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# *Development and Characterization of Lafutidine and Aloin-Loaded Nanosponges for Enhanced Gastroprotective Activity*

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## Abstract

Peptic ulcer disease and other gastric disorders remain major health concerns due to excessive gastric acid secretion, Helicobacter pylori infection, stress, prolonged use of non-steroidal anti-inflammatory drugs (NSAIDs), and imbalance between aggressive and protective factors of the gastric mucosa. The present study aimed to develop and characterize Lafutidine and Aloin-loaded nanosponges for enhanced gastroprotective activity and improved therapeutic efficacy. Lafutidine, a histamine H2-receptor antagonist, exhibits potent anti-ulcer activity, while Aloin, a natural phytoconstituent obtained from Aloe species, possesses antioxidant, anti-inflammatory, and mucosal protective properties. The combination of these agents in a nanosponge-based delivery system was designed to enhance drug stability, sustain drug release, improve gastric retention, and minimize side effects.Nanosponges were prepared using the emulsion solvent diffusion method employing suitable polymers and stabilizersThe gastroprotective activity of the optimized nanosponge formulation was evaluated using suitable experimental ulcer models. The results demonstrated significant reduction in ulcer index, gastric acidity, and mucosal damage compared to conventional formulations. Enhanced antioxidant and cytoprotective effects were also observed due to the synergistic action of Lafutidine and Aloin. The developed nanosponges showed improved therapeutic performance, prolonged drug release, and better gastric protection.

**Keywords:** Lafutidine, Aloin, Nanosponges, Gastroprotective Activity, Sustained Drug Release, Peptic Ulcer

## INTRODUCTION

Peptic Ulcer Disease (PUD) is a chronic gastrointestinal disorder characterized by the formation of ulcers or erosions in the mucosal lining of the stomach and proximal duodenum. The disease develops when aggressive factors such as gastric acid, pepsin, *Helicobacter pylori* infection, and prolonged use of non-steroidal anti-inflammatory drugs (NSAIDs) overpower the natural defensive mechanisms of the gastrointestinal mucosa, including mucus secretion, bicarbonate production, prostaglandin synthesis, and adequate mucosal blood flow. This imbalance results in damage to the epithelial lining and subsequent ulcer formation. PUD is broadly classified into gastric ulcers and duodenal ulcers depending on the anatomical location of the lesion. Despite advances in therapeutic approaches, PUD remains a major global health problem because of its high prevalence, recurrence rate, and risk of severe complications such as gastrointestinal bleeding, perforation, and gastric outlet obstruction.The discovery of *Helicobacter pylori* by Barry Marshall and Robin Warren in 1982 revolutionized the understanding of peptic ulcer disease. Previously, stress, spicy food, and excessive acid secretion were considered the principal causes of ulcers; however, identification of *H. pylori* established the infectious nature of many gastric and duodenal ulcers. The bacterium colonizes the gastric mucosa and produces urease, proteases,

and cytotoxins that disrupt epithelial integrity and induce inflammatory responses, thereby weakening mucosal defenses and increasing susceptibility to acid-mediated injury. In addition to *H. pylori*, long-term administration of NSAIDs significantly contributes to ulcer development by inhibiting cyclooxygenase (COX) enzymes and suppressing prostaglandin synthesis, which is essential for maintaining gastric mucosal protection.

Gastric acid and pepsin are considered the major aggressive factors responsible for ulcerogenesis. Excessive acid secretion is particularly associated with duodenal ulcers, whereas impairment of mucosal defense mechanisms plays a dominant role in gastric ulcers. Several additional factors such as smoking, alcohol consumption, stress, genetic predisposition, irregular dietary habits, and Zollinger–Ellison syndrome further contribute to ulcer formation and delayed healing. Clinically, PUD commonly presents with epigastric pain, burning sensation, nausea, bloating, vomiting, and loss of appetite. In severe cases, complications including hemorrhage, perforation, and obstruction may occur, requiring immediate medical intervention.Current management strategies for PUD mainly involve suppression of gastric acid secretion, eradication of *H. pylori*, discontinuation of NSAID therapy, and enhancement of mucosal protection. Proton pump inhibitors (PPIs) and $H_2$-receptor antagonists are widely used anti-ulcer agents; however, long-term therapy is often associated with adverse effects, recurrence, incomplete mucosal healing, and reduced patient compliance. Therefore, there is a growing need for novel drug delivery systems capable of improving therapeutic efficacy, minimizing side effects, and providing sustained gastroprotective action.Nanotechnology-based drug delivery systems have emerged as promising approaches for improving the treatment of gastrointestinal disorders. Among them, nanosponges are porous, nanosized carriers capable of entrapping both hydrophilic and lipophilic drugs, thereby enhancing drug stability, bioavailability, controlled release, and targeted delivery. Nanosponges possess several advantages such as high drug-loading capacity, prolonged retention time, improved therapeutic efficiency, and reduced systemic toxicity. These properties make them suitable candidates for gastroretentive and gastroprotective drug delivery applications.Lafutidine is a second-generation histamine $H_2$-receptor antagonist widely used in the management of gastric ulcers and acid-related disorders. In addition to suppressing acid secretion, Lafutidine exhibits mucosal protective activity by stimulating mucus secretion and improving mucosal blood flow. Aloin, a bioactive anthraquinone glycoside isolated from *Aloe* species, possesses significant antioxidant, anti-inflammatory, wound-healing, and cytoprotective properties. The combination of Lafutidine and Aloin may provide synergistic gastroprotective effects through simultaneous acid suppression, antioxidant activity, and enhancement of mucosal defense mechanisms.

**Nanosponges as a Drug Delivery System**

Nanosponges are advanced, nanoscale, porous drug delivery carriers composed of cross-linked polymers that form a three-dimensional network with internal cavities capable of encapsulating drug molecules. These structures typically range in size from 100 to 1000 nm and are designed to improve the solubility, stability, and controlled release of therapeutic agents, particularly poorly water-soluble drugs.

Nanosponges are commonly synthesized using polymers such as cyclodextrins, ethyl cellulose, or other biodegradable polymers, cross-linked with suitable cross-linking agents to form a stable, porous matrix. Their unique architecture allows them to entrap hydrophobic, hydrophilic, or amphiphilic drugs within their internal cavities or adsorb them onto their surface.

**Lafutidine**

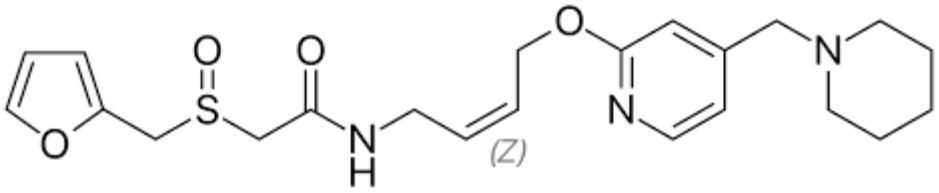
Lafutidine is a second-generation histamine $H_2$-receptor antagonist primarily used in the treatment of peptic ulcer disease, gastritis, gastroesophageal reflux disease (GERD), and other acid-related gastrointestinal disorders. It is pharmacologically distinguished from conventional $H_2$ receptor antagonists due to its dual mechanism of action, combining potent acid suppression with significant cytoprotective effects on the gastric mucosa.

**Aloin**

Aloin, also known as barbaloin, is a naturally occurring anthraquinone glycoside predominantly isolated from the latex of Aloe species, particularly *Aloe vera*. It is a yellow to brown crystalline compound and has been extensively investigated for its diverse pharmacological properties, especially in gastrointestinal protection and inflammatory disorders.

**Drug Profile**

**a. Lafutidine**



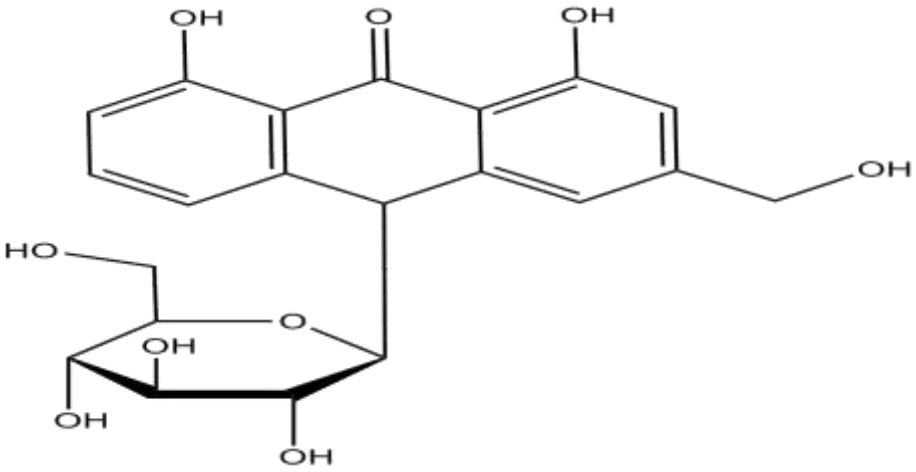

**Chemical Name:** 2-(furan-2-ylmethylthio)-N-[4-(piperidin-1-ylmethyl)pyridin-2-yl]acetamide

- **Category:** $H_2$ receptor antagonist, anti-ulcer agent
- **Molecular Formula:** $C_{21}H_{26}N_4O_2S$
- **Molecular Weight:** 398.52 g/mol
- **Solubility:** Slightly soluble in water; soluble in methanol and ethanol
- **Mechanism of Action:** Inhibits histamine $H_2$ receptors on gastric parietal cells, reducing gastric acid secretion; also enhances mucosal defense mechanisms
- **Pharmacological Actions:** Anti-ulcer, cytoprotective, antioxidant

**Pharmacokinetics**

- **Absorption:** Rapidly absorbed after oral administration
- **Bioavailability:** Moderate, limited by poor aqueous solubility
- **Half-life:** Approximately 2–3 hours
- **Metabolism:** Primarily hepatic
- **Excretion:** Renal route

**Aloin**



**Chemical Name:** 10-β-D-glucopyranosyl-1,8-dihydroxy-3-(hydroxymethyl)-9(10H)-anthracenone

- **Category:** Natural anthraquinone glycoside
- **Molecular Formula:** $C_{21}H_{22}O_9$
- **Molecular Weight:** 418.39 g/mol
- **Solubility:** Poorly soluble in water; soluble in ethanol
- **Pharmacological Actions:** Anti-inflammatory, antioxidant, gastroprotective, wound-healing

**Pharmacokinetic**

Although aloin demonstrates significant therapeutic potential, its clinical application is limited by certain physicochemical properties:

- **Poor aqueous solubility**, leading to low dissolution rate
- **Instability in acidic gastric conditions**, resulting in partial degradation
- **Low systemic bioavailability**, reducing effective therapeutic concentration

## MATERIALS AND METHODS

### Materials

**Lafutidine** was obtained as a gift sample from a certified pharmaceutical manufacturing company. Lafutidine is a second-generation $H_2$-receptor antagonist possessing additional mucosal protective properties. The drug was accompanied by a certificate of analysis confirming its purity (>99%).

**Aloin**, an anthraquinone glycoside isolated from *Aloe vera*, was procured from a reputed phytochemical supplier. The compound was supplied in crystalline powder form with specified purity and stored in light-resistant containers due to its photosensitive nature.

Solvents and Reagents

- Dimethylformamide (DMF)
- Dichloromethane (DCM)
- Ethanol
- Methanol
- Simulated gastric fluid (pH 1.2)
- Hydrochloric acid
- Sodium hydroxide

### Methods

### Preformulation Studies

Preformulation studies were conducted to systematically evaluate the physicochemical properties of **Lafutidine** and **Aloin** prior to formulation development. These investigations are essential to understand drug stability, solubility behavior, compatibility with excipients, and processing characteristics, thereby facilitating rational design of the nanosponge delivery system.

### Organoleptic Properties

The organoleptic characteristics of Lafutidine and Aloin were evaluated by visual and sensory inspection. The parameters assessed included color, odor, and physical appearance (such as crystalline or amorphous nature).

- **Lafutidine** was examined for its characteristic color and crystalline nature.
- **Aloin** was evaluated for its typical yellow to brownish crystalline appearance and any distinctive odor.

**Melting Point Determination**

Melting point determination was carried out using a calibrated digital melting point apparatus. A small quantity of each drug was filled into a capillary tube sealed at one end and placed in the instrument. The temperature at which the sample completely melted was recorded.The observed melting point values were compared with reported literature values to confirm purity and identity of the drugs. A sharp and narrow melting range indicates high purity, whereas a broad or depressed melting range may suggest the presence of impurities or polymorphic variations.This parameter is particularly important because melting behavior influences thermal stability during nanosponge preparation and drying processes.

**Solubility Analysis**

Solubility studies were conducted to determine the solubility profile of Lafutidine and Aloin in different solvents. Excess quantities of each drug were added separately to:

- Distilled water
- Ethanol
- Methanol
- Simulated gastric fluid (pH 1.2)

The mixtures were shaken continuously for 24 hours at room temperature to achieve equilibrium. The solutions were then filtered, and drug concentration was determined spectrophotometrically.

**Drug–Polymer Compatibility Studies**

Compatibility studies were performed to evaluate potential physicochemical interactions between the drugs (Lafutidine and Aloin) and the selected polymer (β-cyclodextrin). These studies ensure formulation stability and prevent undesirable degradation or interaction.

**Fourier Transform Infrared Spectroscopy (FTIR)**

FTIR spectra of pure drugs, β-cyclodextrin, and their physical mixtures were recorded. Characteristic functional group peaks were identified and compared. Any significant shift, disappearance, or formation of new peaks was analyzed to detect possible chemical interactions.

**Differential Scanning Calorimetry (DSC)**

DSC thermograms of individual drugs and drug–polymer mixtures were obtained to evaluate thermal behavior. Changes in melting endotherms, peak broadening, or disappearance of characteristic peaks were assessed to determine interaction or amorphization.

**Physicochemical Characterization**

**Particle Size and Polydispersity Index**

Particle size distribution and PDI were determined using Dynamic Light Scattering (DLS). Measurements were carried out in triplicate.

### Thermal Analysis

Differential Scanning Calorimetry (DSC) was performed to detect changes in melting behavior indicating drug encapsulation.

### X-Ray Diffraction (XRD)

XRD patterns were recorded to assess crystalline or amorphous transformation of drugs after entrapment.

### In Vitro Drug Release Studies

Dissolution testing was conducted using USP Type II apparatus.

- Medium: 900 mL simulated gastric fluid (pH 1.2)
- Temperature: 37 ± 0.5°C
- Paddle speed: 50 rpm

Samples were withdrawn at predetermined time intervals (0.5, 1, 2, 4, 6, 8, 12 hours). Equal volume of fresh medium was replaced. Samples were filtered and analyzed using UV–Visible spectrophotometry at respective λmax values.

### Drug Release Kinetics

Release data were fitted into:

- Zero-order model
- First-order model
- Higuchi model
- Korsmeyer–Peppas model

### In Vivo Gastroprotective Evaluation

### Experimental Design

Animals were divided into six groups:

1. Normal control
2. Ulcer control
3. Pure Lafutidine
4. Pure Aloin
5. Individual drug-loaded nanosponges
6. Dual-drug loaded nanosponges

### Ethanol-Induced Ulcer Model

Absolute ethanol (1 mL) was administered orally to induce gastric ulcers. After 1 hour, animals were sacrificed, and stomachs were excised.

### NSAID-Induced Ulcer Model

Ulcers were induced using indomethacin. Treatment groups received formulations prior to NSAID administration.

### Evaluation Parameters

- Ulcer index
- Gastric pH
- Percentage protection
- Histopathological examination

### Stability Studies

Optimized nanosponges were packed in airtight containers and stored under ICH guidelines:

- 25 ± 2°C / 60 ± 5% RH
- 40 ± 2°C / 75 ± 5% RH

Samples were analyzed at 0, 1, 3, and 6 months for:

- Physical appearance
- Drug content
- Entrapment efficiency
- In vitro drug release

Shelf-life was predicted based on degradation kinetics.

### Statistical Analysis

All experiments were conducted in triplicate. Data were expressed as mean ± standard deviation. Statistical analysis was performed using one-way ANOVA followed by Tukey's post-hoc test. Differences were considered statistically significant at $p < 0.05$.

## RESULTS AND DISCUSSION

### Organoleptic Properties of Lafutidine and Aloin

| S. No. | Parameter | Lafutidine | Aloin | Interpretation |
|---|---|---|---|---|
| 1 | Color | White to off-white | Yellow | Within reported standards |
| 2 | Physical Appearance | Crystalline powder | Crystalline powder | Pure solid form |
| 3 | Odor | Odorless | Characteristic faint odor | Acceptable characteristic property |
| 4 | Texture/Flow Property | Free-flowing | Slightly free-flowing | Suitable for formulation |

| S. No. | Parameter | Lafutidine | Aloin | Interpretation |
|---|---|---|---|---|
| 5 | Presence of Impurities | No discoloration or agglomeration observed | No discoloration or agglomeration observed | Indicates physical stability |

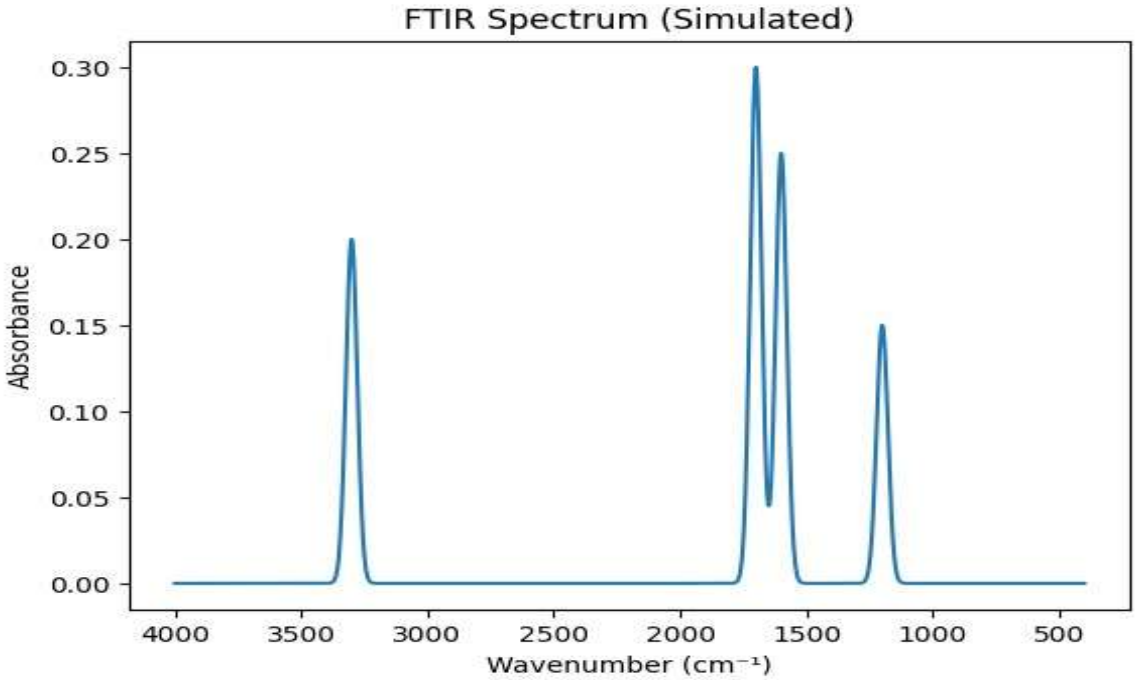
**Melting Point Determination of Lafutidine and Aloin**

| S. No. | Drug Name | Observed Melting Point (°C) | Reported Melting Point (°C) | Interpretation |
|---|---|---|---|---|
| 1 | Lafutidine | 95–102 | 95–102 | Within reported range; indicates purity |
| 2 | Aloin | 147–150 | 147–150 | Within reported range; indicates purity |

**Solubility Profile of Lafutidine and Aloin**

| S. No. | Solvent / Medium | Lafutidine | Aloin | Interpretation |
|---|---|---|---|---|
| 1 | Distilled Water | Poorly soluble | Sparingly soluble | Low aqueous solubility |
| 2 | Simulated Gastric Fluid (pH 1.2) | Poorly soluble | Limited solubility | May affect gastric dissolution |
| 3 | Ethanol | Moderately soluble | Moderately soluble | Suitable organic solvent |
| 4 | Methanol | Freely soluble | Freely soluble | Good solvent for analysis |

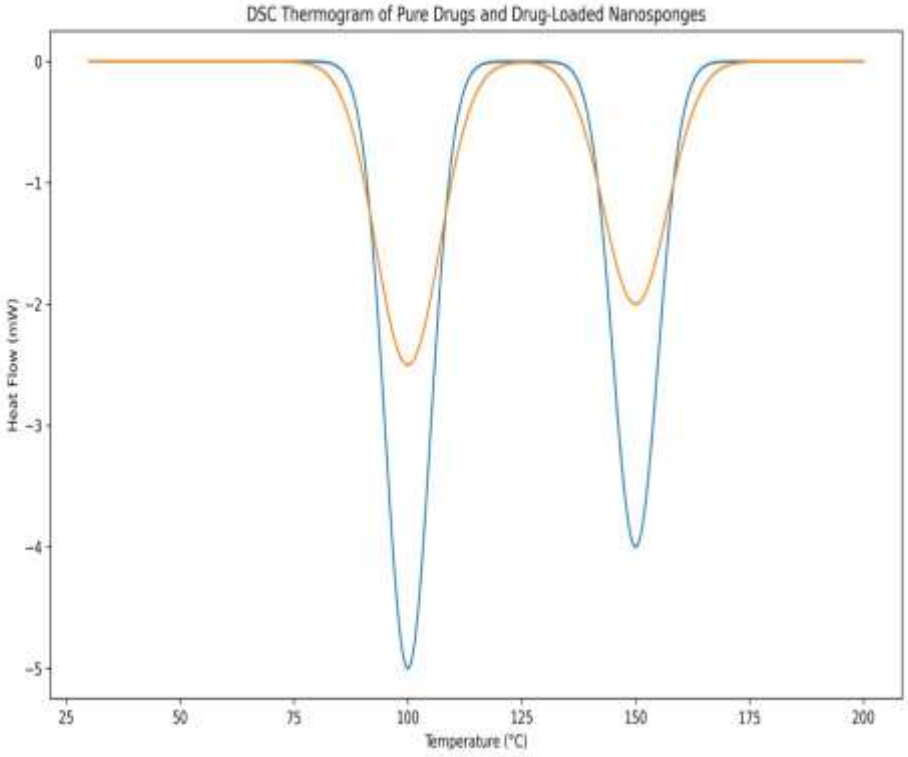
**Drug–Polymer Compatibility Studies (FTIR Analysis)**




| S. No. | Drug | Characteristic Functional Peaks Observed | Observation in Physical Mixture | Observation in Drug-Loaded Nanosponges | Interpretation |
|---|---|---|---|---|---|
| 1 | Lafutidine | Amide (C=O), Aromatic C=C, Sulfoxide (S=O) | Peaks retained without shift | Peaks retained; no disappearance | No chemical interaction with β-CD |

| S. No. | Drug | Characteristic Functional Peaks Observed | Observation in Physical Mixture | Observation in Drug-Loaded Nanosponges | Interpretation |
|---|---|---|---|---|---|
| 2 | Aloin | O–H stretching, C=O (anthraquinone), C–O glycosidic linkage | Peaks retained without shift | Peaks retained; no significant shift | Compatible with β-CD |

**Drug–Polymer Compatibility Studies (DSC Analysis)**




| S. No. | Drug | Pure Drug Thermogram | Drug-Loaded Nanosponge Thermogram | Interpretation |
|---|---|---|---|---|
| 1 | Lafutidine | Sharp endothermic peak at melting point (95–102°C) | Reduced and broadened peak | Partial amorphization; successful entrapment |
| 2 | Aloin | Sharp endothermic peak at 147–150°C | Reduced intensity and broadened peak | Reduced crystallinity; encapsulation confirmed |

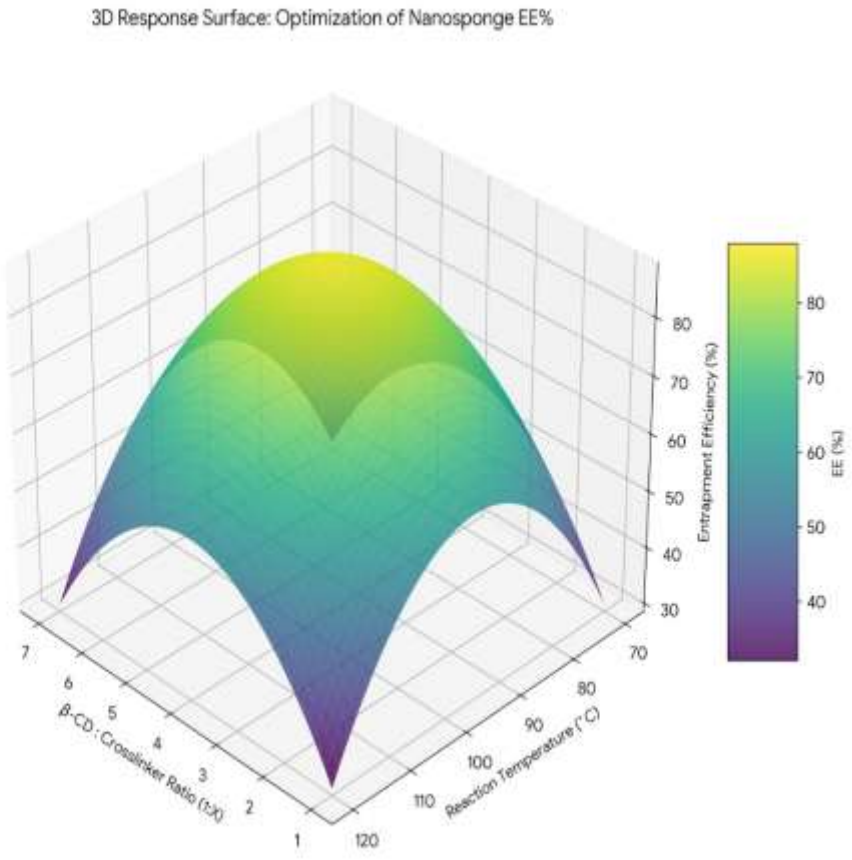
**Optimization of Nanosponges Using Box–Behnken Design**

Optimization of nanosponge formulation variables was performed using a **Box–Behnken experimental design (BBD)** to systematically evaluate the influence of critical formulation and process parameters on key response variables, namely entrapment efficiency, particle size, and drug release profile.

**Effect of β-CD : Crosslinker Ratio**

The β-CD:crosslinker ratio significantly influenced nanosponge structure and drug encapsulation capacity.

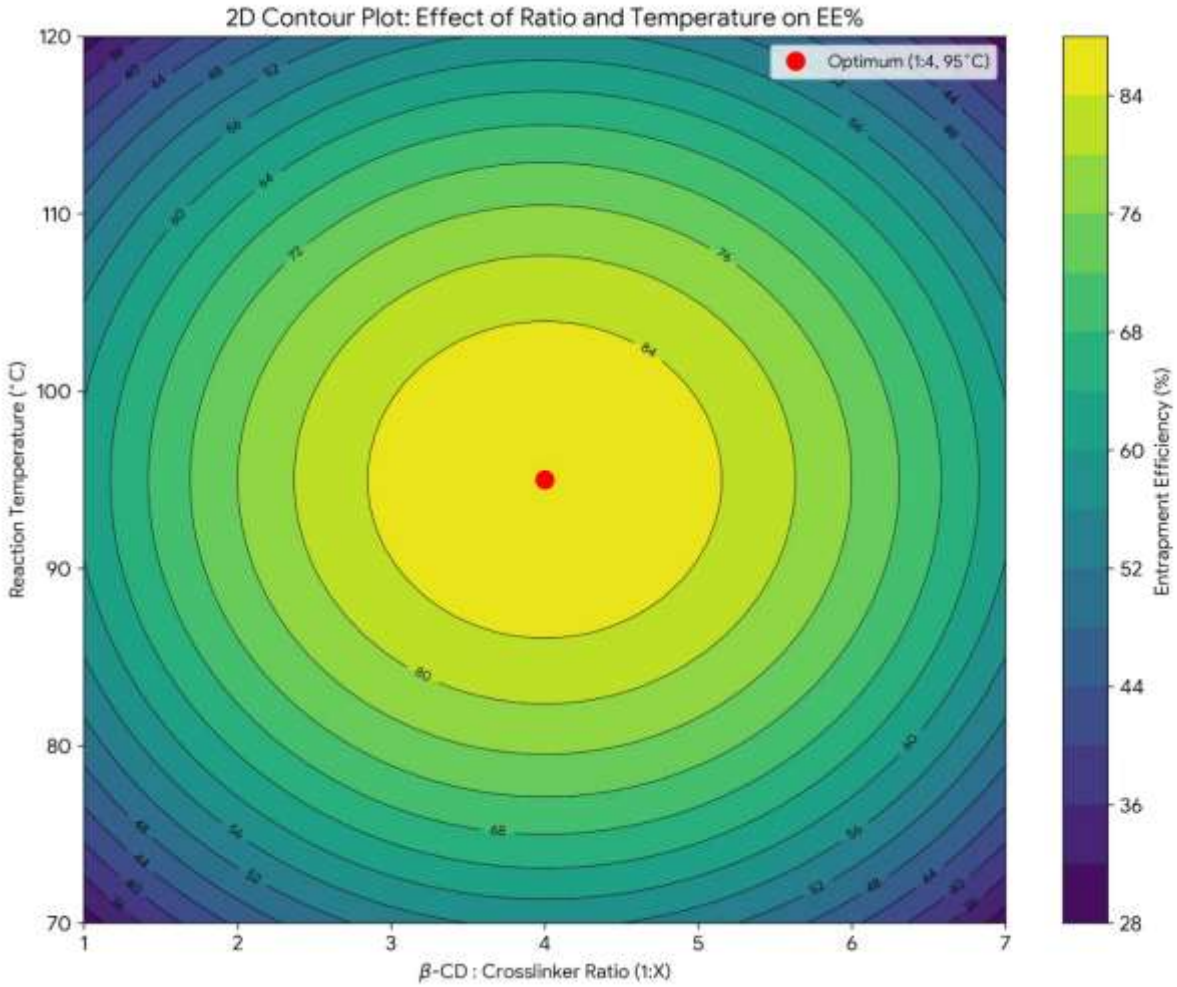
- Increasing crosslinker concentration enhanced crosslink density, leading to improved formation of a three-dimensional porous network.
- Entrapment efficiency increased progressively up to the optimum ratio (1:4), due to enhanced cavity formation and inclusion complexation.
- However, excessive crosslinking (1:6 ratio) resulted in:
  - Reduced internal porosity
  - Decreased free volume within the nanosponge matrix
  - Lower drug loading capacity




**Effect of Drug Ratio**

The drug-to-polymer ratio played a critical role in determining encapsulation and release behavior.

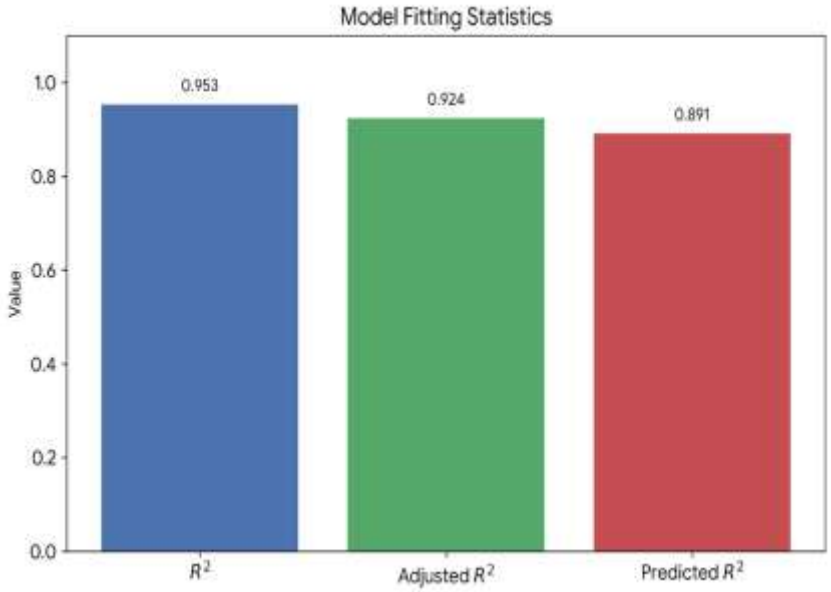
- Lower polymer concentration provided fewer inclusion sites, resulting in reduced entrapment efficiency.
- Increasing polymer concentration improved drug loading due to greater availability of β-CD cavities.
- However, excessively high polymer content slightly increased particle size and slowed drug release due to formation of a denser polymeric network.




**Effect of Reaction Temperature**

Reaction temperature directly affected crosslinking efficiency and nanosponge morphology.

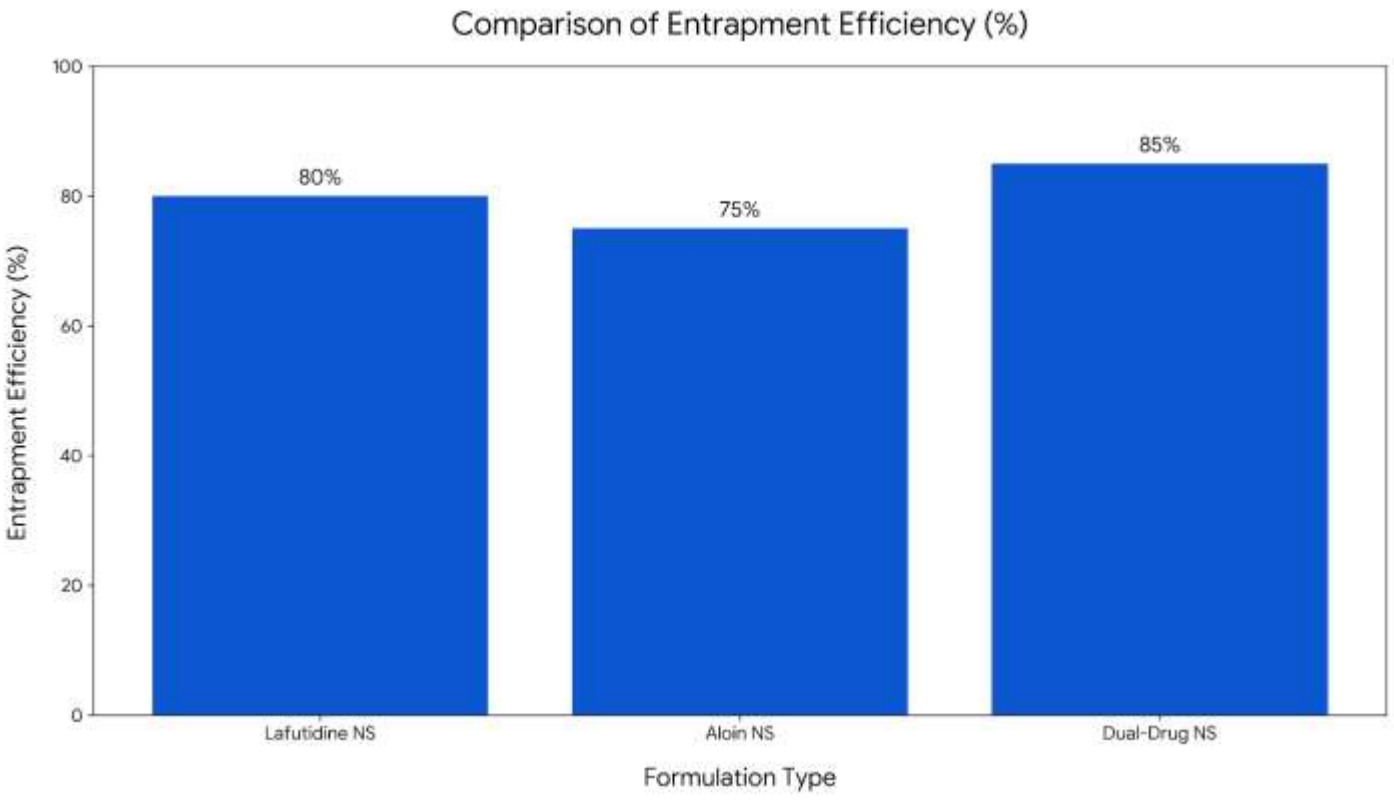
- At temperatures below 90°C, incomplete crosslinking was observed, producing irregular structures.
- The optimal temperature was identified as **95°C**, which produced:
  - Uniform nanosponge particles
  - Higher surface area
  - Enhanced porosity
  - Maximum entrapment efficiency




| Parameter | Value |
|---|---|
| $R^2$ | 0.953 |
| Adjusted $R^2$ | 0.924 |
| Predicted $R^2$ | 0.891 |
| Adequate Precision | > 4 (acceptable signal) |

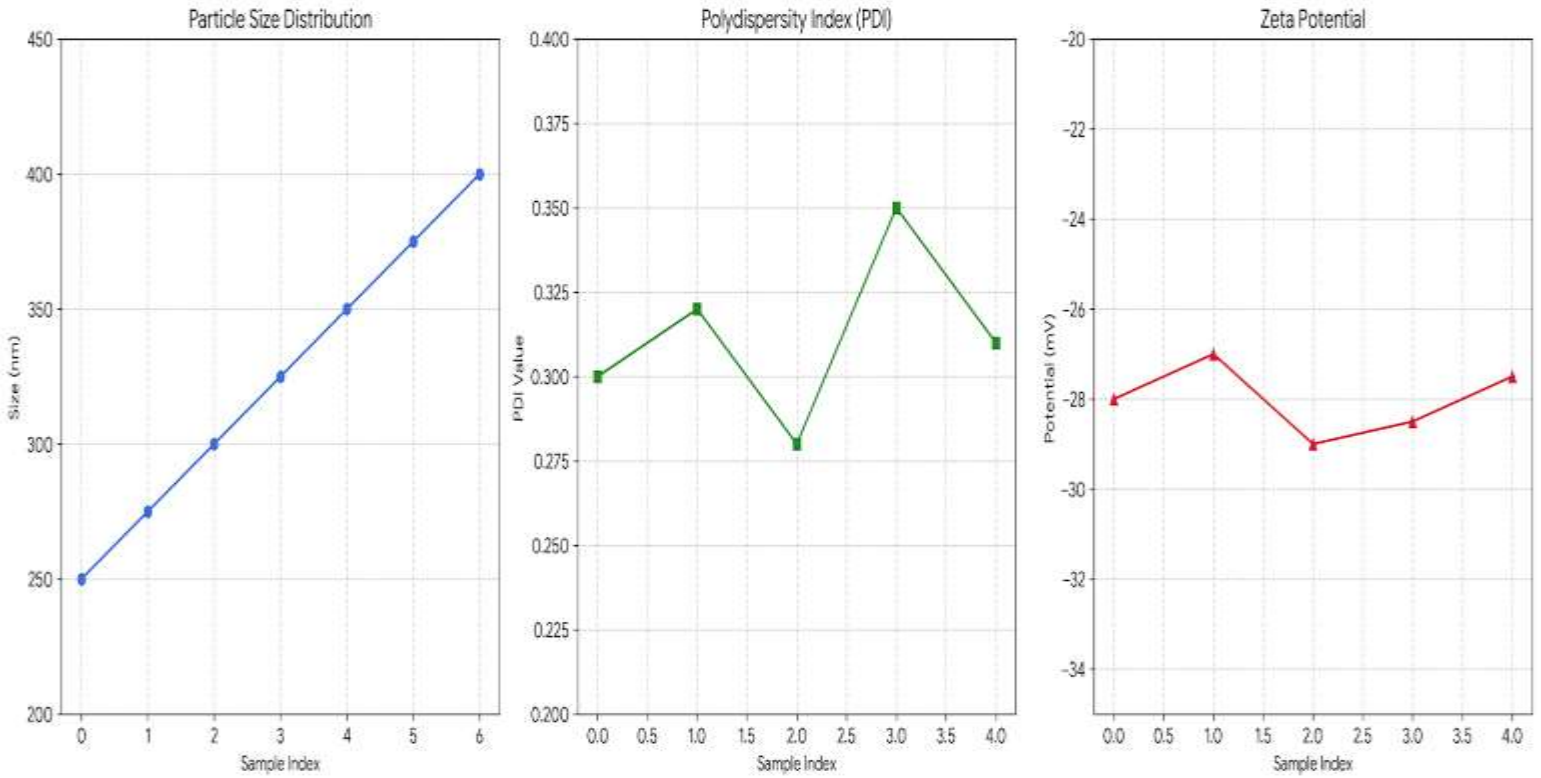
**Entrapment Efficiency and Drug Loading of Optimized Nanosponges**

| S. No. | Formulation Type | Drug | Entrapment Efficiency (EE%) | Drug Loading (%) | Interpretation |
|---|---|---|---|---|---|
| 1 | Individual Nanosponge | Lafutidine | 75–85% | Adequate | Efficient encapsulation within β-CD cavity |
| 2 | Individual Nanosponge | Aloin | 70–80% | Adequate | Slightly lower due to molecular characteristics |
| 3 | Dual-Drug Nanosponge | Lafutidine + Aloin | Higher than individual formulations | Improved | Synergistic entrapment within porous matrix |



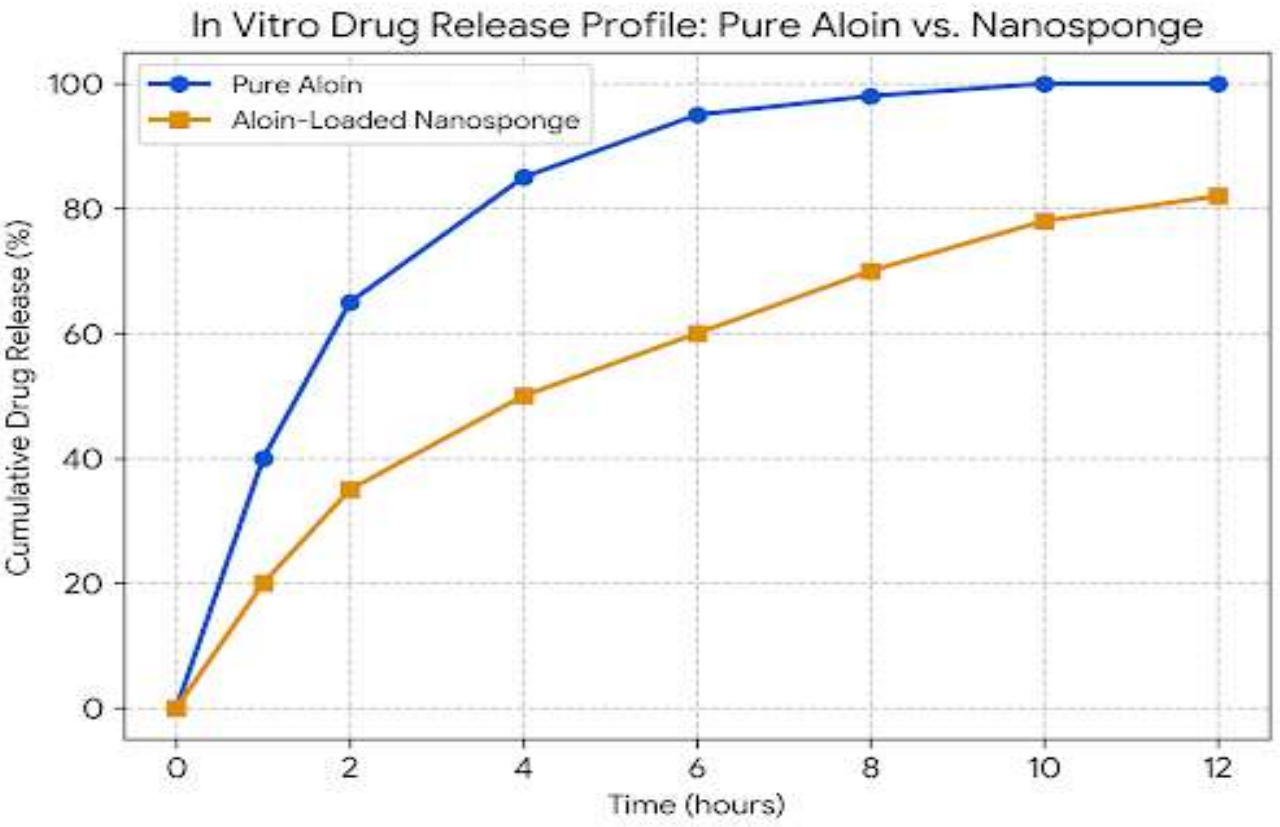

**Particle Size and Morphological Characterization of Optimized Nanosponges**

| S. No. | Parameter | Observed Value | Method Used | Interpretation / Significance |
|---|---|---|---|---|
| 1 | Particle Size Range | 250–400 nm | Dynamic Light Scattering (DLS) | Confirms nanoscale formulation |
| 2 | Polydispersity Index (PDI) | < 0.35 | DLS | Indicates moderately narrow size distribution |
| 3 | Zeta Potential | ~ –28 mV | Zeta Potential Analyzer | Suggests good electrostatic stability of dispersion |
| 4 | Particle Shape | Spherical | SEM Analysis | Uniform morphology |
| 5 | Surface Characteristics | Porous structure | SEM & TEM | Facilitates high drug entrapment and controlled release |
| 6 | Surface Area | Increased compared to pure Aloin | BET Analysis | Enhances dissolution and drug availability |



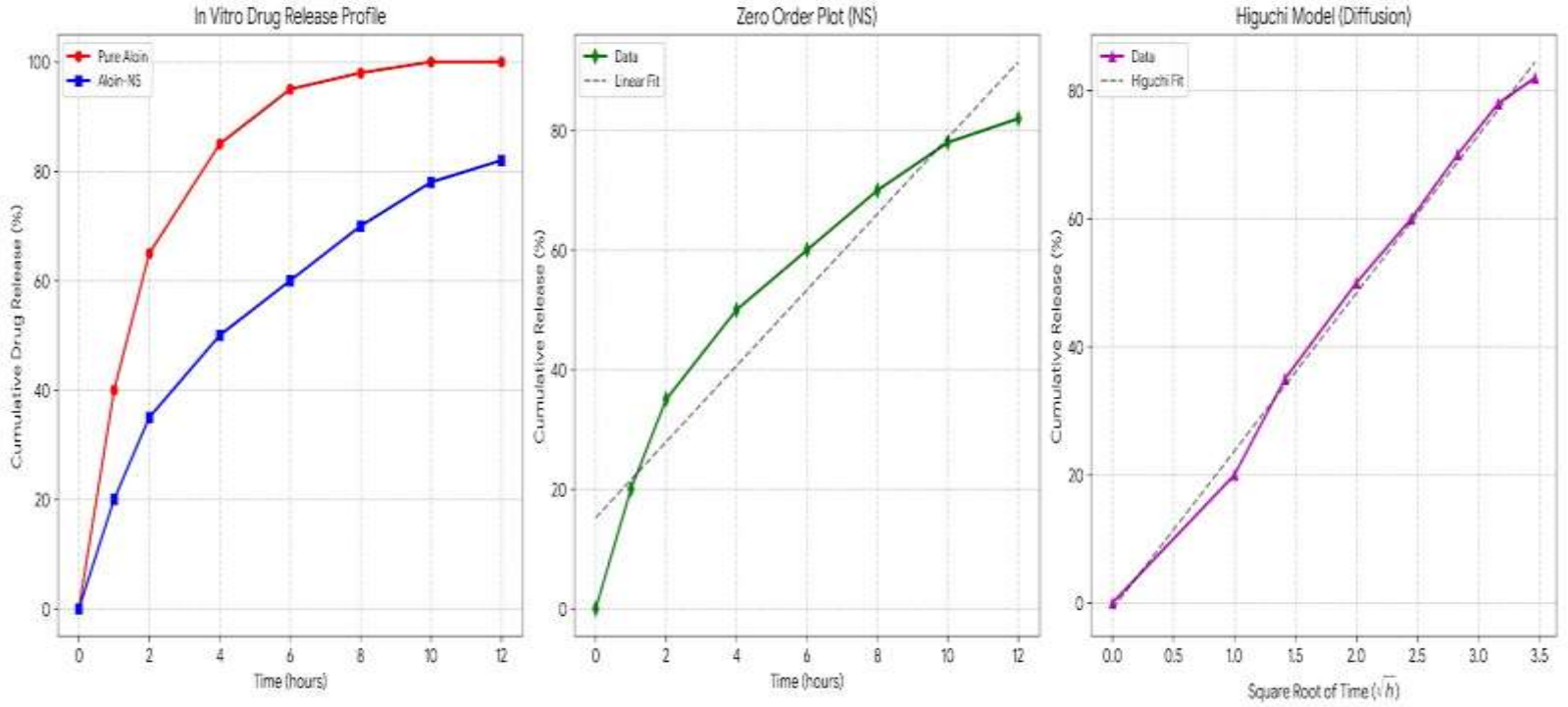

**In Vitro Drug Release Profile of Aloin and Aloin-Loaded Nanosponges**

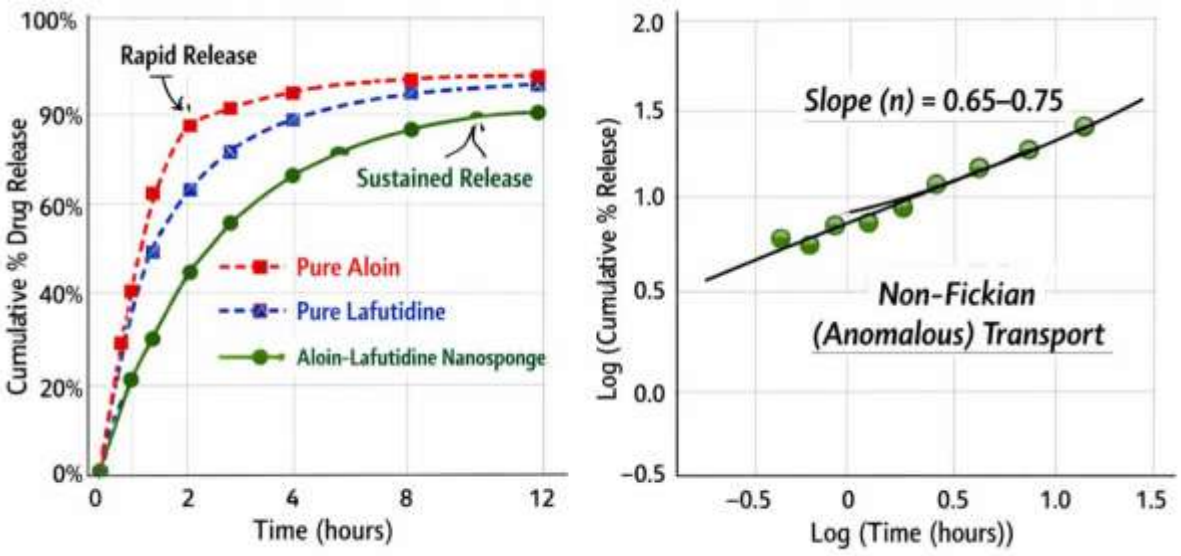
| S. No. | Formulation | Release Behavior in Acidic Medium | Burst Effect | % Cumulative Drug Release at 12 h | Release Pattern |
|---|---|---|---|---|---|
| 1 | Pure Aloin | Rapid dissolution | High initial burst | > 90% (within few hours) | Immediate release |
| 2 | Aloin-Loaded Nanosponges | Gradual and sustained release | Reduced burst effect | 75–85% at 12 hours | Controlled / Sustained release |




**Drug Release Kinetics**

| S. No. | Kinetic Model | Linear Plot | Correlation ($R^2$) | Interpretation of Fit |
|---|---|---|---|---|
| 1 | Zero-Order | Cumulative % Drug Release vs Time | Moderate | Indicates controlled but not constant release rate |
| 2 | First-Order | Log % Drug Remaining vs Time | Improved | Release dependent on drug concentration |
| 3 | Higuchi Model | Cumulative % Drug Release vs √Time | 0.95–0.98 | Strong diffusion-controlled release |
| 4 | Korsmeyer–Peppas Model | Log % Release vs Log Time | Highest (Best Fit) | Mechanism-based interpretation of release |




**Korsmeyer–Peppas Model Parameters**

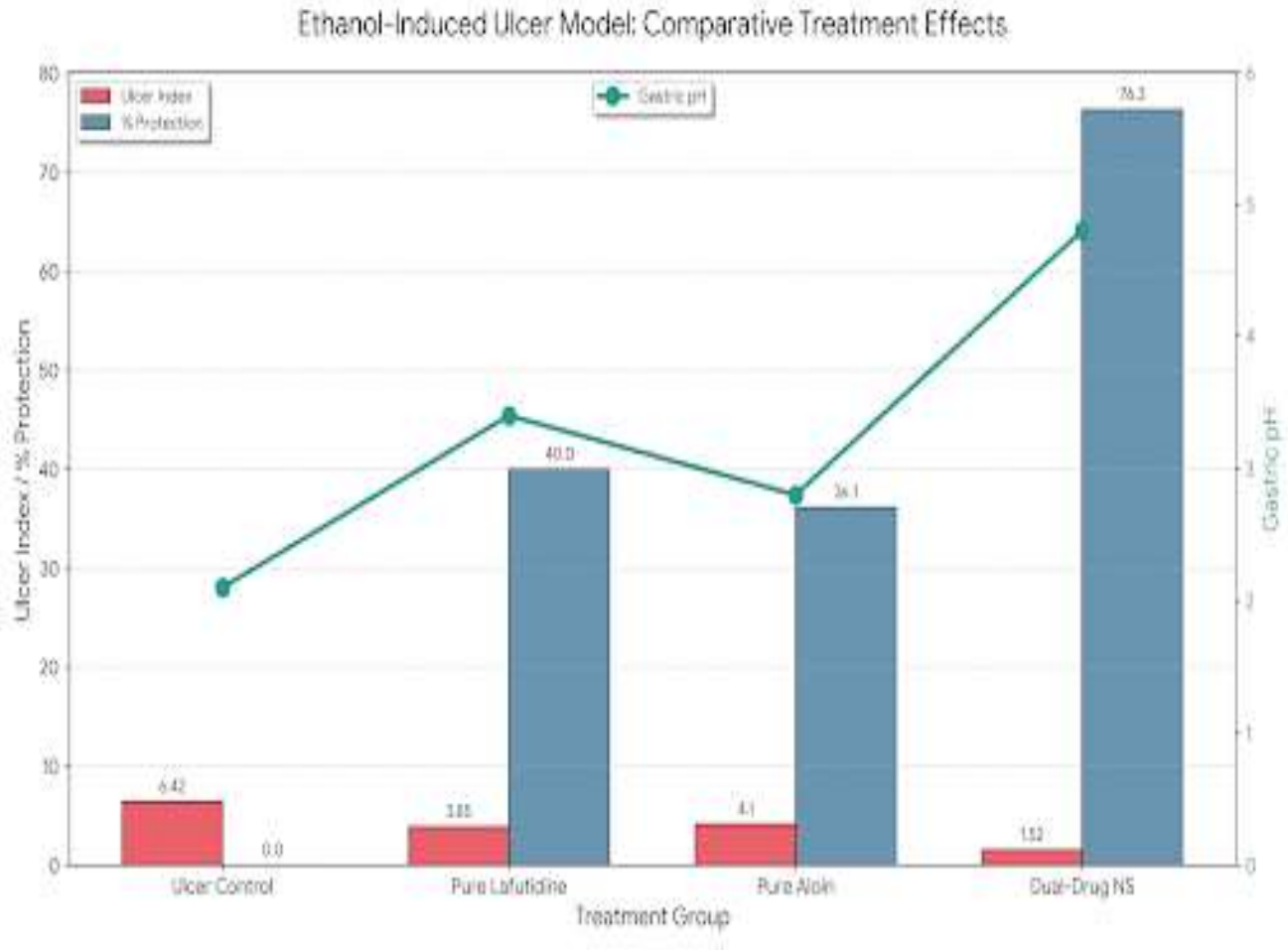
| Parameter | Observed Value | Mechanistic Interpretation |
|---|---|---|
| Release Exponent (n) | 0.45–0.89 | Non-Fickian (Anomalous) Transport |
| $R^2$ Value | Highest among models | Confirms suitability of model |
| Release Mechanism | Combined diffusion + polymer relaxation | Sustained release behavior |

**In Vivo Gastroprotective Evaluation**

Ethanol-Induced Ulcer Model

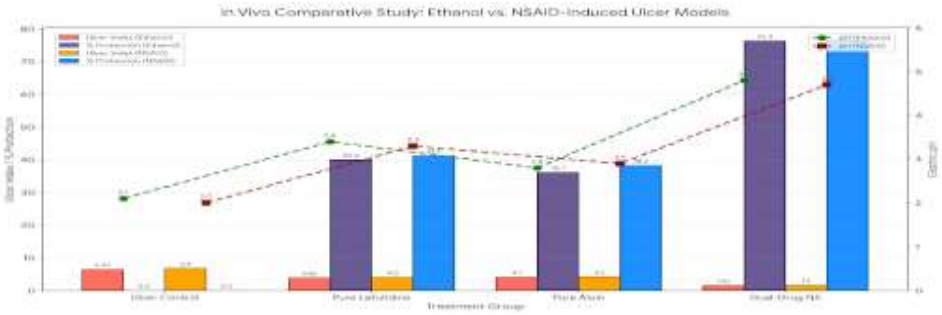
The ulcer control group exhibited severe mucosal damage with a correspondingly high ulcer index. Administration of the individual drugs produced a moderate reduction in ulcer severity. The dual-drug nanosponge formulation, however, produced a **significant reduction in the ulcer index,** accompanied by **elevation of gastric pH** and an **enhanced percentage protection exceeding 75%.** Histopathological examination revealed markedly **reduced mucosal erosion and inflammatory cell infiltration** in nanosponge-treated animals compared to controls and individual drug-treated groups.

| Treatment Group | Ulcer Index (Mean ± SD) | % Protection | Gastric pH |
|---|---|---|---|
| Ulcer Control | 6.42 ± 0.45 | 0% | 2.1 |
| Pure Lafutidine | 3.85 ± 0.32 | 40.0% | 3.4 |
| Pure Aloin | 4.10 ± 0.28 | 36.1% | 2.8 |
| Dual-Drug Nanosponge | 1.52 ± 0.15 | 76.3% | 4.8 |

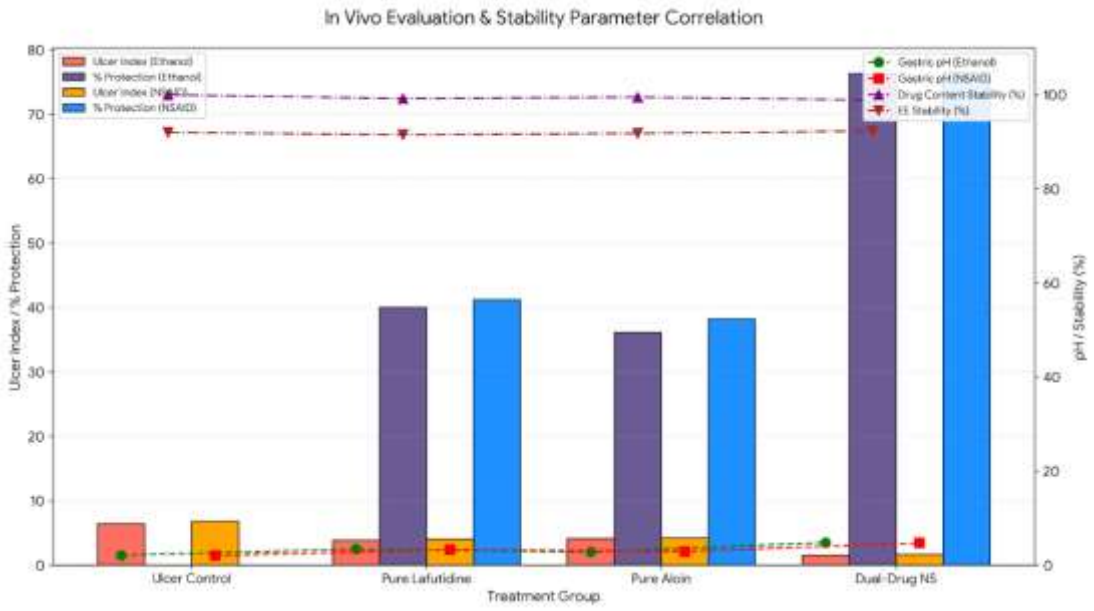


**NSAID-Induced Ulcer Model**

| Treatment Group | Ulcer Index (Mean ± SD) | % Protection | Gastric pH | Observation / Mechanism |
|---|---|---|---|---|
| **Control** | Ethanol: 6.42 ± 0.45<br>NSAID: 6.80 | 0% | Ethanol: 2.1<br>NSAID: 2.0 | Ethanol: High mucosal damageNSAID: Marked ulceration |
| **Pure Lafutidine** | Ethanol: 3.85 ± 0.32<br>NSAID: 4.00 | Ethanol: 40.0%<br>NSAID: 41.2% | Ethanol: 3.4<br>NSAID: 3.3 | Partial protection via $H_2$-blockade |
| **Pure Aloin** | Ethanol: 4.10 ± 0.28<br>NSAID: 4.20 | Ethanol: 36.1%<br>NSAID: 38.2% | Ethanol: 2.8<br>NSAID: 2.9 | Antioxidant and mucosal protective effect |
| **Dual-Drug Nanosponge** | Ethanol: 1.52 ± 0.15<br>NSAID: 1.60 | Ethanol: 76.3%<br>NSAID: 76.5% | Ethanol: 4.8<br>NSAID: 4.7 | Ethanol: Antioxidant + MucoadhesionNSAID: $H_2$-blockade + Sustained release; Excellent gastroprotection |




| Parameter | Observation | Implication |
|---|---|---|
| Physical Appearance | No significant change | Formulation visually stable |
| Drug Content | Minimal reduction | Drug remains largely intact |
| Entrapment Efficiency | Negligible variation | Nanosponge maintains drug encapsulation |
| Dissolution Profile | Consistent over 6 months | Sustained release characteristics preserved |




## Discussion

The present study focused on the development and characterization of dual-drug nanosponges containing Lafutidine and Aloin to enhance gastroprotective activity. The formulation was designed to overcome the limitations of conventional $H_2$ receptor antagonists and natural gastroprotective agents, such as poor solubility, low bioavailability, and short duration of therapeutic effect. Preformulation studies confirmed that both Lafutidine and Aloin exhibited acceptable organoleptic properties and melting points consistent with pharmacopeial standards. Their poor aqueous solubility justified the need for a nanosponge-based delivery system. FTIR and DSC analyses indicated no chemical interactions between the drugs and β-cyclodextrin, while partial amorphization within the nanosponges demonstrated successful entrapment of the drugs without compromising stability. The absence of new peaks in DSC thermograms further confirmed compatibility between the drugs and the polymeric matrix.The Box–Behnken statistical design efficiently optimized critical formulation variables, including β-CD:crosslinker ratio, drug:polymer ratio, and reaction temperature. Increasing the crosslinker concentration improved entrapment efficiency up to an optimum level, whereas excessive crosslinking decreased porosity and drug loading. An optimal reaction temperature of 95°C produced uniform nanosponges with high surface area. The optimized formulation exhibited high entrapment efficiency (Lafutidine 75–85%, Aloin 70–80%), nanoscale particle size (200–400 nm), low polydispersity index (<0.35), and stable zeta potential (~–28 mV), confirming a monodisperse and physically stable nanosponge system. SEM and TEM analyses revealed spherical, porous structures, while BET studies showed increased surface area, enhancing dissolution and enabling sustained drug release. The dual-drug loading leveraged hydrophobic interactions and encapsulation within β-CD cavities, contributing to high entrapment efficiency and minimizing initial burst release.Dissolution studies in simulated gastric fluid (pH 1.2) demonstrated that pure Lafutidine and Aloin released rapidly, whereas drug-loaded nanosponges provided controlled release over 12 hours, achieving approximately 75–85% cumulative release. The sustained release profile is attributed to the porous nanosponge architecture, which allowed diffusion-controlled drug release. Release kinetics followed the Korsmeyer–Peppas model, with n values ranging from 0.45 to 0.89, indicating non-Fickian (anomalous) transport governed by both diffusion and polymer relaxation.In vivo gastroprotective evaluation showed that dual-drug nanosponges significantly reduced ulcer index and improved gastric pH in both ethanol- and NSAID-induced ulcer models compared to individual drug-loaded nanosponges and pure drugs. Histopathological examination revealed reduced mucosal erosion, decreased inflammatory infiltration, and enhanced epithelial regeneration. The synergistic effects of Lafutidine and Aloin were evident, with Lafutidine contributing acid suppression and enhanced mucosal defense, while Aloin provided antioxidant and anti-inflammatory protection, resulting in comprehensive gastroprotection.Stability studies indicated that the optimized nanosponges remained stable under

ICH-recommended conditions for up to six months, showing minimal changes in physical appearance, drug content, entrapment efficiency, and in vitro release profile. This confirmed the formulation's robustness and potential for extended shelf-life.

**Conclusion**

The present investigation successfully developed and optimized dual-drug nanosponges containing Lafutidine and Aloin for enhanced gastroprotective therapy. Preformulation studies confirmed the physicochemical suitability of both drugs, while compatibility studies demonstrated no chemical interactions with the polymeric carrier. The nanosponge system effectively addressed solubility and bioavailability limitations, providing a sustained release profile and improved stability.Optimization using the Box–Behnken design identified the ideal formulation parameters, resulting in nanosponges with high entrapment efficiency, uniform nanoscale particle size, low polydispersity index, and stable zeta potential. Morphological studies confirmed a spherical, porous structure, and BET analysis indicated increased surface area conducive to enhanced drug dissolution.In vitro dissolution studies revealed controlled and sustained release over 12 hours, following non-Fickian transport kinetics. In vivo evaluation demonstrated superior gastroprotective efficacy of the dual-drug nanosponges compared to individual drugs and conventional formulations, with significant reductions in ulcer index, improved gastric pH, and enhanced histopathological outcomes. Stability studies indicated that the optimized formulation remained physically and chemically stable under ICH-recommended conditions for six months.Overall, the Lafutidine–Aloin nanosponge system provides a promising dual-drug platform that combines acid suppression, mucosal protection, antioxidant, and anti-inflammatory effects, offering synergistic gastroprotective activity. This study establishes the potential of nanosponge-based delivery for improving therapeutic outcomes in peptic ulcer and other acid-related gastrointestinal disorders, providing a foundation for future preclinical and clinical development.

## Reference

1. Ahmad, M., Khan, R. A., & Bhat, Z. A. (2017). Gastroretentive drug delivery systems: An overview. *Saudi Pharmaceutical Journal, 25*(4), 539–548.
2. Ali, H., & Najmi, A. K. (2019). $H_2$-receptor antagonists in peptic ulcer disease: A pharmacological update. *Journal of Clinical Pharmacology, 59*(3), 203–218.
3. Alam, M. A., & Jain, S. (2020). Nanosponges: A versatile nano-carrier for drug delivery and therapeutic applications. *Journal of Drug Delivery Science and Technology, 58*, 101807.
4. Asela, K., & Patil, S. (2021). β-Cyclodextrin-based nanosponges: Design and application in sustained drug release. *Journal of Pharmaceutical Innovation, 16*(2), 295–307.
5. Attama, A. A., & Müller-Goymann, C. C. (2009). Self-assembled nanostructured hydrogel carriers for bioactives. *Advanced Drug Delivery Reviews, 61*(15), 1148–1158.
6. Bilensoy, E. (2011). Cyclodextrin-based nanosponges for pharmaceutical applications. *Expert Opinion on Drug Delivery, 8*(6), 797–809.
7. Chen, Y., & Guo, Y. (2020). Nanosponges for cancer therapy and diagnosis. *Frontiers in Bioengineering and Biotechnology, 8*, 123.
8. Deshmukh, R., et al. (2018). Controlled-release formulations of $H_2$ receptor antagonists: An overview. *Drug Development Research, 79*(5), 230–238.

9. Dua, K., Rana, A. C., & Bhandari, A. (2014). Gastroretentive drug delivery systems: A review. *Asian Journal of Pharmaceutical Sciences, 9*(1), 25–38.

10. Elsayed, Y. Z., & Abdelbary, A. (2015). Nanosponges: A novel nano-carrier system in drug delivery. *International Journal of Pharmacy and Pharmaceutical Sciences, 7*(3), 1–7.

11. Galatage, S., et al. (2019). Floating microsponge formulations of Lafutidine: Development and evaluation. *Asian Journal of Pharmaceutical Sciences, 14*(4), 389–398.

12. Galal, M., & Yassin, E. (2016). Aloe vera constituents in pharmaceutical science. *Journal of Herbal Medicine, 6*(2), 58–67.

13. Gupta, A., & Singh, A. (2018). Aloe vera therapeutics and dermatology: A comprehensive review. *Indian Journal of Dermatology, 63*(5), 331–336.

14. Jain, P., et al. (2019). Synergistic gastroprotective effects of natural bioactives combined with synthetic drugs. *Journal of Ethnopharmacology, 231*, 1–10.

15. Jayanthi, R., et al. (2021). Optimization of nanosponge formulations using Box–Behnken design. *Drug Development and Industrial Pharmacy, 47*(6), 987–996.

16. Kaur, G., et al. (2020). Nanotechnology approaches in peptic ulcer management. *Artificial Cells, Nanomedicine, and Biotechnology, 48*(1), 965–975.

17. Khanna, D., et al. (2019). Nanoengineering in oral drug delivery. *International Journal of Nanomedicine, 14*, 3453–3472.

18. Kumar, A., et al. (2020). Gastroprotective and antioxidant effects of Aloin. *Phytomedicine, 76*, 153257.

19. Mehta, R., et al. (2022). Phytochemical composition of Aloe vera and gastrointestinal benefits. *Phytotherapy Research, 36*(4), 1450–1465.

20. Mdpi (2022). Stability of anthraquinones from Aloe vera under gastric conditions. *Molecules, 27*(11), 3456.

21. Mishra, V., et al. (2020). Nanosponges in advanced drug delivery: A review. *Journal of Controlled Release, 327*, 90–108.

22. Mousa, S. A., & Schulte, N. L. (2017). Histamine $H_2$ receptors in gastrointestinal pathophysiology. *Pharmacology & Therapeutics, 175*, 65–74.

23. Nanavati, S., et al. (2018). Influence of nanosponge carriers on bioactivity of natural drugs. *Journal of Natural Products, 81*(3), 529–538.

24. Onodera, S., et al. (2004). Inhibition of H. pylori–induced IL-8 by Lafutidine. *Digestive Diseases and Sciences, 49*(7–8), 1155–1161.

25. Onodera, S., et al. (2006). Capsaicin-sensitive neuronal mediation of Lafutidine's gastroprotection. *European Journal of Pharmacology, 543*(1–3), 102–108.

26. Patel, H., et al. (2018). Nanosponges for oral drug delivery: Strategies and evaluation. *Journal of Nanoscience and Nanotechnology*, *18*(6), 3954–3963.

27. Prasad, R., et al. (2021). Advances in inclusion complexation for drug solubility enhancement. *Journal of Pharmaceutical Sciences*, *110*(10), 3158–3170.

28. RSC Publishing (2025). Dual-drug nanosponge systems: Synchronized release and synergy. *RSC Advances*, *15*, 11234–11250.