RESEARCH PAPER

Design, Optimization, and Comprehensive Evaluation of Mucoadhesive Gastro-Retentive Tablets of Silymarin and Glycyrrhizin Using a QbD-Driven Approach

Misbah Sultana Abdul Kausar Badewale[1, 2*] and Varsha Siddheswar Tegeli[2]

[1]Research Scholar, Punyashlok Ahilyadevi Holkar Solapur University, Solapur-Pune National Highway, Kegaon, Solapur-413255, Maharashtra, India*
[2]Associate Professor, D.S.T.S. Mandal's College of Pharmacy, Solapur-413255, Maharashtra, India
*[*]**Corresponding Author:** Ms. Misbah Sultana Abdul Kausar Badewale, Assistant Professor, Gandhi Natha Rangaji College of Diploma Pharmacy, Solapur.*
Email: misbahp1@yahoo.com

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ABSTRACT
The present study focuses on the design, optimization, and comprehensive evaluation of mucoadhesive gastro-retentive tablets of silymarin and glycyrrhizin using a Quality by Design (QbD)-driven approach. Silymarin and glycyrrhizin are bioactive compounds with limited oral bioavailability due to poor aqueous solubility and short gastric residence time. The mucoadhesive gastro-retentive tablet formulation was developed to enhance gastric retention, prolong drug release, and improve therapeutic efficacy. A systematic QbD approach was employed to optimize the formulation variables, including the concentration of mucoadhesive polymers (e.g., chitosan, carbopol) and release-retarding polymers. The tablets were evaluated for physicochemical properties, mucoadhesive strength, swelling index, in vitro drug release, and ex vivo residence time. The optimized formulation demonstrated satisfactory mucoadhesive properties, sustained release profile, and improved stability. The results indicate that the QbD-driven development of mucoadhesive gastro-retentive tablets is a promising strategy for enhancing the oral bioavailability of silymarin and glycyrrhizin, offering a potential therapeutic benefit for liver-related disorders.

Keywords: Silymarin; Glycyrrhizin; Mucoadhesive; Gastro-retentive; Quality by Design (QbD); Sustained release.
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1. INTRODUCTION

Liver disorders, including hepatic inflammation, fibrosis, and toxin-mediated injury, continue to pose substantial global health challenges and necessitate the development of effective hepatoprotective therapies [1]. In recent years, herbal bioactives have emerged as promising candidates due to their broad-spectrum antioxidant, anti-inflammatory, antifibrotic, and immunomodulatory activities. Among these, Silymarin, a flavonolignan complex derived from *Silybum marianum*, and Glycyrrhizin, a triterpenoid saponin obtained from *Glycyrrhiza glabra*, are extensively recognized for their clinical hepatoprotective potential. Silymarin promotes hepatic regeneration, inhibits lipid peroxidation, and stabilizes hepatocyte membranes, while Glycyrrhizin modulates inflammatory mediators, exerts antiviral effects, and protects hepatic tissue from structural and functional degeneration [2].

Despite their strong pharmacological profiles, both phytoconstituents exhibit poor aqueous solubility, limited permeability, and extensive first-pass metabolism, leading to suboptimal bioavailability following oral administration [3-4].

Gastro-retentive drug delivery systems (GRDDS) address these challenges by maintaining the dosage form in the stomach for extended periods, thereby optimizing absorption of drugs with preferential uptake in the upper GIT. Among GRDDS, mucoadhesive systems offer distinct advantages, as they adhere to gastric mucosa and resist peristaltic movement, ensuring sustained residence and prolonged drug release. Polymers such as Carbopol 974P, employed in this study for its superior mucoadhesive strength and favorable safety profile, hydrate upon contact with gastric fluid to form a cohesive gel barrier that anchors the dosage form and modulates drug diffusion [5-6].

The combination of Silymarin and Glycyrrhizin is scientifically justified based on their complementary mechanisms of hepatoprotection. Silymarin primarily reduces oxidative stress and stabilizes hepatocyte membranes, while Glycyrrhizin suppresses inflammatory cytokines such as TNF-α and IL-6, enhances hepatocyte regeneration, and exhibits antifibrotic activity, rendering the combination advantageous for chronic liver disorders [7]. Their similar solubility behavior in acidic environments further supports co-formulation. FTIR

**Author for Correspondence: misbahp1@yahoo.com*

compatibility studies conducted in this work confirmed the absence of chemical interactions between the two drugs and excipients, validating their suitability for incorporation into a single controlled-release matrix [8].

In alignment with current regulatory and industrial expectations, the present study adopts a Quality by Design (QbD) framework to systematically develop and optimize mucoadhesive gastro-retentive tablets of Silymarin and Glycyrrhizin. The research encompasses comprehensive pre-formulation assessment including solubility profiling, wavelength selection, and drug–excipient compatibility supported by spectrophotometric and FTIR analyses [9]. A Central Composite Design (CCD), generated using Design Expert® software, was employed to evaluate the influence of critical material attributes (Carbopol 974P and PVP K30 concentrations) on key response variables such as mucoadhesive strength, swelling index, and in-vitro release kinetics. The statistical outputs, including ANOVA and predictive modeling, confirmed the significance of a quadratic model for optimizing formulation performance [10].

Subsequent evaluations of flow properties, compression characteristics, mechanical strength, drug content uniformity, swelling behavior, mucoadhesion, and dissolution profiles enabled the selection of an optimized formulation capable of sustaining drug release for up to 18 hours with robust mucoadhesive performance. Overall, the study integrates phytopharmaceutical science with advanced gastro-retentive technology under a QbD-guided framework, offering a rational and clinically relevant approach for enhancing the therapeutic potential of Silymarin and Glycyrrhizin in liver disease management [11,12].

2. MATERIALS AND METHODS

2.1 Materials

Silymarin and Glycyrrhizin were procured as gift samples of analytical grade. The excipients included Carbopol 974P (mucoadhesive polymer), PVP K30 (binder), Lactose monohydrate and Microcrystalline Cellulose (MCC) (diluents), and Colloidal Silicon Dioxide (glidant). All chemicals used for analytical procedures—including methanol, hydrochloric acid (0.1 N), and phosphate buffer pH 6.8—were of reagent grade. Double-distilled water was used throughout the study.

2.2 Pre-formulation Studies

2.2.1 Solubility Studies

The solubility of Silymarin and Glycyrrhizin was assessed in water, 0.1 N HCl, methanol, and phosphate buffer (pH 6.8). An excess quantity of drug (≈100 mg) was added to 5 mL of each solvent and shaken for 24 h using a mechanical shaker. The samples were filtered through a 0.45 µm syringe filter, diluted suitably, and analyzed at 288 nm (Silymarin) and 250 nm (Glycyrrhizin) using a UV–Visible spectrophotometer [13].

2.2.2 Wavelength Selection

Standard solutions (10 µg/mL) of Silymarin and Glycyrrhizin in 0.1 N HCl were scanned from 190–400 nm using a UV–Visible spectrophotometer. The λmax was found to be 288 nm for Silymarin and 250 nm for Glycyrrhizin [14].

2.2.3 Calibration Curve

Standard stock solutions were prepared and diluted to yield 0–20 µg/mL for Silymarin and 0–15 µg/mL for Glycyrrhizin in 0.1 N HCl. Absorbance values were recorded at their respective λmax and calibration curves were constructed [15].

2.2.4 Drug–Excipient Compatibility Studies (FTIR)

Fourier Transform Infrared (FTIR) spectroscopy was performed using the KBr pellet method. Pure drugs, polymers, and optimized formulations (before and after stability exposure at 40 °C / 75% RH for 4 weeks) were scanned in the range 4000–400 cm^{-1}. Spectra were examined for potential chemical interactions [16].

2.3 Prototype Development

Five preliminary formulations (Trials 1–5) were prepared using direct compression to determine suitable concentrations of polymer and binder. Powder blends were passed through a #40 mesh, mixed geometrically, lubricated, and compressed. Tablets were evaluated for hardness, friability, thickness, and overall integrity. Trial 5 exhibited optimal mechanical characteristics and was selected for further optimization [17].

2.4 Formulation of Mucoadhesive Gastro-retentive Tablets

Nine formulations (F1–F9) were prepared using direct compression. Each 400 mg tablet contained fixed amounts of Silymarin (40 mg), Glycyrrhizin (40 mg), MCC (75 mg), and colloidal silicon dioxide (8 mg), while concentrations of Carbopol 974P (40–60 mg) and PVP K30 (50–70 mg) were varied according to the design matrix.

Powder blends were mixed uniformly, lubricated, and compressed using a rotary tablet press with a 10 mm flat punch [18].

2.5 Experimental Design (QbD-Based Optimization)

A Central Composite Design (CCD) with two independent factors was used:

- **A:** PVP K30 (50–70 mg)
- **B:** Carbopol 974P (40–60 mg)

The primary response modeled was:

- Mucoadhesive Strength (g / N)

Design Expert (Version 13) generated 9 experimental runs, including factorial, axial, and center points. ANOVA was performed to determine model significance and predict optimized factor levels [19].

2.6 Evaluation of Pre-Compression Parameters

2.6.1 Bulk and Tapped Density

Powder blend was poured into a graduated cylinder to record bulk volume, then subjected to 100 taps to determine tapped volume. Density values were used to calculate Carr's Index and Hausner Ratio.

2.6.2 Angle of Repose

Flowability was evaluated using the fixed-funnel method, and the angle of repose was calculated using:

$$Angle\ of\ Repose\ (\theta) = \frac{tan^{-1} height(cms)}{radius(cms)}$$

2.6.3 Carr's Index and Hausner Ratio

Calculated from bulk and tapped densities using standard equations to assess compressibility and flow [20].

2.7 Evaluation of Post-Compression Parameters

2.7.1 Hardness

Measured using a Monsanto hardness tester, expressed as kg/cm².

2.7.2 Thickness and Diameter

Determined using a digital Vernier caliper (accuracy 0.01 mm).

2.7.3 Friability

Ten tablets were weighed and rotated at 100 rpm for 4 min in a Roche friabilator. Percent weight loss was calculated.

2.7.4 Weight Variation

Ten tablets were weighed individually and compared to the average weight.

2.7.5 Drug Content

Powder equivalent to one tablet was dissolved in methanol, sonicated for 30 min, filtered, diluted, and analyzed at 288 nm and 250 nm.

2.8 Swelling Index

Each tablet (W_1) was placed in 200 mL of 0.1 N HCl at 37 °C ± 0.5°C. Tablets were removed at predetermined intervals (1–18 h), blotted, and reweighed (W_2). Swelling index was calculated:

SI= (W2- W1)/W1

2.9 In-Vitro Mucoadhesive Strength

Fresh sheep stomach mucosa was fixed on a platform, and the tablet was adhered to the mucosal surface. Weight was gradually added until detachment occurred. Mucoadhesive force (N) was calculated using:

$$Adhesion\ Force\ (N) = \frac{Mucoadhesive\ Strength}{1000} \times 9.81$$

2.10 In-Vitro Drug Release Studies

Drug release was evaluated using USP Type II (Paddle) apparatus containing 900 mL of 0.1 N HCl at 37 ± 0.5°C and 50 rpm. Samples (5 mL) were withdrawn at predetermined intervals up to 18 hours, filtered, and analyzed spectrophotometrically. Withdrawn volume was replaced with fresh medium [21].

2.11 Statistical and Kinetic Data Analysis

Release data were fitted to kinetic models (Zero-order, First-order, Higuchi, Korsmeyer–Peppas) to elucidate the release mechanism. Optimization results and model predictions were generated using Design Expert.

2.12 Stability Studies

Optimized formulations were stored at 40°C ± 2°C / 75% RH ± 5% for 30 days. Post-study evaluations included drug content, mucoadhesive strength, swelling, and release profile comparisons [22].

3. RESULTS AND DISCUSSION

3.1 Pre-formulation and Analytical Characterization

The preliminary solubility studies demonstrated that both Silymarin and Glycyrrhizin exhibit limited aqueous solubility but improved solubility in acidic and organic media. Silymarin showed comparatively higher solubility in 0.1 N HCl, whereas Glycyrrhizin exhibited superior solubility in methanol, confirming their suitability for gastro-retentive delivery where acidic gastric conditions prevail. These findings justified the selection of a gastric retention approach to enhance drug availability (Table 1 and Table 2).

Table 1: Results of Solubility of Silymarin

Solvent	Absorbance	Conc (µg/ml)	Dilution	Actual Conc (mg/ml)
Water	0.156	3.78	10	0.038
0.1N HCl	0.373	9.58	100	0.953
Methanol	0.172	4.20	100	0.420
Phosphate buffer pH 6.8	0.314	7.96	100	0.796

Table 2: Results of Solubility of Glycyrrhizin

Solvent	Absorbance	Conc (µg/ml)	Dilution	Actual Conc (mg/ml)
Water	0.635	11.71	100	1.171
0.1N HCl	0.106	2.02	100	0.202

Methanol	0.782	14.41	500	7.203
Phosphate buffer pH 6.8	0.165	3.10	100	0.310

UV spectrophotometric analysis revealed well-defined absorption maxima at 288 nm for Silymarin and 250 nm for Glycyrrhizin, ensuring reliable analytical quantification (Figure 1 and Figure 2). The calibration curves for both drugs showed excellent linearity within the studied concentration ranges, confirming method accuracy and suitability for dissolution and content analysis (Table 3 and Table 4)

Table 1: Results of Calibration curve of Silymarin

Conc (µg/ml)	Absorbance
0	0.000
4	0.177
8	0.322
12	0.466
16	0.617
20	0.763

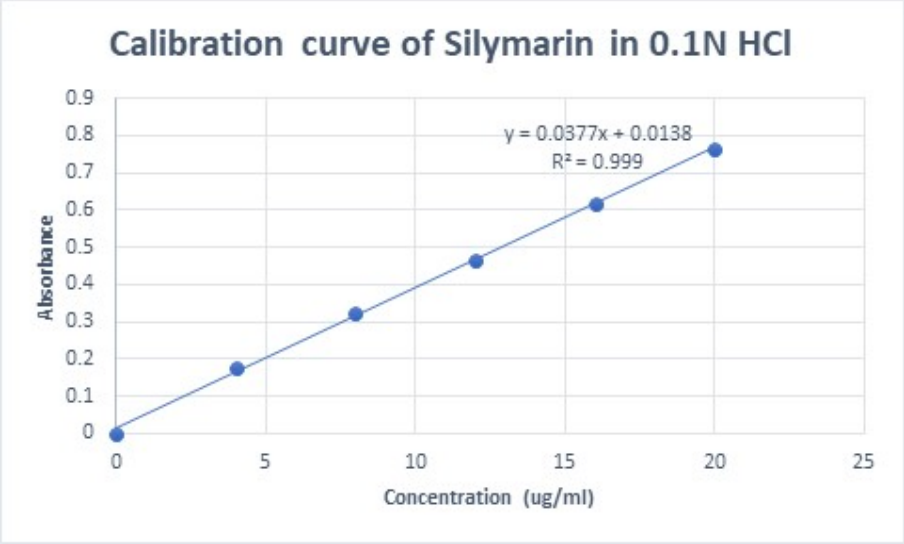

Figure 1: Calibration curve of Silymarin

Table 2: Results of Calibration curve of Glycyrrhizin

Conc (µg/ml)	Absorbance
0	0.000
3	0.164
6	0.317
9	0.481
12	0.645
15	0.824

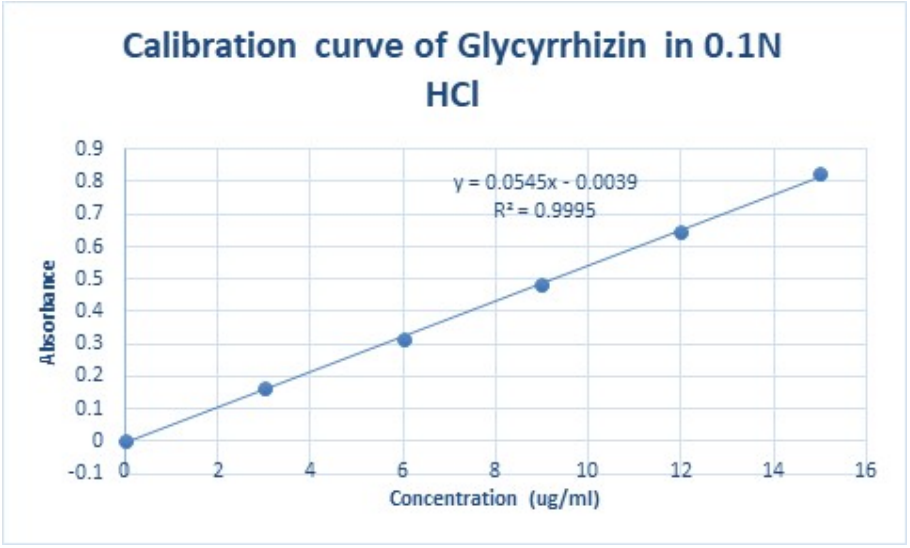

Figure 2: Calibration curve of Glycyrrhizin

3.2 Drug–Excipient Compatibility

FTIR studies confirmed the chemical stability of Silymarin and Glycyrrhizin both individually and in combination with Carbopol 974P, PVP K30, lactose monohydrate, MCC, and colloidal silicon dioxide. The preservation of characteristic functional group peaks without shifts or disappearance confirmed the absence of drug–drug and drug–excipient interactions. Representative FTIR spectra are presented in Figure 3. These findings validate the physicochemical compatibility of all formulation components, ensuring formulation stability during processing and storage

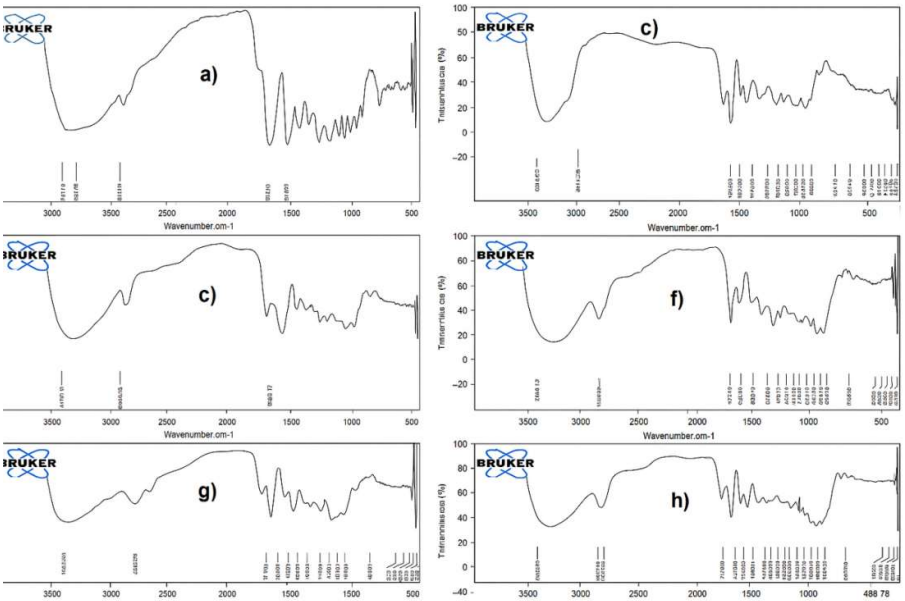

Figure 3: FTIR spectra of Silymarin, Glycyrrhizin, and their compatibility with formulation excipients: *(a) FTIR spectrum of Silymarin; (b) FTIR spectrum of Glycyrrhizin; (c) IR spectrum of Silymarin and Glycyrrhizin; (d) FTIR spectrum of Silymarin and Glycyrrhizin with Carbopol 974P; (e) IR spectrum of Silymarin and Glycyrrhizin with PVP K30; (f) IR spectrum of Silymarin and Glycyrrhizin with Lactose Monohydrate; (g) IR spectrum of Silymarin and Glycyrrhizin with Microcrystalline Cellulose; (h) IR spectrum of Silymarin and Glycyrrhizin with Colloidal Silicon Dioxide*

3.3 Prototype Development

Prototype trials (Trial 1–Trial 5) revealed a progressive improvement in mechanical properties with incremental increases in polymer and binder concentrations (Table 3). Early batches exhibited brittleness, indicating insufficient matrix integrity. Trial 5 demonstrated optimal hardness, thickness, and handling characteristics, confirming the importance of balanced Carbopol 974P and PVP K30 levels for tablet robustness. Consequently, Trial 5 was selected for further QbD-based optimization.

Table 3: Prototype development

Constituents	Trial 1 (mg)	Trial 2 (mg)	Trial 3 (mg)	Trial 4 (mg)	Trial 5 (mg)
Silymarin	40	40	40	40	40
Glycyrrhizin	40	40	40	40	40
Carbopol 974P	80	150	50	50	60
PVP K30	30	30	50	50	60
Lactose	-	-	100	60	117
MCC (q.s.)	46	76	54	54	75
CSD (2%)	4	4	6	6	8
Total	240	340	340	300	400

3.4 Pre-compression Evaluation

All formulation blends (F1–F9) exhibited acceptable flow properties, with bulk and tapped densities supporting uniform die filling. Angle of repose values below 27° indicated excellent flow behavior. Carr's Index and Hausner ratios further confirmed good compressibility and suitability for direct compression. Among all batches, F6 showed the most favorable flow and packing behavior, minimizing the risk of weight variation during compression (Table 4).

Table 4: Pre-Compression Evaluation Parameters of Powder Blends (F1–F9)

Batch	Bulk Density	Tapped Density	Angle of Repose (°)	Carr's Index (%)	Hausner Ratio
F1	4.25 ± 0.12	4.69 ± 0.32	24.9 ± 0.01	9.38 ± 0.03	1.10 ± 0.06
F2	3.56 ± 0.13	3.82 ± 0.16	24.6 ± 0.02	6.81 ± 0.06	1.07 ± 0.09
F3	3.91 ± 0.19	4.32 ± 0.24	24.9 ± 0.02	9.49 ± 0.05	1.10 ± 0.11
F4	5.03 ± 0.14	5.69 ± 0.23	25.7 ± 0.03	11.60 ± 0.03	1.13 ± 0.09
F5	3.78 ± 0.21	4.32 ± 0.14	25.4 ± 0.03	12.50 ± 0.05	1.14 ± 0.13
F6	4.26 ± 0.17	4.69 ± 0.14	23.5 ± 0.01	9.17 ± 0.04	1.10 ± 0.06
F7	4.92 ± 0.25	5.32 ± 0.19	24.5 ± 0.03	7.52 ± 0.06	1.08 ± 0.13
F8	3.34 ± 0.15	3.83 ± 0.23	26.1 ± 0.04	12.79 ± 0.08	1.15 ± 0.12
F9	4.62 ± 0.12	4.99 ± 0.15	24.3 ± 0.02	7.41 ± 0.07	1.08 ± 0.14

3.5 Post-compression Characteristics

Compressed tablets demonstrated satisfactory mechanical strength, with hardness values ranging between 5.8–7.2 kg/cm². Thickness and diameter remained uniform across batches. Friability values were well below pharmacopeial limits (<1%), confirming resistance to abrasion. Weight variation and drug content uniformity were within acceptable limits for both Silymarin and Glycyrrhizin, with F6 exhibiting near-ideal content uniformity. These results confirm precise blending and compression control (Table 5).

Table 5: Post-Compression Evaluation of Mucoadhesive Gastro-Retentive Tablets (F1–F9)

Batch	Hardness (kg/cm²)	Thickness (mm)	Friability (%)	Weight Variation (mg)	Diameter (mm)	Silymarin Content (%)	Glycyrrhizin Content (%)
F1	6.1 ± 0.3	3.1 ± 0.1	0.31 ± 0.06	408 ± 2.1	9.4 ± 0.3	97.30 ± 2.3	98.25 ± 1.6
F2	5.9 ± 0.2	2.9 ± 0.2	0.42 ± 0.03	394 ± 2.3	10.5 ± 0.5	95.36 ± 3.6	94.23 ± 2.1
F3	6.9 ± 0.3	2.7 ± 0.3	0.26 ± 0.03	404 ± 1.2	8.7 ± 0.6	98.21 ± 1.9	96.87 ± 1.9
F4	6.3 ± 0.4	2.9 ± 0.3	0.35 ± 0.09	384 ± 2.3	9.4 ± 0.3	96.33 ± 3.2	96.78 ± 1.8
F5	5.8 ± 0.5	3.4 ± 0.4	0.29 ± 0.06	392 ± 1.6	10.9 ± 0.5	96.57 ± 1.3	96.06 ± 0.9
F6	6.5 ± 0.4	3.2 ± 0.2	0.23 ± 0.05	402 ± 2.1	10.2 ± 0.5	100.20 ± 1.8	99.30 ± 1.4
F7	6.2 ± 0.3	2.8 ± 0.2	0.34 ± 0.06	396 ± 2.5	9.6 ± 0.3	97.36 ± 1.5	99.36 ± 2.4
F8	6.1 ± 0.2	3.0 ± 0.1	0.39 ± 0.03	400 ± 1.2	8.8 ± 0.4	98.33 ± 1.8	96.78 ± 1.7
F9	7.2 ± 0.3	2.6 ± 0.3	0.43 ± 0.04	398 ± 2.5	9.7 ± 0.2	99.35 ± 0.5	97.56 ± 1.3

3.6 Swelling Behavior

*Author for Correspondence: misbahp1@yahoo.com

Swelling studies demonstrated gradual hydration and gel layer formation over 18 h for all formulations (Table 6). Higher polymer concentrations resulted in increased swelling indices, enhancing matrix integrity and diffusion control. Formulations F6, F7, and F9 exhibited superior swelling behavior, which is essential for sustained release and prolonged gastric residence.

Table 6: Results for Swelling index of GR Tablets

Swelling Index (%)									
Time (hrs.)	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
0	0	0	0	0	0	0	0	0	0
1	3.12	5.32	4.85	6.21	5.29	7.11	5.52	3.52	8.52
2	14.21	16.35	17.25	18.67	16.86	18.93	20.14	17.25	20.32
4	29.74	32.45	32.64	34.74	32.84	31.69	36.21	32.65	34.51
8	58.71	63.54	67.85	68.25	60.32	65.34	66.33	67.21	70.21
12	69.23	78.45	74.32	80.29	78.65	81.23	81.42	83.54	85.27
18	79.87	87.67	95.21	97.85	92.21	103.81	100.88	99.36	101.22

3.7 In-Vitro Drug Release

Both drugs exhibited controlled and sustained release over 18 h (Tables 7 & 8; Figures 4 & 5). Minimal initial burst release confirmed effective matrix formation. Formulations F2 and F6 showed the highest cumulative release for both drugs while maintaining extended release profiles, attributed to balanced polymer hydration and diffusion-controlled release mechanisms.

Table 7: In-vitro drug Release of Silymarin

Silymarin									
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
0.5	1.21	2.74	1.09	1.15	2.58	3.03	2.04	1.65	1.04
1	3.56	4.03	3.22	3.10	5.01	4.68	3.84	4.20	3.08
2	8.59	9.84	8.66	7.89	11.65	10.99	8.54	9.44	8.54
4	19.24	20.30	21.54	18.41	21.55	22.06	17.85	18.54	15.66
6	29.41	30.21	31.54	29.57	31.85	33.12	28.22	28.41	29.54
8	41.28	43.20	45.21	41.06	45.98	46.23	40.85	42.55	41.52
12	59.87	64.88	63.25	61.22	62.84	65.47	61.47	62.54	60.21
15	78.33	81.33	77.25	71.45	78.21	83.11	72.33	74.87	71.62
18	86.81	97.66	91.65	87.07	93.28	97.56	88.47	91.83	83.72

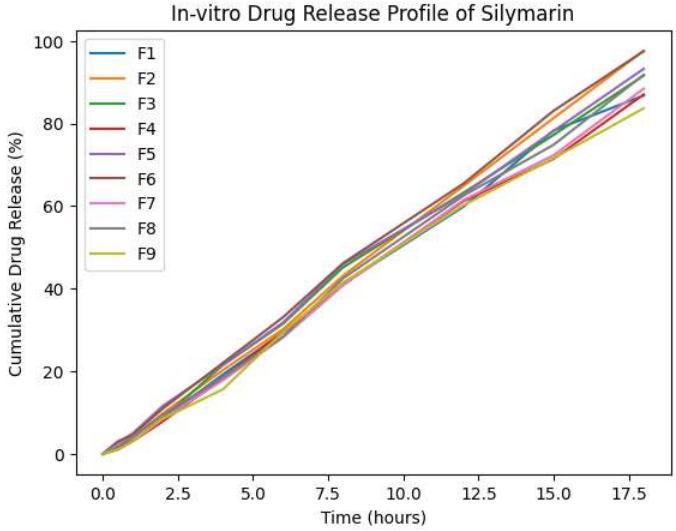

Figure 4: In-vitro Drug Release Profile of Silymarin

Table 8: In-vitro drug Release of Glycyrrhizin

Glycyrrhizin

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
0.5	1.02	2.18	1.87	1.65	1.87	2.14	2.18	1.84	2.02
1	4.18	4.07	3.84	3.56	4.03	5.71	3.98	4.08	4.33
2	8.14	7.65	8.62	8.26	8.76	9.47	8.74	9.85	10.85
4	14.22	15.31	14.35	15.78	14.96	16.55	16.87	14.89	16.52
6	28.21	30.45	28.54	29.65	28.74	30.46	31.52	36.54	37.14
8	40.25	41.25	43.21	43.87	46.85	44.38	43.52	42.66	45.32
12	62.08	63.74	65.18	63.47	63.26	62.64	63.21	62.37	61.21
15	73.65	74.32	77.66	74.25	77.69	79.37	74.25	75.14	72.54
18	85.49	95.88	88.91	86.05	91.57	94.61	87.15	90.18	82.83

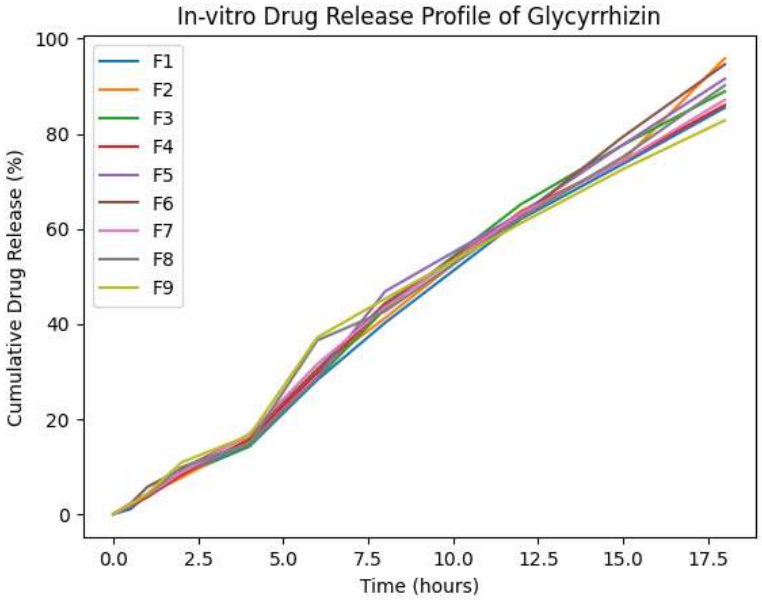

Figure 5: In-vitro Drug Release Profile of Glycyrrhizin

3.8 Mucoadhesive Strength and QbD Optimization

Mucoadhesive strength increased significantly with Carbopol 974P concentration (Table 9). QbD analysis using Central Composite Design revealed a statistically significant quadratic model ($p < 0.001$), with Carbopol concentration exerting the greatest influence on mucoadhesion. Response surface plots (Figures 6, 7 & 8) illustrated the optimized design space, identifying F6 as the optimal formulation with maximum mucoadhesive strength and balanced release characteristics.

Table 9: Results of In-vitro Mucoadhesive Strength

Batches	Mucoadhesive Strength (g)	Adhesion Force (N)
F1	29.1 ± 0.3	0.2855
F2	39.2 ± 0.1	0.3846
F3	36.1 ± 0.5	0.3541
F4	29.3 ± 0.2	0.2874
F5	37.4 ± 0.7	0.3669
F6	39.4 ± 0.2	0.3865
F7	33.8 ± 0.4	0.3316
F8	36.2 ± 0.2	0.3551
F9	27.9 ± 0.3	0.2737

Quality by Design (QbD)–Based Optimization of Mucoadhesive Strength

A Quality by Design (QbD) approach was employed to optimize the mucoadhesive strength of gastro-retentive tablets using response surface methodology. A Central Composite Design (CCD) was generated using Design-Expert® software (Version 13.0.5.0), incorporating two independent formulation variables: PVP K30 (A) and Carbopol 974P (B). Both factors were studied at three levels within the concentration ranges of 50–70 mg and 40–60 mg, respectively. Mucoadhesive strength was selected as the critical quality attribute (CQA). A total of nine experimental runs were performed in randomized order, and the experimental design along with observed responses is presented in Table 10.

Table 10: Central Composite Design (CCD) Matrix for Optimization of Mucoadhesive Strength

Run	PVP K30 (mg)	Carbopol 974P (mg)	Mucoadhesive Strength
1	60	40	29.1
2	70	60	39.2
3	60	50	36.1
4	70	40	29.3
5	50	60	37.4
6	60	60	39.4
7	50	50	33.8
8	70	50	36.2
9	50	40	27.9

Note: Mucoadhesive strength expressed as detachment force (g).

Model Fitting and Statistical Evaluation

Model fitting analysis indicated that the quadratic model was the most appropriate, exhibiting the highest adjusted and predicted coefficients of determination. The statistical validity of the model was confirmed by ANOVA, summarized in Table 11.

Table 11: ANOVA for Quadratic Model of Mucoadhesive Strength

Source	Sum of Squares	df	Mean Square	F-value	p-value
Model	159.35	5	31.87	256.09	0.0004*
A – PVP K30	5.23	1	5.23	42.00	0.0075*
B – Carbopol 974P	147.02	1	147.02	1181.37	<0.0001*
AB	0.04	1	0.04	0.32	0.6104
A^2	1.62	1	1.62	13.02	0.0366*
B^2	5.44	1	5.44	43.75	0.0070*
Residual	0.37	3	0.12	—	—
Total	159.72	8	—	—	—

*Statistically significant ($p < 0.05$)

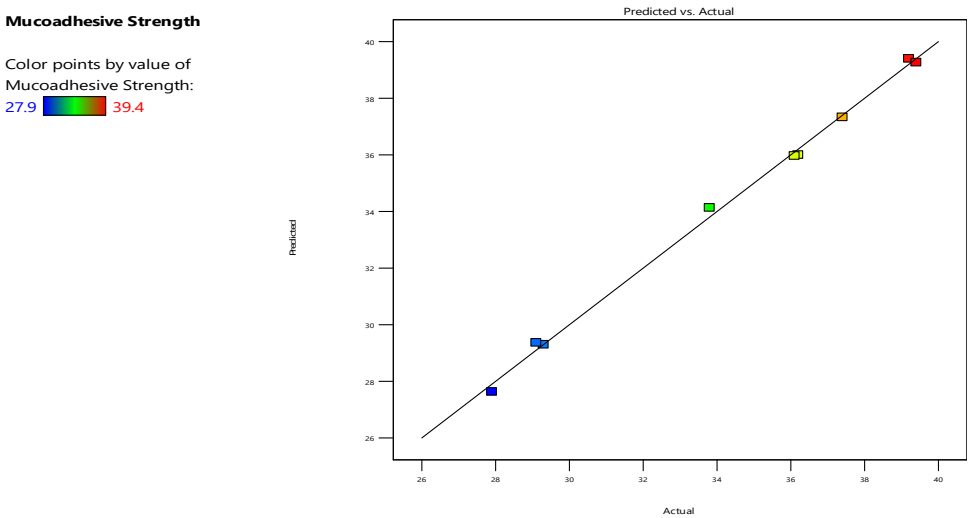

Figure 6: Contour plot showing the combined effect of PVP K30 and Carbopol 974P concentrations on mucoadhesive strength of gastro-retentive tablets.

*Author for Correspondence: misbahp1@yahoo.com

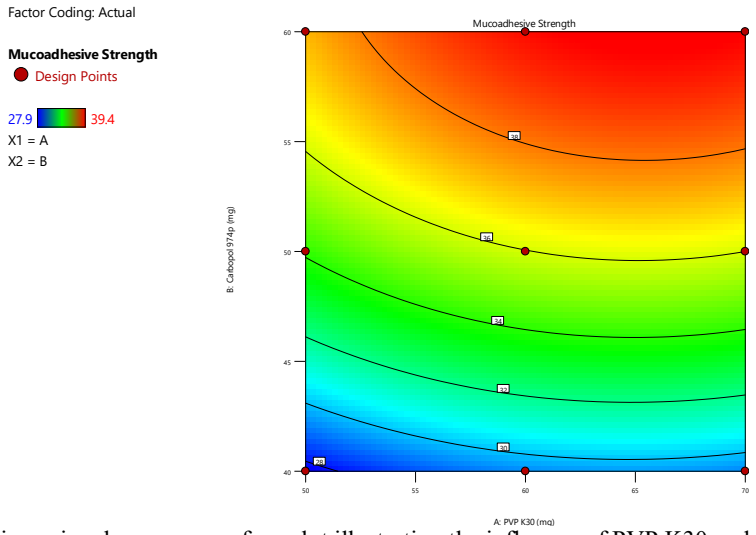

Figure 7: Three-dimensional response surface plot illustrating the influence of PVP K30 and Carbopol 974P on mucoadhesive strength.

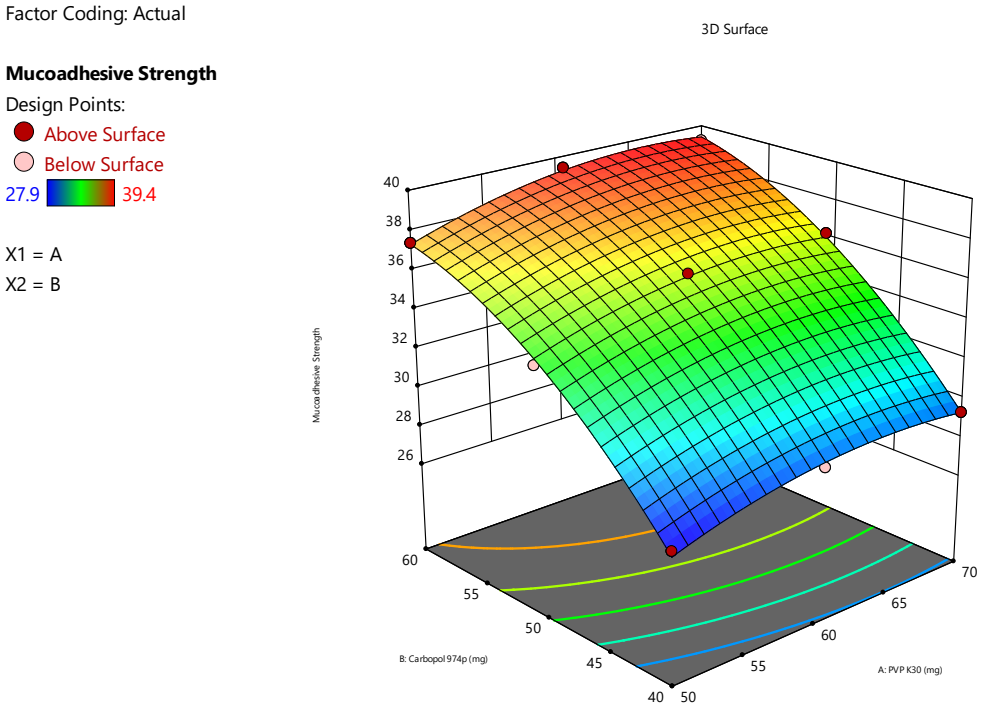

Figure 8: Predicted versus experimental values of mucoadhesive strength, demonstrating excellent agreement between model predictions and observed data.

3.9 Stability Assessment

Accelerated stability studies showed no significant changes in drug content, swelling behavior, mucoadhesive strength, or dissolution profile, confirming formulation stability under stressed conditions.

4. CONCLUSION

The present study successfully demonstrated the rational development and optimization of mucoadhesive gastro-retentive tablets containing Silymarin and Glycyrrhizin using a Quality by Design (QbD)–driven approach. Comprehensive preformulation and compatibility studies confirmed the suitability of the selected drugs and excipients for formulation into a stable controlled-release system. Application of Central Composite Design enabled systematic evaluation of critical formulation variables, identifying Carbopol 974P as the dominant factor influencing mucoadhesive strength and release behavior. The optimized formulation exhibited excellent flow and compression characteristics, uniform drug content, strong mucoadhesion, and sustained drug release for up to 18 hours with minimal initial burst effect. In-vitro release profiles and swelling behavior indicated diffusion-controlled release supported by robust matrix formation. Stability studies further confirmed formulation integrity

under accelerated conditions. Overall, the QbD-guided gastro-retentive system offers a promising strategy to enhance the bioavailability and therapeutic efficacy of Silymarin and Glycyrrhizin, supporting its potential application in the long-term management of chronic liver disorders.

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6. AUTHORSHIP STATEMENT

M.S.A.K.B. and V.S.T. jointly contributed to the conceptualization and design of the study. Supervision of the research work was carried out by V.S.T. Both authors were responsible for providing the necessary resources, while M.S.A.K.B. handled the procurement of materials. Data collection and processing were performed by M.S.A.K.B., with data analysis and interpretation carried out collaboratively by M.S.A.K.B. and V.S.T. The literature review was conducted by both authors. M.S.A.K.B. prepared the original draft of the manuscript, and V.S.T. critically reviewed and edited the manuscript. All authors have read and approved the final version of the manuscript.

7. CONFLICT OF INTEREST STATEMENT

The authors declare that there are no conflicts of interest, financial or otherwise, related to the publication of this manuscript.

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