RESEARCH PAPER

DESIGN, FORMULATION AND EVALUATION OF THIOLATED CHITOSAN-BASED GASTRO RETENTIVE FEBUXOSTAT TABLETS

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ABSTRACT

This study aimed to enhance the gastric residence time and bioavailability of febuxostat by creating gastro-retentive mucoadhesive floating tablets. This study compared the mucoadhesive properties of natural polymers and improved these polymers through thiolation. Tablets containing 40 mg of febuxostat were prepared via direct compression using sodium bicarbonate and citric acid as the gas-generating agents. Natural gums (guar and xanthan) and unmodified chitosan were tested for mucoadhesion and drug release control properties. Chitosan's mucoadhesive strength and matrix integrity were improved by adding thiol groups using thioglycolic acid. The thiolated chitosan formulation (F2) showed significantly higher mucoadhesive strength (72.8 ± 2.6 g), a floating lag time under 120 s, and sustained drug release (89.7 ± 1.7%) over 12 h. Drug release followed the Korsmeyer–Peppas model, indicating a non-Fickian diffusion. A factorial design confirmed that the polymer concentration significantly affected mucoadhesion and drug release. This thiolated chitosan system shows promise for improving the delivery of drugs with limited gastric residence and poor solubility.

Keywords: Febuxostat, thiolated chitosan, gastro retentive, mucoadhesion, swelling index, Design of Experiments, Korsmeyer–Peppas kinetics.

How to cite this article: Pathan SD, Datkhile SV, Gaikwad SD, Ramteke K, Bhalekar SM, Walunj KB, Padwal PN, Wagh SA. Design, Formulation and Evaluation of Thiolated Chitosan-Based Gastro Retentive Febuxostat Tablets. Int J Drug Deliv Technol. 2026;16(56s): 928-938. DOI: 10.25258/ijddt.16.56s.100

Source of support: Nil.

Conflict of interest: None.

1. INTRODUCTION:

Gouty arthritis is a chronic inflammatory disorder caused by the accumulation of uric acid and deposition of monosodium urate crystals in joints. Febuxostat, a selective xanthine oxidase inhibitor approved in 2009, is widely used for gout management, especially in patients intolerant to allopurinol. However, febuxostat exhibits limited oral bioavailability due to its poor aqueous solubility and localized absorption in the upper gastrointestinal tract. Conventional tablets provide insufficient gastric residence time, leading to fluctuating plasma drug levels and reduced therapeutic efficiency. To overcome these limitations, gastro-retentive drug delivery systems have been developed to prolong gastric retention and sustain drug release (Khanna Dinesh, 2012), (Michael E. Ernst, 2009).

Floating matrix tablets prepared with hydrophilic polymers and effervescent agents offer prolonged gastric buoyancy and controlled drug release. Chitosan is commonly used because of its biocompatibility and mucoadhesive properties, while thiolated chitosan provides enhanced adhesion through disulfide bond formation with gastric mucin. In the present study, gastro-retentive floating-mucoadhesive febuxostat tablets were developed using chitosan, thiolated chitosan, guar gum, and xanthan gum. The thiolated chitosan formulation was optimized using a 2^2 factorial design and evaluated for physicochemical properties, swelling, mucoadhesion, drug release, and release kinetics. (Basel Kamel, 2017), (Mohamed H. Abu Elella, 2024), (Rajesh Pahwa, 2012), (Tamer M.

M. Ways, 2018), (Daniela Silva, 2020), (Jung Soo Sohn, 2023), (Zeba Saifi, 2025).

2. MATERIALS AND METHODS:

2.1 Study Site:

All the experimental work described in this study was conducted at the Arni Analytical Training Centre located in Nashik, India, under controlled laboratory conditions that followed standard protocols for pharmaceutical research.

2.2 Materials:

Febuxostat and all excipients were obtained from the Arni Analytical Training Center, Nashik, India. Chitosan, thiolated chitosan, guar gum, and xanthan gum were used as matrix polymers, while HPMC K4M served as the release-retarding polymer. MCC PH-102 was used as a diluent, sodium bicarbonate and citric acid as gas-generating agents, PVP K30 as a binder, and magnesium stearate with talc as lubricant and glidant. All materials used were of analytical or pharmaceutical grade.

2.3 Synthesis of Thiolated Chitosan:

Thiolated chitosan was synthesized by conjugating thioglycolic acid with chitosan using EDAC as a coupling agent. Chitosan was dissolved in 1% acetic acid, followed by the addition of thioglycolic acid and EDAC, and the mixture was stirred under nitrogen for 24 h at room temperature. The formed thiolated chitosan was precipitated with ethanol, purified, vacuum-dried at 40 °C for 48 h, and characterized for free thiol content using Ellman's reagent. (Tamer M. M. Ways, 2018), (Andreas Bernkop-Schnürch, 2012), (Javed Iqbal, 2012).

2.4 Drug–Excipient Compatibility Study:

Drug–excipient compatibility was evaluated using UV-visible spectrophotometry by analyzing 1:1 physical mixtures of febuxostat and excipients over a wavelength range of 200–400 nm using a Shimadzu UV-1800 spectrophotometer. The spectra were compared with that of pure febuxostat for changes in wavelength, peak shape, or absorbance. The absence of significant spectral shifts indicated compatibility between febuxostat and the excipients, although the method could not detect solid-state interactions or polymorphic changes. (Michael E. Aulton, 2018), (Gopal Krishna Dash, 2021), (Sunil P. Chaudhari, 2022).

2.5 Formulation of Gastroretentive Tablets:

Four febuxostat floating tablet formulations (F1–F4) were prepared by direct compression using different gastro-retentive polymers. Each tablet contained febuxostat, HPMC K4M, sodium bicarbonate, citric acid, PVP K30, MCC PH-102, magnesium stearate, and talc, with a total weight of 200 mg. All ingredients were sieved, blended uniformly, and compressed using a rotary tablet press with 8 mm punches at a compression force of 10 kN. Formulations were prepared in triplicate batches and evaluated in triplicate. (Michael E. Aulton, 2018), (Tadros, 2010), (Amit Kumar Nayak, 2010), (H. Shah Viral, 2012).

Table 1. Formulation of Thiolated Chitosan based Gastroretentive Tablets:

Ingredient (mg/tablet)	F1	F2	F3	F4
Febuxostat	40	40	40	40
Chitosan	60	—	—	—
Thiolated Chitosan (TCh)	—	60	—	—
Guar Gum	—	—	60	—
Xanthan Gum	—	—	—	60
HPMC K4M (base; 32 mg = 16% w/w)	32	32	32	32
Sodium Bicarbonate	24	24	24	24
Citric Acid	8	8	8	8
PVP K30	12	12	12	12
Magnesium Stearate	2	2	2	2
Talc	2	2	2	2
Microcrystalline Cellulose	20	20	20	20
Total Weight (mg)	**200**	**200**	**200**	**200**

2.6 Pre-compression Evaluation:

Before compression, powder blends were evaluated according to USP <1174> for bulk density, tapped density, Carr's index, Hausner's ratio, angle of repose, and moisture content using standard instruments. All measurements were performed in triplicate, and results were expressed as mean ± standard deviation. (Michael E. Aulton, 2018), (Convention, 2023), (Ankit Patel, 2021).

2.7 Post-compression Evaluation:

The prepared tablets were evaluated for post-compression parameters including weight variation, thickness, hardness, friability, and drug content uniformity using standard pharmacopeial methods. Drug content was determined by UV–visible spectrophotometry at 315 nm after dissolving the tablet in 0.1 M hydrochloric acid. All tests were performed in triplicate, and results were expressed as mean ± standard deviation. (USPC, United States Pharmacopeia Convention (USPC), 2018), (USP, United States Pharmacopeia Convention (USPC), 2025).

2.8 In Vitro Floating:

Floating lag time and total floating duration were evaluated using USP dissolution apparatus II in 900 mL of simulated gastric fluid (0.1 M HCl, pH 1.2) at 37 ± 0.5 °C and 50 rpm. Floating lag time was recorded as the time required for the tablet to float, while floating duration was the total time the tablet remained buoyant. All tests were conducted in

triplicate and expressed as mean ± standard deviation. (Ankur Rajora, 2022), (Minal P. Shraddha, 2025).

2.9 Swelling Index:

The swelling index of the tablets was determined by a gravimetric method using simulated gastric fluid (pH 1.2) at 37 ± 0.5 °C. Pre-weighed tablets were periodically removed, blotted to remove excess moisture, and reweighed up to 12 h. The swelling index was calculated from the weight gain of the tablets. All experiments were performed in triplicate, and results were expressed as mean ± standard deviation.

$$\mathbf{SI}\ (\%) = \frac{(\boldsymbol{Wt} - \boldsymbol{W0})}{\boldsymbol{Wo}} \times \mathbf{100}$$

Where W0 is the initial weight of the dry tablet, and Wt is the weight of the swollen tablet at time t. Each experiment was conducted in triplicate (n = 3), and the mean ± standard deviation was used to express the results (Rajesh Kumar, 2023), (Hiral Patel, 2022).

2.10 Mucoadhesive Strength:

Mucoadhesive strength was evaluated using fresh goat stomach mucosa as the biological membrane. The mucosal tissue was equilibrated in simulated gastric fluid (pH 1.2) at 37 ± 0.5 °C, and tablets were attached under a preload force before measuring the detachment weight using a modified physical balance. Mucoadhesive strength was recorded as the minimum weight required to detach the tablet from the mucosal surface. All tests were performed in triplicate, and results were expressed as mean ± standard deviation. (Nafee N. A., 2004), (Chawla Gurpreet, 2003), (Deepti Kharia, 2022).

2.11 In vitro drug release:

In vitro drug release studies were performed using USP dissolution apparatus II at 50 rpm and 37 ± 0.5 °C. Tablets were initially tested in simulated gastric fluid (pH 1.2) for 2 h, followed by phosphate buffer (pH 6.8) for the remaining period. Samples were withdrawn at predetermined intervals, filtered, and analyzed at 315 nm using a UV–Visible spectrophotometer, while maintaining sink conditions. All studies were conducted in triplicate, and results were expressed as mean ± standard deviation. (Ankur Rajora, 2022), (Sabyasachi Dash, 2010), (Rakesh Sharma, 2021).

2.12 Drug Release Kinetic Modelling:

Drug release data were fitted to zero-order, first-order, Higuchi, and Korsmeyer–Peppas kinetic models using the PK Solver add-in for Microsoft Excel to determine the drug release mechanism. The best-fit model was selected based on the highest R^2 and lowest AIC values. Statistical analysis of mucoadhesive strength and 12 h drug release among formulations was performed using one-way ANOVA followed by Tukey's HSD test at $p < 0.05$ using GraphPad Prism 9.0.

$$\frac{\boldsymbol{Qt}}{\boldsymbol{Q\infty}} = \mathbf{k} - \mathbf{t}^{\boldsymbol{n}}$$

Where K= is the rate constant, n= is the release exponent, Q∞ = is the total drug content, and Qtr. = is the cumulative drug released at time t. (Juergen Siepmann, 2011), (Yong Zhang, 2010).

2.13 Design of Experiments:

The thiolated chitosan formulation (F2) was optimized using a 2^2 factorial design with center-point replicates, considering thiolated chitosan and HPMC K4M concentrations as independent variables. Mucoadhesive strength and cumulative drug release at 12 h were selected as responses. Design-Expert software was used for statistical analysis, polynomial modeling, response surface plotting, and ANOVA to evaluate the effects of formulation variables at $p < 0.05$. (Bhupinder Singh, 2018), (Montgomery, 2019).

$$\mathbf{Y=\beta0+\beta1X1+\beta2X2+\beta12X1X2}$$

3 RESULTS:

3.1 Characterisation of Thiolated Chitosan:

FTIR spectroscopy confirmed successful thiolation of chitosan by showing a characteristic S–H stretching peak at 2550–2570 cm^{-1} in thiolated chitosan. Minor shifts in hydroxyl and amide regions indicated interaction with thioglycolic acid. Ellman's assay showed a free thiol content of 412.6 ± 18.3 µmol/g polymer, confirming successful synthesis of thiolated chitosan.

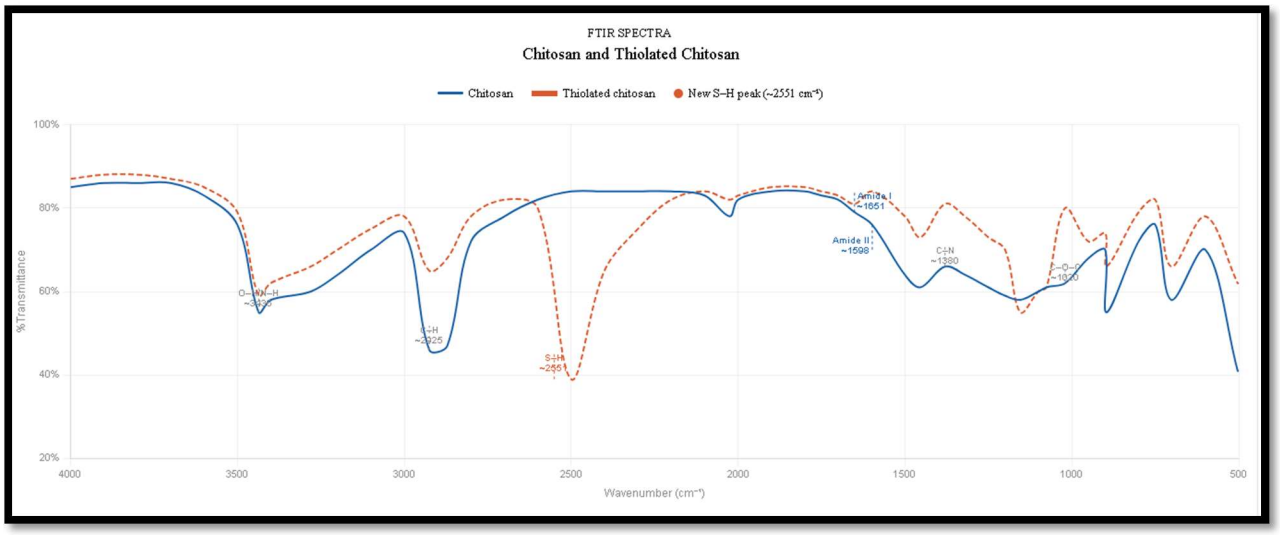


***Figure 1. FTIR Spectra of Chitosan And* FTIR Spectra of Thiolated Chitosan**

3.2 Pre-compression Evaluation:

Pre-compression studies showed that all powder blends possessed satisfactory flow and compressibility properties suitable for direct compression. Carr's index, Hausner's ratio, and angle of repose values were within acceptable pharmacopeial limits, indicating good flow behavior. Moisture content remained below 5% for all formulations, with F2 showing the lowest value, possibly due to increased hydrophobicity from thioglycolyl substitution.

Table 2. Pre-compression evaluation:

Parameter	F1 (Chitosan)	F2 (Thiolated Chitosan)	F3 (Guar Gum)	F4 (Xanthan Gum)	Acceptable Limit
Bulk Density (g/cm³)	0.421 ± 0.012	0.435 ± 0.009	0.412 ± 0.014	0.418 ± 0.011	—
Tapped Density (g/cm³)	0.512 ± 0.015	0.528 ± 0.011	0.498 ± 0.017	0.506 ± 0.013	—
Carr's Compressibility Index (%)	17.77 ± 0.82	17.42 ± 0.64	17.27 ± 0.91	17.39 ± 0.75	≤ 25
Hausner's Ratio	1.216 ± 0.018	1.211 ± 0.012	1.209 ± 0.022	1.210 ± 0.016	≤ 1.25
Angle of Repose (°)	28.4 ± 0.93	27.6 ± 0.71	27.1 ± 1.04	27.8 ± 0.88	< 30
Moisture Content (%)	2.84 ± 0.21	2.61 ± 0.18	3.12 ± 0.24	2.97 ± 0.22	≤ 5

3.3 Post-compression Evaluation:

All formulations complied with pharmacopoeial limits for weight variation, hardness, friability, and drug content uniformity, indicating good tablet quality. Formulation F2 showed the highest hardness and lowest friability, suggesting superior mechanical strength due to enhanced intermolecular interactions within the thiolated chitosan matrix. F2 also exhibited the longest disintegration time and the shortest floating lag time, while all formulations remained buoyant for more than 12 h, confirming effective gastro-retentive floating behavior.

Table 3. Post-compression evaluation:

Parameter	F1	F2	F3	F4	Acceptable Limit
Weight Variation (mg)	199.4 ± 1.2	200.1 ± 0.9	199.6 ± 1.3	199.8 ± 1.0	±5%
Hardness (kg/cm²)	6.8 ± 0.31	7.4 ± 0.24	6.5 ± 0.38	6.7 ± 0.29	5–8
Thickness (mm)	4.82 ± 0.06	4.85 ± 0.04	4.79 ± 0.08	4.81 ± 0.05	—
Friability (%)	0.52 ± 0.04	0.41 ± 0.03	0.61 ± 0.05	0.57 ± 0.04	<1
Disintegration Time (min)	128 ± 4	162 ± 5	141 ± 6	149 ± 5	—

Drug Content (%)	99.12 ± 0.82	99.74 ± 0.61	98.84 ± 0.94	99.03 ± 0.78	95–105
Swelling Index at 12 h (%)	142.3 ± 4.8	218.6 ± 5.2	185.4 ± 6.1	176.8 ± 5.7	—
Mucoadhesive Strength (g)	38.4 ± 2.1	72.8 ± 2.6	54.3 ± 3.0	49.6 ± 2.8	—
Floating Lag Time (s)	82 ± 6	68 ± 4	91 ± 7	87 ± 5	<120
Total Floating Time (h)	>12	>12	>12	>12	>12
Drug Release at 12 h (%)	61.4 ± 2.2	89.7 ± 1.7	76.3 ± 2.3	71.8 ± 2.0	—

3.4 Swelling Index:

The formulations showed noticeable differences in swelling behavior, with the swelling index following the order F2 > F3 > F4 > F1 at 12 h. Formulation F2 exhibited the highest swelling capacity, likely due to the hydrophilic nature of thiolated chitosan and disulfide bond formation, which enhanced water retention and matrix expansion. This improved swelling behavior may contribute to prolonged gastric retention and sustained drug release.

3.5

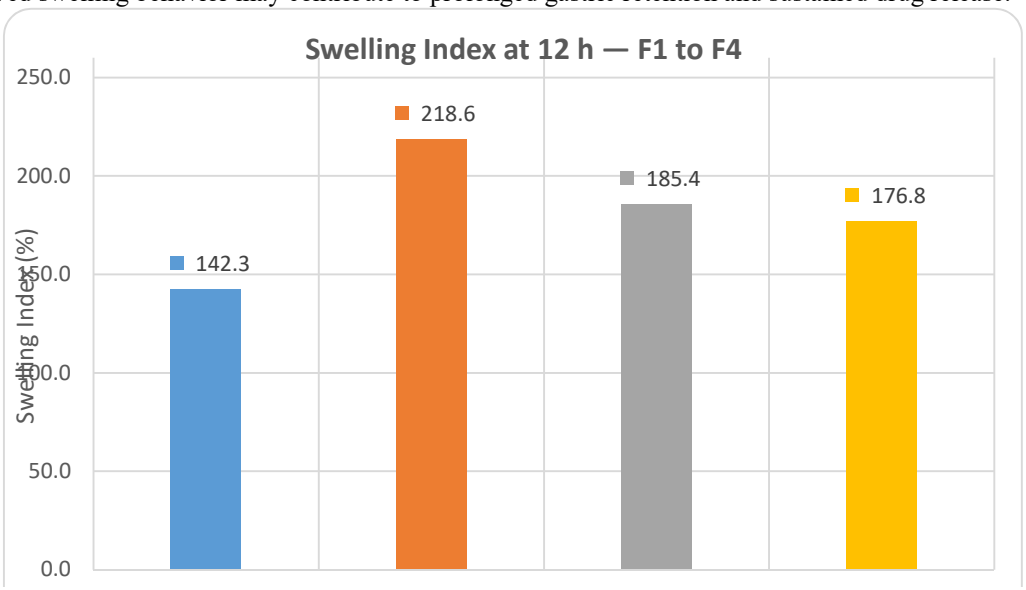


Figure 2. Graph of Swelling Index

Mucoadhesive Strength:

Mucoadhesive strength varied significantly among the formulations, with F2 showing the highest value compared to F1, F3, and F4. Statistical analysis confirmed that the differences were significant ($p < 0.05$). The enhanced mucoadhesion of F2 was attributed to free thiol groups in thiolated chitosan, which form covalent disulfide bonds with gastric mucus, while guar gum and xanthan gum formulations exhibited moderate adhesion through weaker intermolecular interactions.

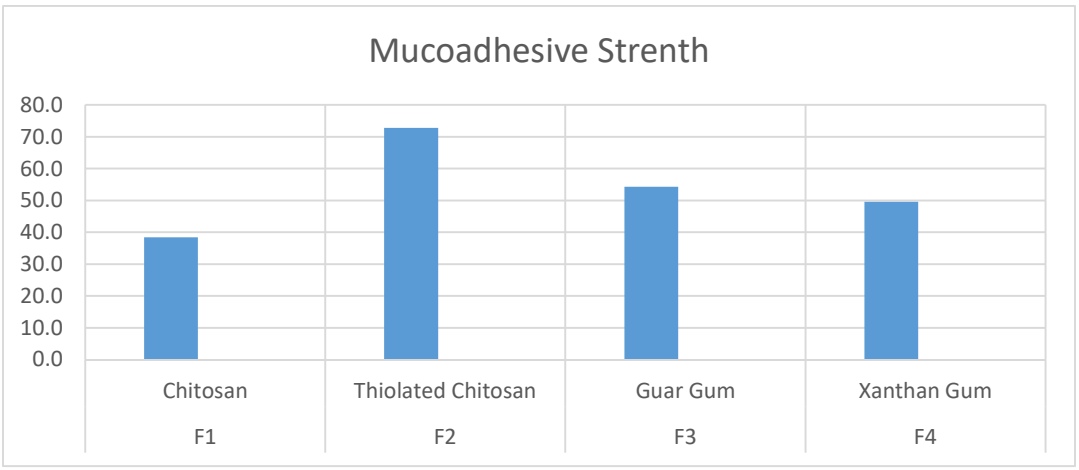


Figure 3. Graph of Mucoadhesive Strength

3.6 In Vitro Drug Release:

The pure drug suspension showed rapid drug release within 2 h, confirming the absence of a release-retarding matrix. Among the formulations, F2 exhibited the highest cumulative drug release at 12 h, followed by F3, F4, and F1, with statistically significant differences among formulations ($p < 0.05$). The sustained-release behavior of F2 was attributed to the formation of a dense hydrated matrix by thiolated chitosan, which controlled drug diffusion. Drug release from F2 best followed the Korsmeyer–Peppas model, indicating anomalous non-Fickian transport involving both diffusion and polymer relaxation.

Table 4. In Vitro Drug Release:

Time (h)	F1 (%)	F2 (%)	F3 (%)	F4 (%)	Pure Drug (%)
1	8.2 ± 0.6	9.4 ± 0.4	8.7 ± 0.7	8.5 ± 0.5	38.4 ± 1.2
4	26.8 ± 1.3	33.2 ± 0.9	29.6 ± 1.4	28.1 ± 1.2	89.6 ± 2.4
8	49.7 ± 1.8	63.8 ± 1.3	57.4 ± 1.9	53.6 ± 1.7	98.4 ± 2.8
12	61.4 ± 2.2	89.7 ± 1.7	76.3 ± 2.3	71.8 ± 2.0	99.4 ± 3.0

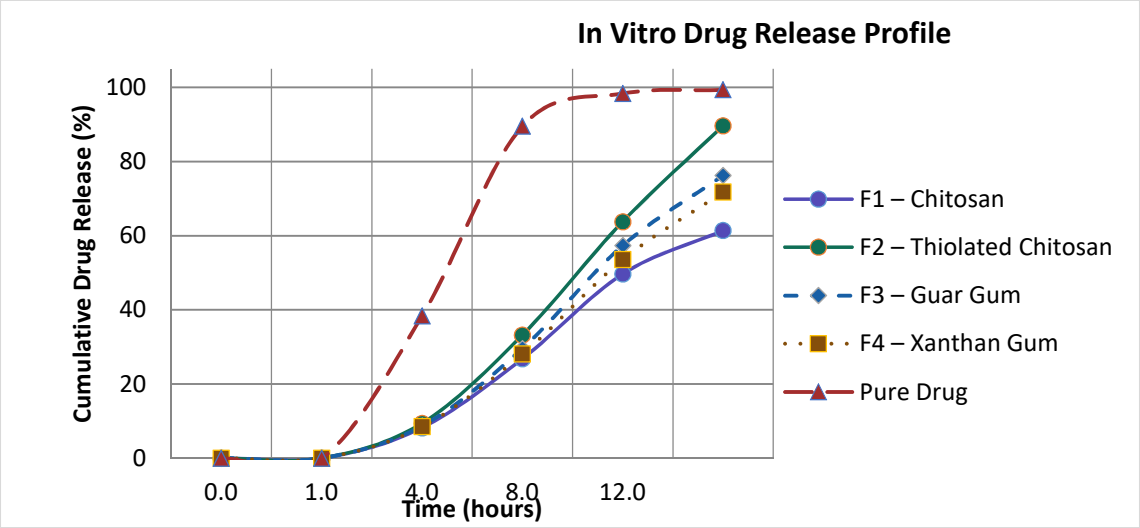


Figure 4. Graph of In Vitro Drug Release

3.7 Drug Release Kinetics:

Among the evaluated kinetic models, the Korsmeyer–Peppas model showed the best fit for formulation F2 with the highest R^2 value, indicating controlled drug release through anomalous non-Fickian transport involving both diffusion and polymer relaxation. This behavior was attributed to the hydrated and viscoelastic thiolated chitosan matrix. Formulations F1, F3, and F4 also exhibited anomalous transport behavior but showed comparatively lower release control than F2.

Table 5. Drug Release Kinetics:

Formulation	Zero-Order R^2	First-Order R^2	Higuchi R^2	Korsmeyer–Peppas R^2	n Value	Release Mechanism	Best-Fit Model
F1	0.9421	0.9684	0.9812	0.9876	0.512	Anomalous transport	Korsmeyer–Peppas
F2	0.9614	0.9711	0.9894	0.9962	0.624	Anomalous transport	Korsmeyer–Peppas
F3	0.9387	0.9612	0.9798	0.9841	0.537	Anomalous transport	Korsmeyer–Peppas
F4	0.9318	0.9574	0.9763	0.9819	0.521	Anomalous transport	Korsmeyer–Peppas

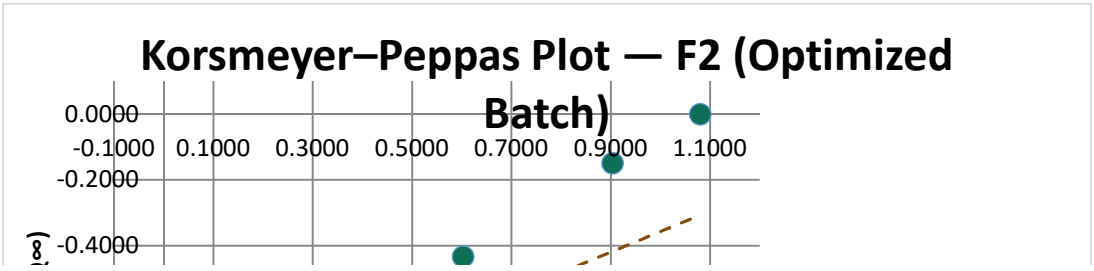
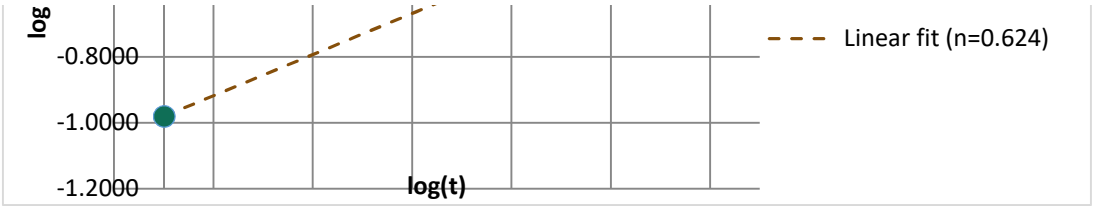


Figure 5. Graph of Korsmeyer–Peppas Plot — F2 (Optimized Batch)



3.8 Design of Experiments DOE Results:

Table 6 contains the complete factorial design matrix, which is 2^2 with three center-point replicates, as well as the corresponding response values. The analysis of the DOE produced the polynomial regression equations that explain the relationship between the two replies, Y1 and Y2, and the independent variables, X1 and X2.

Y1 (Mucoadhesive Strength) = 72.81 + 14.81•X1 + 5.94•X2 + 6.83•X1•X2

Y2 (Drug Release at 12h) = 86.57 + 5.74•X1 + 3.74•X2 + 2.28•X1•X2

Table 6. Experimental Design Matrix and Observed Responses for the 2^2 Full Factorial Design of Thiolated Chitosan Gastroretentive Tablets:

Run	X_1 (Coded)	X_2 (Coded)	Polymer Concentration (% w/w)	HPMC K4M Concentration (mg/tablet)	Mucoadhesive Strength (g)	Drug Release at 12 h (%)
1	−1	−1	15	28	54.2 ± 1.8	74.3 ± 1.4
28	+1	−1	25	28	78.6 ± 2.1	83.7 ± 1.7
32	−1	+1	15	36	61.4 ± 1.9	79.8 ± 1.6
36	+1	+1	25	36	92.3 ± 2.4	91.2 ± 1.9
5 (CP)	0	0	20	32	72.8 ± 2.0	89.7 ± 1.7
6 (CP)	0	0	20	32	73.1 ± 1.8	88.9 ± 1.5
7 (CP)	0	0	20	32	72.4 ± 1.9	89.2 ± 1.8

ANOVA results showed that the polynomial models for mucoadhesive strength and 12 h drug release were statistically significant ($p < 0.0001$). Polymer concentration had the greatest influence on both responses, followed by HPMC K4M concentration and their interaction. Increased polymer and binder concentrations enhanced mucoadhesion and sustained drug release, while non-significant lack-of-fit values confirmed the reliability of the developed models.

Table 5. Response of Mucoadhesive Strength:

Source	SS	df	MS	F-value	p-value	Significance
Model	1486.72	4	371.68	84.32	<0.0001	Significant
X_1 (Polymer Concentration)	894.41	1	894.41	202.90	<0.0001	Significant
X_2 (HPMC K4M concentration)	312.64	1	312.64	70.93	0.0009	Significant
X_1X_2	186.24	1	186.24	42.26	0.0030	Significant
Residual	13.22	3	4.41	—	—	—
Lack of Fit	7.18	1	7.18	2.39	0.2614	Not Significant
Pure Error	6.04	2	3.02	—	—	—
Total	1499.94	7	—	—	—	—

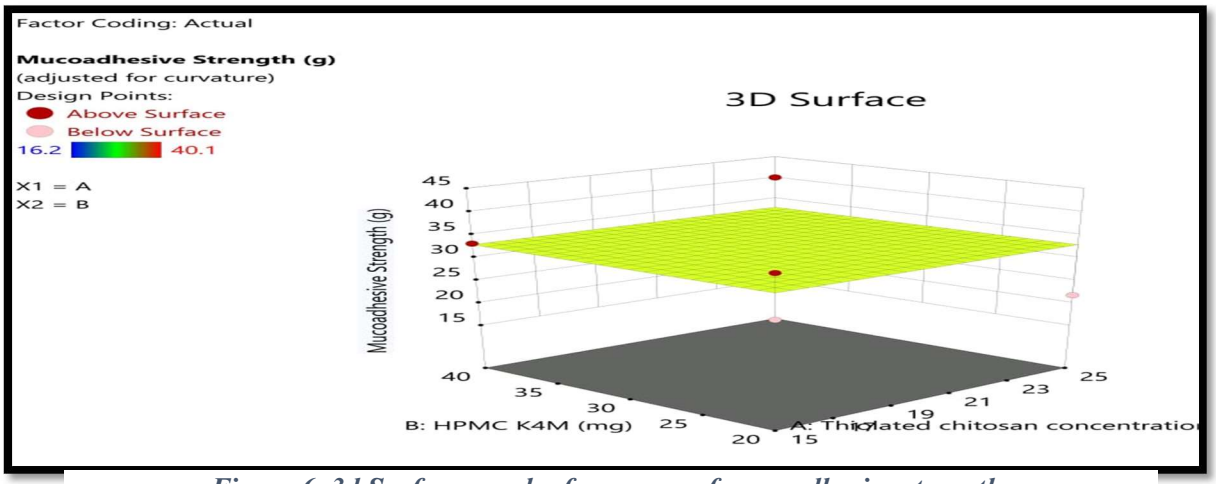


Figure 6. 3d Surface graph of response of mucoadhesive strength:

Table 6. Response: Drug Release at 12 h:

Source	SS	df	MS	F-value	p-value	Significance
Model	322.16	4	80.54	47.18	<0.0001	Significant
X_1 (Polymer Concentration)	168.08	1	168.08	98.43	0.0002	Significant
X_2 (HPMC K4M concentration)	109.41	1	109.41	64.06	0.0013	Significant
X_1X_2	41.78	1	41.78	24.46	0.0159	Significant
Residual	5.12	3	1.71	—	—	—
Lack of Fit	2.84	1	2.84	2.49	0.2558	Not Significant
Pure Error	2.28	2	1.14	—	—	—
Total	327.28	7	—	—	—	—

Optimization using the desirability function targeted maximum mucoadhesive strength and 85–95% drug release at 12 h. The optimized formulation contained a higher concentration of thiolated chitosan with a moderate binder level. Experimental responses closely matched predicted values with less than 2% variation, confirming the validity and

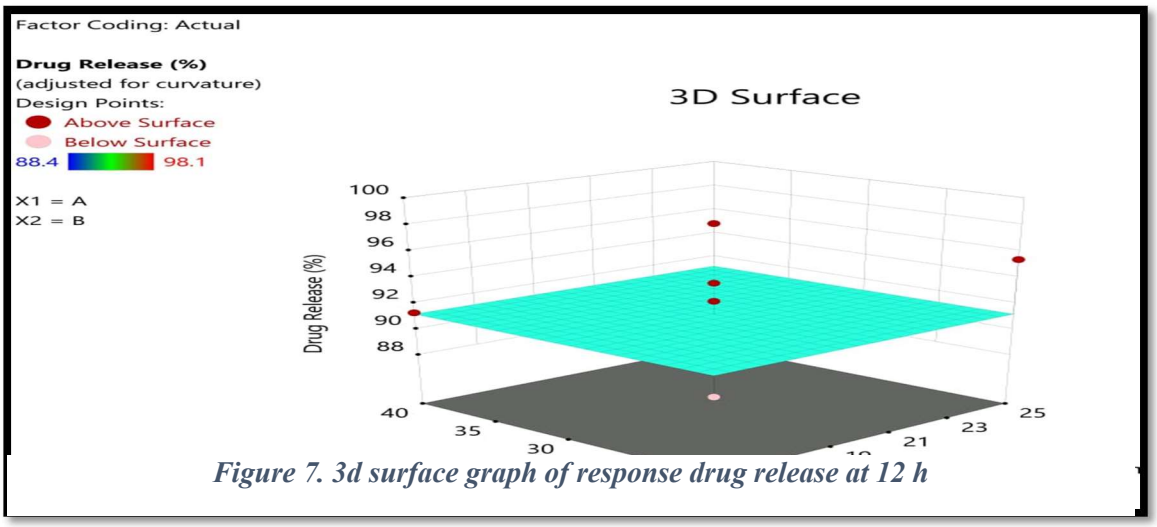


Figure 7. 3d surface graph of response drug release at 12 h

predictive accuracy of the statistical model.

4. DISCUSSION:

The present study aimed to develop a gastro-retentive floating-mucoadhesive febuxostat tablet system to overcome the limitations of conventional oral therapy. Floating-mucoadhesive technology was selected because the combination of buoyancy and mucoadhesion provides prolonged gastric retention. Among all formulations, thiolated chitosan-

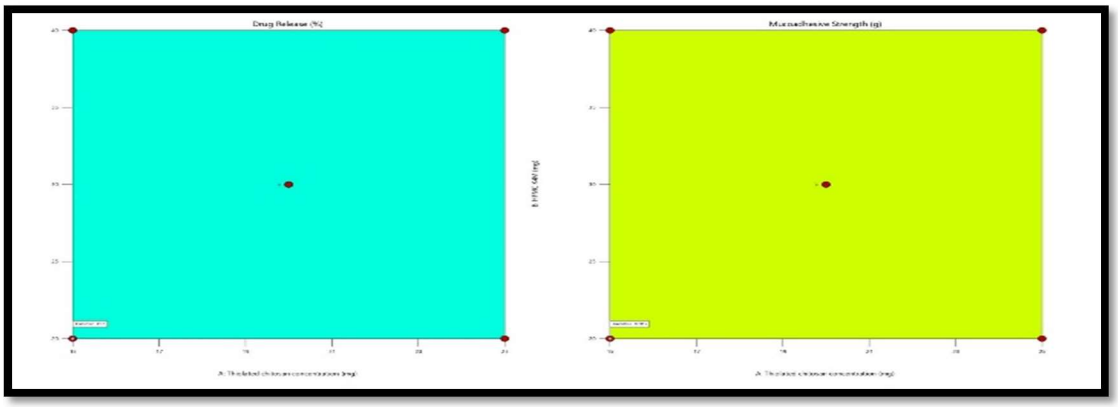


Figure 8. Graph of optimization of Mucoadhesive strength and drug release at 12 h

based formulation F2 showed superior performance due to enhanced mucoadhesion, swelling, and sustained drug release. The improved mucoadhesion was attributed to the formation of covalent disulfide bonds between thiol groups of thiolated chitosan and cysteine-rich regions of gastric mucin, along with electrostatic interactions. Thiolated chitosan

also exhibited higher swelling behavior because of its hydrated crosslinked gel network, which improved water retention and prolonged drug diffusion.

Drug release from F2 followed anomalous non-Fickian transport involving both diffusion and polymer relaxation mechanisms. Dynamic disulfide bond rearrangement in the thiolated chitosan matrix contributed to controlled drug release, unlike guar gum and xanthan gum formulations. DOE analysis confirmed that polymer concentration significantly affected mucoadhesion and drug release. The prolonged buoyancy and sustained release of F2 support its potential for once-daily febuxostat therapy.

5. CONCLUSION:

The study demonstrated that thiolated chitosan-based gastro-retentive floating-mucoadhesive febuxostat tablets showed superior performance compared to chitosan, guar gum, and xanthan gum formulations, with the highest mucoadhesive strength, swelling index, and sustained drug release over 12 h. The enhanced performance was attributed to covalent disulfide bond formation between thiol groups and gastric mucin. Drug release from the optimized formulation followed anomalous non-Fickian transport, indicating combined diffusion and polymer relaxation mechanisms. Overall, thiolated chitosan proved to be a promising polymer for gastro-retentive delivery of febuxostat and other BCS Class II drugs. However, further studies involving stability testing, in vivo pharmacokinetic evaluation, and advanced solid-state characterization are required before clinical application.

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