RESEARCH PAPER

Formulation And Evaluation Of Gastro-Retentive Oral Floatable In-Situ Gel Of Ranolazine For Sustained Drug Release

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Abstract

The present study aimed to develop and evaluate a gastro-retentive oral floatable in-situ gel formulation of Ranolazine for sustained drug delivery and improved bioavailability. In-situ gel systems remain in liquid form before administration and undergo sol-to-gel transition in the gastric environment, thereby enhancing gastric retention and providing controlled drug release. In this study, pectin and HPMC K4M were used as primary polymers to formulate nine batches (F1–F9) of Ranolazine in-situ gel using the ion-activated gelation method. Sodium citrate and calcium chloride were incorporated to regulate gelation behavior and provide ionic cross-linking.

All formulations were evaluated for physicochemical parameters including physical appearance, pH, viscosity, in-vitro gelation, floating behavior, drug content, water uptake, and in-vitro drug release. The results indicated that increasing polymer concentration significantly influenced viscosity, gel strength, floating duration, and drug release characteristics. Among all batches, formulation F8 demonstrated optimal performance with suitable pH (8.60 ± 0.01), high viscosity (20768 ± 50 cP), rapid gelation (+++), prolonged floating time (14 hours), and maximum drug content (98.00 ± 0.18%). The formulation exhibited sustained drug release, achieving 99.78% cumulative release within 9 hours. Release kinetic analysis revealed that drug release followed the Korsmeyer–Peppas model, indicating anomalous transport mechanisms.

Stability studies performed for three months showed no significant changes in physicochemical properties or drug release behavior. In-vivo pharmacokinetic evaluation in rabbits demonstrated enhanced bioavailability of the optimized formulation, with higher AUC (1764.08 ng·h/ml) and prolonged Tmax (6 h) compared to the reference product. The findings confirm that the optimized gastro-retentive in-situ gel formulation of Ranolazine provides sustained drug release, prolonged gastric retention, and improved systemic exposure, making it a promising approach for effective oral drug delivery.

Keywords: Ranolazine, In-situ gel, Gastro-retentive drug delivery, Oral floatable system, Sustained release, Pectin, HPMC K4M, Pharmacokinetics.

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1. Introduction

The development of in-situ gelation systems has received considerable attention in the last few years. In situ gel delivery systems are capable of continuous drug release while maintaining a constant drug concentration in the blood plasma. In- situ gel systems are liquid at room temperature but converted into gels when they come into contact with physiological body fluids. Gel formation depends on many factors, such as temperature modulation, pH changes, presence of ions, ultraviolet radiation, electrical sensitivity and enzymes that release the active substance in-situ gels are suspensions or solutions that, after reaching a certain point, undergo gelation [1]. is Physical and chemical changes including body fluid exposure or UV exposure external triggers ion concentration, pH, temperature, availability of specific molecules or ions and others, a steady state plasma drug concentration profile can be generated from in situ gels using sustained drug release. So that the drug is effectively absorbed from the gel and improves bioavailability.

Compared to conventional drug formulations, in-situ gel delivery systems have potential advantages such as simple manufacturing process, ease of administration, low frequency of administration, improved compliance and patient comfort. In-situ gels are liquid drugs that can be easily applied to sites

of absorption. A firm gel forms at the site of drug absorption [2]. It is able to prolong the release time of the drug. Natural and synthetic polymers can be used to form gels in situ. In situ gel formation is induced by one or a combination of different stimuli, such as pH-sensitive, temperature- sensitive and ionic cross-linking polymers. Recent advances in peritoneal route and liquid in situ oral gels allowed us to exploit changes in physical specificity in different regions of the GI tract to enhance drug absorption and improve bioavailability. Polymer solutions known as gels in situ, depending on the temperature of the application site, ionic strength or pH and the formation of a gel system. The mechanism of this formation process uses polymeric materials in response to external stimulation, therefore, under physiological conditions, the polymer undergoes a reversible phase transition from of a solution to a gel by changing its dispersion or conformational state emphasizing the advantages of fluids and gels, these gels vary widely in their application prospects for drug delivery such as oral administration, ocular administration, nasal systems and implants [3].

2. Formulation Study and Development

ngredients (gm)	**Formulation Code**								
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
Ranolazine	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Pectin	1	1	1	1	1.5	1.5	1.5	1.5	2
HPMC K4M	0.1	0.2	0.3	0.4	0.4	0.5	0.6	0.7	0.8
Sodium Citrate	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25
Calcium Chloride	0.065	0.065	0.065	0.065	0.065	0.065	0.065	0.065	0.065
Methyl Paraben	0.09	0.09	0.09	0.09	0.09	0.09	0.09	0.09	0.09
Propyl Paraben	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01
Deionized Water	Up to 50 ml	Up to 50 ml	Up to 50 ml	Up to 50 ml	Up to 50 ml	Up to 50 ml	Up to 50 ml	Up to 50 ml	Up to 50 ml

3. Method of Preparation Preparation of In Situ Gelling Systems

In situ gelling systems were prepared using varying concentrations of pectin and HPMC K4M to study their effect on gelation behavior and drug release characteristics. Initially, the required quantities of pectin were dispersed in cold deionized water and stirred continuously using a magnetic stirrer until a uniform solution was obtained. Separately, HPMC K4M at varying concentrations was dissolved in water and then gradually added to the pectin solution with continuous stirring to ensure proper mixing and homogeneity.

To the above polymeric solution, sodium citrate (0.5% w/v) and calcium chloride (0.13% w/v) were added and dissolved completely. Sodium citrate acted as a complexing agent to prevent premature gelation, while calcium chloride served as a source of calcium ions required for gel formation. Subsequently, Ranolazine pure drug (2.5 g) was added to the solution and stirred until it was uniformly dispersed[4].

4 Evaluation of Gastro-Floatable In-Situ Gel Formulations

Physical Appearance

All prepared Ranolazine in-situ gel formulations were visually inspected for color, clarity, homogeneity, and consistency under adequate lighting against a white background. The absence of particulate matter, turbidity, phase separation, or precipitation confirmed physical stability and uniformity.

pH Measurement

The pH of the formulations was determined using a calibrated digital pH meter (standardized with pH 4.0 and 7.0 buffers). A 1% w/v dispersion was prepared in distilled water, and measurements were performed in triplicate. The mean pH values were found to be within the acceptable range for gastric administration.

Viscosity Measurement

Viscosity was measured using a Brookfield Viscometer (DV-II+ Pro) with spindle No. 02 at 50 rpm. Readings were recorded after 3 minutes when torque values were within 70–80%. The study evaluated the effect of polymer concentration on flow behavior and gelation characteristics.

In-Vitro Gelation Study

Gelation ability was assessed by adding 10 mL of formulation to 500 mL of 0.1 N HCl (pH 1.2). Gel formation time and duration were visually observed and graded as (+), (++), or (+++) based on onset and

integrity of gel formed under simulated gastric conditions.

In-Vitro Floating Study

Floating behavior was evaluated using USP Dissolution Apparatus Type II (paddle method) containing 0.1 N HCl (pH 1.2) at 37 ± 0.5 °C and 50 rpm. Floating lag time and total floating duration were recorded to assess gastroretentive potential.

Drug Content Estimation

Drug content was determined spectrophotometrically at 272 nm after appropriate dilution with 0.1 N HCl. Samples were sonicated, filtered, and analyzed against a standard calibration curve. Percentage drug content was calculated using:

$$\%\ Drug\ Content = \frac{\text{Practical Drug Content}}{\text{Theoretical amount of drug}} \times 100$$

Water Uptake Study

Swelling behavior was evaluated by measuring the weight gain of the formed gel in acidic medium over 6 hours. Percentage water uptake was calculated using:

$$\%\ Water\ Uptake = \frac{(W2-W1)}{W1} \times 100$$

Where,

W_1 = Initial weight of gel

W_2 = Weight of gel after water uptake

In-Vitro Drug Release

Drug release was studied using USP Apparatus II in 900 mL of 0.1 N HCl (pH 1.2) at 37 ± 0.5 °C and 50 rpm for 10 hours. Samples were withdrawn at predetermined intervals and analyzed at 272 nm. Studies were conducted in triplicate.

Release Kinetics

Release data were fitted to Zero-order, First-order, Higuchi, and Korsmeyer–Peppas models. The model with the highest R^2 value was considered the best fit. The release exponent (n) from the Korsmeyer–Peppas model indicated the mechanism of drug release (Fickian diffusion, anomalous transport, or Case-II transport).

Stability Studies

Stability studies were conducted as per ICH guidelines under accelerated conditions (40 ± 2 °C/75 ± 5% RH) for six months. The optimized formulation was evaluated for pH, viscosity, gelation behavior, floating properties, and in-vitro drug release. No significant changes were observed, indicating good stability and suitability for further development.

In-Vivo Pharmacokinetic Evaluation of Optimized Formulation and Reference Product [5].

The pharmacokinetic study was conducted to compare the oral bioavailability of the optimized Ranolazine gastro-retentive in-situ gel with a marketed reference product. The objective was to evaluate systemic drug exposure and validate the in-vitro performance with in-vivo data.

Dose Calculation and Ethical Approval

The animal equivalent dose was calculated from the human dose (80 mg/60 kg) using CDER-recommended body surface area conversion:

The calculated rabbit dose was **4.15 mg/kg**, corresponding to approximately **8.3 mg per rabbit** (1.8–2 kg body weight).

The study was approved by the Institutional Animal Ethical Committee (CPCSEA approval no. 1566/PO/Re/S/11/CPCSEA) and conducted in accordance with CPCSEA guidelines.

Study Design

A parallel study design was employed using **healthy New Zealand white rabbits** (1.8–2 kg), divided into two groups (n = 6 each):

- **Group I (Test):** Optimized Ranolazine in-situ gel formulation
- **Group II (Reference):** Marketed formulation (tablet powder dispersed in water)

Animals were fasted for 12 hours before and after dosing, with free access to water. Formulations were administered orally using gavage.

Blood Sampling and Analysis

Blood samples (1–2 mL) were collected from the marginal ear vein at predetermined intervals. Plasma was separated by centrifugation (5000 rpm, 10 min, 4°C) and stored at −20°C until analysis.

Plasma Ranolazine concentrations were determined using a validated bioanalytical method. Pharmacokinetic parameters were calculated using non-compartmental analysis.

Pharmacokinetic Parameters Evaluated [6].

The following parameters were determined from plasma concentration–time profiles:

- **Cmax (ng/mL):** Maximum plasma concentration
- **Tmax (h):** Time to reach Cmax
- **Kel (h^{-1}):** Elimination rate constant
- **t½ (h):** Elimination half-life

- **AUC_{0}–t (ng·h/mL):** Area under the curve up to last measurable concentration
- **AUC_{0}–∞ (ng·h/mL):** Total systemic exposure

Significance of the Study

Comparative evaluation of Cmax, Tmax, AUC, and t½ enabled assessment of:

- Rate and extent of absorption
- Relative bioavailability
- Bioequivalence between test and reference formulations
- Correlation of in-vitro release with in-vivo performance

The optimized in-situ gel formulation demonstrated improved gastro-retentive behavior and comparable pharmacokinetic performance relative to the marketed product, supporting its potential for enhanced therapeutic efficacy.

5. Evaluation of Formulation [7,8].

Physical Appearance and pH

All pectin-based in-situ gel formulations of Ranolazine were evaluated for clarity, homogeneity, gelation behavior, and pH prior to administration. Visual inspection showed a uniform white, cream-like appearance with smooth consistency. No particulate matter, phase separation, sedimentation, or air entrapment was observed, confirming proper polymer dispersion and formulation stability.

All formulations exhibited rapid sol-to-gel transition upon exposure to 0.1 N HCl (pH 1.2), forming coherent and stable gels without fragmentation. Gelation occurred due to ionic cross-linking of pectin and sodium alginate with calcium ions under acidic conditions, indicating suitability for gastro-retentive delivery.

The pH values ranged from **8.09 ± 0.01 to 8.60 ± 0.01**, indicating mildly alkaline formulations. This alkaline pH prevents premature gelation during storage while ensuring rapid gel formation in the stomach. Low standard deviation values (≤ 0.03) confirmed excellent reproducibility. Among all batches, **F8 (8.60 ± 0.01)** showed the highest pH, suggesting improved sol stability before administration.

Viscosity Measurement

Viscosity was measured using a Brookfield viscometer at 30 rpm. Viscosity increased progressively from **10978 ± 42 cps (F1)** to **20768 ± 50 cps (F8)**, demonstrating a polymer concentration-dependent increase in rheological strength. This rise is attributed to enhanced polymer chain entanglement and intermolecular interactions at higher polymer concentrations.

Torque values showed minimal variability (SD ≤ 0.27), indicating uniform rheological behavior and absence of phase separation.

Formulation **F8** exhibited the highest viscosity (20768 ± 50 cps) and torque (83.94 ± 0.26), reflecting a dense and robust polymeric network. The formulation maintained an optimal balance between pourability in the sol state and strong gel integrity after gelation, making it suitable for sustained gastro-retentive drug delivery.

In-Vitro Gelation Study

Gelation capacity was evaluated in simulated gastric fluid (pH 1.2) and graded as:

- (+) Gel formed slowly and dispersed rapidly
- (++) Gel formed immediately and remained for a few hours
- (+++) Gel formed immediately and remained for an extended period

Formulations **F7, F8, and F9** demonstrated (+++) gelation capacity, forming strong and intact gels that persisted for more than 12 hours. The enhanced gel strength is attributed to higher pectin concentration, which promotes stronger ionic cross-linking and formation of a dense three-dimensional matrix.

Among these, **F8** showed the best overall performance, combining rapid gelation, prolonged integrity, optimal viscosity, alkaline pH stability, and previously established buoyancy characteristics.

In-Vitro Floating Study

The floating behavior of Ranolazine in-situ gel formulations was evaluated in 0.1 N HCl (pH 1.2) at 37 ± 0.5 °C. Floating lag time and total floating duration were recorded as key indicators of gastro-retentive potential.

All formulations exhibited rapid buoyancy, with lag times ranging from **50.65 ± 0.17 sec (F6)** to **60.78 ± 0.12 sec (F8)**, indicating floatation within approximately one minute. Floating duration ranged from **10.00 ± 0.05 h (F1)** to **14.00 ± 0.06 h (F8)**. Increased polymer concentration improved gel strength and CO_2 entrapment, thereby prolonging buoyancy.

Formulation **F8** demonstrated the longest floating duration with acceptable lag time, confirming its superior gastro-retentive performance.

Drug Content Estimation

Drug content ranged from **85.00 ± 0.25% (F1)** to **98.00 ± 0.18% (F8)**, complying with pharmacopoeial limits (85–115%). Low standard deviation values (≤ 0.25%) confirmed uniform drug distribution and reproducibility.

Lower drug content in early batches (F1–F3) may be attributed to weaker gel matrices and lower polymer concentration. Increased polymer content improved drug entrapment efficiency. Formulation **F8** exhibited the highest drug content and minimal variability, indicating optimized formulation parameters and maximum drug incorporation.

Water Uptake Study

Water uptake values ranged from **2.71 ± 0.04 g/g (F1)** to **8.01 ± 0.05 g/g (F8)**. Increased polymer concentration enhanced gel hydration and swelling capacity.

Formulations F7–F9 showed high swelling behavior, with **F8** demonstrating maximum water uptake while maintaining gel integrity. Optimal swelling supports prolonged buoyancy and controlled drug diffusion without compromising mechanical stability.

In-Vitro Drug Release Study

Drug release was evaluated in 0.1 N HCl (pH 1.2). All formulations exhibited an initial burst release followed by sustained release.

Formulation **F8** showed a controlled initial release (61.14 ± 0.31%) and achieved **99.78 ± 0.19% cumulative release at 9 hours**, indicating efficient and prolonged drug delivery. In contrast, formulations with lower polymer content (F1–F3) showed slower and less sustained release due to weaker gel matrices.

The optimized release profile of F8 is attributed to balanced polymer concentration, effective cross-linking, appropriate swelling, and stable gel integrity.

Table no. 1 : In-Vitro Drug Release Study

Time (hrs)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
1	6.90 ± 0.42	8.84 ± 0.40	5.86 ± 0.38	3.21 ± 0.36	5.21 ± 0.35	6.76 ± 0.34	8.52 ± 0.33	1.14 ± 0.31	8.13 ± 0.34
2	0.46 ± 0.39	2.89 ± 0.37	8.81 ± 0.36	6.42 ± 0.35	8.73 ± 0.33	0.01 ± 0.31	5.56 ± 0.30	6.19 ± 0.28	0.73 ± 0.32
3	2.38 ± 0.38	5.42 ± 0.36	2.09 ± 0.34	8.91 ± 0.32	1.22 ± 0.31	4.73 ± 0.29	7.48 ± 0.28	8.83 ± 0.27	2.61 ± 0.30
4	5.98 ± 0.35	0.68 ± 0.33	9.16 ± 0.31	6.44 ± 0.30	7.63 ± 0.29	9.68 ± 0.28	2.32 ± 0.26	4.42 ± 0.25	2.76 ± 0.26
5	7.89 ± 0.34	3.61 ± 0.32	2.04 ± 0.30	7.52 ± 0.28	9.24 ± 0.27	3.97 ± 0.26	5.14 ± 0.24	8.38 ± 0.23	5.24 ± 0.24
6	9.78 ± 0.33	5.84 ± 0.31	4.79 ± 0.29	0.32 ± 0.27	2.11 ± 0.26	5.06 ± 0.25	8.76 ± 0.23	2.35 ± 0.22	0.12 ± 0.23
7	1.76 ± 0.32	0.63 ± 0.30	8.42 ± 0.28	3.04 ± 0.26	5.40 ± 0.25	8.75 ± 0.24	6.92 ± 0.22	8.92 ± 0.21	7.64 ± 0.21
8	3.96 ± 0.31	5.73 ± 0.29	2.35 ± 0.27	8.99 ± 0.25	1.72 ± 0.24	6.25 ± 0.23	3.66 ± 0.21	4.85 ± 0.20	5.96 ± 0.20
9	2.12 ± 0.30	3.71 ± 0.28	0.99 ± 0.26	6.15 ± 0.24	8.61 ± 0.23	5.92 ± 0.22	0.37 ± 0.21	9.78 ± 0.19	0.21 ± 0.20

Figure 1: Cumulative drug profile of in situ gel batch F1 to F3

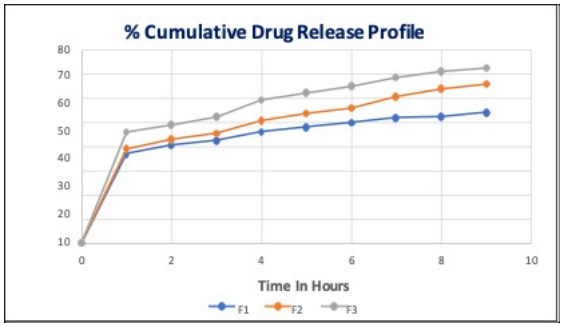

Figure 2: Cumulative drug profile of in situ gel batch F4 to F6

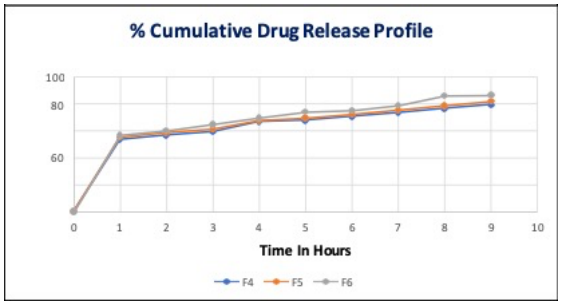

Figure 3: Cumulative drug profile of in situ gel batch F7 to F9 Table

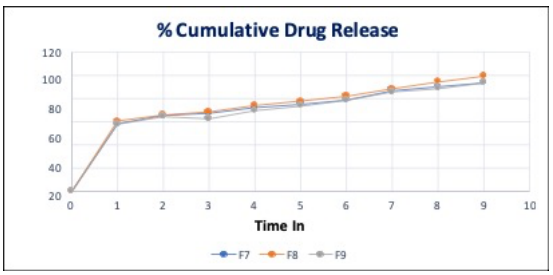

Table no. 2: Kinetic Model Fitting for Optimized Formulation (F8)

Time in Hours	% CDR	% CDR nreleased	Log of % drug nreleased	Log Time	QRT	Log % CDR
1	61.14	38.86	0.3010	0	1	.7863
4	74.42	25.58	0.1485	.60206	2	.8716
8	94.85	5.15	0.1476	.90309	2.82	.9770
9	99.78	0.22	0.0861	954243	3	.9990

Table 3: Kinetic study of Oral Floatable In-Situ Gel of Ranolazine

Formulation Code	Zero Order R2	First Order R2	Higuchi R2	Korsmeyer eppa's- model	
				R2	lope n
F1	0.978	0.798	0.931	0.993	0.573
F2	0.975	0.628	0.975	0.972	0.551
F3	0.994	0.792	0.963	0.987	0.635
F4	0.986	0.631	0.985	0.989	0.947
F5	0.981	0.675	0.971	0.980	0.874
F6	0.971	0.786	0.968	0.977	0.937
F7	0.989	0.862	0.987	0.984	0.943
F8	0.992	0.982	0.996	0.995	0.764
F9	0.990	0.921	0.991	0.991	0.847

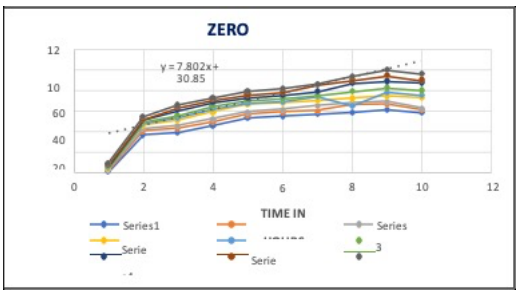

Figure 4: Zero order equation for All Batches of Oral Floatable In-Situ gel of Ranolazine

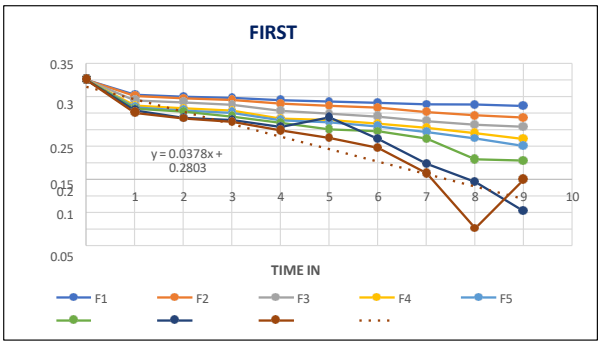

Figure 5: First order equation for All Batches of Oral Floatable In-Situ gel of Ranolazine

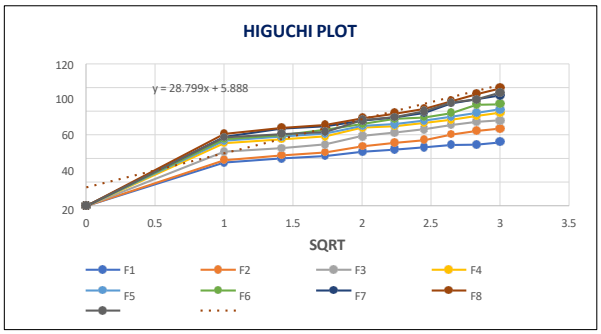

Figure 6 : Higuchi Plot for All Batches of Oral Floatable In-Situ gel of Ranolazine

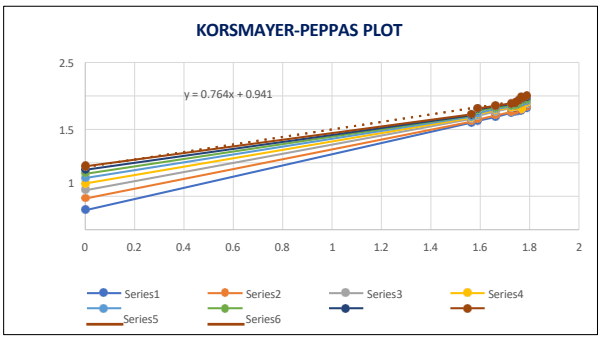

Figure 7: Korsmeyer-Peppas Plot for All Batches of Oral Floatable In-Situ gel of Ranolazine

Stability Study of Optimized Oral Floatable *In Situ* Gel Formulation [9,10].

The optimized formulation (F8) was subjected to

comprehensive stability studies over a period of three months under standard storage conditions, namely room temperature and protection from light, in order to assess its physicochemical stability, formulation integrity, and suitability for long-term storage. Stability evaluation is a critical requirement in pharmaceutical development, as it ensures that the formulation retains its intended quality, safety, and therapeutic performance throughout its shelf life. Accordingly, key parameters including pH, gelling capacity, viscosity, and drug content were systematically monitored at predetermined intervals (initial, 1, 2, and 3 months).

pH Stability

The pH of oral in-situ gel formulations is an important parameter that affects formulation stability, drug integrity, and gelation behavior in the gastric environment. The optimized formulation **F8** showed an initial pH of **8.60**, indicating a mildly alkaline environment that helps maintain the formulation in a sol state during storage and prevents premature gelation.

During the stability study, the pH slightly decreased to **8.11 after one month**, which may be due to minor interactions between formulation components or absorption of atmospheric carbon dioxide. At **two months**, the pH increased to **8.65**, suggesting good buffering capacity of the polymeric system. After **three months**, the pH was recorded as **8.58**, which is very close to the initial value.

Overall, only minimal fluctuations in pH (**8.11–8.65**) were observed during the three-month study, indicating good physicochemical stability of the formulation. These results confirm that the optimized formulation maintains a stable alkaline environment suitable for preserving drug stability and ensuring proper sol-to-gel transition upon administration.

Gelling Capacity

Gelling capacity is an important parameter for gastroretentive in-situ gel systems, as it determines the ability of the formulation to transform from sol to gel upon contact with gastric fluid. The gelling capacity of the optimized formulation **F8** was evaluated by introducing the formulation into **simulated gastric fluid (0.1 N HCl)** and observing the rate and strength of gel formation.

Initially, formulation **F8 exhibited +++ gelling capacity**, indicating immediate and strong gel formation with good structural integrity. During the **one-, two-, and three-month stability studies**, the formulation consistently showed +++ **gelling behavior**, with no changes in gel strength or gelation time.

The gel formation occurs due to **ionic cross-linking between calcium ions and polymer chains of pectin and sodium alginate**, forming a stable three-dimensional gel network. The consistent gelling performance throughout the study indicates that formulation **F8 maintains its functional integrity during storage**, ensuring effective gastric retention and sustained drug release.

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Viscosity Profile

Viscosity is an important parameter for oral in-situ gel systems as it influences rheological stability, ease of administration, and gel formation in the gastric environment. The viscosity of the optimized formulation **F8** was measured using a Brookfield viscometer at a constant spindle speed.

Initially, the formulation showed a viscosity of **20,764 cP**, indicating a stable and well-structured polymeric system suitable for maintaining homogeneity and proper flow properties. After **one month**, the viscosity slightly decreased to **20,125 cP**, which may be due to minor rearrangement of polymer chains during storage. At **two months**, the viscosity increased to **20,648 cP**, suggesting stabilization of the polymer network. After **three months**, the viscosity was **20,512 cP**, which is very close to the initial value.

Overall, the viscosity remained within **±3% of the initial value**, indicating good rheological stability of the formulation. These minor variations are typical for polymeric systems and do not affect pourability, gel formation, or sustained drug release behavior.

Drug Content Stability

Drug content analysis was performed to evaluate the chemical stability of **Ranolazine** in the optimized formulation **F8** during storage. Initially, the drug content was **97 ± 0.4%**, indicating uniform drug distribution within the polymeric matrix.

After **one month**, the drug content slightly decreased to **96 ± 0.2%**, suggesting minimal drug loss. At **two months**, the value remained stable at **96 ± 0.9%**, indicating consistent drug retention. After **three months**, the drug content was **95.8 ± 0.6%**, which is still within acceptable limits.

Overall, the minor variations observed during the stability study indicate that the formulation maintains good **chemical stability and uniform drug distribution**, confirming the suitability of formulation **F8** for further development.

Table 4: Stability testing of optimized batch formulation

haracterization	Initial	Month	Months	Months
pH	8.60	8.11	8.65	8.58
elling Capacity	+++	+++	+++	+++
Viscosity (cP)	20,764	20,125	20,648	20,512
Drug Content (%)	7 ± 0.4	96 ± 0.2	96 ± 0.9	95.8 ± 0.6

Stability Study of Drug Release

The optimized oral floatable in-situ gel formulation **F8** was evaluated for drug release stability under accelerated conditions (**40 ± 2°C and 75 ± 5% RH**) according to ICH guidelines. Initially, the formulation showed a controlled and sustained release pattern, with **61.14% drug release at 1 hour** and nearly complete release (**99.78%**) at **9 hours**.

After **1, 2, and 3 months** of storage, the drug release profiles remained almost unchanged. The release at **1 hour** was **61.09%, 60.97%, and 60.92%**, respectively, while the cumulative release at **9 hours** was **99.64%, 99.20%, and 99.15%**, indicating only negligible variation.

Overall, the minimal differences in drug release during the stability study confirm that the **polymeric gel matrix remained stable**, maintaining its controlled release characteristics. These results demonstrate that the optimized formulation **F8** possesses good physical and chemical stability during storage.

Table 5: Cumulative % Drug Release Profile During Stability Study

Time (hrs)	Initial	After 1 Month	After 2 Months	After 3 Months
0	0	0	0	0
1	61.14	61.09	60.97	60.92
2	66.19	66.10	66.01	65.95
3	68.83	68.75	68.32	68.29
4	74.42	74.35	74.19	74.12
5	78.38	78.12	78.04	77.98
6	82.35	82.29	82.16	82.10
7	88.92	88.81	88.47	88.41
8	94.85	94.72	94.58	94.50
9	99.78	99.64	99.20	99.15

In-Vivo Pharmacokinetic Evaluation of Optimised Formulation and Reference Product [11,12].

Linearity curve: The standard calibration curve was found to be in the range of 10 to 400 ng/ml. The regression coefficient (r) is greater than or equal to 0.999. Data is presented in Table 6.

Table 6: Linearity curve values of Ranolazine

concentration(µg/ml)	%Area ratio
10	0.0063
20	0.0127
30	0.0195
80	0.0503
200	0.1257
240	0.1510
320	0.1993
400	0.2480

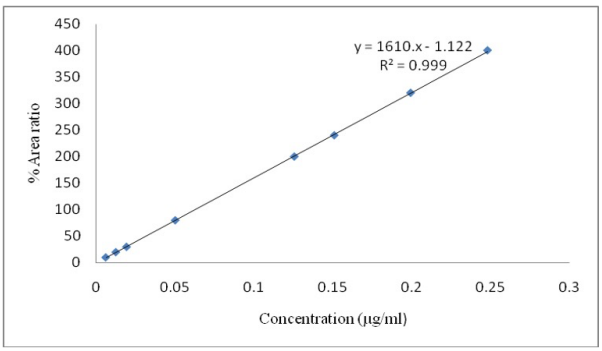

Figure 8: Linearity curve of Ranolazine

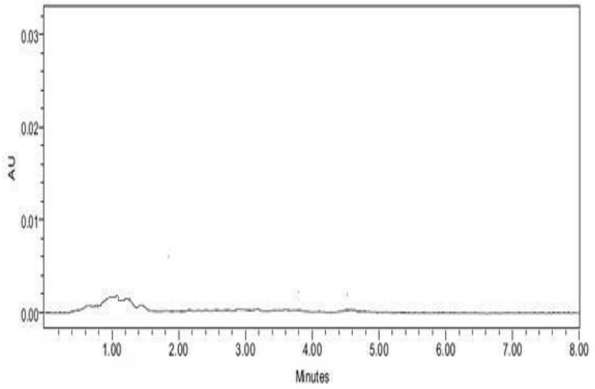

Figure 9: Chromatogram of the extracted Blank plasma sample

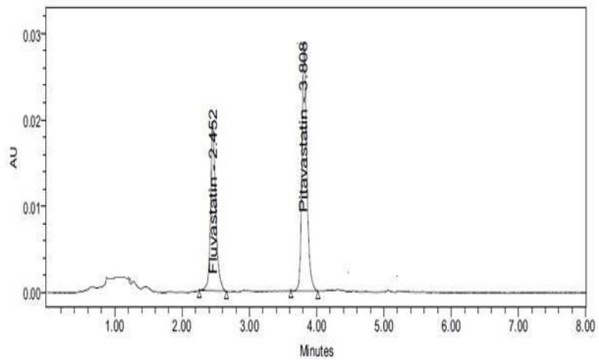

Figure 10: Chromatogram of Pitavastatin (Internal Standard) spiked blank plasma sample

Table 7: *In vivo* plasma data of test and reference:

Time (hrs)	Test (ng/ml)	Reference (ng/ml)
0.5	12.84±0.23	21.36±0.03
1	38.46±0.16	49.42±0.19
2	55.26±0.11	99.42±0.19
3	89.98±0.57	115.36±0.03
4	103.86±0.34	162.42±0.19
6	156.35±0.01	83.89±0.03
8	132.58±0.15	42.35±0.02
12	45.36±0.29	21.75±0.32
18	29.54±0.53	9.36±0.32
24	12.62±0.12	2.85±0.26

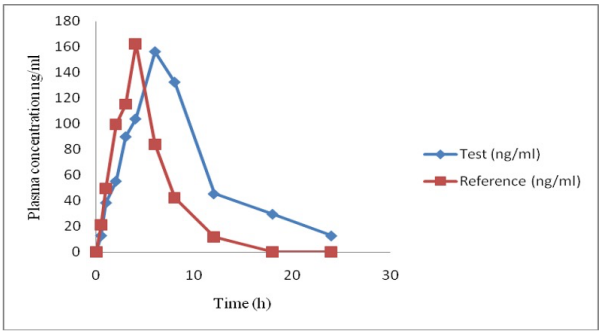

Figure 11: *In vivo* drug plasma data of test and reference product

In Vivo Plasma Drug Concentration Profile of Test and Reference Formulations [13].

Table 5.4 presents a comparative pharmacokinetic evaluation of the test and reference formulations based on plasma drug concentration–time profiles measured over 24 h. The data (ng/ml) illustrate differences in absorption rate, peak plasma concentration (C_max), and duration of systemic exposure, which are critical determinants of therapeutic performance and dosing suitability.

At 1 h post-administration, the reference formulation exhibited a higher plasma concentration (49.42 ± 0.03 ng/ml) than the test formulation (38.46 ± 0.16 ng/ml), indicating faster initial absorption. This trend continued at 2 h and 3 h, where the reference product reached 99.42 ± 0.19 ng/ml and peaked at 115.36 ± 0.03 ng/ml, while the test formulation showed comparatively lower values of 55.26 ± 0.11 ng/ml and 89.98 ± 0.57 ng/ml, respectively. These findings suggest rapid absorption kinetics for the reference formulation, consistent with immediate-release behavior.

At 4 h, the test formulation demonstrated a marked rise in plasma concentration (103.86 ± 0.57 ng/ml), approaching the reference value (162.42 ± 0.03 ng/ml), indicating the onset of sustained absorption. By 6 h, a crossover occurred: the test formulation reached 156.35 ± 0.01 ng/ml, surpassing the reference product, which had begun to decline. This shift highlights the prolonged release characteristics of the test formulation and its ability to maintain therapeutic plasma levels for an extended period.

In-Vivo Pharmacokinetic Parameters

Table 8 : Pharmacokinetic Parameters of Test and Reference Formulation

Parameters	Test	Reference
AUC (0-∞) ng.h/ml	1764.08±0.04	1053.99±0.01

C max ng/ml	156.35±0.12	162.42±0.19
T(max) (hrs)	6±0.03	4±0.02
MRT (h)	2.84±0.11	1.69±0.14
$k_e(h^{-1})$	0.12±0.01	0.18±0.03
t1/2(hrs)	5.77±0.12	3.85±0.11

Pharmacokinetic Analysis of Optimized Test and Reference Formulations

Pharmacokinetic parameters of the optimized test formulation and conventional reference formulation were analyzed using Kinetica™ 5.0 software to compare their absorption, bioavailability, and elimination characteristics based on in vivo plasma concentration–time data. The test formulation, a gastro-retentive oral floatable *in situ* gel, was designed for sustained drug release, whereas the reference formulation represented a conventional immediate-release system.

Area Under the Curve (AUC):

The test formulation demonstrated a markedly higher AUC (1764.08 ng·h/ml) than the reference product (1053.99 ng·h/ml), corresponding to a 67.5% increase in systemic exposure. This indicates enhanced bioavailability, likely resulting from prolonged gastric residence and sustained drug release.

Peak Plasma Concentration (C_max) and T_max:

The reference formulation showed a slightly higher C_max (162.42 ng/ml) compared to the test formulation (156.35 ng/ml), reflecting rapid absorption typical of immediate-release systems. However, the test formulation exhibited a longer T_max (6 h vs. 4 h), confirming its controlled-release behavior and smoother plasma concentration profile.

Relative Bioavailability and MRT:

Relative bioavailability of the test formulation was 1.67, indicating substantially improved systemic availability. Mean Residence Time was also prolonged (2.84 h vs. 1.69 h), demonstrating extended circulation of the drug.

Elimination Parameters:

The elimination rate constant was lower for the test formulation (0.12 h^{-1}) than for the reference (0.18 h^{-1}), with a corresponding increase in half-life (5.77 h vs. 3.85 h). These findings confirm slower clearance and sustained systemic exposure.

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