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Design and Pharmacokinetic Evaluation of Ciprofloxacin Sustained Release Tablets

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ABSTRACT

The present study is an attempt to develop and evaluate the sustained release tablet formulations (oral) of ciproflocacin hydrochloride utilizing chitosan based in situ forming polyelecrolyte complex as retardant polymer. The traditional method of wet granulation was used to prepare various formulations. A 1% w/w solution of chitosan in 1% acetic acid (cooled to about 4 ^{o}C and neutralized) was used as binder to granulate the drug mixed with anionic polymers like xanthan gum and sodium starch glycolate and other excipients. A number of characteristics were assessed for the tablets, including thickness, hardness, friability, drug content, and uniformity of weight. The in vitro drug release studies were conducted for 12 hrs, in 500 ml of HCl + KCl buffer [(pH 1.5) for 2 hr], for 8 hrs in mixed phosphate buffer (pH 6.8) and again for 2 hr at pH 7.5 utilizing mixed phosphate buffer, using USP type II apparatus running at 50 rpm. The pharmacokinetic parameters were examined by using various mathematical models (zero order, Higuchi, first order, Korsmeyer – Pepps equations and Hixson – crowell) to investigate and elucidate the mechanism of drug from various formulations/ tablets. The drug release studies confirmed the sustained release of drug for 12 hrs. From the dissolution profile comparison of two formulations, it was also confirmed that the change in anionic polymer from one to two had no effect on the dissolution profiles of the formulations. The polyelectrolyte complex formation (in situ) between chitosan and anionic polymers had been revealed by XRD studies of polyelectrolyte complex gels.

KEYWORDS: ***Chitosan, Sodium Starch Glycolate, Xanthan Gum, Polyelectrolyte complex, ciprofloxacin hydrochloride.***

INTRODUCTION

It is not so easy to create sustained-release (single-unit) oral dosage forms for hydrophilic medicines, which are extensively soluble (10 mg/ml) in gastric fluids and also have high dose, because of the drug delivery system's burst release of the loaded medication and limitation on the number of rate-controlling excipients (due to high drug dosages) that can be utilized to create a formulation that has a size appropriate for oral administration [1]. A straightforward, yet incredibly efficient drug delivery method that can demonstrate a fairly steady rate of dissolution over a lengthy duration is therefore needed. After an examination of the literature, it was discovered that poly-electric complexes between polymers with opposing charges result in polymeric carriers that can be utilized to regulate the release of these medications from dosage forms, both initially and continuously. This may be explained by the resulting polymeric carriers' high degree of organization and dense, crystal-like shapes [2]. Therefore the present study attempts to design sustained release tablets of ciprofloxacin hydrochloride by using chitosan solution as binder and sodium starch glycolate or xanthan gum as excipients. The in situ formation of polyelectrolyte complexes was expected when the tablet encountered the acidic dissolution medium (HCL + KCl buffer, pH – 1.5). This approach was expected to sustain the release of drug i.e. ciprofloxacin hydrochloride due to high degree of organization and dense crystal – like structure of the polyelectrolyte complexes formed between cationic polymer chitosan and anionic polymers xanthan gum or sodium starch glycolate [3].

MATERIALS AND METHODS

Materials: Ciprofloxacin hydrochloride (CPZ) was supplied by Saphinx Life Sciences, Vill. Barotiwala, Ponta Saib, Distt. Sirmour (HP) and Well Treat Pharama, H. No. 922, Ward No. 5, Vishal Nagar, Rohtak (Haryana) as gift sample. The Chitosan (CH) (Low molecular weight), Xanthan gum (XG), Sodium Starch Glycolate (SSG), Lactose, purified Talc, Magnesium stearate and other excipients were purchased from Singhla Scientific Industries, 5309/27, Punjabi Mohalla, Ambala cantt (Haryana). Every auxiliary chemical and excipient that was used was of the analytical and pharmaceutical grades, respectively.

Methods: Pre- formulation studies:

Drug – polymer interaction studies: The drug – polymer interaction studies were performed using Fourier-transform infrared spectroscopy (FTIR). Since it was anticipated that there would be no interaction, the FTIR spectra of physical mixes of the drug and polymers were not recorded. So to study the interactions 1% w/v solution of drug in distilled water was mixed with 1% w/v solution of polymers in suitable medium (distilled water or 1% acetic acid). The mixture was kept at 37 ºC for 2 hr. After that the mixture was dried and FTIR spectra were recorded on Spectrum BX of PerkinElmer (USA) by using KBr pellet technique.

Polymer – polymer interaction studies: Fourier-transform infrared spectroscopy (FTIR) and differential scanning calorimetry (DSC) were used in the polymer-polymer interaction investigations. Physical mixes of polymers were not subjected to DSC thermograms and FTIR spectra because it was not anticipated that these would show any interactions between cationic and anionic polymers. There is a good chance that these interactions will occur, though, upon exposure of formulations to the acidic dissolution medium (0.1 M HCl, pH 1.5). Thus, in order to investigate how Chitosan and SSG or XG interact the polymers were mixed in ratio of 1:1 and packed in dialysis pouch (molecular weight cut – off – 1200) previously activated by boiling in Phosphate buffer having pH 7.4 for 30 min according to the experimental protocol shown below in table- 1.

Table-1 Experimental protocol for polymer – polymer interaction study

Sr. No.	Sample Code	Sample composition
1	T-1	Chitosan (CH) + Sodium Starch Glycolate (SSG)
2	T-2	Chitosan (CH) + Sodium Starch Glycolate (SSG)+ Xanthain Gum (XG)
3	T-3	Chitosan (CH) + Xanthain Gum (XG)

These sealed bags were kept at pH 1.5 (HCl+ KCl buffer) maintained at 37± 2 ºC in a basket type USP dissolution apparatus for 2 hrs. During the exposure gel formation occurred. After being removed from the dialysis bags, the contents (gelled) were dried overnight at 60 ºC in an oven. For these dried samples (gels), DSC thermograms and FTIR spectra were recorded.

Preparation of polymeric binder solution: Following the application of compression force, the binders are utilized to hold the various elements of a tablet/ Caplet together. The binder solution was prepared by dissolving chitosan (CH) in 1% acetic acid solution to produce 1% w/v solution. The solutions was cooled to 4ºC and then neutralized by 1M Sodium bicarbonate solution by maintaining the temperature at 4ºC throughout the process [2].

Preparation of Sustained release tablets: Using a traditional wet granulation method, the sustained release tablets were prepared as mentioned in table -2. The binder solution prepared in 1% acetic acid was used to granulate the mixture of drug and excipients. After passing through sieve number 10 the damp mass was dried overnight in a hot air oven at 60 ºC. Following their passage through sieve number 20, the dry granules were lubricated and compacted

into tablets using a single rotating tablet compression machine [3]. About 100 tablets were compressed for each formulation.

Table – 2 Composition of sustained release tablets containing ciprofloxacin hydrochloride along with different anionic polymers sodium starch glycolate and xanthan gum.

Sr. No.	Formulation Code	Ciprofloxacin hydrochloride (mg)	Sodium Starch Glycolate (mg)	Xanthan Gum (mg)	Lactose (mg)	Mg. Stearate (mg)	Talc (mg)	Binder (Chitosan solution in 1% acetic acid)
1	CPZ 1	750	---	----	100	27	9	1%w/v
2	CPZ 2	750	50	----	50	27	9	1%w/v
3	CPZ 3	750	25	25	50	27	9	1%w/v

Evaluation of Sustained release Tablets:

Pre- compression parameters:

Moisture content: Moisture content of dried granules was determined by using IR moisture balance. The pan of balance was released by removing the lock bar. The zero of scale was made to coincide with reference mark by rotating the right hand side knob in clockwise direction. The sample granules were spread evenly on the pan and granules were added till the pointer coincides with the reference mark and zero of scale. The IR lamp was turned on and temperature was set 100 – 110 ºC. The sample was exposed to the set temperature for 10 – 15 min. The right hand side knob was rotated in opposite direction to bring the pointer in line with reference mark. The reading of scale coinciding with reference mark and pointer would indicate the moisture content of sample. To ensure the complete removal of moisture the samples was again exposed to same temperature for 10 min. until pointer position was unchanged.

Drug content: For assay the granules/ powder equivalent to 50 mg of ciprofloxacin hydrochloride were shaken with distilled water (50 ml) in a volumetric flask (100 ml) for 10 min. The volume was made up by adding water and solution was filtered by using whatman filter paper. The filtrate (5 ml) was taken in volumetric flask (100 ml) and volume was adjusted by adding distilled water. Again the resultant solution (5 ml) was taken in volumetric flask (100 ml) and volume was adjusted by adding distilled water. From this final solution the test sample (1ml) was withdrawn and then centrifuged for 15minutes at 10000 rpm. The absorbance spectra of solution against water as blank were measured at λ_{max} of Ciprofloxacin Hydrochloride i.e. 276 nm. The drug content was calculated by using formula:

Drug content = Concentration X Dilution Factor, Drug Content = $\frac{\textbf{Drug Content (mg)}}{\textbf{Label Claim(mg)}}$ x**100** [4, 5, 6, 7]

Bulk density: The known weight of granules (20 gm) was put in a graduated cylinder of bulk density apparatus gently and volume occupied was noted. The bulk density was calculated by using the formula – **Bulk density = Weight / Volume occupied.**

Tapped density: The known weight of granules (20 gm) was put gently in a graduated cylinder of bulk density apparatus and apparatus was operated for 100 tapings. After 100 tapings volume occupied by granules was noted and tapings were repeated until volume remained unchanged. Tapped volume was noted after tapings. The tapped bulk density was calculated by using the formula – **Tapped density = Weight / Tapped volume.**

Hausners' ratio: It is a number that is correlated to flow ability of powder/ granules. The Hausners' ratio was determined by using formula – **Hausners' ratio = Tapped bulk density/ Bulk density**. This ratio determine the flow properties of granules. The ideal range for good flow properties should be 1.2 – 1.5.

Carr's consolidation index (Percent compressibility): The percent compressibility or Carr's consolidation index was calculated by using the formula **– Percent compressibility = [(Tapped density – Bulk density) × 100]/ Tapped density.** The Carr's consolidation index is indirectly related to the relative flow rate, cohesiveness and particle size.

Angle of repose: The largest possible angle between surface of powder/ granules' pile and a horizontal plane is referred as the angle of repose. This was measured by passing a known weight of granules through a funnel having 30 mm stem opening on a glass plate. When the granules were emptied from funnel, the piles' height (h) and piles' radius (r) were measured with ruler. The angle of repose was calculated by using formula – **Angle of repose (Ɵ) = $\tan^{-1}$ h/r**. The flow properties of powder or granules are measured by the angle of repose [8, 9].

Swelling index: To determine the swelling index each drug and polymers were mixed in ratio of 1:1 and packed in dialysis pouch (molecular weight cut – off - 1200) previously activated by boiling in Phosphate buffer having pH 7.4 for 30 min, according to experimental protocol shown below in table- 3.

Table – 3 Composition of polyelectrolyte complex gels to determine swelling index

Sr. No.	Sample Code	Composition
1	CPZ 2	Ciprofloxacin hydrochloride + CH + SSG
2	CPZ 3	Ciprofloxacin hydrochloride + CH + SSG + XG

Each previously weighted sample was first kept in HCL + KCl buffer (having pH 1.5) for 2 hr. and the sample was weighed after every 30 min. After that each sample was transferred in to mixed phosphate buffer (pH 7.4) for 8 hrs and each sample was weighed after every 1 hr until three same consecutive readings were obtained. The swelling index was determined from the formula – **Swelling index = [(Final weight – initial weight) × 100]/ initial weight** [8].

X - Ray Diffraction (XRD) studies: The X – Ray Diffraction studies were conducted on X –ray diffractometer, Miniflex 600, Rigaku Corporation, Tokyo, Japan. These studies were conducted to ensure the formation of Poly Electric Complex by the interaction between Chitosan and anionic polymers i.e. Sodium starch glycolate and xanthan gum when exposed to acidic environment. For the study the samples were prepared by mixing each drug and polymers in ratio of 1:1 and packing in dialysis pouch (molecular weight cut – off - 1200) previously activated by boiling in Phosphate buffer having pH 7.4 for 30 min according to the experimental protocol shown below in table - 4. The XRD thermograms of test samples were also compared with that of pure compounds.

Table – 4 Composition of Polyelectrolyte complex gels for X- ray diffraction studies

Sr. No	Sample Code	Composition
1	G- 1	Chitosan (CH) + Sodium starch glycolate (SSG)
2	G – 2	Chitosan (CH) + Sodium starch glycolate (SSG) + Xantan Gum (XG)
3	G – 3	Ciprofloxacin hydrochloride + CH + SSG
4	G - 4	Ciprofloxacin hydrochloride + CH + SSG + XG

These samples in sealed bags were kept at pH 1.5 (HCl + KCl buffer) maintained at 37± 2 ^{o}C in a basket type USP dissolution apparatus for 2 hrs. During the exposure gel formation occurred. After being removed from the dialysis bags, the contents (gelled) were dried overnight at 60 ^{o}C in an oven. To ascertain if the fine powder samples were crystalline or amorphous, they were continuously scanned at room temperature between 10^{o} to 80^{o} (2Ɵ) at 30 kV accelerating voltage, 15 mA current and at scanning speed of 10 ^{o}C/min [10].

Post- compression parameters:

Friability test: Required number of tablets (20) were weighed after dusting to find the initial weight. The sample was then placed in friabilator and machine was operated for 4 minutes or 100 revolutions. The tablets were again weighted after dusting to note down the final weight. The % friability was determined by using the formula – **Friability = [(Initial weight – final weight)/ initial weight] × 100.** There should be less than 1% friability, ideally.

Uniformity of Weight: 20 tablets for each formulation were taken for this test. Twenty tablets were weighed, and the average weight was determined. Next, a weight was taken for each tablet separately and the average weight was subtracted from individual weight of each tablet to find out difference. The deviation was calculated by determining the percent weight variation by using formula – Percent weight variation = [(individual weight – average weight) × 100]/ average weight. If no unit exceeds the double of the given limit and no more than two tablets fall outside the designated deviation limit, the sample passes the test [8, 9].

Drug content: The drug content of tablets of each formulation was determined by performing assay mentioned in the pre – compression parameters under drug content of granules [4, 5, 6, and 7].

Hardness testing: The Monsanto hardness tester was utilized to determine the hardness of formulated tablets. Three tablets from each formulation were taken randomly. The tablet was placed between anvil and spindle (diametrically) of tester and screw was rotated (clockwise) to hold the tablet. The scale was adjusted to coincide zero of scale with pointer. The screw was again rotated (clockwise) until tablet was broken. The reading on scale give the hardness (force required to break the tablet) of tablet. Ideally a tablet should have hardness value 4 -10 kg/cm^2.

Thickness testing: A vernier caliper was used to measure the thickness of formulated tablets**.** The thickness was determined for three tablets form each formulation (selected randomly). The tablet was placed between the larger jaws of caliper and jaws were tightened to hold the tablet. The tablet thickness was determined from readings of main scale and vernier scale [8, 9].

In vitro dissolution studies: The test was conducted utilizing USP type II apparatus at a paddle speed of 50 rpm. For first 2 hr 500 mL of HCl + KCl buffer (pH 1.5) was used as dissolution media, for next 8 hr mixed phosphate buffer with (pH 6.8) and mixed phosphate buffer (pH 7.5) for last 2hr. Samples of 3ml were collected at various time points (after 0.5, 1.0, 1.5, 2.0, 3.0, 4.0, 5.0, 6.0, 7.0, 8.0, 9.0, 10.0, 10.5, 11.0, 11.5 and 12.0 hr) until 12 h and the same amount of fresh media was added after each sample withdrawal. A UV spectrophotometer was used to measure the concentration of free drug at 276 nm [8, 9, 11].

Dissolution profile comparison: The dissolution profiles of formulations CPZ 2 and CPZ 3 were compared by using model independent approach that uses similarity factor (f_2) and difference factor (f_1) determination. The f_1 and f_2 values must be near 0 (up to 15) and 100 (more than 50), respectively, for profiles to be deemed similar [12, 13, 14].

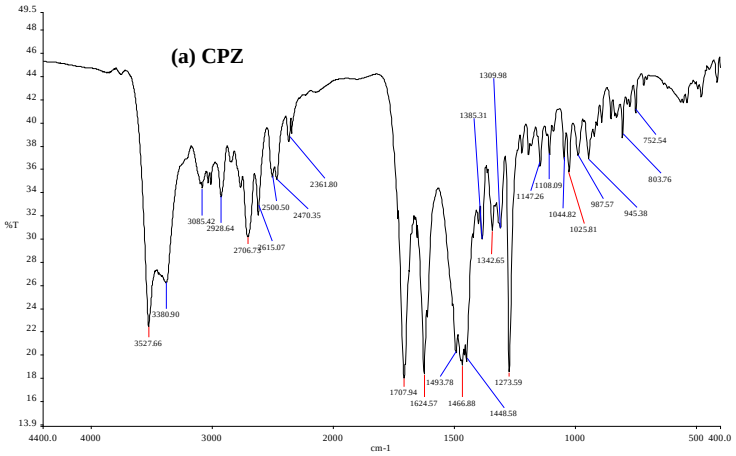
Drug release kinetics: To study the exact mechanism of drug release from various formulations, drug release data was analyzed/ tested with following mathematical models:

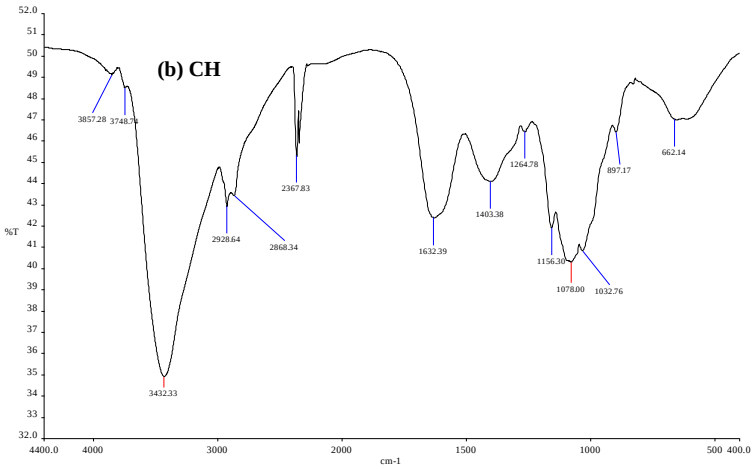
a. Zero – order equation
b. First – order equation
c. Higuchi square root law
d. Hixson – Crowell cube root law
e. Korsmeyer – Peppas equation [3,15, 16] .

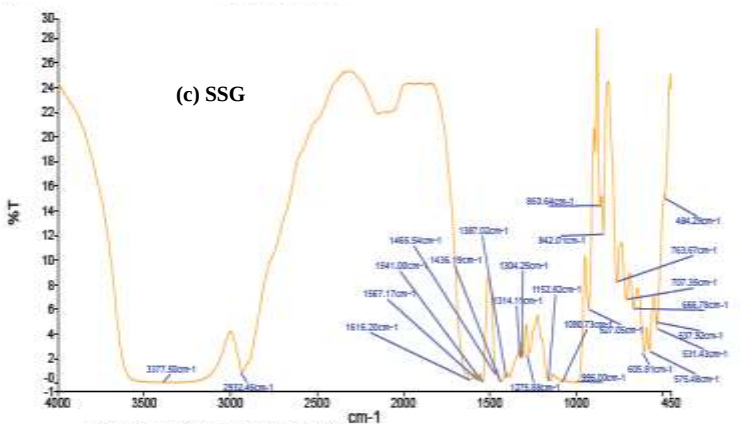
RESULT AND DISCUSSION

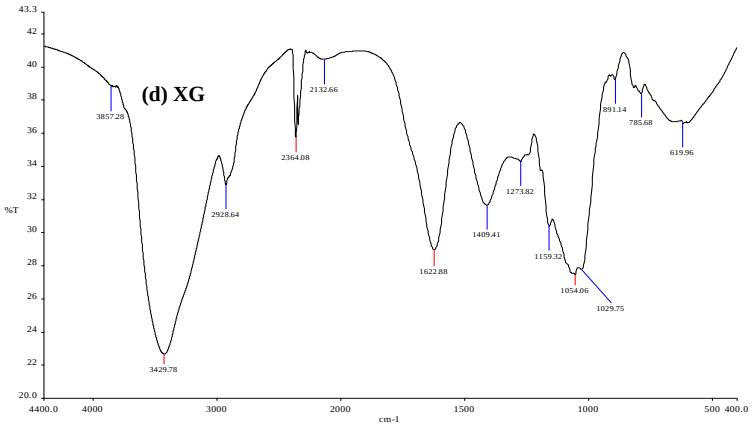
Pre- formulation studies:

Drug – polymer interaction studies: The spectra (FTIR) of pure CPZ (Fig. 1a) exhibited characteristic peaks at 3527, 3085, 2928, 1707 and 1624 cm^{-1} corresponding to –OH stretching vibrations of carboxylic group, alkene and aromatic –CH stretching, carbonyl and quinolones C=O stretching, respectively[5, 6, 17]. The spectra of chitosan (low molecular weight) (Fig. 1b) showed major peaks at 3423, 1632 and 1403 cm^{-1} because of amide I, II and CH and OH bending respectively [2, 3, 18]. In the FTIR spectra of SSG (Fig. 1c) the prominent characteristic peaks were observed at 3377, 2932, 1616, 1567 and 1436 cm^{-1} due to -OH stretching, $-CH_2$ symmetrical stretching, carbonyl group, asymmetric and symmetric –COO vibrations respectively [19]. The characteristic peaks observed in the FTIR spectra of XG (Fig. 1d) at 3429, 2928, 1622, 1409 and 619 cm^{-1} because of OH stretching of carbohydrates, $-CH_2$ asymmetric stretching, -CO stretching of acetate, CH, CH_2 and OH in plane bending in carbohydrates and pyranose ring respectively [2, 3, 20]. The FTIR spectra of sample containing solution mixture of CPZ + CH (Fig. 1e), CPZ + SSG (Fig. 1f) and CPZ + XG (Fig. 1g) did not exhibit interaction with drug due to presence of intact major peaks of Ciprofloxacin hydrochloride.









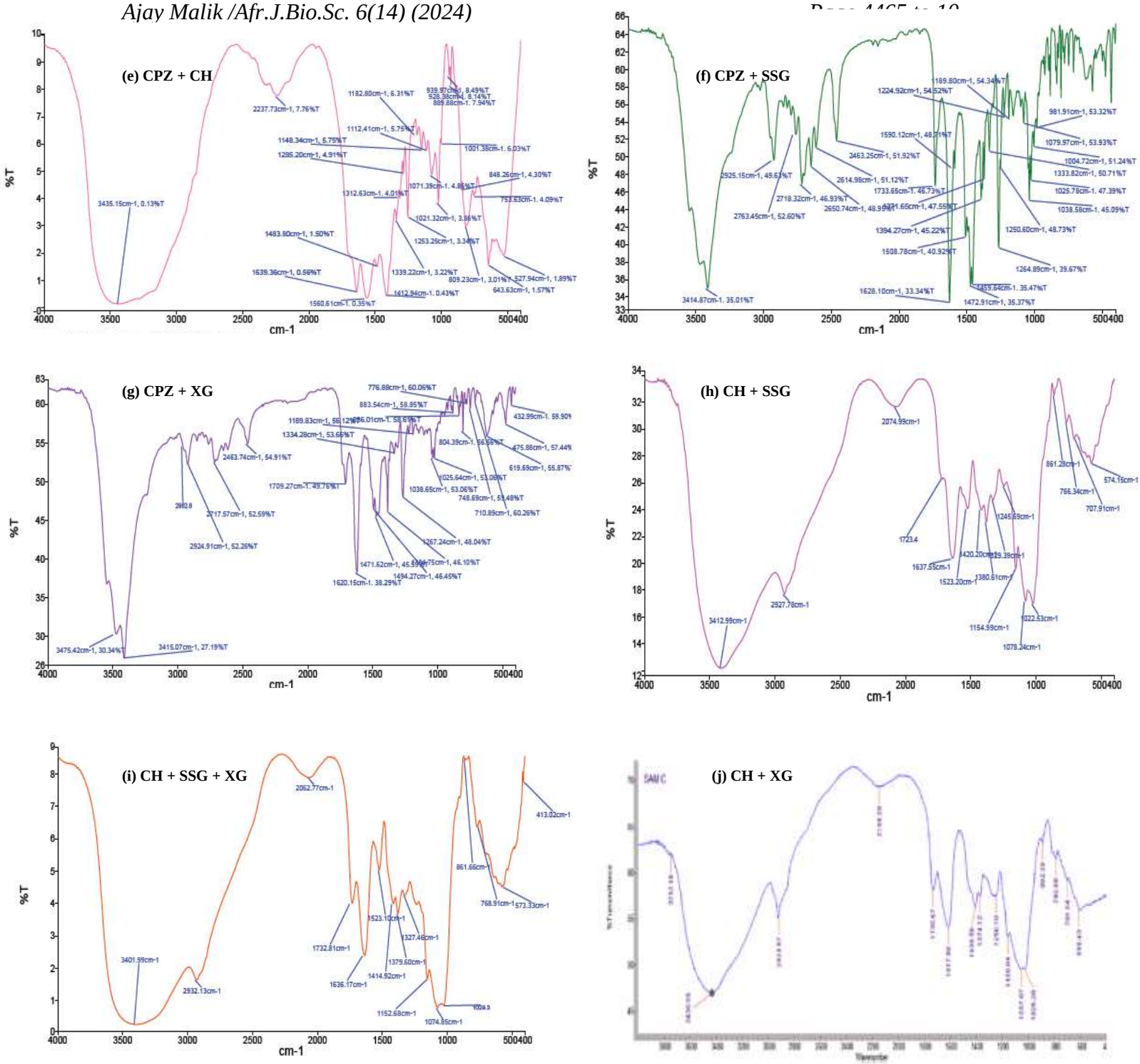


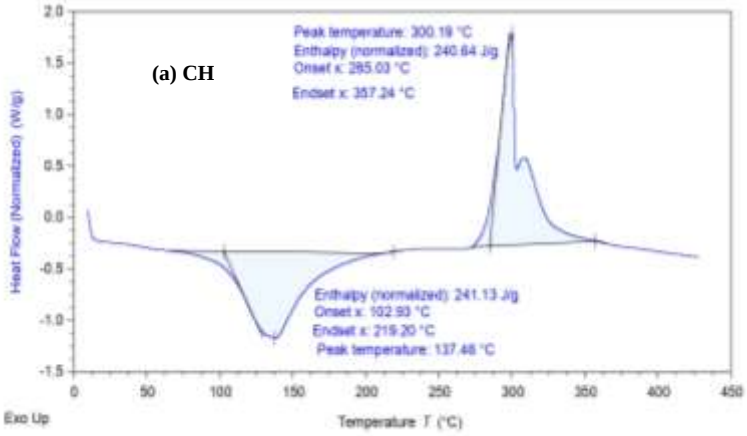
Fig. 1. FTIR spectra of : (a) Ciprofloxacin hydrochloride (b) Chitosan (Low molecular weight) (c) SSG (d) XG (e) CPZ + CH (solutions) (f) CPZ + SSG (solutions) (g) CPZ + XG (solutions) (h) CH + SSG (dried gel) (i) CH + SSG + XG (dried gel) (j) CH + XG (dried gel).

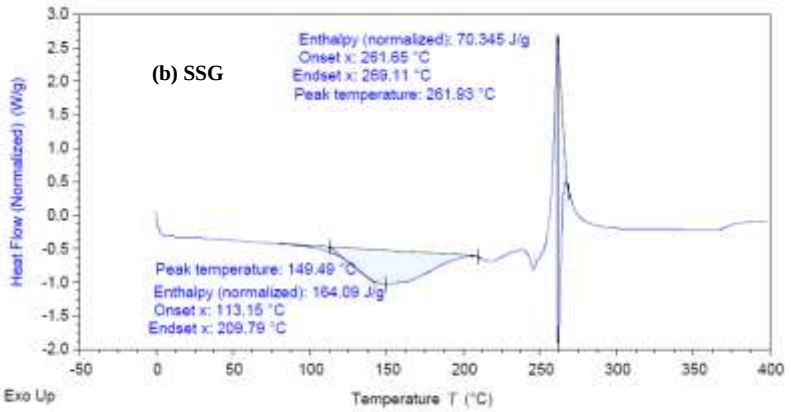
Polymer – Polymer interaction studies:

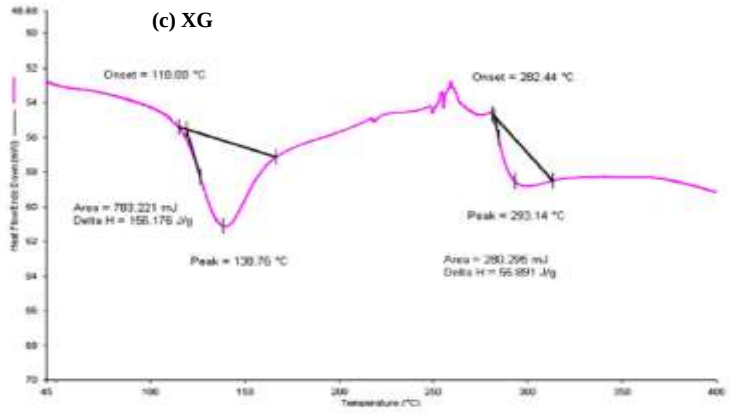
FTIR characterization: The spectra of dried PEC gel sample of CH + SSG (Fig. 1h) exhibited interaction between CH and SSG to form PECs. The –C=O stretching band of –C=O group at 1637 cm^{-1} in SSG spectra was shifted to lower wave number (present at 1616 cm^{-1} in FTIR spectra of SSG) showed the interaction of amino group of CH with carboxylic group of SSG. The –NH bending vibration peak at 1523 cm^{-1} (was absent in pure polymers) indicate the formation of ionic bonds. The spectra of dried PEC gel sample of CH + SSG + XG (Fig. 1i) also confirmed the interaction between carboxylic group of SSG and XG and amino group of CH to form PECs because of shifting of–

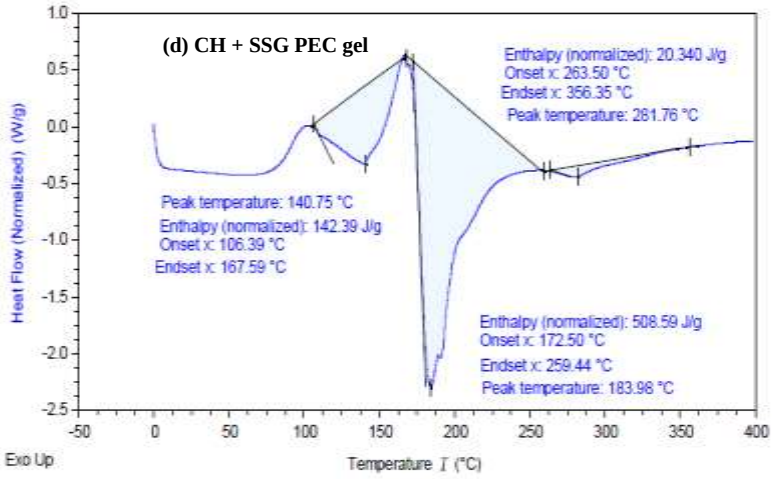
C=O stretching peak of –C=O group to lower wave number. The –NH bending vibration peak at 1523 cm^{-1} (was absent in pure polymers) indicate the formation of ionic bonds. The interaction between CH and XG was also suggested by the FTIR spectra of CH + XG (Fig. 1j) dried PEC gel. The shifting of –C=O stretching peak due to vibrations of –C=O group in XG to lower wave number (at 1736 cm^{-1}) showed the interaction of amino group of CH with carboxylic group of XG. The –NH bending vibration peak at 1523 cm^{-1} (was absent in pure polymers) indicate the formation of ionic bonds. The shifting in absorption bands in the spectra indicated the environmental change around –C=O and Amide – I [2, 3, 19].

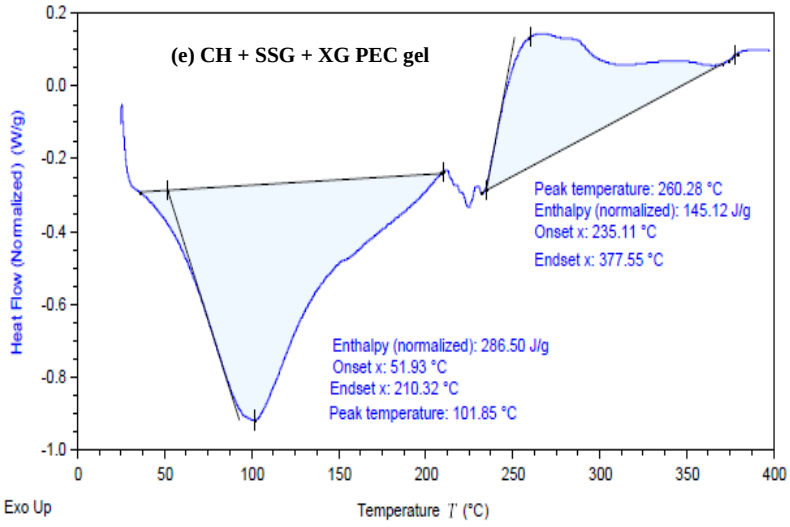
DSC characterization: The melting temperature, crystallinity change, and potential interactions between the polymers were all determined using DSC. Fig. 2 displays DSC thermograms of polymers and dried gels of polymer combinations.











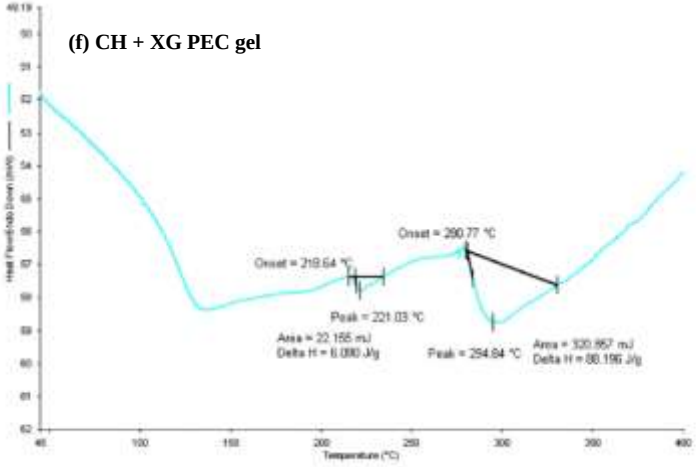


Fig. 2. Thermograms - DSC (exo up) of: (a) CH (Low molecular weight) (b) SSG (c) XG (d) CH + SSG (dried PEC gel) (e) CH + SSG + XG (dried PEC gel) (f) CH + XG (dried PEC gel)

The DSC thermogram of pure Chitosan (Fig. 2a) comprised of one endothermic peak at 137.46 ^{0}C showing melting of CH and one exothermic peak 300.19 ^{0}C exhibiting the thermal degradation of amine units [2, 3, 21, 22]. In the DSC thermogram of SSSG (Fig. 2b) the dehydration of was exhibited by peak at 149.49 ^{0}C and exothermic peak at 269.11 ^{0}C is due to charing of SSG and is also related to thermal degradation of amine units [18]. In thermogram of XG (Fig. 2c) the melting point was shown by broad endothermic peak one at 293 ^{0}C and second broad endothermic peak at 138.7 ^{0}C exhibited loss of water [2, 3]. In thermogram of CH + SSG (T -1) dired gel (Fig. 2d) the interaction between polymers was confirmed by presence of three endothermic peaks. The glass transition of PEC was shown by the first endothermic peak at around 140 ^{o}C. The melting of PEC was exhibited by second endothermic peak at 183 ^{o}C. The third weak endothermic peak was observed at 281 ^{o}C. The individual thermograms of CH and SSG do not have the endothermic peak at 183 ^{o}C. The DSC thermogram of CH + SSG + XG (T -2) dired gel (Fig. 2e) sample had one endothermic peak at 101.85 ^{0}C attributed to loss of water from PEC gel and one exothermic peak at 260.28 ^{0}C due to slow degradation of PEC gel. The formation of PECs between CH, SSG and XG was exhibited by the appearance of DSC thermogram. The three endothermic peaks observed in the thermogram of Chitosan + XG (T -3) dired gel (Fig. 2f) indicated the formation of PECs. The loss of water from PEC gel was exhibited by the peak around 145 ^{0}C and melting point of PEC gel was shown by the peak at 294.84 ^{0}C. The individual thermograms of CH and XG did not have the endothermic peak present at 221 ^{0}C.

Evaluation of Sustained release Tablets:

Pre- compression parameters: The values of all the pre compression parameters evaluated were found within the specified limits (Table 5) [7, 8], showing that the powder blend is suitable for compression into tablets.

Table 5 Pre – compression characterization.

Parameters		CPZ 1	CPZ 2	CPZ 3
Moisture content (% w/w ± SD) n= 3		3.67 ± 0.6	4.0 ± 1.0	4.3 ± 0.6
Drug content (% w/w ± SD) n= 3		98.16 ± 1.0	98.48 ± 0.9	98.80 ± 1.7
Bulk Density (g/cm^3 ± SD) n= 3	Before Lubrication	0.59 ± 0.01	0.55 ± 0.01	0.53 ± 0.02
	After Lubrication	0.64 ± 0.02	0.55 ± 0.04	0.56 ± 0.05
Tapped Density (g/cm^3 ± SD) n= 3	Before Lubrication	0.63 ± 0.04	0.62 ± 0.04	0.61 ± 0.02
	After Lubrication	0.73 ± 0.02	0.69 ± 0.03	0.70 ± 0.02
Hausners' ratio ± SD, n= 3	Before Lubrication	1.1 ± 0.1	1.2 ± 0.1	1.2 ± 0.1
	After Lubrication	1.2 ± 0.1	1.2 ± 0.1	1.2 ± 0.1
Carr's index (% ± SD) n= 3	Before Lubrication	7.8 ± 0.1	12.5 ± 0.4	16.5 ± 0.5
	After Lubrication	14.1 ± 0.6	14.0 ± 0.5	13.0 ± 0.2
Angle of repose (Θ^o ± SD) n= 3	Before Lubrication	26.5 ± 0.6	26.2 ± 0.8	26.1 ± 1.0
	After Lubrication	29.2 ± 0.8	29.2 ± 0.9	29.2 ± 1.1

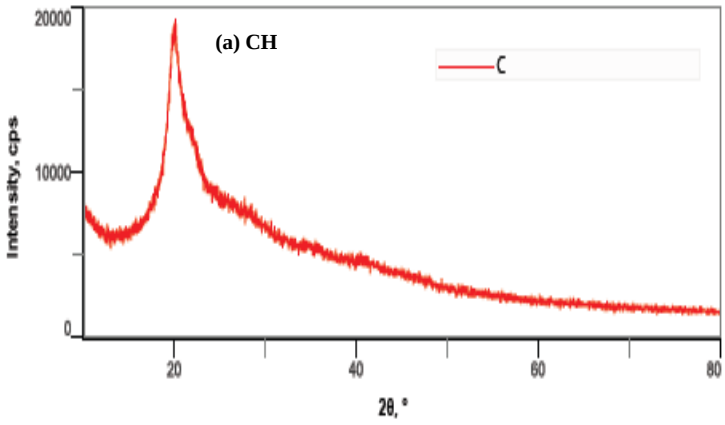
Swelling index: The swelling behavior of PEC gel of different formulations had showed that the swelling of gel was more in acidic medium (found in range of 144 – 159%) than alkaline medium (found in range of 42 – 81%) due to formation of polyelectric complex in acidic medium (Table 6).

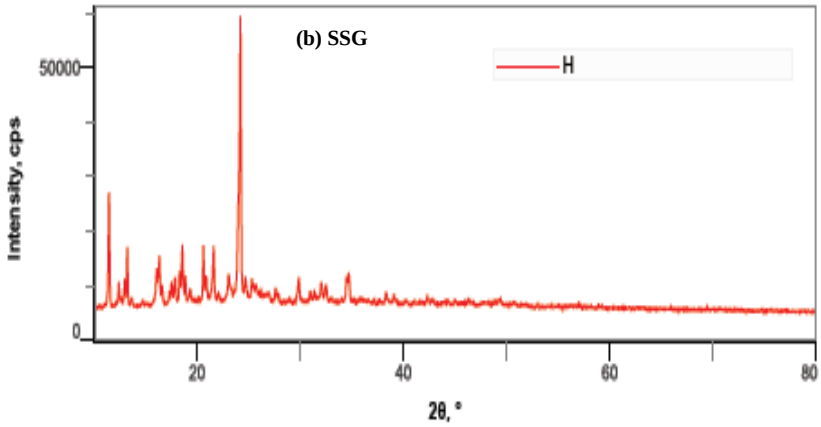
Table 6 Swelling index of PEC gels

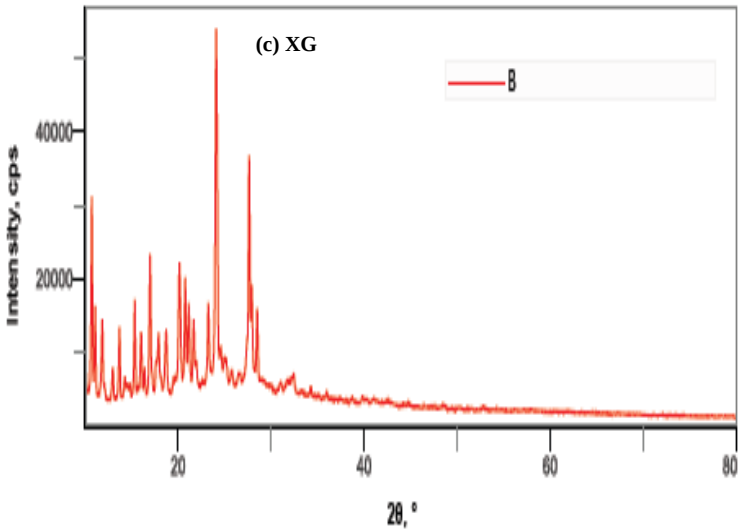
Sr. No	Formulation Code	Swelling Index (% ± SD) n= 3		
		In pH 1.5 (after 2hr)	In pH 7.4 (after 8hr)	Overall (after 10hr)
1	CPZ 2	146.0 ± 1.7	79.6 ± 1.6	343.8 ± 1.2
2	CPZ 3	156.4 ± 2.0	44.5 ± 1.6	275.9 ± 4.2

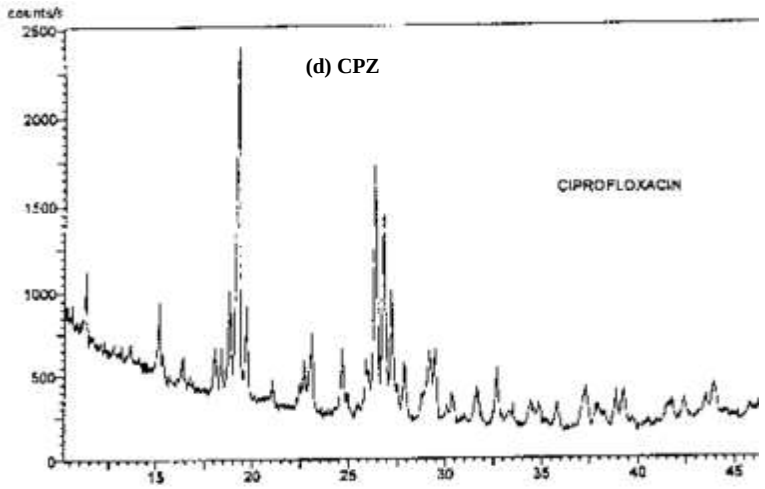
X- ray Diffraction studies: The two broad peaks one at 2Θ = 10^o exhibiting the packing of glycosidic chains in the amorphous region and second at 2Θ = 20^o exhibiting crystalline packing of chitosan chains were observed in the XRD diffractogram of CH (Fig 3a). The diffractogram also showed weak peaks at 2Θ = 11 – 13^o attributed to inter-chain hydrogen bonding [23, 24]. The XRD diffractogram of SSG (Fig. 3b) exhibited prominent peaks at 2Θ =19 – 20^o corresponding to the reflection from the crystalline planes of the starch molecule. The additional peaks at 2Θ around 10-11° and 22-23° were also frequently observed and may be attributed to specific packing arrangements within the SSG structure. The less intense peaks at 2Θ around 5-6°, 15-16°, and 27-28° may be seen depending on the preparation method and crystallinity of the SSG sample [25, 26]. The XRD diffractogram of XG (Fig. 3c) showed peaks at 2θ = 15 to 35^o. The characteristic peak was observed at 2θ = 20°. The weaker peaks at 2Θ around 16-17° and 23-25° attributed to the presence of ordered regions within the polymer chains or interactions with other molecules [27, 28, 29]. The XRD diffractogram of CPZ showed sharp characteristic peaks in the region of 2Θ = 20 to 40^o [30]. The XRD diffractogram of CH + SSG (Fig. 3e) dried PEC gel (G1) showed various peaks at 2θ= 28.28^o, 40.46^o, 50.08^o, 66.3^o and 73.66^o which were not present in pure compounds. The diffractogram of CH + SSG + XG (Fig. 3f) dried PEC gel (G2) showed peaks at 2θ= 22.48^o, 23.18^o, 23.93^o, 26.6^o and 44.34^o. The difftactogram of CPZ + CH + SSG (Fig. 3g) dried PEC gel (G3) showed peaks at 2θ= 10.92^o, 18.8^o, 19.2^o, 21.0^o, 23.0^o, 24.6^o, 26.42^o, 29.12^o, 30.32^o, 34.96^o, 39.14^o and 50.54^o. There were numerous new peaks in the diffractogram of CPZ + CH +

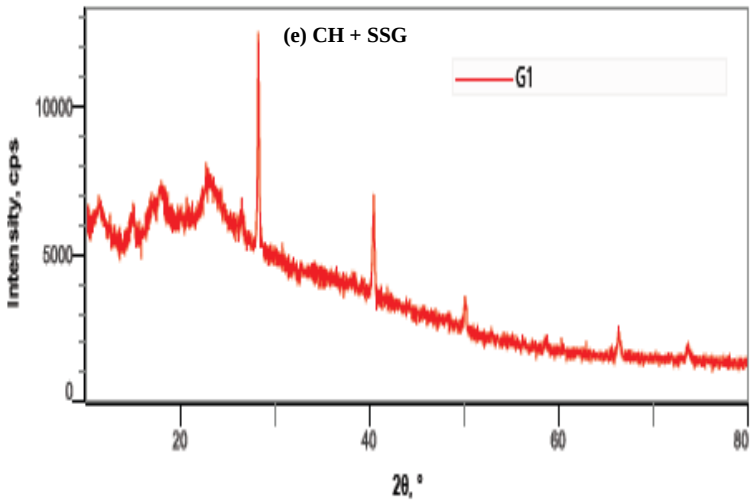
SSG + XG (Fig. 3h) dried PEC gels (G4) which were not present in the individual diffractograms of drug and polymers. Some characteristic peaks were showed at 2θ= 11.28º, 15.0º, 18.88º, 19.28º, 19.74º, 23.1º, 24.74º, 26.52º, 27.96º, 29.18º, 30.46º, 31.6º, 37.26º, and 43.58º. The presence of numerous new peaks in the diffractogram which were not present in the individual diffractograms of drug and polymers, suggest the increase in crystallinity of dried gel due to formation of PECs.

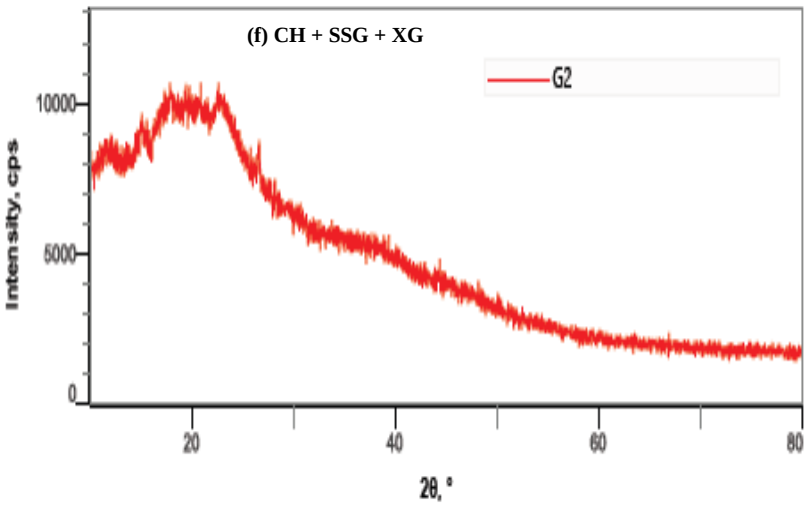


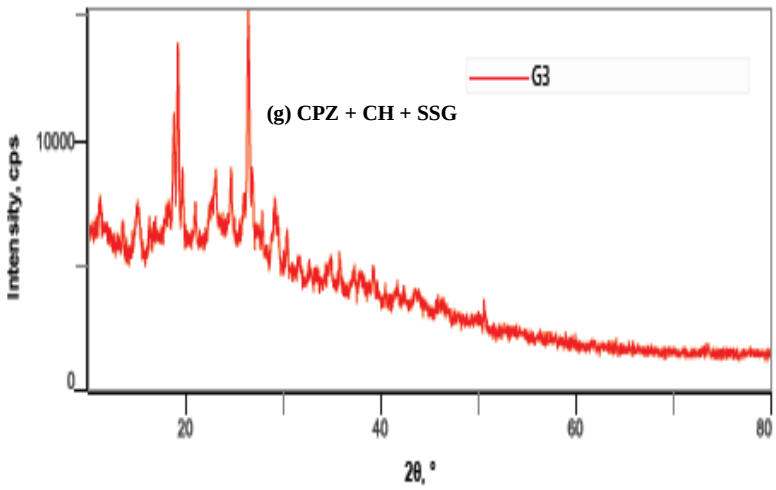












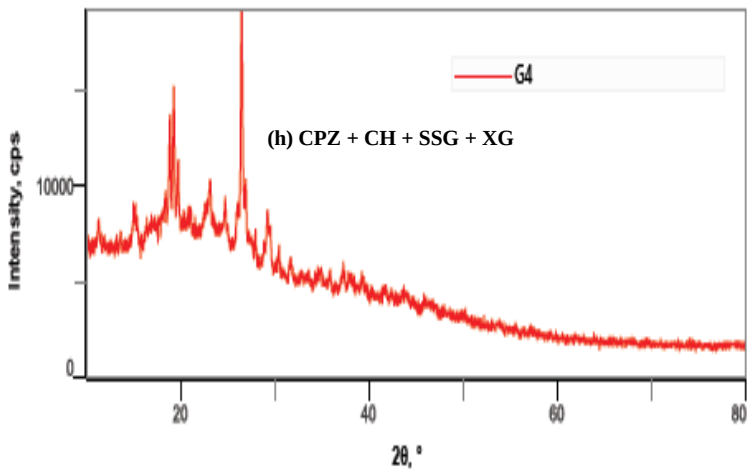


Fig. 3 XRD Diffactograms of: (a) CH, (b) SSG, (c) XG, (d) CPZ, (e) CH + SSG, (f) CH + SSG + XG, (g) CPZ + CH + SSG, (h) CPZ + CH + SSG + XG

Post – compression parameters: All the batches of prepared tablets had a uniform smooth texture and structure confirmed by visual inspection. All the formulations passed the fiability test as they had less than 1% friability. The weight variation of all formulations was between 3 to 4% and individual deviations were found within the specified limits. So the formulations also passed the weight variation test. The drug content and hardness of formulation was found within the range of 97 to 99% and 4 to 5.5 Kg/cm^2. The thickness of formulations was found between 5.1 to 5.3 mm (Table 7) [8, 9].

Table 7 Post- compression characterization of sustained release tablets

Formulation Code	Friability (% ± SD) (n= 3)	Weight (mg ± SD) (n=20)	Drug content (% ± SD) (n= 3)	Hardness (kg/cm^2 ± SD) (n = 3)	Thickness (mm ± SD) (n= 3)
CPZ 1	0.85 ± 0.04	898.5 ± 4.3%	98.3 ± 1.0	4.5 ± 0.5	5.2 ± 0.1
CPZ 2	0.82 ± 0.02	901.0 ± 4.3%	98.0 ± 1.3	5.0 ± 0.5	5.2 ± 0.1
CPZ 3	0.83 ± 0.02	879.8 ± 3.7%	97.7 ± 1.5	4.8 ± 0.7	5.2 ± 0.06

In vitro drug release studies: A plot of % cumulative drug release versus time is shown in Fig. 4. It was observed that the formulation CPZ 1 showed 99% drug release within 2 hrs, indicating the burst drug release from the formulation. The formulations CPZ 2 and CPZ 3 exhibited 97% and 98% drug release respectively in 12 hrs, indicating the sustained release for 12 hr [5, 8, 9, 31].

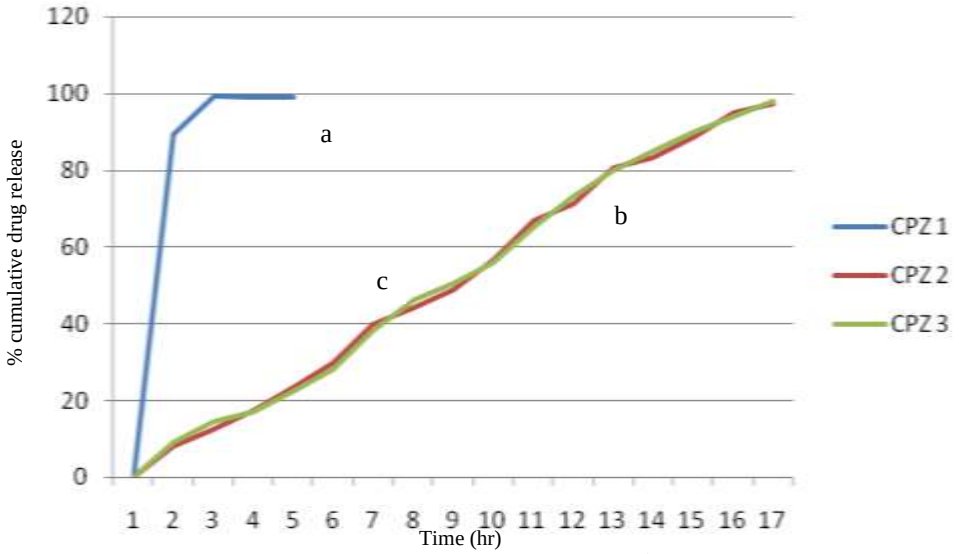


Fig. 4 Cumulative % drug release v/s time graph of: (a) CPZ 1, (b) CPZ2 (c) CPZ 3

Dissolution profile comparison: The f_2 and f_1 values for formulations CPZ 2 and CPZ 3 containing ciprofloxacin hydrochloride indicated the similarity in the dissolution profiles of these formulations. This similarity also showed

that the change in type of anionic polymer from SSG alone in CPZ 2 to SSG + XG in CPZ 3 did not affect the dissolution profile of formulations (Table 8) [12, 13]**.**

Table 8 Dissolution profile comparison

Sr. No.	Formulation code for profile comparison		Similarity factor	Difference factor	Inference
	Test	Reference	(f_2)	(f_1)	
1	CPZ 2	CPZ 3	84	2	Similar

Drug release kinetics: After fitting the dissolution data into various kinetic models it was observed that R^2 value of CPZ 1 was higher for first order equation, which exhibited that the drug release from the formulation depends on drug concentration and hence followed first order release. The drug release from this formulation followed super case II transport mechanism (n higher than 1) characterized by higher speed of solvent penetration in the matrix. The formulation did not show the sustained release. Formulations CPZ 2 and CPZ 3 followed zero – order release. Regarding *n* values, formulation CPZ 2 showed non – Fickian mechanism ($0.5<n<1$) of drug release, indicating the release of CPZ depend on its solubility, swelling and erosion of the PECs. The formulation CPZ 3 also exhibited super case II transport, indicating the rate of solvent diffusion is higher than the swelling of PEC and is the drug release determining factor (Table 9) [3, 5, 16].

Table 9 Data of drug release kinetic study

Sr. No.	Formulation code	R^2 Values					*n* (release exponent)
		Zero order	First order	Higuchi	Hixson - crowell	Korsmeyer- Pepps	
1	CPZ 1	0.624	0.943	0.848	0.823	0.037	1.15
2	CPZ 2	0.995	0.824	0.947	0.926	0.719	0.81
3	CPZ 3	0.996	0.805	0.944	0.921	0.706	1.21

CONCLUSION

The present study was performed to design and evaluate the oral sustained release tablets of ciproflocacin hydrochloride using chitosan based in situ forming polyelecrolyte complex as retardant polymer. The results of this study had indicated that the polyelecrolyte complex formed between chitosan and anionic polymers like SSG and XG had proven an excellent excipent for designing sustained release oral formulations of hydrophilic drugs. These PECs not only provide a sustained drug release but also prevent the initial burst release of drug. The formulated tablets were physically stable. The FTIR, XRD and DSC analysis verified the formation of in situ PECs between CH and SSG/ XG. The formulations had shown sustained release up to 12hr with zero – order release kinetics. The dissolution profiles were found independent of change in type of anionic polymer as confirmed by release profile comparison.

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