Chitosan/ Alginate/ Gelucire in-situ Gelling System for Oral Sustained Delivery of Paracetamol for Dysphagic Patients

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ABSTRACT

The study aims to formulate an oral in-situ gel for sustained paracetamol delivery, targeting pediatric and geriatric patients. A blend of sodium alginate, chitosan, and Gelucires was used to create the gel. Characterization techniques, such as rheology and in vivo bioavailability tests on rat models, were employed. The in-situ gel transitioned into a gel-matrix system in 0.1N HCl, effectively controlling the release of paracetamol at different pH levels (1.2, 5.4, and 6.8). Gels made solely of sodium alginate or sodium alginate-chitosan exhibited rapid drug release at pH 6.8. The formulation containing paracetamol in a Gelucire (G33/01):3-3% sodium alginate - chitosan ratio of 1:1:4 w/w showed an extended drug release time of over 8 hours. Bioavailability in rats revealed a higher time to maximum concentration (Tmax) and lower peak concentration (Cmax) but comparable mean residence time (MRT) and area under the curve (AUC0-∞) to commercial formulations. The gel's synergistic blend of chitosan, sodium alginate, and Gelucire G33/01 ensures a sustained release of paracetamol, making it a promising drug delivery system for vulnerable populations like children and the elderly.

Keywords: *In situ* gel matrix system; chitosan; alginate; Gelucires; Paracetamol; Sustained release.

INTRODUCTION

In-situ gelling systems are utilized for targeted drug delivery and employ different mechanisms of gelation in vivo. These mechanisms are designed to meet specific requirements for drug release and anatomical targets [1-8]. These systems transform from a liquid sol-state to a gel upon encountering specific environmental triggers, such as temperature, enzymes, pH, or ions [9-13]. Temperature-induced gelation involves polymers that undergo a transition from a liquid state to a gel state at body temperature [14], making them suitable for various applications where a minimally invasive approach is preferred. pH-induced gelation refers to the process where polymers undergo sol-to-gel transitions in response to pH variations [15], allowing for precise drug release in regions characterized by distinct pH levels. Enzyme-triggered gelation is a targeted approach that responds to specific enzymes found in particular tissues [16], enabling precise drug delivery in localized areas. Ion-induced gelation refers to the process in which polymers undergo gelation when exposed to specific ions [17]. This phenomenon has practical applications in various fields, such as wound healing, where the concentration of ions at the site of application fluctuates. Each mechanism provides distinct benefits for precise and controlled drug administration, influenced by the environmental factors of the specific tissue and the interplay between the drug and

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polymer. Nonetheless, the intrinsic mechanical fragility of the polymers involved often results in premature erosion, prompting research into methods like polymer blending, grafting, cross-linking, and mixed-matrix approaches to enhance their structural integrity. Blending polymers is an especially effective yet economical strategy to modulate the physical properties of in-situ gels, making them highly relevant for oral administration in populations with dysphagia and those of pediatric or geriatric age. Paracetamol (PA), commonly delivered through tablets or liquids, offers an excellent model drug for these systems, as its extended release has been successfully achieved via in-situ gel formation using polymers of both natural and synthetic origins [18-23]. This study introduces a novel blend consisting of Gelucire® (G), a highly hydrophobic lipid material, with a dual hydrophilic polymer matrix of chitosan (CS) [24, 25] and sodium alginate (SA) [26]. This blend is designed to form an in-situ gel matrix in the stomach for sustained PA release, addressing the limitations associated with the rapid diffusion of hydrophilic drugs [27]. Both CS and SA are biocompatible polysaccharides with unique ionic properties [28-37], while Gelucire® serves as an amphiphilic lipid material with specific fat-soluble or water-dispersible characteristics [38].

MATERIALS AND METHODS

Sodium alginate was obtained as a gift from AL Taqaddom Pharmaceutical Industries Co. (Protanal® LF 120M, Guluronic acid: 35-45% and Mannuronic acid: 55-65%, Lot No.: S20653, FMC BioPolymer A/S, Drammen, Norway). Chitosan was obtained as a gift from the Jordanian Pharmaceutical Manufacturing Co. LTD., JPM (250 KDa with 96% degree of deacetylation, JBICHEM, Shanghai, China). Chitin was obtained as a gift from JPM (200 *M*m, JBICHEM, Shanghai, China). Gelucire® (a saturated polyglycolysed glycerides; Gelucire® grades 33/01, 39/01, and 43/01 were a gift from Gattefosse, France). Paracetamol (Standard of PA, Water Content: 0.1%, Potency: 99.2%) was kindly supplied from Hikma, Jordan. Revanin® (250 mg/ 5 ml) is a commercially available paracetamol suspension manufactured by the Arab Pharmaceutical Manufacturing Co. LTD., APM, Salt, Jordan. All other chemicals and reagents used were either of analytical or pharmaceutical grades.

Preparation of Paracetamol Gel Formulations

Paracetamol: Alginate and Paracetamol: Alginate-Chitosan Formulations:

Three formulations with SA alone were prepared at concentrations of 3%, 4.5%, and 6% (D1, D2, D3) as shown in Table 1.

Table 1 The composition of the in-situ gel formulations (D1, D2, D3, N1, N2, and N3) containing Paracetamol (PA), Sodium Alginate (SA), and Chitosan (CS).

Formula	Contents Ratio w/w	PA (g)	SA colloidal dispersion			The Polymeric Phase		
			3 % w/w (g)	4.5 % w/w (g)	6 % w/w (g)	SA-CS 3-3 % w/w (g)	SA-CS 4.5-4.5% w/w (g)	SA-CS 6-6% w/w (g)
D1	1:4	10	40	-	-	-	-	-
D2	1:4	10	-	40	-	-	-	-
D3	1:4	10	-	-	40	-	-	-
N1	1:4	10	-	-	-	40	-	-
N2	1:4	10	-	-	-	-	40	-
N3	1:4	10	-	-	-	-	-	40

Binary combinations of sodium alginate with chitosan (SA-CS) were prepared at concentrations of 3-3%, 4.5-4.5%, and 6-6% (N1, N2, N3). These combinations were created by dissolving the respective polymers in de-

ionized water, allowing overnight stabilization at 4°C, and subsequently adding paracetamol. The mixtures were then homogenized under specific conditions.

Paracetamol: Gelucire: Chitosan-Alginate Formulations:

Formulations F01-F18 were generated using various Gelucires and SA-CS combinations, as shown in Table 2.

Table 2 The composition of gel formulations (F01 – F18) containing Paracetamol (PA), Gelucire (G), Sodium Alginate (SA), and Chitosan (CS).

Grade of Gelucire®	PA : G : SA-CH Gel					
	(1 : 1 : 4) w/w Ratio			(1 : 1 : 8) w/w Ratio		
	(SA-CS) % w/w			(SA-CS)) % w/w		
	(3-3%)	(4.5-4.5%)	(6-6%)	(3-3%)	(4.5-4.5%)	(6-6%)
G 43/01	F1	F2	F3	F4	F5	F6
G 39/01	F7	F8	F9	F10	F11	F12
G 33/01	F13	F14	F15	F16	F17	F18

A lipidic phase was initially prepared by melting Gelucire and incorporating PA. This phase was combined with different polymeric phases (3-3%, 4.5-4.5%, or 6-6% w/w CS-SA) using a mechanical stirrer (RZR 2041, Heidolph, Germany) at 300 rpm.

Paracetamol: Gelucire: Alginate Formulations:

Three formulations, namely F19, F20, and F21, were prepared without Chitosan, utilizing a 1:1 w/w lipidic phase of PA: G43/01, PA: G39/01, or PA: G33/01 and a 3% SA colloidal dispersion. These were heated and allowed to stabilize overnight at 4°C.

Paracetamol: Gelucire: Chitin-Alginate Formulations:

Formulations F22, F23, and F24 were prepared by replacing chitosan with chitin in a 3-3% w/w ratio, precisely replicating formulations F1, F7, and F13. Each formulation was prepared in triplicate to ensure consistency and reliability.

Rheological Studies

Viscosity measurements were performed at 25 °C with a cone and plate viscometer (Anton Paar Physica MCR 301, Graz-Austria, Type P-PTD 200-62). The viscometer had a cone of 0.994˚ angle and 50.005 mm diameter. Each gel formulation was tested in triplicate over a shear rate range of approximately 2-100 s^{-1} with a gap width of 0.05 mm. Tested each gel in triplicates.

Measurement of *in Vitro* Drug Release

The release of PA from the gel formulations was conducted using the USP paddle method (apparatus II). An appropriate amount of each formulation, equivalent to 250 mg of PA, was accurately weighed and introduced into the dissolution medium using a tip-free disposable syringe. The dissolution medium was maintained at 37±0.5°C with an agitation rate of 50 rpm. To mimic the physiology of the gastrointestinal tract, a gradient pH-dissolution media of 1000 ml volume was employed, starting with 0.1N HCl for 2 hours, changing to pH 5.4 for an additional 2 hours by adding 16.9g trisodium phosphate salt, and finally changing to pH 6.8 by adding 5.4g of the same salt until the end of the test. At predetermined time intervals, 5 ml samples were withdrawn and immediately replenished with pre-warmed fresh medium. Subsequently, the PA content in the samples was analyzed spectrophotometrically at λmax 243 nm. The results, obtained from six determinations, were expressed as the percentage of PA released (USP 30-NF 25, 2007). Each test was performed in triplicate to ensure accuracy and reproducibility.

Elucidation of the Release Mechanism

The drug release pattern was evaluated using four model-dependent kinetic models: zero-order release kinetics, Higuchi's square root of time equation [39], Korsmeyer–Peppas power law equation, and Hixson–Crowell's cube root of time equation [40, 41]. The correlation coefficient, R^2, values evaluated the goodness of fit. The complete dataset of dissolution time was utilized to analyze and elucidate the release mechanism.

Animal Experiments

Twelve male Sprague Dawley rats, weighing 250–315 g, were procured from Al-Yarmouk University Biological Center (Irbid, Jordan) and housed in the Petra University Animal Care Unit (Amman, Jordan) under standard conditions of temperature (22±2°C) and humidity. The rats were allowed to acclimate for a period of 10 days before commencing the experiments. All animal procedures adhered to the guidelines of FELASA (Federation of European Laboratory Animal Science Associations), and the study protocol was reviewed and approved by the Animal Care Committee of the Scientific Research Council of Petra University (approval number: 1223).

On the day of the experiment, the rats underwent a 24-hour fasting period with free access to water. The rats were randomly divided into two groups, with six rats in each group. The first group was administered a 30 mg/kg oral dose of the PA-gel preparation via a metal oral gavage needle (Harvard Apparatus, UK). The second group received a similar dose of a PA commercial suspension, Revanin® (7.5 mg in 0.6 ml, equivalent to 30 mg/kg).

At predetermined time intervals, namely 0, 0.25, 0.5, 1, 2, 3, 4, 6, and 8 hours, blood samples were collected for each group by pooling one blood drop obtained from the tip of the tail (around 35 µl blood/drop) from each rat. The pooled samples were collected in 0.5 ml EDTA blood tubes and centrifuged at 3000 rpm for 5 minutes. The plasma was then collected and stored at -20°C until analysis. The experiment was repeated (n=6) to ensure the reliability and consistency of the results.

In situ Gelling Ability Examination

The animals underwent a 24-hour fasting period with free access to drinking water prior to the administration of the experimental formula using a metallic oral gavage needle. The gel-forming capacity of the formula was assessed by administering approximately 1.3 g and 0.33 g of the formula into the stomachs of rats and mice (n=3 for each group).

Paracetamol Assay

The plasma samples were assayed using HPLC (Shimadzu LC-10A with a Shimadzu SPD-10A detector at a wavelength of 254 nm) according to a previously described method with minor modifications [42]. On the day of analysis, the samples were vortexed for 1 minute, from which 0.150 ml was withdrawn, and the volume was completed with water to 0.5 ml. 50 µl of a 30% perchloric acid solution was added to each tube to precipitate proteins. The samples were vortexed for 1 minute and centrifuged at 6000 rpm for 10 minutes. Finally, 20 µl of the supernatant was injected into a column (150 mm × 4.6 mm i.d. and packed with Inertsil-ODS). Elution was carried out using the KH_2PO_4 (0.1M)-Isopropanol-tetrahydrofuran system in a ratio of 100:1.5:0.1 v/v, and the pH was adjusted to 3.7 using phosphoric acid.

Pharmacokinetic Analysis

The values of the maximum PA plasma concentration (Cmax) and the time of its occurrence (Tmax) were obtained directly from a concentration–time profile. For other pharmacokinetic parameters, the concentration-time data were analyzed using computer-based pharmacokinetic software, WinNonlin® version 5.2.1 (Pharsight Corporation, Mountain View, CA, USA). The area under the plasma level–time curves (AUC) and moment plasma level–time curves (AUMC) were calculated by the trapezoidal method, and the ratio of AUC and AUMC was used to estimate the mean residence time (MRT) of the drug. The program used a minimum of three data points to compute the terminal elimination rate constant (Kel).

Statistical Analysis

Unpaired t-tests, using Prism GraphPad, were carried out to compare the pharmacokinetic parameters of the gel formulation (test) and the commercial suspension (reference). P values of <0.05 were considered significant.

RESULTS AND DISCUSSION

In Vitro Release Studies

In vitro release studies elucidate the efficacy and limitations of various paracetamol (PA) gel formulations. Formulations D1, D2, and D3, which solely incorporated sodium alginate (SA), manifested soft alginic acid gels upon interaction with 0.1 N HCl. However, these SA-only systems showed suboptimal sustained drug release properties, particularly at higher pH values. Figure 1 illustrates this rapid drug release and highlights the suboptimal nature of SA as a sole vehicle for drug delivery.

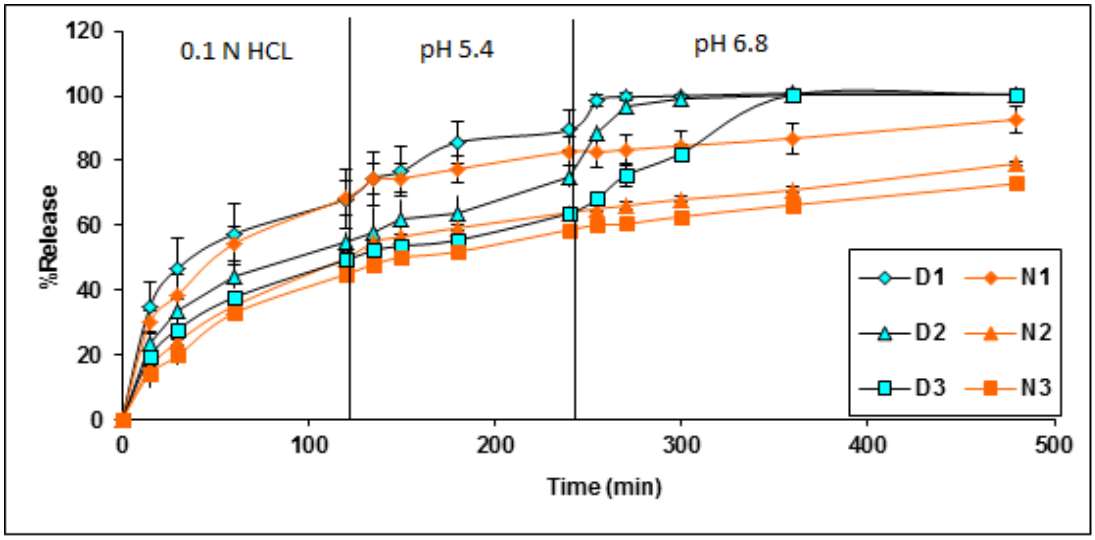

Figure 1 Drug release profiles of PA formulations D1, D2, and D3 with SA as the sole matrix. The data show suboptimal sustained release at higher pH levels.

Such behavior is attributable to the pH-sensitive disintegration of the SA gel in the basic intestinal phase, posing a risk of dose dumping, especially in cases of rapid gastric emptying [43]. To overcome these limitations, SA was blended with chitosan (CS) in formulations N1, N2, and N3. This binary polymeric system displayed advantageous features from both polymers and mitigated their individual drawbacks, thus offering a more effective drug release transition from gastric to intestinal phases [44]. The hybrid SA-CS gel showcased pH-responsive behavior, where the polycationic nature of CS allowed for in-situ gelation in the stomach, prolonging gel structural integrity upon reaching the intestine [45]. Figure 2 shows that among these hybrid formulations, N3 exhibited the most sustained drug release pattern, specifically, a reduction of drug release from 68.48 ± 5.47% to 44.84 ± 1.39% at the end of the acidic stage (2h).

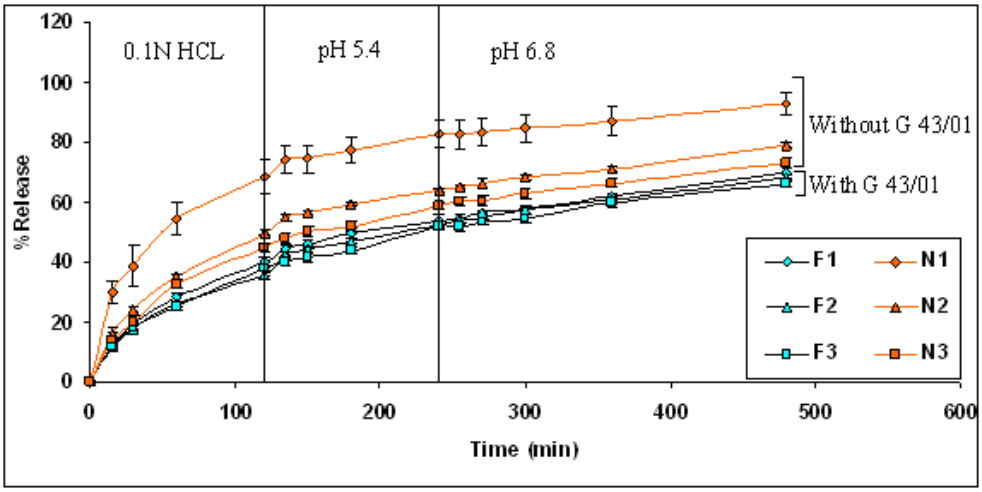

Figure 2 Comparative dissolution profile of in-situ gel formulations containing Gelucire G 43/01 (F1, F2, and F3) with those without Gelucire (N1, N2, and N3).

A novel approach was the inclusion of lipidic material G (G33/01, G39/01, or G43/01) to SA-CS gels in formulations F1-F18. This further reduced drug release, ascribed to changes in matrix hydrophobicity and increased diffusion path length. Notably, formulations incorporating PA:G at a 1:1:4 molar ratio (F1, F2, F3, F7, F8, F9, F13, F14, and F15) demonstrated statistically indistinguishable drug release kinetics, as delineated in Figures 3A, 3B, and 3C.

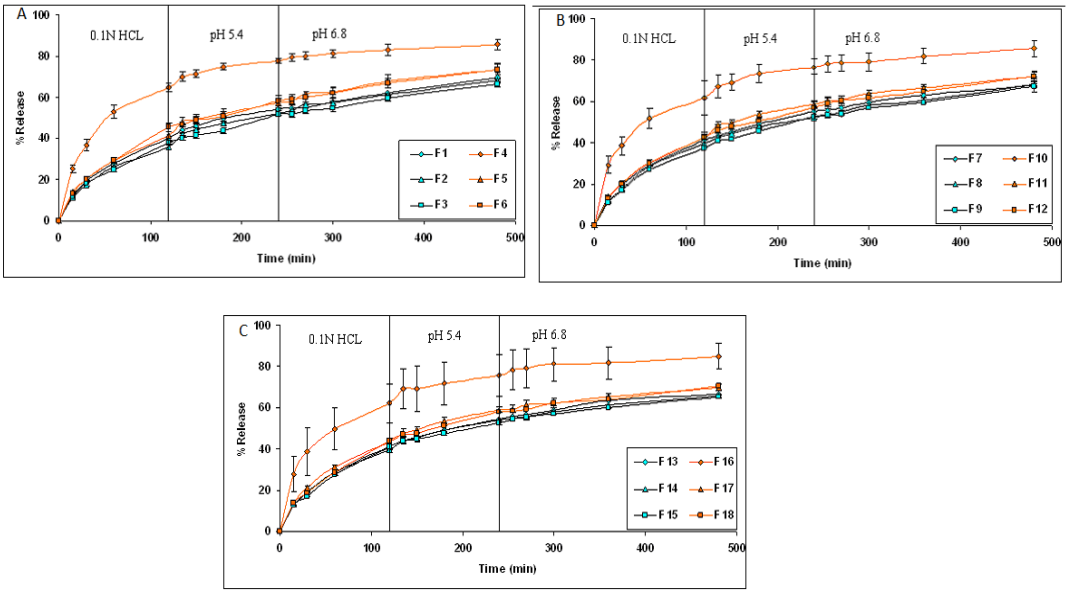

Figure 3 Comparative dissolution profiles of different in-situ gel formulations.

Alterations in SA-CS polymeric concentration from an initial 3%-3% to a subsequent 6%-6% did not induce significant changes in these release parameters. In contrast, formulations with an enhanced 1:1:8 SA-CS ratio (F4, F10, F16) exhibited augmented drug release kinetics, as corroborated by Figures 3A, 3B, and 3C. This increased release is ostensibly attributable to the augmented hydrophilic nature of the polymer matrix. The gel matrices were promptly formed in vitro upon contact with acidic dissolution media (pH 1.2) and also in the in-situ stomachs of rats and mice, as illustrated in Figure 4.

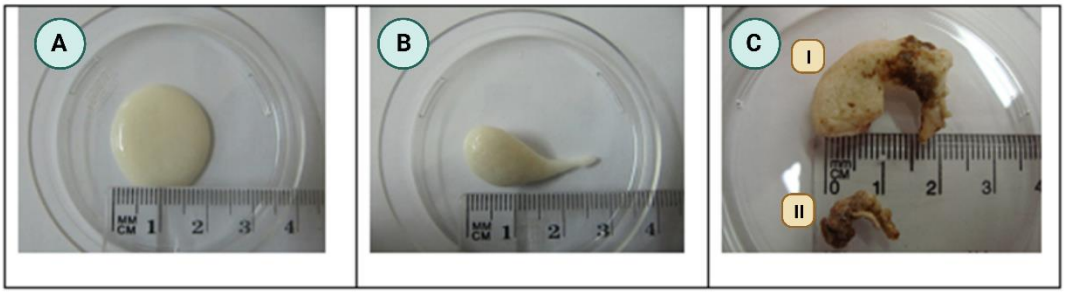

Figure 4 Photographs of the PA: G33/01: CH – AL (1: 1: 4 ratio) gel: (A) before and (B) after addition to the acid media and (C) in-situ rat (I) and mouse (II) stomach 30 min after administration

In vivo studies performed on rats confirmed the rapid in vitro gel formation at acidic pH (pH 1.2). Formulations F1, F7, and F13, which displayed optimal sustained release, were further benchmarked against a commercial PA product (Revanin®, APM), which exhibited complete immediate drug release within 5 minutes, as shown in Figure 5.

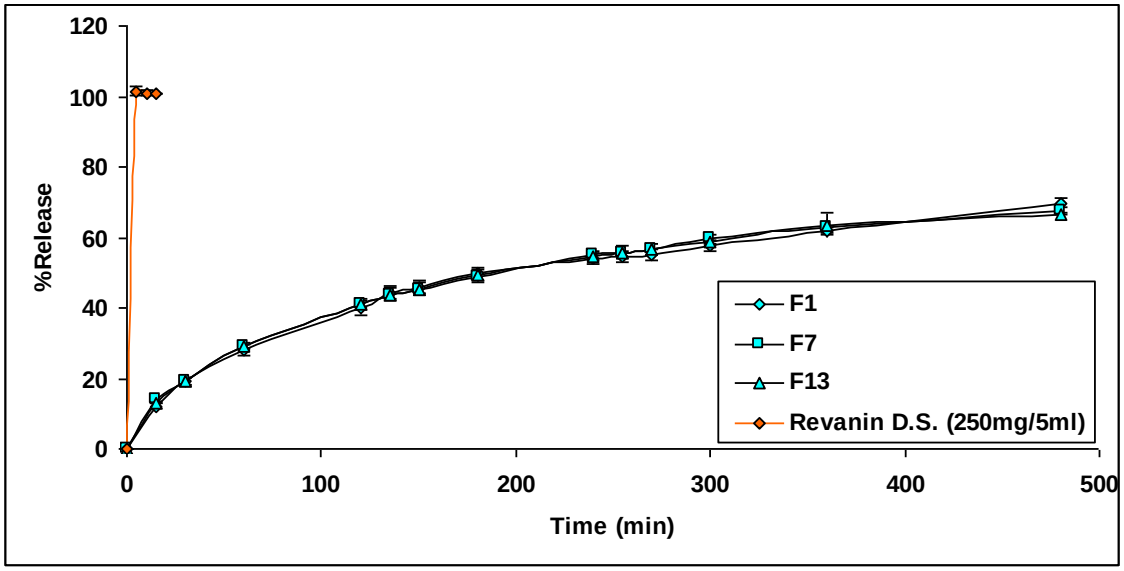

Figure 5 Paracetamol release profiles from Formulas F01, F07, F13 and the commercial PA immediate release suspension (Revanin®, APM)

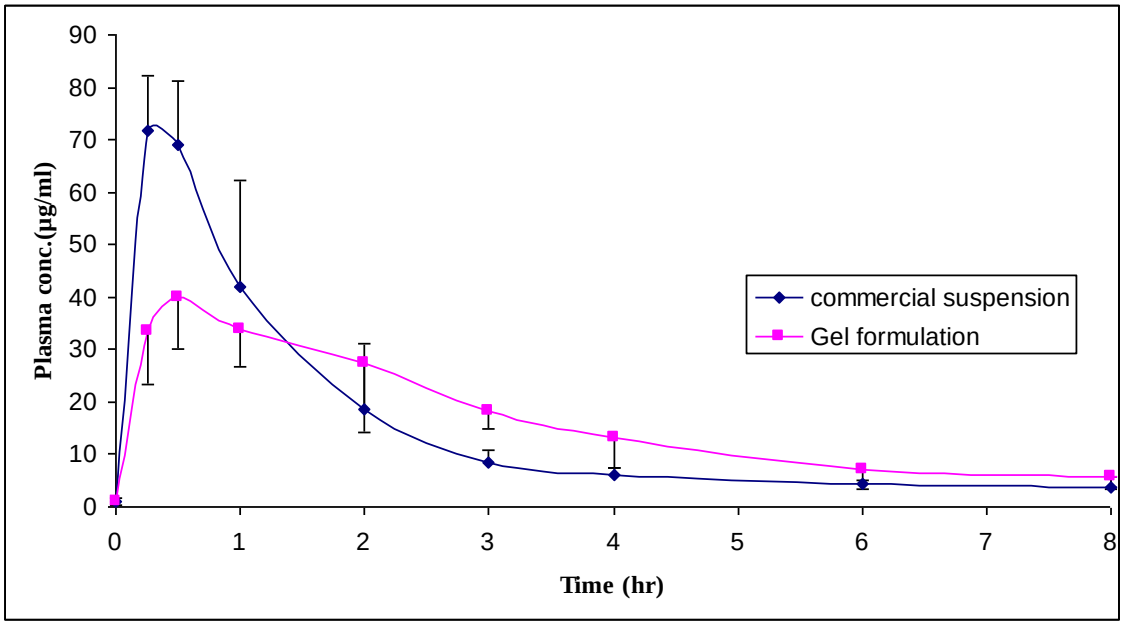

Figure 6 Plasma concentrations of paracetamol in rats after oral administration of commercial suspension and gel formulation (F16). Each value represents the mean ± S.E. of six independent experiments (n=6).

Analysis of the Release Pattern

Table 3 presents the regression parameters obtained after fitting various release kinetic models to the in vitro dissolution data of formulations F1, F4, F7, F10, F13, and F16.

Table 3 Statistical parameters of the various in-situ gel formulations after fitting drug release data into various release kinetic models

Model		F01	F07	F13	F04	F10	F16
Zero-order	r^2	0.8762	0.8728	0.8585	0.7185	0.7729	0.7603
	K_0	0.0012	0.0011	0.0011	0.0012	0.0011	0.0011
First-order	r^2	0.9581	0.9506	0.9376	0.8804	0.9168	0.8999
	K_1	-0.0022	-0.0021	-0.0021	-0.0035	-0.0034	-0.0034
Higuchi	r^2	0.9771	0.978	0.9713	0.8849	0.9217	0.9138
	K_H	0.0315	0.0311	0.0310	0.0333	0.0316	0.0322
Peppas equation	r^2	0.9854	0.9938	0.991	0.9822	0.9897	0.9913
	N	0.5077	0.4838	0.4998	0.4595	0.3647	0.3861
	K_P	-1.4731	-1.4119	-1.4496	-1.1225	-0.9551	-0.9987
Hixson-Crowell	r^2	0.9349	0.9276	0.9139	0.8292	0.8728	0.8571
	K_C	-0.0006	-0.0006	-0.0006	-0.0008	-0.0008	-0.0008

The goodness of fit using different models was ranked in the following order: Korsmeyer-Peppas > Higuchi > first order > Hixson-Crowell cube root law > Zero order. By employing the Korsmeyer-Peppas model, the obtained "n" values for all tested formulations ranged from 0.45 to 0.50. These "n" values indicate that both drug diffusion and polymer relaxation (swelling/erosion) mechanisms are involved in the drug release process.

Viscosity Study

The rheological profiles of the formulated gels have significant implications for their oral administration efficacy. Figure 7 elucidates the shear-dependent viscosity characteristics, revealing a direct correlation between increased viscosity and the melting points of incorporated G constituents.

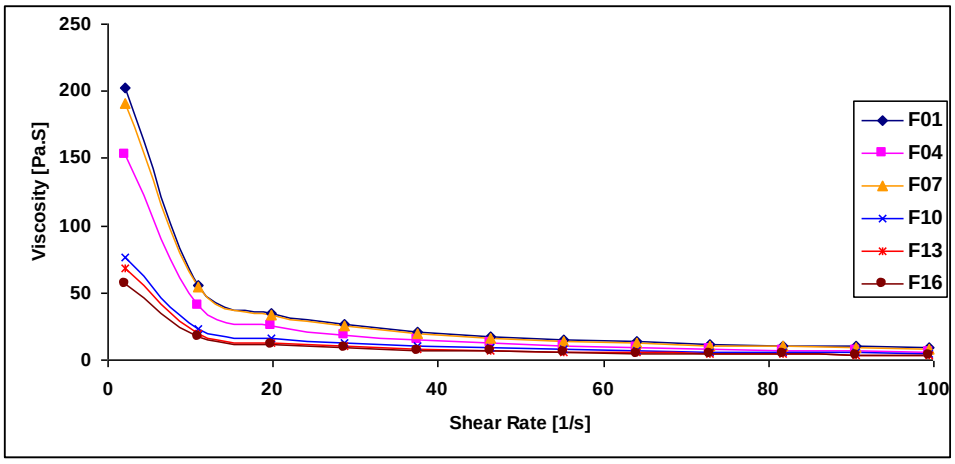

Figure 7 The effect of Shear rate [1/s] dependency of the viscosities of Formulas F01, F04, F06, F10, F13 and F16.

Figure 8 further corroborates the pseudoplastic behavior of the formulations, as evidenced by decreasing apparent viscosities upon incremental shear rate alterations.

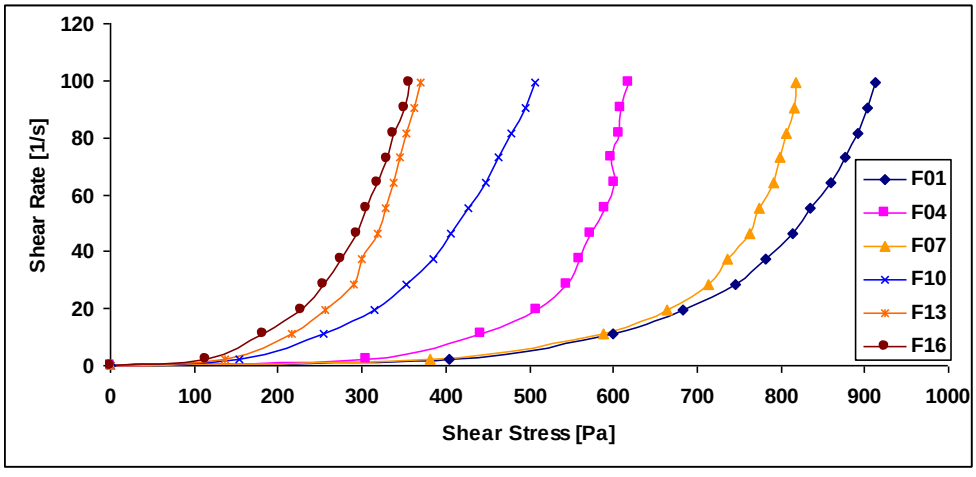

Figure 8 The Flow Curve of Formulas F01, F04, F07, F10, F13 and F16.

Quantitatively, the yield stress values for formulations F16, F13, F10, F4, F7, and F1 ranged from 265 to 750 Pascal-seconds. A pivotal observation was that a two-fold augmentation in the SA-CS polymer ratio resulted in a commensurate decrease in viscosity. In this context, formulations F10, F13, and F16 emerged as favorable candidates for oral administration, attributed to their lower viscosity profiles. Crucially, formulation F16 was subjected to subsequent in vivo evaluations.

***In Vivo* Study**

The release of PA from formulation F16 following oral administration was monitored by determining plasma drug levels. The gelation of this formulation was confirmed by visual observation of the stomach contents, which showed the presence of a distinct matrix mass (as seen in Fig. 4). Figure 6 compares PA levels from the gel with those following oral administration of the commercial suspension. The formed gel was capable of releasing the drug in a sustained manner, providing a relatively consistent plasma concentration profile. The obtained AUC0–∞, MRT, Cmax, Tmax, and t1/2 are summarized in Table 4 along with those published using the same drug and animal models.

Table 4 Comparison of bioavailability parameters of paracetamol administered from the commercial suspension, gel formed in situ in rat stomach (F16)

dosage form	C_{max}	*Tmax*	AUC	MRT	$t_{1/2}$
Gel formulation (F16)	41.0 ± 0.5	0.50 ± 0.08	177.71± 26.4	5. 4 ± 0.7	4.5 ± 1.2
Commercial suspension	74.8 ± 1.2	0.25 ± 0.09	164.3 ± 44.6	4.8 ± 0.9	4.4 ± 0.9

Significantly higher peak time, t_{max} (0.50 ± 0.09 *vs.* 0.25 ± 0.08, *P<0.003*), and lower values of peak concentration, C_{max} (41.0±0.50 *vs* 74.0±1.2, *P<0.001*) were exhibited by the test gel versus the commercial suspension. The area under the curve up to infinite time, $AUC_{0-\infty}$ (177.1±26.4 *vs* 164.3±44.5, *P<0.05*) for the gel and suspension were not significantly different, indicating the similar extent of absorption of the sustained test gel to the reference commercial suspension. The obtained values compare well with those reported earlier (refer to Table 4) in the same animal model.

It is interesting to note the similarity in mean residence times (MRT) between the gel and the commercial suspension. The sustained release effect of the gel formulation results from the gel structure's resistance to the drug's diffusion, whereas that of the suspension arises from the reservoir effect of the suspended particles as they slowly dissolve in the intestine. This result aligns with previous findings [3].

CONCLUSIONS

One of the most commonly used methods to achieve an in-situ gel in the stomach involves combining an anionic polysaccharide with a source of cations, typically calcium. However, excessive calcium intake can be harmful to hypercalcemic patients, and calcium ions may interact unfavorably with certain drugs. This study presents an alternative approach by using a combination of CS and SA without calcium. There is a potential synergistic effect between these two polysaccharides that enhances gel consistency. The mechanism of in-situ gelation relies on the formation of a crosslinked network between the polymers. The addition of hydrophobic Gelucires further enhances gel consistency. These formulations form a gel matrix system immediately upon contact with 0.1N HCl and in the rat stomach in situ. Such a matrix can sustain the release of PA throughout the gastrointestinal tract (65% release after 8 hours). Gelucire® types with similar HLB values and melting points ranging from 33 to 43°C showed no significant differences ($p < 0.05$), likely due to their

similar hydrophobicity. This preparation offers a system with suitable viscosity, easy swellability, prolonged drug action time, and reduced drug administration frequency.

Statements and Declarations

Conflicts of interest: There are no conflicts to declare.

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Authors' contributions

Al-Sayed Sallam: Conceptualization and Formal analysis. Inam Al-Naji, Ruaa Al-Ajeeli: Methodology and Formal analysis. Nidal A. Qinna: Methodology and Resources. Faisal Al-Akayleh, Mayyas Al-remawi, Mai Khanfar: Formal analysis and Writing - Original Draft. Ahmed S.A. Ali Agha: Validation, Software, and Visualization.

Conflict of Interest: The authors declare no conflict of interest.

Statement of Human and Animal Rights

The animal studies were performed after receiving approval of the Institutional Animal Care and Use Committee (IACUC) in the University of Petra (IACUC approval No. A1/9/2021).

Availability of data and materials: Available upon request

Competing interests: The authors declare that none of them have a competing interest.

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نظام التجلئة الموقعي للكيتوزان/الجيلاتين/جيلوسير للتوصيل المُستدام عن طريق الفم للباراسيتامول للمرضى الذين يعانون من صعوبة في البلع

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ملخص

تهدف الدراسة إلى تطوير نظام تركيبة تعطى عن طريق الفم وتكون جل داخل المعدة نتيجة تعرضها لدرجات الحموضة العالية في المعدة ويُحقق توصيل مُستدام للباراسيتامول، مُستهدفًا الفئات العمرية الصغيرة والكبيرة. تم استعمال مزيج من الجينات الصوديوم، الكيتوزان، وجيلوسير. تم التوصيف التركيبة باستخدام تقنيات مثل التفحص الحراري التفاضلي، وطيف الأشعة تحت الحمراء ، واللزوجة. أظهر النظام قدرة على التحكم الفعّال في إطلاق الدواء في مستويات مختلفة من دراجات الحموضة. أفضل التركيبات أظهرت وقت إطلاق يتجاوز الـ8 ساعات. تم اختيار النظام المناسب بناء على دراسات اللزوجة والدراسات البيولوجية.

الكلمات الدالة: نظام مصفوفة الجل الموضعي، كيتوزان، ألجينات الصوديوم، جيلوسير، باراسيتامول، إطلاق مُستدام.

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