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FORMULATION AND EVALUATION OF ALBUTEROL GASTRO RETENTIVE FORMULATION USING NATURAL POLYMERS BY APPLYING FACTORIAL DESIGN

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ABSTRACT

The present study aimed to formulate and optimize gastro-retentive floating tablets of Albuterol for sustained drug release and improved gastric retention. Albuterol, a β2-agonist used in the treatment of asthma and chronic obstructive pulmonary disease, has a short half-life and requires frequent dosing. To overcome this limitation, floating tablets were prepared by direct compression using varying concentrations of Xanthan gum (X1), Sodium alginate (X2), and Sodium bicarbonate (X3) as per a 2^3 full factorial design. Eight formulations (F1–F8) were evaluated for pre- and post-compression parameters, floating lag time, total floating duration, and in-vitro drug release over 11 hours. Drug release kinetics were analyzed using Zero-order, First-order, Higuchi, and Korsmeyer–Peppas models. The optimized formulation showed controlled release, acceptable hardness, friability, and short floating lag time with prolonged buoyancy. Statistical analysis through Design-Expert software revealed significant main and interaction effects among variables, and an optimized batch was identified using desirability function. The study concluded that gastro-retentive drug delivery of Albuterol using natural polymers is a promising approach to enhance therapeutic efficacy by prolonging gastric residence and reducing dosing frequency.

Keywords: Albuterol; Xanthan gum; Sodium alginate; Sodium bicarbonate; Natural Polymers

INTRODUCTION

Albuterol is a BCS class III drug with high solubility and low permeability: Albuterol sulfate is highly soluble across the physiological pH range (1–7.5). According to BCS guidelines, a drug is considered highly soluble if the highest dose strength is soluble in ≤250 mL water over the pH range of 1–6.8. Albuterol meets this criterion **[1, 2]**. Despite good solubility, Albuterol has low intestinal permeability, meaning that it is not readily absorbed across the gastrointestinal membrane. Its absorption is often incomplete and subject to significant inter-individual variability **[3]**. It is absorbed primarily in the small intestine, but limited by efflux transporters and potential metabolism. Oral Bioavailability is approximately 40–50% (due to first-pass metabolism and low permeability) **[4]**.

Gastro-retentive drug delivery systems (GRDDS) are designed to prolong the gastric residence time of dosage forms, improving bioavailability and therapeutic efficacy of drugs with narrow absorption windows. Albuterol, a β2-adrenergic agonist, is used in the treatment of asthma and related respiratory disorders. Due to its short half-life, controlled delivery systems like floating tablets are essential to maintain plasma drug levels over extended periods. The current study aims to develop and optimize a gastro-retentive tablet formulation of Albuterol using a factorial design approach.

MATERIALS AND METHODS

Materials:

Albuterol, Xanthan Gum (XG), Sodium Alginate (SA), Sodium Bicarbonate ($NaHCO_3$), Microcrystalline Cellulose (MCC), Lactose, Talc, and Magnesium Stearate were obtained from standard suppliers.

Methadology:

Formulation of Gastro-Retentive Tablets:

A 2^3 full factorial design was employed to evaluate the effect of XG, SA, and $NaHCO_3$ on drug release (at 11h) and floating lag time (FLT). Eight formulations were prepared using direct compression **(Table 1)**. The excepients used are microcrystalline cellulose (MCC), lactose, talc and magnesium stearate. All ingredients were accurately weighed, passed through a 60-mesh sieve, and blended uniformly. Magnesium stearate and talc were added at the final stage. Tablets were compressed using a single-punch tablet machine fitted with 8 mm flat punches. Pre- and post-compression studies were conducted for the optimized batch **[24]**. Analysis was performed using Design-Expert® software. The software generated polynomial equations, response surface plots, interaction plots, and desirability functions to identify the optimized formulation **[25]**.

Table 1: Composition of Albuterol Gastro Retentive formulations using 2^3 full factorial design DoE

Batch	Xanthan Gum (mg)	Sodium Alginate (mg)	$NaHCO_3$ (mg)	Albuterol (mg)	Talc (mg)	Mg Stearate (mg)	MCC + Lactose (mg)	Total Weight (mg)
F1	25	25	12.5	4	5	2.5	176	250
F2	50	25	12.5	4	5	2.5	151	250
F3	25	50	12.5	4	5	2.5	151	250
F4	50	50	12.5	4	5	2.5	126	250
F5	25	25	25	4	5	2.5	163.5	250
F6	50	25	25	4	5	2.5	138.5	250
F7	25	50	25	4	5	2.5	138.5	250
F8	50	50	25	4	5	2.5	113.5	250

Pre-Compression Evaluation:

A standard calibration curve of Albuterol

A standard calibration curve of Albuterol was constructed by measuring the absorbance of drug solutions in 0.1N HCl at 224 nm. The concentrations ranged from 0 to 10 µg/Ml **[26]**. FTIR spectroscopy was performed to evaluate possible interactions between Albuterol and the excipients used in the formulation. The spectra of pure drug and the physical mixture were recorded in the range of 4000–400 cm^{-1} **[27]**.

Angle of Repose

The fixed funnel method was used to determine flowability. A funnel was fixed, and the powder was allowed to flow freely onto a surface. The angle formed was calculated using: $\theta = \tan^{-1}(h / r)$ Where h is the height and r is the radius of the heap **[28]**.

Carr's Index and Hausner Ratio:

Carr's Index and Hausner Ratio are key pre-compression parameters used to assess the flow properties of powders or granules in pharmaceutical formulation.

These two indices are based on the bulk and tapped densities of the powder. They help to quantify the powder's flow ability and compressibility. Bulk density (BD) was determined by transferring accurately weighed 25–50 g of powder and transferred into 100 mL graduated cylinder. Measured Bulk Volume (V_0) without tapping (Bulk Volume). Tapped Density (TD) is the mass of powder divided by the volume after mechanically tapping a measuring cylinder where the final Volume (Vf = Tapped Volume) **[29, 30]**.

$BD = W / V_0$. (Without tapping).

TD = Mass of powder (g) / Tapped volume (mL)

Post-Compression Evaluation and Analysis Methods

Twenty tablets were individually weighed using a digital balance, and the average weight was recorded to ensure weight uniformity as per pharmacopeial limits. The thickness and diameter of the tablets were measured using a Vernier caliper, which is crucial for packaging and dose consistency **[31]**. Tablet hardness was assessed using a Monsanto hardness tester. Three tablets were selected randomly, and the average of their breaking force was recorded in kg/cm^2. Hardness is critical for mechanical

resistance during handling and transport **[32]**.

Friability was tested using a Roche friabilator using twenty tablets **[33]**

Friability (%) = ((Initial Weight − Final Weight) / Initial Weight) × 100

Drug Content Uniformity

Five tablets were powdered and a quantity equivalent to one tablet was dissolved in 0.1N HCl. The solution was filtered and analyzed using UV spectrophotometry at 276 nm to determine the drug content **[34]**.

Floating Behavior

Floating Lag Time (FLT) was determined by placing one tablet in 250 mL of 0.1N HCl (pH 1.2) maintained at 37 ± 0.5°C. The time taken for the tablet to float was recorded as FLT. Total Floating Time (TFT) is the duration for which the tablet remained buoyant on the medium surface **[35]**.

In-vitro Drug Release Study

Drug release studies were conducted using the USP Type II (paddle) apparatus. Tablets were placed in 900 mL of 0.1N HCl (pH 1.2), stirred at 50 rpm and maintained at 37 ± 0.5°C. 5 mL samples were withdrawn at hourly intervals up to 11 hours, replaced with fresh medium, filtered, and analyzed spectrophotometrically at 276 nm. The in-vitro drug release data obtained from the dissolution study were fitted into various kinetic models to determine the release mechanism of Albuterol from the gastro-retentive tablets. The models applied include zero order, first order, Higuchi Model and Korsmeyer–Peppas Model **[36]**. The model that provided the highest coefficient of determination (R^2) was considered the best fit to describe the drug release mechanism of the formulation.

RESULTS AND DISCUSSION

All formulations (F1–F8) showed good flow properties as indicated by their angle of repose (23.64°–29.28°), bulk density (0.216–0.300 g/cm³), and tapped density (0.230–0.270 g/cm³). Hausner ratios were within the acceptable range (1.12–1.22), indicating fair to good flow ability. Carr's Index values ranged between 11.42–16.67%, suggesting acceptable compressibility **(Table 2)**. These results confirmed that the blends were suitable for direct compression without requiring granulation.

Table 2: Pre-compression parameters of Albuterol Gastro Retentive tablets

Formulation code	Angle of repose (0)±SD	Bulk density (gm/cm)±SD	Tapped density (gm/cm)±SD	Hausner ratio (HR)±SD	Carr's index (Ic)±SD
F1	26.43±0.726	0.216±0.010	0.260±0.010	1.18±0.010	15.39±0.594
F2	25.06±0.556	0.225±0.020	0.260±0.010	1.15±0.060	15.72+0.357
F3	28.46±0.471	0.234+0.015	0.270±0.026	1.19±0.010	13.28±0.640
F4	29.28±0.746	1.22±0.005	0.266±0.015	0.238+0.010	16.01±0.512
F5	25.64±0.312	0.300±0.010	0.230±0.011	1.19±0.009	16.67±0.560
F6	24.85±0.665	0.224±0.010	0.262±0.011	1.12±0.006	11.42±0.511
F7	23.64±0.112	0.216±0.010	0.230±0.011	1.18±0.010	15.39±0.594
F8	24.84±0.632	0.225±0.020	0.262±0.011	1.15±0.060	15.72+0.357

 # All the values are expressed as mean± SD. (n=3)

Post-Compression Parameters:

The data showed a linear increase in absorbance with concentration, indicating that Albuterol follows Beer–Lambert's Law in the tested range. Regression Equation: $y = 0.050x + 0.001$. Correlation Coefficient (R^2): 0.999. This confirms that the method is suitable for quantifying Albuterol in 0.1N HCl with high accuracy and precision. The FTIR spectrum of the physical mixture displayed all characteristic peaks of Albuterol without any significant shift, disappearance, or formation of new peaks. This indicates that no chemical interaction occurred between the drug and the excipients. The FTIR study confirmed that Albuterol is chemically compatible with the excipients used in the gastro-retentive tablet formulation.

All tablets passed the uniformity tests. Tablet weights were around 250 mg (±5%), thickness ranged from 2.12 to 2.28 mm, and diameter remained consistent (\~9 mm). Hardness values ranged from 3.35 to 4.94 kg/cm², indicating satisfactory mechanical strength. Friability values were below 1% for all batches, fulfilling pharmacopeial standards. Drug content ranged from 96.36% to 99.67%, confirming uniform distribution of Albuterol. These findings indicate that the tablets had sufficient hardness and friability for withstanding mechanical handling **(Table 3)**.

Table 3: Post-compression evaluation of Albuterol Gastro Retentive tablets

Formulation code	Weight variation Average wt in(mg)	Hardness (Kg/cm²)	Diameter in(mm)	Thickness in(mm)	Friability (%)	Drug content uniformity (%)	FLT
F1	199.58+0.934	3.355±0.208	9.34±0.577	2.245±0.057	0.756±0.057	99.672±0.612	90
F2	200.5±0.885	4.943±0.115	9.32±0.577	2.144±0.066	0.592±0.055	97.564±0.407	45
F3	195.6±0.824	4.856±0.115	9.65±0.577	2.126±0.055	0.759±0.015	99.044+0.817	50
F4	200.04±0.889	3.987±0.155	9.00±0.000	2.250 0.000	0.671±0.010	99.486±0.147	65
F5	200.3±0.833	4.401±0.200	8.65±0.577	2.285±0.057	0.764±0.011	98.592+0.391	75
F6	200.2±0.952	4.132±0.115	8.67±0.577	2.129±0.010	0.766±0.090	96.362+0.305	85
F7	200.3±0.833	4.401±0.200	8.65±0.577	2.285±0.057	0.764±0.011	98.592+0.391	80
F8	200.2±0.952	4.132±0.115	8.67±0.577	2.129±0.010	0.766±0.090	96.362+0.305	81

All the values are expressed as mean± SD. (n=3)

The floating lag time ranged from 45 seconds (F2) to 90 seconds (F1). All tablets floated for more than 12 hours, indicating successful formulation of floating tablets. Sodium bicarbonate, used as the gas-generating agent, played a key role in ensuring buoyancy. Formulations with higher concentrations of $NaHCO_3$ (F5–F8) showed shorter lag times and longer floating duration, confirming its crucial role **(Table 3 & Figure 2)**. The drug release profile was studied over 11 hours in 0.1N HCl. The cumulative percentage drug release for different batches at 11 hours were: **(Figure 2)**. F1: 78.47%; F2: 76.28%; F3: 79.82%; F4:98.36%; F5: 85.74%; F6: 78.27%; F7:

85.74%; F8: 78.27%. Formulation F4 exhibited the highest drug release (98.36%) at 11 hours, attributed to higher concentrations of both Xanthan gum and Sodium alginate. The presence of natural polymers created a strong gel matrix, which prolonged the release of Albuterol. The formulation maintained floating behavior during the entire release period. The in-vitro release data of all formulations were fitted into Zero-order, First-order, Higuchi, and Korsmeyer–Peppas models. Most formulations showed higher correlation with Higuchi model, indicating a diffusion-controlled drug release mechanism. Additionally, the Korsmeyer–Peppas model, revealed an 'n' value between 0.45 and 0.89, suggesting, non-Fickian (anomalous) transport, where both diffusion and polymer erosion were involved.

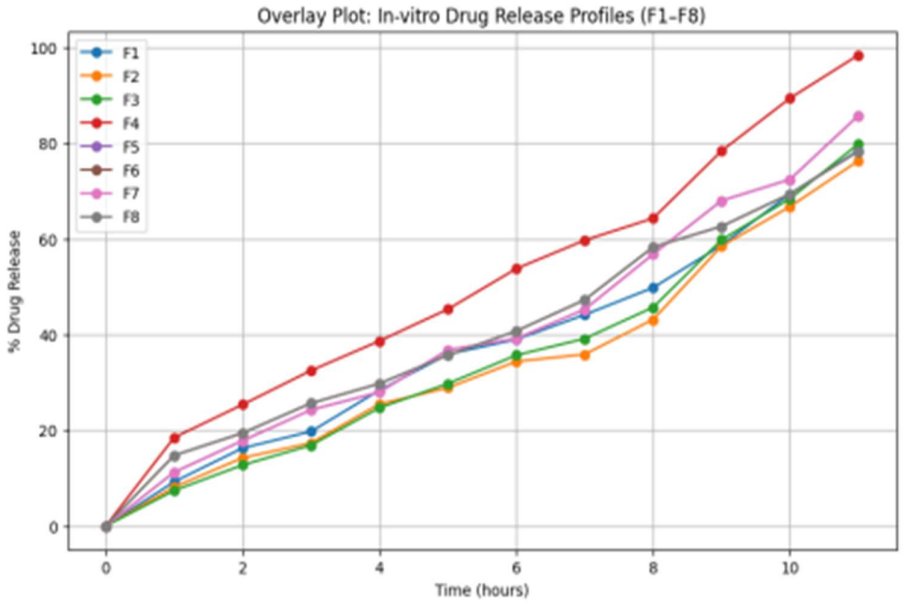

Figure 2: Drug release profile of F1 to F8 formulations. h representing the interaction of natural polymers on drug release kinetics

The ANOVA results revealed that both Xanthan Gum (X_1) and Sodium Alginate (X_2) had a significant positive effect on drug release at 6 hours ($p < 0.05$). Higher levels of these polymers enhanced swelling and matrix formation, resulting in prolonged drug release. However, Sodium Bicarbonate (X_3), used as a gas-forming agent, did not show a statistically significant impact on drug release within the evaluated range ($p > 0.05$). Interaction terms such as X1×X2 had marginal significance, indicating potential synergistic effects between the polymers that may further influence the release profile. FLT was significantly affected by all three main factors. Sodium Bicarbonate (X1) was the most influential factor ($p < 0.001$), which is expected due to its role in

CO_2 generation that enables tablet buoyancy. Xanthan Gum (X1) and Sodium Alginate (X3) also significantly contributed to increasing the FLT ($p < 0.05$), likely due to enhanced gel barrier formation. However, all interaction terms among the factors were found to be statistically non-significant ($p > 0.05$), suggesting that their combined effects do not notably alter FLT within the studied levels. Overall, the ANOVA analysis confirmed the significant roles of polymer concentration and gas-forming agent in controlling the drug release and floating behavior of the gastro-retentive system. These insights were instrumental in selecting the optimized formulation (F4), which achieved a balance between sustained release and rapid buoyancy.

The 3D surface plots (a & e) and contour plots (b & f) demonstrate the combined influence of Xanthan Gum (X1) and Sodium Alginate (X2) on drug release and FLT when NaHCO3 is at its high level (25 mg). Drug release increased significantly with higher concentrations of both polymers, indicating a synergistic swelling and matrix-retaining effect. FLT also increased moderately, suggesting that a thicker polymeric gel layer forms in the presence of high NaHCO3 and polymer levels, which delays tablet submersion and supports floating.

Plots c & g (3D) and d & h (contour) reflect the same relationships when $NaHCO_3$ is kept at its low level (12.5 mg). Drug release at low gas-former concentration is more dependent on the polymer blend. Notably, FLT decreased due to reduced CO2 generation, but polymer matrix thickness still contributed to buoyancy, especially at higher levels of Xanthan Gum. These plots reveal that polymer ratio adjustment can partly compensate for low $NaHCO_3$ in sustaining both release and floating performance. The desirability function plot (i) in **Figure 3** represents the multi-objective optimization of formulation parameters. It indicates that an ideal combination of high polymer concentrations (especially XG and SA) and intermediate $NaHCO_3$ yields the best compromise between maximum drug release and acceptable FLT. **Figure 3** confirms the interactive role of hydrophilic polymers and gas-forming agent in controlling the gastro-retentive behavior of Albuterol tablets. Both individual and combined effects influence the targeted responses, and design space optimization helps identify the most suitable formulation range.

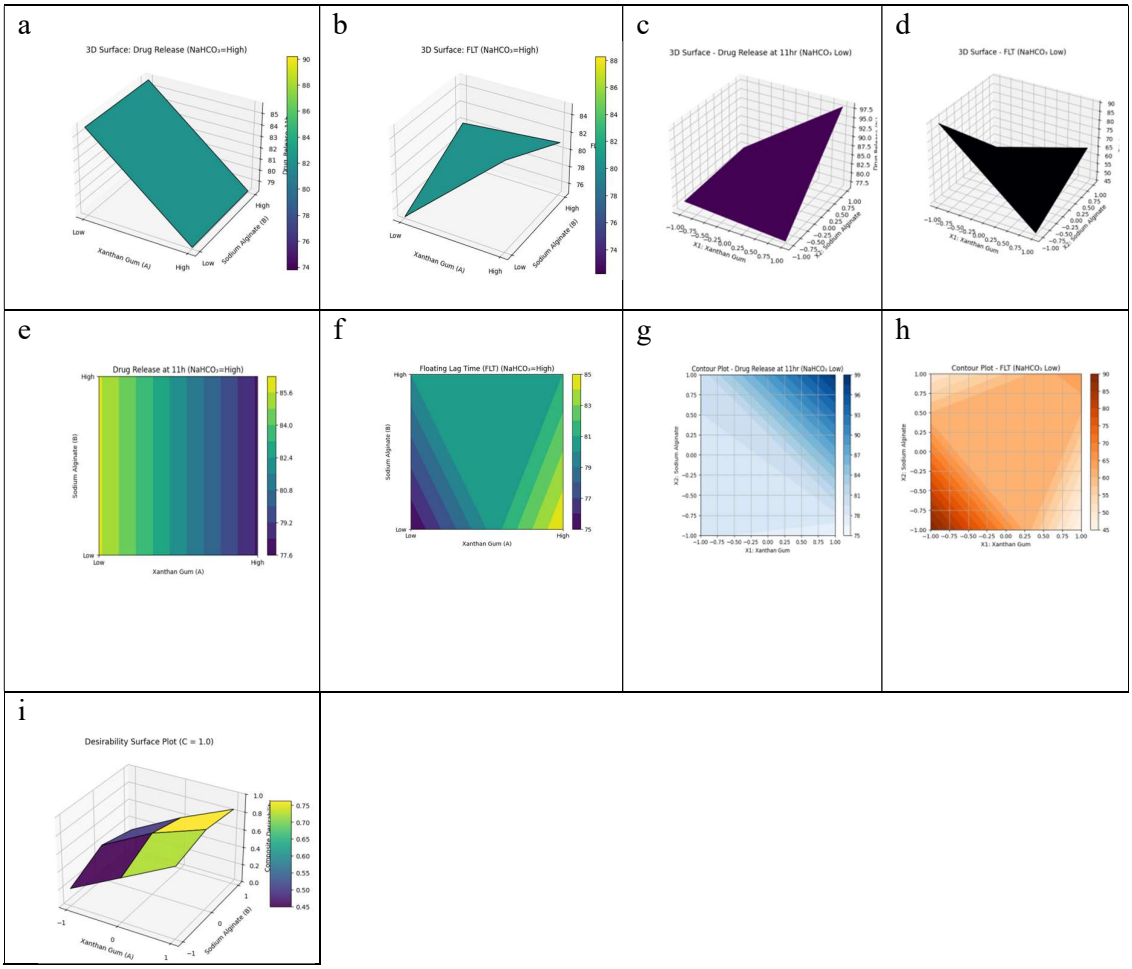

Figure 3: a & b; e & f are the 3D surface plots and counter plots showing the effect of polymers on Drug release and floating time at high concentrations of sodium bicarbonate. c & d; g & h are the 3D surface plots and counter plots showing the effect of polymers on Drug release and floating time at low concentrations of sodium bicarbonate. I is the out of the box desirability 3D plot.

Based on the results of the 2^3 full factorial design analysis of gastro-retentive Albuterol tablets, the optimal formulation was given in **Table 4** was selected using the criteria of maximum drug release at 11 hours and acceptable floating lag time (FLT).

Table 4: Ingredients of Selected Optimized Batch: F4

S. No.	Component	Amount (mg)
1	Xanthan Gum	50
2	Sodium Alginate	50
3	Sodium Bicarbonate	12.5
4	Albuterol	4
5	Talc	5
6	Magnesium Stearate	2.5
7	MCC + Lactose	126
8	Total Weight	250

The results demonstrated that both Xanthan gum and Sodium alginate effectively sustained drug release when used alone or in combination. Sodium bicarbonate was essential for achieving floating behavior, as its concentration determined the lag time and duration of floatation. The factorial design approach enabled understanding of factor effects and interactions with minimal experimental runs. The optimized formulation showed promising characteristics for a gastro-retentive system, potentially improving bioavailability and patient compliance in the management of asthma. It demonstrated the highest drug release at the 6-hour mark along with an acceptable floating lag time, making it suitable for gastro-retentive delivery of Albuterol.

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