FORMULATION, OPTIMIZATION AND CHARACTERISATION OF ORAL FLOATING *IN-SITU* GEL OF LOVASTATIN

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Abstract

This study aimed to develop and optimize an oral floating in-situ gel of Lovastatin to enhance bioavailability and therapeutic efficacy. Lovastatin was characterized using UV estimation, FTIR, and DSC to confirm its suitability. A 3^2 factorial design was employed to optimize the gel formulation, varying sodium alginate and pectin to achieve desirable viscosity and dissolution properties. Nine formulations were prepared with sodium alginate, pectin, HPMC, and other excipients using the hot plate technique. These formulations were evaluated for pH, viscosity, and drug content, gelation capacity, floating lag time, and floating duration. Drug release studies in 0.1N HCl demonstrated sustained release over 12 hours. FTIR and DSC analyses confirmed no interaction between Lovastatin and excipients, ensuring formulation stability. The optimized gel exhibited excellent gelling capacity, prolonged buoyancy, and controlled release, enhancing drug performance and patient compliance.

Key words: floating drug delivery system; in-situ gel; Lovastatin; controlled release; 3^2 factorial design; sodium alginate; pectin.

1. Introduction

In recent years, Floating Drug Delivery Systems (FDDS) have become a significant advancement in oral drug delivery, particularly for drugs that have specific absorption windows in the stomach or upper small intestine. FDDS are designed to float in the gastric environment due to their lower density compared to gastric fluids, which allows for prolonged gastric retention. This extended retention enhances drug absorption by keeping the drug in contact with the absorption sites for an extended period. Various dosage forms, including tablets, capsules, microspheres, and films, have been developed using FDDS technologies. Among these innovations, in-situ gelling systems have emerged as a notable advancement. These systems transition from a liquid state to a gel upon exposure to physiological conditions, providing sustained and localized drug release [1].

However, several challenges remain in the development and application of FDDS. Traditional floating systems often face issues with maintaining consistent buoyancy, achieving controlled drug release, and ensuring stability within the complex gastric environment. Additionally, individual variability in gastric emptying rates can lead to inconsistent therapeutic outcomes, affecting the efficacy of FDDS. In-situ gelling systems, while promising, encounter difficulties in optimizing gelation properties and ensuring that the gel remains buoyant and effective throughout the desired duration [2].

To address these challenges, this research focuses on developing advanced in-situ gelling systems designed for improved gastric retention and controlled drug release. By utilizing natural polymers such as sodium alginate and pectin, known for their gelation properties in the presence of gastric fluids, we aim to enhance gel stability and buoyancy. Sodium alginate, derived from brown seaweed, and pectin, a polysaccharide that gels in the presence of calcium ions, are selected for their ability to form robust gels that can sustain drug release while remaining buoyant in the stomach. Optimizing these polymers will address the performance issues associated with traditional FDDS and in-situ gelling systems [3,4].

This study aims to develop and evaluate Lovastatin-loaded in-situ gelling systems using sodium alginate and pectin. Lovastatin, an HMG-CoA reductase inhibitor with low oral bioavailability due to significant first-pass metabolism, is chosen to benefit from improved gastric retention and sustained release. The research involves preliminary studies, including UV estimation, Fourier-transform infrared spectroscopy (FTIR), melting point determination, and differential scanning calorimetry (DSC), to assess the compatibility of Lovastatin with the excipients and optimize the formulation. By advancing the development of these systems, the research will contribute valuable insights into enhancing drug bioavailability for therapeutic applications and improving natural polymer-based gelling systems for more effective drug delivery [5].

2. Materials and Methods

2.1. Estimation of Lovastatin by Ultraviolet Spectroscopy

2.1.1. Preparation of Standard Stock Solution of Lovastatin:

A standard stock solution of Lovastatin was prepared by dissolving 10 mg of pure Lovastatin in 50 ml of methanol in a 100 ml volumetric flask. The volume was adjusted to 100 ml with methanol, resulting in a concentration of 100 µg/ml[6].

2.1.2. Calibration Curve of Lovastatin in Methanol:

From the standard stock solution, various dilutions were prepared. Aliquots of 1 ml, 1.5 ml, 2 ml, 2.5 ml, 3 ml, 3.5 ml, 4 ml, 4.5 ml, and 5 ml were transferred into 25 ml volumetric flasks and diluted to the mark with methanol. The final concentrations were 4, 6, 8, 10, 12, 14, 16, and 18 µg/ml. The absorbance of these solutions was measured to construct a calibration curve within Beer's law range of 2-25 µg/ml [7].

2.1.3. Melting Point Determination:

The melting point of Lovastatin was determined using the open capillary method. Lovastatin was packed into a capillary tube, which was then heated in a melting point apparatus. The temperature at which melting began was recorded in triplicate, and the average melting point was calculated [8].

2.2. Compatibility Studies of Drug and Excipients

2.2.1. FT-IR Spectroscopy:

Compatibility of Lovastatin with excipients was assessed using Fourier-transform infrared (FT-IR) spectroscopy. Pellets were prepared by mixing the drug and polymers with potassium bromide (KBr) in a 1:100 ratio. The FT-IR spectra of Lovastatin, sodium alginate, and pectin were compared to evaluate the interactions between the drug and excipients [9].

2.2.2. Differential Scanning Calorimetry (DSC):

DSC was employed to analyze the thermal behavior and potential interactions between Lovastatin and polymers. The instrument was calibrated using Indium. Samples were sealed in aluminum pans, and the heating rate was set at 100°C/min under a nitrogen atmosphere[10].

2.3. Formulation Design Using 3^2 Factorial Design

2.3.1. Factors and Levels:

A 3^2 factorial design was utilized to formulate the floating oral in-situ gel. Sodium alginate and pectin were the two independent variables, each tested at three levels: low, medium, and high. This resulted in a factorial matrix of nine experimental formulations shown in Table 1.

Table 1. Experimental Combinations of Sodium Alginate and Pectin in Full Factorial Design

Sl no	Sodium Alginate (g)	Pectin (g)
1	0.3	0.3
2	0.3	0.5
3	0.3	0.7
4	0.5	0.3
5	0.5	0.5
6	0.5	0.7

7	0.7	0.3
8	0.7	0.5
9	0.7	0.7

2.4. Preparation of Floating Oral In-Situ Gel

The floating oral in-situ gel was formulated using a hot plate technique. Calcium chloride (cross-linking agent) and sodium citrate (neutralizing agent) were added to 100 ml of distilled water in a beaker. Sodium alginate and pectin were then mixed into 40 ml of this solution and heated to 60°C while stirring until completely dissolved. Hydroxypropyl methylcellulose (HPMC) was added, and the temperature was adjusted to 40°C. The solution was cooled to room temperature. Separately, Lovastatin was dissolved in 20 ml of the calcium chloride and sodium citrate solution using a sonicator. This drug solution was mixed into the polymer solution at room temperature [11,12]. The remaining excipients (sodium bicarbonate, sodium saccharine, and sodium benzoate) were added, and the final volume was adjusted to 100 ml with distilled water. The formulation table of floating oral in-situ gel was shown in table 2.

Table 2. Formulation Table

Sl no	**Ingredients (g)**	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
1	Lovastatin	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4
2	Sodium Alginate	0.3	0.3	0.3	0.5	0.5	0.5	0.7	0.7	0.7
3	Pectin	0.3	0.5	0.7	0.3	0.5	0.7	0.3	0.5	0.7
4	HPMC	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
5	Sodium Bicarbonate	1	1	1	1	1	1	1	1	1
6	Sodium Citrate	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25
7	Calcium Chloride	0.075	0.075	0.075	0.075	0.075	0.075	0.075	0.075	0.075
8	Sodium Saccharine	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
9	Sodium Benzoate	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
10	Distilled Water	qs	qs	qs	qs	qs	qs	qs	qs	qs

2.5. Evaluation of Prepared Floating Oral In-Situ Gel

2.5.1. pH Measurement:

The pH of 1 ml of each gel formulation was diluted to 25 ml with distilled water and measured using a pH meter. Measurements were taken in triplicate and averaged.

2.5.2. Viscosity of Formulated Suspension:

Viscosity was measured using a Brookfield viscometer DV-2P with spindle TL6. The sample was tested at various speeds (20, 30, 50, 60, 100, and 200 rpm), and the viscosity was recorded in cps. Measurements were performed in triplicate and averaged [13].

2.5.3. Viscosity After Gelling:

The viscosity after gelling was assessed using the Brookfield viscometer DV-2P with spindle L4. The gel was prepared by mixing the suspension with 100 ml of 0.1 N HCl. Viscosity measurements were taken at the same speeds as before, with data recorded in cps and averaged over triplicate tests[14].

2.5.4. Drug Content Estimation:

Drug content was determined by extracting 10 ml of the gel formulation (equivalent to 40 mg of Lovastatin) into a 100 ml volumetric flask. The solution was mixed with 50–70 ml of 0.1 N HCl and sonicated for 30 minutes. The volume was adjusted to 100 ml with 0.1 N HCl, filtered, and 10 ml of the filtered solution was diluted to 100 ml with 0.1 N HCl. The drug content was measured spectrophotometrically at 238 nm. Measurements were repeated in triplicate and averaged [15].

2.5.5. Gelation Time/In-Vitro Gelling Capacity:

The in-vitro gelling capacity was assessed by adding 10 ml of simulated gastric fluid (0.1 N HCl, pH 1.2) to a glass test tube containing 1 ml of each formulation. The time taken for the suspension to form a gel-like structure upon contact with the simulated fluid was recorded. Gelation capability was classified based on gelation time and duration [16].

2.5.6. Floating lag time:

The floating lag time of each formulation was measured by adding 1 ml of the prepared gel to 10 ml of 0.1 N HCL in a glass test tube. The time taken for the gel to start floating on the surface of the HCL solution was recorded using a timer [17].

2.5.7. Duration of floating:

The duration of floating was assessed by observing how long each formulation remained floating in 10 ml of 0.1 N HCL. The time was recorded from the moment the gel began to float until it sank [18].

2.5.8. In-vitro drug release studies:

In-vitro drug release was evaluated using a USP type II dissolution apparatus with a paddle stirrer at 50 rpm. The dissolution medium was 900 ml of 0.1 n HCL at 37 ± 0.5°c. A 10 ml aliquot of the prepared suspension was placed in the dissolution medium. Samples (8 ml each) were withdrawn at 0, 1, 2, 4, 6, 8, 10, and 12 hours, filtered through Whattman filter paper, and analyzed spectrophotometrically at 238 nm to determine the drug content. Measurements were taken in triplicate, and the average values were used for analysis[19-20].

3. Results

3.1. Analytical Studies

3.1.1. UV Spectra of Lovastatin:

The UV spectra of Lovastatin were recorded using methanol as the solvent. Lovastatin exhibited a maximum absorbance (λmax) at **238 nm**. The UV spectrum provides a key analytical method for quantitative estimation of Lovastatin shown in figure1.

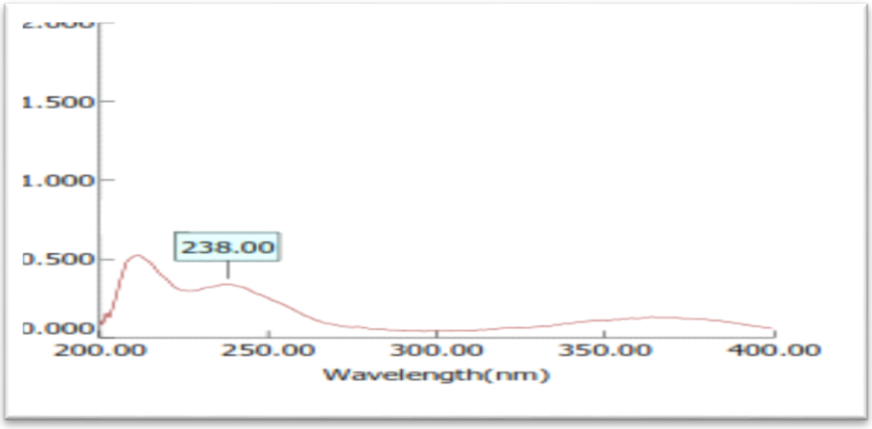

Figure 1. UV spectra of Lovastatin

3.1.2. Standard Calibration Curve of Lovastatin in Methanol:

A calibration curve was constructed for Lovastatin using methanol as the solvent. The absorbance values for different concentrations of Lovastatin (ranging from 0 to 18 µg/ml) were recorded, and the results are summarized in Table 3.

Table 3. Calibration Curve of Lovastatin in Methanol

Concentration (µg/ml)	Absorbance (±SD) (n=3)
0	0
2	0.112 ± 0.01
4	0.225 ± 0.02
6	0.349 ± 0.02
8	0.419 ± 0.04
10	0.529 ± 0.015
12	0.628 ± 0.02
14	0.735 ± 0.04
16	0.861 ± 0.03
18	0.945 ± 0.03

3.1.3. Standard Calibration Curve of Lovastatin:

A standard calibration curve was plotted using the absorbance values obtained for the various concentrations of Lovastatin.(Figure 2) The linear regression analysis of the standard curve is as follows:

- **Slope**: 0.0523
- **Intercept**: 0.01
- **Correlation Coefficient (R^2)**: 0.9986

The equation for the calibration curve, based on the linear regression analysis, is:

Absorbance=0.052X+0.01

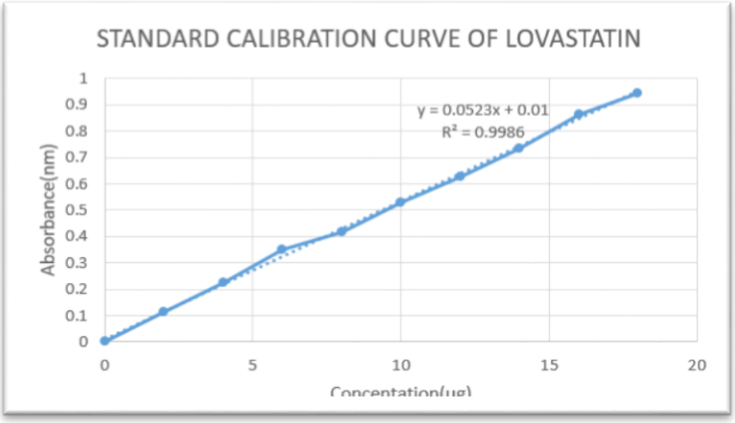

Figure 2. Standard calibration curve of Lovastatin

3.2. Preliminary Studies

3.2.1. Melting Point Determination:

The melting point of Lovastatin was determined using the open capillary method. Lovastatin starts melting at **154°C** and completely melts at **174.5°C**, which aligns with the reported literature values, indicating the purity of the drug sample.

3.2.2. FTIR Spectrum of Pure Drug Lovastatin:

The FTIR spectrum of pure Lovastatin was recorded, and the characteristic peaks of functional groups were identified (Table 4, Figure 3). The results showed the presence of significant functional groups such as hydroxyl, amides, carboxylic acids, and C-H stretching, confirming the drug's structure.

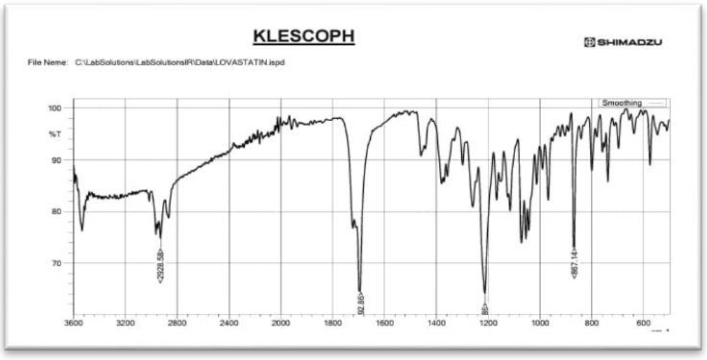

Figure 3. FTIR spectra of pure drug

Table 4. FTIR Spectral Peaks of Pure Drug Lovastatin

Functional Group	Wavelength (cm^{-1})
Hydroxyl (-OH)	2928.58
Amides (N-H)	1692.86
Carboxylic acid (C=O)	1212.86
C-H stretching	867.14
C=C stretching	1428.12

3.2.3. FTIR Spectrum of Physical Mixture (Lovastatin + Sodium Alginate + Pectin)

The FTIR spectrum of the physical mixture of Lovastatin and excipients (Sodium Alginate + Pectin) was also recorded. The results are summarized in Table 5, Figure 4. where the presence of functional groups remained consistent, indicating no significant interaction between the drug and the excipients.

Figure 4. FTIR spectra of physical mixture of drug and polymers

Table 5. FTIR Spectral Peaks of Physical Mixture of Lovastatin and Excipients

Functional Group	Wavelength (cm^{-1})
Hydroxyl (-OH)	1700.00
Amides (N-H)	1984.29
Carboxylic acid (C=O)	2928.58
C-H stretching	3391.44
C=C stretching	1811.23

The absence of any major changes in the FTIR spectra of the physical mixture, compared to the pure drug, indicates that there is no significant interaction between the drug and the excipients under the given conditions.

3.2.4. Differential Scanning Calorimetry (DSC) of Pure Drug Lovastatin

The DSC analysis of pure Lovastatin was performed to evaluate its thermal properties. The DSC thermograph showed a characteristic endothermic peak at **171.68°C**, which corresponds to the melting point of Lovastatin. The thermal profile confirmed the purity of the drug, as it aligns with the reported literature values. DSC spectra of pure drug was shown in figure 5.

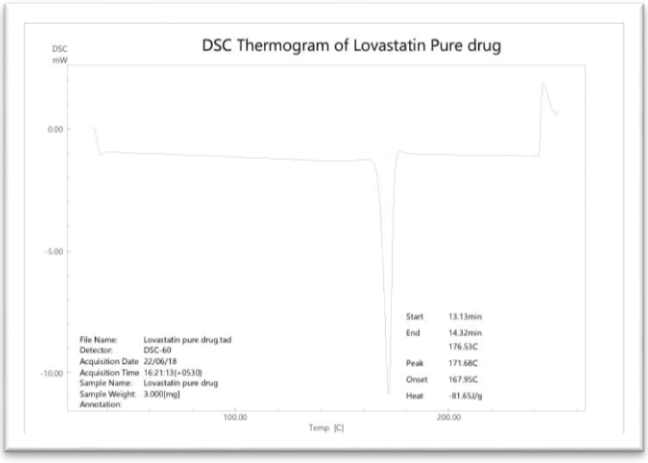

Figure 5. DSC spectra of pure drug

3.3. Evaluation parameters of all nine formulations

3.3.1. Drug Content:

The drug content for all nine formulations ranged from **94.1±0.21% to 98.4±0.57%**, which indicates that the formulations had a consistent and reliable drug-loading capacity. This ensures the desired dosage is maintained across all batches, with F3 formulation demonstrating the highest drug content.

3.3.2. pH:

The pH values for all formulations were within a narrow range of **4.0±0.01 to 4.1±0.03**. This slightly acidic pH ensures the formulation is suitable for oral administration and does not cause irritation to the gastric mucosa. The small variation indicates excellent consistency in the formulation process.

3.3.3. Gelation Time:

The gelation time for all formulations was recorded as **<10 seconds**, which is desirable for in-situ gel formulations as it indicates that the solution quickly transitions to a gel upon administration, forming a stable structure for drug release.

3.3.4. Floating Lag Time:

The floating lag time for all formulations was less than 1 minute, ensuring that the formulation floats almost immediately after administration. This rapid floating behavior is essential for maintaining the formulation in the upper gastrointestinal tract, where it can deliver the drug more effectively over a prolonged period.

3.3.5. Duration of Floating:

All formulations exhibited a floating duration of **more than 12 hours**, which is essential for a sustained drug release system. All the evaluation parameters of formulations were shown in Table 6.

Table 6. Evaluation parameters of Formulations

Sl no	Drug content (%)	pH	Gelation time(sec)	Floating lag time(min)	Duration of floating(hr)
1	98.4±0.57	4.1±0.01	<10	<1	>12
2	97.1±1.92	4.0±0.02	<10	<1	>12
3	98.4±0.04	4.1±0.01	<10	<1	>12
4	96.1±1.74	4.1±0.03	<10	<1	>12
5	95.1±0.43	4.0±0.03	<10	<1	>12
6	97.6±1.92	4.1±0.2	<10	<1	>12
7	94.1±0.21	4.0±0.02	<10	<1	>12
8	95.1±0.32	4.1±0.03	<10	<1	>12
9	94.6±0.04	4.0±0.01	<10	<1	>12

3.3.6. Viscosity of floating oral *in-situ* gel before gelling:

All formulations exhibited shear-thinning behavior with decreasing viscosity at higher RPMs,(Table 7) which is characteristic of pseudoplastic fluids. Formulations F8 and F9 showed the highest viscosities across the RPM range, indicating higher resistance to flow in suspension. This suggests that these formulations might have a more complex or concentrated gel-forming matrix.

Table 7. Viscosity of suspension

Sl no	20rpm	30rpm	50rpm	60rpm	100 rpm	200 rpm
F1	1178±22	777±8	465±7	395±8	220±5	115±7
F2	1256±14	884±5	495±13	425±6	222±8	120±4
F3	1480±15	954±9	510±7	455±5	235±6	126±7
F4	1375±10	912±12	520±8	465±6	246±4	128±8
F5	1442±82	950±16	535±8	472±4	258±8	131±6
F6	1466±12	960±12	545±5	451±7	267±4	135±7
F7	1378±13	965±15	562±6	456±9	273±7	138±4
F8	1490±14	975±12	577±7	476±7	285±8	144±7
F9	1498±16	985±8	588±7	492±7	297±7	147±8

3.3.7. Viscosity of floating oral *in-situ* gel after gelling:

There was a marked increase in viscosity after gelation for all formulations, demonstrating effective gel formation. The highest viscosities were observed for formulations F9, F8, and F3, indicating the formation of stronger gel networks. Formulation F9, in particular, exhibited the highest viscosity at lower RPMs, suggesting a more robust gel structure. This implies that F9 could provide better stability and a longer floating duration in the gastrointestinal tract compared to the other formulations(Table 8).

Table 8. Viscosity of floating oral *in-situ* gel after gelling

Sl no	RPM					
	20rpm	**30rpm**	**50rpm**	**60rpm**	**100 rpm**	**200 rpm**
F1	20864±42	10330±34	6839±26	5783±28	3572±37	2134±22
F2	22479±36	11276±24	8785±42	6266±46	3992±27	2130±28
F3	26438±25	14643±42	9875±62	8494±46	4454±20	2893±28
F5	24838±62	13282±52	9685±34	7629±42	5252±18	2423±36
F6	24728±54	14892±25	10577±27	8583±35	5493±19	2293±25
F7	25423±56	13739±34	11628±16	7932±44	4343±42	2432±18
F8	27893±64	15608±43	10637±43	8607±42	5992±29	2773±22
F9	28698±75	15830±29	11229±54	8823±26	5893±35	2930±16

Values expressed as mean± S.D, n=3

3.3.8. Comparison of Viscosity Data:

The viscosity of the gels was significantly higher than that of the suspensions, confirming the successful transition from a flowable state to a gel-like consistency. This increase in viscosity is crucial for ensuring prolonged gastric retention and controlled drug release.

3.3.9. *In-vitro* drug release studies of all nine formulations:

In the in-vitro drug release studies,(Table 9, Figure 8) the cumulative percentage drug release (CDR) over 12 hours varied among the nine formulations. At 1 hour, F1 showed the highest release at 32.21%, while F3 had a lower release of 27.92%. By 4 hours, F1 and F2 reached 57.03% and 55.25% CDR, respectively, with F3 at 46.96%. At the 12-hour mark, F1 achieved 99.13% release, F2 reached 98.42%, and F3 showed a release of 97.82%. These results indicate that F1 and F2 provided a more rapid and complete drug release compared to the other formulations, highlighting their effectiveness for applications requiring high and swift drug release.

Table 9. *In-vitro* drug release oral *in-situ* gel

TIME (hrs)	Percent cumulative drug release								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	32.21	29.42	27.92	24.65	24.13	21.31	21.31	21.32	21.31
2	39.44	31.64	29.60	27.50	29.56	29.60	30.16	27.57	27.75
3	43.66	36.11	33.32	30.21	33.32	30.26	31.35	30.12	31.84
4	57.03	55.25	46.96	33.29	42.8	40.07	42.51	32.68	36.11
5	61.26	59.12	59.37	39.90	48.13	44.63	45.63	40.10	41.78
6	63.12	64.57	61.39	42.21	51.22	49.56	55.53	46.89	43.89
7	78.41	65.03	64.27	51.43	57.10	57.13	59.74	52.55	55.31
8	84.41	82.24	65.37	56.86	65.61	62.37	64.57	57.06	57.03
9	92.009	85.35	83.02	76.03	73.69	76.27	68.81	65.57	64.68
10	96.06	95.02	85.96	77.34	84.78	81.37	76.77	76.24	72.26
11	99.13	98.42	94.09	78.66	90.48	89.44	83.43	84.78	78.41
12			97.82	93.06	93.66	93.46	91.71	89.44	83.18

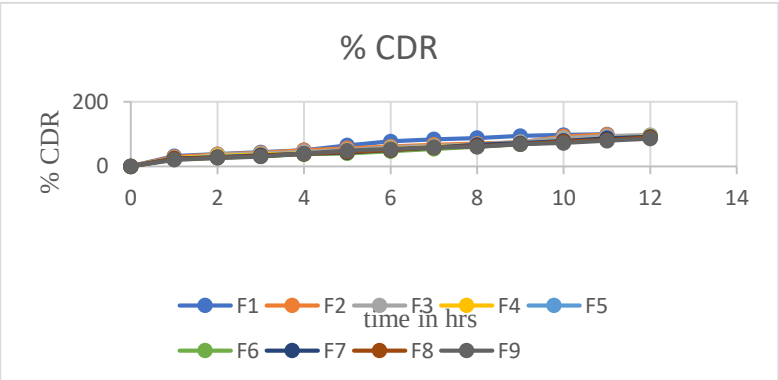

Figure 8. Cumulative percent of drug release

3.3.10. VISCOSITY OF SOL & GEL OF OPTIMIZED FORMULATION :

For the optimized formulation, viscosity measurements of the suspension revealed a shear-thinning behavior, with viscosities decreasing from 1482 ± 15 cps at 20 RPM to 129 ± 7 cps at 200 RPM, indicating a pseudoplastic flow characteristic. Upon gelling, the viscosity increased substantially, reaching 26,781 ± 27 cps at 20 RPM and decreasing to 2,877 ± 24 cps at 200 RPM. This notable increase in viscosity after gelation confirms the successful formation of a robust gel network, which is essential for maintaining prolonged gastric retention and controlled drug release. The significant difference in viscosity between the suspension and the gel underscores the effectiveness of the gelation process in achieving the desired rheological properties for the floating oral in-situ gel.

Table 10. Viscosity of sol and gel of optimized formulation

RPM	Viscosity of suspension in Cps	viscosity of gel in Cps
20	1482±15	26781±27
30	944±8	14489±42
40	524±7	9867±62
60	463±5	8276±45
100	248±6	4437±20
200	129±7	2877±24

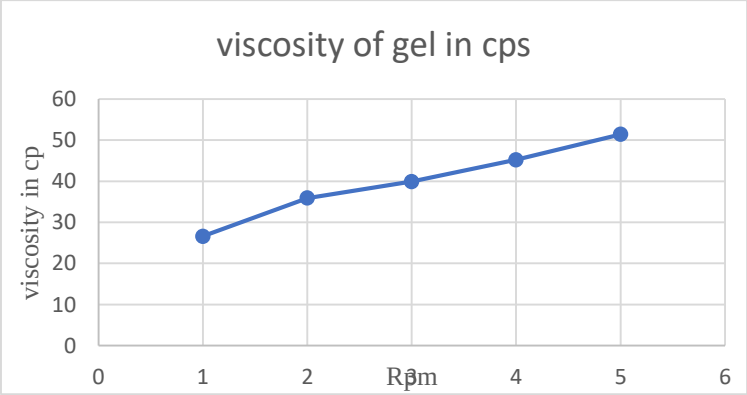

Figure 9. Viscosity of optimized formulation

3.3.11. Percent CDR of optimized formulation

For the optimized formulation, the in-vitro drug release profile demonstrated a well-controlled and consistent release over the 12-hour period. (Table 10, Figure 10) Initially, the release was moderate but progressively increased, indicating an effective and sustained release mechanism. The formulation showed a continuous rise in drug release, reaching a high level by the end of the observation period. This behavior highlights the formulation's ability to maintain a prolonged release, ensuring extended therapeutic efficacy.

Table 10. Percent CDR of optimized formulation.

Time in Hrs	% CDR
1	26.7
2	36.9
3	39.5
4	45.3
5	52.4
6	58.3
7	63.9
8	67.05
9	75.8
10	86.8
11	94.7
12	97.2

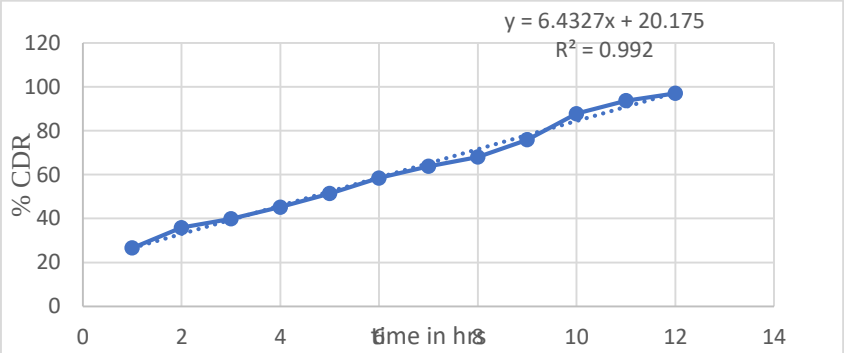

Figure 10. Percent CDR of optimized formulation.

4. Conclusion

In conclusion, the development and optimization of oral floating in-situ gels for Lovastatin have proven to be successful across multiple parameters. Utilizing a 3^2 factorial design facilitated the precise formulation of nine different gels, each demonstrating desirable characteristics. The formulations exhibited appropriate pH levels and effective gelation, ensuring stability and consistency. The floating duration of the gels was satisfactory, with formulations maintaining buoyancy over extended periods. Notably, the cumulative drug release from the formulations ranged between 96.54% and 99.13% over 12 hours, indicating a controlled and sustained release profile. Viscosity measurements before and after gelation confirmed the gels' ability to maintain desirable consistency, crucial for prolonged gastric retention. Stability studies demonstrated that Lovastatin remained stable within the gel matrix throughout the storage period. The optimized formulations, especially F1 and F2, showed significant potential for enhancing bioavailability and therapeutic efficacy of Lovastatin, while also improving patient compliance through their sustained release and effective floating properties. These findings suggest that the developed gels are promising candidates for further clinical evaluation, offering potential advancements in oral drug delivery systems.

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