Factors influencing optimization of polyelectrolyte complex as raft systems containing ondansetron hydrochloride

Mina Safa Aziz*, Methaq Hamad Sabar*, Ali Mahmoud Jasim Al-Samydai**

Department of Pharmaceutics, College of Pharmacy, Mustansiriyah University, Baghdad, Iraq.

**** Department of pharmaceutics and pharmaceutical technology, College of Pharmacy, Al-Ahliyyah Amman University, Amman, Jordan.***

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Corresponding Author email:
mina_safaa@uomustansiriyah.edu.iq
Orcid: https://orcid.org/0009-0006-8262-0183

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Abstract:

Gastroretentive drug delivery systems (GRDDSs) are highly promising methods for the enhancement of the bioavailability and therapeutic effectiveness of some orally administered medications. The present review focused on gastroretentive film drug delivery methods, specifically developed to extend the duration of medication presence in the stomach which is most likely to enhance their absorption and efficacy.

HCl release by evaluating key formulation and process parameters. The complexation technique was used to prepare PEC by adjusting Chitosan molecular weight and cross-linker concentration (1% and 2%). Formulations were assessed for drug content, buoyancy, raft strength, and *in vitro* drug release. Analytical methods such as FTIR, DSC, and FE-SEM confirmed PEC formation and structural properties. Drug release kinetics were modeled using mathematical equations. The finding demonstrates that increased Chitosan molecular weight and cross-linker concentration improved raft stability, buoyancy, and drug release control. The optimal formulation (F6) showed high drug content (94.8%), drug loading (11.9%), and sustained drug release over 12 hours. In conclusion, the optimized PEC raft system effectively prolonged Ond. HCl release offers a promising platform for drugs requiring extended gastric retention and controlled release.

Keywords: Chitosan, Polyelectrolyte complex, Ondansetron hydrochloride, Sodium alginate.

العوامل المؤثرة في صياغة وتحسين مجمع البولي إلكتروليت كأنظمة طوف تحتوي على الأوندانسيترون هيدروكلوريد

مينا صفاء عزيز*، ميثاق حمد صبار*، علي محمود جاسم الصميدعي**

***فرع الصيدلانيات، كلية الصيدلة، الجامعة المستنصرية، بغداد، العراق.*

***قسم الصيدلانيات والتكنولوجيا الصيدلانية، كلية الصيدلة، جامعة عمان الأهلية، عمان، الأردن.*

الخلاصة:

تعزز أنظمة توصيل الأدوية المحتجزة في المعدة التوافر البيولوجي للأدوية من خلال إطالة وقت الإقامة في المعدة. توفر أنظمة تشكيل الطوافة القائمة على مجمعات البولي إلكتروليت (PEC) إطلاق خاضع للأدوية للرقابة، خاصة بالنسبة لأدوية مثل الأوندانسيترون هيدروكلوريد (Ond. HCl) ، الذي يحتوي على توافر حيوي محدود ونصف عمر قصير. تهدف هذه الدراسة إلى صياغة وتحسين نظام طوف قائم على PEC باستخدام الكيتوسان وألجينات الصوديوم من اجل اطلاقOnd. HCl المستدام

عن طريق تقييم بارامترات الصياغة والعملية الرئيسية. تم استخدام تقنية التشابك المعقدة لإعداد PEC عن طريق ضبط الوزن الجزيئي للكيتوسان، وتشكيل مركب البوليمر الدوائي، وتركيز المادة المساعدة على التشابك (1٪ ،2٪). تم تقييم التركيبات من حيث كفاءة انحباس الدواء، والطفو، وقوة الطوافة، وسلوك الانتفاخ وتحرير الدواء في المختبر. أكدت الطرق التحليلية مثل FTIR وDSC وFE-SEM تكوين PEC وخصائصه الهيكلية. تم تصميم حركية إطلاق الدواء باستخدام المعادلات الرياضية. توضح النتيجة أن زيادة الوزن الجزيئي للكيتوسان وتركيز المادة المساعدة على التشابك أدى إلى تحسين استقرار الطوافة والطفو والتحكم في تحرير الدواء. أظهرت التركيبة المثلى (F6) كفاءة عالية في الانحباس (94.8٪)، وتحميل الدواء (11.9٪)، واستمرار تحرير الدواء على مدار 12 ساعة. في الخلاصة أدى نظام الطوافة PEC المحسن إلى إطالة أمد تحرير Ond. HCl بشكل فعال. يوفر منصة واعدة للأدوية التي تتطلب الاحتفاظ احتباسا ممتد في المعدة وتحرر متحكم فيه.

الكلمات المفتاحية: الكيتوسان، مجمعات البولي إلكتروليت، الأوندانسيترون هيدروكلوريد، ألجينات الصوديوم

Introduction

The increasing incidence of gastrointestinal illnesses and the constraints of traditional drug delivery techniques present substantial obstacles to successful therapeutic management, notwithstanding progress in pharmaceutical sciences. Oral drug delivery continues to be the predominant and most convenient method for administering drugs owing to its simplicity, patient adherence, and cost efficiency. This is especially beneficial for medications necessitating systemic effects, as it obviates the requirement for intrusive treatments. However, this method presents multiple physiological issues, including a variable gastric emptying rate that differs among individuals, a short gastrointestinal transit time, and the presence of an absorption window in the upper small intestine for various medications resulting in variable plasma drug concentrations, requiring multiple doses and diminishing patient compliance (1, 2).

Advanced approaches have been established to address these constraints, among them gastro-retentive drug delivery systems that remain in the upper gastrointestinal tract for prolonged durations, enabling controlled drug release at a predetermined rate. This extends the duration between doses, augmenting patient adherence and raising medication efficacy (3). Technological approaches for gastro-retentive systems encompass a mucoadhesive system, floating system, magnetic system, ion exchange resin, expandable system, unfoldable system, and raft-forming system (4, 5). In a recent study aimed to design and optimize gastro-retentive floating minitablets of ondansetron using HPMC K15M and Carbopol 971, the study successfully demonstrated that ondansetron floating minitablets are a promising gastro-retentive delivery system for prolonged emesis control in chemotherapy patients (6). Also, a previous study aimed to formulate and optimize an effervescent gastroretentive tablet of Ond. HCl using a [3. sup .2] factorial design (7). Another previous study aimed to formulate gastro retentive floating hydro dynamically balanced drug delivery system of Ond. HCl (8 mg) employing various low-density polymers by using a direct compression technique (8).

The raft formation system generates a continuous, viscous gel upon interaction with the gastric fluid layer, referred to as the raft. Due to its lower bulk density, the gel layer remains buoyant over the gastric fluid. Consequently, the system sustains its buoyancy in the stomach without influencing the gastric emptying rate for an extended period. When the system is submerged in gastric contents, the medicine is progressively released at the designated rate from the system (9, 10). A recent study

developed a raft-forming suspension of famotidine to improve the oral bioavailability of narrow absorption window drugs by enhancing gastric residence time (GRT) and preventing gastro-esophageal reflux disease (GERD). The formulation aimed to prolong drug release and provide effective anti-reflux action, demonstrating the potential for improved therapeutic outcomes (11). Another recent study aimed to formulate a novel raft-forming system incorporating curcumin-Eudragit® EPO solid dispersions that were developed to prolong gastric residence time and provide controlled release of curcumin for treating gastric ulcers. Solid dispersions were prepared using a solvent evaporation method at a 1:5 curcumin-to-Eudragit® EPO ratio to enhance solubility and dissolution. The raft-forming formulations, composed of Sodium alginate and calcium carbonate, formed a gelled raft within 1 minute and sustained buoyancy in acidic conditions, releasing 60–85% of curcumin over 8 hours; the findings highlight the potential of raft-forming systems for stomach-specific delivery of poorly soluble lipophilic drugs like curcumin (12).

Ondansetron is a short-acting serotonin 5-HT3 receptor antagonist utilized for the control of nausea and vomiting. This medication is eliminated from the body by the liver and kidneys. Its bioavailability is approximately 60%, protein binding ranges from 70% to 76%, it is metabolized in the liver, and the half-life is short, approximately 3-5 hours (13-15).

Polymeric drug delivery systems are primarily engineered to administer active pharmaceuticals effectively. Among numerous polymeric drug delivery methods, polyelectrolyte complex (PEC) has emerged as an efficient form of polymeric carrier for drug delivery systems (16). A PEC is characterized as a macromolecular substance including repeating units that dissociate into a highly charged polymeric molecule when introduced to an ionizing solvent (e.g., H_2O), resulting in either a positively or negatively charged polymeric chain. The charge on the repeating units of the PEC is neutralized by smaller counter ions with opposite charges, which help maintain electroneutrality (16, 17). Chitosan (CS), a cationic polysaccharide produced from the deacetylation of chitin sourced from marine crustaceans, is extensively utilized as a cationic polymer owing to its advantageous safety and biocompatibility properties. The amalgamation of chitosan with other anionic polymers can enhance gastric retention and extend the release of medicines (18, 19). In a recent study, mucoadhesive microbeads were developed for the controlled release of Ond. HCl, the microbeads were fabricated using chitosan as a mucoadhesive polymer and sodium tripolyphosphate (Na-TPP) as a cross-linking agent via the ionotropic gelation technique, and the results suggest that Ondansetron-loaded Chitosan microbeads are a promising drug delivery system for sustained release, reducing dosing frequency and improving therapeutic efficacy (20). Another recent investigation aimed to synthesize and characterize CS – Sod. alginate PEC for use as an active excipient in formulating fast-dispersible phenytoin sodium tablets. The PEC was formed via ionic cross-linking of the polymers and evaluated for micromeritic properties and flow behavior, which were found suitable for tablet formulation; the findings suggest that the chitosan–alginate PEC is a promising excipient for developing fast-dispersible tablets with enhanced drug delivery properties (21).

This study seeks to develop a complex incorporating Ond. HCl enables the final formulation to remain buoyant by creating a raft over gastric fluids for prolonged drug release, enhancing bioavailability and patient adherence. The development of a PEC raft-forming formulation made from two

oppositely charged hydrophilic polymers (CS – Sod. alginate) has not been recorded thus far, highlighting the originality of this research.

Materials

All materials used in the research were purchased. Ondansetron hydrochloride dihydrate powder Qufu Hongly Chemical Industry Co., Ltd (China). High M.wt. Chitosan Powder (CS_{HP}) (1000-2000 cps) Glentham Life Science Ltd. (United Kingdom, UK). Medium M.wt. Chitosan Powder (CS_{MP}) (200-400 cps) Rhawn Chemical Technology Co. (Shanghai, China). Low M.wt. Chitosan Powder (CS_{LP}) (<200 cps) Rhawn Chemical Technology Co. (Shanghai, China). Sodium alginate (Sod. alginate) Powder Sigma-Aldrich. Calcium Chloride ($CaCl_2$) Central Drug House (P) Ltd. (Gujarat, India). Sodium Hydroxide (NaOH) ACS Chemicals (Gujarat-India). Glacial acetic acid solution ACS Chemicals (Gujarat-India). Hydrochloric acid solution Thomas Baker (Chemicals) Pvt. Ltd. Hard gelatin capsule size 00 Liaoyang Sinotech Technology Development Co., Ltd.(Shanghai, China).

Preparation of raft forming PEC of Ond. HCl

Different formulations of raft-forming PEC of Ond. HCl was prepared using oppositely charged polymers, as shown in Table 1. (22)

First step: A Cationic CS gel solution was prepared by dissolving it in 2% acetic acid solution using a magnetic stirrer with constant agitation. The mixture was left overnight in the lab at room temperature to ensure it was completely dissolved and formed a homogenous gel.

Second step: The drug (20 mg) was dissolved in the CS gel solution, and continuous mixing was performed for approximately half an hour until a homogenous mixture of (CS - drug) gel dispersion formed.

Third step: Sodium alginate (anionic polymer) was dissolved in deionized water using a magnetic stirrer. It was then slowly added to the mixture of (CS - drug) while continuously stirring at high speed. In this step, the pH was adjusted to roughly (5-5.5) using 4% NaOH, achieving the optimal condition for electrostatic interaction until a homogeneous, strong, and stable complex was achieved.

Additional step: For the formulation containing a cross-linker, $CaCl_2$ was prepared in different concentrations (1% and 2%) by dissolving the required weight in a small amount of deionized water. Then, it was added to the (CS - drug) mixture and mixed for 30 min.

Fourth step: The resulting complex was applied to a glass petri dish and dried in an oven at 40 ℃ overnight. Then, it was stored in a desiccator for future testing purposes. Weigh the amount of the prepared complex containing the equivalent of 20 mg drug and then load it into a hard gelatin capsule size 00 for further study (14, 23).

Table 1. Composition of the investigated PEC raft forming formulations containing 20 mg of Ond. HCl.

Formula code	Formula components				
	CS_{HP} (mg)	CS_{MP} (mg)	CS_{LP} (mg)	Sod. alginate (mg)	$CaCl_2$
F1	120	—	—	60	—
F2	—	120	—	60	—
F3	—	—	120	60	—
F4	120	—	—	—	—
F5	120	—	—	60	1%
F6	120	—	—	60	2%

*All formulation contains 20 mg of the drug

Evaluation of the Raft Forming System

Assessment of % drug content and % drug loading

A quantity of dried complex containing an equivalent of 20 mg of the drug was broken down and accurately weighed. Then, it was transferred into a beaker containing 100 mL of 0.1 N HCl (pH 1.2) and kept for 24 hr with occasional shaking using a high-speed magnetic stirrer at 37 ± 0.5 °C. The solution was then filtered through a 0.45 µm syringe filter, then using a 50 mL volumetric flask, 1 mL of filtered sample was diluted with 0.1 N HCl (pH 1.2) up to 50 mL. The solution absorbance was measured at 310 nm. Drug content and drug loading percentage were calculated according to the following formula (24, 25):

$$\%\ \textbf{drug content} = \frac{\textbf{Actual drug content}}{\textbf{Theoretical drug content}} * \textbf{100} \qquad \textbf{Eq. (1)}$$

$$\%\ \textbf{drug loading} = \frac{\textbf{amount of Ond.HCL in PEC particulate}}{\textbf{weight of PEC particulate}} * \textbf{100} \qquad \textbf{Eq. (2)}$$

Determination % yield

The practical weight of the complex was determined after drying using an electrical balance, and then the % yield of the complex was determined using this equation (18, 26):

$$\%\ \textbf{yeild} = \frac{\textbf{practical weight of complex}}{\textbf{theoritical weight of complex}} * \textbf{100} \qquad \textbf{Eq. (3)}$$

***In vitro* buoyancy assessment**

The floating lag time (FLT) and total floating time (TFT) were used to evaluate the buoyancy properties of the floated complex. A precise amount of the dried complex, containing the equivalent of 20 mg of the drug, was weighed., loaded into a hard gelatin capsule, and transferred into a 100 mL beaker containing 100 mL of 0.1N HCl (pH 1.2) solution and stirred using a magnetic stirrer at a medium temperature of 37 ± 0.5 °C and a rate of 50 rpm. The duration necessary for the dissolution of the capsule's gelatin shell and the complex to float to the top of the medium and form a raft called FLT was recognized and calculated. Then, the beaker was removed from the stirrer and left for 24 hr to determine the duration of floating (TFT) (27) .

Measurement of raft strength

The raft's strength was evaluated using a double-pan balance, as seen in Figure 1. The raft PEC formulations were immersed in a 250 mL beaker containing 150 mL of 0.1 N HCl solution, which was maintained at 37 ºC. The beaker was positioned on the left side of the pan and balanced by adding another 250 mL beaker with 150 mL of water on the right-side pan. Throughout the experiment, an L-shaped metal wire probe with a diameter of 1.2 mm was inserted into the left-side beaker and maintained just beneath the surface of the HCl solution during the raft development process. The raft PEC formulation was applied to the beaker holding the HCl solution, facilitating the formation of the raft on the surface. Then, water was gradually removed from the beaker positioned on the right pan using a plastic dropper until the L-shaped wire moved upward. The amount of water withdrawn was then measured, and this measurement represented the raft strength in milligrams (28).

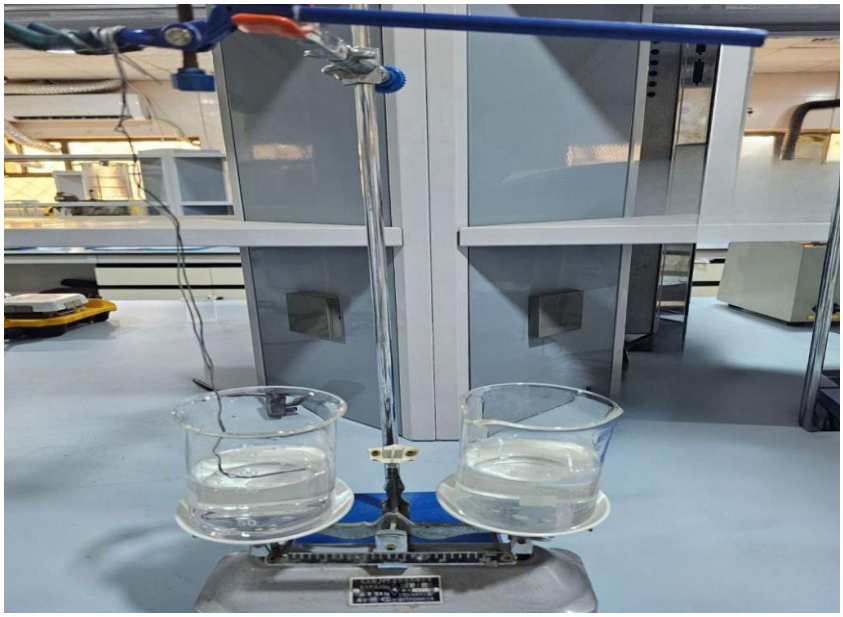

Figure 1. Double pan balance and the wire probe used for raft strength measurement (modified method).

Raft weight and volume

A graduated beaker containing 150 mL of 0.1N HCl was used. The weight (W_1) and volume (V1) of the beaker before the addition of the capsule were measured. Then, the capsule was placed in the beaker and permitted to settle for several minutes, allowing it to form a raft; the weight of the beaker after raft formation (W2) and the position reached by each raft at the top were noted on the outside of the beaker as (V_2) recorded.

The weight of the raft was measured using the following equation (28):

$$\textbf{Raft weight} = \textbf{W2} - \textbf{W1} \qquad \textbf{Eq. (4)}$$

The raft volume was determined using the equation (28):

$$\textbf{Raft volume} = \textbf{V2} - \textbf{V1} \qquad \textbf{Eq. (5)}$$

***In vitro* dissolution studies**

A study was conducted to analyze the dissolution of Ond. HCl capsules in a solution of 900 mL 0.1 N HCl with a pH (1.2) using the dissolution device USP Type II (paddle type) set at 50 rpm and temperature of 37 ºC. Capsules were inserted into each of the device jars, and at predetermined intervals, 5 mL from each sample was withdrawn and replaced with an equivalent amount of fresh dissolution medium. Subsequently, the samples were filtered using 0.45 µm syringe filters and analyzed using a UV-visible spectrophotometer at a wavelength of 310 nm. The trials were performed in triplicate, and the mean value was reported (29).

Variables affecting the release of Ond. HCl

Effect of molecular weight (M.wt) of Chitosan

Three formulas (F1, F2, and F3) with a ratio of (CS: Sod. alginate) (2:1) were used to study the effect of changing the M.wt of chitosan on the *in vitro* drug release from the complex.

Effect of addition of anionic polymer to drug: cationic polymer PEC

The *in vitro* release profiles of F1 (CS: Sod. alginate) and F4 (CS: Ond. HCl) PEC were compared to evaluate their *in vitro* drug release behaviors.

Effect of cross-linking agent concentration

Different concentrations of the cross-linking agent $CaCl_2$ (1% and 2%) were used in the formulations (F5 and F6), respectively. to examine their impact on enhancing ionic interactions between (CS_{HP} - Sod. alginate) and compare it to F1, which was formulated without the cross-linking agent.

Kinetic Drug Release Modeling

The Ond. HCl cumulative concentration released from the formulated complex-forming raft capsules at various time intervals was analyzed using zero-order kinetics, first-order kinetics, Higuchi model, and Korsmeyer-Peppas model to elucidate the drug release process (30).

Zero order model:	$Q_t = Q_0 + K_0t$	**Eq. (6)**
First order model:	$\text{Log } Q_t = \log Q_0 - K_1t/2.303$	**Eq. (7)**
Higuchi model:	$Q_t = k_H (t)^{0.5}$	**Eq. (8)**
Korsmeyer-Peppas model:	$\text{Log } [M_t / M_\infty] = \log K_{KP} + n \log t$	**Eq. (9)**

Where Q_t Represents the amount of drug released in time t., Q_0 Represents the initial amount of the drug in the dosage form., K_0 Represents the zero-order release constant., K_1 Is the first-order release constant., K_H Denotes the Higuchi dissolving constant indicative of the formulation Attributes. Mt/M_∞ Denotes the fraction of drug released at time t. K_{KP} Is a constant influenced by the structural and geometric attributes of the system. n Is a diffusional release exponent that characterizes the transport mechanism.

Identification of the optimal formulation

The optimal formulation of PEC raft formulation was chosen for further investigation: FTIR analyses, DSC, and FE-SEM.

Morphological examination

Surface morphology was analyzed at different resolutions via a field emission scanning electron microscope (FE-SEM). The samples were allowed to air dry before being attached to glass stubs using pre-applied double-sided glue. The stub was later placed in a fine-coat ion sputter for gold deposition, and the surface morphology for optimum formula F6 was examined at a 30 kV accelerating voltage using an Inspect F50 SEM (Netherlands) (31).

Differential Scanning Calorimetry (DSC)

Differential Scanning Calorimetry (DSC) examines the drug's melting point and confirms complex formation in optimum formula F6. In this technique, a sample weighing around 3 mg was placed in aluminum pans and subjected to analysis. The temperature range for analysis is from 25 °C to 400 °C, with a heating rate of 5 °C/min. The absence of an aluminum baking pan is used as a reference in this analysis. A non-reactive environment was created within the calorimeter to ensure no chemical reactions occur by continuously replacing the air with nitrogen gas at 50 mL per minute (32).

Fourier transforms infrared spectroscopy (FTIR)

A small amount of the Ond. HCl, polymers, and PEC formulation loaded drug sample, approximately 5 mg, was ground, mixed with KBr, and compressed to form a KBr disc. The disc was analyzed in a spectrum range between 400-4000 cm^{-1} to investigate the purity of the drug and polymer and to confirm the formation of the complex (33, 34).

Analytical statistics

The statistical analysis was conducted utilizing IBM SPSS Statistics V26 using a one-way analysis of variance (ANOVA), with a P value below 0.05 deemed significant. All experiments were conducted in triplicate. Results were presented as the mean ± SD.

Results

Evaluation of the Raft Forming System

Assessment of % drug content, % yield, % drug loading, and *in vitro* buoyancy.

According to the results in Table 2., all prepared PEC raft formulations showed a high drug content in the range of (95 % - 96 %) except for F4, which shows low drug content (65 %). The drug loading and the yield percentage for all formulations (F1 –

F6) were in the range (9.8 % - 12 %), and (80 % - 85.4 %) respectively.

The FLT for all formulations (F1 – F6) was instantaneous right away from the time the capsule opened, which was 5 min. The TFT shows non-significant differences between formulations except for F4, which sank after 1 hr, as seen in Table 2 and Figure 2.

Table 2. % Drug content, % drug loading, % yield, and buoyancy characteristic of the PEC raft forming formulations (n=3, mean ± SD).

Formula number	% Drug content	% Drug loading	% yield	TFT (hr)	
F1	95 ± 0.816	10.5± 0.495	85.4 ± 1.23	> 12	
F2	96 ± 0.712	12 ± 0.374	82 ± 1.314	> 12	
F3	96 ± 0.315	12 ± 0.572	80.2 ± 0.942	> 12	
F4	65 ± 0.05	9.8 ± 1.190	80 ± 1.180	1	
F5	95.7 ± 0.510	12 ± 1.472	81 ± 1.87	>12	
F6	94.8 ± 0.471	11.9 ± 1.186	84.4 ± 1.72	>12	

***FLT was instantaneous for all formulations.

Figure 2. The floating behavior of polyelectrolyte complex raft formulation.

Raft weight, volume, and strength

The raft strength ranged from 7.05 ± 0.13 to 7.9 ± 0.13 g, as assessed by the modified balance method. The weight and volume of the raft varied from 0.102 ± 0.15 to 0.303 ± 0.18 g and from 4 ± 0.35 to 5 ± 0.33 mL, respectively, as shown in Figure 3.

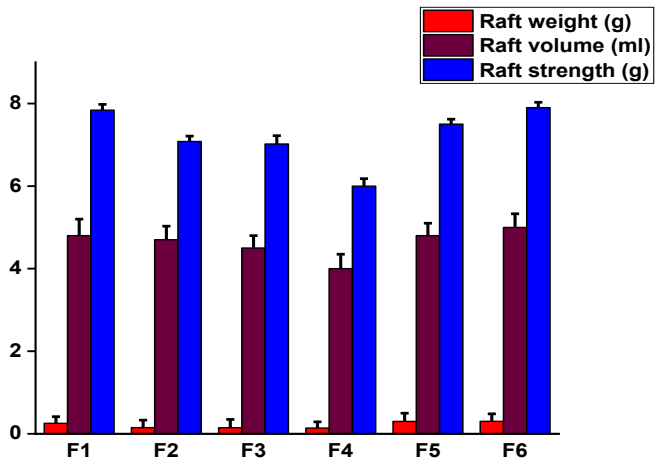

Figure 3. The assessment criteria for PEC raft-forming formulations.

Variables affecting PEC raft formulation

Effect of molecular weight of CS on *in vitro* drug release

The *in vitro* release profiles of different M.wt CS for the formulations (F1, F2, and F3) are shown in Figure 4. The release values of F1 containing high M.wt CS at 2 hr was 45% ± 0.05, and at 8 hr was 80% ± 0.01; on the other hand, 95% of the drug was released at the first 2 hr from F2, and F3 containing medium and low M.wt CS respectively. It was noted that an increase in M.wt of chitosan resulted in a significant ($p<0.05$) delay in drug release.

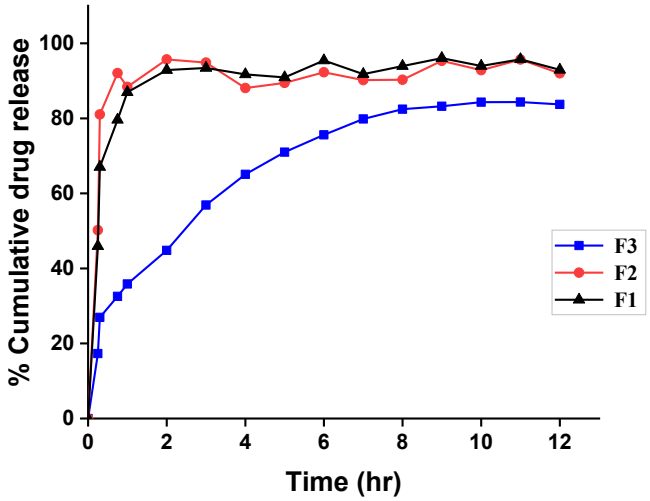

Figure 4. Effect of Chitosan M.wt on Ond. HCl release from PEC raft forming formulations.

Effect of addition of anionic polymer to drug: cationic polymer PEC

The *in vitro* release profiles of F1 (CS: Sod. alginate) and F4 (CS: Ond. HCl) formulations demonstrated distinct drug release patterns over 12 hours, as seen in Figure 5. In the initial 2 hours, both formulations exhibited a release of approximately 45%. However, by the 5-hour mark, F4 reached a cumulative drug release of 60%, after which it plateaued and maintained a steady state until the 12-hour time point. In contrast, F1 showed a more sustained release profile, with 70% of the drug released at 5 hours, followed by a continued increase in release, ultimately reaching 85% by 12 hours. These results indicate a significant ($p<0.05$) release retardation in F1 compared to F4, as evidenced by the slower release kinetics of F1, which contrasts with the earlier steady state achieved by F4.

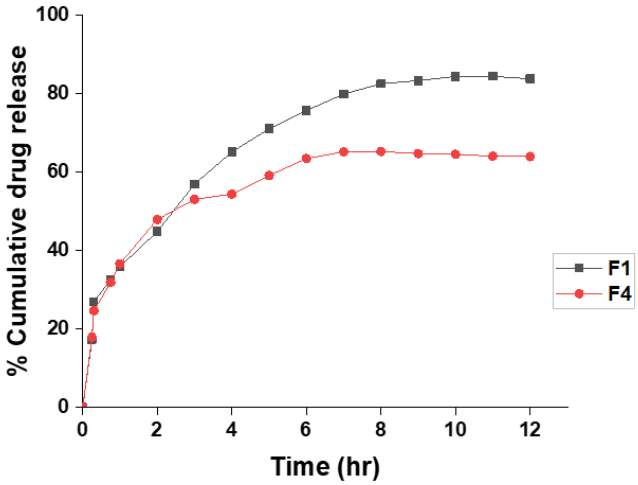

Figure 5. ***In vitro*** **release of Ond. HCl from (CS_{HP}: Ond. HCl) and (CS_{HP}: Sod. alginate) PEC.**

Effect of cross-linking agent concentration

The impact of $CaCl_2$ concentration as an ion crosslinking agent on Ond. HCl release is displayed in Figure 6. At first 2 hr, F5 displayed burst release of 71% ± 0.006 compared to F6 and F1, which displayed 39 % ± 0.02 and 45% ±0.05 drug release respectively. At 8 hr, F5 and F6 showed 95 % ± 0.211 and 84% ± 0.165 drug release, respectively. compared to F1 that shows 80% ± 0.01 drug release. The drug release continuously raised slowly for F6, while for F5 and F1, it ended at 8 hr. The findings demonstrate that elevating the concentration of $CaCl_2$ from 1% (F5) to 2% (F6) significantly ($p < 0.05$) influenced the reduction of the drug release rate.

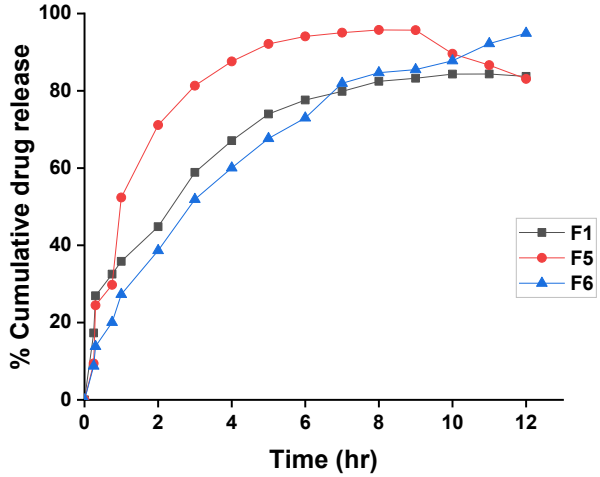

Figure 6. Effect of cross-linker $CaCl_2$ concentration on *in vitro* Ond. HCl release from CS_{HP} – Sod. alginate PEC.

Analysis of the mathematical model of drug release kinetic

The dissolution data of different formulations were evaluated using various kinetic models to assess their in vitro release patterns, as detailed in Table 3.

Table 3. Drug release kinetic of PEC-prepared formulations.

Formula code	Zero-order		First order		Higuchi		Korsmeyer Peppas		
	K_0 (min^{-1})	R^2	K_1 (min^{-1})	R^2	K_H (mg. $min^{½}$)	R^2	K_{kp} (mg. min^{-n})	R^2	n
F1	0.323	0.5983	0.005	0.8339	4.310	**0.9870**	5.831	0.9950	**0.438**
F2	2.831	0.9776	0.050	**0.9947**	14.185	0.9899	7.725	1	**0.691**
F3	2.400	0.9475	0.039	0.9973	12.115	**0.9994**	1.492	1	**0.545**
F4	0.222	0.3288	0.004	0.6712	3.708	**0.9224**	8.270	0.9868	**0.349**
F5	0.794	**0.9601**	0.010	0.9282	5.173	0.8130	0.311	0.9728	**1.241**
F6	0.302	0.9144	0.005	**0.9909**	3.856	0.9557	1.627	0.9925	**0.675**

Choosing the optimal formula

Formula F6 was identified as the optimal PEC raft-forming formulation based on the results, which include high drug content, drug loading, yield, and good floating ability of (94.8%, 11.9%, 84.4%, and >12 hr), respectively. It also has good raft properties (weight, volume, and strength). Furthermore, it exhibited a sustained *in vitro* release profile for 12 hr without burst release. This optimum formula was further characterized to confirm complex formation.

Morphological examination

The FE-SEM of PEC of pure CS powder, pure Sod. alginate powder and CS - Sod. alginate loaded with Ond. HCl is shown in Figure 7. The chitosan powder was distributed evenly without aggregation and appeared as large, irregularly shaped flakes.

The rough and layered morphology is typical of chitosan, as it tends to form sheet-like structures due to its polymeric nature (35, 36). The SEM image of Sod. alginate shows a homogeneous and highly porous rough surface with cavities (37, 38). While the surface morphology of PEC reveals irregular aggregated particles with particle sizes that fluctuate throughout the micron range.

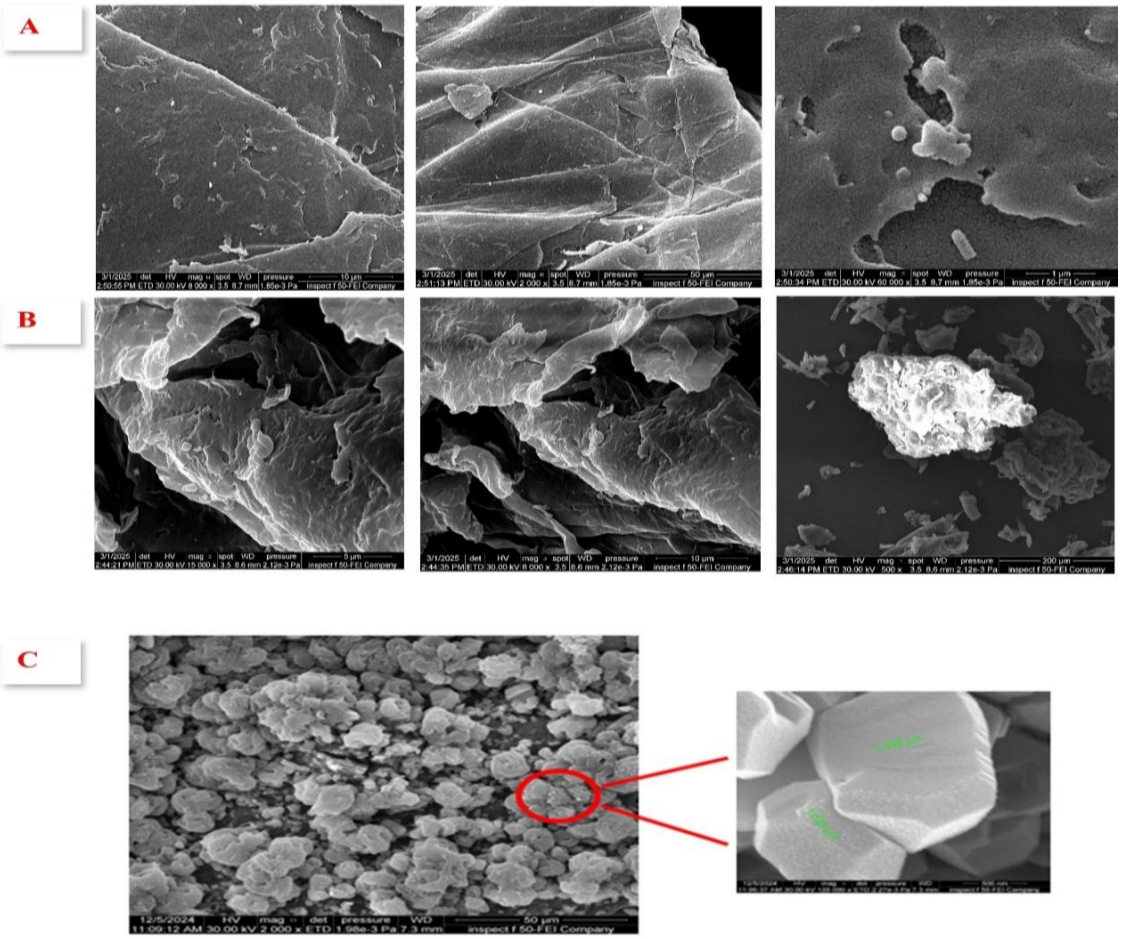

Figure 7. FE-SEM of pure CS powder (A), pure Sod. alginate powder (B) and PEC of CS_{HP}: Sod. alginate crosslinked with 2% $CaCl_2$ (C).

Differential scanning colorimetric

The DSC thermograms of Ond. HCl, CS, Sod. alginate and the dried PEC loaded with the drug are presented in Figure 8. Pure Ond. HCl exhibits a pronounced endothermic peak at a temperature of 185 °C. The distinctive endothermic peak corresponds to the melting temperature of Ond. HCl. Also, a large endotherm was detected at 85 °C, corresponding to the dehydration process in Ond. HCl, as it is a dihydrate (39, 40). The DSC thermogram of pure CS exhibited an endothermic peak at around 85 °C, indicating water evaporation. A significant exothermic peak was seen around 280 °C, indicative of the gradual decomposition of CS (41, 42). The DSC thermogram of pure Sod. alginate exhibited an endothermic peak at around 100

°C, signifying the presence of bound water or moisture since it's a hydrophilic polymer, and an exothermic peak at around 260 °C, suggesting the onset of Sod. alginate decomposition (43). Dried PEC of CS – Sod. alginate loaded Ond. HCl showed an endothermic peak around 100 °C, which may be associated with the vaporization of water from the hydrophilic polymer group and the dihydrate moiety of the drug. The sharp endo thermic peak of HCl has disappeared. The peaks associated with CS and Sod. alginate vanished, and a new peak emerged at around 200 °C (44-46).

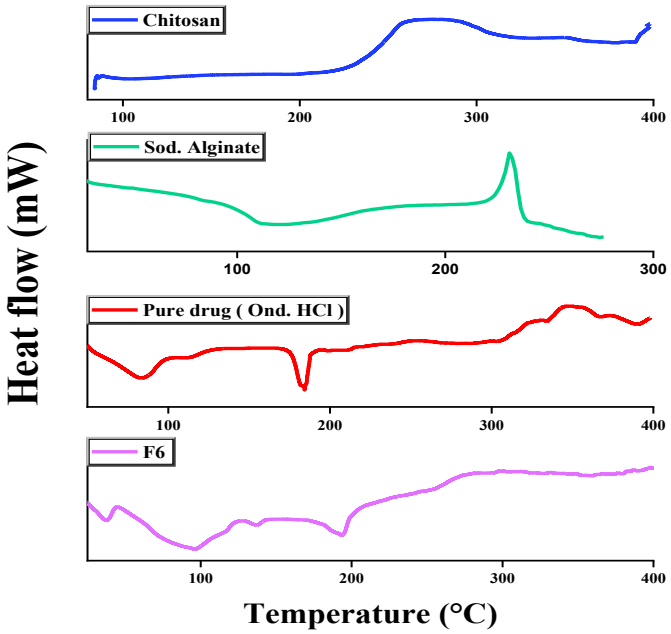

Figure 8. DSC of pure drug, Chitosan, Sodium alginate, and optimum formula F6.

Fourier transform infrared spectroscopy (FT-IR)

The FTIR spectrum of pure Ond. HCl, Chitosan, Sod. alginate and optimum formula (F6) are depicted in Figure 9. The key FTIR spectral changes are summarized in Table 4., highlighting shifts and new peaks that confirm PEC.

Table 4: FTIR Characteristic Peaks of Pure Ond. HCl, Chitosan, Sodium alginate, and optimum formula (F6).

Sample	Characteristic Peaks (cm^{-1})	Functional Group / Vibration Assignment
Pure Ond. HCl	3483.44	Broadband O-H stretching of H_2O
	3408.29	N-H stretching
	1280.73	C-N stretching
	1635.64	C=O stretching in an aromatic ketone ring
	1531.48	C=C aromatic stretching
	2900, 756.10	C-H stretching and bending
Chitosan (CS)	3466, 3302	Broadband O-H and $-NH_2$ stretching
	2872	Symmetric C-H stretching
	1654	C=O stretching (amide I band)
	1593	N-H bending (amide II band)
	1153	C-O stretching vibration
Sodium alginate	1633.5,1407.6	Asymmetrical and Symmetrical COO^- stretching vibration
	3406	O-H stretching
Physical mixture + drug	1639, 3483.44	Peaks of the drug still present with no significant difference
Dried PEC (F6)	1417	Shift in COO^- symmetric stretching from 1407 cm^{-1}
	1556.43, 1454	New peaks indicating PEC formation

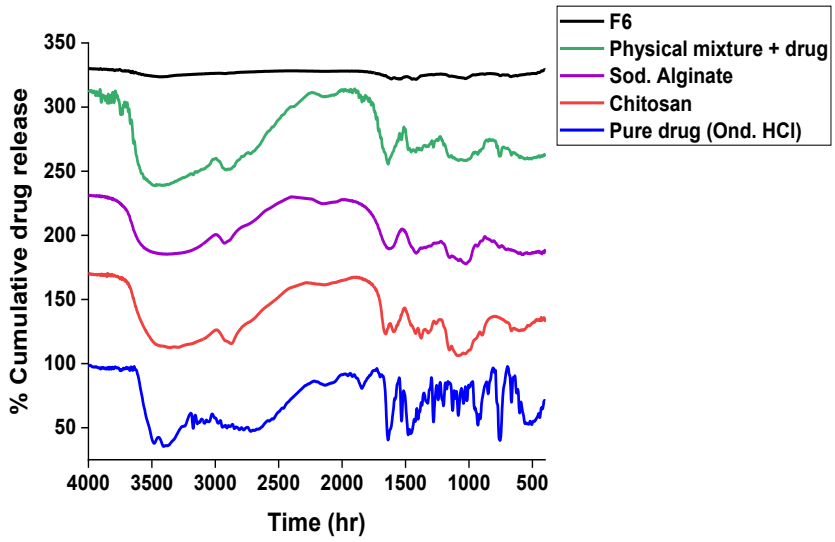

Figure 9. FTIR of Sodium alginate, Chitosan, pure drug, and optimum formula (F6)

Discussion

Evaluation of raft forming system

Assessment of % drug content, % drug loading, % yield, and *in vitro* buoyancy.

The high drug content, drug loading, and yield observed across all prepared PEC raft formulations indicate the successful formation of a stable PEC between CS and Sod. alginate. This interaction enhances drug retention within the matrix, demonstrating the effectiveness of the selected polymers and formulation technique. The formulation method proved to be reliable and efficient in achieving high drug incorporation. However, the lower drug content observed in **F4 (CS_{HP}: Ond. HCl)** suggests a weaker electrostatic interaction, leading to a less stable PEC structure with reduced drug retention capability (24, 25). In the buoyancy study, the PEC raft-forming system exhibited a density lower than that of gastric fluids (1.004 g/mL), ensuring prolonged floating time and minimal lag time. This buoyancy is attributed to the electrostatic interaction between the cationic CS and anionic Sod. alginate, forming a viscous gel that swells upon contact with gastric fluid. The swelling process entraps air within the matrix, contributing to a low-density structure that remains float for an extended duration. Chitosan alone in F4 could not achieve the same floating behavior due to its inability to form a sufficiently buoyant structure, further emphasizing the necessity of sodium alginate in the formulation (47). Samanta, Nayak, et al. (2023) developed a single-unit hydrodynamically balanced system for ofloxacin delivery using oppositely charged ionic polymers. The buoyancy test revealed excellent flotation in simulated gastric fluid (pH 1.2) for 6 hours with no lag time. This was attributed to the rapid hydration and swelling of the hydrophilic polymer matrix, forming a buoyant mass (48).

Raft weight, volume, and strength

Concerning raft weight, volume, and strength, as the CS M. wt increases, a rigid and more stable complex will be formed with Sod. alginate that will result in better raft properties (49, 50). Furthermore, adding a crosslinker to (CS-Sod. alginate) enhances the gel matrix's strength, resulting in improved raft properties. F4 lacking Sod. alginate exhibits lower strength, weight, and volume compared to other formulations emphasizing the importance of the presence Sod. alginate and its role in forming a stable, rigid complex with desired raft properties (51, 52).

***In vitro* release study**

Effect of molecular weight of CS on *in vitro* drug release

The molecular weight of CS plays a crucial role in controlling the drug release profile of the formulated PEC. As the molecular weight of CS increases, drug release is significantly reduced. This can be attributed to the longer polymer chains of high molecular weight chitosan (CS_{HP}), which enhance polymer entanglement and restrict drug diffusion (53, 54). High molecular weight chitosan exhibits increased viscosity and when combined with Sod. alginate, which also possesses inherent viscosity, forms a dense and strong network. This strong interaction reduces matrix porosity and enhances polymer chain entanglement, thereby limiting the penetration of the dissolution medium and subsequently hindering drug release. In contrast, formulations containing **low- and medium-molecular weight chitosan** form a less compact structure with greater porosity. The reduced viscosity and shorter polymer chains lead to a more open network, facilitating faster diffusion of the medium and promoting enhanced drug release (55). Čalija, Cekić, et al. 2011 found that Drug release behavior was clearly influenced by drug/polymer ratio, Chitosan molecular

weight and its concentration, and hardening time in chitosan solution (56). Another study on the effect of molecular weights of CS was investigated on the release of allantoin-loaded Chitosan nanoparticles; according to the result, it was discovered that the molecular weight of CS had an impact on the rate at which allantoin was released from the CS nanoparticles (57).

Effect of addition of anionic polymer to drug: cationic polymer PEC

The limited ability of the (CS - Ond. HCl) complex to retard drug release, compared to the (CS – Sod. alginate) complex, can be attributed to three primary factors. Firstly, chitosan contains positively charged amine groups ($–NH_3^+$) that can form hydrogen bonds and ionic interactions with the hydroxyl and carbonyl functional groups of Ond. HCl, these interactions are not sufficiently strong to create a dense and compact network. In contrast, the PEC formed between (CS – Sod. alginate) exhibits a more strong and cohesive structure due to stronger electrostatic interactions between the cationic groups of chitosan and the anionic carboxylate groups of alginate. This structural difference results in faster drug diffusion in the CS-Ond. HCl complex. Secondly, CS demonstrates pH-dependent behavior, particularly in acidic media, where it undergoes protonation, leading to increased solubility and rapid swelling. In the absence of a stabilizing anionic polymer, such as Sod. alginate, the swelling of CS is not adequately controlled. This uncontrolled swelling accelerates the erosion of the polymer matrix, leading to faster drug release. The lack of a dual-polymer system to modulate swelling and erosion significantly diminishes the ability of the CS-Ond. HCl complex to sustain drug release. Lastly, the high solubility of ondansetron hydrochloride in acidic media further contributes to the rapid release mechanism. The drug's solubility in low-pH environments promotes a diffusion-driven release process. Without the incorporation of an additional polymer to enhance the structural integrity of the matrix, the drug readily diffuses out of the system once chitosan begins to degrade. These factors collectively explain the limited drug release retardation observed in the CS-Ond. HCl complex, underscoring the importance of polymer selection and matrix stabilization in controlling drug release kinetics (58, 59). In previous studies, it has been well-documented that the formation of polyelectrolyte complexes between cationic and anionic polymers results in a robust and stable network due to strong electrostatic interactions (60, 61).

Effect of cross-linking agent percentage

The concentration of calcium chloride ($CaCl_2$) as a crosslinking agent plays a crucial role in controlling the drug release behavior of the PEC system. Increasing the concentration of calcium chloride ($CaCl_2$) from **1% (F5) to 2% (F6)** significantly enhances the stability and structural integrity of the PEC matrix, leading to a notable reduction in the drug release rate. This effect can be attributed to the higher availability of **Ca^{++} ions**, which promote increased crosslinking with polymer chains, particularly with Sod. alginate, forming a denser and more compact **two-dimensional network structure** within the matrix, leading to a higher density of the polymer matrix and, consequently, an increase in the diffusional path. This restricts the penetration of the dissolution medium and slows down the release of the drug (62). This is consistent with previous studies, where formulations with a greater degree of crosslinking exhibited superior structural durability compared to those with a lower degree of crosslinking (63). Another earlier study demonstrates the role of ionic cross-linking in forming a three-dimensional network that

provides structural stability and increases the viscosity of the alginate solution, which enhances the formation of the alginate matrix (64). In contrast, **F1**, which lacks a crosslinking agent, exhibits a more open polymer structure, allowing faster penetration of the dissolution medium and facilitating drug diffusion. The absence of ionic crosslinking results in a weaker gel matrix with lower structural integrity, leading to an accelerated drug release profile (65). A similar observation was seen in a previous study to assess the impact of polymer cross-linking on improving drug loading and guaranteeing continuous drug release. By fabrication of multilayer polyelectrolyte films designed for buccal distribution of benzydamine, it was observed that the drug release from the non-cross-linked polyelectrolyte multilayers occurred promptly, with about 90% of the loaded benzydamine released within 30 minutes while cross-linking led to the formation of stable and porous structures with enhanced drug loading and extended release capacity (66).

Analysis of the mathematical model of drug release kinetic

The kinetic model analysis provided insight into drug release mechanisms from the prepared PEC raft formulations. It was noted that the R^2 value for formulations F2 and F6 showed the highest R^2 when analyzed under first-order release kinetics, indicating that the release is concentration-dependent. F1, F3, and F4 formulations followed the Higuchi model, indicating that the primary processes influencing drug release are the penetration of the dissolving medium, followed by the dissolution of the drug and its diffusion across the gel layer. The R^2 value for formulation F5 was elevated when analyzed under zero-order kinetics, indicating that the drug release rate from this formulation is independent of the drug concentration (67, 68). The Korsmeyer-Peppas analysis revealed that most formulations followed Anomalous non-Fickian transport, suggesting that both the diffusion of the drug from the hydrated matrix and the relaxing of the polymer influence drug release. The exception was F6, which exhibited **super Case-II transport** (69-71).

Morphological examination

The irregular surface shape aligns with polyelectrolyte complexation; wherein electrostatic interactions may induce such aggregation. The lack of smooth, crystalline formations indicates successful complexation and encapsulation of Ond. HCl within the CS-Sod. alginate matrix (72, 73).

Differential scanning colorimetric

The DSC results confirm the formation of a PEC between CS and Sod. alginate, incorporating Ond. HCl. The disappearance of the broad endothermic peak of pure Ond. HCl suggests that the drug is no longer in its crystalline form but is instead molecularly dispersed within the complex, contributing to its stabilization. The shifts in the characteristic peaks of CS and Sod. alginate further supports the successful formation of a stable PEC structure, which enhances drug encapsulation and controlled release properties (43, 74).

Fourier transform infrared spectroscopy (FT-IR)

The FTIR analysis confirmed the purity of the individual components, as all characteristic functional group peaks correspond to Ond. HCl, CS, and Sod. alginate was present in their respective spectra. The absence of additional or unexpected peaks indicates that no chemical degradation or impurity was introduced during the formulation process. Moreover, the observed shift in the **carboxylate (COO^-)**

bands in the PEC formulation strongly suggests the formation of a polyelectrolyte complex between chitosan and sodium alginate. This shift is indicative of electrostatic interactions between the positively charged amino groups of CS and the negatively charged carboxylate groups of Sod. alginate, supporting the successful formation of a stable complex (75-77).

Conclusion

This research effectively developed and refined a PEC-based raft-forming device for the prolonged release of Ond. HCl. The analysis revealed that critical formulation parameters, such as chitosan molecular weight and cross-linker concentration, substantially affected the raft's mechanical strength, buoyancy, drug content, and *in vitro* release profile. Among the evaluated formulations, F6, CS: Sod. alginate crosslinked with 2% $CaCl_2$ proved to be the most effective formulation due to its exceptional drug content, loading capacity, and prolonged drug release over 12 hours without a burst release. The strong electrostatic interactions between CS and Sod. alginate, augmented by cross-linking, facilitated the development of a stable and strong raft structure. Analytical methods, such as FTIR, DSC, and FE-SEM, validated the effective production of PEC and drug encapsulation. The new raft-forming method exhibited significant potential for improving Ond. HCl bioavailability and therapeutic efficacy. This methodology may be modified for additional medications exhibiting comparable pharmacokinetic difficulties, facilitating the development of sophisticated gastro-retentive drug delivery systems in forthcoming pharmaceutical applications.

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