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Research Article

Development and Evaluation of Ca^{+2} Ion Cross-Linked Carboxymethyl Xanthan Gum Tablet Prepared by Wet Granulation Technique

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Abstract. The objective of this work was to study the release behavior of prednisolone from calcium-cross-linked carboxymethyl xanthan gum (CMXG) tablets in dissolution medium having different pH values prevailing in the gastrointestinal lumen. Xanthan gum (XG) was derivatized to CMXG which was then cross-linked *in situ* with Ca^{+2} ion during wet massing step of tablet preparation. Fourier transform infrared (FTIR) spectroscopy and differential scanning calorimetry studies did not show any drug-polymer interaction although the drug underwent solid-state transformation during compression as evident from X-ray diffraction analysis. *In vitro* release study demonstrated that increase in the amount of Ca^{+2} ion decreased the drug release, and beyond a certain amount, the drug release increased. While increase in both drug load and tablet crushing strength decreased the drug release, increase in exposure time in acid solution of pH 1.2 increased the overall release of the drug. The mechanism of drug release was non-Fickian/anomalous. The results indicated that variation in the amount of Ca^{+2} ion can modulate the drug release from CMXG matrix tablets as needed.

KEY WORDS: carboxymethyl xanthan gum; drug release; *in situ* cross-linking.

INTRODUCTION

In recent years, natural polysaccharides have evoked tremendous interest in the design of modified release drug delivery systems due to their nontoxicity, low cost, availability, biosafety, and biodegradability (1). In addition, because of their wide range of molecular weight, varying chemical composition, and large number of derivable groups on molecular chains, polysaccharides easily lend themselves for various chemical modifications (2). Modification of native polysaccharides, achieved through chemical derivatization (e.g., carboxymethylation, grafting, etc.), chemical cross-linking (with glutaraldehyde, epichlorhydrin), and ionic cross-linking (with Ca^{+2}, Ba^{+2}, Al^{+3} ions), offers many new functional properties to meet their needs in design of drug delivery system (3). Several polysaccharides such as alginate (4, 5), guar gum (6, 7), katira gum (8), tamarind gum (9), and pectin (10, 11) have been derivatized and/or cross-linked to have tailor-made products of various types for drug delivery devices.

Xanthan gum (XG) is an extracellular heteropolysaccharide produced by fermentation of gram-negative bacterium *Xanthomonas campestris*. Most of the investigations related to XG, either alone or in combination with other polymers, involved design of sustained-release matrix tablets (12–15). However, there is no report on release pattern of a drug from derivatized and cross-linked XG matrix.

In the present investigation, XG was derivatized to carboxymethyl xanthan gum (CMXG), cross-linked with Ca^{+2} ion and converted into tablet by wet granulation method. This method provides a greater possibility of more effective and different degrees of cross-linking between CMXG and metal ion.

The objective of this study was to evaluate the effect of the amount of Ca^{+2} ion on release behavior of prednisolone from the tablets. Another aspect of this study was to evaluate whether the cross-linked CMXG tablets could prevent or minimize premature release in the upper gastrointestinal tract and provide release of major amount of the drug in 10 h during which the tablets might reach the colon. The effect of other variables such as tablet crushing strength, drug load, and pretreatment time in acid solution was also investigated. Prednisolone (PDL) has been used as a model drug in this study.

MATERIALS AND METHODS

Materials

Prednisolone (PDL) was obtained as gift sample from Mepro Pharmaceuticals Pvt. Ltd., Mumbai, India. Xanthan gum (SD Fine Chem, Mumbai, India), monochloro acetic acid and calcium chloride dihydrate ($CaCl_2$) (Merck Specialities Pvt. Ltd., Mumbai, India), and all other chemicals of analytical grade were obtained commercially. Double-distilled water was used throughout the study.

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Preparation of Tablets

Required amount of CMXG, which was derivatized from XG following the method reported earlier (16), and PDL (passed through #60 mesh BS screen) were manually blended and converted into a damp, cohesive mass with required amount of $CaCl_2$ solution. The cohesive mass was passed through #18 mesh BS screen. The resulting granules were dried in a tray dryer 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 5.5-mm punch in a 10 station rotary minipress tablet machine (RIMEK, Karnavati Engineering Ltd., Gujarat, India). The tablets were prepared using different CMXG/$CaCl_2$ ratio, crushing strength (3.5–5.5 kg/cm^2), and drug load (5–20 mg). Fifty tablets of each formulation were prepared in duplicate. The composition of the tablets is shown in Table I.

Physical Characteristics of Tablets

Weight Variation Test

Twenty tablets were weighed individually in an electronic pan balance (XB 600 M-C, Precisa, Switzerland). The weight of each tablet was compared with the average weight of the tablets.

Crushing Strength of Tablets

Crushing strength of the tablets was determined using Monsanto type Tablet Hardness Tester (Campbell Electronics, Mumbai, India), and average value of 10 determinations was reported.

Thickness of Tablets

The thickness of each tablet was measured with a Digimatic Caliper (CD-6"CS, Mitutoyo Corporation, Japan), and average of 10 determinations was calculated.

Friability Test

Ten tablets were weighed and placed in the plastic drum of a Friabilator (EF2, Electro Lab, Mumbai, India). After 100 revolutions, the tablets were dedusted with a soft brass and reweighed. The percentage of weight loss was calculated.

PDL Content in Tablets

A tablet was crushed in a glass mortar and transferred quantitatively with methanol in a stoppered conical flask. The flask was shaken in a mechanical shaker for 4 h. The mixture was filtered and an aliquot, following suitable dilution, was analyzed at 243 nm using Microplate Spectrophotometer (Multiskan GO, Thermo Scientific, USA). The drug content was determined using a calibration curve constructed in methanol. Drug content of each of the 10 tablets was compared with the average drug content of the tablets.

Fourier Transform Infrared Analysis

Fourier transform infrared (FTIR) spectra of CMXG, PDL, physical mixture, and PDL-loaded tablet were recorded in a FTIR spectrophotometer (Perkin Elmer, RX-1, UK). The samples were mixed with KBr and converted into pellets at 6-ton pressure using a hydraulic press. The spectra were taken in the wave number region of 4,000–400 cm^{-1}.

Differential Scanning Calorimetry Study

Differential scanning calorimetry (DSC) thermograms of CMXG, PDL, physical mixture, and PDL-loaded tablet were

Table I. Composition of Matrix Tablets

Formulation code	Amount of drug (mg)	CMXG (mg)	$CaCl_2$ (mg)	CMXG/$CaCl_2$ ratio	Magnesium stearate (mg)	Crushing strength (kg/cm^2)
Effect of CMXG/$CaCl_2$ ratio						
FX1	10	100	00	1:0	1	5
FX2	10	83.3	16.7	5:1	1	5
FX3	10	66.7	33.3	2:1	1	5
FX4	10	60	40	1.5:1	1	5
FX5	10	50	50	1:1	1	5
Effect of crushing strength						
FX6	10	60	40	1.5:1	1	3.5
FX7	10	60	40	1.5:1	1	4.5
FX8	10	60	40	1.5:1	1	5.5
FX9	10	75	25	3:1	1	3.5
FX10	10	75	25	3:1	1	4.5
FX11	10	75	25	3:1	1	5.5
Effect of drug load						
FX12	5	60	40	1.5:1	1	5
FX4	10	60	40	1.5:1	1	5
FX13	20	60	40	1.5:1	1	5

CMXG carboxymethyl xanthan gum

obtained using Perkin Elmer (Pyris Diamond TG/DTA, Singapore) differential scanning calorimeter which was calibrated against indium. Weighed amount (5.86 to 9.88 mg) of a sample was kept in a hermetically sealed aluminum pan and heated at a scan speed of 10°C/min over a temperature range of 30–300°C under a constant nitrogen flow at 150 ml/min.

X-Ray Diffraction Study

The qualitative X-ray diffraction studies of CMXG, PDL, physical mixture, and PDL-loaded tablet were performed using an X-ray diffractometer (ULTIMA-III, Rigaku, Japan). The powdered samples were scanned from 5–80° diffraction angle (2θ) range under the following measurement conditions: source; Ni-filtered Cu-Kα radiation (λ=1.54 Å); voltage 45 kv; current 30 mA; and scan speed 5°/min.

In Vitro Drug Release Study

In vitro drug release study was carried out in USP-II tablet dissolution rate test apparatus (TDP-06P, Electro Lab, Mumbai, India) at 37±0.5°C and 100 rpm speed under sink condition following the method described in Indian Pharmacopoeia 2010 (17) 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) trisodium 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 up to 10 h in 905 ml of dissolution medium. During the dissolution study, a 5 ml aliquot was withdrawn from the dissolution medium at predetermined time and replaced with 5 ml of the fresh respective fluid warmed at 37°C. The aliquots were filtered through Whatman (No. 1) filter paper. The absorbance was measured at 248 nm for both acid solution and buffer solutions of pH 7.4 and 6.8 using Microplate Spectrophotometer (Multiskan GO, Thermo Scientific, USA). The amount of drug released from the tablet was determined using calibration curves drawn in the respective medium.

Statistical Analysis

Each formulation was prepared in duplicate, and each analysis was duplicated. The effect of variation in CMXG/$CaCl_2$ ratio on drug release was analyzed by analysis of variance (ANOVA, single factor) with the aid of GraphPad Prism (Version 3.0). Difference was considered significant when $p<0.001$.

Data Treatment

Diffusion Coefficient of Drug

For the determination of diffusion coefficient (D_c) of PDL from the tablets, equivalent spherical diameter (cm) of the tablets was calculated from the relationship: $d=(6r_ch)^{1/3}$, where d, r_c, and h represent equivalent spherical diameter, radius, and height (cm) 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 (18):

$$D_c = \pi(r\theta/6M_\alpha)^2 \quad (1)$$

where r is the equivalent spherical radius of tablet, 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 (s), and M_α is the total amount of drug loaded.

Drug Release Mechanism

The release data up to 60% of drug release were fitted to power law Eq. (2) (19).

$$M_t/M_\alpha = kt^n \quad (2)$$

where M_t/M_α represents the drug released at time t, k is a constant incorporating the structural and geometric characteristics of the matrix tablets, and n denotes the diffusional exponent indicative of transport mechanism. In case of tablet, n=0.45 indicates Fickian diffusion, $0.45<n<0.89$ indicates non-Fickian/anomalous transport, n=0.89 is for case II transport, and $n>0.89$ indicates super case II transport (20, 21).

Mean Dissolution Time

The mean dissolution time in minute (MDT) was calculated from Eq. (3) (22) using the values n and k obtained from Eq. (2).

$$\mathrm{MDT} = (n/n+1)\, k^{-1/n} \quad (3)$$

RESULTS AND DISCUSSION

Physical Characteristics of Tablet

Weight variation test revealed that weight of none of the 20 tablets deviated by more than ±7.5% of the average weight (17).

The friability of the tablets was less than 1% and within the pharmacopoeial limit (17). However, the friability of the tablets FX6 and FX9 having lower crushing strength of 3.5 kg/cm^2 was 1.04 and 1.12%, respectively.

Thickness of the tablets did not vary by more than ±5% of the average thickness (3.56 mm).

PDL Content in Tablets

PDL content of each of the 10 tablets was within 85 to 115% of the average drug content.

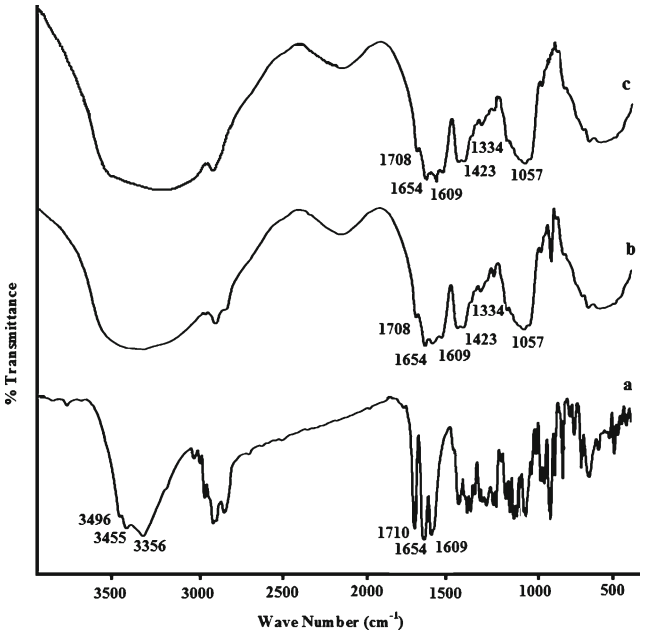

Fig. 1. FTIR spectra of (*a*) PDL, (*b*) physical mixture, and (*c*) PDL-loaded tablet

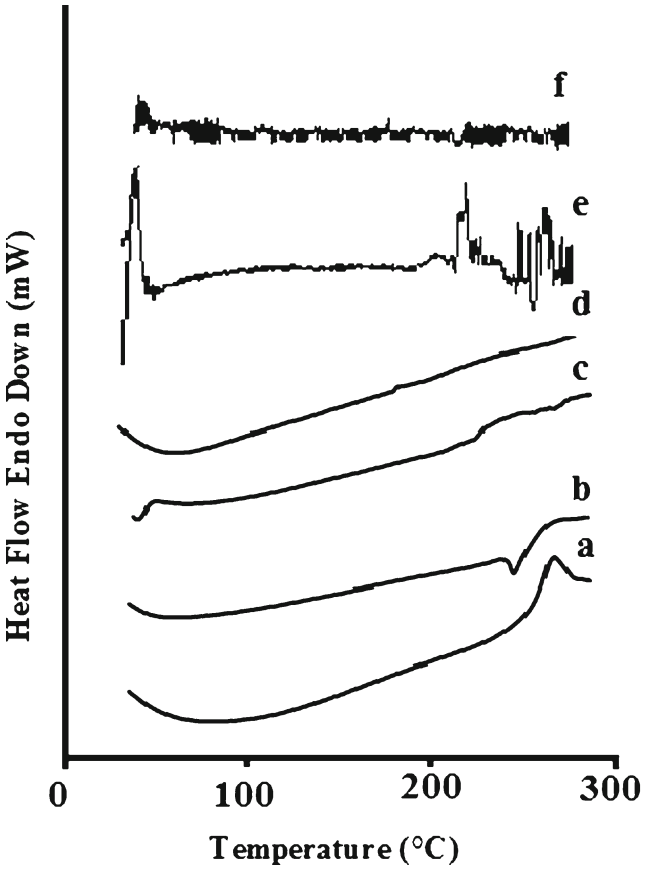

Fig. 2. DSC thermograms of (*a*) CMXG, (*b*) PDL, (*c*) physical mixture, (*d*) PDL-loaded tablet, (*e*) derivative DSC of physical mixture, and (*f*) derivative DSC of PDL-loaded tablet

Drug-Excipients Compatibility Study

Chemically, prednisolone is trihydroxy pregna-1,4-diene-3,20-dione. FTIR spectrum of the drug is shown in Fig. 1(a). Peaks at 3,496, 3,455 and 3,356 cm^{-1} for three –OH groups, 1,609 cm^{-1} for diene, and 1,654 and 1,710 cm^{-1} for 3,20-dione were considered for identification of the drug. FTIR spectrum of physical mixture of PDL, CMXG, and $CaCl_2$ is shown in Fig. 1(b). A broad shallow peak extending from about 3,100–3,600 cm^{-1} was considered for –OH groups; peaks at 1,609, 1,423, 1,334 and 1,057 cm^{-1} were respectively for C=O group of pyruvate, symmetric COO^- group of glucuronic acid, –CO– stretching of O-carboxymethyl group, and –C-O-C– stretching of acetal group of CMXG. FTIR spectrum of PDL-loaded matrix tablet (Fig. 1(c)) showed that the peaks at 3,496, 3,455 and 3,356 cm^{-1} for –OH groups of the drug overlapped with the broad shallow peak extending from 3,100–3,600 cm^{-1} of CMXG. The peaks for dione of the drug appeared at 1,654 and 1,708 cm^{-1}; the peak for diene at 1,609 cm^{-1} appeared to overlap with C=O stretching of pyruvate of CMXG. The spectrum of the tablet also showed the presence of peaks for –CO– stretching of O-carboxymethyl and –C-O-C– stretching of acetal groups of CMXG. FTIR study indicated the presence of characteristic bands of the drug in the tablet almost at the same wave numbers.

The DSC thermograms of CMXG, PDL, physical mixture, and drug-loaded tablet are shown in Fig. 2. Prednisolone exhibited a sharp melting endotherm at 244°C. CMXG showed an initial broad endotherm between 70 and 80°C due to loss of moisture present in CMXG. An exothermic peak due to decomposition of CMXG was obtained at around 280–282°C. However, the melting endotherm of the drug could not be clearly detected in either physical mixture or tablet. Although derivative DSC of the thermogram of the physical mixture showed the endothermic peak of the drug at 244°C, no endothermic melting peak of the drug was evident even after derivative DSC of the thermogram of the tablet. This indicates possible solid-state transformation of the drug during tableting.

The X-ray diffractograms of CMXG, PDL, physical mixture, and drug-loaded tablet are shown in Fig. 3. Five reflections to the interplanner distances of 5.76, 5.65, 5.50, 5.14, and 5.07 Å, respectively, at 15.36, 15.68, 16.10, 17.22, and 17.48 2θ were taken into account for assessing solid-state transformation of the drug in tablet. Physical mixture showed reflection to the interplanner distances of 5.73, 5.62, 5.47, 5.13, and 5.05 Å, respectively, at 15.44, 15.76, 16.18, 17.28, and 17.56 2θ with however reduced intensity due to dilution of drug with polymer. Drug-loaded tablet did not show any characteristic peaks of the drug. This demonstrated that the crystalline nature of the drug was retained in the physical mixture but lost in the tablet. It is inferred from the above results that crystalline PDL was converted into amorphous form during compression.

Drug Release

The results of PDL release from matrix tablets prepared with only CMXG or CMXG/$CaCl_2$ in different ratios are shown in Fig. 4. The release of the drug from tablet FX1, which was prepared with only CMXG, was slow liberating 13.26±0.68% of the loaded drug in acid solution in 2 h, and

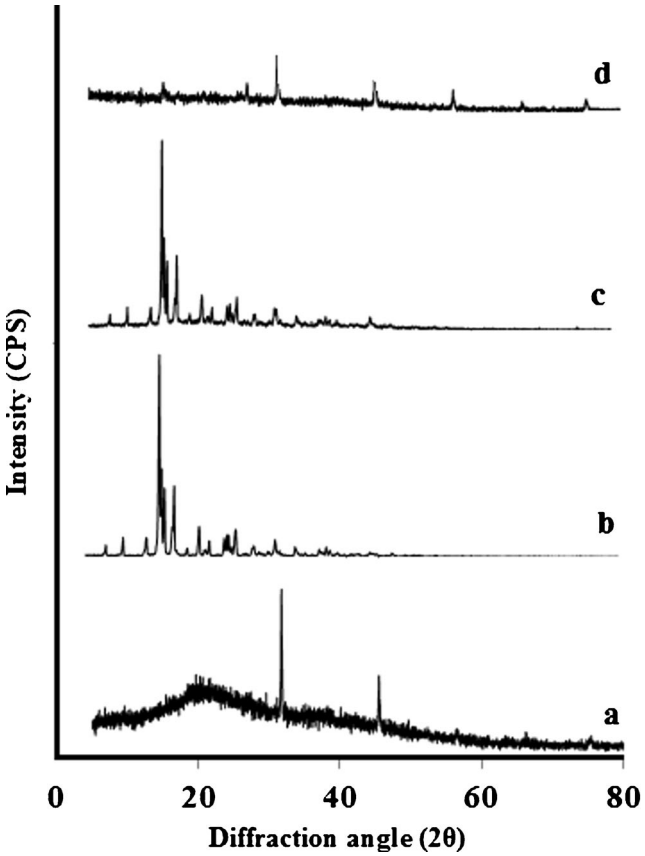

Fig. 3. XRD patterns of (*a*) CMXG, (*b*) PDL, (*c*) physical mixture, and (*d*) PDL-loaded tablet

no initial burst effect was observed. Change in pH of the dissolution medium to 7.4 and thereafter to 6.8 did not produce any abrupt increase in drug release. Instead, FX1 tablet released 25.22±1.77 and 50.84±0.98% drug, respectively, in 5 and 10 h in a gradual manner. Addition of $CaCl_2$ in the tablet matrix altered the drug release considerably in a different way. Increase in the amount of $CaCl_2$ as in tablets FX2 (CMXG/$CaCl_2$=5:1), FX3 (CMXG/$CaCl_2$=2:1), and FX4 (CMXG/$CaCl_2$=1.5:1) decreased the drug release. Tablet FX4 produced the slowest release liberating 05.27±0.10, 11.86±0.37, and 20.06±0.43% drug, respectively, in 2, 5, and 10 h. However, further increase in the amount of $CaCl_2$ as in tablets FX5 (PCMGG/$CaCl_2$=1:1) increased the drug release. Addition of $CaCl_2$ beyond the above amount made wet granulation very difficult. Tablet FX5 produced the fastest release liberating 11.51±0.26, 31.90±0.57, and 84.94±0.66% drug in 2, 5, and 10 h, respectively. To further ascertain the variation in drug release due to addition of $CaCl_2$ in the matrix, MDT was calculated using Eq. (3). Table II shows that MDT increased significantly ($p<0.001$) with increase in the amount of $CaCl_2$, and after a certain amount of $CaCl_2$, MDT decreased.

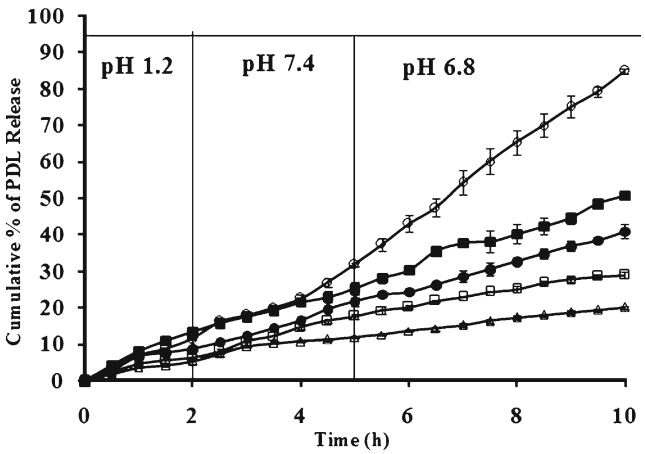

Fig. 4. PDL release from matrix tablets in acidic solution of pH 1.2 for 2 h followed by in buffer solution (pH 7.4 and 6.8). CMXG/$CaCl_2$ 10:0 (FX1, *black square*), 5:1 (FX2, *black circle*), 2:1 (FX3, *white square*), 1.5:1 (FX4, *white triangle*), 1:1 (FX5, *white circle*); n=4, maximum SD=± 3.60

Table II. Mean Dissolution Time and Diffusion Coefficient of Drug Calculated from the Release Profile of Various Tablets

Formulation code	MDT (min) (mean±SD, n=4)	Diffusion coefficient (cm^2/s) (mean±SD, n=4)
FX1	31.45 (0.42)	6.5×10^{-06} (4.41×10^{-07})
FX2	40.64 (1.74)	4.44×10^{-06} (7.55×10^{-08})
FX3	48.18 (1.78)	2.56×10^{-06} (1.17×10^{-07})
FX4	59.45 (0.44)	1.03×10^{-06} (5.41×10^{-08})
FX5	39.21 (0.66)	2.18×10^{-05} (1.59×10^{-06})

MDT mean dissolution time, *SD* standard deviation

When a tablet of CMXG is brought in contact with water, the carboxylic groups introduced on the backbone of the polymer as well as the existing carboxylic group on the trisaccharide side chain ionize, repel each other and leads to uncoiling of the double-helix structure of xanthan molecules exposing many hydrophilic groups in water and inducing hydrogen bond formation. Such interaction leads to the formation of viscous polymer solution around the tablet surface (23, 24). Release of drug from a hydrophilic matrix tablet depends on the viscosity of the swollen region that in turn is a function of the amount of polymer in the matrix (15). Since FX1 tablet was composed of 90% CMXG, a highly viscous polymer solution having considerable mechanical strength was formed around the tablet surface that acted as a barrier to diffusion of drug. Rapid formation of viscous polymer solution around the tablet surface and poor aqueous solubility of PDL were responsible to prevent initial burst effect. The viscous polymer 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. This sequence of events coupled with pH-independent solubility of PDL (209.37 mg/l in acid solution of pH 1.2 and 202.08 mg/l in buffer solution of pH 7.4 at 27°C) produced gradual drug release.

$CaCl_2$, which was added in tablets FX2 to FX5, dissolved in water during the wet massing step of tablet preparation and generated Ca^{+2} ion. The liberated Ca^{+2} ion reacted with the carboxyl groups of CMXG *in situ* and thus cross-linked the free carboxyl group of CMXG. Similar ionic cross-link between Ca^{+2} ion and alginate (25, 26), carboxymethyl guar (6, 27), and pectin (11, 28) have been reported. The cross-link restricts the mobility of the polymer chains and results in the formation of a true gel layer in contact with water around the

Table III. Effect of Crushing Strength and Drug Load on Release of Prednisolone Represented in Terms of AUC in 10 h

Formulation code[a]	Crushing strength (kg/cm^2)	AUC (%h)	Formulation code[b]	Crushing strength (kg/cm^2)	AUC (%h)	Formulation code[c]	Drug load (mg)	AUC (%h)
FX6	3.5	26.85 (0.53)	FX9	3.5	39.10 (0.21)	FX12	5	23.97 (0.23)
FX7	4.5	12.11 (0.08)	FX10	4.5	23.27 (0.07)	FX4	10	9.88 (0.05)
FX8	5.5	8.06 (0.04)	FX11	5.5	13.61 (0.09)	FX13	20	8.48 (0.28)

Mean±SD, $n=4$
AUC area under the curve
[a] $CMXG/CaCl_2=1.5:1$
[b] $CMXG/CaCl_2=3:1$
[c] $CMXG/CaCl_2=1.5:1$

tablet surface (29). Increase in cross-linking agent produces higher cross-link density inducing higher gel strength (28) and reduces macromolecular mesh size (30) and, hence, decreases drug diffusion through the gel layer. 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), and the results are shown in Table II. Increase in the amount of $CaCl_2$ up to a certain level decreased the diffusion coefficient of the drug, and further increase in the amount of $CaCl_2$ increased the diffusion coefficient.

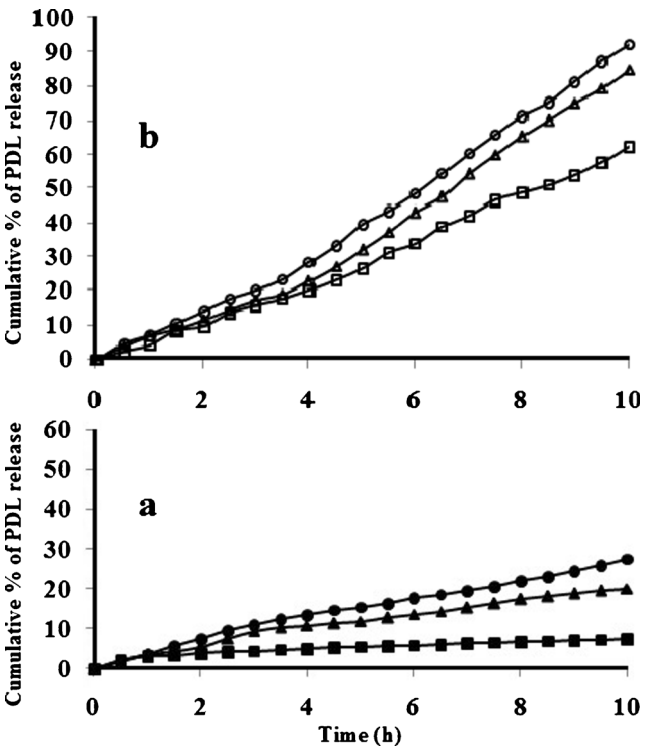

Fig. 5. Effect of pretreatment time of tablet in acid solution (pH 1.2) on PDL release. **a** $CMXG/CaCl_2$ 1.5:1, 5 kg/cm^2, 0.5 h (*black square*); 2 h (*black triangle*); 3 h (*black circle*); **b** $CMXG/CaCl_2$ 1:1, 5 kg/cm^2, 0.5 h (*white square*); 2 h (*white triangle*); 3 h (*white circle*); $n=4$, maximum SD=±1.49)

Increase in the amount of $CaCl_2$ in the tablets reduced the swelling of the matrices, and at the highest level of $CaCl_2$, the matrix-swelling decreased considerably and erosion of the matrix started earlier (data not shown). These observations highlighted the effect of *in situ* cross-linking between a certain amount of Ca^{+2} ion and CMXG on retardation of drug release. The results are in agreement with the reports that increase in calcium content decreases the drug release from Ca^{+2} ion cross-linked pectin and alginate matrix tablets, and beyond a critical concentration of Ca^{+2} ion, drug release increases due to either weakening of the gel strength of the polymer caused by excessive cross-linking by Ca^{+2} ions resulting in a nonhomogenous pectin matrix (10, 31) or channeling effect of Ca^{+2} ions present in excess to that required for cross-linking of alginate (4).

The effect of crushing strength (3.5 to 5.5 kg/cm^2) of tablets on drug release was studied on two sets of tablets prepared with $CMXG/CaCl_2$ in a ratio of 3:1 and 1.5:1. To compare the effect of crushing strength of tablets on drug release, area under the curves (AUCs) of release *versus* time curves were calculated using trapezoidal rule. Within a time period, decrease in the value of AUC is an indication of slower drug release and *vice versa*. Table III shows that increase in crushing strength of the tablets decreased the value of AUC.

This observation was found with both the tablet formulations prepared using CMXG and $CaCl_2$ in a ratio of 1.5:1 and 3:1. It has been reported that release of drugs from hydrophilic matrix tablets is independent of compression force as it is the gel porosity rather than the tablet porosity that determines the drug release (32). Although inconclusive without further experimentation, it can be hypothesized that increase in compression force might have altered the swelling and erosion characteristics of the tablets inducing change in drug release. The results further substantiated the previous observation that increase in calcium content decreases the drug release as this phenomenon was observed in the tablets prepared with three different crushing strengths.

The effect of drug load on the release of PDL was studied with the tablets prepared using $CMXG/CaCl_2$ ratio of 1.5:1 and having a crushing strength of 5 kg/cm^2. Table III shows that increase in drug load from 5 to 20 mg decreased the values of AUC. Generally, increase in drug content increases

Table IV. Release Parameters (Exponent n and Kinetic Constant k) of PDL from Matrix Tablets

Formulation code	Release exponent (n) (mean ± SD, n=4)	Kinetic constant (k) (mean ± SD, n=4)	Correlation coefficient (r)
FX1	0.802 (0.0144)	0.877 (0.0130)	0.993
FX2	0.868 (0.0263)	0.721 (0.0259)	0.989
FX3	0.864 (0.0251)	0.622 (0.0197)	0.991
FX4	0.789 (0.0145)	0.528 (0.0091)	0.989
FX5	1.032 (0.0088)	0.800 (0.0165)	0.980
FX6	0.969 (0.0217)	0.703 (0.0187)	0.981
FX7	0.694 (0.0223)	0.660 (0.0156)	0.993
FX8	0.616 (0.0136)	0.606 (0.0213)	0.974
FX9	0.943 (0.0231)	0.765 (0.0167)	0.985
FX10	0.890 (0.0176)	0.750 (0.0098)	0.994
FX11	0.858 (0.0097)	0.559 (0.0112)	0.996
FX12	0.923 (0.0186)	0.841 (0.0214)	0.996
FX13	0.713 (0.0198)	0.500 (0.0135)	0.979

SD standard deviation

the concentration gradient of the drug between the tablet and external dissolution medium and results in higher drug release. However, the release of a drug from a polymer matrix depends not only on the diffusion of drug but also on relaxation of the polymer on solvent penetration. The solvent front penetration rate has been found to be the lowest in a matrix containing the highest drug content (33). At low drug load, larger pore fraction results in higher swelling inducing faster drug release. On the other hand at higher drug load, the higher crystalline domain of the drug formed in the matrix causes reduction as well as shrinkage of pores in the matrix and produces slower drug release. Decrease in drug release with increase in drug load from bead-type dosage form has been reported (34–36).

The gastric empting time of tablets may vary from 1 to 3 h depending on the physiological and disease condition as well as the presence or absence of food. The different exposure time in acid solution may change the characteristics of a matrix in which an acidic pendant group is introduced and subsequently cross-linked ionically. To assess the effect of variable exposure time in acid solution on overall drug release, the dissolution study of FX4 and FX5 tablets was conducted in acid solution for 0.5, 2, or 3 h, and after each specified time, the pH of the dissolution medium was changed to pH 7.4 and 6.8.

The drug release profiles of tablet FX4 (Fig. 5a) after various pretreatment in acid solution indicated that as the residence time of the tablet in acid solution was increased, the drug release also increased. Similar observation was noted for tablet FX5 (Fig. 5b). As the exposure time in acid solution was increased, conversion of Ca-CMXG to CMXG also increased. Subsequent increase in pH of dissolution medium accentuated the charge repulsion between the ionized carboxylic groups inducing increase in gel porosity and thus produced higher release.

Release Mechanism

In an attempt to evaluate the mechanism of drug release, the data up to 60% PDL release from various tablets were fitted in power law Eq. (2), and the results are shown in Table IV. Mechanism of drug release from uncross-linked and calcium-cross-linked CMXG tablets (FX1–FX4) was non-Fickian/anomalous as the values of the release exponent n were confined within 0.789 to 0.868. However, for tablet FX5, which was prepared with the highest amount of $CaCl_2$, the mechanism of drug release was found to be super case II transport (n=1.032). The mechanism of drug release from tablets containing higher drug loads (FX4 and FX 13) and crushing strength (FX7,FX8 and FX10, FX11) were found to be anomalous except for tablets containing lowest drug load (FX13) and crushing strength (FX6 and FX9) that appeared to be super case II transport. Except for tablet FX5, increase in the amount of $CaCl_2$, drug load, and tablet crushing strength decreased the kinetic constant (k) indicating increase in retardation of drug release.

CONCLUSION

PDL-loaded matrix tablets were developed by an industrially feasible wet granulation method using CMXG as a hydrophilic polymer which was cross-linked *in situ* with Ca^{+2} ions. Variables such as CMXG/$CaCl_2$ ratios, drug load, crushing strength, and pretreatment time in acid solution were found to modulate the drug release to a different extent. The study also revealed that the drug release from all the formulations was considerably less in 5 h, a time period during which the formulation are expected to cross the upper gastrointestinal region. However, none of the formulation, barring FX5, was able to release the loaded drug rapidly in 10 h during which the formulations might be located in the colon. The tablet FX5 which was prepared with CMXG/$CaCl_2$ ratio of 1:1 released major portion of the drug in 10 h although the premature release was slightly higher than the other formulations. It is concluded from the preliminary study that the tablet FX5 appears to be a promising formulation for further modification to design a device for colon delivery of drug.

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