RESEARCH ARTICLE

Optimizing Verapamil Hydrochloride *In-situ* Delivery: A Strategic Formulation Approach using Box-Behnken Design for Enhanced Performance and Comprehensive Evaluation of Formulation Parameters

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ABSTRACT

This study focuses on formulating and assessing an *in-situ* gastro-retentive gel for precise delivery of verapamil hydrochloride to the stomach, aiming to extend its residence time and improve targeted delivery. Gels were synthesized *in-situ* using a cation-controlled gelation method, incorporating varied blends of pectin and HPMCK4M. Design Expert's box behnken design was employed to assess responses such as buoyancy lag time, water uptake, and cumulative drug discharge. Results revealed that the developed gels exhibited a total float time exceeding 10 hours, with formulation T-2 showing the least floating lag time and a cumulative drug release of 99.40 ± 3.24% over 10 hours. This suggests effective prolongation of the gastric residence time, enabling controlled verapamil hydrochloride release. Additional evaluations, including appearance, pH, viscosity, *in-vitro* gel formation, drug content, density, and gel force, supported the robustness of the developed gels. Subsequent *in-vitro* dissolution and stability studies affirmed consistent active ingredient content, highlighting formulation stability over time. In conclusion, this study demonstrates that the *in-situ* gels effectively extend gastric residence time, facilitating controlled verapamil hydrochloride release, marking significant advancements in drug delivery systems and targeted drug delivery within the gastrointestinal tract.

Keywords: Formulation, Gastro-retentive, *In-situ*, Release, Verapamil.

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INTRODUCTION

Oral drug delivery systems (ODDS) play a pivotal role in pharmaceutical formulations, offering a convenient and patient-friendly mode of administering therapeutic agents. These systems encompass a diverse range of technologies and formulations designed to deliver drugs through the oral route, leveraging the gastrointestinal tract's extensive surface area and permeability.[1] Various oral dosage forms, including tablets, capsules, liquids, and oral disintegrating tablets, cater to different patient needs and preferences. The versatility of oral drug delivery extends to controlled-release formulations, allowing for drug release for a prolonged time, and novel technologies like nanoparticle-based formulations, enhancing drug solubility and bioavailability. The oral route's ease of administration promotes patient adherence, making it a preferred choice for chronic treatments. As researchers continue to innovate in this field, advancements in targeted drug delivery, biocompatible materials, and personalized medicine are shaping the future of ODDS, contributing to improved therapeutic outcomes and enhanced patient well-being.[2]

Gastro-retentive drug delivery systems (GRDDS) represent an innovative method to address challenges associated with oral drug administration. These systems are intended to protract the dwelling time of drug formulations within the stomach, offering a solution to issues like irregular gastrointestinal tract movement, incomplete drug discharge, and limited duration of drug action.[3] The key objective of GRDDS is to enhance

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drug absorption and bioavailability by ensuring an extended and controlled release of active components. Various strategies are employed in developing these systems, such as floating, bioadhesive, and expandable systems, each tailored to achieve prolonged gastric retention. Floating systems, for example, utilize buoyant materials to remain on the stomach surface, while bioadhesive systems adhere to the gastric mucosa, preventing premature drug discharge.[4] The versatility of GRDDS enables researchers to explore *in-situ* drug delivery systems (DDS), aiming to further extend gastric residence time and enhance drug discharge kinetics. This evolving field holds significant promise for optimizing drug delivery, offering potential benefits in terms of increased therapeutic efficacy and improved patient compliance. As researchers continue to delve into the intricacies of GRDDS, the potential for innovative and effective drug delivery solutions is poised to advance pharmaceutical science and patient care.

Calcium channel blockers (CCBs) constitute a class of medications widely used in the management of cardiovascular conditions. By doing so, CCBs exert vasodilatory effects, reducing peripheral vascular resistance and decreasing myocardial contractility. This dual action makes them valuable in treating hypertension, angina pectoris, and certain arrhythmias. The therapeutic efficacy of CCBs extends beyond cardiovascular conditions,[5] with some applications in migraine prophylaxis and Raynaud's phenomenon. Despite their widespread use, vigilant deliberation of individual patient features and possible side effects, such as edema, constipation, and heart rate irregularities, is crucial for optimizing their clinical utility. Calcium channel blockers continue to be pivotal in cardiovascular medicine, contributing significantly to the management of various cardiovascular disorders.[6]

Verapamil hydrochloride is a well-established medication belonging to the class of CCBs. This dual action results in vasodilation, decreased peripheral vascular resistance, and reduced myocardial contractility, making it effective in treating conditions such as hypertension, angina pectoris, and certain arrhythmias. Verapamil is classified as a non-dihydropyridine CCB, distinguishing it from other members of its class. Beyond its cardiovascular applications, verapamil has demonstrated utility in treating migraines and certain neurological disorders. Verapamil hydrochloride remains a valuable and versatile medication in clinical practice, contributing significantly to the management of various cardiovascular and related conditions.[7]

In-situ, gels represent an innovative class of DDS designed to address challenges associated with conventional formulations. These gels undergo a phase transition upon administration, transforming from a liquid to a gel state in response to specific physiological triggers or environmental conditions, such as temperature, pH, or ions present in the target site. This unique property allows for localized and extended drug discharge, enhancing therapeutic efficacy. In the context of drug delivery, *in-situ* gels offer several advantages, including prolonged residence time at the target site, improved bioavailability, and reduced systemic side effects. The versatility of *in-situ* gels extends their applicability to various administration routes, including ophthalmic, nasal, and oral, providing a tailored approach for different therapeutic needs[8].

This research is centered on creating and assessing a gastro-retentive gel specifically formulated to accurately deliver VMH to the stomach to prolong residence time and optimize drug delivery at the targeted site. The synthesis of these gels involved *in-situ* formation utilizing a cation-controlled gelation method, incorporating varied combinations and concentrations of pectin and HPMCK4M.

MATERIALS AND METHODS

Verapamil hydrochloride was procured from Sun Pharma, Mumbai as a sample. The following chemicals were sourced from Fischer, Bangalore: Carbopol 934P, calcium carbonate, calcium chloride, HPMC K4M, methylparaben, pectin, propylparaben, sodium alginate, and sodium citrate. All utilized constituents were of analytical reagent (AR) grade, and the experiments were conducted using double-distilled water.

Preparation of *In-situ* Gels

A cation-controlled gelation method was employed to formulate an *in-situ* floating gel for VMH. The procedure involved dissolving varying concentrations of polymer in distilled water and, sodium citrate and calcium chloride under incessant rousing at 800 rpm using a magnetic stirrer (at 70°C). Later, conserving beneath 40°C, different concentrations of VMH and calcium carbonate were introduced, and the subsequent gel was enthused to achieve an unvarying dispersal.[9,10] Stabilizers were then incorporated, and the final *in-situ* gel was stored in an amber bottle for subsequent use (Table 1).

Evaluation

Exterior and pH

The visual attributes of the gels underwent meticulous examination, and the pH values of the *in-situ* gel solutions containing VMH were thoroughly assessed at a temperature of 25°C utilizing a precise digital pH meter. To ensure accuracy in the analysis, each formulation underwent three independent pH measurements, and the average value obtained was diligently recorded, contributing to a comprehensive characterization of the formulations.[11]

In-vitro gelation

To assess the *in-vitro* gelling capacity, a gelling solution was prepared using an HCl solution (0.1 N, pH 1.2). Subsequently, 1-mL of each formulation was introduced into 10 mL of the gelling solution, upholding a constant temperature of 37 ± 1°C. The gelation process initiated as the formulation interacted with the gelling solution. The evaluation of gelation capacity considered both the time taken for gelation and the duration of gel formation. The assessment employed a scoring system, details of which can be inserted here, encompassing various parameters to comprehensively evaluate the *in-vitro* gelling performance[12].

- "+": Gelling in few seconds and disperses rapidly
- "++": Gels instantly and float for 10 hours
- "+++": Gels instantaneously and float for > 10 hours

Table 1: Various trials of VMH *in-situ* gel formulations

Trials	*VMH (mg)*	*Pectin (mg)*	*HPMC K4M (mg)*	*C-934P (mg)*	*SC (mg)*	*$CaCl_2$ (mg)*	*$CaCO_3$ (mg)*	*MP (mg)*	*PP (mg)*	*DW (q.s) (mL)*
T-1	40	0.50	0.40	0.25	0.30	0.20	0.50	0.10	0.05	100
T -2	40	1.00	0.40	0.25	0.30	0.20	0.50	0.10	0.05	100
T -3	40	0.50	0.80	0.25	0.30	0.20	0.50	0.10	0.05	100
T -4	40	1.00	0.80	0.25	0.30	0.20	0.50	0.10	0.05	100
T -5	40	0.39	0.60	0.25	0.30	0.20	0.50	0.10	0.05	100
T -6	40	1.10	0.60	0.25	0.30	0.20	0.50	0.10	0.05	100
T -7	40	0.75	0.32	0.25	0.30	0.20	0.50	0.10	0.05	100
T -8	40	0.75	0.88	0.25	0.30	0.20	0.50	0.10	0.05	100
T -9	40	0.75	0.60	0.25	0.30	0.20	0.50	0.10	0.05	100

VMH: Verapamil Hydrochloride; HPMC: Hydroxyl Propyl methyl Cellulose; C-934P: Carbopol 934P; SA: Sodium alginate; SC: sodium citrate; $CaCl_2$: calcium chloride; $CaCO_3$: calcium carbonate; MP: Methyl paraben; PP: Propyl paraben; DW: Distilled water

Viscosity

The viscosities of various *in-situ* gels were determined using a Brookfield viscometer (DV-II+Pro digital). The assessment included placing 20 mL of each sample in a beaker. The T-shaped shaft was precisely lowered vertically to the center of the cup, ensuring it did not touch the bottom. Viscosities were measured at 50 rpm, and the temperature was meticulously upheld throughout the procedure. To enhance accuracy, the average of three measurements was considered for each viscosity assessment.[13]

Buoyancy

The USP-II dissolution device (Electrolab, India) was utilized for the *in-vitro* buoyancy assessment. In this study, 10 mL of the VMH *in-situ* gel was introduced into the container, which was filled with 0.1 N HCl of pH 1.2 (37 ± 0.5°C) to replicate physiological conditions. The study observed and recorded two crucial parameters: The float delay time, representing the duration for the formulation to achieve buoyancy, and the total float time, indicating the overall duration the formulation remained afloat. These measurements provided valuable insights into the buoyancy characteristics of the *in-situ* gel and its behavior in simulated gastric environments.[14]

Density

The formulation's density was determined utilizing the water displacement method. In this process, 10 mL of the preparation was decanted into 50 mL of 0.1 N HCl, initiating gelation. Subsequently, the resulting gel was carefully transferred into a graduated cylinder to facilitate sedimentation. Both the volume and weight of the formed gel were then meticulously measured. The combination of these precise volume and weight measurements allowed for the gel density estimation using the water displacement method. This method offers an accurate means to determine density by considering the volume of water displaced when the gel is introduced.[15]

Gel strength

In the conducted study, a specific gravity of 30 g was applied to the formed gel. A 50 g weight was centrally placed on the surface of the gel and permissible to pass over it. The duration taken for the weight to descend 5 cm over the set gel was considered as an indicator of its strength. Three readings were recorded for each test to ensure accuracy and reliability, and the average of these readings was calculated. This approach was adopted to comprehensively evaluate the gel strength, providing a representative measure of its resistance to the applied force.[16]

VMH content

A double-beam UV–visible spectrophotometer (Shimadzu, Japan) was utilized to assess the VMH gratified in the *in-situ* gel. In this procedure, 10 mL of the formulation, equal to 100 mg of VMH, was thawed in 80 mL of 0.1 N HCl (pH 1.2). The mixture underwent continuous stirring with a magnetic stirrer for -hour. Subsequently, the subsequent solution was drinkable and thinned with 0.1 N HCl to achieve a total volume of 100 mL. The drug content was determined by measuring absorption using a UV-visible spectrophotometer at a specific wavelength of 278 nm, chosen based on VMH's characteristics. The UV–vis spectrophotometer provided a quantitative analysis of the VMH level in the *in-situ* gels, contributing crucial information to the comprehensive characterization of the formulations.[17]

Water uptake

The formulation was introduced into a solution comprising 0.1 N HCl. Utilizing a water bath under precise temperature control the formulation solution underwent gelation. The gel was removed and then dried. The original weight of the gel was recorded. Subsequently, distilled water (10 mL) was introduced to the gel and poured off at 30-minute intervals. The weight of the gel was noted during each interval, facilitating the calculation of weight changes over time. This systematic procedure provided a structured approach to evaluating how the gel evolved in terms of weight during the specified intervals.[18]

In-vitro VMH discharge

VMH discharge was conducted using a USP type II apparatus operating at 50 rpm and a temperature of 37 ± 0.5°C (medium consisted of 0.1 N HCl). An *in-situ* gel equal to 40 mg of VMH

(10 mL) was introduced into the dissolution medium while upholding a temperature of 37°C ± 0.5°C. At each designated interval, a sample was collected, and absorbance measured with UV spectrophotometry at 278 nm was then employed to analyze the filtered samples, providing a comprehensive assessment of the VMH discharge profile over the specified time intervals.[19]

Optimization of in-situ gel by factorial design

The development of a novel drug formulation often involves an iterative process, where various combinations are tested to achieve satisfactory but not necessarily optimal outcomes. To systematically and cost-effectively enhance the formulation process, this study employed optimization techniques, specifically response surface methodology (RSM), with the assistance of Design Expert software. The results underwent multiple regression analysis, leading to the formulation of equations describing the influence of independent variables on selected responses. The dependent variables encompassed critical parameters such as the floating lag time (Y_1), water uptake (Y_2), and the % of cumulative drug discharge at various time points [2h (Y_3), 4h (Y_4), and 8h (Y_5)]. This approach allowed for a more structured and efficient exploration of the formulation space, facilitating the identification of optimal conditions for the desired drug delivery system. The optimization process considered two independent factors, namely pectin level (X1) and HPMC level (X2). High and low values for each factor were coded as +1 and -1, respectively, with the mean coded as zero. The selected ranges for each factor were determined based on preliminary studies. This experimental design was chosen for its capacity to offer sufficient degrees of freedom to assess both the main effects and interactions between factors. The application of response surface methodology provides a systematic and efficient exploration of the formulation space, aiding in the identification of optimal conditions for attaining the anticipated drug discharge profile. This approach enhances the precision and effectiveness of the formulation process by allowing a more targeted investigation of the factors influencing the presentation of the drug delivery system.[20]

Figure 1: *In-vitro* gelation of the *in-situ* gel formulation

Accelerated stability studies

These studies were carried out at 40 ± 2°C and 75 ± 5% relative humidity (RH). Throughout this period, the formulations underwent thorough examinations to assess any potential changes in appearance, active ingredient content, pH, *in-vitro* buoyancy, and drug discharge. These evaluations were designed to ascertain the stability of the formulations under varied storage conditions, offering crucial insights into their resilience and integrity over an extended period. Adherence to ICH guidelines ensures that the stability of the data generated is reliable and can be extrapolated to predict the formulation's performance under different environmental conditions.[21,22]

RESULTS AND DISCUSSION

Appearance and pH

Our investigation thoroughly examined the visual attributes and pH measurements of pharmaceutical formulations, specifically gels labeled T-1 to T-9. All formulations consistently exhibited a greenish-yellow appearance, indicating a uniform and visually appealing presentation. The pH measurements ranged from 7.87 ± 0.05 (T-4) to 7.02 ± 0.07 (T-8), falling within the acceptable range for oral drugs. This suggests that the formulations are unlikely to induce oral irritation. Importantly, the solutions upheld a fluid consistency at room temperature without any symbols of gelation. This distinctive implies that the gels continue in a liquid state until encountering gastric fluid. Overall, the visual presentation and pH measurements validate the aesthetic appeal of the formulations and affirm their suitability for oral administration. Meeting the necessary criteria for patient adherence and oral acceptability, these formulations demonstrate promising attributes for pharmaceutical use. Garala *et al.,* 2013 were prepared *in-situ* gels and found the clear white coloured gel.[23]

In-vitro Gelation

In our study, all formulations underwent a comprehensive *in-vitro* gelation analysis, and their gelation properties were systematically assessed by a standardized scale ranging from ++ to +++ (refer to Table 2). Notably, each gel demonstrated real gelation, with trials T-2 and T-6 exhibiting direct gelation and sustaining the gel state beyond 10 hours. Conversely, the remaining formulations displayed commendable gelation properties, upholding the gel for the projected 10 hours duration. The aptitude of these gels to rapidly get into a gel and withstand it for more time frame indicates a superior gelling capacity. This beneficial property holds significance for *in-situ* gelation systems, facilitating prolonged retention in the gut and ensuring a prolonged discharge (Figure 1), such observations were also seen by Kesarla *et al.,* in 2016.[24]

Viscosity

The viscosity ranged from 235.8 ± 4.7 to 361.3 ± 4.4 cps (Table 2). Viscosity, representing a fluid's resistance to flow, is a key parameter in ODDS. Striking an optimal viscosity is essential to balance fluidity for easy administration with sufficient thickness for adherence and retention at the target site, such

as the gastrointestinal tract. Our formulations' measured range of viscosities indicates a tailored approach to achieve the desired flow characteristics for effective oral delivery. Considering viscosity in formulation design is particularly crucial for ensuring patient compliance, as formulations with appropriate viscosity are more likely to be easily swallowed, ensuring consistent dosing. Moreover, viscosity influences the residence time of the formulation in the gastrointestinal tract, impacting drug absorption and therapeutic effectiveness. Therefore, our comprehensive assessment of formulation viscosities provides appreciated visions into these ODDS's design and probable performance, contributing to their overall efficacy and patient adherence.

The observed viscosity trend reveals a direct and notable correlation between increasing levels of the gelling polymer and the rising viscosity of the formulations. This correlation is ascribed to the heightened cross-linking of the polymer molecules, leading to a more intricate network structure and an elevation in viscosity. Notably, the augmentation of sodium alginate and gellan gum levels, in particular, resulted in a significant increase in viscosity. These conclusions underscore the polymer level's pivotal role in deciding the gels' viscosity. By strategically adjusting the polymer content, precise control over viscosity becomes feasible, ensuring it aligns within the optimal range for easy administration to patients. The viscosity results of the gels conform to the prescribed standards for orally administered drugs. The significant increase in viscosity at higher polymer levels signifies the gel's capacity to achieve the reliability required for effective drug delivery.

This discovery holds paramount importance for optimizing the characteristics of the formulation, ensuring its adherence to the necessary criteria for effective oral administration, and consequently, enhancing overall patient compliance. In essence, this aspect of the study provides valuable insights into the tunability of the formulation, offering a practical means to tailor its viscosity to meet specific requirements for optimal ODDS.

In-vitro Buoyancy

The primary objective of this study was to assess the float delay time and total float time of the generated gel formulations, with summarized outcomes presented in Table 2. The results indicate that trial T-2 exhibited superior buoyancy properties compared to the other *in-situ* gels. This particular formulation demonstrated rapid gel formation within 30 seconds, notably faster than the remaining formulations. Additionally, all the gels remained afloat for > 10 hours, indicating a prolonged duration of buoyancy.

The ability of these gels to quickly form a gel and float for more time is beneficial for GRDDS. This characteristic leads to prolonged drug discharge, contributing to extended therapeutic effects.

Based on these results, T-2 emerges as the top-performing formulation among those tested, demonstrating immediate gel formation and an uninterrupted time of flotation. These formulations exhibit promising potential for extended drug discharge and improved therapeutic outcomes. The combination of rapid gel formation and prolonged buoyancy positions them as particularly promising candidates for GRDDS, offering enhanced control over drug discharge kinetics and potentially improving patient treatment outcomes.

VMH Content

The presented findings, detailed in Table 3, offer a comprehensive overview of the %content of the active ingredient in the various formulations under investigation. Remarkably, the active ingredient content consistently fell within a narrow range across all formulations, specifically ranging from 78.69 ± 3.62% to 95.36 ± 2.54%. This outcome reflects a uniform distribution of the active ingredient under the specified standards outlined in the relevant monograph. Notably, the T-2 trial stands out as particularly noteworthy, demonstrating the highest % of VMH content. Trial T-2, in particular, exhibited the highest VMH levels.

Table 2: Physical assets of the *in-situ* gels

Trials	*Physical look*	*pH*	*Gelling capability*	*Viscosity (cps)*	*Buoyancy lag time (s)*	*Total floating time (h)*
T-1	White	7.54 ± 0.07	++	285.8 ± 6.3	53 ± 2	>10
T -2	White	7.04 ± 0.41	+++	351.2 ± 1.6	45 ± 6	>10
T -3	White	7.65 ± 0.45	++	295.7 ± 4.4	55 ± 2	>10
T -4	White	7.87 ± 0.05	++	341.2 ± 2.3	49 ± 5	>10
T -5	White	7.58 ± 0.08	++	345.6 ± 3.8	54 ± 4	>10
T -6	White	7.19 ± 0.14	+++	361.3 ± 4.4	40 ± 3	>10
T -7	White	7.74 ± 0.14	++	341.2 ± 2.1	51 ± 2	>10
T -8	White	7.02 ± 0.07	++	235.8 ± 4.7	59 ± 1	>10
T -9	White	7.47 ± 0.06	++	339.7 ± 1.3	56 ± 2	>10

Values in mean ± SD; n = 3; ++: immediate gel formation and up to 10 h floating;
+++: immediate gel formation >10 h floating

The significance of these results lies in the consistent and high %content of VMH in these specific formulations. This uniformity is crucial for ensuring the reliability and reproducibility of the formulations, supporting their potential effectiveness in delivering the intended therapeutic dose. The elevated content of pectin and medium levels of HPMC K4100 in trial T-2 further suggests its potential as an optimized candidate, showcasing a robust presence of the active ingredient within the formulated gel.

Overall, these findings contribute valuable insights into the quality and uniformity of the active ingredient distribution across the tested formulations. This uniformity is pivotal for ensuring the efficacy and consistency of the pharmaceutical product, reinforcing the potential of these formulations to deliver reliable therapeutic outcomes.

Water Uptake

The % of water content in a DDS is a critical factor influencing drug discharge, as it directly impacts the diffusion of water into the polymer matrix, subsequently affecting drug discharge through diffusion or dissolution mechanisms. In this study, the % of water absorption by the gels was assessed over 2 hours, revealing a range between 15.6 ± 0.1% and 31.5 ± 0.6%. Notably, the T-3 trial demonstrated superior water absorption after 2 hours compared to the other *in-situ* gels. The higher levels of polymers, specifically pectin and HPMC K4M, in these trials resulted in greater water absorption by the gel.

The increased water absorption observed in T-3 suggests an enhanced ability of these formulations to absorb water, potentially contributing to improved drug delivery properties. This heightened water absorption is beneficial as it facilitates deeper diffusion into the polymer matrix, which may enable a faster and well-organized drug-release process. The capacity of T-3 to absorb a greater amount of water implies a potential benefit in terms of optimizing drug delivery characteristics, indicating these formulations as promising candidates for further exploration in the development of effective *in-situ* gels.

Density

The study conducted measurements of the densities of gastro retentive *in-situ* floating gels, revealing values ranging from 0.632 ± 0.06 to 0.782 ± 0.04 g/cm³. Importantly, these measured densities are lower than that of stomach contents (1.004 g/cm³). This low density is crucial for achieving buoyancy in gastric fluid, ensuring prolonged gastric retention. The buoyancy of these formulations facilitates extended drug discharge, thereby enhancing therapeutic efficacy.

These systems prevent rapid passage through the gut, supporting their suitability for prolonged exposure and absorption in the upper gastrointestinal tract. Confirming the desired low density reinforces the potential of these formulations for GRDDS, suggesting their capability to improve therapeutic outcomes through prolonged retention and extended drug release. The findings underscore the significance of the buoyant properties of these *in-situ* floating gels for effective drug delivery in the gastrointestinal environment.

Gel Strength

Gel strength, a critical parameter for resisting peristaltic movements *in-vivo*, was measured in this study and yielded values ranging from 55.07 ± 3.44 to 68.25 ± 1.19 seconds. Trial T-4, with a higher value, exhibited notably strong gel resistance. The enhanced gel strength in T-4 can be attributed to elevated levels of pectin and lesser HPMC K100M, fostering stronger gel structures. These polymers contribute to increased cross-linking and gelation capacity.

The robust gel strength observed in T-4 is crucial for upholding integrity in the gastrointestinal tract during transportation, a vital characteristic of GRDDS. This strength ensures extended drug discharge and holds promise for improved therapeutic outcomes. The favorable gel strength position of T-4 in the study suggests its potential as a candidate for DDS that requires prolonged discharge, contributing to the overall efficacy of the formulated gels.

***In-vitro* Drug Discharge**

The study conducted VMH (active ingredient) discharge over 10 hours using 0.1 N HCl as the dissolution medium, and the drug release pattern is visually depicted in Figure 2. Results indicated that formulations with higher levels of pectin and lower HPMC K4M exhibited an increased and extended drug discharge. Among the tested trials, T-2 demonstrated the highest drug discharge, representing that these gels successfully achieved extended VMH release throughout the entire 10 hours.

The elevated pectin levels and low levels of HPMC K4M in T-2 are likely contributors to their effective control and prolongation of drug discharge. The extended drug release observed in T-2 can be attributed to the unique properties of the polymers utilized, such as pectin and HPMC K4M, which are known for their capacity to form a gel matrix and regulate drug release through diffusion or dissolution mechanisms. The higher polymer levels in T-2 likely resulted in the formation of a more robust and prolonged gel matrix, contributing to the observed extended drug release profile.

This finding is particularly promising for these formulations, as it suggests their potential to provide prolonged therapeutic effects, reducing the frequency of dosing and potentially improving patient compliance. The extended drug discharge profile observed in T-2 underscores its suitability for GRDDS, offering a promising avenue for optimizing therapeutic outcomes.

Factorial Design

An *in-situ* oral gel was successfully developed through the application of the ionic cross-linking method, achieving optimization for extended drug discharge lasting up to 10 hours using Design Expert's Box-Behnken Design (BBD). The amounts of pectin (X_1) and HPMC (X_2) were chosen as independent variables in the formulation process. Characterization of the prepared batches encompassed various parameters, including gelation capacity, water absorption, active ingredient content, formulation viscosity, and pH. All

Table 3: VMH content, water uptake, gel strength, and density of the *in-situ* gels

Trials	*Drug content (%)*	*Water uptake (%)*	*Gel strength (sec)*	*Density (g/cm^3)*
T-1	84.29 ± 3.69	21.3 ± 0.3	58.05 ± 1.31	0.685 ± 0.05
T-2	95.36 ± 2.54	16.5 ± 0.8	59.88 ± 0.65	0.632 ± 0.06
T-3	78.69 ± 3.62	31.5 ± 0.6	57.36 ± 2.28	0.684 ± 0.01
T-4	80.74 ± 1.24	17.5 ± 0.7	68.25 ± 1.19	0.767 ± 0.08
T-5	81.35 ± 2.65	23.6 ± 0.4	59.74 ± 2.08	0.709 ± 0.06
T-6	89.65 ± 4.51	15.6 ± 0.1	65.98 ± 1.97	0.782 ± 0.04
T-7	86.98 ± 5.29	19.3 ± 0.3	55.07 ± 3.44	0.679 ± 0.05
T-8	85.85 ± 4.61	30.2 ± 0.6	59.22 ± 1.64	0.681 ± 0.01
T-9	91.96 ± 1.82	31.4 ± 0.8	55.71 ± 2.52	0.668 ± 0.04

Values in mean ± SD; n = 3

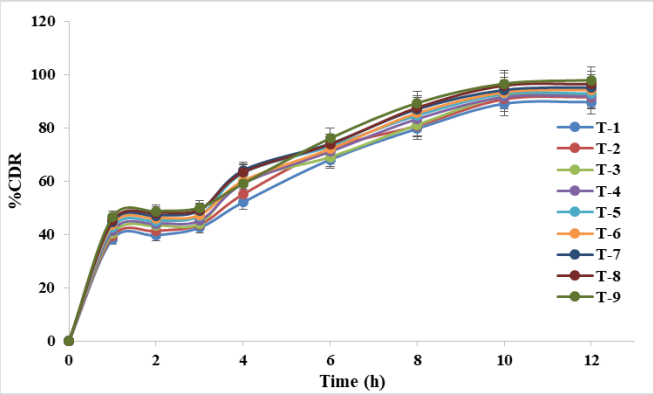

Figure 2: Drug discharge from the *in-situ* gel formulations

these parameters met acceptable standards, obviating the need for additional statistical analysis.

For statistical analysis, the % of cumulative drug discharge at different time points (2, 4, and 8 hours) served as the dependent variable. Design Expert software (version 12, Stat-Ease Inc, Minneapolis, MN) was employed for this purpose. The use of this comprehensive approach facilitated a thorough evaluation and optimization of the *in-situ* oral gel formulation, ensuring extended drug discharge. This systematic methodology underscores the robustness of the developed formulation, laying the groundwork for potential applications in CDDS. The final equations in terms of coded factors were enlisted below:

Floating lag time=+56.00-4.22A+2.16B+0.5AB-4.63A²-0.6250B²

Water uptake in 120 minutes= +31.50-3.76A+3.33B-2.30AB-6.07A²-3.49B²

CDR@2 =+92.90+1.90A-1.87B-0.55AB-0.8750A²-1.78B²

CDR@4 =+95.10+1.50A-1.70B-1.13AB-0.3787A²-1.45B²

CDR@8 =+97.80+1.34A-1.35B-0.8750AB-0.5875A²-1.41B²

The data underwent statistical analysis utilizing the analysis of variance (ANOVA) test, and quadratic models were constructed to identify the optimized batch. The quadratic model proved to be adequate in explaining the responses, particularly in the context of gel viscosity and percent cumulative drug discharge (%CDR). Gel viscosity was found to be significantly influenced by the levels of sodium alginate and pectin. As the polymer level increased, complexation and cross-linking with calcium ions also increased, resulting in an elevation in gel viscosity. Kurniawansyah *et al.,* 2020 observed such relations using Poloxamer 407 by full factorial design.[25]

The %CDR exhibited an inverse relationship with the levels of pectin and HPMC K4M. The drug discharge from the *in-situ* gel was primarily influenced by the amount of pectin, where increased cross-linking led to reduced drug discharge from the gel matrix. Higher levels of pectin resulted in increased cross-linking, leading to decreased drug discharge. Conversely, a higher level of HPMC K4M resulted in a less viscous gel, promoting greater drug discharge.

The statistical analysis revealed the significant influence of polymer levels on key parameters, with sodium alginate and pectin affecting gel viscosity and HPMC K4M influencing drug discharge from the gel matrix. This nuanced understanding, derived from the statistical analysis, provides valuable insights into the interplay of formulation components and their impact on critical properties, contributing to the optimization of the *in-situ* oral gel for extended drug discharge.

Contour plots, exemplified in Figure 3, serve as graphical representations illustrating the influence of two independent variables, namely the amounts of pectin and HPMC K4M, on the response variables, i.e., floating lag time, water uptake, CDR-2h, CDR-4h, and CDR-8h. The identified optimal values for these inputs were 0.7418 mg of pectin and 0.9803 mg of HPMC K4M, representing the preferred amounts conducive to achieving desired outcomes in drug discharge. The contour plots reveal the impact of pectin and HPMC K4M level variations on %CDR at specific time intervals. Barse *et al.,* 2018, optimized such formulation using 3^2 full factorial design.[26]

These graphical representations offer a comprehensive understanding of the relationship between input variables and the desired drug discharge outcomes at different time points, aiding in the identification of optimal formulation (Figure 4) conditions for extended drug discharge.

Accelerated Stability Studies

The formulation (T-2) displayed exceptional stability throughout an accelerated stability study, with no significant alterations observed in form and buoyancy%. Even under

Table 4: BBD layout with the result of responses

Trials	*Factors*		*Responses (%CDR at different intervals)*				
	A:Pectin (mg)	*B:HPMC K4M (mg)*	*Floating lag time (s)*	*Water uptake (%)*	*CDR-2h (%)*	*CDR-4h (%)*	*CDR-8h (%)*
T-1	0.5	0.5	53	21.3	90.1	92.8	95.2
T-2	1.25	0.5	45	16.5	94.7	97.85	99.4
T-3	0.5	1	55	31.5	87.4	91.51	94.1
T-4	1.25	1	49	17.5	89.8	92.04	94.8
T-5	0.34467	0.75	54	23.6	88	91.8	94.5
T-6	1.40533	0.75	40	15.6	93.8	96.32	98.6
T-7	0.875	0.396447	51	19.3	91.7	94.2	96.7
T-8	0.875	1.10355	59	30.2	86.5	89.62	93.1
T-9	0.875	0.75	56	31.5	92.9	95.1	97.8

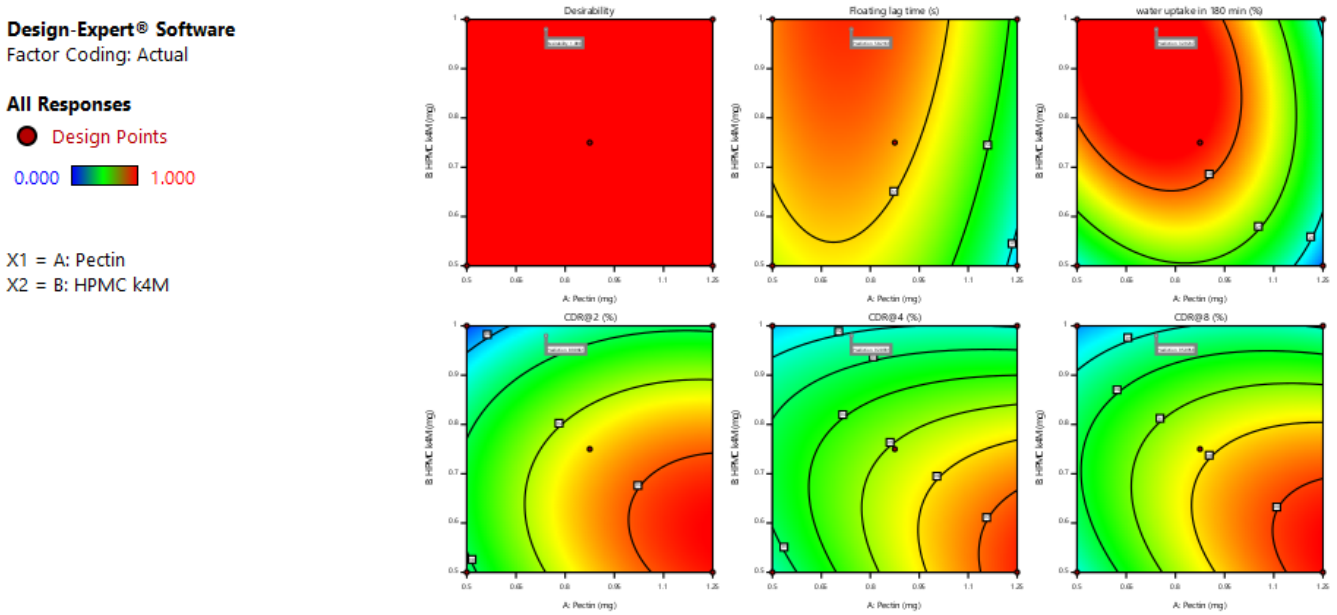

Figure 3: Contour plots of inputs on the responses

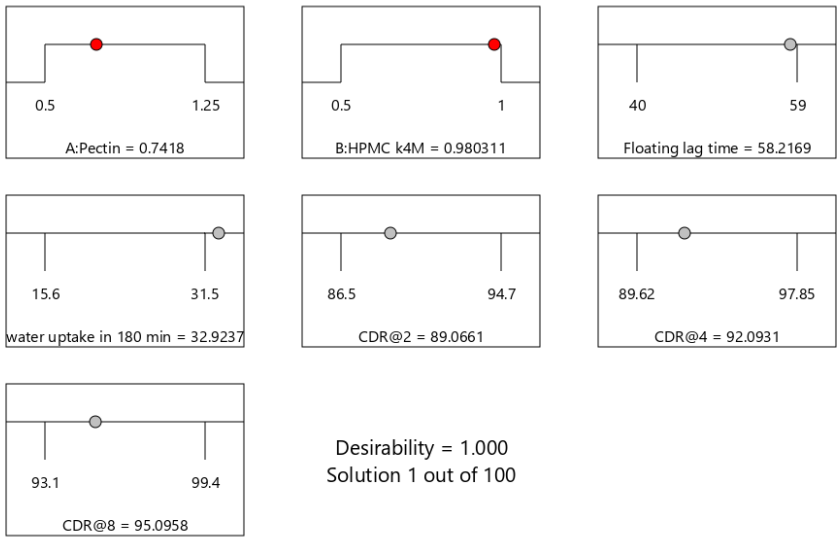

Figure 4: Desirable values of the responses

stressed storage conditions for 6 months, the VMH content within these formulations remained stable, and there were no noteworthy differences in drug discharge over this period. These results strongly indicate the stability of the *in-situ* gels, particularly T-2, under storage conditions, suggesting their potential to uphold quality and performance over time. This robust stability is crucial for ensuring the reliability and effectiveness of pharmaceutical formulations, emphasizing the suitability of T-2 for extended drug delivery applications.

CONCLUSION

In summary, this research has successfully focused on developing an *in-situ* floating gelation system, offering a promising solution to challenges associated with conventional drug delivery methods. The systematic exploration of various formulation parameters has yielded significant results, showcasing the potential of this innovative approach. Introducing a cohesive gel matrix into the stomach, leading to the formation of a floating gel *in-situ*, presents several advantages. Notably, T-2 trials have emerged as standout performers, demonstrating immediate gelation, prolonged flotation time, consistent active ingredient content, and favorable gel strength. These formulations exhibited superior water absorption, controlled and extended drug discharge, and a density conducive to flotation and extended gastric retention. These comprehensive findings align seamlessly with the research objectives, affirming the effectiveness and significance of the developed formulation. The research outcomes contribute valuable insights to the field, emphasizing the potential of gastroretentive *in-situ* gelation systems to significantly enhance drug delivery and bioavailability. The results highlight improved drug delivery competence, extended drug discharge, enhanced gastric retention, and optimized therapeutic efficacy. In essence, the study underscores the promising performance of this innovative drug delivery system, paving the way for advancements in drug delivery technologies and their potential applications in therapeutic contexts.

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