RESEARCH PAPER

Formulation and Evaluation of a Floating Oral In-Situ Gel of Risedronate Sodium for Sustained Gastro-Retentive Drug Delivery

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ABSTRACT
Risedronate Sodium has low oral bioavailability and is mainly absorbed in the upper GI tract, requiring a gastro-retentive system for better efficacy. This study developed floating oral in situ gels using Sodium Alginate, HPMC K100M, Carbopol 934P, and Calcium Carbonate to prolong gastric retention and sustain drug release. Ten formulations were evaluated for key properties and drug release. Formulation F6 showed optimal viscosity, gel strength, rapid buoyancy (<30 s), and sustained release (~90% in 12 h) with zero-order kinetics. Stability studies confirmed its robustness. This gastro-retentive gel offers improved bioavailability and patient compliance through once-daily dosing.
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INTRODUCTION

Oral drug delivery remains the most preferred route of administration because of its convenience, patient compliance, and cost-effectiveness. However, conventional dosage forms often suffer from fluctuations in plasma levels and short residence times in the gastrointestinal tract, leading to reduced therapeutic efficiency of drugs with narrow absorption windows or poor bioavailability (1,2). To overcome these limitations, gastro-retentive drug delivery systems (GRDDS) have gained increasing attention, as they are designed to remain in the stomach for extended periods and release drugs in a controlled manner (3).

Floating in situ gels represent an advanced form of GRDDS that undergoes sol-to-gel transformation when exposed to gastric fluid. These formulations offer dual advantages: they float on gastric contents owing to internal gas generation and form a strong gel matrix capable of sustaining drug release (4). Hydrophilic polymers such as Sodium Alginate, HPMC and Carbopol are widely used in in situ gel systems because of their ability to swell, form strong physical networks, and provide prolonged gastric retention (5,6). Furthermore, floating in situ gels are easy to administer as liquids and are converted into gels only after reaching the stomach, improving safety and patient acceptance compared to solid gastroretentive dosage forms (2).

Risedronate Sodium is a third-generation bisphosphonate commonly prescribed for the management of osteoporosis and bone metabolic disorders. Although highly potent, it suffers from extremely low oral bioavailability (<1%) owing to its poor permeability and limited absorption in the upper gastrointestinal tract (7). Patients must remain upright and fast after administration to minimize esophageal irritation, which affects compliance. Therefore, a gastro-retentive formulation that ensures prolonged residence in the stomach and sustained drug release can improve therapeutic outcomes and patient adherence is needed.

In this context, floating oral in situ gel technology offers high potential for Risedronate Sodium by enabling controlled release at its primary absorption site while maintaining gastric retention and minimizing dosing frequency. Although floating in situ gels have been explored for various drugs, limited research is available on Risedronate Sodium using a multi-polymer system incorporating Sodium Alginate, HPMC and Carbopol for optimized buoyancy and release control. Thus, the present study was undertaken to develop and evaluate a floating oral in situ gel of Risedronate Sodium with the objectives of prolonging gastric residence, sustaining drug release, and improving overall therapeutic performance.

MATERIALS AND METHODS

2.1 Materials

Misoprostol was used as the model. The polymers and excipients used in the formulation included Poloxamer 407, Poloxamer 188, Hydroxypropyl Methylcellulose (HPMC), Carbopol 934P, Sodium Alginate, Calcium Carbonate, and Sodium Citrate. All reagents and solvents used were of analytical grade. Distilled water was used to prepare the formulations.

2.2 Pre-formulation Studies

2.2.1 Characterization of Misoprostol

The melting point of misoprostol was determined using the capillary tube method, following the USP guidelines. A fixed quantity of misoprostol was packed in a capillary tube and heated using a digital melting point apparatus, and the temperature at which the last particle liquefied was recorded.

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2.2.2 Drug–Excipient Compatibility Study

Physical and chemical compatibility studies were conducted between misoprostol and selected excipients.

Physical compatibility: Drug–excipient mixtures were stored at room temperature and at 40°C/75 ± 2% RH, and observed periodically for changes in color or appearance.

Chemical compatibility: FTIR spectroscopy was performed using a Shimadzu FTIR 8400 spectrometer over the range of 4000–400 cm^{-1}. Samples (drug, drug + excipient mixture, and optimized formulation) were compressed with KBr to form pellets, and spectra were recorded to detect potential interactions.

2.3 Preparation of Oral In-Situ Gel of Misoprostol

In situ gel formulations were prepared using the cold method.

1. Poloxamer 407 and Poloxamer 188 were dissolved in cold distilled water (4°C) under continuous magnetic stirring until a clear solution was obtained (overnight).
2. HPMC and Carbopol 934P were separately dispersed in warm distilled water (40–50°C), stirred to avoid lumps, and allowed to hydrate for 2–4 h.
3. The hydrated HPMC/Carbopol dispersion was slowly added to the Poloxamer solution with continuous stirring.
4. Sodium Alginate was dissolved in warm distilled water (~60°C), hydrated, and incorporated into the polymer blend.
5. Misoprostol was dissolved in ethanol/water and added to the polymeric base with gentle stirring to ensure uniform distribution.
6. Calcium Carbonate was incorporated as a gas-generating agent just before the final volume makeup.
7. The pH was adjusted to 6.4–6.8 using 0.1 N NaOH/0.1 N HCl, and sodium citrate was added to prevent premature gelation.
8. Final formulations were stored in amber-colored containers at 4–8°C to maintain the sol state prior to administration

2.4 Evaluation of In-Situ Gel

Table 1. Evaluation Parameters and Analytical Methods Used for In-Situ Gel Formulations

Parameter	Method
Appearance & Clarity	Visual inspection
pH	Measured using calibrated pH meter (triplicate average)
In-vitro Gelation	1 mL formulation added to 5 mL simulated gastric fluid (0.1 N HCl, pH 1.2) at 37°C and gelation behavior rated (+)/(++)/(+++)
Viscosity	Brookfield Viscometer (DV-II + Pro), spindle S21, 50 rpm
In-vitro Buoyancy	USP Type II apparatus; floating lag time and total floating duration recorded
Water Uptake	Gel mass change monitored every 30 min after adding water and decanting
Density of Gel	Weight/volume of 10 mL gel formed in 0.1 N HCl
Gel Strength	Time required for 50 g weight to penetrate 5 cm through 30 g of gel
Drug Content	5 mL formulation equivalent to 3 mg drug in 0.1 N HCl; analyzed at 281 nm by UV-spectrophotometer
In-vitro Drug Release	USP Type II (paddle) in 500 mL 0.1 N HCl, 37°C, 50 rpm; aliquots withdrawn at intervals and analyzed at 281 nm

2.5 Release Kinetics

The drug release data of the optimized formulation were fitted to zero-order, first-order, Higuchi, Hixson–Crowell, and Korsmeyer–Peppas models to determine the release mechanism and rate. The diffusion exponent (n) of the Korsmeyer–Peppas model was used to characterize the release mechanism.

2.6 Stability Studies

The optimized formulation was subjected to accelerated stability testing as per ICH guidelines at 40 ± 2 °C / 75 ± 5% RH for 1 month. Samples were withdrawn at 0 and 30 days and evaluated for visual appearance, pH, floating behavior, gelation capacity, drug content, and in vitro release performance.

RESULT

3.1 Identification of Drug

The identity of Risedronate Sodium was confirmed using UV spectrophotometry. A 0.1 N HCl solution was prepared by diluting 8.5 mL of concentrated hydrochloric acid to 1000 mL with distilled water. An accurately weighed amount of Risedronate Sodium (10 mg) was dissolved in methanol and diluted to 100 mL to obtain a stock solution of 100 µg/mL.

To determine the maximum absorbance wavelength (λmax), 1 mL of the stock solution was diluted to 10 mL with methanol to obtain a 10 µg/mL working solution. The solution was scanned in the wavelength range of 200–400 nm, and λmax was observed at 262.0 nm, confirming the characteristic absorption peak of Risedronate Sodium.

For the calibration curve, serial dilutions of the stock solution were prepared at concentrations of 2, 4, 6, 8, 10, and 12 µg/mL using methanol. The absorbance of each dilution was measured at 262.0 nm using 0.1 N HCl as a blank. The calibration plot demonstrated excellent linearity across the tested concentration range, establishing the suitability of the

method for the accurate quantitative estimation of Risedronate Sodium in the formulated system. Table 2

Table 2: Preparation of standard calibration curve of Risedronate Sodium in 0.1N HCL

Concentration (µg/mL)	Absorbance at λmax (262 nm)
0	0
2	0.125
4	0.247
6	0.356
8	0.473
10	0.592

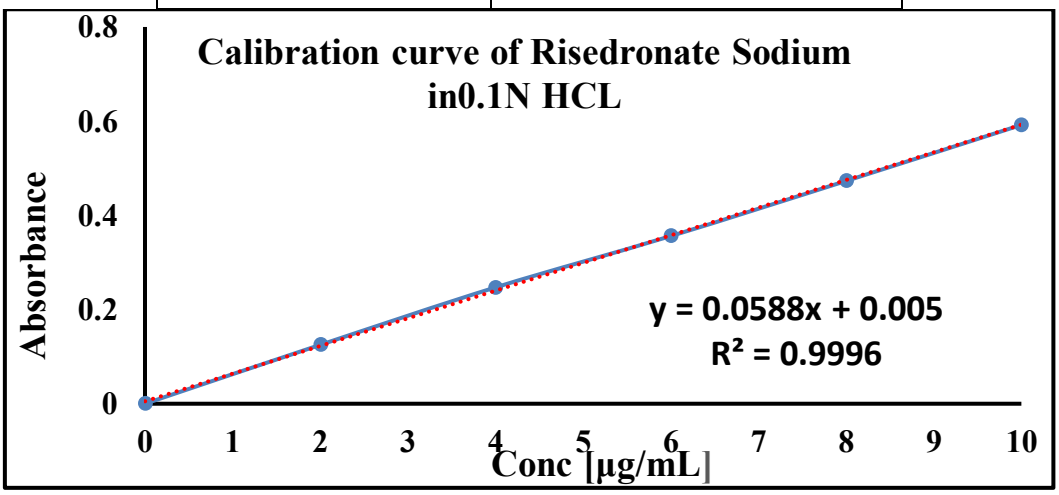

Figure 1: Calibration curve of Risedronate Sodium in 0.1 N HCL

The maximum absorbance wavelength (λmax) of Risedronate Sodium was found to be 262 nm. The standard calibration curve, as shown in Figure 6.1, demonstrated excellent linearity within the selected concentration range, with a correlation coefficient (R^2 = 0.9996). These findings confirm that the UV spectrophotometric method is highly reliable for the identification and quantitative estimation of Risedronate Sodium. The established calibration curve enables the accurate determination of Risedronate Sodium concentration in pharmaceutical formulations and analytical studies. Figure 1

Melting Point of Risedronate Sodium

The melting point of Risedronate Sodium was determined using the capillary tube method. The drug exhibited a melting point of 252°C, which is consistent with the reported range for Risedronate Sodium, confirming its purity and thermal stability.

Drug–Excipient Compatibility Study

Drug–excipient compatibility was evaluated to ensure that the selected excipients did not interact with Risedronate Sodium and were suitable for formulation development. This study aimed to assess the physical and chemical compatibility between the drug and the polymers used in the in situ gel system.

Physical Compatibility Study:

Table 3: Physical Compatibility of Drug and Excipients

S. No.	Drug and Excipients	Description and Condition		
		Initial	At room temperature	At 40ºC ± 2ºand75%RH±2% (in 30 days)

			10	20	30	10	20	30
1.	Risedronate Sodium	White Crystalline Powder	NC	NC	NC	NC	NC	NC
2.	Risedronate Sodium + Sodium Alginate	Off-White Powder	NC	NC	NC	NC	NC	NC
3.	Risedronate Sodium + HPMC K100M	)ff -White Powder	NC	NC	NC	NC	NC	NC
4.	Risedronate Sodium +Carbopol 934P	)ff -White Powder	NC	NC	NC	NC	NC	NC
5.	Risedronate Sodium + Calcium Carbonate	)ff -White Powder	NC	NC	NC	NC	NC	NC

**NC - No Change*

Physical compatibility was assessed over 10, 20, and 30 days at both room temperature and accelerated conditions (40 ± 2°C / 75 ± 5% RH). No visible changes in color or appearance were observed in any of the drug–excipient mixtures throughout the study period. These results confirm that Risedronate Sodium is physically compatible with the selected excipients. Tablel 3

Chemical Compatibility Study:

A drug–excipient interaction study was performed using Fourier-transform infrared (FTIR) spectroscopy. FTIR spectra of the pure drug, individual polymers, and the physical mixture of Risedronate Sodium with excipients were recorded using a Shimadzu FTIR-8400S spectrophotometer in the wavenumber range of 4000–400 cm^{-1}. The spectra were evaluated to identify any possible shifts, disappearance, or appearance of characteristic peaks, which would indicate physicochemical interactions between the drug and the excipients.

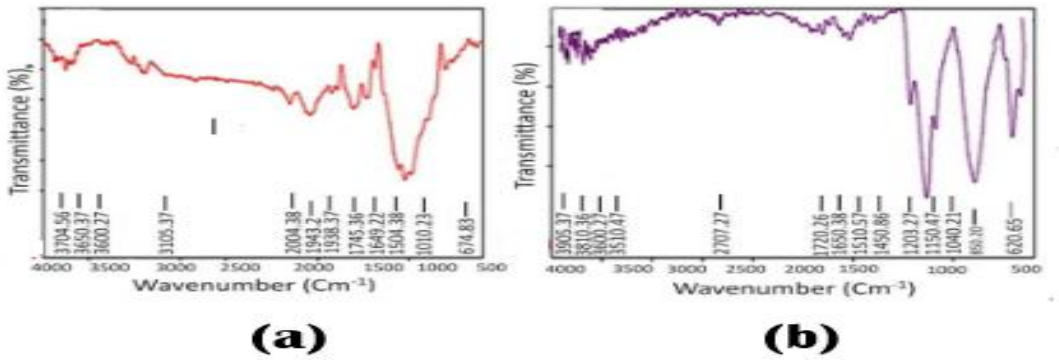

Figure 2: (a) FTIR of Risedronate Sodium (B) Optimized formulation F6

The FTIR spectrum of pure Risedronate Sodium exhibited distinct characteristic peaks corresponding to its functional groups, confirming the identity and purity of the drug. A prominent peak at 1028.56 cm^{-1} indicated aliphatic P=O stretching, while the absorption band at 2923.91 cm^{-1} corresponded to C–H stretching vibrations. Additional signals between 1400 and 1600 cm^{-1} were attributed to C=C and C=N stretching, supporting the presence of aromatic structural features. Collectively, these spectral observations confirm the presence of hydroxyl, carbonyl, ether, and aliphatic groups, consistent with the established chemical structure of Risedronate Sodium. The FTIR spectrum of the optimized formulation (F6), containing Risedronate Sodium with HPMC, Carbopol 934P, and Sodium Alginate, retained the major characteristic peaks of the drug. A C–H stretching band observed near 2707 cm^{-1} reflects the presence of aliphatic chains contributed by both the drug and polymers. The C=N stretching signal near 1650 cm^{-1} also remained apparent, although slightly broadened or shifted, suggesting possible hydrogen bonding or weak physical interactions between the drug and polymeric matrix rather than chemical degradation. Minor peak broadening without the disappearance of key functional bands indicates the molecular dispersion of the drug within the polymer network without structural modification. Figure 2. Therefore, FTIR analysis confirmed that no significant chemical interactions occurred between Risedronate Sodium and the selected excipients, establishing their compatibility for formulation development.

Formulation Of Risedronate Sodium Oral In Situ Gel

The prepared formulations (F1-F10) of Risedronate Sodium oral floating *in situ* gel are shown in Figure 3.

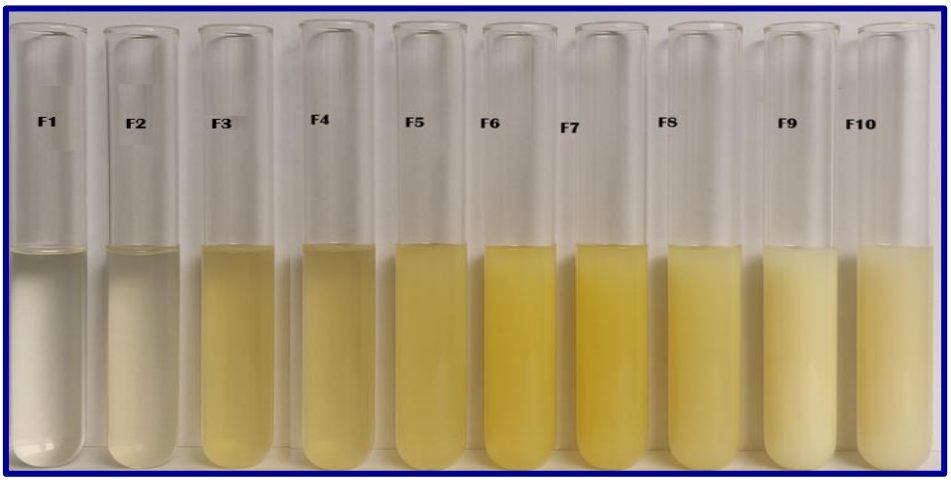

Figure 3: Prepared formulations of Risedronate Sodium oral In situ gel

Physical Appearance

The visual appearance of the formulations was evaluated, as it plays a significant role in patient acceptability and compliance. All formulations (F1–F10) were examined for color, clarity, and pourability. As shown in Table 4, all formulations were transparent to slightly yellow and remained easily pourable, indicating uniformity and the absence of premature gelation at room temperature.

Table 4: Physical appearance of formulated In situ gel

The formulations were free flowing and did not produce any gelation at room temperature.

Sr.No.	Formulation Code	Appearance	Pourability
1	F1	Transparent	Easily Pourable
2	F2	Transparent	Easily Pourable
3	F3	Slight yellow	Easily Pourable
4	F4	Slight yellow	Easily Pourable
5	F5	Slight yellow	Easily Pourable
6	F6	yellow	Easily Pourable
7	F7	yellow	Easily Pourable
8	F8	Slight yellow	Easily Pourable
9	F9	White	Easily Pourable
10	F10	White	Easily Pourable

pH of Risedronate Sodium Oral In-Situ Gel

Table 5: pH of In situ gel formulations

Sr. No.	Formulation Code	pH*
1	F1	6.70 ± 0.02
2	F2	7.10 ± 0.02
3	F3	7.15 ± 0.02

4	F4	7.25 ± 0.02
5	F5	7.29 ± 0.02
6	F6	7.30 ± 0.02
7	F7	7.37 ± 0.02
8	F8	7.30± 0.02
9	F9	7.33 ± 0.02
10	F10	7.30 ± 0.02

*n=3

The pH of all formulations was evaluated to ensure their suitability for oral administration and to avoid mucosal irritation. As shown in Table 5, the pH values of the formulations ranged from 6.70 to 7.37, with all samples falling within the physiologically acceptable salivary pH range (6.2–7.6). These results indicate that the developed oral in situ gels are unlikely to cause irritation upon administration and are suitable for oral use.

In-Vitro Gelation Study

The gelation behavior of the formulations was evaluated in 0.1 N HCl (pH 1.2) to simulate gastric conditions, and the extent of gel formation was graded on an ordinal scale ranging from + to +++ (Table 6). Formulations F1–F3 exhibited weak gelation (+), forming gels rapidly but losing their integrity within a short period. In contrast, F4–F10 exhibited strong gelation (+++), producing firm gels that remained intact for extended durations

Table 6: Gelling capacity of formulated Oral *In situ* gel of Risedronate Sodium

Sr. No.	Formulation Code	Gelling capacity
1	F1	+
2	F2	+
3	F3	+
4	F4	+++
5	F5	+++
6	F6	+++
7	F7	+++
8	F8	+++
9	F9	+++
10	F10	+++

(+) : Gels in few seconds, disperses rapidly

(++) : Gelation immediate, remains for few hours

(+++) : Gelation after few minutes, remains for extended period

All formulations underwent an immediate sol-to-gel transition upon contact with an acidic medium, confirming the responsiveness of the polymer system. Gel formation was driven by the release of calcium ions from the calcium citrate complex, which became entrapped within the polymeric network and facilitated the cross-linking of sodium alginate and HPMC K100M, with or without Carbopol 934P. This ionic and hydrogen bond-mediated crosslinking results in the formation of stiff and stable gels, which are essential for prolonged gastric retention and controlled drug release.

Viscosity of Risedronate Sodium Oral In-Situ Gel

The viscosity of the formulations was evaluated at 25°C using a Brookfield viscometer at 50 rpm to assess the flow characteristics of the liquid gel prior to administration. As shown in Table 7, the viscosity increased progressively from 120 ± 2.25 cps (F1) to 356 ± 2.21 cps (F10) with increasing polymer concentration. Formulations containing higher levels of

sodium alginate, HPMC K100M, and Carbopol 934P demonstrated greater viscosity due to enhanced chain entanglement and hydration of the hydrophilic polymers. The observed rheological profile indicates that the polymer composition plays a pivotal role in modulating the gel consistency. Importantly, all formulations maintained a sufficiently low viscosity at room temperature to remain easily pourable while possessing the potential to transform into a strong gel under gastric conditions. Figure 4.

Table 7: Viscosity of formulated Oral In situ gel of Risedronate Sodium

S.No.	Formulation Code	Viscosity (centipoise)*
1	F1	120 ± 2.25
2	F2	145 ± 1.53
3	F3	186 ± 2.62
4	F4	212 ± 3.58
5	F5	238 ± 2.52
6	F6	260 ± 2.52
7	F7	284 ± 5.03
8	F8	319 ± 3.16
9	F9	343 ± 3.51
10	F10	356 ± 2.21

*n=3

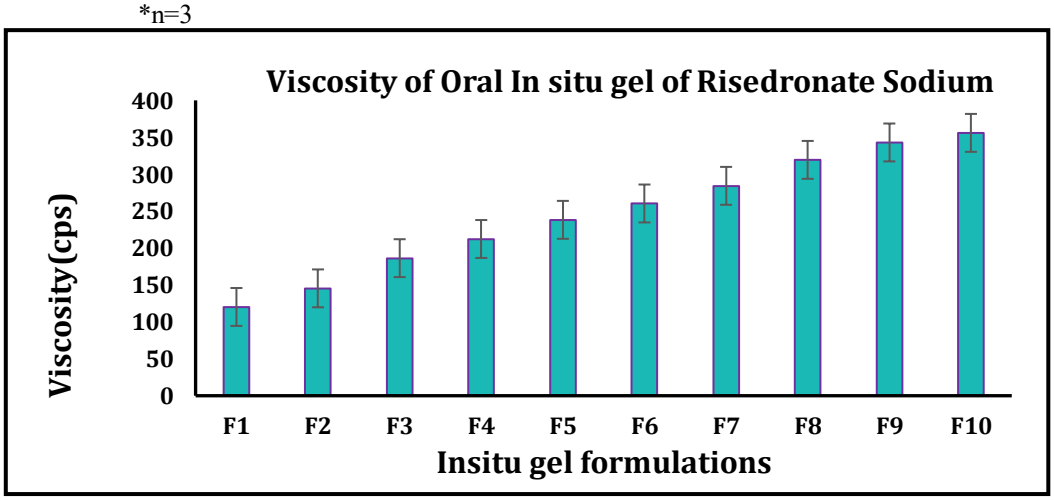

Figure 4: Viscosity of In situ gel of Risedronate Sodium formulations

All formulations demonstrated satisfactory viscosity and flow characteristics at room temperature; however, a clear concentration-dependent increase in viscosity was observed with increasing polymer concentrations. Formulations containing higher concentrations of sodium alginate and HPMC K100M exhibited greater viscosity due to enhanced polymer chain entanglements and hydration. The addition of secondary polymers, particularly Carbopol 934P, further contributed to an incremental increase in viscosity, reflecting its strong thickening and swelling behavior.

Among all formulations, F10 exhibited the highest viscosity (356 cps), attributable to its elevated content of HPMC (0.5%), Carbopol 934P (0.2%), and sodium alginate (3%). The rheological profile confirmed that variations in polymer composition play a critical role in modulating the consistency of the oral in situ gel system, which is essential for regulating gel strength and drug release performance under gastric conditions.

In-Vitro Buoyancy Study

The floating behavior was evaluated to determine the gastroretentive efficiency of the in situ gel formulations. Floating lag time, defined as the time required for a formulation to ascend to the surface of the dissolution medium after administration, is

a critical parameter for floating drug delivery systems. A shorter lag time ensures that the formulation remains in the stomach and avoids premature intestinal transit.

All formulations produced buoyant gels upon contact with the gastric simulated medium owing to in situ generation and entrapment of CO_2, triggered by the reaction of the gas-forming agent within the polymeric matrix. The trapped gas reduced the density of the gel to below that of gastric fluid (~1.004 g/cm³), enabling its flotation.

The polymer composition significantly influenced the buoyancy performance. Higher concentrations of HPMC K100M, Carbopol 934P, and sodium alginate enhanced gel viscosity and structural integrity, thereby improving gas entrapment and prolonging floating duration. The floating lag time and total floating duration for all formulations are summarized in Table 8

Table 8: In vitro buoyancy of Floating Oral In situ gel of Risedronate Sodium

Sr.No.	Formulation Code	Floating lag time(s)*	Floating duration (hrs.)
1	F1	45 ± 2	5
2	F2	42 ± 4	7
3	F3	37 ± 2	9
4	F4	36 ± 2	11
5	F5	32 ± 4	>12
6	F6	30 ± 2	>12
7	F7	28 ± 2	>12
8	F8	25 ± 4	>12
9	F9	23 ± 2	>12
10	F10	21 ± 1	>12

*n=3

The floating mechanism of the in situ gel is attributed to the entrapment of carbon dioxide generated from the gas-forming agent within the polymeric matrix, which decreases the density of the formulation to below that of gastric fluid (~1.004 g/cm³), enabling buoyancy. The composition and concentration of polymers, particularly HPMC K100M, Carbopol 934P, and sodium alginate, play critical roles in this process, as increased viscosity and gel strength promote more efficient gas entrapment and consequently reduce lag time.

The floating duration represents the total period during which the formulation remains buoyant in the gastric environment and is an essential indicator of gastroretentive performance. A floating duration exceeding 12 h is desirable, as it enables prolonged residence of the dosage form in the stomach and supports controlled drug release.

Formulations with higher polymer concentrations generally demonstrated extended floating durations due to greater gel integrity and resistance to erosion. However, excessive viscosity may delay gel formation and increase the floating lag time, underscoring the need for an optimized balance. Among all formulations, F10 exhibited the shortest floating lag time (21 s) and maintained buoyancy for more than 12 h, attributable to its high gel strength and robust polymer matrix.

Density of Risedronate Sodium Oral In-Situ Gel

Density plays a critical role in determining the buoyancy of gastroretentive drug delivery systems. For an in situ gel to float in the gastric environment, its density must be equal to or lower than that of gastric fluid (~1.004 g/cm³).

As presented in Table 9, the density of all formulations ranged between 0.980 ± 0.001 and 0.999 ± 0.001 g/cm³, confirming that each formulation possessed a density lower than that of gastric fluid. The reduced density can be attributed to entrapped CO_2 bubbles within the crosslinked polymer matrix, which lowers the overall mass-to-volume ratio of the gel.

The density data correlated well with the buoyancy results, indicating that all formulations were capable of floating and remaining in the stomach for prolonged periods. This property is essential for ensuring extended gastric retention and sustained drug release, thereby enhancing the therapeutic performance of the gastroretentive in situ gel system.

Table 9: Density of formulated In situ gel

Sr.No.	Formulation Code	Density (g/cm3)
1	F1	0.980 ± 0.001
2	F2	0.983 ± 0.002
3	F3	0.985± 0.002
4	F4	0.987 ± 0.001
5	F5	0.989 ± 0.001
6	F6	0.990 ± 0.001
7	F7	0.994 ± 0.001
8	F8	0.997 ± 0.001
9	F9	0.999 ± 0.001
10	F10	0.102± 0.001

*n=3

Measurement of Gel Strength of Risedronate Sodium Oral In situ Gel

Gel strength is a critical parameter that reflects the mechanical integrity of the gelled mass and its ability to withstand gastric peristalsis. As shown in Table 10, all formulations exhibited satisfactory gel strength, with values ranging from 14.8 ± 0.6 s (F1) to 42.7 ± 1.23 s (F10).

A gradual increase in gel strength was observed with higher concentrations of HPMC K100M, Carbopol 934P, and sodium alginate, indicating that the polymer composition directly influences the rigidity of the formed gel. Formulation F1, which contained the lowest polymer content, exhibited the weakest gel structure, whereas F10, which contained the highest polymer concentration, demonstrated the strongest gel network.

These results confirmed that higher gel strength contributed to improved resistance against mechanical stress, enabling the gel to maintain its structural integrity in the stomach for longer periods. Consequently, formulations with greater gel strength are more likely to support prolonged gastric retention and extended drug release, which are desirable attributes of gastro-retentive delivery systems.

Table 10: Gel strength of formulated In situ gel

Sr. No.	Formulation Code	Average gel Strength(s)*
1	F1	14.8 ± 0.6
2	F2	18.2 ± 1.15
3	F3	22.6 ± 0.58
4	F4	24.9± 0.58
5	F5	29.3± 1.53
6	F6	32.5 ± 1.15
7	F7	35.4 ± 1.53
8	F8	37.7 ± 1.00
9	F9	40.8 ± 1.40
10	F10	42.7 ± 1.23

*n=3

Percentage Water Uptake by Risedronate Sodium In situ Gel

Table 11: Percentage water uptake of In situ gel formulations

Time (mins)	%Water uptake by the formulations									
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
30	28.50	26.87	24.35	22.5	21.02	19.80	17.10	15.50	14.80	13.65
60	40.45	37.98	35.80	33.56	31.20	30.04	28.95	27.07	26.57	24.84
90	62.50	59.05	56.10	54.84	52.83	50.21	48.19	47.92	46.20	45.90
120	70.56	69.80	66.75	63.37	61.90	60.09	58.10	57.19	55.58	54.06

Water uptake plays a critical role in controlling drug diffusion from polymeric matrices, as the extent of hydration influences both gel swelling and erosion dynamics of the matrices. The percentage water uptake of all formulations was evaluated at predetermined time intervals, and the results are presented in Table 11.

A clear trend was observed between the polymer concentration and water absorption capacity. Formulations with lower polymer content (F1–F3) exhibited the highest water uptake, reaching 70.56% at 120 min for F1. Their relatively weak gel matrices allow for greater penetration of the aqueous medium, resulting in enhanced swelling. In contrast, increasing the polymer concentration (F4–F10) produced a denser and more cross-linked gel network, thereby restricting water diffusion into the matrix. For example, F10 demonstrated the lowest water uptake (54.06% at 120 min), reflecting its rigid and compact structure.

The combination of sodium alginate, HPMC K100M, and Carbopol 934P synergistically contributed to hydration control. Sodium alginate forms an ionically cross-linked gel barrier through interaction with calcium ions, while Carbopol imparts mucoadhesive strength, and HPMC supports the maintenance of viscosity and swelling resistance. This integrated polymer system allows the gel to retain its integrity, maintain buoyancy, and regulate hydration.

Formulations F5–F7 displayed water uptake values ranging from 61.90% to 58.10% at 120 min, striking an optimal balance between hydration and structural rigidity. Such behavior is favorable for sustained and controlled drug release, where adequate swelling facilitates drug diffusion without excessive gel erosion.

Drug Content of Risedronate Sodium Oral In Situ Gel

Drug content uniformity is an essential quality parameter for ensuring accurate dosing and therapeutic efficacy of pharmaceutical formulations. The percentage drug content of the developed in situ gels is presented in Table 12

Table 12: Percentage drug content of formulated In situ gel

Sr. No.	Formulation Code	Drug content (%)
1	F1	95.50
2	F2	99.10
3	F3	96.90
4	F4	95.10
5	F5	99.04
6	F6	98.10
7	F7	97.59
8	F8	98.36
9	F9	99.35
10	F10	99.40

All formulations demonstrated acceptable drug loading, with drug content values ranging from 95.10% to 99.40%, indicating a uniform dispersion of Risedronate Sodium throughout the polymeric matrix. The high degree of uniformity suggests that

the preparation method was efficient in minimizing drug loss during processing and preventing drug segregation during the gel formation. These results further confirm that polymer incorporation and formulation variables did not adversely affect drug entrapment.

In vitro Dissolution Study of Formulated Risedronate Sodium Oral In situ Gel

An in vitro dissolution study was conducted to evaluate the release pattern of Risedronate Sodium from the formulated oral in situ gels, and the results are presented in Table 13and Figure 8. All formulations showed a time-dependent increase in drug release, confirming sustained-release behavior.

A significant influence of polymer composition on drug release kinetics was observed. Formulations with lower polymer concentrations (F1–F3) displayed the most rapid release, with F1 achieving 95.5% drug release at 12 h, attributable to its weaker gel matrix that facilitates faster hydration, erosion, and diffusion of the drug. Conversely, formulations with higher polymer concentrations (F8–F10) exhibited significantly slower release rates due to the formation of a dense, highly cross-linked gel network that restricted water penetration and drug diffusion. Among these, F10 showed the slowest release (83.9% at 12 h), consistent with its high sodium alginate, HPMC K100M, and Carbopol 934P content.

Formulations F5–F7 demonstrated intermediate release profiles, maintaining a balance between matrix hydration and structural integrity, making them suitable for sustained release. The overall release behavior indicated that increasing the polymer concentration enhanced the gel strength and reduced erosion, resulting in prolonged and controlled drug release.

Table 13: In vitro Drug release of Formulated Risedronate Sodium Oral In situ Gel

Time (min.)	Percentage Drug Release									
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
0.5	22	19	17	15	14	13	12	11	10	9
1	28	25	22	20	19	18	17	16	15	13
1.5	34	33	32	30	28	26	25	23	21	20
2	38	37	35	34	32	30	29	27	25	23
3	45	43	41	38	37	35	33	30	28	25
4	54	51	50	48	46	43	42	39	37	35
5	65	63	60	58	55	52	49	47	45	42
6	70	68	66	64	60	58	56	53	50	48
7	76	73	71	70	68	66	64	63	61	60
8	78	76.4	74.5	72.3	70,1	68.5	65.4	64.1	67.2	69
9	82.4	80.1	78.3	76.5	75.2	74.2	73.1	72.5	71.3	70.4
10	85.3	84.1	83.6	82.7	80.2	79.1	78.4	77.2	76.3	75.4
11	89.1	88	86	84	83	82.7	81.5	80.5	78.5	76.7
12	95.5	93.7	92.6	91.9	90.4	90.2	88	86	84.2	83.9

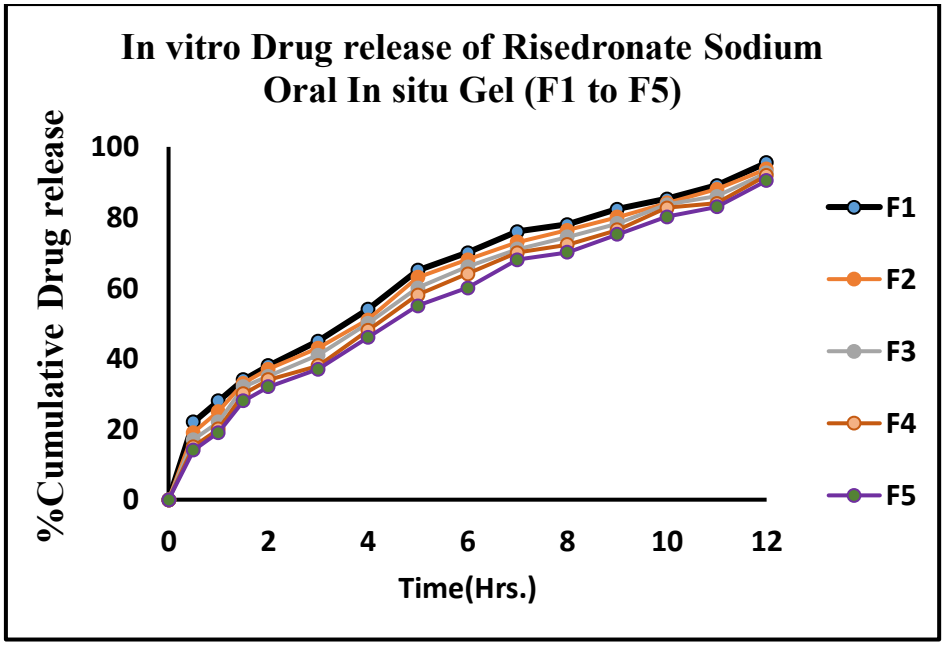

Figure 5: In vitro Drug release of Risedronate Sodium Oral In situ Gel (F1 to F5)

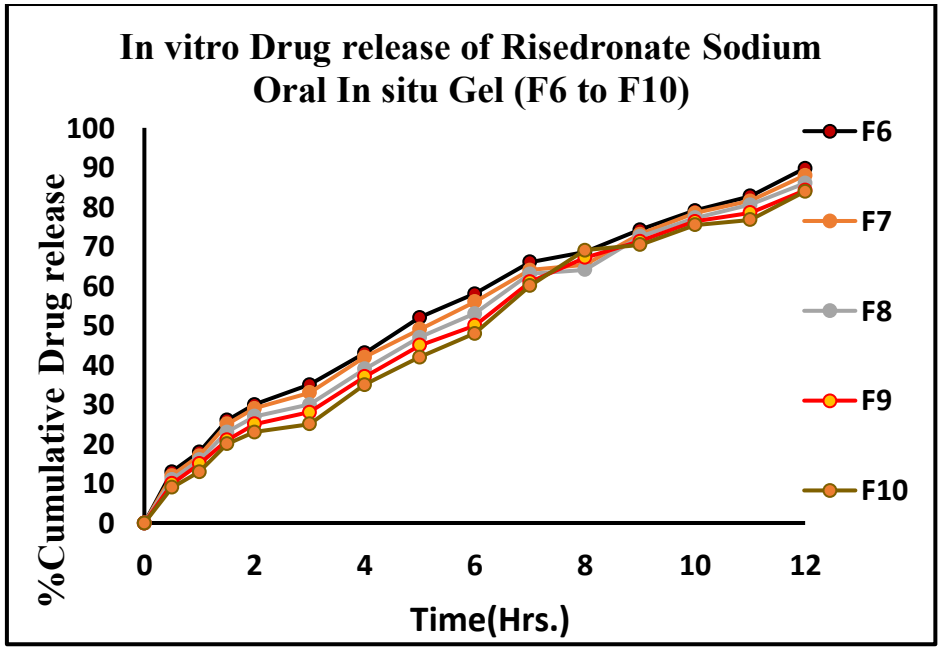

Figure 6: In vitro Drug release of Risedronate Sodium Oral In situ Gel (F6 to F10)

The in vitro drug release behavior of the floating in situ gel formulations (F1–F10) was predominantly influenced by the type and concentration of the hydrophilic polymers used: sodium alginate, HPMC K100M, and Carbopol 934P. Upon contact with gastric fluid, these polymers hydrate and undergo sol-to-gel transformation, forming a viscous three-dimensional network that regulates the hydration, swelling, erosion, and diffusion of Risedronate Sodium. Each polymer selectively contributed to the modulation of drug release. Sodium alginate facilitated rapid gelation through ionic crosslinking with calcium ions, forming an initial diffusion barrier. Carbopol 934P, a pH-responsive mucoadhesive polymer, swelled extensively in the acidic gastric environment and further reinforced gel structure for sustained release. HPMC K100M, a high-viscosity cellulosic polymer, enhances matrix strength by retaining absorbed water and forming a swelling-controlled diffusion layer, thereby significantly reducing drug mobility.

Formulations F1–F3, which contained lower polymer concentrations, produced loosely structured gel matrices that hydrated and eroded rapidly, resulting in faster drug release. These formulations released more than 80–85% of the drug within 10 h, indicating limited gel resistance to diffusion. F4–F6, which contained moderate polymer concentrations, exhibited a more balanced release profile. The synergistic

effect of Carbopol 934P and HPMC K100M led to improved mechanical integrity while allowing controlled diffusion, achieving 90–92% cumulative release over 10–12 h. In contrast, formulations F7–F10, characterized by high polymer content, generated dense and highly cross-linked matrices with high gel strength and viscosity. These features markedly restricted water penetration and matrix erosion, yielding slower and prolonged drug release, with 84–88% cumulative release at 12 h. However, owing to the highly compact gel network, a slight initial lag in drug diffusion was observed.

Among all formulations, F6 was identified as the optimum formulation. It exhibited the most favorable balance of sodium alginate, HPMC K100M, and Carbopol 934P, resulting in an ideal interplay between hydration, gel integrity, and diffusion. F6 sustained drug release for 12 h with approximately 90% cumulative release, which is appropriate for once-daily administration. It also demonstrated moderate swelling behavior (44% water uptake at 120 min), preventing premature erosion while maintaining consistent diffusion. Furthermore, F6 exhibited excellent buoyancy characteristics, with minimal floating lag time and a floating duration exceeding 12 h, indicating efficient gas retention and robust gel mechanical strength.

Taken together, the results highlight that polymer composition governs the mechanistic pathway of drug release through modulation of swelling, erosion, and diffusion, and formulation F6 displayed the most desirable performance for sustained gastro-retentive delivery of Risedronate Sodium.

Selection Of Optimized Formulation

The selection of the optimized formulation was based on a comprehensive evaluation of all physicochemical and performance parameters. Among the ten developed in situ gel formulations, F6 emerged as the optimal formulation.

Formulation F6 exhibited a desirable sustained-release profile, extending drug release up to 12 h with approximately 90% cumulative release, indicating its suitability for prolonged delivery of Risedronate Sodium. In addition, F6 demonstrated an excellent balance of key performance characteristics, including appropriate viscosity for pourability, high gel strength, favorable buoyancy behavior (short floating lag time and >12 h floating duration), suitable density, and uniform drug content. This combination of properties ensured prolonged gastric retention while maintaining controlled hydration and diffusion properties.

Overall, the results highlight that formulation F6 provides the most optimal interplay between gel integrity, mechanical stability, and drug-release kinetics, making it the most promising candidate for the gastro-retentive oral delivery of Risedronate Sodium.

In Vitro Release Kinetics

In-Vitro Release Kinetics

To elucidate the mechanism of drug release from the optimized formulation (F6), the in-vitro release data were fitted to various kinetic models, and the coefficient of determination (R^2) values were calculated (Table 14). The best-fit model was selected based on the highest R^2.

As shown in Table 14, formulation F6 demonstrated the highest linearity with the zero-order model (R^2 = 0.9950), indicating that drug release occurred at a constant rate independent of drug concentration, a characteristic of controlled-release systems. The release profile also showed a good correlation with the Higuchi (R^2 = 0.9730) and Hixson-Crowell (R^2 = 0.9825) models, suggesting that both diffusion through the polymer matrix and dissolution of the matrix contributed to drug release.

Further mechanistic analysis using the Korsmeyer–Peppas model showed excellent linearity (R^2 = 0.9960), and the release exponent (n) was greater than 0.45, confirming an anomalous (non-Fickian) transport. This indicates that the release of Risedronate Sodium from the in situ gel is governed by a combination of polymer relaxation/swelling and diffusion-controlled mechanisms.

Collectively, the kinetic modelling results revealed that the optimized formulation (F6) followed zero-order release kinetics with a non-Fickian diffusion mechanism, achieving sustained and controlled drug release over 12 h.

Table 14: R2 Values of various Kinetic Models of Optimized formulation (F6)

Kinetic Models	Coefficient of Determination (R2)
Zero order	0.9950
First Order	0.9250
Higuchi	0.9730
Hixon-Crowell	0.9825
Korsmeyer -Peppas	0.9960

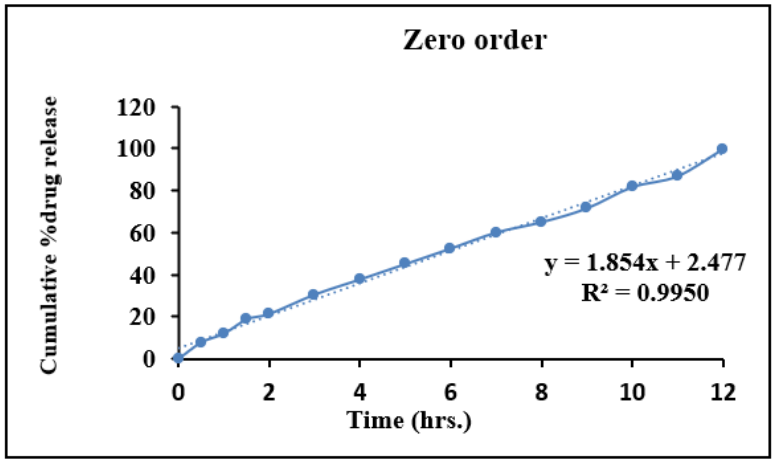

Figure 7: Zero order plot for optimized Risedronate Sodium Oral In situ Gel (F6)

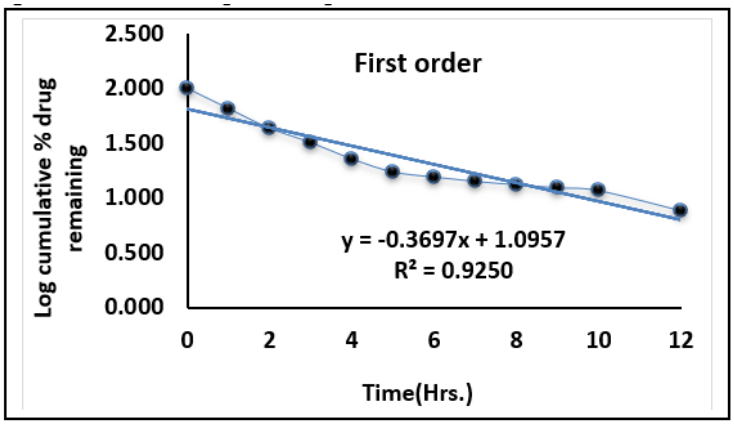

Figure 8: First order plot for optimized Risedronate Sodium Oral In situ Gel (F6)

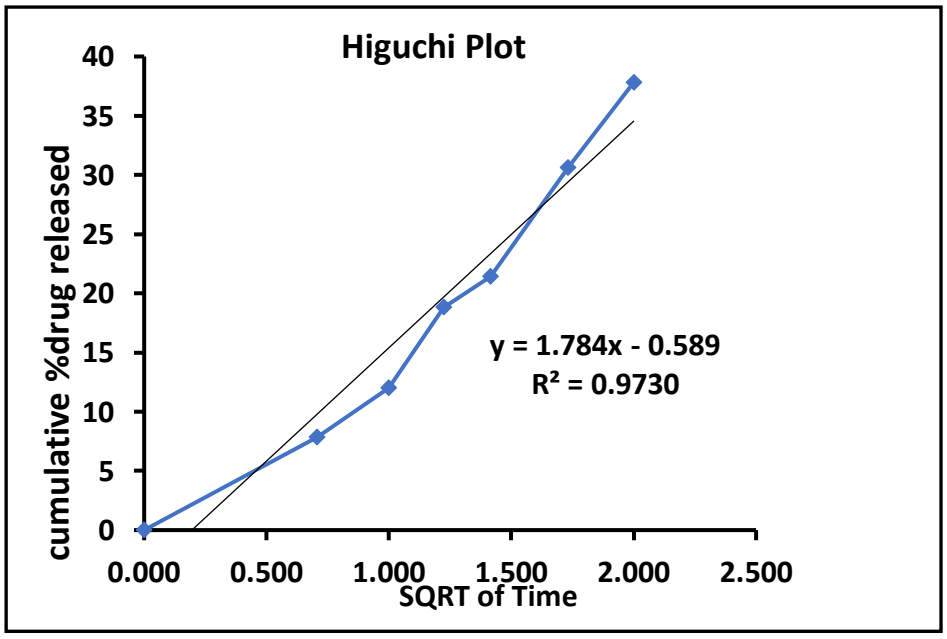

Figure 9: Higuchi plot for optimized Risedronate Sodium Oral In situ Gel (F6)

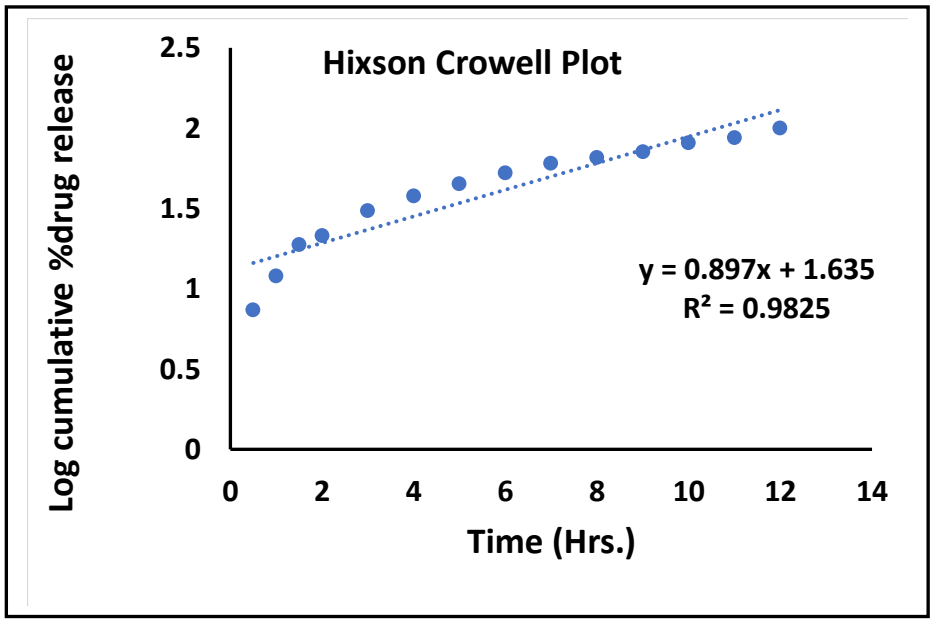

Figure 10: Hixson Crowell Plot for optimized Risedronate Sodium Oral In situ Gel (F6)

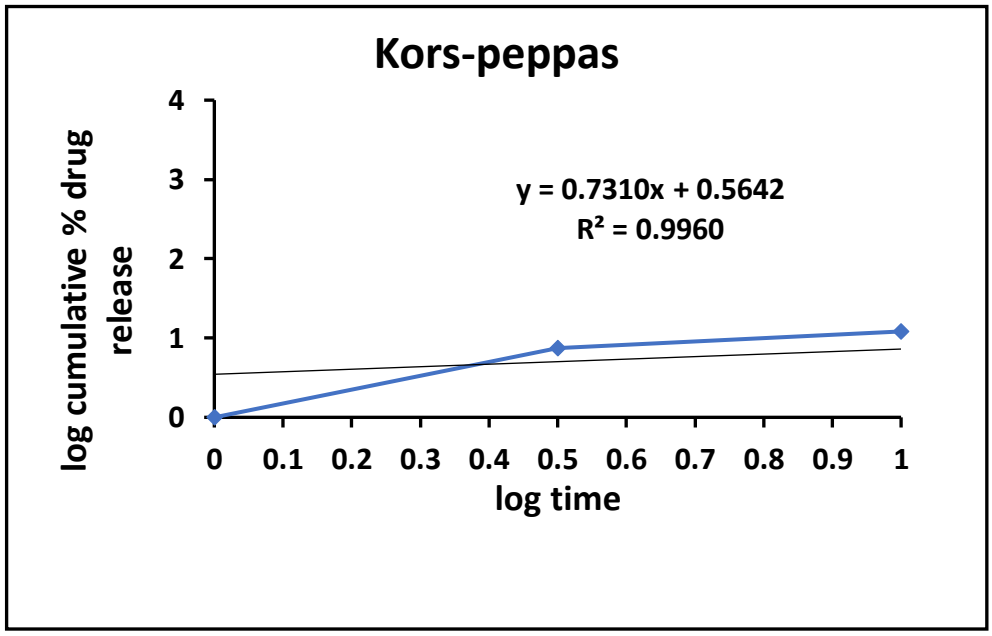

Figure 11: Kors –peppas Plot for optimized Risedronate Sodium Oral In situ Gel (F6)

Stability Studies

The optimized formulation (F6) was subjected to accelerated stability testing in accordance with ICH guidelines at 40 ± 2 °C / 75 ± 5% RH for a period of one month. The results of the stability evaluation are presented in Table 15

No significant changes were observed in the visual appearance, pourability, or gelling capacity of the formulation during the study period. The pH remained stable (7.30 ± 0.02 initially and 7.29 ± 0.20 after one month), indicating the absence of chemical degradation or polymer–drug interactions under stress conditions. The floating lag time and floating duration remained unchanged (≤30 s and >12 h, respectively), confirming that the buoyancy and gas-entrapping efficiency were retained over time.

Similarly, only minimal variation was noted in viscosity (260 ± 2.52 cps initially and 258 ± 2.10 cps after one month), demonstrating the stability of the gel structure and the polymer network. The drug content remained consistent throughout the study (98.10% initially and 98.06% after one month), confirming the absence of drug loss or degradation during the study period.

Overall, the accelerated stability data confirmed that formulation F6 remained physically, chemically, and functionally stable for at least one month, demonstrating its suitability for long-term storage and commercial translatio

Table 15: Stability data for Optimized Formulation – F6

Parameter	Condition:40±2ºC/75±5%RH	
	Initial	After1 month
Visual Appearance	White	White
Pourability	Easily pourable	Easily pourable
pH*	7.30 ± 0.02	7.29± 0.2
Gelling capacity	+++	+++
Floating Lag time(s)*	30± 2	30± 2
Floating duration (hours)	>12	>12
Viscosity(cps)*	260 ± 2.52	258± 2.10
Drug content(% w/v)	98.10	98.06

*n=3

Table 16: Cumulative % drug release of Optimized formulation- F6 for stability test

Time(hrs)	Condition:40±2ºC/75±5%RH	
	(%CDR) Initial	(%CDR) After 1 month
0	0	0
0.5	13	12.94
1	18	17.30
1.5	26	25.65
2	30	28.20
3	35	34.36
4	43	42.10
5	52	51.60
6	58	56.59
7	66	64.40
8	68.5	66.20
9	74.2	72.35
10	79.1	77.40

11	82.7	80.50
12	90.2	89.70

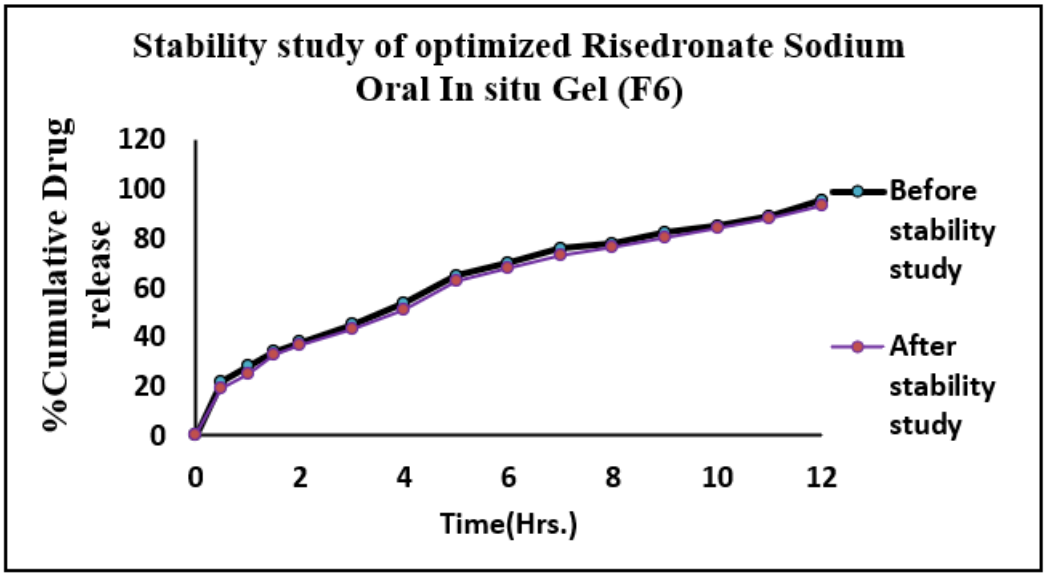

Figure 12: Invitro release of optimized Risedronate Sodium oral insitu gel (6) at stability study

To assess the effect of storage conditions on the release characteristics of the optimized formulation, the in vitro drug release profile of F6 was evaluated before and after one month of accelerated stability testing (40 ± 2 °C / 75 ± 5% RH). The cumulative percentage drug release values are presented in Table 16.

The release profiles obtained before and after storage were comparable across all time points. At the end of 12 h, the cumulative drug release was 90.2% initially and 89.7% after one month, indicating only a marginal and statistically insignificant difference. The similarity of the profiles demonstrates that the polymer network, gel integrity, and diffusion-controlled release mechanism remained unaffected under accelerated conditions.

Overall, these results confirm that the optimized formulation retained its sustained-release behaviour, buoyancy characteristics, and drug-loading efficiency during storage, further supporting the stability and robustness of formulation F6 for long-term gastro-retentive application.

DISCUSSION

The objective of the present investigation was to formulate a floating oral in situ gel of Risedronate Sodium to prolong gastric residence time and sustain drug release. Risedronate Sodium exhibits poor bioavailability and is primarily absorbed in the upper gastrointestinal tract; therefore, gastro-retentive systems can significantly enhance its therapeutic performance and patient compliance compared to conventional dosage forms (7,8).

Drug–excipient compatibility studies confirmed that the selected polymers and additives did not chemically interact with Risedronate Sodium. The FTIR spectra retained all major functional groups of the drug, consistent with earlier reports indicating that Sodium Alginate, HPMC, and Carbopol do not chemically alter bisphosphonate drugs (3,9). Therefore, the selected excipients were suitable for the development of a stable in situ gel system.

All formulations-maintained pH values within the physiological salivary range, ensuring their suitability for oral administration without causing irritation. Similar findings have been reported in earlier studies on floating in situ gels, where neutral pH helped maintain patient acceptability and improved formulation stability (2). Viscosity and gel strength increased proportionally with polymer concentration, consistent with the well-established swelling and hydration behaviors of HPMC and Carbopol in hydrophilic matrix systems (6).

The buoyancy and density results confirmed efficient CO_2 entrapment and prolonged gastric retention. Sodium Alginate reacts with calcium ions to promote ionic cross-linking and gel formation, whereas Carbopol and HPMC enhance viscosity and mechanical strength, contributing to a longer floating duration (3,10). The floating duration exceeding 12 h observed for formulations F5–F10 aligns with the reported requirements for sustained gastric residence in gastro-retentive delivery systems.

Drug release was significantly influenced by the polymer concentration. The faster release from F1–F3 was attributed to thinner and less compact gel matrices, whereas the highly cross-linked structure of the polymer-rich formulations (F8–F10) markedly restricted matrix hydration and drug diffusion, consistent with observations in other sustained in situ gel formulations (1,11). Among all formulations, F6 exhibited the most desirable drug release profile (~90% at 12 h), appropriate for once-daily administration.

Kinetic modelling revealed zero-order release with a strong correlation to the Korsmeyer–Peppas model and a release exponent indicating non-Fickian diffusion. This demonstrates that both swelling- and diffusion-controlled mechanisms contributed to drug release, consistent with gastro-retentive hydrophilic polymer matrices (12).

Stability studies confirmed that formulation F6 retained its physicochemical characteristics, buoyancy performance, and drug release profile without significant changes during storage. This supports its suitability for long-term pharmaceutical applications and commercialization, in line with ICH guidelines and previous reports on in situ gel stability (13).

Overall, the results demonstrate that a floating oral in situ gel system containing Sodium Alginate, HPMC K100M and Carbopol 934P can effectively sustain the gastric residence and release of Risedronate Sodium for up to 12 hours. The optimized formulation F6 represents a promising alternative to conventional tablets, offering enhanced bioavailability, prolonged drug action, and improved dosing convenience.

CONCLUSION

The present study successfully developed a floating oral in situ gel of Risedronate Sodium with the objective of prolonging gastric residence time and providing sustained drug release. Compatibility studies confirmed that the selected polymers—Sodium Alginate, HPMC K100M and Carbopol 934P—were chemically and physically compatible with the drug and suitable for formulation development. All prepared formulations demonstrated acceptable physicochemical characteristics, including physiological pH, appropriate viscosity, efficient sol-to-gel transition in an acidic medium, and excellent buoyancy performance.

The in vitro release study revealed a clear influence of polymer concentration on drug release kinetics, with higher polymer levels producing a more sustained release profile owing to denser gel matrices and reduced erosion. Among the ten formulations, F6 was identified as the optimized formulation, as it exhibited a desirable balance of viscosity, gel strength, floating ability (>12 h), and sustained drug release (~90% at 12 h). Kinetic modelling confirmed that F6 followed zero-order release behavior with a non-Fickian diffusion mechanism, indicating that both swelling and diffusion governed drug release.

Accelerated stability studies demonstrated that the optimized formulation retained its physicochemical integrity, buoyancy, and drug-release characteristics during storage, confirming its robustness and suitability for long-term application.

Overall, the findings of this study indicate that floating oral in situ gel technology represents a promising gastro-retentive platform for Risedronate Sodium delivery, offering the advantages of prolonged gastric retention, sustained release, reduced dosing frequency, and improved therapeutic effectiveness. However, the present work is limited to in-vitro evaluation and short-term accelerated stability testing, and it does not include in-vivo gastro-retention, pharmacokinetic validation, or long-term stability assessment. Therefore, further studies are recommended to confirm the in-vivo floating behavior, bioavailability enhancement, and safety profile of the optimized formulation (F6) through animal/human studies. Additionally, extended stability studies as per ICH guidelines, scale-up trials, and optimization of patient-friendly packaging and dosing conditions are suggested to support clinical translation and commercialization of this gastro-retentive delivery system.

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Conflict of Interest

The authors declare that there are no conflicts of interest regarding the publication of this study. This study was conducted purely for academic and scientific purposes, and no financial or non-financial benefits were received from any commercial or industrial organization that could influence the outcome of this research

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