Design and *In Vitro* Evaluation of Pentoxifylline-Polyelectrolyte Complex Tablets

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ABSTRACT

The study evaluates the possibility of using polyelectrolyte complexes (PECs) in the form of mucoadhesive matrix tablets to achieve a prolonged drug release profile of Pentoxifylline suitable for peroral administration. PECs were formed by different ratios and combination of polymers (chitosan–alginate, chitosan-carbopol and chitosan–carrageenan) and were dried by lyophilisation. Characterization was performed by Fourier Transform-Infrared (FT-IR) spectroscopy and X-Ray Diffraction (XRD) studies. The tablets were formulated by direct compression method. The influence of polymer ratio on drug release was studied by swelling index and dissolution studies and *ex-vivo* studies gave the bioadhesive strength. The formulation were subjected to accelerated stability testing as per ICH guidelines. The release data were examined kinetically. All the lyophilized PECs had some degree of prolonged release properties. The chitosan-carbopol complex matrices CC4 and CC3 were the best candidates compared to the other systems in prolonging the drug release profile of Pentoxifylline.

Keywords: Carbopol 934P, Carrageenan, Chitosan, Pentoxifylline, Polyelectrolyte complex, Sodium Alginate.

INTRODUCTION

The occurrences of charge-charge interactions between ionic polymers and drugs were considered to be a negative event when the ionic polymers are used as excipients in pharmaceutical formulations. In these systems release of drugs may be strongly affected by the occurrence of charge-charge interactions. However, in recent years these negative events of polymer-drug and polymer-polymer interactions have been exploited positively for controlled drug release.[1,2]

The interaction between two oppositely charged polymers results in the formation of a complex, termed as polyelectrolyte complex. This PECs meet the profile of requirements of biocompatible polymer systems and can be adapted to meet the various requirements like carrier substances and components for active substances. Polyelectrolyte complexes are the association complexes formed between oppositely charged particles (e.g. polymer-polymer, polymer-drug and polymer-drug-polymer). These are formed due to electrostatic interaction between oppositely charged polyions.[3] This avoids the use of chemical cross linking agents, thereby reducing the possible toxicity and other undesirable effects of the reagents.

Our interest in the polymers chitosan, alginate, carbopol, and carrageenan is based on the fact that our country is an important producer of these polysaccharides. At the same time, since our national pharmaceutical industry uses basic technology for the manufacture of solid dosage forms, most of the procedures are based on dry granulation techniques.

Pentoxifylline, a synthetic xanthine derivative, is an analogue of theophylline and inhibits phosphodiesterase. Pentoxifylline and its metabolites improve the flow properties of blood by decreasing its viscosity in patients with chronic peripheral arterial disease, this increases blood flow to the affected microcirculation and

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enhance tissue oxygenation.[4] Pentoxifylline is rapidly and almost completely absorbed from the GIT following oral administration, but the drug faces the problem of extensive first-pass metabolism in the liver.[5] It has short half-life of 1.6 hours and low oral availability (19 ± 13%). Therefore it needs to be formulated in such a way that its bioavailability is increased when administered perorally.

An attempt was made to design a system of PEC tablets in which the properties of different polymers are made use. Chitosan chosen as the common polymer for all the combination of PECs has the property of ionizing at acidic pH and swelling, good bioadhesion and biodegradability. Sodium Alginate, Carbopol and Carageenan have good swelling, bioadhesion and biodegradable property. The PECs tablets formed are expected to adhere to the stomach mucous lining, swell and form a matrix which prolongs the drug release.

MATERIALS AND METHODS

The following materials were used in this study: Pentoxifylline was procured as gift sample from Anu's Laboratory, Hyderabad, India; Chitosan was purchased from CFID, Cochin. Carbopol 934P and Sodium alginate was purchased from CDH (P) Ltd. New Delhi. I-Carrageenan (Irish Moss) was purchased from HiMedia, Mumbai. All other chemicals used were of analytical grade.

Preparation of PECs

Polyelectrolyte complexes of the different ratios of polymers were prepared as shown in Table 1. The chitosan-sodium alginate polyelectrolyte complexes were prepared from chitosan solution of 4% w/v in 1% v/v acetic acid solution and Sodium alginate solution of 4% w/v in water.

The chitosan-carbopol polyelectrolyte complexes were prepared from chitosan solution of 4% w/v in 1% v/v acetic acid solution and carbopol solution of 4% w/v in water.

Table 1: Ratios of Polymers used in PEC Formation

Code	Chitosan-sodium alginate	Chitosan-carbopol	Chitosan-carrageenan pH 5	Chitosan-carrageenan pH 4
C1	1:1	–	–	–
C2	1:4	–	–	–
C3	–	1:1	–	–
C4	–	1:4	–	–
C5	–	–	1:1	–
C6	–	–	1:4	–
C7	–	–	–	1:1
C8	–	–	–	1:4

The chitosan-carrageenan polyelectrolyte complexes were prepared from chitosan solution of 4% w/v in 1% v/v acetic acid solution and carrageenan solution of 4% w/v in sodium acetate buffer at pH 5 and pH 4 respectively.

Each solution was heated separately at 70–80ºC. Both solutions were mixed at 75ºC with agitation until the mixture reached room temperature. Then it was left to rest for 2 hr. The polyelectrolyte complex was thoroughly washed with distilled water and was then separated from water by centrifugation for 30 minute at 10000 rpm. Thereafter, the polyelectrolyte complex was again submerged in distilled water and left at 9ºC for 48 hr. Then the centrifugation step was repeated. Finally the polyelectrolyte complexes were dried to constant weight by lyophilisation. Freeze Dryer (Table Top) - Daihan Labtech was used for lyophilization.

The polyelectrolyte complexes of all the polymer combinations prepared were rapidly solidified by transferring small portions with a Pasteur pipette onto the inner surface of a cold flask rotating in methanol bath at 50°C. After a certain layer thickness was obtained, the flask was attached to the vacuum adapter of the lyophilizer. The solvent was sublimed under pressure of 8–10 mmHg and condensed. Lyophilized preparations were stored in desiccators at room temperature. The PECs formed were milled by trituration and classified by sieving through 100 mesh sieve.[6,7]

Characterization of PECs

Fourier transform infrared spectroscopy (FT-IR)

The IR spectra were recorded on SHIMADZU 8201 PC FT IR SPECTROMETER using a thin film supported on KBr pellets. 1 to 2% of PECs of Pentoxifylline from each combination of polymers were mixed and ground to a fine powder. The PECs were finely ground by Nujol mulling technique. The mixture was processed within the pelletizer to get thin homogeneous films or pellets. The pellets formed where placed in IR sample holder and the spectrum was run. The spectrums were measured in cm^{-1}.

X-ray diffraction

The powder X-ray diffraction patterns of PECs were recorded using a Philips PW-1729 X-ray diffractrometer. PECs were mounted on a goniometer and gradually rotated while being bombarded with X-rays, producing a diffraction pattern of regularly spaced spots.

Preformulation studies

The powders of polymers and drug are characterized by bulk density, tapped density, Carr's consolidation index and angle of repose.

Table 2: Composition of Pentoxifylline PEC Tablets

Formulations	Pentoxifylline (mg)	Chitosan (mg)	Carbopol (mg)	Carrageenan (mg)	Sodium alginate (mg)	Magnesim stearate (mg)	Talc (mg)
CC1	400	200	–	–	200	8	8
CC2	400	80	–	–	320	8	8
CC3	400	200	200	–	–	8	8
CC4	400	80	320	–	–	8	8
CC5	400	200	–	200	–	8	8
CC6	400	80	–	320	–	8	8
CC7	400	200	–	200	–	8	8
CC8	400	80	–	320	–	8	8

Formulation of Pentoxifylline PEC tablets

Lyophilized complexes were directly compressible and were formulated into tablets by the direct compression method in Mini press I tablet compression machine, using the formula given in Table 2.

Evaluation of Pentoxifylline PEC tablets

The physicochemical properties like hardness, friability, weight variation and drug content estimation were evaluated as per the methods specified in British Pharmacopoeia 2012 and Indian Pharmacopoeia 2010.

Swelling

One tablet from each formulation was weighed individually (W_1) and placed separately in petridishes containing 10 ml of hydrochloric acid buffer (pH 1.2). After regular intervals (2, 4, 6 and 8 hours), the tablets were carefully removed from petridishes and excess water was removed using filter paper. The swollen tablets were reweighed (W_2) and swelling index of each tablet was calculated using the following equation and expressed in percentage.[8,9]

$$\text{Swelling index} = \frac{W_2 - W_1}{W_1} \times 100 \qquad \text{(Eq.1)}$$

In-vitro drug release studies

The *in vitro* drug release studies of the tablets were performed by using USP dissolution apparatus –type II (paddle type), using 900 ml of 0.1 N hydrochloric acid (pH 1.2) as the dissolution medium maintained at 37 ± 0.5ºC and rotated at 50 rpm. Aliquots were withdrawn at specified time intervals over a 8-hour period and immediately replaced with fresh dissolution medium. The drug content in the withdrawn samples was determined spectrophotometrically at 268 nm using a UV spectrophotometer (JascoV-530, Japan).

Ex vivo bioadhesion

Tablets bioadhesion was assessed by the measurement of detachment force required to separate the tablet from the substrate (porcine gastric mucosa) on which it was previously applied. Several techniques have been reported in literature for the measurement of bioadhesive strength by use of spring balance connected to the table support digital balance connected to recorder or universal tensile testing apparatus (Figure 1).[10]

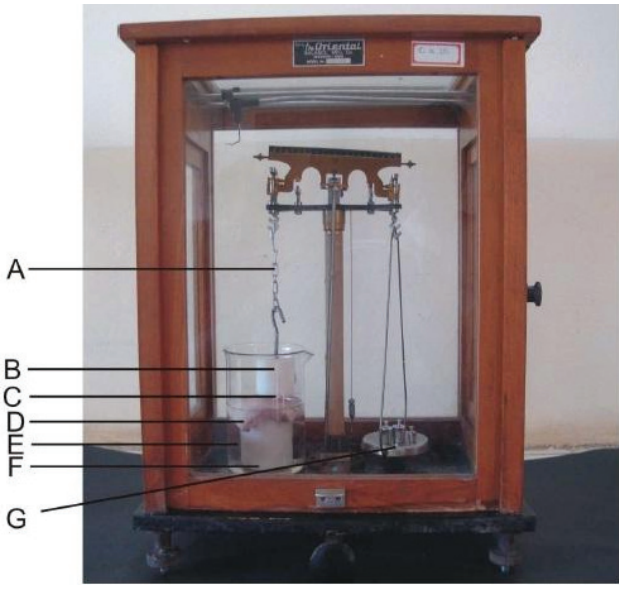

Figure 1: Bioadhesion test apparatus.
A: Hanging chain
B: Teflon block A
C: Tablet
D: Porcine gastric mucosa
E: Glass beaker
F: Teflon block B
G: Right side pan with weights

RESULTS AND DISCUSSION

Characterization of PECs

Fourier transform infrared spectroscopy (FT-IR)

The disappearance of peaks at 1601 cm^{-1} for ($-NH_3$) of chitosan and 1407 cm^{-1} for $-COO^-$ of alginate and broadening of peaks around 3500–3100 cm^{-1} indicating enhancement of hydrogen bonding, was observed in

chitosan-sodium alginate complex indicating the formation of polyelectrolyte complex.

Peaks of –NH group was observed at 1595 cm^{-1} for chitosan and that of –CO group of carboxylic acid for carbopol was observed at 1715 cm^{-1}. The overlapping peak of –NH and $–COO^-$ was observed at 1550 cm^{-1} confirming the formation of complexes between chitosan and carbopol.

Similarly the polyelectrolyte complex formation between chitosan and carrageenan was observed by the shifting of the peaks from 1595 cm^{-1} for –NH of chitosan and 1446.4 cm^{-1} for $–SO_4^{2-}$ of carrageenan to 1560.1 cm^{-1} for $–NH_3^+$ and 1419.4 cm^{-1} for $–SO_4^{2-}$ in the complex. The FT-IR spectra are shown in Figure 2.

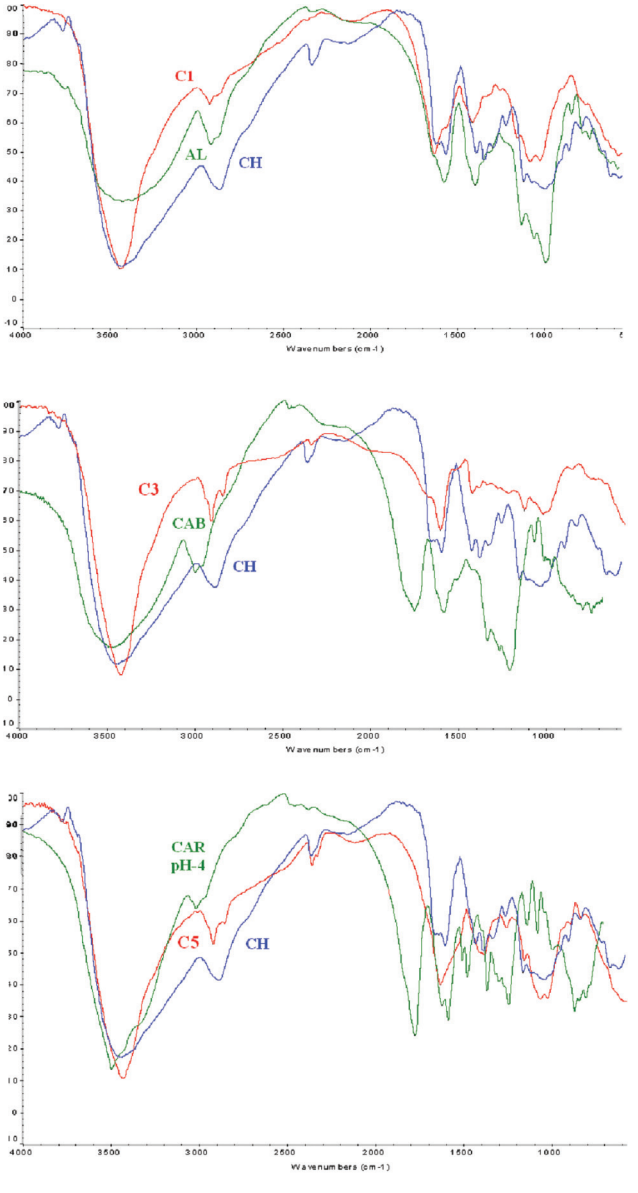

Figure 2: Comparative FT-IR spectra of chitosan (CH), sodium alginate (AL), and carbopol (CAB), with the respective PEC of chitosan and sodium alginate (C1), PEC of chitosan and carbopol (C3), carageenan at pH-4 (CAR pH-4) and PEC of chitosan and carageenan at pH-4 (C5).

X-ray diffraction

The X-ray diffraction patterns of pure polymers were found to be crystalline in nature and that of the PECs were found to be amorphous. This confirmed the formation of complex between the pair of polymers. The X-ray diffraction patterns are shown in Figure 3.

Preformulation

The bulk densities of PECs were found to be within the range of 0.713–0.873 gm/cc, while tapped densities were within the range of 0.812–0.954 gm/cc. The Carr's index of PECs were determined from the bulk and tapped densities and were found to be within the range of 5.1– 6.7. They can be said to have "excellent flow properties" as their Carr's index values lay between 5 to 15%. The values have been mentioned in Table 3.

Swelling index

The swelling index was calculated with respect to time. As time increases, the swelling index was increased,

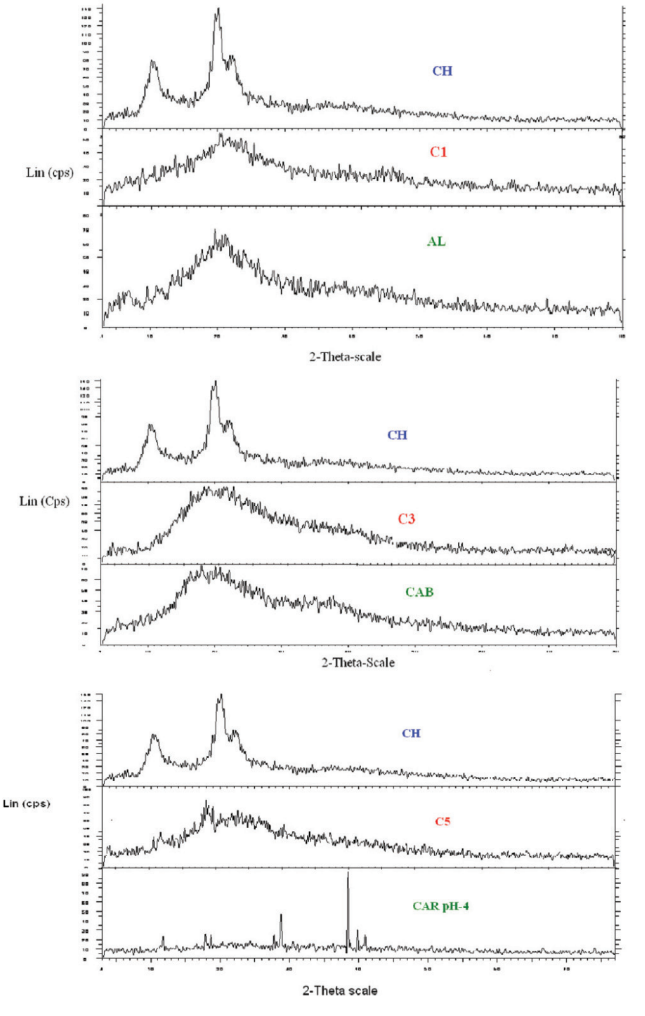

Figure 3: Comparison of XRD patterns of chitosan (CH), sodium alginate (AL), and carbopol (CAB), with the respective PEC of chitosan and sodium alginate (C1), PEC of chitosan and carbopol (C3), carageenan at pH-4 (CAR pH-4) and PEC of chitosan and carageenan at pH-4 (C5).

Table 3: Powder Properties of PECs

Powder properties	C1	C2	C3	C4	C5	C6	C7	C8
Bulk density (gm/cc)	0.83	0.82	0.82	0.87	0.79	0.71	0.76	0.75
Tapped density (gm/cc)	0.90	0.89	0.91	0.87	0.83	0.81	0.95	0.93
Angle of repose (°)	30.6 ± 0.87	29.8 ± 0.33	29.9 ± 0.65	30.03 ± 0.66	35.65 ± 0.72	32.19 ± 0.39	31.28 ± 0.25	30.65 ± 0.71
Carr's index	6.5	6.2	5.35	5.43	6.3	5.1	5.4	6.7

because weight gain by PEC tablet was increased proportionally with rate of hydration up to 6 hours. Later on, it decreases gradually due to dissolution of outermost gelled layer of PEC tablet into dissolution medium. The direct relationship was observed between swelling index and change in ratio of polymers, and as ratio changes i.e from 1:1 to 1:4, swelling index was increased as shown in Figure 4. Amoung different combination of polymers used, the swelling index of chitosan-carbopol PECs (CC4 > CC3) was observed to be high followed by chitosan-alginate (CC2 > CC1) and chitosan-carrageenan (CC6 > CC5 > CC7 > CC8).

In vitro drug release

It has been observed that the cumulative percent drug release decreases with increasing ratio of polymers in PECs and swelling index. The reason attributed to this fact is slow erosion of the gelled layer from the PEC tablets containing higher ratio (1:4) of polymers. This slow release is because of the formation of a thick interpolymer gel structure that delays drug release from tablet matrix, where hydration of individual polymer particles results in extensive swelling. As a result of rheology of hydrated product, the swollen particles coalesce. This results in a continuous viscoelastic matrix that fills the interstices, maintaining the integrity of the tablet, and retarding further penetration of the dissolution medium. This was evident from the release profiles (Figure 5). The overall sustained release performance of used polymer systems were found to be in order; chitosan-carbopol > chitosan-alginate > chitosan-carrageenan.

Drug release mechanism

Different kinetic equations (zero order, first order and higuchi's equation) were applied to interpret the release rate from matrix system. The best fit with higher correlation (R^2) ranges from 0.9904 to 1 for all the formulations.

As observed from the Table 4 the n values of R^2 for all the formulations were high enough to evaluate the drug dissolution behavior.

The hydrophilic polymers such as sodium alginate, chitosan and carrageenan show swelling in presence of liquid solvent due to polymer relaxation and is characterized by the formation of a gel-like network surrounding the system. The mechanical property of the surface hydrated gelatinous barrier plays an important role in over all drug release rate. As it is desirable for a sustained release device to deliver drug in zero order kinetics, our results showed high correlation coefficient among the formulation for zero order release. In our formulations it is found that the fluid enter through the cracks and pores of the matrix with diffusion of drug through the matrix insignificantly which is best described by Higuchi's$t^{1/2}$ model.

The value of n had no significant relationship with the diffusion of hydrophilic polymers contained in the

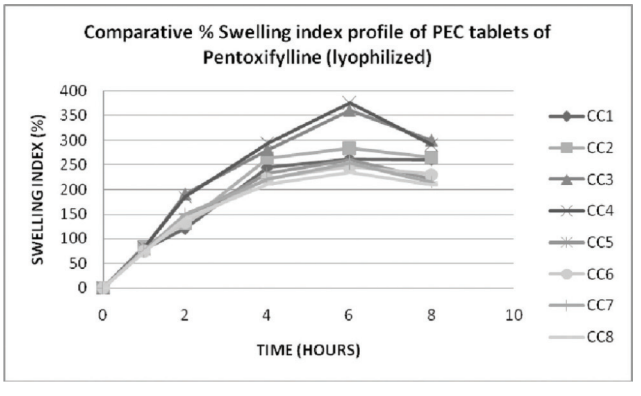

Figure 4: Comparative % swelling index profile of PEC tablets of Pentoxifylline.

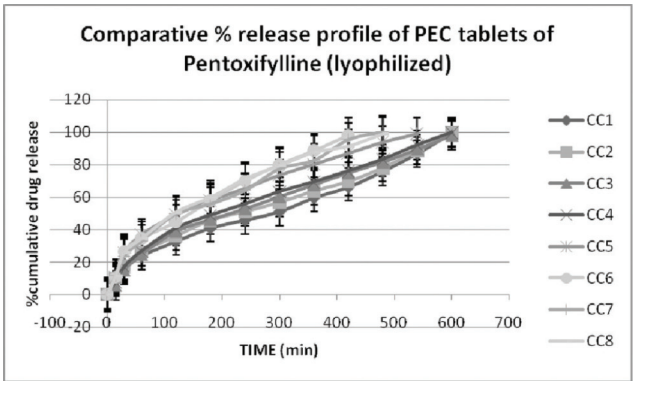

Figure 5: Comparative % release profile of PEC tablets of Pentoxifylline.

Table 4: Comparison of Different Orders of in Vitro Release of Drug from PEC Matrix Tablets of Pentoxifylline

Formulation	Zero-order	First-order	Higuchi model
CC1	y = 0.5371x + 53.262 **R^2** = 0.98	y = –0.001x + 1.9584 **R^2** = 0.98	y = 0.25x **R^2** = 1
CC2	y = 0.5547x + 264.81 **R^2** = 0.97	y = –0.0062x + 1.7209 **R^2** = 0.95	y = 3.6673x + 47.029 **R^2** = 0.99
CC3	y = 0.5972x + 170.05 **R^2** = 0.97	y = –0.0035x + 1.9209 **R^2**= 0.91	y = 4.3604x + 17.496 **R^2** = 0.99
CC4	y = 0.5952x + 225.38 **R^2** = 0.97	y = –0.0049x + 1.8141 **R^2** = 0.97	y = –4.3504x + 68.659 **R^2** = 0.99
CC5	y = 0.6326x + 304.34 **R^2** = 0.94	y = –0.012x + 1.7325 **R^2** = 0.99	y = 4.4526x + 51.196 **R^2** = 0.99
CC6	y = 0.8228x + 286.25 **R^2** = 0.97	y = –0.0102x + 1.6717 **R^2** = 0.95	y = 5.108x + 46.432 **R^2** = 0.99
CC7	y = 0.7418x + 311.81 **R^2** = 0.97	y = –0.0112x + 1.6213 **R^2** = 0.98	y = 4.8997x + 52.376 **R^2** = 0.99
CC8	y = 0.7256x + 318012 **R^2** = 0.95	y = –0.0128x + 1.6582 **R^2** = 0.97	y = 4.8518x + 53.709 **R^2** = 0.99

formulation. This observation was in agreement with the finding of (Nokhodchi *et al*).[11]

Ex vivo bioadhesion

The bioadhesive strength was determined in terms of weight required to detach the tablet form the porcine gastric mucosa. The selected polymers are known to swell readily on contact with the hydrated mucus membrane. This glass-rubbery transition provides polymers plasticization, resulting in a large adhesive surface for maximum contact with mucin and flexibility to the polymer chains for interpenetration with mucin. Increasing the polymer ratio provide more adhesive sites and polymer chains for interpenetration with mucin resulting in augmentation of bioadhesive strength (up to 26.3 gram force). CC4 and CC3 showed the best bioadhesion results followed by CC2 and CC1 as in Table 5. The formulations showed bioadhesion time on sheep buccal mucosa from 11 hour to 16 hour. This indicate that the formulations have ability to remain localize on specific sites on mucosal membrane.

Table 5: Bioadhesive Strengths of PEC Tablets of Pentoxifylline

Formulation	Bioadhesive strength (gm)
CC1	22.63 ± 0.32
CC2	23.07 ± 0.49
CC3	23.66 ± 0.76
CC4	25.72 ± 0.64
CC5	22.61 ± 0.92
CC6	20.80 ± 0.84
CC7	22.00 ± 0.93
CC8	21.78 ± 0.43

CONCLUSION

The choitosan-carbopol, chitosan–alginate systems were better than the chitosan–carrageenan system as a prolonged drug release matrix system because the drug release is controlled at low percentage of the polymers in the formulation. The chitosan-carbopol, chitosan–alginate system showed higher mean dissolution time than the chitosan–carrageenan system. In the case of the system chitosan–carrageenan, the high capacity of carrageenan to promote the entry of water into the tablet could be responsible for the main mechanism of drug release, i.e. disintegration instead of the swelling of the matrix. Chitosan-carbopol system proved to be better compared to chitosan-alginate system in case of swelling index and dissolution time. The bioadhesive strength observed for chitosan-carbopol system and chitosan-alginate system could help the systems to be localized in the acidic pH of stomach for the prolonged period of time. The promising swelling property and bioadhesive strength of the PECs could prove to prolong the effect of Pentoxifylline.

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