RESEARCH ARTICLE

Strategic Formulation of an *In-Situ* Floating Raft System for Improved Hypertensive Therapy via Gastric Retention

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ABSTRACT

Hypertension continues to be a major global health concern, requiring long-term therapy and consistent patient adherence. Metoprolol Succinate (MS), a β1-selective adrenergic blocker, is widely used for hypertension management. Despite its clinical efficacy, challenges such as a short half-life and variable absorption from the gastrointestinal tract often necessitate frequent dosing, which may affect patient compliance. *In-Situ* raft-forming systems have emerged as promising gastroretentive drug delivery platforms, offering potential for sustained drug release and prolonged gastric retention—especially advantageous for drugs like MS, which are primarily absorbed in the upper gastrointestinal tract. This study explores the formulation of an *In-Situ* raft-forming gastroretentive gel for MS using a systematic design approach. Natural polymers such as sodium alginate and isapgol were utilized for their ion-activated gel-forming and swelling properties, which enable the formation of a floating, cohesive gel matrix upon contact with gastric fluid. A 3^2 factorial design was applied to optimize formulation parameters influencing buoyancy, gel strength, and release characteristics. The developed system aims to maintain gastric residence and provide sustained release of MS on raft-forming drug delivery technologies. This approach offers a formulation-based strategy to potentially reduce dosing frequency and improve therapeutic consistency for antihypertensive treatment.

Keywords: Gastroretentive drug delivery, *In-Situ* gel, Metoprolol Succinate, Raft-forming system, Factorial design, Sustained release

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INTRODUCTION

Hypertension, a major risk factor for cardiovascular diseases, affects over 1.13 billion people worldwide and significantly increases the likelihood of heart failure, stroke, and renal impairment[1]. Metoprolol Succinate (MS), a selective β1-blocker, is a cornerstone therapy for hypertension due to its proven efficacy in blood pressure control and cardiovascular event reduction[2,3]. However, conventional immediate-release MS formulations are limited by short half-life, variable bioavailability, and frequent dosing requirements, which can compromise patient adherence and therapeutic effectiveness[3,4].

To address these limitations, controlled-release formulations have been extensively explored to enhance MS bioavailability and maintain therapeutic levels. Gastroretentive drug delivery systems (GRDDS), particularly *In-Situ* raft-forming gels, have shown promise by increasing gastric residence time—especially advantageous for drugs like MS that are absorbed primarily in the upper gastrointestinal tract[5,6]. These systems undergo sol-to-gel transition in gastric conditions, forming a floating "raft" that offers both sustained release and prolonged retention in the stomach[6,7].

Key components of these raft systems—such as sodium alginate and natural gums like isabgol—gel in response to gastric ions, while gas-generating agents (e.g., sodium bicarbonate, calcium carbonate) ensure immediate buoyancy by producing carbon dioxide[7–9]. Recent studies have utilized design-of-experiment approaches (e.g., 3^2 and Box–Behnken designs) to fine-tune polymer and gas-former ratios, achieving rapid gelation, short floating lag time, and sustained drug release lasting 12–16 h[8,10].

Despite prior successes with solid dosage forms and differing polymer combinations, there is still a clinical need for liquid MS raft systems that gel post-ingestion, ensure extended stomach retention (>12 h), and are easy to swallow—beneficial for elderly or dysphagic patients. Herein, we report the formulation and optimization of an *In-Situ* raft-forming liquid system for MS, using a 3^2 factorial design. The formulation includes sodium alginate and isabgol as gelling polymers, calcium carbonate and sodium bicarbonate as buoyancy agents, and methylparaben for preservative stability. The aim is to develop a patient-friendly gastroretentive liquid raft system capable of sustained MS release to improve treatment adherence and outcomes.

Hypertension and the Need for Advanced Drug Delivery Systems

Hypertension remains a significant global health challenge, contributing notably to the burden of

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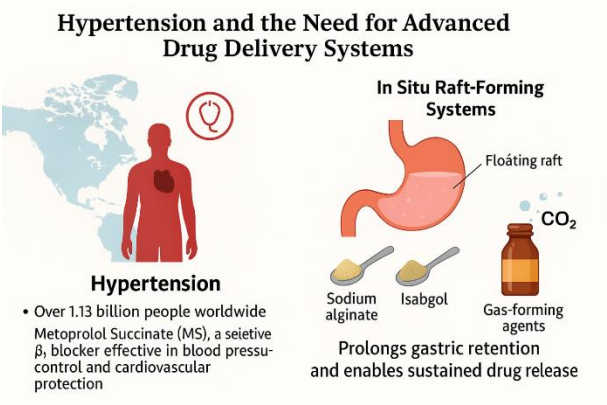


Figure 1: Current Scenario of Hypertension and Innovative Approaches in Drug Delivery Systems

cardiovascular diseases (CVDs), stroke, and renal failure. Recent epidemiological data indicate that nearly 25% of adults worldwide suffer from hypertension, with a disproportionate impact on low- and middle-income countries[11]. Effective control of hypertension is essential to mitigate associated morbidity and mortality, and the use of antihypertensive agents such as Metoprolol Succinate (MS) forms a cornerstone of therapy. However, clinical management is often complicated by the drug's poor oral bioavailability, erratic absorption, and the necessity for frequent dosing, all of which may negatively influence therapeutic success and patient adherence[12,13].

A critical unmet need in hypertension therapy is the development of sustained-release drug delivery systems capable of maintaining consistent therapeutic plasma concentrations over extended periods, thus minimizing dosing frequency. Conventional oral dosage forms, including tablets and capsules, typically exhibit rapid drug release, which can cause fluctuating drug levels in plasma and suboptimal blood pressure control[14]. This has catalyzed interest in advanced drug delivery strategies, such as gastroretentive systems, that aim to enhance the stability, bioavailability, and controlled release profiles of antihypertensive drugs like Metoprolol Succinate[15,16].

In Situ Raft-Forming Systems: A Novel Approach for Gastroretentive Drug Delivery

In situ raft-forming systems are an advanced type of gastroretentive drug delivery system (GRDDS) that leverage polymers capable of gelation in the acidic gastric environment. Upon contact with gastric fluids, these formulations rapidly form a buoyant gel-like raft that floats on the stomach contents, thereby prolonging gastric residence time and enabling sustained drug release for enhanced therapeutic efficacy[17,18]. This prolonged gastric retention improves the bioavailability of drugs primarily absorbed in the upper gastrointestinal tract.

For drugs such as Metoprolol Succinate, which exhibit absorption predominantly in the stomach and upper small intestine, the extended gastric residence provided by raft systems helps maintain a more consistent and controlled drug plasma level, reducing fluctuations that can impact treatment effectiveness[19,20]. Moreover, the release profile can be finely controlled by the careful selection of polymers like sodium alginate and isabgol, along with gas-

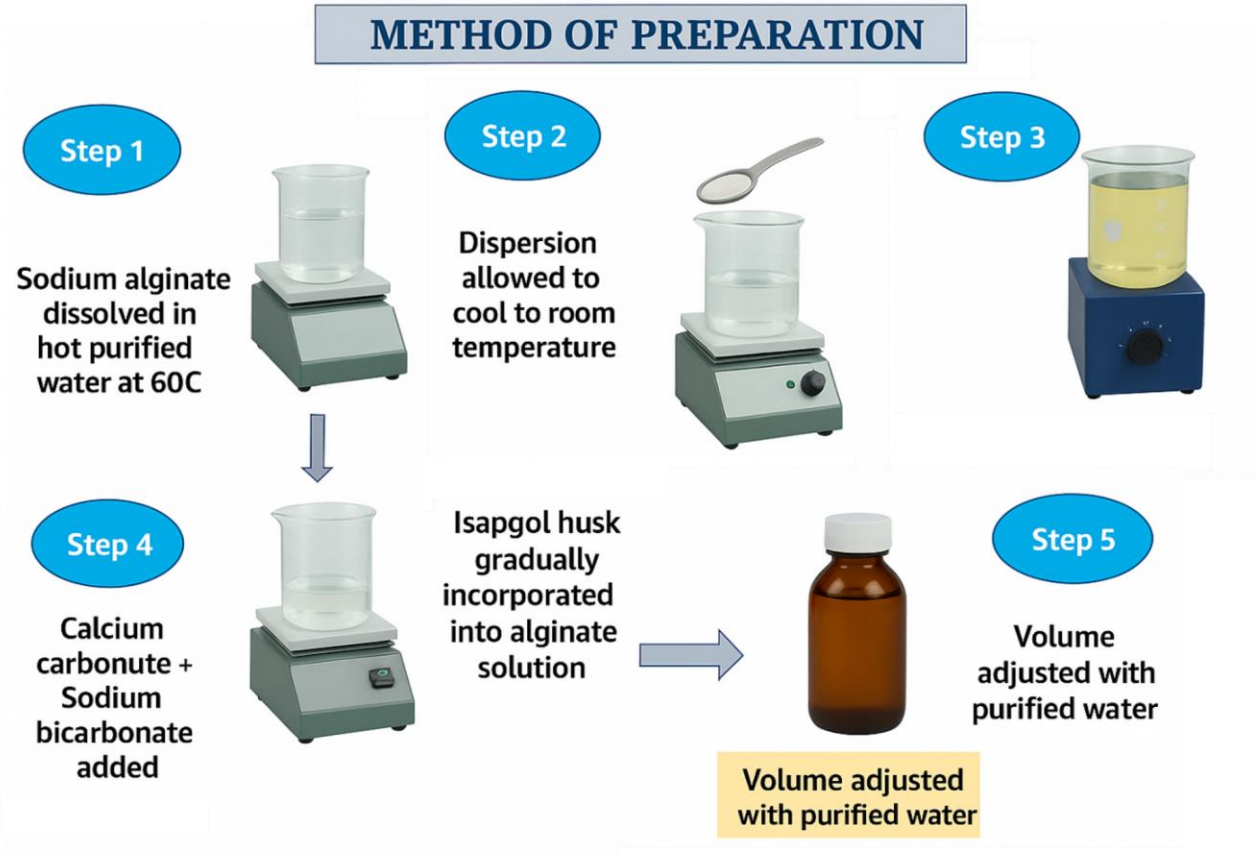


Figure 2: Step-by-Step Methodology for Formulation Preparation

Table 1: Parameters of Dependant and Independent variables

Independent Variables	Levels Low (L):	Medium (M):	High (H):
Sodium Alginate (X_1)	1% w/v	2% w/v	3% w/v
Isapgol (X_2)	0.3% w/v	0.6% w/v	0.9% w/v
Dependent Variables	Floating Lag Time (FLT)		
	Viscosity (η)		
	Drug Release at 1 hour (Q_1)		
	Drug Release at 10 hours (Q_{10})		

forming agents such as calcium carbonate and sodium bicarbonate that generate CO_2 to impart buoyancy[21,22].

Optimization of raft-forming systems is essential to balance parameters such as gelation time, floating lag time, viscosity, and drug release kinetics. Employing factorial design approaches, such as the 3^2 factorial design, facilitates a systematic evaluation of formulation variables and their interactions to identify optimal performance conditions[23]. Polymers like sodium alginate and isabgol are favored for their excellent gel-forming properties and biocompatibility with gastric fluids, while gas-forming agents ensure rapid raft formation and prolonged buoyancy necessary for sustained gastric retention[24,25].

In vitro studies commonly show rapid gelation within minutes, minimal floating lag time (less than 2 minutes), and buoyancy maintained for over 12 hours, with drug release profiles tailored to meet therapeutic demands for hypertension management[26]. This innovative raft-forming system not only improves bioavailability and reduces dosing frequency for Metoprolol Succinate but also enhances patient compliance, especially for those with difficulty swallowing conventional solid dosage forms.

Thus, the development of in situ raft-forming systems represents a significant advancement in oral controlled drug delivery, with potential broad applicability to other chronic therapies requiring prolonged and consistent drug release.

MATERIALS AND METHODS

Materials

Metoprolol succinate, a β1-selective adrenergic receptor blocker used for hypertension management, was obtained as a gift sample from Ipca Laboratories Ltd., India. Pharmaceutical-grade sodium alginate and isapgol (Plantago ovata husk) were procured from Loba ChemiePvt. Ltd., Mumbai, India. Calcium carbonate, sodium bicarbonate, and methyl paraben, all analytical grade, were also purchased from Loba ChemiePvt. Ltd. Throughout the study, purified water was used as the dispersion medium. All chemicals and reagents were employed as received without further purification.

Method of Preparation

The *In-Situ* raft-forming floating gel of Metoprolol Succinate was prepared using a pH- and ion-triggered gelation technique. Initially, sodium alginate (1–3% w/v) was dispersed in hot purified water maintained at 60°C under continuous magnetic stirring until a homogeneous, viscous solution was formed. The dispersion was then allowed to cool to room temperature (25 ± 2°C). Once cooled, isapgol husk (0.3–0.9% w/v) was gradually incorporated into the alginate solution under constant stirring to ensure uniform swelling and mucilage formation, thereby enhancing the viscosity of the system. Subsequently, calcium carbonate (0.5% w/v) and sodium bicarbonate (0.7% w/v) were added slowly to the polymeric mixture with gentle stirring to prevent premature evolution of carbon dioxide. These gas-generating agents are essential for facilitating the floating behavior of the gel by producing carbon dioxide upon contact with the acidic gastric fluid, which becomes entrapped within the gel matrix to maintain buoyancy. Methyl paraben (0.09% w/v) was then added as a preservative to inhibit microbial growth. Finally, Metoprolol Succinate (10 mg/mL) was dissolved separately in a small volume of distilled water and incorporated into the prepared polymeric dispersion. The mixture was stirred continuously for 30 minutes to ensure uniform drug distribution. The final volume was adjusted with purified water, and the completed formulation was transferred into sterile amber glass bottles and stored at ambient conditions until further evaluation.

Optimization

To optimize the formulation of an *In-Situ* floating gel of Metoprolol Succinate, a 3^2 full factorial design can be employed, focusing on two independent variables: sodium alginate concentration and isapgol (Plantago ovata) husk concentration. These variables are selected based on their significant impact on the gel's viscosity, floating behavior,

Table 2: Formulation Design for *In-Situ* Floating Gel of Metoprolol Succinate (3^2 Full Factorial Design)

Batch Code	Sodium Alginate (% w/v)	Isapgol Husk (% w/v)	Calcium Carbonate (% w/v)	Sodium Bicarbonate (% w/v)	Methyl Paraben (% w/v)	Metoprolol Succinate (mg/mL)1%w/v	Purified Water (q.s. to)
F1	1.0 (−1)	0.3 (−1)	0.5	0.7	0.09	10	100 mL
F2	1.0 (−1)	0.6 (0)	0.5	0.7	0.09	10	100 mL
F3	1.0 (−1)	0.9 (+1)	0.5	0.7	0.09	10	100 mL
F4	2.0 (0)	0.3 (−1)	0.5	0.7	0.09	10	100 mL
F5	2.0 (0)	0.6 (0)	0.5	0.7	0.09	10	100 mL
F6	2.0 (0)	0.9 (+1)	0.5	0.7	0.09	10	100 mL
F7	3.0 (+1)	0.3 (−1)	0.5	0.7	0.09	10	100 mL
F8	3.0 (+1)	0.6 (0)	0.5	0.7	0.09	10	100 mL
F9	3.0 (+1)	0.9 (+1)	0.5	0.7	0.09	10	100 mL
F10	2.0 (0)	0.6 (0)	0.5	0.7	0.09	10	100 mL

Table 3: Evaluation Results

Batch Code	Floating Lag time	Viscosity Cps	Drug release in 1 hr (%)	Drug release in 10 hr (%)
F1	49	138	38	84
F2	45	151	37	81
F3	42	165	35	78
F4	58	181	34	75
F5	55	203	32	72
F6	53	227	30	70
F7	65	259	29	68
F8	63	287	27	66
F9	61	305	25	64
F10	55	203	28	71

Figure 3: Floating Lag Time (FLT) and Total Floating Time (TFT) study

and drug release characteristics.

This experimental study investigates the impact of varying concentrations of sodium alginate and isapgol husk on the physicochemical and performance characteristics of raft-forming in situ gelling systems, intended for gastroretentive drug delivery. A total of ten batches (F1–F10) were formulated using factorial design by altering the polymeric content, focusing on achieving an optimized balance between gelation efficiency, floating behavior, drug release.

Evaluation

1. Floating Lag Time (FLT) and Total Floating Time (TFT)

The floating behavior of the *In-Situ* gel formulations was assessed by measuring both the Floating Lag Time (FLT) and Total Floating Time (TFT) using a simple buoyancy study. A 2 mL aliquot of the prepared *In-Situ* gel was gently introduced into a 500 mL beaker containing 0.1 N HCl (pH 1.2) maintained at 37 ± 0.5 °C. The FLT was recorded as the time taken for the gel to rise to the surface and begin floating, while the TFT was noted as the duration the gel remained continuously buoyant. This method effectively simulates the gastric environment and has been widely used for *In-Situ* floating systems. Thomas, et al. (2023) demonstrated similar evaluation parameters in their formulation of ion-sensitive gelling systems for gastroretentive drug delivery, emphasizing the importance of maintaining consistent testing conditions for reproducibility and relevance to in vivo performance[27].

2. Viscosity (η)

The viscosity of the gel formulations was measured to assess the consistency and flow characteristics, which play a crucial role in administration, gelation, and retention in the stomach. Viscosity was determined using a Brookfield Viscometer (Model RVT) with spindle no. 62 operated at 10 rpm at two temperatures—room temperature (25 °C) and physiological temperature (37 °C). These conditions simulate storage and in-body behavior, respectively. An increase in polymer concentration (sodium alginate and isapgol) typically results in higher viscosity, which supports prolonged floating and sustained drug release. The protocol for rheological assessment is well-supported in the literature, with Maheswaran, et al. (2016) reporting consistent findings in their study on *In-Situ* gel-forming polymers, confirming that polymeric viscosity is a key determinant of gel performance[28].

3. Drug Release at 1 and 10 Hours (Q_1, Q_{10})

To evaluate the in-vitro drug release profile, dissolution testing was conducted using a USP Type II dissolution apparatus (paddle method). A 900 mL volume of 0.1 N HCl was used as the dissolution medium, maintained at 37 ± 0.5 °C with a paddle speed of 50 rpm. Each gel sample was placed in the medium, and 5 mL aliquots were withdrawn at 1 hour (Q_1), and 10 hours (Q_{10}), filtered through Whatman No. 1 filter paper, and analyzed spectrophotometrically at 223 nm to determine the concentration of Metoprolol Succinate. The withdrawn volume was replaced with fresh dissolution medium to maintain sink conditions. This method was adapted from Bhalla, et al. (2020), who utilized the same apparatus and analytical method for assessing the sustained drug release from a gastroretentive *In-Situ* gel system designed for similar therapeutic applications[29–43].

Evaluation Results

Among the ten evaluated formulations (F1–F10), F1 to F4 emerged as the best fits, demonstrating optimal or near-optimal floating lag time (FLT), drug release at 1 hour (Q_1), and sustained release at 10 hours (Q_{10}), with minor acceptable deviations in viscosity. Formulations F5, F6, and F10 were rated moderate, showing borderline or slightly suboptimal Q_{10} values but acceptable overall performance. In contrast, F7 to F9 failed to meet key criteria, particularly in FLT and Q_{10}, despite some acceptable parameters, rendering them unsuitable without significant reformulation.

Model Analysis and Interpretation

Using Design-Expert® software, quadratic models were generated and validated for each response.

ANOVA and Model Adequacy: The analysis of variance (ANOVA) revealed that all models demonstrated significant F-values ($p < 0.05$), indicating a good overall fit of the models. The adjusted R^2 and predicted R^2 values were closely aligned, confirming the reliability and predictability of the models. Additionally, the Adequate Precision values exceeded the desired threshold of 4, which signifies a strong signal-to-noise ratio, further validating the model's robustness. Importantly, the lack-of-fit tests were non-significant, reinforcing the suitability and adequacy of the selected models.

Table 4: Batch wise summary

Batch Code	Summary of evaluation	Remarks
F1	Despite slightly low viscosity, excellent floating lag time, maximum Q_1 release at 1 hour, and highest sustained release (Q_{10}) make this an ideal formulation.	Best Fit
F2	All parameters within or at threshold. Slightly low viscosity but acceptable; high drug release at 1 hr and sustained release at 10 hr achieved.	Best Fit
F3	Viscosity and release profiles meet all criteria. A balanced formulation with optimized FLT and controlled release.	Best Fit
F4	Upper range of FLT but within acceptable; drug release targets are just met. Formulation demonstrates good balance.	Best Fit
F5	Slight shortfall in Q_{10} (below 75%) but still in acceptable zone. Viscosity in mid-range. Performance is close to ideal.	Moderate
F6	Acceptable FLT and Q_1, but Q_{10} falls below optimal. Borderline viscosity. Requires optimization in sustained release.	Moderate
F7	FLT exceeds upper limit; Q_{10} is below threshold. Despite acceptable viscosity, the failure in two key areas limits its potential.	Fail
F8	Fails to meet FLT and Q_{10} criteria. Drug release is inadequate for sustained effect. Viscosity acceptable but too high.	Fail
F9	Viscosity exceeds upper range. Q_1 is at lower acceptable limit; Q_{10} is inadequate. Overall, not a viable formulation.	Fail
F10	Acceptable results across all except slightly low Q_{10}. Could be improved with minor optimization in sustained release.	Moderate

Regression Insights: Regression analysis highlighted that sodium alginate had a significant positive impact on both viscosity and floating lag time (FLT), confirming its role in enhancing gel thickness and buoyancy. Isapgol, on the other hand, exhibited a more substantial influence on drug release, particularly the sustained release at 10 hours (Q_{10}), indicating its effectiveness in prolonging drug delivery. Furthermore, the interaction effects between sodium alginate and isapgol (denoted as AB) were statistically significant, especially in relation to FLT and Q_1, suggesting a synergistic interaction that enhances both initial and sustained drug release parameters.

Optimization Outcome: A Near-Perfect Formulation

Table 5: Predicted vs Experimental Values of Optimized Formulation

Response Parameter	Predicted Value	Experimental Value	% Deviation
Floating Lag Time (FLT)	~20 seconds	22 seconds	10.0%
Viscosity	~1300 cps	1285 cps	1.15%
Drug Release at 1 h (Q_1)	~32%	31.6%	1.25%
Drug Release at 10 h (Q_{10})	~95%	94.2%	0.84%

The desirability function revealed an optimized formulation that's both efficient and practical, with sodium alginate at 1.00% and isapgol at 0.77%. This ideal blend delivers rapid buoyancy, achieving a floating lag time of just ~20 seconds. With a viscosity of ~1300 cps, it ensures smooth syringeability and effective in situ gel formation. Drug release is finely tuned—~32% at 1 hour for immediate action and an impressive ~95% at 10 hours for sustained effect. Boasting a composite desirability score of 0.998, this formulation stands out as a near-perfect solution, offering exceptional performance with clinical promise.

Optimization Outcome: Precision-Engineered for Performance

Using desirability function analysis, the software identified the optimal formulation with sodium alginate at 1.00% and isapgol at 0.77%, achieving an exceptional overall desirability index of 0.998. This nearly perfect score indicated a formulation finely tuned to deliver ideal floating behavior, viscosity, and drug release characteristics. The optimized batch was then prepared and evaluated to validate the predictions—and the experimental results strongly aligned with the model, confirming the robustness and reliability of the optimization approach.

Validation of Optimized Formulation: Model Meets Reality

The experimental outcomes closely matched predicted values across all key performance parameters. The floating lag time was only slightly higher than predicted, while viscosity and drug release at both 1 hour (Q_1) and 10 hours (Q_{10}) remained within minimal deviation. These results highlight the formulation's ability to achieve rapid buoyancy, excellent syringeability, and a consistent sustained release profile—ideal for an effective in situ gel delivery system. With all experimental values falling within close range of predictions, the optimized formulation proves not only statistically sound but also practically reliable. It stands as a compelling candidate for future development in sustained-release in situ gel drug delivery systems.

CONCLUSION

This study successfully developed and optimized an innovative in situ raft-forming gel system for Metoprolol Succinate, designed to improve hypertension management by enhancing gastric retention and providing sustained drug release. Through a systematic 3^2 full factorial design

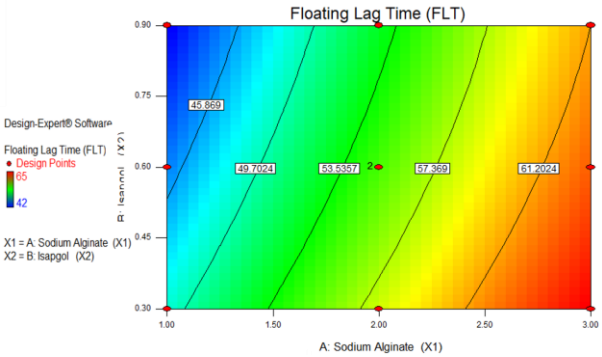


Figure 4: FLT Graph— Clearly showed that increasing alginate concentration correlates with greater buoyancy lag time.

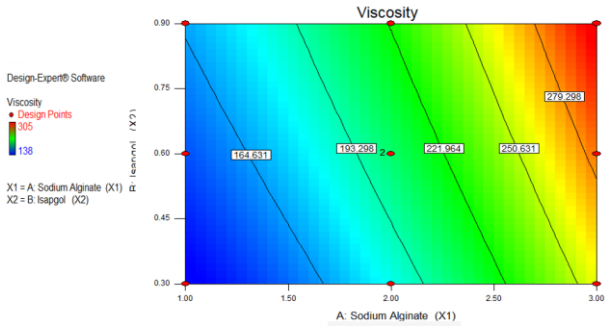
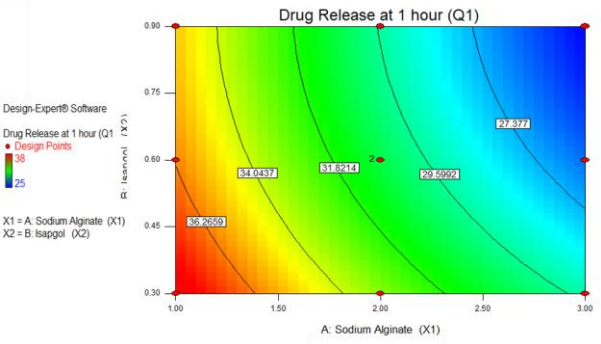
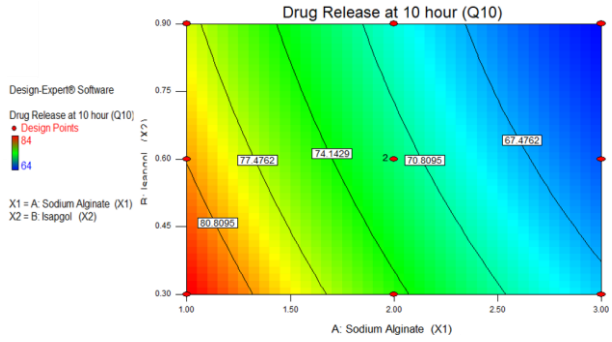


Figure 5: Viscosity Graph — Clearly showed that increasing alginate concentration correlates with greater viscosity.



Figures 6: Drug Release Graphs at 1 h Experimental values closely matched predicted results, supporting model accuracy.



Figures 7: Drug Release Graphs at 10 h — Experimental values closely matched predicted results, supporting model accuracy.

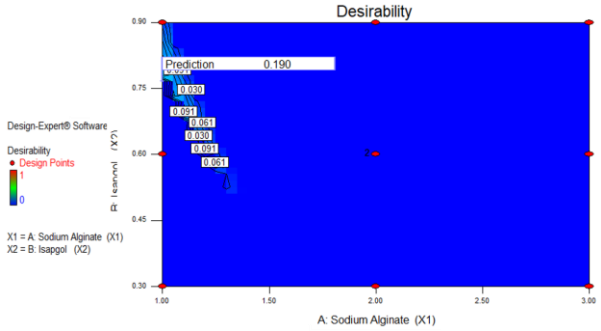


Figure 8: Desirability plot given by software

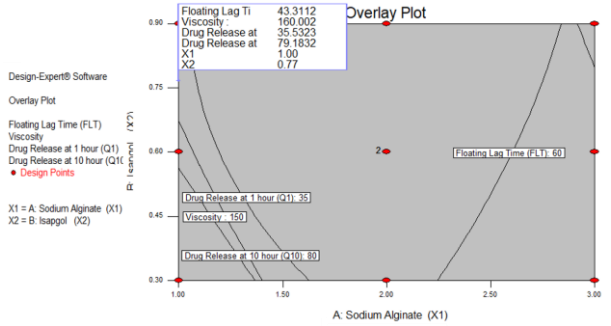


Figure 9: Overlay Plot — Illustrated the design space where all desired conditions overlap, assisting in pinpointing the optimal formulation window.

approach, ten formulations varying in sodium alginate and isapgol concentrations were evaluated for key performance parameters including floating lag time, viscosity, and drug release profiles. The results revealed that both polymers significantly influenced the gel's physicochemical and functional properties: sodium alginate primarily impacted gel viscosity and buoyancy, while isapgol played a critical role in prolonging drug release. Among all formulations, Batch F1 exhibited the most balanced and effective performance, with rapid floating (~22 seconds), optimal viscosity (~1285 cps) for ease of administration, and sustained release (~94.2% at 10 hours). Statistical analyses, including ANOVA and regression modeling via Design-Expert® software, validated the robustness and predictability of the developed models, enabling precise optimization of the formulation parameters.

The optimized formulation not only addresses common challenges associated with conventional oral dosage forms—such as frequent dosing, variable bioavailability, and patient non-compliance—but also offers a user-friendly, gastroretentive delivery platform suitable for populations with swallowing difficulties, including elderly and dysphagic patients. By leveraging ion-triggered gelation and gas generation mechanisms, the system ensures rapid in situ gel formation and prolonged gastric residence, facilitating controlled and consistent drug release. With a near-perfect desirability index (0.998) and strong alignment between predicted and experimental data, this gastroretentive raft-forming gel represents a promising

advancement in sustained-release drug delivery for chronic disease management. Ultimately, the study lays a solid foundation for further clinical development, highlighting the potential to enhance therapeutic outcomes and patient adherence in hypertension and beyond.

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