Journal of Neonatal Surgery
ISSN(Online):2226-0439
Vol.14, Issue 24s (2025)
https://www.jneonatalsurg.com

OPEN ACCESS

Chitosan based in situ forming Polyelectrolyte Complexes: A Novel approach for Designing Sustained Release Formulation

Ajay Malik*[1], Navneet Verma[1], Vijay Sharma[1], Vibhu Sahani[2]

[1]FacultyofPharmacy, IFTM University, Moradabad, Uttar Pradesh, India
[2]Department of Pharmacy, LLM Medical College, Meerut, Uttar Pradesh, India

***Corresponding Author:**

Ajay Malik

Research Scholar, Faculty of Pharmacy, IFTMUniversity, Moradabad, Uttar Pradesh -244001 (India)

Email ID: ajaymalik.malik9@gmail.com

Citethis paper as: Ajay Malik, Navneet Verma, Vijay Sharma, Vibhu Sahani (2025) Chitosan based in situ forming Polyelectrolyte Complexes: A Novel approach for Designing Sustained Release Formulation. *Journal of Neonatal Surgery*, 14 (24s), 836- 846

ABSTRACT

The present study is an attempt to develop and evaluate the sustained release tablet formulations (oral) of paracetamol utilizing chitosan based in situ forming polyelecrolyte complex as retardant polymer. The traditional method of wet granulation was used to create various formulations. A 1%w/w solution of chitosan in1% acetic acid (cooled to about 4 ^{o}C and neutralized) was used as binder to granulate the drug mixed with anionic polymer (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 2hr],for 8hr in mixed phosphate buffer (pH6.8) and again for 2hr at pH7.5 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, firstorder, Korsmeyer– Pepps equations and Hixson– crowell) to investigate and elucidate the mechanism of drug release from the various formulations/ tablets. The drug release studies confirmed the sustained release of drug for12hrs.The polyelectrolyte complex formation (in situ) between anionic polymers and chitosan had been revealed by XRD studies of polyelectrolyte complex gels

Keywords: *Chitosan, Sodium Starch Glycolate, Xanthan Gum, Polyelectrolyte complex, paracetamol.*

1. INTRODUCTION

It is very challenging to create sustained-release (single-unit) oral dosage forms for hydrophilic medicines, which are extensively soluble (10mg/ml) in stomach 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 straight forward, 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]. Thus, the current work aims to create sustained release tablet formulations of paracetamol by using chitosan solution as binder and sodium starch glycolate as excipient. The in situ formation of polyelectrolyte complexes was expected when the tablet encountered the acidic dissolution medium (0.1 NHCL, pH–1.5).It was anticipated that this strategy would maintain the drug's release sustained due to high molecular organization and dense crystalline structure of the polyelectrolyte complexes formed between cationic polymer chitosan and anionic polymer sodium starch glycolate [3].

2. MATERIALSANDMETHODS

Materials: Paracetamol (PCM) 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), 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 with1%w/v solution of polymers in suitable medium (distilled water or 1% acetic acid).The mixture was kept at 37ºC for 2hr. After that the mixture was dried and FTIR spectra were recorded on Spectrum BX of Perkin Elmer (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 the formulations to the acidic dissolution medium (0.1 N HCl, pH 1.5). Thus, in order to investigate how chitosan and SSG interact the polymers were mixed in ratio of 1:1 and packed in dialysis membrane (molecular weight cut – off - 1200) previously activated by boiling for 30 min in Phosphate buffer (pH7.4). These sealed bags were kept at pH 1.5 (0.1NHCl) 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 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 1.0 M 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 -1. The binder solution prepared in1% acetic acid was used to granulate the mixture of drug and excipients. The damp mass was passed through sieve number10 and dried at 60 ºC overnight in a hot air oven. 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.

Table1. Formulations of sustained release tablets

Sr. No.	Formulation Code	Paracetamol (mg)	Sodium Starch Glycolate (mg)	Lactose (mg)	Mg. Stearate (mg)	Talc (mg)	Binder (Chitosan solution in 1% acetic acid)
1	PCM1	750 mg	---	100	27	9	1%w/v
2	PCM2	750 mg	50	50	27	9	1%w/v

Evaluation of Tablets:

Pre-compression characterization:

Moisture content: Moisture content of dried granules was determined by using IR moisture balance [4].

Drug content: The assay of paracetamol was performed by UV method with UV Spectrophotometer (UV-1800), Shimadzu. For assay The granules/ powder equivalent to about 0.15 mg of paracetamol were added to 0.1 M NaOH (50 ml) taken in a volumetric flask (200 ml). The solution was diluted with distilled water (100ml) and shaken for 15 min. More water was added to produce 200ml. The contents were mixed and filtered through whatman filter paper. The filtrate (10ml) was diluted to100ml with distilled water. The resulting solution (10ml) was added to 0.1M NaOH (10ml) and solution was diluted to 100ml with distilled water and mixed. From this final solution, test sample (1ml) was withdrawn and absorbance spectra of solution against water as blank were measured at $\lambda_{max}$of Paracetamol i.e.257 nm [5,6,7,8].The formula used to calculate the drug content:

Drug content= Concentration × Dilution Factor,

$$\text{Drug Content} = \frac{\text{Drug Content (mg)}}{\text{Label Claim (mg)}} \times 100$$

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 no further change in volume was observed. The volume occupied after tapings is called tapped volume. The tapped bulk density was calculated by using the formula – **Tapped density = Weight / Tapped volume.**

Hausners' ratio: It is a number corresponds to flow ability of granules/ powder. The formula to determine Hausners' ratio – **Hausners' ratio = Tapped bulk density/ Bulk density**. This ratio determines 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.** Particle size, cohesiveness, and relative flow rate are all indirectly correlated with the Carr's consolidation index.

Angle of repose: The largest possible angle between surface of powder or granules' pile and a horizontal plane is reffered to 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 formula to determine angle of repose – **Angle of repose (Θ) = $\tan^{-1}$ h/r**. The flow properties of powder or granules are measured by the angle of repose [4, 9].

Swelling index: To determine the swelling index each PCM, CH and SSG were mixed in ratio of 1:1 and packed in dialysis membrane (molecular weight cut–off-1200), previously activated by boiling for 30min in Phosphate buffer (pH 7.4). The previously weighted sample was first kept in 0.1N HCL (having pH 1.5) for 2 hr. and the sample was weighed after every 30min. After that each sample was transferred into mixed phosphate buffer (having pH 7.4) for 8 hrs and each sample was weighed after every 1hruntil three same consecutive readings were obtained. The formula for determining swelling index – **Swelling index = [(Final weight – initial weight) × 100]/ initial weight** [9, 10].

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 Sodium starch glycolate 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 membrane (molecular weight cut–off -1200) previously activated by boiling for 30min in Phosphate buffer (pH7.4) according to the experimental protocol shown below in table-2. The XRD thermograms of test samples were also compared with that of pure compounds.

Table2. Composition of Polyelectrolyte complex gels for X-ray diffraction studies

Sr. No	Sample Code	Composition
1	G-1	Chitosan (CH) + Sodium starch glycolate (SSG)
3	G-7	Paracetamol + CH + SSG

These samples in sealed bags were kept at pH 1.5 (0.1N HCl) 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. To ascertain if the fine powder samples were crystalline or amorphous, they were continuously scanned at room temperature between 10º to 80º (2Θ)at 30kV accelerating voltage,15mAcurrent and at scanning speed of 10 ºC/min.[10, 11].

Post-compression parameters:

Friability test: Required number of tablets (20) was weighed after dusting to find the initial weight. The sample was then putinRochefriabilatorandmachinewasusedfor4minutesor100revolutions.Thetabletswereagainweightedafterdusting 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: For the test 20 tablets of each formulation were used. The tablets (i.e.20) were weighed and average weight was calculated. Then each tablet was weighed individually and the difference in weight was determined by deducting average weight from individual weight of each tablet. The deviation from average weight 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 [9, 10].

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, 7, 8].

Hardness testing: The Monsanto hardness tester was utilized to determine the hardness of formulated tables. Three tablets were arbitrarily selected from each formulation. The tablet was placed between anvil and spindle (diametrically) of tester and screw was rotated (clock wise) 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 [4, 9].

In vitro dissolution studies: The test was conducted utilizing USP type II apparatus at paddle speed of 50 rpm. A 500 mL of 0.1N HCl (pH 1.5) was used as dissolution media for first 2hr, mixed phosphate buffer (pH6.8) for next 8hr 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) until12 hand 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 243 nm. [12, 13, 14, 15].

Drug release kinetics: The various mathematical models were used to examine and test drug release data in order to determine the precise mechanism of drug release from different formulations were Zero – order equation, First – order equation, Higuchi square root law, Hixson – Crowell cube root law and Korsmeyer – Peppas equation [3, 16, 17].

3. RESULTANDDISCUSSION

Pre- formulation studies:

Drug – polymer interaction studies: In the spectra (FTIR) of pure PCM (Fig. 1a) characteristic peaks observed at 3326, 3162- 3035, 1655, 1610 and 1506 cm^{-1} corresponding to –OH vibrations, CH_3 stretching, C= O stretching, C= C stretching and Asymmetrical bending in C-H bond, respectively. The peaks observed at 1564 and 1259 - 1226 cm^{-1} were due to NH amide – II bending and C-N (aryl) stretching vibrations. The peaks due to C-C stretching, Symmetrical bending in C-H, C-O stretching, para- distributed aromatic ring and out of plane ring deformation of phenyl ring were observed at 1441, 1370 – 1327, 1171, 837 and 518 cm^{-1}, respectively [2, 18, 19].The spectra of chitosan (low molecular weight) (Fig. 1b) showed major absorption bands at 3423, 1632 and1403cm^{-1} because of amide I, II and CH and OH bending respectively [2,3,20]. 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 [21]. The spectra of the sample containing solution mixture of PCM + CH (Fig. 1d) and PCM + SSG (Fig. 1e) exhibited no interaction with drug due to presence of intact major peaks of Paracetamol.

Polymer–Polymer interaction studies:

FTIR characterization: The spectra (FTIR) of PEC gel sample (dried) of CH + SSG (Fig.1f) exhibited interaction between CH and SSG to form PECs. The peak at 1637cm^{-1} due to –C=O stretching vibrations of –C=O group in SSG 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 1523cm^{-1} (was absent in pure polymers) indicate the formation of ionic bonds.

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. 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 [2,3,22,23]. In the DSC thermogram of SSSG (Fig. 2b) the dehydration 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 [21]. In thermogram of CH + SSG dired gel (Fig. 2c) theinteraction 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.

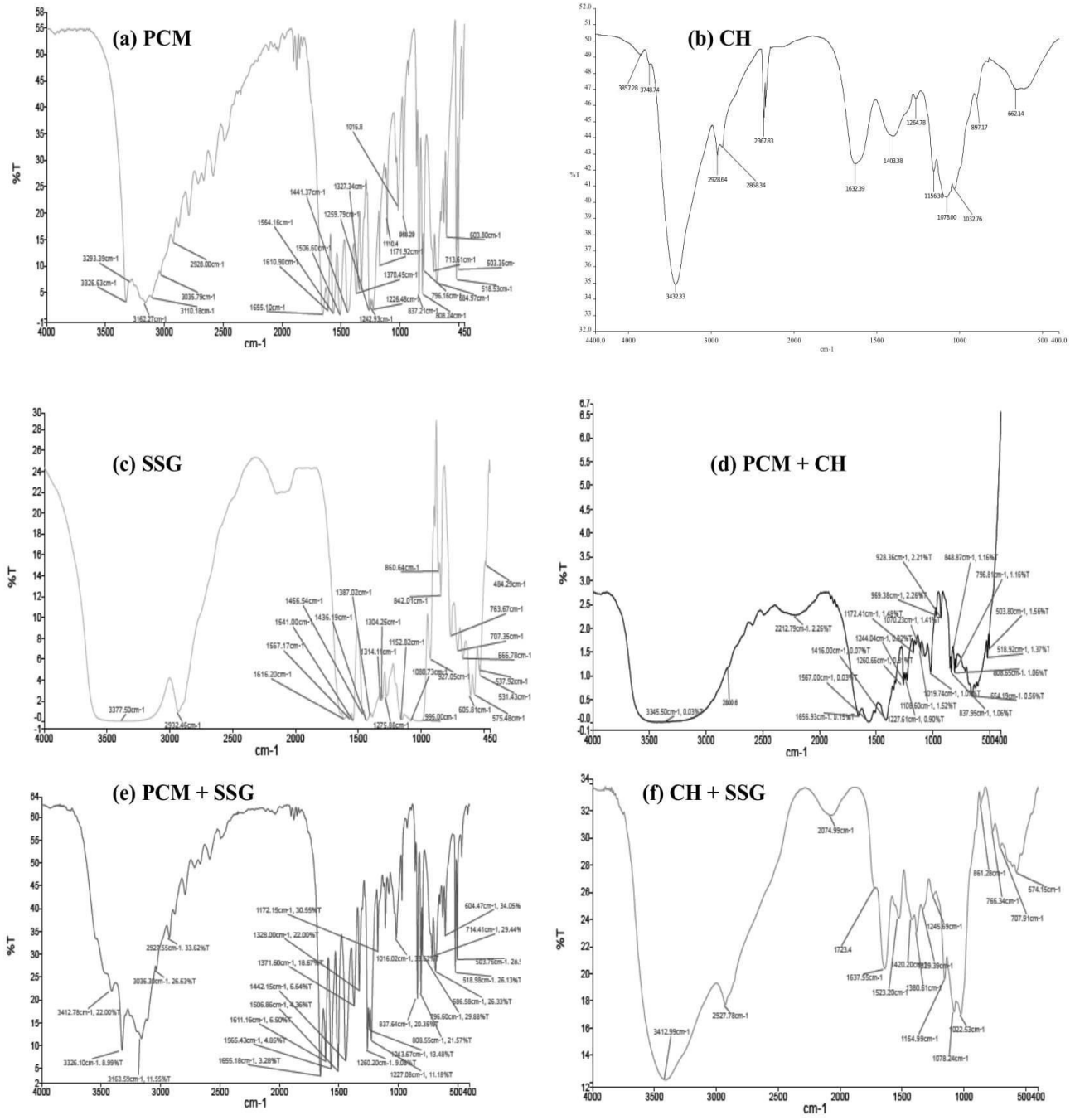
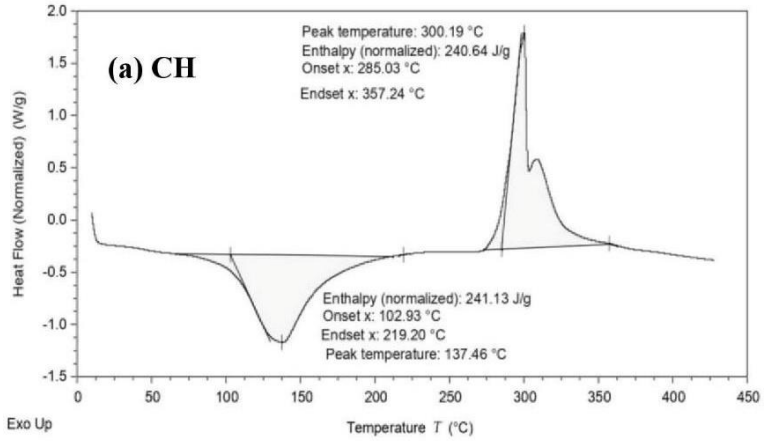
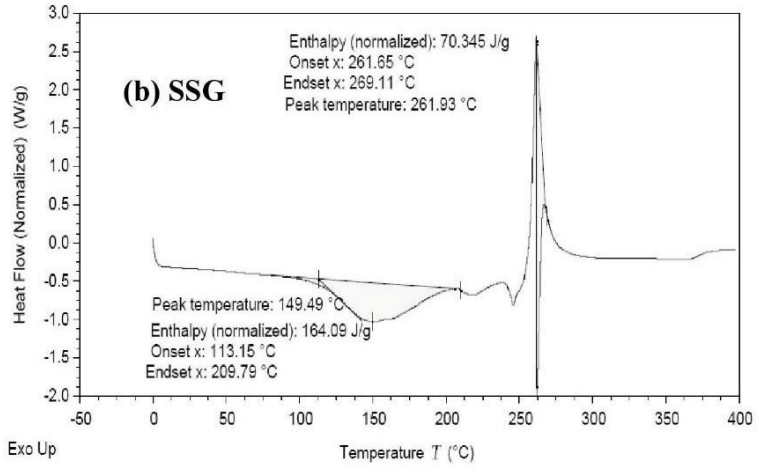


Figure1. Spectra (FTIR) of: (a) Paracetamol (PCM), (b) Chitosan (Low molecular weight) (CH), (c) SSG, (d) PCM + CH (solutions) (e) PCM + SSG (solutions) (f) CH + SSG (dried gel)





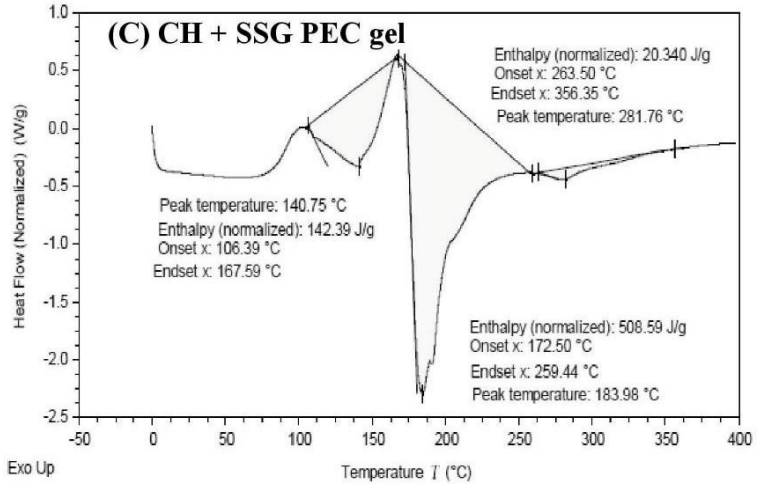


Figure2. Thermograms (DSC) (exoup) of: (a) CH (Low molecular weight) (b) SSG (c) CH + SSG (driedPEC gel)

Evaluation of Tablets:

Pre- compression characterization: The observed values of all parameters were found within the limits specified (Table 3), showing that the powder blend is suitable for compression into tablets.

Table3. Pre- compression characterization

Parameters		PCM1	PCM2
Moisture content (%w/w)		1.3±0.58	1.7±0.58
Drug content (%w/w)		98.86± 2.1	98.37± 0.9
Bulk Density (g/cm^3)	Before Lubrication	0.47± 0.02	0.46± 0.02
	After Lubrication	0.58± 0.05	0.53± 0.04
Tapped Density (g/cm^3)	Before Lubrication	0.63± 0.03	0.61± 0.02
	After Lubrication	0.74±0.03	0.66± 0.04
Hausners' ratio	Before Lubrication	1.3±0.06	1.4±0.1
	After Lubrication	1.3±0.06	1.2±0.1
Carr's index (%)	Before Lubrication	25.2± 0.8	25.4± 1.1
	After Lubrication	21.7± 0.8	13.8± 0.8
Angle of repose (Ɵ^o)	Before Lubrication	36.1± 0.9	33.2± 1.0
	After Lubrication	28.6± 0.9	27.1± 1.1

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

Swelling index: The swelling behavior of PECgel (of PCM2) had showed more swelling in acidic medium than alkaline medium due to formation of polyelectric complex in acidic medium (Table 4).

Table4. Swelling index of PEC gel in different mediums

Sr. No	**Formulation Code**	**Swelling Index(%w/w)**		
		In pH 1.5 (after 2hr)	**In pH 7.4 (after 8hr)**	**Overall (after10hr)**
1	PCM2	183.2± 2.4	42.2± 1.8	298.3± 1.8

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

X- ray Diffraction studies: The XRD diffractogram of CH + SSG (Fig. 3a) 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 [24, 25, 26, 27]. There were numerous new peaks in the diffractogram of Paracetamol, Chitosan and Sodium starch glycolate dried PEC gel (G7) (Fig. 3b) which were not present in the individual diffractograms of drug and polymers [28, 29, 30]. Some characteristic peaks were showed 2θ=11.96^o, 13.68^o, 15.38^o, 16.62^o, 18.02^o, 20.24^o, 23.34^o, 24.22^o, 26.4^o, 27.04^o, 28.18^o, 32.66^o, 36.68^o and 40.34^o. 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.

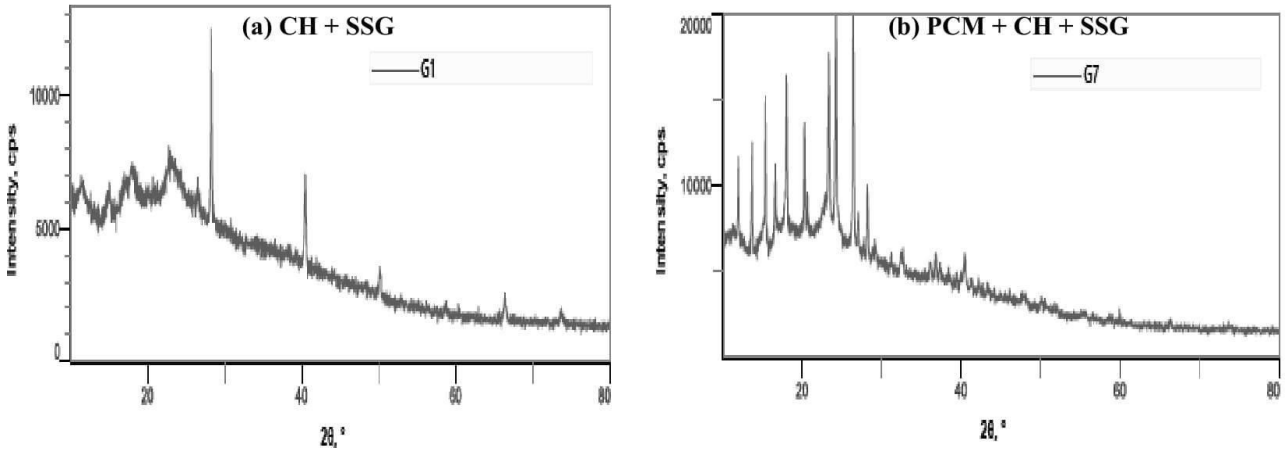


Figure3. XRD Diffractograms of: (a) CH + SSG and (b) PCM + CH + SSG

Post–compression parameters: All the batches of prepared tablets had a uniform smooth texture and structure confirmed by visual inspection. All the formulations had less than 1% friability and hence passed the test. The weight variation of all formulations was between 3 to 5% 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 96 to 99% and 4 to 5.5 Kg/cm^2. The thickness of formulations was found between 4.1 to 4.3 mm (Table 5) [9, 10].

Table5. Post-compression characterization of sustained release tablets

Formulation Code	Friability (%)	Weight (mg)	Drug content (%)	Hardness (kg/cm^2)	Thickness (mm)
PCM1	0.80± 0.02	888.0± 4.3%	98.5± 2.1	5.4±0.8	6.6±0.06
PCM2	0.73± 0.02	888.3± 4.1%	98.6± 2.3	6.1±0.4	6.5±0.1

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

In vitro drug release studies: A plot of % cumulative drug release versus time is shown in Fig. 4. It was observed that the formulation PCM1 showed about 99% drug release within 2hrs, indicating the burst drug release from the formulation. The formulation PCM 2 exhibited 97% drug release in 12 hrs, indicating the sustained release for 12 hr [2, 31, 32, 33].

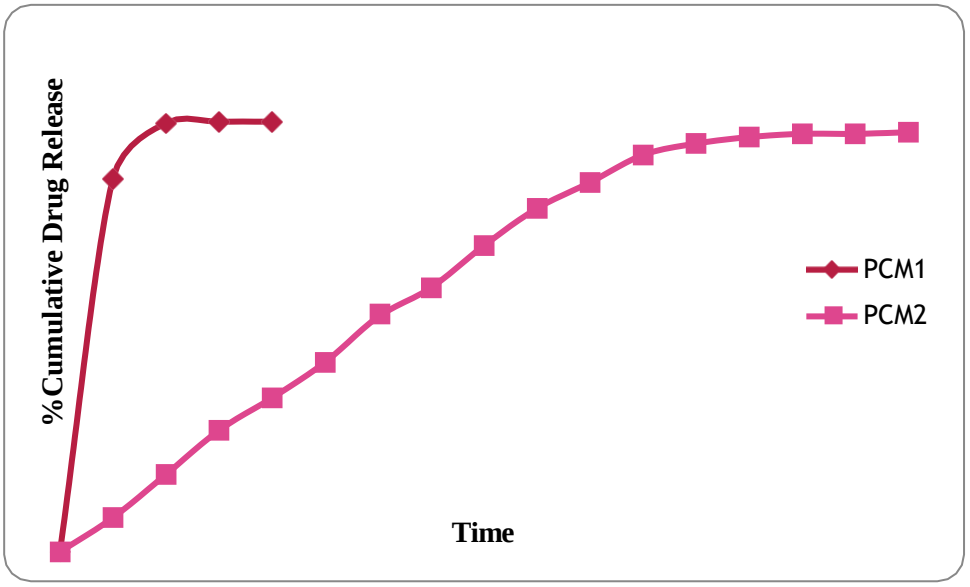


Figure4. Cumulative % drug release v/s time graph of: (a) PCM 1 and PCM 2

Drug release kinetics: After fitting the dissolution data into various kinetic models it was observed that R^2 value of PCM 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. Higuchi drug release pattern was followed by formulation PCM 2 as indicated by Highest R^2 value. Regarding *n* values, formulation PCM 2 followed Fickian release mechanism (n<0.5), indicating that the ordinarydiffusion was the governing factor for drug release form the PECs. (Table 6) [2, 9, 17, 34, 35, 36, 37].

Table6. 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	PCM1	0.704	0.962	0.914	0.882	0.023	1.04
2	PCM2	0.932	0.978	0.994	0.944	0.688	0.42

4. CONCLUSION

The goal of the current study was to develop and assess paracetamol oral sustained release tablets 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 polymer SSG 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 and degradation (in acidic medium) of drug. The formulated tablets were physically stable. The FTIR, DSC and XRD analysis confirmed the formation of in-situ PECs between CH and SSG. The formulations had shown sustained release up to 12hr with zero – order release kinetics.

ACKNOWLEDGEMENT

The authors are grateful to Prof. Anurag Verma, Principal, School of Pharmacy, Teerthanker Mahaveer University (TMU), Moradabad U. P. for providing guidance for the completion of this research manuscript. We also express our gratitude to Prof. Vikas Kumar, Principal DK Pharma college, Rewari, Haryana and Dr. Parveen Kumar Goyal, Professror, Dept. of Pharmacy, PIET, Panipat (Haryana) for their support and encouragement during this work.

REFERENCES

[1] Madhusudhan pogula, S. Nazeer,; Extended Release Formulation, International Journal OfPharmacy & TechnologySSN:0975-766X,Dec-2010|Vol.2| IssueNo.4|625-684.

[2] Niharika Lal, Juhi Dubey, Praveen Gaur, Navneet Verma, Anurag Verma,; Chitosan based in situ forming polyelectrolytecomplexes:Apotentialsustaineddrugdeliverypolymericcarrierforhighdosedrugs,Jr. MaterialsScienceandEngineering,PublishedbyElsevierC79(2017)491–498.

[3] AnuragVerma,AshokK.Bansal,AmitavaGosh,JayantaK.Pandit,Lowmolecularmasschitosanascarrier for hydrodynamically balanced system for sustained delivery of ciprofloxacin hydrochloride, Acta Pharm.62(2012) 237 – 250.

[4] IndianPharmacopoeia2018,GovernmentofIndia,MinistryofHealth&FamilyWelfare,Publishedbythe Indian PharmacopoeiaCommission, Ghaziabad, 2018.

[5] BeheraS,GhantyS,AhmadF,SantraS,BanerjeeS.,2012.UV-visiblespectrophotometricmethod developmentandvalidationofassayofparacetamoltabletformulation.JAnalBioanalTechniques,3(6):151- 7.

[6] NandrePartikAshok,Dr.GulamJavedKhan.,2022.ASimpleUV–VIS–SpectrophotometricAssayStudy onDifferentBrandsofParacetamol.WorldJournalofPharmaceuticalSciences,Vol.8,Issue9,186-193.

[7] SawantR,Bhangale L,JoshiR,LankeP,2010.Validatedspectrophotometricmethods forsimultaneous estimation of Paracetamol, Domperidone and Tramadol HCl in pure and tablet dosage form. Journal of chemical metrology, 4(1): 21.

[8] Tabbouche O. S, Soukkariyyeh I, Naji M and Alwan T., 2013. Validation of A UV-Spectrophotometric MethodForTheAssayAndPurityofParacetamolinSolutionsForIVInfusion,AndComparisonofMarketedBrands. InternationalJournalofPharmacy,3(1):24-27

[9] Heyam Saad Ali, Gazala Afreen Khan, Babiker M.A. Elhaj, Mai Al Ajaji and Rasha Saad, 2016. Evaluation & formulation of paracetamol matrix sustained release tablets using natural polymers. Journal of Innovations in PharmaceuticalandBiologicalSciences(JIPBS),Vol3(4),85-91.

[10] N. C. Ngwuluka, B. A. Idiakhoa, E. I. Nep, I. Ogaji and I. S. Okafor, 2010. Formulation and evaluation of paracetamol tablets manufactured using the dried fruit of Phoenix dactylifera Linn as an excipient. Research in Pharmaceutical Biotechnology, Vol. 2(3), pp.25-32,

[11] GhulamAbbasa,MuhammadHanifa,MahtabAhmadKhana.pHresponsivealginatepolymericraftsfor controlleddrugreleasebyusingboxbehnkenresponsesurfacedesign.DesignedMonomersandPolymers, 2017, Vol. 20, No. 1, 1–9.

[12] Lee B.J. Ryu S.G. and Cui J.H., 1999. Formulation and release characteristics of hydroxypropyl methylcellulose matrixtabletcontainingmelatonin.DrugDevIndPharm,22:493-501.

[13] Lee, M.-H.; Chun, M.-K.; Choi, H.-K., 2008. Preparation of Carbopol/Chitosan interpolymer complex as a controlled release tablet matrix; effects of complex formation medium on drug release characteristics.Arch.Pharm. Res., 31, 932–937.

[14] ShashankSoni,VeermaRam,AnuragVerma.UpdatesonApproachestoIncreasetheResidenceTimeofDrug in the Stomach for Site Specific Delivery: Brief Review.International Current Pharmaceutical Journal, 2018, 6(11): 81-91

[15] The United States Pharmacopoeia 32 National Formulary 27, United States Pharmacopoeia convention, Inc., Rockville, MD, 2009; 2907.

[16] Skelly,J.P.,G.L.Amidon,W.H.Barr, L.Z.Benet,J. E.Carter,J.R.Robinson,V.P.Shah,andA.Yacobi, 1990, "In Vitro and In Vivo Testing and Correlation for Oral Controlled/Modified- Release Dosage Forms," Pharmaceutical Research, 7:975-982.

[17] Paulo Costa, Jose Manuel Sousa Lobo.Modeling and comparison of dissolution profiles- Review. European Journal ofPharmaceuticalSciences 13 (2001)123–133.

[18] SocratesG.,InfraredCharacteristicGroupFrequencies,JohnWiley&Sons,NewYork(2004).

[19] DaniVR.OrganicSpectroscopy.TataMcGraw-HillPublishingCompanyLimited,NewDelhi,1995;86-168.

[20] LeonidaM,Ispas-SzaboP,MateescuMA.Self-stabilizedchitosananditscomplexeswithcarboxymethylstarch asexcipientsindrugdelivery.BioactMater.2018,8;3(3):334-340.

[21] PrudhviRajVadamala,SaravanakumarK,YugandharBaiah.FormulationDesignandCharacterizationof

Orally Disintegrating Tablet of Rizatriptan Using Different Superdisintegrants, Ymer (2022), Vol. 21, Issue 11, 1181 – 1191.

[22] DhawadiP,Prerna,JagtapN,Ramanand,Characterizationoftheglasstransitiontemperatureofchitosanand itsoligomersbyTemperatureModulatedDifferentialScanningCalorimetry,PelagiaResearchLibrary,2012, 3/3; 1372 - 1382.

[23] Dong Y, Ruan Y, Wang H, Zhao Y and Bi D, Studies on Glass Transition Teperature of Chitosan with Four Techniques,JournalofAppliedPolymerScience,vol.-3,2004;1553–1558.

[24] 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,Volume 50, Issue 3,2023,Pages 290-299.

[25] Santosh Kumar and Joonseok Koh. Physiochemical, Optical and Biological Activity of Chitosan-Chromone DerivativeforBiomedicalApplications.InternationalJournalofMolecularSciences,May2012,13,6102- 6116; doi:10.3390/ijms13056102.

[26] PratikN. Bhandari, DavidD. Jones, MilfordA. Hanna.Characterizationofsodiumstarchglycolateprepared using reactive extrusion and its comparisons with a commercial brand VIVASTAR®P. Industrial Crops andProducts, 2013, Vol. 41, 324 – 330.

[27] Ganesh Chaulang, Piyush Patel,Sharwaree Hardikar, Mukul Kelkar, Ashok Bhosale, Sagar Bhise. Formulationand Evaluation of Solid Dispersions of Furosemide in Sodium Starch Glycolate. Tropical Journal ofPharmaceutical Research,February 2009; 8 (1): 43-51.

[28] In-Chun Wang, Min-Jeong Lee, Da-Young Seo, Hea-Eun Lee, Yongsun Choi, Woo-Sik Kim, Chang-Sam Kim, Myung-YungJeong,GuangJinChoi.,2011.PolymorphTransformationinParacetamolMonitoredbyIn-line NIRSpectroscopyduringaCoolingCrystallizationProcess.AAPSPharmSciTech,764–770.

[29] Touraj Ehtezazi,MarwanAlgellay,YamirIslam,MattRoberts,NicolaM.Dempster,SatyajitD.Sarker,2017. The Application of 3D Printing in the Formulation of Multilayered Fast Dissolving Oral Films. Journal of Pharmaceutical Sciences xxx, 1-10.

[30] Judyta Cielecka-Piontek,Anna Stasilowicz, Mikolaj Mizera, Ewa Tykarska, Kornelia Lewandowska, Andrzej Miklaszewski, 2019. The Possibility of UsingX-RayPowderDiffraction, InfraredandRamanSpectroscopy In The Study Of The Identification of StructuralPolymorphs of Acetaminophen. Acta Poloniae Pharmaceutica nDrug Research, Vol. 76 No. 6 pp. 997– 1004.

[31] Khushi Chouksey, Ayush Sahu, Kuldeep Ganju, 2022. Formulation and Evaluation of CiprofloxacinHydrochlorideSustainedReleaseTabletsUsingHibiscusRosaSinensisMucilage.JournalofAdvanced Scientific Research; 13 (8): 71-78.

[32] SenthilKumarKrishnan,MohammadGulzarAhmed,B.Ramesh,RamakrishnaT.,2012.Designand Evaluation of Chitosan Based Oral Controlled Release Matrix Tablets of Glipizide. International Journal of Universal Pharmacy and BioScience, 1(2), 130– 139.

[33] ArifulIslam,Md.Arifuddin,Md.RakibUddin,JakiaSultana,FarjanaChowdhury,RumanaFerdushi. Dissolution Study of Tramadol HCl Sustained Release Matrix Tablet from HPMC K4M. World Journal of PharmaceuticalResearch,2015,Vol.4,Issue12,1447-1459.

[34] HiguchiT,1963.Mechanismofsustainedactionmedication.Theoreticalanalysisofrateofreleaseofsolid drugsdispersedinsolidmatrices.J.Pharm.Sciences;52:1145-1149.

[35] SubalChandraBasak,KesevanSenthilKumar,MurugesanRamalingam,2008.Designandrelease characteristics of sustained release tablet containing metformin HCl, Brazilian Journal of Pharmaceutical Sciences,vol. 44, n. 3, 477 – 483.

[36] Barnabas Wilson, Patel Pritesh Babubhai, Moothandassery Sankarakutty Sajeev, Josephine Leno Jenita, S. R. BrahmaniPriyadarshini,2013.Sustainedreleaseentericcoatedtabletsofpantoprazole:Formulation,invitro and in vivo evaluation. Acta Pharm. 63:131–140.

[37] Md.ShozanMondal,SharifMd.Abuzar,Md.ArifulIslam,Md.TauhidulIslamandMd.SharifurRahman, 2015. Sustain Release Formulation and Evaluation of Ciprofloxacin Sustain Release Tablet and Its Comparison withMarketProduct.InternationalJournalofLifeSciencesandReview,Vol.1(4):124-136...

.