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CHITOSAN-BASED IN-SITU FORMING POLYELECTROLYTE COMPLEXES FOR CIPROFLOXACIN SUSTAINED RELEASE TABLETS

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ABSTRACT
Background: It is not straightforward to create sustained-release (single-unit) oral dosage forms for hydrophilic medicines, which are highly soluble (10 mg/mL) in gastric fluids and have a high dose. This study is an attempt to utilize biopolymer Chitosan-based Polyelectrolyte complex as a retardant to develop and evaluate the sustained release tablet formulations (oral) of Ciprofloxacin hydrochloride. **Methodology:** Sustained-release tablets were prepared using the traditional wet granulation method, employing a neutralized chitosan solution (1% w/w) at 4°C in 1% acetic acid as the binder. Formulated tablets were assessed for pharmacopoeial and non-pharmacopoeial parameters, as well as in vitro 12-hour drug release studies. The different mathematical models were utilized to examine the pharmacokinetic parameters and elucidate the mechanism of drug release. **Results and discussion:** The sustained release of the drug for 12 hrs was confirmed through the in vitro release studies. Both formulations, CFX 2 and CFX 3 exhibited 97% and 98% cumulative drug release, respectively, after 12 hr. The dissolution profiles of both formulations were shown to be unaffected by the change in anionic polymers from one to two, as confirmed by dissolution profile comparison studies, with values of similarity factor (f_2) 84 and of difference factor (f_1) 2. The XRD studies confirmed the in situ formation of a polyelectrolyte complex between chitosan and anionic polymer, as evidenced by the presence of additional peaks in the diffractograms. **Conclusion:** The polyelectrolyte complexes not only provide a sustained drug release but also prevent the initial burst release of the the drug.

INTRODUCTION

Problem Statement: 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 highly efficient drug delivery method is therefore needed that can demonstrate a relatively steady rate of dissolution over an extended duration. In light of the above problem, the study aimed to design sustained-release tablets of ciprofloxacin hydrochloride using a chitosan solution as the binder and sodium starch glycolate or

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xanthan gum as excipients. It has been reported that poly-electrolyte complexes, formed between polymers with opposing charges, result in polymeric carriers that can regulate the release of medications from dosage forms, both initially and continuously [2]. It can be justified by the resulting polymeric carriers' high degree of organization and dense, crystal-like shapes. The in situ formation of polyelectrolyte complexes was expected when the tablet encountered the acidic dissolution medium (0.1 N HCL, pH – 1.5). This approach was expected to sustain the release of the drug, i.e., ciprofloxacin hydrochloride, due to the high degree of organization and dense, crystal-like structure of the polyelectrolyte complexes formed between the cationic polymer chitosan and the anionic polymers xanthan gum or sodium starch glycolate [3].

MATERIALS AND METHODS

Materials: Ciprofloxacin hydrochloride (CFX) was supplied by Saphinx Life Sciences, Vill. Barotiwala, Ponta Saib, Distt. Sirmour (HP) and Well Treat Pharma, H. No. 922, Ward No. 5, Vishal Nagar, Rohtak (Haryana) as a gift sample. The Chitosan (CTS) (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.

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 the drug in distilled water was mixed with 1% w/v solution of polymers in a suitable medium (distilled water or 1% acetic acid). The mixture was kept at 37°C for 2 hours. After that, the mixture was dried and FTIR spectra were recorded on the Spectrum BX of PerkinElmer (USA) by using the 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, however, upon exposure of the formulations to the acidic dissolution medium (0.1 N HCl, pH 1.5). Thus, to investigate the interaction between Chitosan (CTS) and SSG or XG, the polymers were mixed in a 1:1 ratio. Sample T-1 contained CTS + SSG, sample T-2 contained CTS + SSG + XG, and sample T-3 contained CTS + XG. These samples were packed individually in dialysis pouches (molecular weight cut–off 1200) that had been previously activated by boiling in Phosphate buffer with a pH of 7.4 for 30 minutes. These sealed bags were kept at pH 1.5 (0.1 N HCl) and maintained at 37±2°C in a basket-type USP dissolution apparatus for 2 hours. During the exposure, gel formation occurred. After being removed from the dialysis bags, the contents (in a gel form) were dried overnight at 60°C 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 together. The binder solution was prepared by dissolving chitosan (CTS) in 1 1% acetic acid solution to produce 1 1% w/v solution. The solutions were cooled to 4°C and then neutralized with a 1M Sodium bicarbonate solution, maintaining the temperature at 4 °C 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 1. 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 ˚C. 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.

EVALUATION OF SUSTAINED-RELEASE TABLETS

Pre-compression parameters

Moisture content: The Moisture content of dried granules was determined by using an IR moisture balance. The pan of balance was released by removing the lock bar. The zero of scale was set to coincide with the reference mark by rotating the right-hand

side knob in a 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 the scale. The IR lamp was turned on, and the temperature was set to 100 – 110°C. The sample was exposed to the set temperature for 10–15 minutes. The right-hand side knob was rotated in the opposite direction to align the pointer with the reference mark.

Reading the scale, which coincides with the reference mark, and the pointer would indicate the moisture content of the sample. To ensure the complete removal of moisture, the samples were again exposed to the same temperature for 10 min. until the 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 the solution was filtered using Whatman filter paper. The filtrate (5 ml) was taken in a volumetric flask (100 ml), and the volume was adjusted by adding distilled water. Again, the resultant solution (5 ml) was taken in a volumetric flask (100 ml), and the 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 the solution against water as blank were measured at λmax of Ciprofloxacin Hydrochloride, i.e., 276 nm[4],[5],[6],[7]. The drug content was calculated by using the formula.

$$\boldsymbol{Drug\ Content = Concentration \times Dilution\ factor}$$

Bulk density: The known weight of granules (20 g) was gently placed in a graduated cylinder of the bulk density apparatus, and the volume occupied was noted. The bulk density was calculated by using the formula.

$$\boldsymbol{Bulk\ density = \frac{Weight}{Volume\ occupied}}$$

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

$$\boldsymbol{Tapped\ density = \frac{Weight}{Tapped\ volume}}$$

Hausner's ratio: It is a number that is correlated to the flowability of powder or granules. The Hausners' ratio was determined by using the formula

$$\boldsymbol{Hausners'\ ratio = \frac{Tapped\ bulk\ density}{Bulk\ density}}$$

This ratio determines the flow properties of granules. The ideal range for good flow properties is 1.2–1.5.

Carr's consolidation index (Percent compressibility): The % compressibility or Carr's consolidation index was calculated by using the formula –

$$\%\ \boldsymbol{compressibility} = \frac{[(\boldsymbol{Tapped\ density\ -\ Bulk\ density}) \times \mathbf{100}]}{\boldsymbol{Tapped\ density}}$$

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 the surface of a powder/ granules' pile and a horizontal plane is referred to as the angle of repose. This was measured by passing a known weight of granules through a funnel having a 30 mm stem opening on a glass plate. When the granules were emptied from the funnel, the piles' height (h) and the piles' radius (r) were measured with a ruler. The flow properties of powder or granules are measured by the angle of repose[8],[9]. The angle of repose was calculated by using the formula

$$\boldsymbol{Angle\ of\ repose}\ (\theta) = \boldsymbol{tan^{-1}\ h/r}$$

Swelling index: To determine the swelling index, each drug and polymer were mixed in a 1:1 ratio. Sample CFX 2 contained CFX, CTS, and SSG, and sample CFX 2 had CFX, CTS, and SSG XG. These samples were packed individually in dialysis pouches (molecular weight cut–off 1200) that had been previously activated by boiling in Phosphate buffer with a pH of 7.4 for 30 minutes. Each previously weighted sample was first kept in 0.1 N HCl (pH 1.5) for 2 hours, and the sample was weighed after every 30 minutes. After that, each sample was transferred into a mixed phosphate buffer (pH 7.4) for 8 hours, and the sample was weighed every hour until three consecutive readings were obtained. The swelling index [8] was determined from the formula –

$$\boldsymbol{Swelling\ index} = \frac{[(\boldsymbol{Final\ weight - Initial\ weight}) \times \mathbf{100}]}{\boldsymbol{Initial\ weight}}$$

X-Ray Diffraction (XRD) studies: The X–ray diffraction studies were conducted on an X-ray diffractometer, Miniflex

600, from Rigaku Corporation, Tokyo, Japan. These studies were conducted to ensure the formation of Poly Electric Complex through the interaction between Chitosan and anionic polymers, specifically sodium starch glycolate and xanthan gum, when exposed to an acidic environment. For the study the samples were prepared by mixing each drug and polymers in ratio of 1:1, sample G – 1 containing CTS + SSG, sample G – 2 having CTS + SSG + XG, sample G – 3 having CFX + CTS + SSG and sample G – 4 containing CFX + CTS + SSG + XG. These samples were packed individually in dialysis pouches (molecular weight cut–off 1200) that had been previously activated by boiling in Phosphate buffer with a pH of 7.4 for 30 minutes. The XRD thermograms of test samples were also compared with those of pure compounds. These samples, in sealed bags, were kept at pH 1.5 (0.1 N HCl) and maintained at 37 ± 2 °C in a basket-type USP dissolution apparatus for 2 hours. During the exposure, gel formation occurred. After being removed from the dialysis bags, the contents (in a gel form) were dried overnight at 60°C in an oven. To determine if the fine powder samples were crystalline or amorphous, they were continuously scanned at room temperature between 10 °C and 80 °C (2 °C/min) at an accelerating voltage of 30 kV, a current of 15 mA, and a scanning speed of 10 °C/min [10].

POST- COMPRESSION PARAMETERS

Friability test: The Required number of tablets (20) was weighed after dusting to find the initial weight. The sample was then placed in a friabilator, and the machine was operated for 4 minutes or 100 revolutions. The tablets were weighed again after dusting to record their final weight. There should be less than 1% friability, ideally. The % friability was determined by using the formula

$$\boldsymbol{Friability} = \frac{[(\boldsymbol{Initial\ weight} - \boldsymbol{Final\ weight}) \times \mathbf{100}]}{\boldsymbol{Initial\ weight}}$$

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 with the zero point, as indicated by the pointer. The screw was again rotated (clockwise) until tablet was broken.

The reading on the scale indicates the hardness (the force required to break the tablet) of the tablet. Ideally, a tablet should have a hardness value of 4-10 kg/cm².

Uniformity of Weight: 20 tablets for each formulation were taken for this test. Twenty tablets were weighed, and the average weight was determined. Next, the weight of each tablet was taken separately, and the average weight was subtracted from the individual weight of each tablet to determine the difference. The deviation was calculated by determining the percent weight variation by using the formula

$$\boldsymbol{Percent\ weight\ variation} = \frac{[(\boldsymbol{individual\ weight} - \boldsymbol{average\ weight}) \times \mathbf{100}]}{\boldsymbol{average\ weight}}$$

If no unit exceeds twice 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 for each formulation was determined by performing the assay mentioned in the pre-compression parameters, as described in the drug content of granules [4],[5],[6],[7].

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

In vitro dissolution studies: The test was conducted utilizing a USP type II apparatus at a paddle speed of 50 rpm. For the first 2 hours, 500 mL of 0.1 N HCl (pH 1.5) was used as the dissolution medium. For the next 8 hours, a mixed phosphate buffer (pH 6.8) and a mixed phosphate buffer (pH 7.5) were used. For the last 2 hours, a mixed phosphate buffer (pH 7.5) was used. 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 CFX 2 and CFX 3 were compared using a model-independent approach that involves determining the similarity factor (f2) and difference factor (f1). 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[11],[12],[13].

Drug release kinetics: To study the exact mechanism of drug release from various formulations, drug release data were analyzed/ tested with the 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],[14],[15].

Table 1: Composition of sustained release tablets containing ciprofloxacin hydrochloride along with different anionic polymers, sodium starch glycolate, and xanthan gum.

S No.	Formulation Code	CFX (mg)	SSG (mg)	XG (mg)	Lactose (mg)	Mg. Stearate (mg)	Talc (mg)
1	CFX 1	750	---	----	100	27	9
2	CFX 2	750	50	----	50	27	9
3	CFX 3	750	25	25	50	27	9

RESULT AND DISCUSSION

Pre-formulation studies

Drug – polymer interaction studies: The spectra (FTIR) of pure CFX(Figure 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],[16]. The spectra of chitosan (CTS) (low molecular weight) (Figure 1b) showed major peaks at 3423, 1632, and 1403 cm-1 because of amide I, II, and CH and OH bending, respectively [2],[3],[17]. In the FTIR spectra of SSG (Figure 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 [18]. The characteristic peaks observed in the FTIR spectra of XG (Figure 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],[19]. The FTIR spectra of the sample containing a solution mixture of CFX + CTS (Figure 1e), CFX + SSG (Figure 1f), and CFX + XG (Figure 1g) did not exhibit interaction with the drug due to the presence of intact major peaks of Ciprofloxacin hydrochloride.

Polymer – Polymer interaction studies

FTIR characterization: The spectra of the dried PEC gel sample of CTS + SSG (Figure 1h) exhibited interaction between CTS and SSG to form PECs. The –C=O stretching band of the –C=O group at 1637 cm-1in SSG spectra was shifted to a lower wave number (present at 1616 cm-1 in FTIR spectra of SSG), showing the interaction of the amino group of CTS with the carboxylic group of SSG. The –NH bending vibration peak at 1523 cm^{-1} (which was absent in pure polymers) indicates the formation of ionic bonds. The spectra of the dried PEC gel sample of CTS + SSG + XG (Figure 1i) also confirmed the interaction between the carboxylic group of SSG and XG and the mino group of CTS to form PECs because of the shifting of the–C=O stretching peak of the –C=O group to a lower wave number. The –NH bending vibration peak at 1523 cm^{-1} (which was absent in pure polymers) indicates the formation of ionic bonds. The interaction between CTS and XG was also suggested by the FTIR spectra of CTS + XG (Figure 1j), dried PEC gel. The shifting of the –C=O stretching peak due to vibrations of the –C=O group in XG to a lower wave number (at 1736 cm^{-1}) showed the interaction of the amino group of CTS with the carboxylic group of XG. The –NH bending vibration peak at 1523 cm^{-1} (which was absent in pure polymers) indicates the formation of ionic bonds. The shifting of absorption bands in the spectra indicated environmental changes around –C=O and Amide I [2],[3],[18].

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

The DSC thermogram of pure Chitosan (Figure 2a) comprised of one endothermic peak at 137.46 ^{0}C showing melting of CTS and one exothermic peak 300.19 ^{0}C exhibiting the thermal degradation of amine units[2],[3],[20],[21].In the DSC thermogram ofSSSG (Figure 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[17].

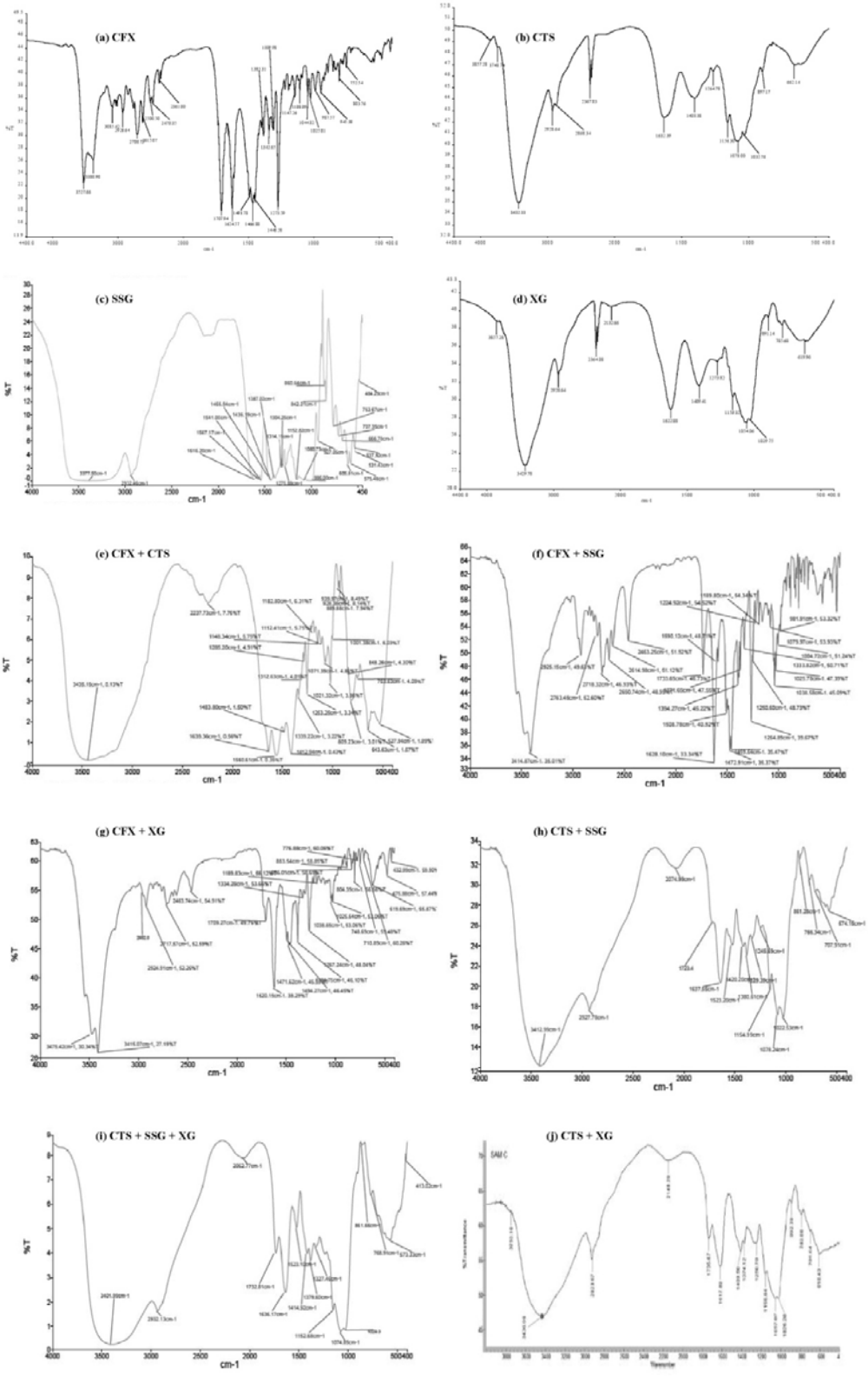

Figure 1. FTIR spectra of : (a) Ciprofloxacin hydrochloride (CFX) (b) Chitosan (CTS) (Low molecular weight) (c) SSG (d) XG (e) CFX + CTS (solutions) (f) CFX + SSG (solutions) (g) CFX + XG (solutions) (h) CTS + SSG (dried gel) (i) CTS + SSG + XG (dried gel) (j) CTS + XG (dried gel).

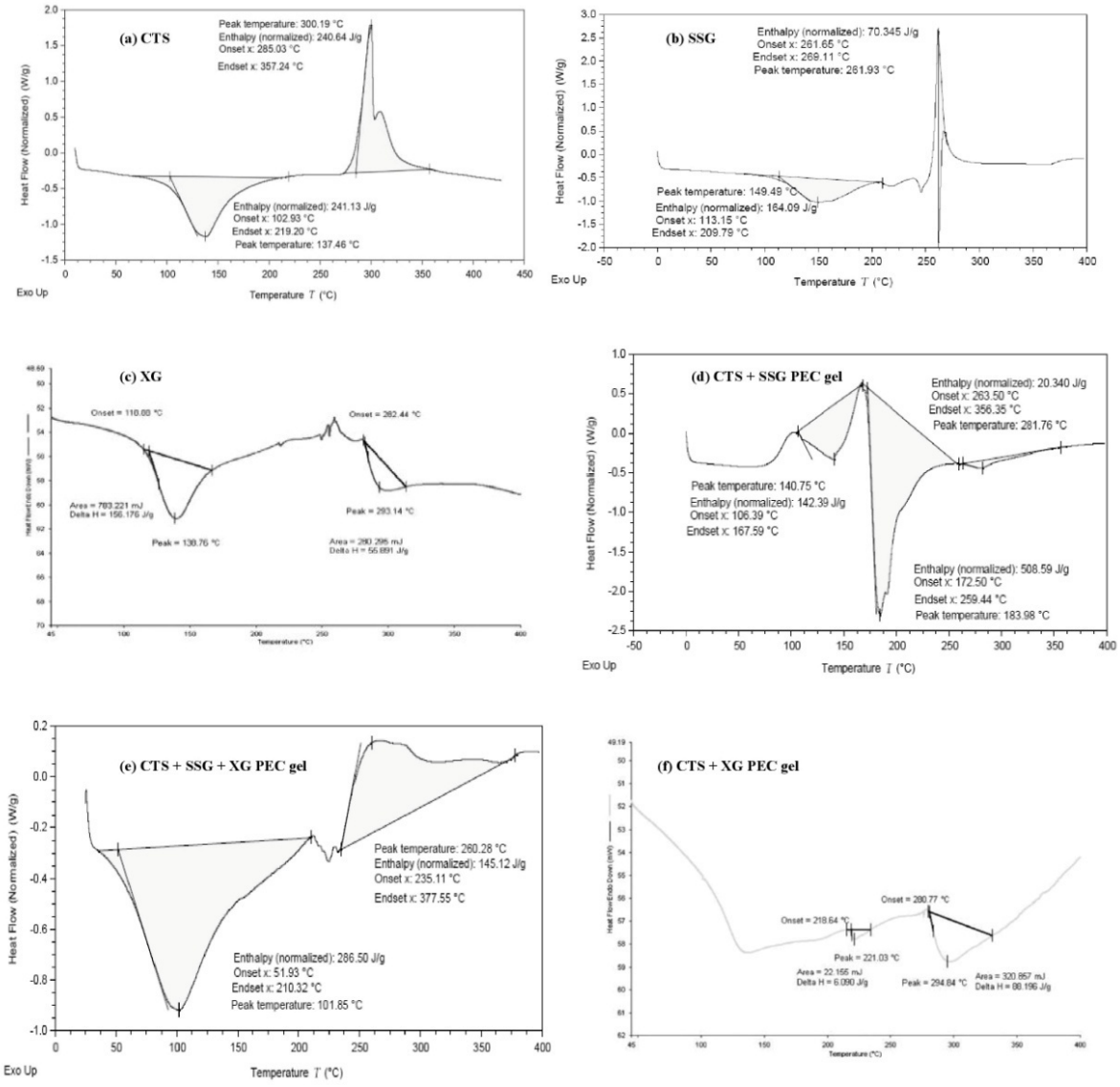

Figure 2. Thermograms - DSC (exo up) of: (a) CTS (Low molecular weight) (b) SSG (c) XG (d) CTS + SSG (dried PEC gel) (e) CTS + SSG + XG (dried PEC gel) (f) CTS + XG (dried PEC gel)

In the thermogram of XG (Figure 2c), a broad endothermic peak showed the melting point at 293 0C and a second broad endothermic peak at 138.7 ^{0}C exhibited loss of water[2],[3]. In the thermogram of CTS + SSG (T-1) dried gel (Figure 2d), the interaction between polymers was confirmed by the presence of three endothermic peaks. The first endothermic peak indicated the glass transition of PEC at approximately 140 °C.

The melting of PEC was exhibited by a second endothermic peak at 183 ^{o}C. The third weak endothermic peak was observed at 281 ^{o}C. The individual thermograms of CTS and SSG do not exhibit an endothermic peak at 183°C. The DSC thermogram of the CTS + SSG + XG (T -2) dried gel (Figure 2e) sample exhibited one endothermic peak at 101.85°C, attributed to the loss of water from the PEC gel, and one exothermic peak at 260.28°C due to the slow degradation of the PEC gel. The appearance of the DSC thermogram exhibited the formation of PECs between CTS, SSG, and XG. The three endothermic peaks observed in the thermogram of Chitosan + XG (T-3) dried gel (Figure 2f) indicated the formation of PECs. A peak was observed in the loss of water from the PEC gel at approximately 145°C, and the melting point of the PEC gel was observed to be 294.84°C. The individual thermograms of CTS and XG did not exhibit an endothermic peak at 221 °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 2 shows that the powder blend is suitable for compression into tablets[7],[8].

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 3).

Table 2: Pre-Compression Characterization

Parameters		CFX 1	CFX 2	CFX 3
Moisture content(% w/w)		3.67 ± 0.6	4.0 ± 1.0	4.3 ± 0.6
Drug content(% w/w)		98.16 ± 1.0	98.48 ± 0.9	98.80 ± 1.7
Bulk Density(g/cm^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)	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	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 (%)	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)	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

All values are expressed as mean ± SD, n = 3

Table 3. Swelling index of PEC gels

SN	Formul-ationCode	Swelling Index (% w/w)		
		In pH 1.5 (after 2hr)	In pH 7.4 (after 8hr)	Overall (after 10hr)
1	CFX 2	146.0 ± 1.7	79.6 ± 1.6	343.8 ± 1.2
2	CFX 3	156.4 ± 2.0	44.5 ± 1.6	275.9 ± 4.2

All values are expressed as mean ± SD, n = 3

X-ray Diffraction studies: The two broad peaks, one at 2Θ = 10ºexhibiting the packing of glycosidic chains in the amorphous region, and the second at 2Θ = 20ºexhibiting crystalline packing of chitosan chains, were observed in the XRD diffractogram of CTS(Figure 3a). The diffractogram also showed weak peaks at 2Θ =11–13˚ attributed to inter-chain hydrogen bonding [22],[23]. The XRD diffractogram of SSG (Figure 3b) exhibited prominent peaks at 2Θ =19 – 20º 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 [24],[25]. The XRD diffractogram of XG (Figure 3c) exhibited peaks at 2θ angles ranging from 15 ° to 35°. The characteristic peak was observed at 2θ = 20°. The weaker peaks at 2Θ around 16-17° and 23-25° are attributed to the presence of ordered regions within the polymer chains or interactions with other molecules[26],[27],[28]. The XRD diffractogram of CFX (Figure 3d) showed sharp characteristic peaks in the region of 2Θ = 20 to 40˚ [29]. The XRD diffractogram of CTS + SSG (Figure 3e), dried PEC gel (G1), showed various peaks at 2θ= 28.28°, 40.46°, 50.08°, 66.3°, and 73.66°, which were not present in pure compounds. The diffractogram of CTS + SSG + XG (Figure 3f) dried PEC gel (G2) showed peaks at 2θ= 22.48º, 23.18º, 23.93º, 26.6º and 44.34º. The difftactogram of CFX + CTS + SSG (Figure 3g) dried PEC gel (G3) showed peaks at 2θ= 10.92º, 18.8º, 19.2º, 21.0º, 23.0º, 24.6º, 26.42º, 29.12º, 30.32º, 34.96º, 39.14º and 50.54º.

There were numerous new peaks in the diffractogram of CFX + CTS + SSG + XG (Figure 3h) dried PEC gels (G4), which were not present in the individual diffractograms of the drug and polymers alone. 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 the drug and polymers, suggests an increase in crystallinity of the dried gel due to the formation of PECs.

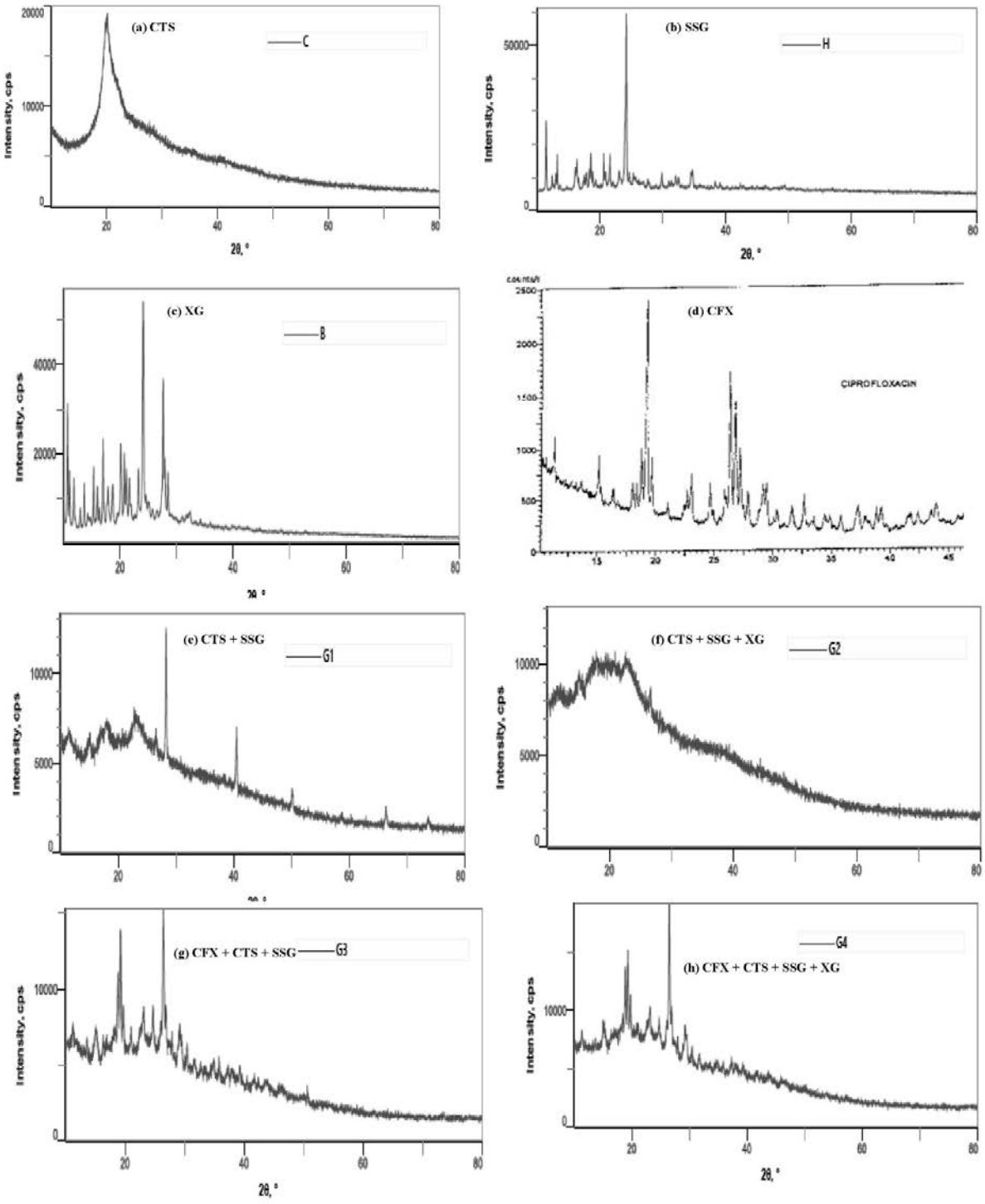

Figure 3. XRD Diffactograms of: (a) CTS, (b) SSG, (c) XG, (d) CFX, (e) CTS + SSG, (f) CTS + SSG + XG, (g) CFX + CH + SSG, (h) CFX + CH + SSG + XG

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 friability test as they had less than 1% friability. The weight variation of all formulations was between 3 to 4% & individual deviations were found within the specified limits. So the formulations also passed the weight variation test. The drug content and hardness of formulation wasfound 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 4)[8],[9].

Table 4. Post- compression characterization of sustained release tablets

Sr. No.	Formulation Code	Friability (%	Weight (mg)	Drug content (% w/w)	Hardness (kg/cm^2)	Thickness (mm)
1	CFX 1	0.85 ± 0.04	898.5 ± 4.3%	98.3 ± 1.0	4.5 ± 0.5	5.2 ± 0.1
2	CFX 2	0.82 ± 0.02	901.0 ± 4.3%	98.0 ± 1.3	5.0 ± 0.5	5.2 ± 0.1
3	CFX 3	0.83 ± 0.02	879.8 ± 3.7%	97.7 ± 1.5	4.8 ± 0.7	5.2 ± 0.06

All values are expressed as mean ± SD, n = 3

In vitro drug release studies: A plot of the percentage of cumulative drug release versus time is shown in Figure 4.It was observed that the formulation CFX 1 showed 99% drug release within 2 hrs, indicating the burst drug release from the formulation. The formulations CFX 2 and CFX 3 exhibited 97% and 98% drug release, respectively, in 12 hrs, indicating the sustained release for 12 hr[5],[8],[9],[30].

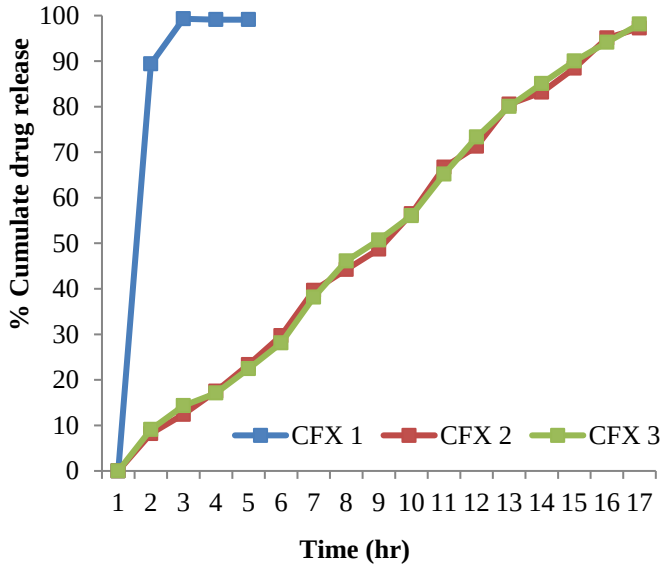

Figure 4. Cumulative % drug release v/s time graph of: (a) CFX 1, (b) CFX 2 (c) CFX 3

Dissolution profile comparison: The f_2 and f_1 values for formulations CFX 2 and CFX 3, containing ciprofloxacin hydrochloride, indicated similarity in the dissolution profiles of these formulations. This similarity also showed that the change in type of anionic polymer from SSG alone in CFX 2 to SSG + XG in CFX 3 did not affect the dissolution profile of formulations (Table 5)[12],[13].

Table 5. Dissolution profile comparison

Formulation code for profile comparison		Similarity factor	Difference factor	Inference
Test	**Ref**	**(f_2)**	**(f_1)**	
CFX 2	CFX 3	84	2	Similar

Drug release kinetics: After fitting the dissolution data into various kinetic models, it was observed that the R^2 value of CFX 1 was higher for the first-order equation, indicating that the drug release from the formulation depends on the drug concentration and thus follows first-order release kinetics. The drug release from this formulation followed a super case II transport mechanism (n> 1), characterized by a higher speed of solvent penetration in the matrix. The formulation did not show sustained release.

Formulations CFX 2 and CFX 3 followed zero–order release. Regarding *n* values, formulation CFX 2 exhibited a non-Fickian mechanism (0.5 < n < 1) of drug release, indicating that the release of CFX depends on its solubility, swelling, and erosion of the PECs. The formulation CFX 3 also exhibited super case II transport, indicating that the rate of solvent diffusion is higher than the swelling of PEC and is the drug release determining factor (Table 6)[3],[5],[15].

Table 6: 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	CFX 1	0.624	0.943	0.848	0.823	0.037	1.15
2	CFX 2	0.995	0.824	0.947	0.926	0.719	0.81
3	CFX 3	0.996	0.805	0.944	0.921	0.706	1.21

CONCLUSION

The present study was conducted to design and evaluate oral sustained-release tablets of ciprofloxacin hydrochloride using a chitosan-based in situ forming polyelectrolyte complex as a retardant polymer. The results of this study indicated that the polyelectrolyte complex formed between chitosan and anionic polymers, such as SSG and XG, has proven to be an excellent excipient 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 the drug. The formulated tablets were physically stable. The FTIR, XRD, and DSC analyses confirmed the formation of in situ PECs between CTS and SSG/XG. The formulations had shown sustained release up to 12 hours with zero–order release kinetics. The dissolution profiles were found to be independent of the change in type of anionic polymer, as confirmed by the comparison of release profiles. The study effectively demonstrated the potential of polyelectrolyte complexes in providing sustained release of drugs with high doses and high aqueous solubility, without significantly increasing the tablet size and without any initial burst release.

Limitations and Future Prospects: Our study demonstrated remarkable significance as a sustained-release formulation of Ciprofloxacin hydrochloride; however, its clinical translation requires in vivo studies to confirm the in vitro-in vivo correlation. Nonetheless, to substantiate the formulation's potential for real-world application, further investigations encompassing scalability and long-term stability assessments are warranted.

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AUTHOR CONTRIBUTION

Vijay Sharma conceived and designed the study. Ajay Malik was responsible for data acquisition, data analysis and interpretation, drafting the manuscript, and performing statistical analysis. Vijay Sharma and Navneet Verma provided critical revision of the manuscript and overall supervision. All authors have read and approved the final manuscript.

FINANCIAL ASSISTANCE

NIL

CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

[1] Mahmoud ZH, Hamrouni A, Kareem AB, Mostafa MA, Jalil alhakim Z, Majeed AH. Synthesis and characterization of chitosan sheet modified by varied weight ratio of anatase (TiO2) nano mixture with Cr(VI) adsorbing. *Kuwait J. Sci.*, **50**, 290–9 (2023) https://doi.org/10.1016/j.kjs.2023.05.006.

[2] Lal N, Dubey J, Gaur P, Verma N, Verma A. Chitosan based in situ forming polyelectrolyte complexes: A potential sustained drug delivery polymeric carrier for high dose drugs. *Mater. Sci. Eng. C. Mater. Biol. Appl.*, **79**, 491–8 (2017) https://doi.org/10.1016/j.msec.2017.05.051.

[3] Verma A, Bansal A, Ghosh A, Pandit J. Low molecular mass chitosan as carrier for a hydrodynamically balanced system for sustained delivery of ciprofloxacin hydrochloride. *Acta Pharm.*, **62**, 237–50 (2012) https://doi.org/10.2478/v10007-012-0013-2.

[4] Moed S, Hall M, Lee N, Costa C P, Rodland E K, Shemirani A I, Clifford K, Desai D, Zaman M H, Quantitative assay for ciprofloxacin and enrofloxacin formulations. *JoGR*,3, e2019044 (2019) https://doi.org/10.29392/joghr.3.e2019044

[5] Mahmoud TY, Hamza IS, Jarallah AL. Spectrophotometric Method for the Determination of Ciprofloxacin in Pure and Pharmaceutical Preparations: Development and Validation. *Engineering Proceedings*, **59(1)**, 164 (2023) https://doi.org/10.3390/engproc2023059164

[6] Al-Omar M. Ciprofloxacin: Analytical Profile. *Profiles Drug Subst. Excip. Relat. Methodol.*, **31**, 179–207 (2005) https://doi.org/10.1016/S0099-5428(04)31005-1.

[7] Prasad AR, Ratna JV. Development and validation of a simple uv-spectrophotometric method for the determination of ciprofloxacin HCl present in taste masked drug resin complex. *Int. J. Appl. Pharm.*, **10**, 37–41 (2018) https://doi.org/10.22159/ijap.2018v10i3.24199.

[8] Sahu A, Chouksey K, Ganju K. Formulation and Evaluation of Ciprofloxacin Hydrochloride Sustained Release Tablets Using Hibiscus Rosa Sinensis Mucilage. *J. Adv. Sci. Res.*, **13**, 71–8 (2022) https://doi.org/10.55218/jasr.202213811

[9] Kahsu A, Aklilu T, Masresh B, Melkam W. Benefits and Risks of Fluoroquinolones Use in Pediatrics: a Review. *Int. J. Life Sci. Rev. Rev. Artic. Int. J. Life Sci. Rev.*, **1**, 169–74 (2015) https://doi.org/10.13040/IJPSR.0975-8232.IJLSR.1.

[10] Mocanu AG, Belu I, Croitoru O, Ciocîlteu MV, Manda CV, Neamtu J. Formulation and Characterization of Ciprofloxacin loaded PLGA Microspheres for Applications in Orthopedic Infections. *Curr Health Sci J*., **43(4)**, 306-310 (2017) https://doi.org/10.12865/CHSJ.43.04.03.

[11] Fahmy S, Abu-Gharbieh E. In vitro dissolution and in vivo bioavailability of six brands of ciprofloxacin tablets administered in rabbits and their pharmacokinetic modeling. *Biomed Res Int.*, **2014**, 590848 (2014) https://doi.org/10.1155/2014/590848.

[12] J. Conceicao, M. Estanqueiro, M. H. Amaral, P. Lobao, P. Costa, J. M. Sousa Lobo. Development and Characterization of Buccal Bilayer Tablets containing Microparticles with Ibuprofen. *Am. J. Med. Sci. Med*.; 2(5):109-114. (2014) https://doi.org/10.12691/ajmsm-2-5-5.

[13] Shah VP, Tsong Y, Sathe P, Liu J-P. In Vitro Dissolution Profile Comparison—Statistics and Analysis of the Similarity Factor, f2. *Pharm. Res.*, **15**, 889–96 (1998) https://doi.org/10.1023/A:1011976615750.

[14] Skelly JP, Amidon GL, Barr WH, Benet LZ, Carter JE, Robinson JR, Shah VP, Yacobi A. In Vitro and in Vivo Testing and Correlation for Oral Controlled/Modified-Release Dosage Forms. *Pharm. Res.*, **7**, 975–82 (1990) https://doi.org/10.1023/A:1015970512368.

[15] Samaha D, Shehayeb R, Kyriacos S. Modeling and comparison of dissolution profiles of diltiazem modified-release formulations. *Dissolution Technol*., **16**, 41–6 (2009) https://doi.org/10.14227/DT160209P41.

[16] Tom RT, Suryanarayanan V, Reddy PG, Baskaran S, Pradeep T. Ciprofloxacin-protected gold nanoparticles. *Langmuir*, **20**, 1909–14 (2004) https://doi.org/10.1021/la0358567.

[17] Leonida M, Ispas-Szabo P, Mateescu MA. Self-stabilized chitosan and its complexes with carboxymethyl starch as excipients in drug delivery. *Bioact. Mater*., **3**, 334–40 (2018) https://doi.org/10.1016/j.bioactmat.2018.04.001.

[18] Shah KA, Li G, Song L, Gao B, Huang L, Luan D, Iqbal H, Cao Q, Menaa F, Lee B-J, Alnasser, S. M., Alshahrani, S. M., & Cui, J. Rizatriptan-Loaded Oral Fast Dissolving Films: Design and Characterizations. *Pharmaceutics*. 14 (12), 2687 (2022) https://doi.org/10.3390/pharmaceutics14122687

[19] Jadhav RL, Beloshe P, Siraj S, Vyankatrao PM. Design, Development, and Characterization of Modified Xanthan Gum Based Novel in situ Gel of Ciprofloxacin Hydrochloride for Ophthalmic Drug Delivery. *Asian J. Pharm.*, **14**, 236–46 (2020) https://doi.org/10.22377/ajp.v14i2.3619.

[20] Lazaridou A, Biliaderis C G. Thermophysical properties of chitosan, chitosan–starch and chitosan–pullulan films near the glass transition *Carbohydrate Polymers*, 48 (2), 179-190 (2002) https://doi.org/10.1016/S0144-8617(01)00261-2

[21] Dong Y, Ruan Y, Wang H, Zhao Y, Bi D. Studies on glass transition temperature of chitosan with four techniques. *J. Appl. Polym. Sci.*, **93**, 1553–8 (2004) https://doi.org/10.1002/app.20630.

[22] Zaid H. Mahmoud, AchrafHamrouni, Asmaa B. Kareem, Mohammed Ahmed Mostafa, ZaharaJalilalhakim, Abdulwahhab H. Majeed. Synthesis and characterization of chitosan sheet modified by varied weight ratio of anatase (TiO2) nano mixture with Cr(VI) adsorbing. Kuwait Journal of Science, 50 (3), 290-299 (2023) https://doi.org/10.1016/j.kjs.2023.05.006.

[23] Kumar S, Koh J. Physiochemical, optical and biological activity of chitosan-chromone derivative for biomedical applications. *Int. J. Mol. Sci.*, **13**, 6102–16 (2012) https://doi.org/10.3390/ijms13056102.

[24] Bhandari PN, Jones DD, Hanna MA. Characterization of sodium starch glycolate prepared using reactive extrusion and its comparisons with a commercial brand VIVASTAR ®P. *Ind. Crops Prod.*, **41**, 324–30 (2013) https://doi.org/10.1016/j.indcrop.2012.04.050.

[25] Chaulang G, Patel P, Hardikar S, Kelkar M, Bhosale A, Bhise S. Formulation and evaluation of solid dispersions of furosemide in sodium starch glycolate. *Trop. J. Pharm. Res.*, **8**, 43–51 (2009) https://doi.org/10.4314/tjpr.v8i1.14711.

[26] Kashaudhan K, Pande PP, Sharma J, Shankar R, Nath A, Chaurasiya A, Kushwaha N. Synthesis and characterization of Xanthan Gum Xanthates and their application for toxic metal ion removal from synthetic wastewater. *J. Dispers. Sci. Technol.*, **0**, 1–15 (2024) https://doi.org/10.1080/01932691.2024.2373932.

[27] Elena VAizquez, SofA-a Piguillem, Santiago Rubio, Jorge DA-az, Hector Baldoni EV and MM. Structural Analysis of Xanthan GUM-FE (III) Capsules. *Acad. J. Chem.*, **5**, 31–40 (2020) https://doi.org/10.32861/ajc.54.31.40.

[28] Zheng M, Lian F, Xiong Y, Liu B, Zhu Y, Miao S, Zhang L, Zheng B. The synthesis and characterization of a xanthan gum-acrylamide-trimethylolpropane triglycidyl ether hydrogel. *Food Chem.*, **272**, 574–9 (2019) https://doi.org/10.1016/j.foodchem.2018.08.083.

[29] Sahoo S, Chakraborti CK, Naik S, Mishra SC, Nanda UN. Structural analysis of ciprofloxacin-carbopol polymeric composites by X-ray diffraction and fourier transform infra-red spectroscopy. *Trop. J. Pharm. Res.*, **10**, 273–80 (2011) https://doi.org/10.4314/tjpr.v10i3.14.

[30] Lee BJ, Ryu SG, Cui JH. Formulation and release characteristics of hydroxypropyl methylcellulose matrix tablet containing melatonin. *Drug Dev. Ind. Pharm.*, **25**, 493–501 (1999) https://doi.org/10.1081/ddc-100102199.