RESEARCH ARTICLE

Studying the Release Characteristics of Naproxen Sustained Release Matrix Tablet Using Natural Polyelectrolytes

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ABSTRACT

Aim: This work involves studying the release characteristics of naproxen sustained release matrix tablet using natural polyelectrolytes and studying some variables affecting the formulation such as the effects of {Polyelectrolyte complexes (PEC) formation, polymer-polymer ratio, anionic polymer type, a molecular weight of Chitosan (CS), type and amount of diluent} on the release rate of naproxen.

Methods: Sixteen formulas were prepared using direct compression with 500 mg total tablet weight. The release properties of naproxen sustained release matrix tablets were investigated using USP dissolution apparatus I (basket). FT-IR spectra of the complexes were studied to indicate the interactions between polyions.

Results: The results showed that the release rate of naproxen was decreased in the formulas that contain PEC comparing to the formulas with a single polymer. The formula containing CSh: SA prepared in the ratio of (3:1) showed the slowest release rate (68.17% of naproxen in 7 hr) and extended the release up to 15 hours. It was seen that the formula containing CSh: XG in 3:1 ratio formed the strongest PEC and the release rate extended up to 20 hour. On the other hand, changing the molecular weight of CS from high to low and the type of diluent from lactose monohydrate to Medicines Control Council (MCC) showed a non-significant increase in the release rate.

Conclusion: Polyelectrolyte complex prepared from cationic polymer CS and anionic polymer of SA, XG, and CG physical mixtures were successfully formed. Formula 13 formed the strongest PEC with a ratio of CS: XG equal to (3:1) which extended the release up to 20 hr.

Keywords: Chitosan, Matrix tablet, Naproxen, Polyelectrolytes, Sustained, Xanthan.

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INTRODUCTION

The PECs have gained an important role in pharmaceutical preparations, especially in the preparation of matrix tablets due to their properties of extending the release of the drug.[1] PECs are formed in a spontaneous manner when combining macromolecules of opposite charges in solution. Certain parameters govern the formation of these complexes include molecular weight, ionic strength, charge density, the type and concentration of salt in the solution, pH, and the intensity of mixing.[2] Different methods have been used to study the interaction among polymers including measurement of turbidity, measurement of pH, ionic strength, viscosity, light scattering, infrared spectroscopy (IR), nuclear magnetic resonance (NMR), thermal analysis, pKa and powder X-Ray diffraction.[3] Chitosan is a polycationic derivative of poly-N-acetyl-D-Glucosamine (chitin), it is widely used in various applications like gels, solutions, films and fibers.[4] Anionic polymers like (pectin, alginate, carrageenan, xanthan gum and carboxymethyl cellulose) can form PECs with the polycation chitosan for extending drug delivery systems.[5] Alginates are copolymers that are unbranched of[1-4] linked β-D-mannuronic acid and α-L-glucuronic acid moieties. Sodium alginate has been broad as a disintegrant in tablets, binders, thickening agents in suspension and emulsion and stabilizer. Sodium alginate has the advantage of being used in matrix system formulation to control drug release since it is a biodegradable polymer and does not need any surgical intervention to be removed.[6] Xanthan gum is an exopolysaccharide that originated from a plant microorganism of *Xanthomas* species. Xanthan gum basically consists of D-glucose-mannose and D-glucuronic acid. Xanthan gum has been broadly used orally and topically in pharmaceutical formulations, cosmetics and as a thickening agent in the food industry. In sustained-release preparations, xanthan gum provides time-dependent release with an extended-release of drug particularly with a polycation, chitosan to form PECs, which retard the release of drugs.[8] In matrix tablet, xanthan gum forms a thick gel layer that when exposed to the dissolution medium, releases the drug slowly by diffusion or erosion of the matrix.[9] Carrageenan is originated from a family

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of sulfated polysaccharides, which are high molecular weight molecules extracted from specific kind of red seaweeds. They basically consist of D-galactose moiety linked in an alternative manner in 3-linked-β-D-galactopyranose and 4-linked- α-D-galactopyranose units. Carrageenan has been used in the preparation of sustained-release matrix tablet because of its physicochemical properties such as high viscosity, high molecular weight, and gelling property.[10] Naproxen is [(+)-(S)-2-(6-methoxynaphthalen-2-yl) propanoic acid],[11] naproxen is an nonsteroidal anti-inflammatory drug (NSAID) treats rheumatoid arthritis and in the relief of pain in cases like headaches.[12] High levels of naproxen in the stomach can cause stomach ulcer and bleed, so that designing a sustained-release form of naproxen can improve this disadvantages resulting in less frequent dosing and less GIT disturbances.[13,14] The aim of this study is to utilize natural polyelectrolytes in the preparation of naproxen as sustained release matrix tablet.

MATERIALS AND METHODS

Materials

Naproxen powder, High molecular weight CS, Carrageenan (CG), polyvinyl pyrrolidone (PVP), and lactose monohydrate were supplied by (Guokang bio-technology, China), Sodium alginate (SA) and Xanthan gum (XG) were provided by (Wuhan Senwayer century, China), Magnesium stearate was supplied by (Scharlab S.L, Spain).

Methods

Preparation of Sustained Release Matrix Tablet of Naproxen

Different formulas were prepared as shown in Table 1 using a direct compression method to produce a 250 mg naproxen sustained release matrix tablets in which the total weight of each tablet was 500 mg. The formulas were prepared using different polymers (CS, SA, XG, and CG) separately as a single polymer and as a physical mixture of two polymers to produce a polyelectrolyte mixture, in addition to other excipients. The powders of each formula were mixed for 15 minutes; the resultant mixture was mixed with magnesium stearate (0.5% w/w) for 1 minute and compressed by the tablet machine into 500 mg tablet.

Fourier Transform Infrared Study (FT-IR)

The FT-IR spectra of CS, CG, XG, SA, (CS/CG) PEC, (CS/XG) PEC and (CS/SA) PEC were obtained using potassium bromide disks in the range of 4000–400 cm^{-1} to confirm complex formation between those polymers.

In vitro release study

The release properties of naproxen sustained release matrix tablets were investigated using USP dissolution apparatus I (basket) at 37 ± 0.5 °C with rotation speed of 100 rpm in 900 ml dissolution medium (HCl solution 1.2) for 2 hours and (phosphate buffer 6.8) at specific times intervals (0.5 , 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20) hour(s) in which samples of 5 mL were withdrawn, and the volume of samples was replaced with 5mL of the same buffer solution. These samples were filtered using a 0.45 –µm millipore filter and analyzed spectrophotometrically at 271 nm for the drug content in both mediums. Each test was done in triplicate.[15,16]

RESULTS AND DISCUSSION

Effect of the formation of polyelectrolyte complex

The release of naproxen from formulas F3, F7, and F8 is shown in Figure 1. Comparing between F3, F7 and F8, it was seen that after 7 hours the release from F7 which contains 200 mg SA was about 93.32% due to the presence of SA which is a pH-sensitive polymer that forms a diffusion barrier on the surface of the tablet that leads to its swelling and erosion in the intestinal fluid and burst the release of the drug.[17] Whereas, the release of naproxen from F8 which contains 200mg CS

Table 1: Different formulas of naproxen as sustained-release tablets

Formula No. / *Substance (mg)*	*F1*	*F2*	*F3*	*F4*	*F5*	*F6*	*F7*	*F8*	*F9*	*F10*	*F11*	*F12*
Naproxen	250	250	250	250	250	250	250	250	250	250	250	250
CS_h	100	50	150	85	70	50		200	150	150	150	150
CS_l										50		
SA	100	100	50	85	70	50	200		50			
XG											50	
CG												50
PVP	25	25	25	25	25	25	25	25	25	25	25	25
Magnesium Stearate	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Lactose monohydrate	22.5	72.5	22.5	52.5	82.5	122.5	22.5	22.5		22.5	22.5	22.5
MCC									22.5			
Total weight (mg)	500	500	500	500	500	500	500	500	500	500	500	500

CS_h:High molecular weight chitosan, SA: Sodium alginate, XG:Xanthan gum, CG:Carrageenan, PVP:Polyvinylpyrrolidone.MCC:Microcrystalline cellulose.

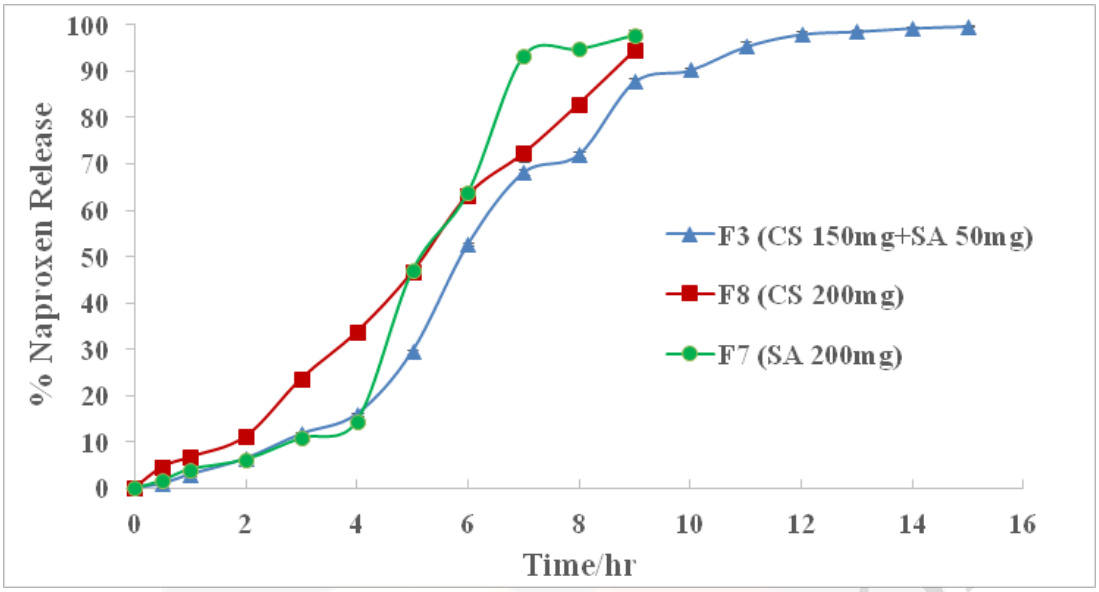

Fig. 1: The effect of the formation of (CSh/SA) PEC on the cumulative release of naproxen at different pH media at 37° (n = 3)

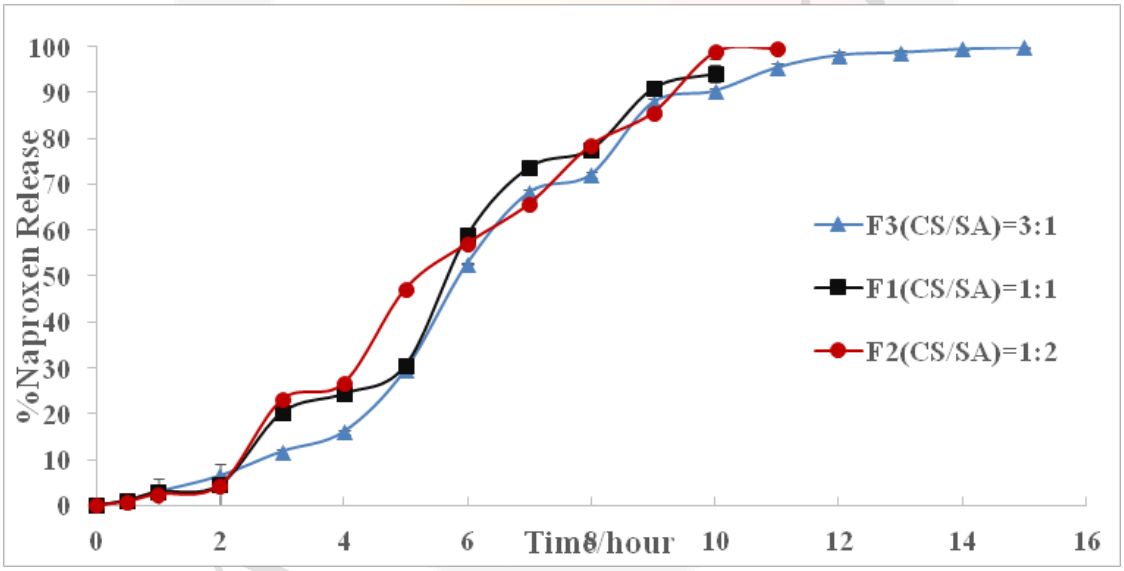

Fig. 2: The effect of the (CS_h/SA) ratio on the cumulative release of naproxen at different pH media at 37° (n = 3)

was 72.21%, after 7 hours due to the presence of CS which acts as a drug carrier and binder to extend the release of the drugs(96).While in F3 which contains 150mg CSh +50mg SA only 68.17% of naproxen was released after 7 hrs and the release was extended to 15 hrs ,so the release was non significantly decreased ($p > 0.05$),the reason behind that is the formation of PEC between CSh and SA through an electrostatic interaction between the protonated amine (NH^{3+}) group in CS and the carboxylate (CO^{O-}) group of SA which solved the problem of pH dependency due to the formation of complex.[18]

Effect of polymer to polymer ratio

The effect of different ratios on the release of naproxen from formulas F1, F2 and F3 are shown in Figure 2. These formulas were prepared by mixing CSh and SA in different ratios (1:1, 1:2 and 3:1) respectively. It was seen that in vitro release of naproxen might be affected by the physicochemical properties of CS and SA since they are pH-dependent. Comparing the release from F1 which contains CSh/SA in a ratio of 1:1 with F2 which contains CSh/SA in a ratio of 1:2 about 30.55% of naproxen was released from F1 during the first 5 hours and about 47.55% of naproxen was released from F2. So, the release of naproxen was significantly increased ($p < 0.05$) only in the first 5 hours due to increased amount of SA in F2 which caused swelling and erosion of the polymer in the intestinal fluid. While in F3 which contains CSh/SA in a ratio of 3:1, F3 showed the slowest release in which released 52.17% of naproxen in 6 hours. The release of F3 was decreased significantly ($p < 0.05$) when the amount of CS increased in the matrix which increased the interaction between the two

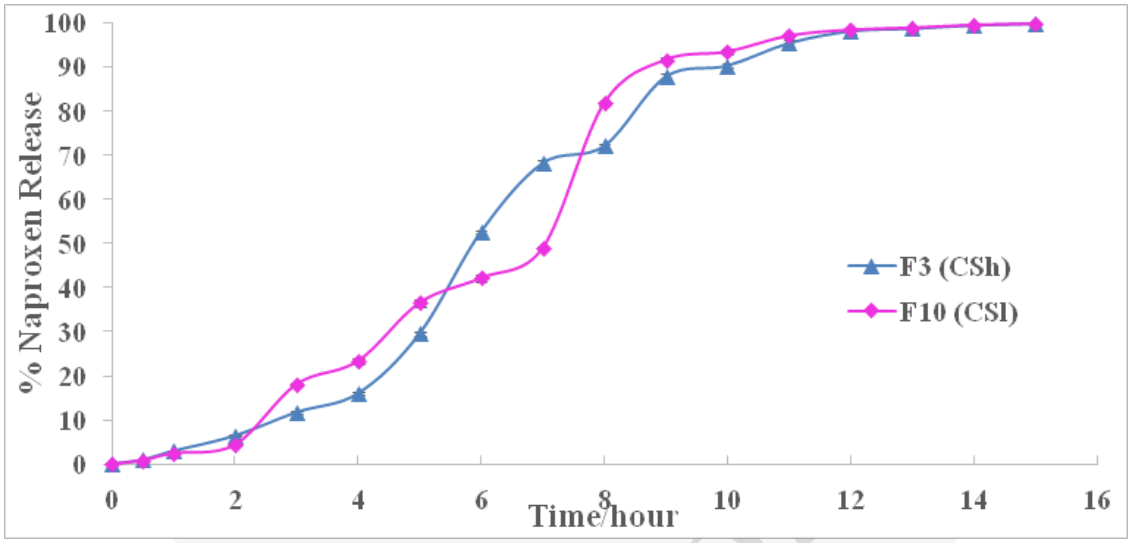

Fig. 3: The effect of the CS_l and CS_h on the cumulative release of naproxen at different pH media at 37° (n = 3)

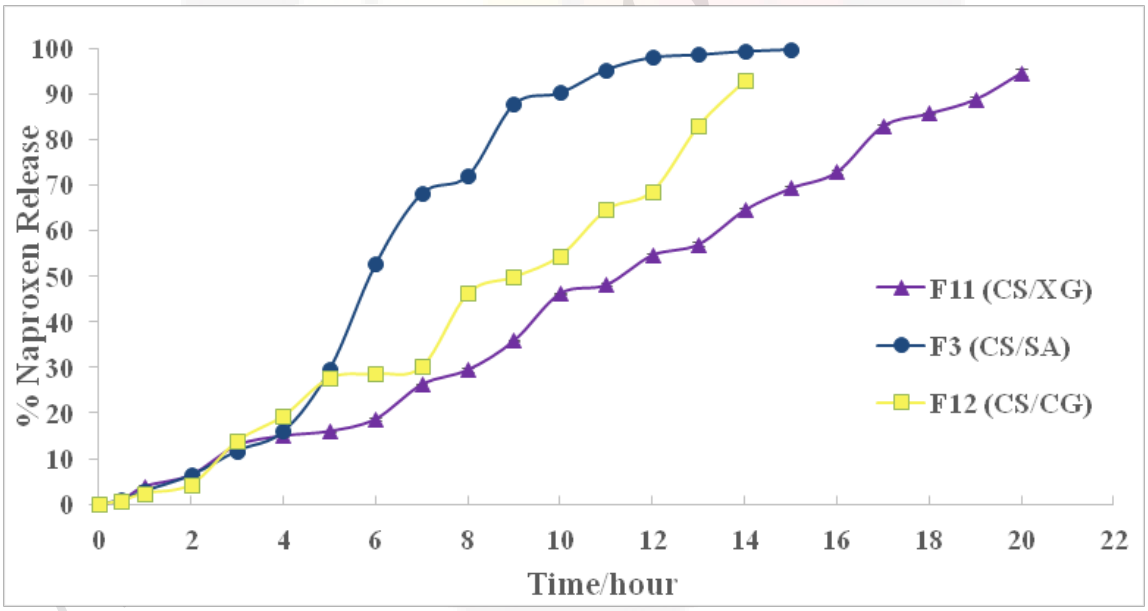

Fig. 4: The effect of the type of anionic polymer on the cumulative release of naproxen at different pH media at 37° (n = 3)

polymers to form a closed network that leads to decrease in the diffusion of the drug outwards of the tablets.[19,20]

Effect of molecular weight of chitosan

Two formulas (F3 and F10) were used to study the effect of the molecular weight of CS on the release of naproxen as shown in Figure 3. Formulas 3 and 10 were prepared using high and low molecular weight CS respectively, it was seen that there was no significant difference ($p > 0.05$) observed in the dissolution profile of naproxen sustained-release tablet when changing from high to low molecular weight CS after one hour where 2.94% of naproxen was released from F3 and 2.44% of naproxen was released from F10 may be due to the fact that CS is not fully reacted with SA to form PEC after one hour (57), also there was no significant ($p > 0.05$) difference in the release of naproxen after 6 hours where 52.71% and 42.14% of naproxen was released from F3 and F10 respectively, but after the 6 hours a slight decrease in the release of naproxen occurred with the increase of CS molecular weight may be to the fact that a similar portion of SA interacted with CS despite the difference in molecular weight of CS.[17]

2.4 Effect of anionic polymer type

To study the effect of the type of anionic polymer SA, XG and CG were used in the preparation of (CSh/SA), (CSh/XG) and (CSh/CG) PECs respectively, the release profiles from these formulations were shown in Figure 4. It was seen that there was no significant difference ($p > 0.05$) in the release rate between the three formulas F3, F11 and F12 at the first 4 hours were 15.99%, 15.02%, and 19.37% respectively.

According to this study, it was seen that the strongest PECs was formed with F11 (CSh/XG) which extended the release of naproxen up to 20 hour may be due to the presence of xanthan gum which is a high molecular weight polysaccharide that formed a highly viscous and hydrated layer on the surface of the matrix tablet allowing the drug to diffuse slowly and to be released by erosion. [21] The release of F3 which contains CSh/SA was significantly increased ($p < 0.05$) due to the presence of SA which has high sensitivity to pH and forms a diffusion barrier on the surface of the tablet that leads to its swelling and erosion in the intestinal fluid and burst the release of the drug.[17] On the other hand, the release of F12which contains CSh/CG was significantly decreased ($p < 0.05$) due to the presence of carrageenan which has a high viscosity and gelling properties that can slow the release rate of the drug.[22]

Effect of diluent type

To study the effect of diluent type, F3 which contains lactose as a diluent was compared with F9 which contains MCC as shown in Figure 5. The results of naproxen release showed no significant difference ($p > 0.05$) at 6 hr in which F3 released 52.71% and F9 released 62.11% of naproxen, but then the release was faster from the formula contains MCC (F9) in comparison with the contains lactose (F3).The faster release rate was seen with MCC due to inherent disintegrant characteristics so quick release of the drug into the dissolution medium from matrix tablets. The results were in agreement with other researchers where rapid release rate of slightly water-soluble drugs (like naproxen) from hydrophilic matrix tablet when changing the diluent from lactose to MCC.[23]

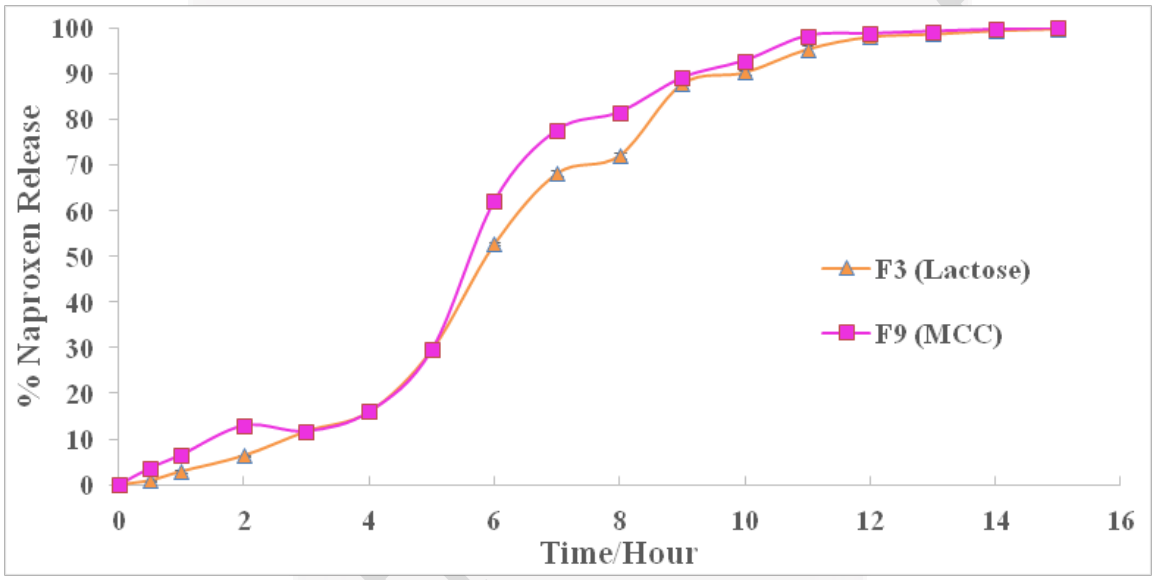

Fig. 5: The effect of the type of diluent on the cumulative release of naproxen at different pH media at 37° (n = 3)

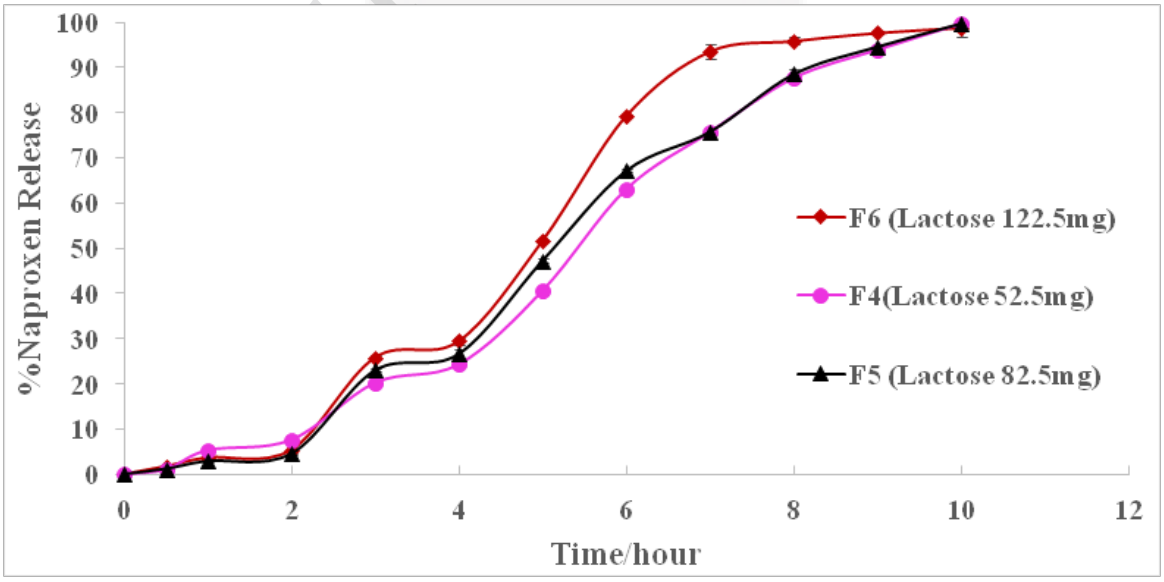

Fig. 6: The effect of the amount of diluent on the cumulative release of naproxen at different pH media at 37° (n = 3)

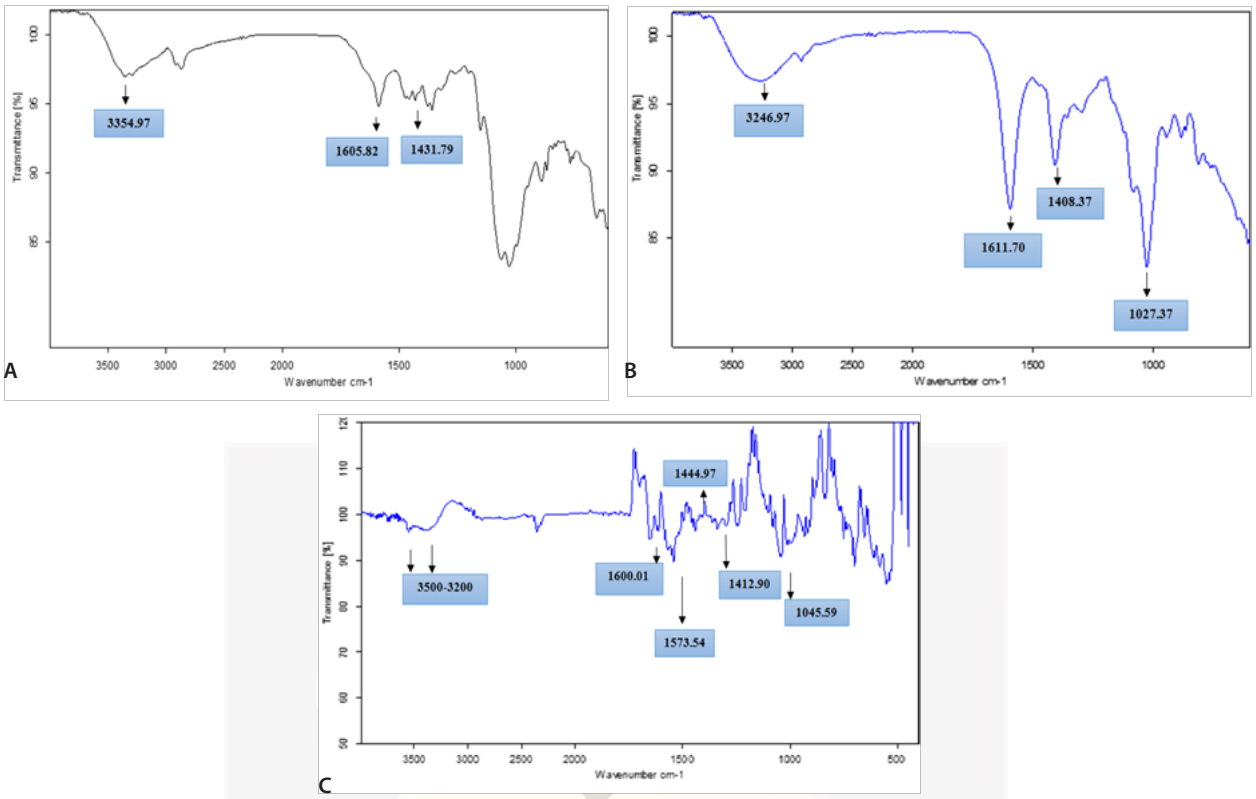

Fig. 7: FTIR spectra of (A) CS, (B) SA, (C) CS/SA PEC

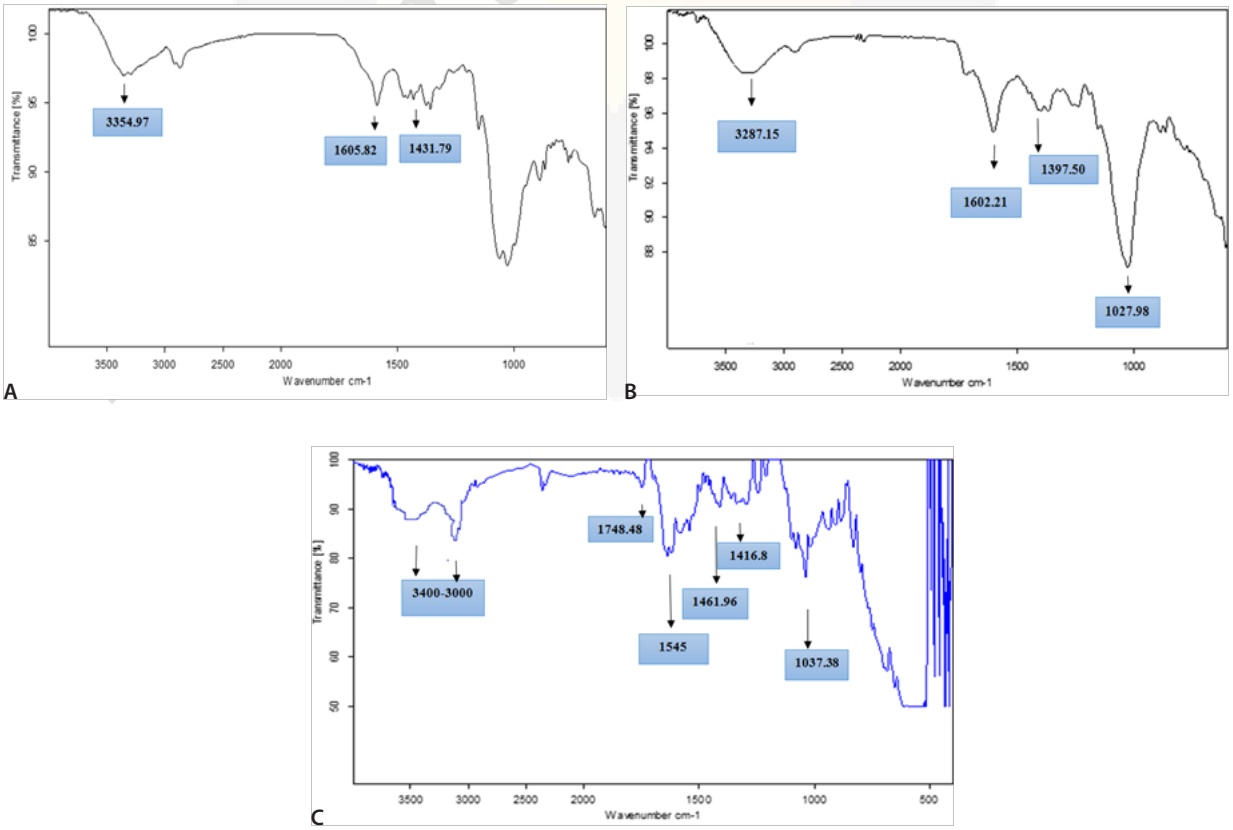

Fig. 8: FTIR spectra of(A)CS; (B)XG; (C) CS/XG PEC

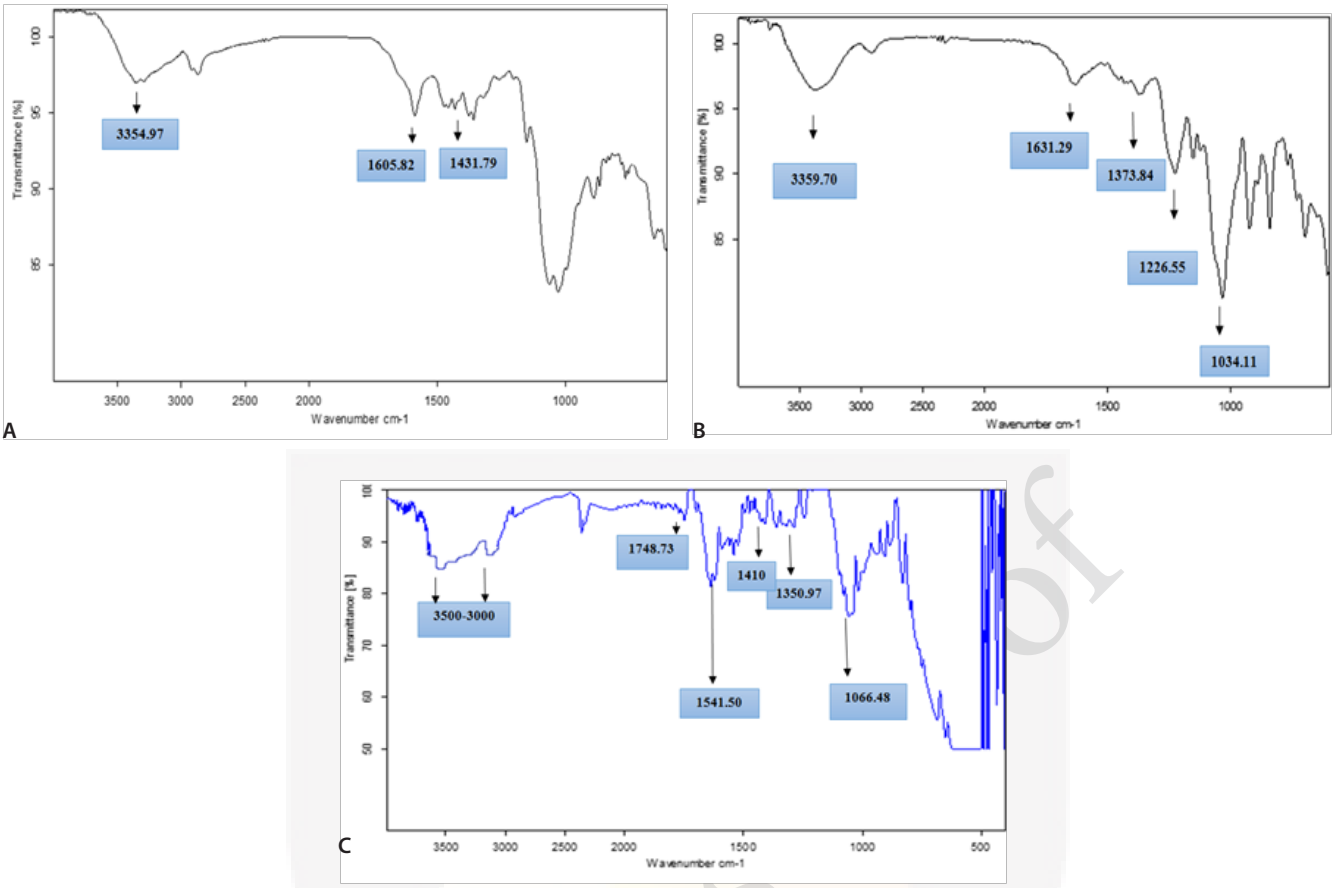

Fig. 9: FTIR spectra of (A) CS; (B) CG; (C) CS/CG PEC

Effect of diluent amount

The effect of diluent amount on the release of naproxen from formulas F4, F5 and F6 are shown in Figure 6. These formulas were prepared by mixing CSh and SA in different amounts of lactose 52.5 mg, 82.5 and 122.5 respectively. It was seen that in vitro release of naproxen might be affected by the amount and the solubility of the diluent. Comparing F4 which contains 52.5mg with F5 which contains 82.5 mg and F6 which contains 122.5 mg of lactose respectively, there was non-significant increase ($p > 0.05$) of naproxen release, at 6 hours the release of naproxen was about 63%, 67.16% and 79.28% from F4,F5 and F6 respectively. The explanation of this increase in the release rate of naproxen is that, as the number of lactose increases, the porosity of swollen matrix increases and the strength of gel decreases which speed up the erosion and release rate since lactose is a water-soluble diluent.[19]

Fourier Transform Infrared (FT-IR) Spectroscopy

The electrostatic interaction between the NH^{3+} group in CS and COO^- in SA, XG, and CG lead to the formation of self-assembled PECs in the dissolution process when the pH of the solution was about 1.2. The PECs were formed as a film on the surface of the tablet.[25,24] In order to confirm the (CS/SA), (CS/XG) and (CS/CG) interactions, tablets were dried and analyzed by FT-IR spectroscopy. Figures 7, 8 and 9 show the FT-IR spectra of each complex. In CS, the bands were shifted 1600.01 cm^{-1} for (C = O) group in the spectrum of (CS/SA) PEC. While in (CS/XG) PEC spectra the bands of CS were shifted to 1545.30 cm^{-1} for (C = O) group. In addition (CS/CG) PEC spectra showed the shifting of CS bands to 1541.50 cm^{-1} for (C = O) group. The IR spectrum of SA, XG, and CG showed the characteristics peaks at 1611.70 $cm^{-1,}$ 1602.21 cm^{-1} and 1631.29 cm^{-1}which represent the stretching of (C = O) group respectively. These bands are shifted to 1573.54 cm^{-}, 1748.48 cm^{-1}, and 1748.73 cm^{-1} respectively.

These results suggested that (CS/SA), (CS/XG) and (CS/CG) PECs were formed through the electrostatic interaction between the ($-COO^-$) group in SA, XG and CG with ($-NH^+$) group in CS respectively.[25-29]

CONCLUSION

Naproxen can be formulated as oral sustained release matrix tablet, using a physical mixture of cationic and anionic polymers to form PECs resulting in less frequent dosing and a reduction in gastric irritation. FTIR spectroscopy showed that PEC could be formed by the electrolyte interaction between ($-CO^{O-}$) group of anionic polymers (SA, XG, and CG) and ($-NH^{3+}$) of cationic polymer CS when the pH of the dissolution was 1.2. Increasing the amount of SA, XG or CG in the formula showed pH-dependent release and was given a faster release rate while the release rate retarded with

increasing PEC strength. Formula 13 formed the strongest PEC with a ratio of CS: XG equal to (3:1) which extended the release up to 20 hours.

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