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Ionic crosslinking of O-carboxymethylated *Albiziaprocera* gum and its effect on rheological changes and drug release from matrix tablets

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ABSTRACT:
In this study, carboxymethylated *Albiziaprocera* gum (CMAP) was cross-linked by Ca^{2+} ions using concentrated calcium chloride solution as the cross-linking agent. The resulting cross-linked CMAP (CCMAP) was evaluated for its rheological properties and release of the drug from its matrix tablet formulation. The cross-linking of carboxymethylated polymer with Ca^{2+} ions restricts the water infiltration rate into the framework of the polymer matrices. As it brought about a decrease in electrostatic repulsion between the polymeric chains resulting in high entanglements with a strong gel network, an increase in the consistency of the gel layer affected the swelling rate and drug release. A dynamic rotational and oscillatory study was performed to analyze the rheological data and investigate the structural integrity of polymers (CMAP and CCMAP). Correlation coefficients (R^2) were used to evaluate the kinetic model for best fitting the drug release data. Based on instrumental analyses of drug-polymer compatibility, Metformin was used as a model drug in the formulations. This study aimed at achieving enhanced functional properties for improved drug release from the polymer core through cross-linking.

KEYWORDS: Carboxymethylated *Albiziaprocera*, Ca^{2+} ion cross-linking, Rheology, Swelling, Drug release kinetics

I.INTRODUCTION

There have been numerous studies that have explored the release behavior of drugs using polysaccharides such asguar gum, locust bean gum, xanthan gum and karaya gum as hydrophilic matrices [1–6].Several efforts are being made to enrich the existing resources, including the search for new polysaccharides and the modification of existing ones.The diversity of chemical compositions and functional groups of native polysaccharides makes them susceptible to modifying chemically [7] by using chemical derivatization, chemical crosslinking, or ionic crosslinking [8]. As a result, custom-built materials can be developed for modulating the release of drugs.

Carbohydrate polymersareproveninthefieldofpharmaceuticals industriesreceiveda lotofattention,especiallyasasite-specificor sustainedreleasedrugdeliverycarrier.*Albiziaprocera* was considered for its biocompatibility and wide availability as a carbohydrate polymer.A.procera is an exudate gum obtained from Albiziatree belonging to Mimosaceae family.A. procera gum contains β-(1→3)-D-galactopyranose units with some β-(1→6)-D-galactopyranose units[9]and α-(1→3)-L-arabinofuranose units [10-13].A key aspect of this study was the conversion of carboxymethylated A. procera (CMAP) into its crosslinking structure (CCMAP) with calcium ions, which was investigated for rheological changes and effects on drug release.In this work, both CMAP and CCMAP matrix tablets were prepared by wet granulation method, and the effect of crosslinking was evaluated on drug release in a comparative manner.

Drug diffusion through entangled polymeric matrices is influenced by many factors, including the gel network size and gel strength[1], which have a direct impact on the viscosity of the polymer solution[2,3].However, the polymeric entanglementdepends on molecular domain of the polymer and the functional groups within it.

Since carboxymethylation affected the inherent rheological characteristics of native polymers due to coulombic repulsion between carboxyl groups, this was reflected in their significant change in drug release characteristics [14].

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In addition, the ionic cross-linking with carboxyl groups attached to carboxymethylated polymer chains may have a significant effect on polymer entanglements, mechanical strength [15], and drug release from polymer matrices [16].In addition to analyzing the drug release and kinetics, the drug-polymer compatibility was also assessed.The rheological properties of the polymer matrix can influence the drug release kinetics, duration, and mechanism. A polymer matrix with high viscosity can slow down the diffusion of drugs through the matrix, resulting in a slower drug release rate [17-19].Similarly; a more elastic matrix can resist swelling, which can reduce the drug release rate. Therefore, understanding the rheological behavior of the polymer matrix is crucial for designing drug delivery systems with desired drug release profiles [20].The results of such studies may be valuable for interpreting the behavior of crosslinked polymers that are essential to optimizing modified release tablets.

II. MATERIALS AND METHODS

Materials

The Metformin hydrochloride (MET) was provided as a gift sample by Stadmed Pvt. Ltd., Kolkata, India. The native A. procera (NAP) was procured from Mizoram University (Mizoram, India).Monochloroacetic acid (99.0%), sodium hydroxide, tri-sodium phosphate dodecahydrate (TSPD) Mol.Wt. 380.119 g/mole and Tri-sodium citrate (TSC) was purchased from LobaChemie Pvt. Ltd. Mumbai, India. calcium chloride dehydrate, andmethanol (99% v/v) analytical reagent grade were purchased from Merk Specialties Pvt. Ltd. Mumbai, India.All other chemicals and reagents used were of analytical grade.

1. Carboxymethylation of*Albiziaprocera*

The carboxymethylation of NAP was carried out by a base-catalyzed reaction.[21]Pulverized native procera gum was sieved through 45 meshes and weighed.The dispersion was prepared by slowly adding powdered NAP (10 g) to aqueous sodium hydroxide solution (45% w/v). To ensure complete hydration, the mixture was placed in a double-walled ice chamber (stainless steel) maintained at a temperature between 0-8°C and agitated vigorously.A solution of monochloro-acetic acid (45.05% in water) of 10 ml was gradually added to the slurry while stirring continuously at a temperature of 15-18ºC.Afterward, the reaction mixture was heated to 75°C in a water bath for one hour with regular stirring, and maintained at room temperature for 24 hours. After precipitating the resulting mass with methanol: water (80:20), it was filtered through 8mm filter paper and washed the filtered cake three to four times with aqueous methanol (80% by volume).To achieve the final pH of the CMAP samples, glacial acetic acid was used for pH adjustment and then methanol was used for washing. Air drying was carried out on the tiny semi-crystalline samples and they were then placed in a hot air oven at 60°C for 24 hours.

2. Degree of substitution (DS)

The amount of CMAP, at 5% w/v, was dispersed in 25 ml of 2M hydrochloric acid, and 2.5 ml of aqueous, 80% v/v methanol was gradually added while stirring for 2-3 hours. Then further 2 ml of aqueous 80% v/v methanol was added. The mixture was filtered and washed with methanol: water (80:20) until the wash showed neutrality on litmus paper. Finally, the residue was washed with pure methanol and air dried for 1-2 hours. Then it was dried in a hot air oven at 60ºC until a constant mass was obtained. 200 mg of dried powdered CMAP was accurately weighed and the sample was added to aqueous 70% v/v methanol and allowed to stand for a few minutes. Then 20 ml of water and 5 ml of 0.5M NaOH solution were added. The mixture was shaken for 3-4 hours until the sample was completely dissolved. The solution was titrated with 0.4M HCl solution using phenolphthalein as an indicator [22] The degree of substitution of the O-carboxymethyl group was determined according to the following equation [15].

$$Ds = [\frac{0.162 \times A_{NaOH}}{1 - 0.058 \times A_{NaOH}}] (1)$$

Where A_{NaOH} is the milliequivalents of NaOH required per gram of sample.

3. Preparation of crosslinked CMAP

Arequired quantity (approx. 10g) of dry basis semi-crystalline CMAP powder was weighed and passed through a BS screen #45. The powderwas then slowly sprinkled into de-ionized water and stirred for 1hour to formslurry. Afterwards, a freshly prepared NaOH solution (2% w/v, 10 ml) was slowly added to the slurry for complete solubilization. Then it was transferred into an aqueous $CaCl_2$ solution (5% w/w, 50 ml) and stirred.The mixture was kept overnight. The next day, the obtained mass was vacuum filtered, and the filtered cake was washed with methanol.

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The resultant cake was dried in a hot air oven at 60°C for 4 hours.After obtaining the dried crosslinked CMAP (CCMAP), it was ground and screened [23-24].

4. FTIR spectrum analysis

CMAP and CCMAP powdered samples were analyzed using a FTIR spectrophotometer (PerkinElmer,RX-1,UK), using the potassium bromide disc technique, in the range of 4000 - 400 cm^{-1}. The disc was prepared using ground samples (2 mg) and KBr (45 mg) at 400 kg cm^{-2} pressure for 10 minutes.

5. Differential Scanning Calorimetry (DSC) study

The thermal analysis of CMAP and CCMAP was carried out on a differential scanning calorimeter (DSC-4000, Perkin-Elmer, USA). The samples were hermetically sealed in an aluminum pan and heated from 30 to 300°C with a nitrogen flow of 20 ml/min at a scan rate of 10°C/min.

6. Rheological studies

The rheological experiments were conducted in a Modular Compact Rheometer (Anton Parr MCR 102, Austria). Throughout the study, standard 1° cone geometry (CP-40) of 40 mm in diameter was used. Each experiment was conducted using 5% (w/v) matrices of CMAP and CCMAP at 25°C. Acidic solution (pH 1.2) and buffer solution (pH 6.7) were used to prepare the polymeric matrices for both polymers.At variable shear rates, the shear viscosity of samples was determined in the dynamic rotational mode.The oscillatory mode was used to study the amplitude sweep and frequency sweep of the polymers against their loss and storage moduli (G' and G").At a fixed angular frequency, the amplitude sweep was carried out with varying strains to induce structural deformation in the entangled polymer, while the frequency sweep was used to study the variation of G' and G" with variable angular frequencies by using a predetermined strain (%) under linear viscoelastic (LVE) regime from the amplitude sweep.

7. Drug-polymer FTIR compatibility study

The FTIR spectra of MET, powdered tablet containing CMAP, and CCMAP were recorded using an FTIR spectrophotometer (Perkin Elmer, RX-1, UK) usingthe KBr pellet technique. The spectra were taken in the wave number region of 4000 –400cm^{-1}.

8. Preparation of matrix tablet

Several ingredients were passed through a #60 mesh BS screen, including powdered CMAP and lactose and microcrystalline cellulose (MCC). The drug was then thoroughly mixed with the polymer and the other ingredients in the weight proportions indicated in Table 1.It was then converted into a moist cohesive mass by adding a sufficient amount of water. After this, the cohesive mass was passed through a #16 mesh BS screen, and the resulting granules were dried in a tray dryer at 60°C until the moisture content reached 2–3% w/w.After passing the dried granules through the #20 mesh BS screen, magnesium stearate (2% w/w) was used to lubricate the blend, and the lubricated blend was then compressed into tablets on a single punch tablet machine using 19.5 mm concave-face oval-shaped tooling (RIMEK, KaranavatiEngineeringLtd., Gujarat, India). In the same manner, MET containing CCMAP tablets were prepared.

Table 1: Matrix tablet Formulations

Sl no.	Ingredients per tablet (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
1	MET	250	250	250	250	250	250	250	250	250	250
2	CMAP	300	400	500	600	700	-	-	-	-	-
3	CCMAP	-	-	-	-	-	300	400	500	600	700
4	Lactose anhydrous	450	350	250	150	100	450	350	250	150	100
5	MCC	80	80	80	80	30	80	80	80	80	30
6	Purified water	qs	qs	qs	qs	qs	qs	qs	qs	qs	qs
7	Magnesium stearate	20	20	20	20	20	20	20	20	20	20

***qs indicate quantity sufficient**

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9. Swelling study

The swelling study of blank (placebo) CMAP and CCMAP matrixtablets was conducted in water, acid solution (pH 1.2) and buffer solution (pH 7.4) using USP II tablet dissolution test apparatus (model TDP-06P, Electrolab, India) at 37 ± 0.5◦C.As a buffer solution, 700 ml HCl solution with pH 1.2 was mixed with 200 ml 0.2 (M) tri-sodium orthophosphate dodecahydrate[25] as the media.In a stainless steel wire mesh basket, a matrix tablet was placed and weighed (Precisa, XB 600 M-C, Switzerland, readability 0.0001 g). Following that, the matrix basket was immersed in 900 ml of the test medium at 37 ± 0.5◦C and stirred at 100 rpm. After a predetermined period of time, the basket containing the hydrated matrix tablet was carefully removed, excess water was blotted, and a new weight was taken.Percentage swelling of the tablets was determined using the following relationship [26]:

$$\% \text{ Swelling } = [\frac{(W_2 - W_1)}{W_1} \times 100] \quad (2)$$

Where, W_1 represents initial weight of the tablet at time 0 and $W_2$is the weight of the tablet at time t after immersion in test medium.

10. Physical characteristics of tablet

A. Weight variation test

In order to determine the weight variation of each formulation, 20 tablets were weighed using an electronic balance (Precisa, XB600 M-C, Switzerland, readability 0.0001 g). According to official procedures, the individual weights of the tablets were compared with the average weights of the tablets[27].

B. Hardness, Thickness and Friability

In each formulation, 10 tablets were randomly taken to examine for hardness and dimension analysis.

The tablet hardness was determined using a pre-calibrated Monsanto hardness tester (Cadmach, Ahmedabad, India). A calibrated digital caliper was used to determine the physical dimensions of the tablets (length, breadth and thickness).

The Roche friabilator (Campbell Electronics, Mumbai, India) was used to test the friability of 20 tablets from each formulation. The friabilator was rotated at 25 rpm for 4 minutes;dedusted tablets were reweighed to determine percentage of weight loss.

C. Drug content of tablet

A total of 20 tablets were weighed and crushed into a fine powder.The powder containing about 0.1 grams of Metformin hydrochloride was accurately weighed and shaken with 70 ml of water for 15 minutesthen diluted to 100 ml with waterand filtered.The filtrate (10 ml) was diluted to 100 ml by adding water and then 10 ml from this dilution was further diluted to 100 ml by adding water.A double beam spectrophotometer (Shimadzu, UV, 2450, Japan) was used to measure the absorbance of the resulting solution (0.01 mg/ml). The contentof $C_4H_{11}N_5$, HCl was calculated, taking 798 as the specific absorbance at 232nm[28].

11. In-vitro drug release study

The matrix tablets were tested for drug release in acid solution (pH 1.2) and phosphate buffer solution (pH 6.8) using the USP II tablet dissolution rate test apparatus (Electrolab, TDP-06P, India).At 37±0.5 °C and 100 rpm, a tablet was immersed in 750 ml of 0.1M hydrochloric acid solution kept in a dissolution vessel. Each aliquot was removed and replenished with fresh medium, kept at 37 ±0.5 °C, at predetermined intervals.Following the operation in the acid environment for two hours, 250 ml of 0.2M trisodium phosphate dodecahydrate solution (previously kept at 37 ± 0.5 ◦C) was added.After adjusting the pH (6.8 ± 0.05)of the medium with 2M sodium hydroxide solution, the dissolution process was conducted for 12 hours. After filtration and suitable dilution, the aliquots were spectrophotometrically analyzed.The measurement of drug release was made at the wavelength of the highest absorbance (λmax) in the respective medium. Analysis of MET was performed at 232 nm and 230 nm in acid and buffer solutions, respectively.

III. RESULTS AND DISCUSSION

Extent of carboxymethylation

NAP is made up of a linear chain of - (1→ 3)-β-D-galactopyranoseunits with some - (1→6)-β-D-galactopyranose units, and some - (1→3)-L-arabinofuranose units[9].The conversion of NAP to CMAP involves the replacement of numerous hydroxyl groups (-OH) groups with O-carboxymethyl groups($-OCH_2-COO^- H^+$). Sodium hydroxide dehydronatesthe hydroxyl groups in NAP by formation of alkoxides during the reaction.The average number of substituted

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carboxymethyl groups per anhydro sugar unit is assigned by DS [14]. It was found that the degree of substitution for this reaction was 0.51.

Figure 1 illustrates the possible structures of CMAP and CCMAP.

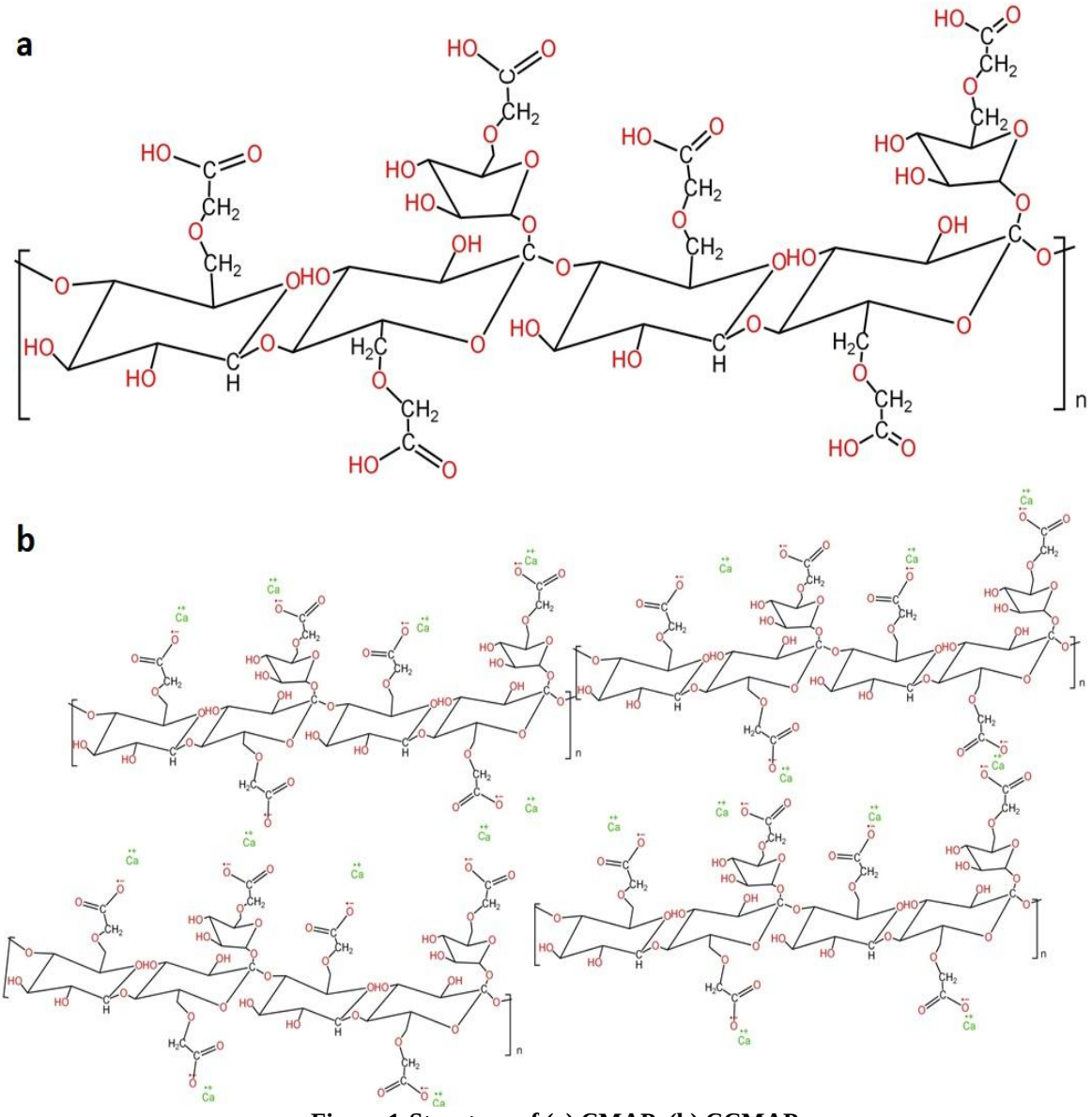

Figure 1:Structure of (a) CMAP, (b) CCMAP.

FTIR spectrum analysis of CMAP and CCMAP

A Fourier transform IR spectrum of CMAP and CCMAP is illustrated in Figure 2.According to Figure 2, The FT-IR spectra of CMAP and CCMAP did not exhibit significant differences in the positions of bands; however, the intensity was different. Based on Figure 2a, CMAP displayed bands of absorption at 2921, 2364.66, 1579.18, 1620, 1457.55, 1420.44, 1315.3 and 1028.74 cm^{-1}, which are representative bands for carbohydrates [29]whilethe absorption bands of CCMAP, were found to be at 2888.3, 2356.41, 1577.12, 1457.56, 1418.38, 1319.42, 1018.43cm^{-1}(Figure 2b).Thus, other than the nominal shifts in the positions of the bands in both polymers, no significant changes were observed.Due to O—H stretching of the hydroxyl groups, a band appeared to be broadened between 3600-3200 cm^{-1} for both polymers (Figure 2a and 2b)[30].In the case of CCMAP, the band for O—H stretching (Figure

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1b)was found to be more intense than CMAP due to crosslinked with Ca^{+2} ions[31].The absorption bands at 2921 cm^{-1} and 2888.3 cm^{-1}were due to the vibrations of C—H stretching. The presence of carboxyl groups (—COO) is indicated by the appearance ofthe characteristic band around 1610-1370 cm^{-1}[32]. The bending vibration of the hydroxyl group (O—H) was observed at 1457 cm^{-1}.The band around 1420-1418 cm^{-1} was attributed to C=O stretching of acid.Since the scissoring of methyl groups (—CH2), bands were detected at 1315 and 1319 cm^{-1}.Several bands were detected at 1018 cm^{-1} and 1020 cm^{-1} as the stretching frequency of >CH—O—CH.

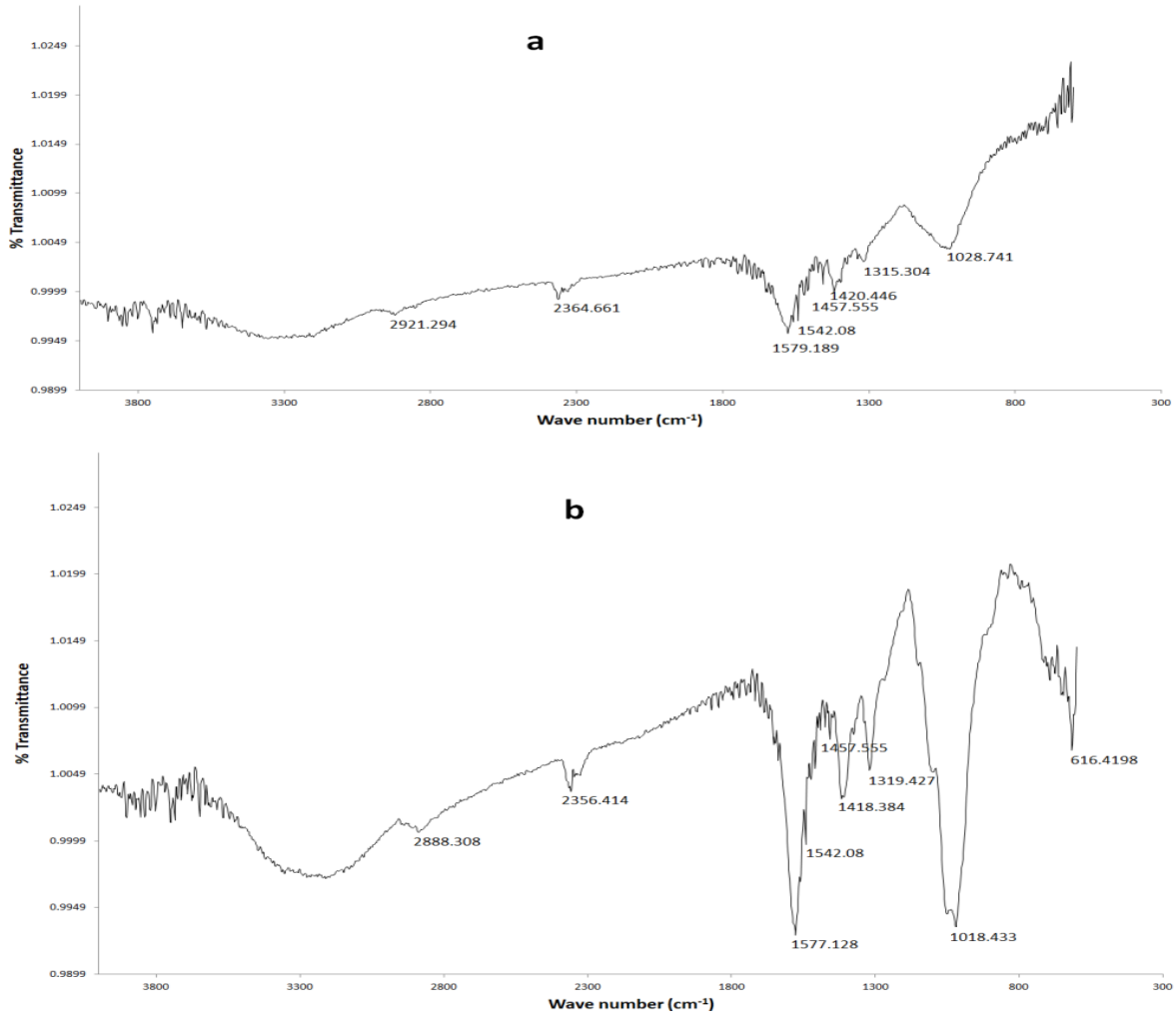

Figure 2: FTIR spectra (a) CMAP, (b) CCMAP.

Differential Scanning Calorimetry (DSC) study

Figure 3 depicts the superimposed plot of diversified DSC thermograms of CMAP and CCMAP. The results indicate that an exothermic event of CMAP occurred at 55.31°C with a heat flow of 20.50 mW. However, the exothermic event of CCMAP shifted at 57.98 °C, 21.06 mW.Based on the DSC profiles of both polymers, each showed an endothermic peak.While CMAP displayed a melting peak at around 261.39°C with a heat flow of 8.57mW, CCMAP showed its melting peak at around 268.7 °C with a heat flow of 8.76mW.Therefore, there was a shift in the melting peak of CCMAP compared to CMAP. In this regard, CCMAP displayed greater thermal stability than CMAP due to the ionic crosslinking [33].

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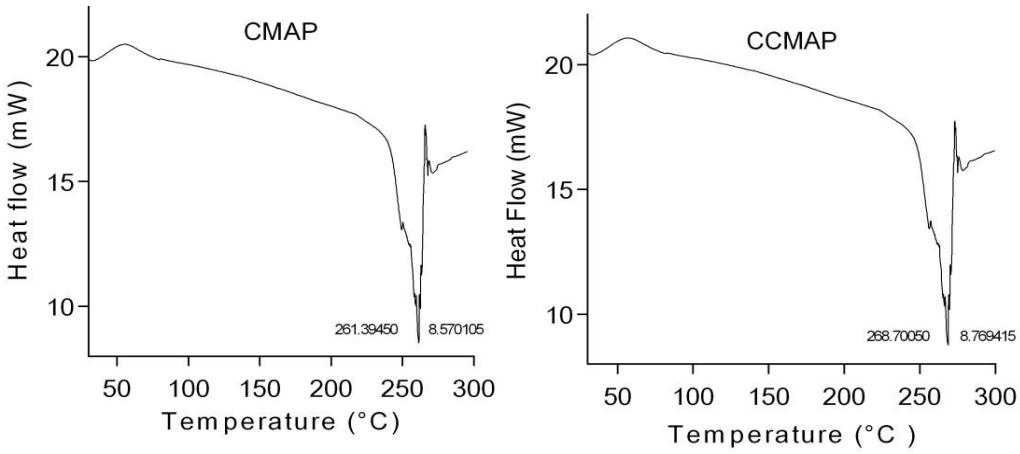
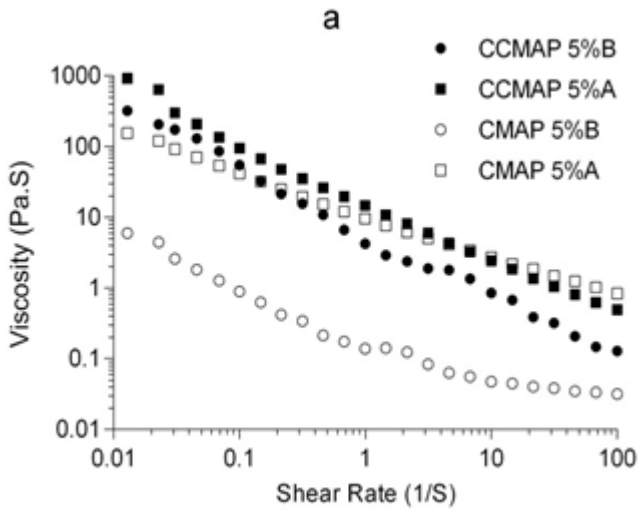


Figure 3:DSC thermograms (a) CMAP, (b) CCMAP.

Rheological studies

The flow curve of CMAP and CCMAP is shown in Figure 4a. The flow curves indicate that the viscosity of the CCMAP matrix at pH 1.2 is greater than the viscosity at neutral pH. Similarly, the viscosity of CMAP at pH 1.2 was higher than the viscosity at pH 6.8. However, when comparing the viscosity profiles of CCMAP and CMAP, it was found that CCMAP was always higher than CMAP. Additionally, both polymers displayed non-Newtonian behavior with the pseudo-plastic flow. The carboxymethyl groups in CMAP matrices are ionized and induce electrostatic repulsion, resulting in polymer disentanglements and viscosity decline[34]. The ionization of carboxymethyl groups was more pronounced at pH 6.8 in comparison to acidic pH.

Due to the crosslinking, the Ca^{++}ions reactedwith carboxylic groups and formed CCMAP (—OCH_2COO^- Ca^{2+}—$OOCH_2CO$—)[35].Thus, Crosslinked polymer chains are prevented from moving and coulombic repulsion between them gets restricted.Therefore, CCMAP chains became highly disentangled and exhibited high viscosity, resulting in the formation of viscoelastic gels.



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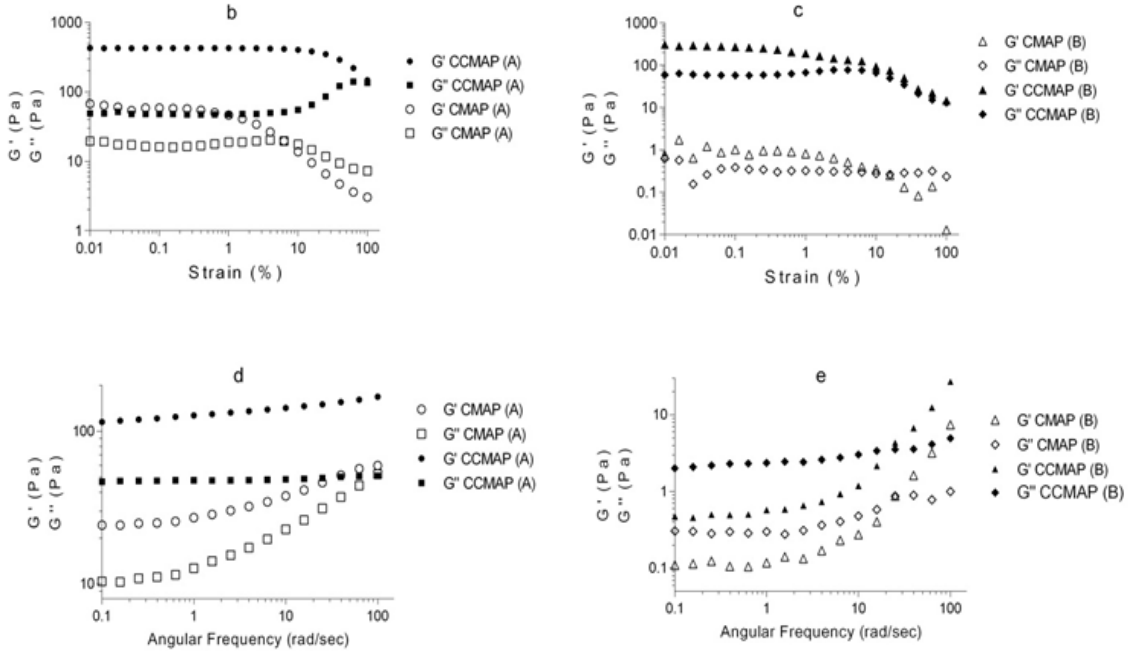

Figure 4:(a) Flow curves : CMAP at pH 1.2 (□), at pH 6.8 (○); CCMAP at pH 1.2 (■), at pH 6.8 (●); (b) Amplitude sweepat pH 1.2: CMAP G′(○), G″ (□); CCMAP G′ (●), G″ (■);(c) Amplitude sweep at pH 6.8:CMAP G′ (∆), G″ (◊); CCMAP G′ (▲), G″ (♦); (d) Frequency sweep at pH 1.2 :CMAP G′ (○), G″ (□); CCMAP G′ (●),G″ (■);(e) Frequency sweep at pH 6.8 :CMAP G′ (∆), G″ (◊); CCMAP G′ (▲), G″ (♦).

Both polymers exhibit amplitude sweep curves illustrated in Figure4b (at pH 1.2) and 4c (at pH 6.8). As a result of linear viscoelasticity, the linear viscoelastic region (LVE) corresponds to the stress varying linearly with strain for the sample under study[36]. The storage modulus G' (Pa) as an elastic response [37] and the loss modulus G' (Pa) as a viscous response of both polymers were varied with variable strain (%) during the amplitude of the deformation.Initially, the polymers will maintain their structural integrity within the LVE, but after a critical strain (%) the structural deformations will begin as the declination of G' exceeds the LVE.Figure 4b indicates that in acidic pH, CCMAP had a critical strain of 2.5%, while CMAP had a critical strain of 0.3%.Crosslinking prevented CCMAP from being ionized, resulting in higher mechanical strength than CMAP. Additionally, CMAP had shorter LVE than CCMAP.However, the critical strain of CCMAP at pH 6.8 was found to be 0.4% while CMAP had 0.1%.It was also observed that the LVE in CCMAP at pH 6.8 became significantly shorter than at pH 1.2. In contrast, the LVE of CMAP at pH 6.8 became more unstable and showed irregular patterns.

As the frequency sweep was performed, the measured critical strain (%)was kept constant within the LVE while the angular frequency (rad/sec) was varied.According to the frequency sweep curves presented in Figure 4d and 4e, CCMAP had higher G' values than CMAP at pH 1.2 and 6.8. However, both polymers have a higher G' value than G" (G'>G").There was a larger difference between G' and G" without crossing each other, indicating a higher degree of rheological stability for CCMAPmatrices at pH 1.2 as compared to CCMAP matrices at pH 6.8[38].The higher values of G' over the G" (G'>G") indicate avisco-elastic structure of CCMAP [39].The high degree of entanglement in CCMAP matrices resulted in a strong gel structure as a result of cross-linking.Conversely, CMAP matrices were found to have weak gel structures as compared to CCMAP matrices.At pH 6.8, both polymers showed crossover points (CMAP at 25.1 rad/sec, G'=G"=0.873, CCMAP at 25.1 rad/sec, G'=G"=3.378) that indicate structural deformation [40].Additionally, the CMAP matrices at pH 1.2 exhibited a weak gel-like structure that lost their elastic energy at pH 6.8 and formed disentangled structure. It is the result of the ionization of

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functional groups (—OCH_2COO^- H^+) of CMAP which leads to electrostatic repulsion, resulting in a decrease in entanglements[41, 42].

Drug-polymer FTIR compatibility study

The FTIR spectra of the drug and the drug-polymer mixture are shown in Figure 5a and b.As a fingerprint of Metformin, the FTIR spectrum (Figure 5a) showed characteristic absorption bands at 3371, 3392, 3176, 1622, 1568, 1167 and 1063 cm^{-1} wavenumbers[43].The absorption bands of MET appeared at 3371, 3392 and 3176 $cm^{-1}$for the amine N—H stretching vibrations. As N—H bonds (in amines) are weaker in polarity than O—H bonds, their absorption bands are less intense and less broad than O—H bands. MET exhibited characteristic bands at 1622 and 1568 cm^{-1} for C—N and C=N respectively. However, the absorption bands at 1620-1580 cm^{-1} are also responsible for N—H bending. In addition, the absorption bands at 1167 and 1063 cm^{-1}were due to C—N stretching. The band at 1475 cm^{-1}wavenumber was due to C—H bending.All of the characteristic bands of the drug were found almost at the same wavelength in the FTIR spectrum obtained from the MET-polymer mixtures (Figure 5b).

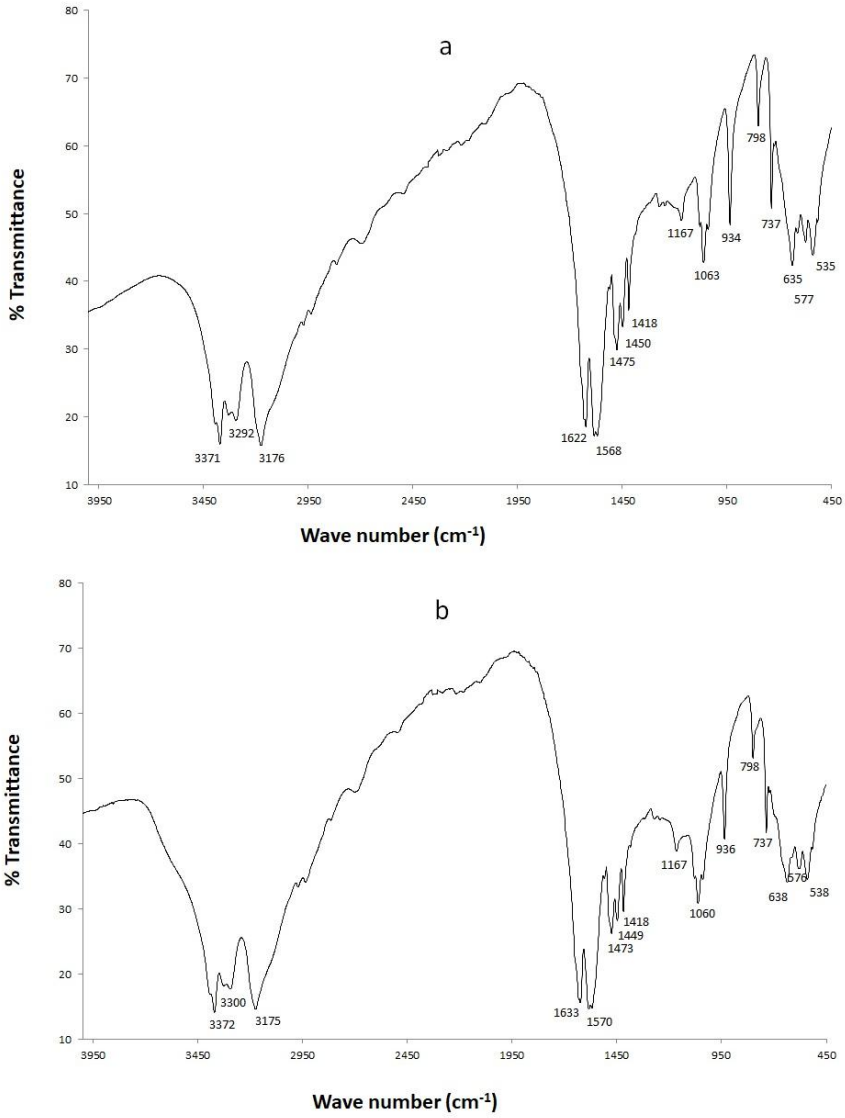

Figure 5:FTIR spectrum (a) Metformin, (b) Metformin-polymer mixture.

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Swelling study

Figure 6a and b illustrate the swelling profiles of CMAP and CCMAP matrices in acidic (pH 1.2) and buffer (pH 6.4) media. In acid media, the % of swelling of blank CMAP tablets wasconsiderably less than in buffer media. However, CMAP tablets in both media exhibited a rapid and greater swelling than blank CCMAP tablets.The calcium crosslinking results in low water penetration velocity and high entanglement in CCMAP matrices, resulting in reduced swelling as compared to CMAP matrix.

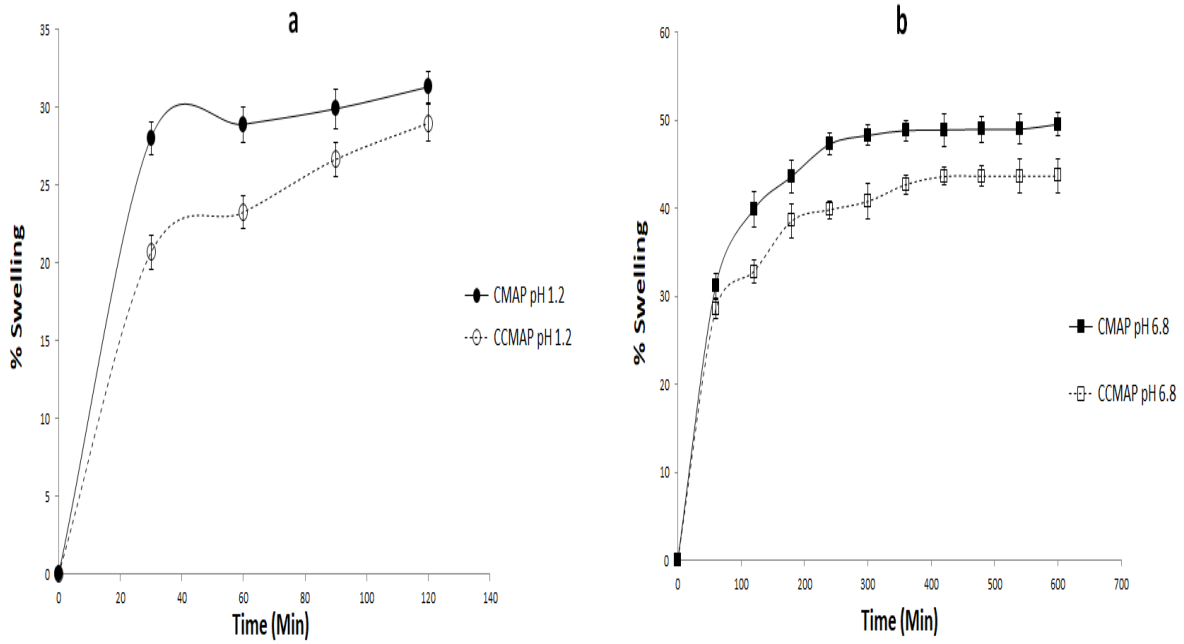

Figure 6:Swelling profiles (a) At pH 1.2: CMAP(●), CCMAP (-○-); (b) At pH 6.8 :CMAP (■), CCMAP (-□-).

Physical characteristics of tablet

The physical characteristics of the tablets were within acceptable limits.A comparison of all the physical characteristics of the tablets of each formulation is presented in Table 2.

Table 2:Physical evaluation of formulated batches of matrix tablet

Formulation code	Average weight (mg) (N=20)	Hardness (Newton/cm^2) (N=10) *	Average thickness (mm) (N=10) *	Average length (mm) (N=10)*	Average breadth (mm) (N=10)*	Friability (%) (N=20) *	Drug content (%) (N=20)
F1	1117.2 ± 2.25%	56.87 ± 0.06	6.1 ± 0.02	19.49 ± 0.011	9.00 ± 0.013	0.67 ±0.026	99.08 ±0.16
F2	1114.6 ± 1.23%	59.82 ± 0.021	5.89 ± 0.01	19.49 ± 0.009	8.99 ± 0.021	0.63 ±0.047	99.13 ±0.21
F3	1108.2 ± 2.06%	61.58 ± 0.028	5.92 ± 0.012	19.42 ± 0.014	9.01 ± 0.017	0.53 ±0.016	101.03 ±0.18
F4	1113.04 ± 4.02%	60.11 ± 0.047	5.96 ± 0.023	19.45 ± 0.011	9.02 ± 0.012	0.57 ±0.031	98.98 ±0.24

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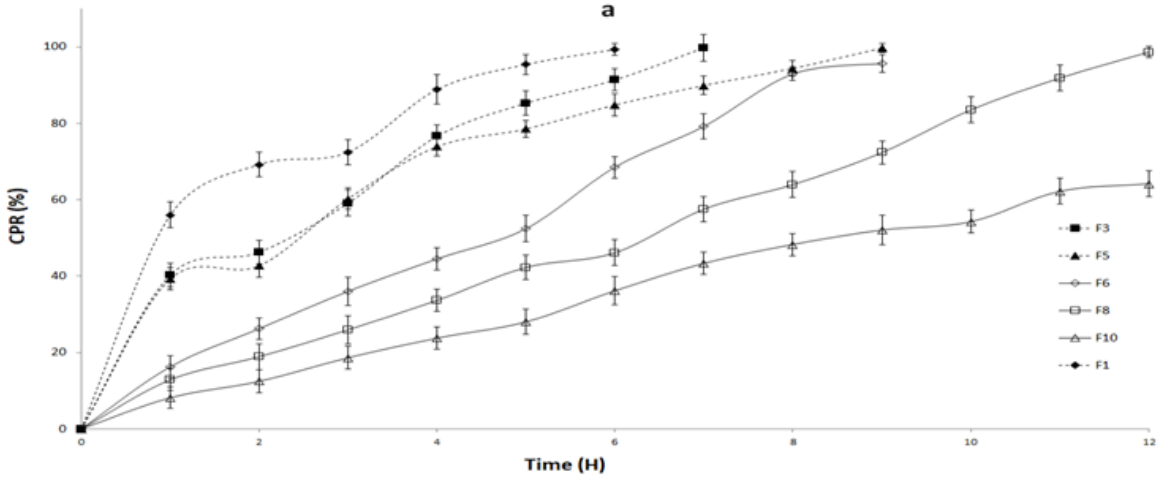
F5	1119.2 ± 2.08%	67.27 ± 0.032	5.99 ± 0.011	19.50 ± 0.01	9.02 ± 0.01	0.48 ±0.01 8	99.01 ±0.19
F6	1122.03 ± 1.04%	64.13 ± 0.016	6.2 ± 0.014	19.49 ± 0.017	8.99 ± 0.023	0.51 ±0.033	100.05 ±0.23
F7	1119.25 ± 2.15%	69.13 ± 0.023	5.98 ± 0.022	19.46 ± 0.013	9.01 ± 0.016	0.35 ±0.0 23	99.69 ±0.22
F8	1121.03 ± 1.29%	68.05 ± 0.051	5.99 ± 0.09	19.48 ± 0.018	9.00 ± 0.023	0.39 ±0.014	99.16 ±0.2
F9	1121.16 ± 1.47%	70.31 ± 0.043	6.1 ± 0.023	19.48 ± 0.012	9.03 ± 0.013	0.23 ±0.021	99.33 ±0.16
F10	1123.05 ± 1.07%	70.01 ± 0.049	5.99 ± 0.013	19.49 ± 0.011	9.00 ± 0.020	0.26 ±0.03	99.43 ±0.22

* N= number of tablets tested; Mean ± SD (n=3)

In-vitro drug release study

Based on the standard calibration curve of MET, the coefficient of correlation (R^2) was obtained and the amount of drug dissolved in each sample was determined. The in-vitro drug release profiles of MET (250 mg) from tablets containing CMAP and CCMAP in each formulation are presented in Figure 7a and b.Based on the entire drug release profiles, CCMAP formulations exhibited prolonged release and became more sustained with increasing polymer concentrations. Conversely, the CMAP formulations exhibited a rapid momentaneous drug release profile. The maximum amount of MET released from the CMAP matrices was 249.25 mg (99.7%) within 9 hours (F5), while CCMAP matrices released 246.6 mg (98.64%) upto 11 hours.The Ca^{++} crosslinking restricted the permeation of water influx into the CCMAP matrices, reduced swelling and promoted the formation of the viscoelastic gel layer.Consequently, these factors contributed to a slower release of drugs.In CMAP matrices, the electrostatic repulsion between the polymeric chains enhanced the mobility, de-coiled structure and weak gel networks lost their structural integrity assisted rapid deformation. Consequently, they permeated water uptake, leading to higher swelling andaccelerated drug release.For CMAP and CCMAP tablets, the AUC values for MET released are presented in Table 3. The drug release data wereanalyzed for two-wayANOVA to determine the significant difference in drug release between different formulations.According to the ANOVA table shown in Table 4 the differences between the drug releases from the two matrices were statistically significant ($P < 0.0001$).



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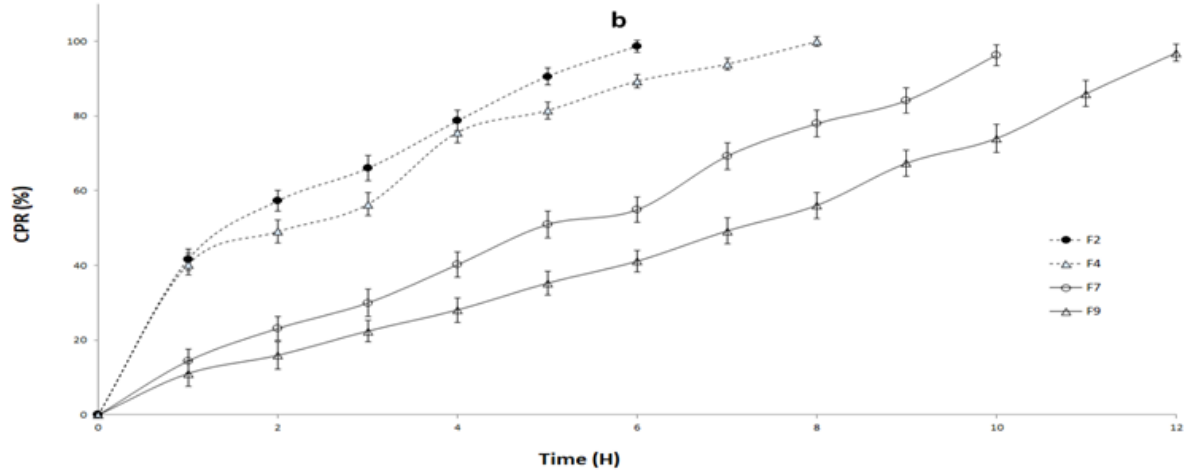

Figure 7: Drug release profiles of MET from CMAP (---) and CCMAP (□) matrix tablets. (a) CMAP formulations: F1 (♦), F3 (■), F5 (▲); CCMAP formulations: F6(◊), F8(□), F10(Δ); (b) CMAP formulations: F2 (●), F4 (△); CCMAP formulations: F7 (○), F9 (Δ).

Table 3: AUC of drug release

Media	Formulations									
	AUC of drug release from CMAP matrix (% mg hrs)					AUC of drug release from CCMAP matrix (% mg hrs)				
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
At pH 1.2	226.475 ± 3.6	175.6083 ± 2.6	158.4708 ± 4.2	162.0625 ±3.6	151.4958 ± 4.8	73.42918 ± 3.2	64.93334 ± 4.2	55.80418 ± 2.9	47.62499 ± 3.5	35.93333 ± 3.7
At pH 6.8	1078.963 ± 4.1	958.5917 ± 4.7	1121.871 ± 3.2	1339.796± 2.9	1533.942 ± 4.4	1159.783 ± 4.2	1232.313 ± 3.7	1495.604± 2.4	1337.525 ± 4.6	1048.558 ± 4.4

* Mean ± SD, n=3

Table 4: Two-way ANOVA table

Two-way ANOVA					
Alpha	0.05				
Source of Variation	% of total variation	P value	P value summary	Significant?	
Row Factor	28.91	<0.0001	****	Yes	
Column Factor	2.679	0.892	ns	No	
ANOVA table	SS	DF	MS	F (DFn, DFd)	P value
Row Factor	46569	12	3881	F (12, 108) = 3.803	P < 0.0001
Column Factor	4315	9	479.4	F (9, 108) = 0.4699	P = 0.8920
Residual	110194	108	1020		
Number of missing values	0				

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The drug release data was analyzed using several kinetic models, including zero-order, first-order, Higuchi, and Korsmeyer-Peppas.In accordance with the obtained results, the release mechanism of different formulations has been determined based on the best fit in several models, as shown in Table 5.Based on the linear regression analysis, the coefficient of correlation coefficient (R^2) indicated that the drug release from CMAP formulations was diffusion controlled and followed the Higuchi model.However, CCMAP followed zero order kinetics (F6 to F9) except for F10 which followed Korsmeyer-Peppas model.As the formulation F10 showed a diffusion exponent of 0.877, it indicates the Anomalous (non-Fickian) diffusion, which implies that the drug was released by both diffusion-controlled andswelling-controlled mechanisms [44].

Table 5:Formulation-specific release kinetics data

Kinetic model	R^2 of Formulations									
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**
zero order	0.965	0.993	0.974	0.968	0.946	**0.991**	**0.996**	**0.996**	**0.986**	0.991
1-st order	0.948	0.962	0.953	0.934	0.889	0.95	0.944	0.949	0.966	0.91
Korsmeyer-Peppas	0.965	0.993	0.958	0.97	0.96	0.989	0.991	0.987	0.978	**0.993**
Higuchi	**0.97**	**0.993**	**0.978**	**0.978**	**0.975**	0.964	0.968	0.958	0.932	0.979

IV.CONCLUSION

The study revealed a decrease in the magnitude of viscosity of CMAP matrices attributed to electrostatic repulsion between carboxymethyl groups caused by the ionization of CMAP. However, cross-linking of O-carboxymethylated procera gum by Ca2+ ions contributed to the formation of entangled structures and high viscoelasticity. The enhanced viscoelastic properties of the CCMAP matrix counteracted the matrix deformation. Eventually, the high viscoelastic CCMAP matrices formed a strong gel layer around the tablet surface which confined water ingress leading to less swelling. Thus the CCMAP tablets provided sustained drug release by controlling the diffusion rate of the drug molecules. Therefore a chemically modified and ionically cross-linked polymer can affect the rheological parameters of the polymer matrix. It is also possible to achieve a specific drug release rate, duration, and mechanism from the flexibility of polymers.

CONFLICT OF INTEREST

In relation to this manuscript, all authors declare that there is no conflict of interest.

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REFERENCES

[1] Sujja-Areevath J, Munday DL, Cox PJ, Khan KA. Relationship between swelling, erosion and drug release in hydrophillic natural gum mini-matrix formulations. European journal of pharmaceutical sciences. 1998 Jul 1;6(3):207-17.

[2] Roy DS, Rohera BD. Comparative evaluation of rate of hydration and matrix erosion of HEC and HPC and study of drug release from their matrices. European Journal of Pharmaceutical Sciences. 2002 Aug 1;16(3):193-9.

[3] Zuleger S, Lippold BC. Polymer particle erosion controlling drug release. I. Factors influencing drug release and characterization of the release mechanism. International Journal of Pharmaceutics. 2001 Apr 17;217(1-2):139-52.

[4] Mughal MA, Iqbal Z, Neau SH. Guar gum, xanthan gum, and HPMC can define release mechanisms and sustain release of propranolol hydrochloride. AapsPharmscitech. 2011 Mar;12:77-87.

[5] Munday DL, Cox PJ. Compressed xanthan and karaya gum matrices: hydration, erosion and drug release mechanisms. International Journal of Pharmaceutics. 2000 Aug 1;203(1-2):179-92.

[6] Sriamornsak P, Thirawong N, Weerapol Y, Nunthanid J, Sungthongjeen S. Swelling and erosion of pectin matrix tablets and their impact on drug release behavior. European

journal of pharmaceutics and biopharmaceutics. 2007 Aug 1;67(1):211-9.
[7] Vyas SP, Khar RK. Controlled drug delivery concepts and advances. vallabhprakashan. 2002;1:411-7.
[8] Prajapati VD, Jani GK, Moradiya NG, Randeria NP. Pharmaceutical applications of various natural gums, mucilages and their modified forms. Carbohydrate polymers. 2013 Feb 15;92(2):1685-99.
[9] Pachuau L, Lalhlenmawia H, Mazumder B. Characteristics and composition of Albiziaprocera (Roxb.) Benth gum. Industrial Crops and Products. 2012 Nov 1;40:90-5.
[10] Zhang J, Akihisa T, Kurita M, Kikuchi T, Zhu WF, Ye F, Dong ZH, Liu WY, Feng F, Xu J. Melanogenesis-inhibitory and cytotoxic activities of triterpene glycoside constituents from the bark of Albiziaprocera. Journal of natural products. 2018 Dec 6;81(12):2612-20.
[11] Avachat AM, Dash RR, Shrotriya SN. Recent investigations of plant based natural gums, mucilages and resins in novel drug delivery systems. Ind J Pharm Edu Res. 2011 Jan;45(1):86-99.
[12] De Paula RCM, Santana SA, Rodrigues JF. Composition and rheological properties of Albizialebbeck gum exudates. Carbohydr. Polym. 2001; 44:133–139.
[13] De Pinto, Leon G, Martinez M, Beltran O, Rincon F, Clamens C, Igartuburu JM, Guerrero R, Vera A. Characterization of polysaccharides isolated from gums of two Venezuelan specimens of Albizianiopoides var. colombiana. Ciencia. 2002;19: 382–387.
[14] Chakravorty A, Barman G, Mukherjee S, Sa B. Effect of carboxymethylation on rheological and drug release characteristics of locust bean gum matrix tablets. Carbohydrate polymers. 2016 Jun 25;144:50-8..
[15] Barai BK, Singhal RS, Kulkarni PR. Optimization of a process for preparing car□ymethyl cellulose from water hyacinth (Eichorniacrassipes). Carbohydrate Polymers. 1997 Mar 1;32(3-4):229-31..
[16] Singh R, Maity S, Sa B. Effect of ionic crosslink on the release of metronidazole from partially carboxymethylated guar gum tablet. Carbohydrate polymers. 2014 Jun 15;106:414-21.
[17] Wang JZ, Ding ZQ, Zhang F, Ye WB. Recent development in cell encapsulations and their therapeutic applications. Materials Science and Engineering: C. 2017 Aug 1;77:1247-60.
[18] Shilpa A, Agrawal SS, Ray AR. Controlled delivery of drugs from alginate matrix. Journal of Macromolecular Science, Part C: Polymer Reviews. 2003 Jan 6;43(2):187-221.
[19] Gupta PK, Bhandari N, Shah H, Khanchandani V, Keerthana R, Nagarajan V, Hiremath L. An update on nanoemulsions using nanosized liquid in liquid colloidal systems. Nanoemulsions-Properties, Fabrications and Applications. 2019 Mar 29;1(1):1-4.
[20] Shaker DS, Ishak RA, Ghoneim A, Elhuoni MA. Nanoemulsion: A review on mechanisms for the transdermal delivery of hydrophobic and hydrophilic drugs. Scientia Pharmaceutica. 2019;87(3):17.
[21] Dodi G, Hritcu D, Popa MI. Carboxymethylation of guar gum: synthesis and characterization. Cellulose chemistry and Technology. 2011 Mar 1;45(3):171
[22] Toğrul H, Arslan N. Production of carboxymethyl cellulose from sugar beet pulp cellulose and rheological behaviour of carboxymethyl cellulose. Carbohydrate Polymers. 2003 Oct 1;54(1):73-82.
[23] Hongbo T, Yanping L, Min S, Xiguang W. Preparation and property of crosslinking guar gum. Polymer journal. 2012 Mar;44(3):211-6.
[24] Huang Y, Yu H, Xiao C. Effects of Ca2+ crosslinking on structure and properties of waterborne polyurethane-carboxymethylated guar gum films. Carbohydrate Polymers. 2006 Nov 23;66(4):500-13.
[25] Indian Pharmacopoeia, vol. I, The Indian Pharmacopoeia Commission, Govern-ment of India, Ghaziabad, 2010
[26] Sriamornsak, P., Thirawong, N., Weerapol, Y., Nunthanid, J., &Sungthongjeen, S.(2007). Swelling and erosion of pectin matrix tablets and their impact on drugreleasebehavior. European Journal of Pharmaceutics and Biopharmaceutics, 67,211–219.
[27] Indian Pharmacopoeia, vol. II, controller of publications, Delhi (2018), pp. 1143-1144

[28] Pharmacopoeia I, Volume II. Published by the controller of Publication. Vol. I, New Delhi. 2007;655.
[29] Yuen SN, Choi SM, Phillips DL, Ma CY. Raman and FTIR spectroscopic study of carboxymethylated non-starch polysaccharides. Food chemistry. 2009 Jun 1;114(3):1091-8.
[30] Sadalage PS, Pawar KD. Production of microcrystalline cellulose and bacterial nanocellulose through biological valorization of lignocellulosic biomass wastes. Journal of Cleaner Production. 2021 Dec 10;327:129462.
[31] Dagar, V., Pahwa, R. and Ahuja, M., 2022. Preparation and Characterization of Calcium Cross-Linked Carboxymethyl Tamarind Kernel Polysaccharide as Release Retardant Polymer in Matrix. Biointerface Res. Appl. Chem, 13, p.111.
[32] Aguir C, M'Henni MF. Experimental study on carboxymethylation of cellulose extracted from Posidoniaoceanica. Journal of applied polymer science. 2006 Feb 15;99(4):1808-16.
[33] Hongbo T, Yanping L, Min S, Xiguang W. Preparation and property of crosslinking guar gum. Polymer journal. 2012 Mar;44(3):211-6
[34] Maiti S, Ray S, Mandal B, Sarkar S, Sa B. Carboxymethyl xanthan microparticles as a carrier for protein delivery. Journal of microencapsulation. 2007 Jan 1;24(8):743-56.
[35] Huang Y, Yu H, Xiao C. Effects of Ca2+ crosslinking on structure and properties of waterborne polyurethane-carboxymethylated guar gum films. Carbohydrate Polymers. 2006 Nov 23;66(4):500-13.
[36] Kaboorani A, Blanchet P. Determining the linear viscoelastic region of sugar maple wood by dynamic mechanical analysis. BioResources. 2014 Jun 5;9(3):4392-409.
[37] Talens P, Castells ML, Verdú S, Barat JM, Grau R. Flow, viscoelastic and masticatory properties of tailor made thickened pea cream for people with swallowing problems. Journal of Food Engineering. 2021 Mar 1;292:110265.
[38] Xiao F, Chen M, Wu S, Amirkhanian SN. A long-term ultraviolet aging effect on rheology of WMA binders. Int. J. Pavement Res. Technol. 2013 Sep 1;6(5):496-504.
[39] Li C, Liu C, Liu J, Fang L. Correlation between rheological properties, in vitro release, and percutaneous permeation of tetrahydropalmatine. AapsPharmscitech. 2011 Sep;12:1002-10.
[40] Rasid IM, Do C, Holten-Andersen N, Olsen BD. Effect of sticker clustering on the dynamics of associative networks. Soft Matter. 2021;17(39):8960-72.
[41] Medina-Torres L, Brito-De La Fuente E, Torrestiana-Sanchez B, Katthain R. Rheological properties of the mucilage gum (Opuntiaficusindica). Food hydrocolloids. 2000 Sep 1;14(5):417-24.
[42] Yan X, Xiao X, Au C, Mathur S, Huang L, Wang Y, Zhang Z, Zhu Z, Kipper MJ, Tang J, Chen J. Electrospinning nanofibers and nanomembranes for oil/water separation. Journal of Materials Chemistry A. 2021;9(38):21659-84.
[43] Smaeel SA, Al-Bayati YK. Determination of trace metformin in pharmaceutical preparation using molecularly imprinted polymer based pvc-membrane. Eurasian Chem. Commun. 2021; 3:812-30.
[44] Arora G, Malik K, Singh I, Arora S, Rana V. Formulation and evaluation of controlled release matrix mucoadhesive tablets of domperidone using Salvia plebeian gum. Journal of advanced pharmaceutical technology & research. 2011 Jul;2(3):163.