution (pH 1.2) and buffer solution (pH 7.4) upto 4 h. The slope of % swelling versus $\sqrt{}$time plot (Table 4) indicated that rate of swelling of the tablets in acid solution was less than that in buffer solution. Hence, the release of the drug should be expected to be less in acid solution than in buffer solution. Higher MNZ release in acid solution could be related to its pH-dependent solubility. The solubility of MNZ is higher (64.8 mg/ml) in acid solution (pH 1.2) than that (10 mg/ml) at pH values between 2.5 and 8.0 at 20 °C (Wu & Fassihi, 2005). It might be possible that certain amount of the drug dissolved from the tablet surface before the formation of gel layer. An initial burst release of water soluble drugs from hydrophilic matrix tablets is not unexpected. (Varshosaz, Tavakoli, & Kheirolahi, 2006).

To understand the mechanism of drug release, the release data upto 60% of MNZ release from various tablets were fitted in Eq. (2). The results (Table 5) can be summarized as follows:

Table 5
Release parameters (exponent n_r and kinetic constant k_r) and zero order release rate of MNZ from tablets.

Formulation code	Release exponent (n_r)	Kinetic constant (k_r)	Correlation coefficient (r)	Zero order release rate constant (%/h)	Correlation coefficient (r)
F1	0.538	1.252	0.973	6.115	0.993
F2	0.590	1.164	0.991	5.774	0.979
F3	0.784	0.958	0.989	5.701	0.989
F4	0.836	0.822	0.983	4.517	0.994
F5	0.692	1.109	0.999	5.002	0.979
F6	0.633	1.320	0.995	8.458	0.971
F7	0.733	1.427	0.998	16.850	0.999

The mechanism of drug release from uncrosslinked and Ca^{2+}-crosslinked PCMGG tablets (F1–F7) was non-Fickian or anomalous as the release exponent (n_r) varied within 0.538–0.836. As the degree of crosslink increased the kinetic constant (k_r) decreased (Tablets F1–F4) and further increase in the amount of calcium content increased the kinetic constant.

It is however, to be noted that the power law expression was developed for uncrosslinked swellable polymer matrix. In order to avoid misinterpretation, the release data were fitted in different kinetic models such as zero order, 1st order, Higuchi and Hixon Crowell equations. As some amount of drug was released from the tablet surface before the matrix swelled and resulted in a burst release, the release data from 1 h to 60% drug release was used to characterize the mechanism of release. It was found that the release could be best explained by zero order kinetic ($r = 0.971–0.999$) (Table 5). The rate of drug release decreased with increase in the degree of crosslinking and beyond a certain concentration the rate of release increased.

4. Conclusion

This study revealed that in situ crosslinking of PCMGG by Ca^{2+} ion changed the viscosity of the gel layer formed around the tablet surface on hydration that influenced water penetration into the matrix inducing considerable change in swelling and erosion of the matrix and consequently in drug release. Thus, variation in calcium content may provide flexibility in achieving desired drug release rate from ionically crosslinked PCMGG tablet. However, another aspect of this work to provide complete release of MNZ in colon while preventing premature release in upper gastrointestinal tract could not be achieved.

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