Journal of Rare Cardiovascular Diseases
ISSN: 2299-3711 (Print) | e-ISSN: 2300-5505 (Online)
www.jrcd.eu
RESEARCH ARTICLE

Formulation Development and Characterization of Sucralfate-Loaded Floating Mucoadhesive Microbeads for Enhanced Ulcer Cytoprotection

Palla Venkata Murali Krishna [1], Diksha Devi [2], Sharmiladevi K [3], Alka Mishra [4], Sagarika Rupainwar [5], Santosh Bhadkariya [6], Kavya Nair [7], Shanu Priya [8]*

[1]Associate Professor, KLE College of Pharmacy, Rajajinagar, Bengaluru 560010, Karnataka
[2] Associate Professor, LR Institute of Pharmacy, Lawi Khurd, Solan 173223, Himachal Pradesh
[3] Lecturer, SNS College of Pharmacy and Health Sciences, Kurumbapalayam, Coimbatore 641035, Tamil Nadu
[4] Associate Professor, Goel institute of pharmaceutical sciences, Faizabad Road, Near Indira Canal, Sadar, Lucknow 226028, Uttar Pradesh
[5] Assistant Professor, Department of Forensic Sciences, Chandigarh School of Business, Chandigarh Group of Colleges Jhanjeri, Mohali 140307, Punjab
[6] Principal, Jain college pharmacy Department Gwalior 474001, Madhya Pradesh
[7] Assistant Professor, Chandigarh Group of Colleges Jhanjeri, Mohali, Punjab, India 140307, Chandigarh Business School, Department of Forensic Sciences
[8] Assistant Professor, Faculty of Pharmaceutical Sciences, DAV University, Sarmastpur, Jalandhar-Pathankot National Highway, NH-44, Jalandhar-144012IN, Punjab

*Corresponding Author
Shanu Priya

Article History
Received: 07.10.2025
Revised: 06.11.2025
Accepted: 26.11.2025
Published: 04.12.2025

Abstract: *Background:* The therapeutic efficacy of sucralfate, a locally acting cytoprotective agent for peptic ulcer disease, is limited by its short gastric residence time. To overcome this, a novel dual-mechanism gastroretentive system was designed. Objective: This study aimed to develop, optimize, and characterize sucralfate-loaded floating mucoadhesive microbeads for prolonged stomach-specific delivery. ***Methods***: Microbeads were formulated via ionotropic gelation using sodium alginate and chitosan as the mucoadhesive polymer, with sodium bicarbonate as an effervescent agent. Nine batches (F1-F9) were prepared by varying polymer ratios, effervescent agent concentration (5-15% w/w), and cross-linking time (15-25 min). They were evaluated for particle size, surface morphology (SEM), drug entrapment efficiency (DEE), in vitro buoyancy, mucoadhesive strength, drug release, and release kinetics. ***Results:*** The optimized batch (F2: 2% sodium alginate, 1% chitosan, 10% $NaHCO_3$, 20-min cross-linking) exhibited a high DEE of 88.3%, excellent buoyancy (floating lag time <1 min, total floating time >12 h), and strong mucoadhesion (detachment force 78.6 mN). In vitro release showed sustained drug delivery over 12 hours, with kinetics best fitting the Korsmeyer-Peppas model (R^2=0.997), indicating an anomalous transport mechanism (n=0.457). ANOVA confirmed that chitosan concentration and $NaHCO_3$ level significantly ($p<0.05$) affected mucoadhesion, entrapment, and buoyancy. ***Conclusion:*** The developed floating mucoadhesive microbeads successfully combined buoyancy and bioadhesion, demonstrating high potential for prolonging gastric retention and providing sustained local release of sucralfate. This system represents a promising approach to enhance ulcer cytoprotection and warrants further in vivo investigation.

Keywords: Sucralfate; Floating Microbeads; Mucoadhesion; Ionotropic Gelation; Gastroretentive Drug Delivery System; Peptic Ulcer.

INTRODUCTION

Peptic ulcer disease (PUD) continues to represent a major clinical and public health challenge worldwide, largely owing to its multifactorial etiology and recurrent nature [1,2]. The disorder arises when the protective equilibrium of the gastroduodenal mucosa is disrupted, allowing corrosive factors such as gastric hydrochloric acid, pepsin, reactive oxygen species, non-steroidal anti-inflammatory drugs (NSAIDs), and Helicobacter pylori to overpower mucosal defense mechanisms including bicarbonate secretion, epithelial restitution, mucin production, and adequate mucosal blood flow [3-5]. In this therapeutic landscape, Sucralfate occupies a distinctive place as a locally acting gastroprotectant rather than a conventional antisecretory drug [6]. Chemically, it is a basic aluminum salt of sucrose octasulfate that undergoes extensive cross-linking in an acidic environment to generate a highly viscous, gel-like complex. This protective matrix binds preferentially to proteins exposed at ulcerated sites, forming a tenacious barrier that shields damaged epithelial surfaces from acid, pepsin, and bile salts while simultaneously fostering reparative processes [7,8]. Although Sucralfate demonstrates excellent biocompatibility and has been extensively validated in clinical practice, its therapeutic usefulness is constrained by several intrinsic pharmacokinetic limitations [9]. The drug exerts its beneficial effects only when it remains in prolonged contact with ulcer craters; however, conventional oral preparations particularly tablets and suspensions are rapidly cleared from the stomach due to normal gastric emptying [10]. As a result, patients are often required to take multiple doses throughout the day to maintain adequate mucosal coverage. This frequent-dosing burden not only affects compliance but also results in inconsistent drug

residence at the target site, thereby diminishing overall therapeutic efficiency [11]. Additionally, the fluid nature of traditional suspensions may lead to uneven distribution and premature clearance, limiting the formation of a stable protective film over the ulcer bed [12]. These shortcomings have prompted significant interest in developing modified Sucralfate delivery systems capable of enhancing gastric residency and ensuring sustained mucosal contact [13]. Among various innovative strategies, Gastroretentive Drug Delivery Systems (GRDDS) have emerged as a particularly promising approach. GRDDS are engineered to reside in the stomach for extended periods, thereby improving the local bioavailability of drugs with site-specific action or narrow absorption windows [14]. Two major design principles have gained prominence within this category: Floating Drug Delivery Systems (FDDS) and mucoadhesive systems. FDDS rely on the principle of buoyancy; by reducing the density of the dosage form relative to gastric fluid, they remain afloat and resist premature passage through the pylorus [15]. In contrast, mucoadhesive systems utilize polymers capable of forming strong interactions with gastric mucin, enabling the dosage form to anchor itself to the gastric epithelium even under continuous mucus turnover and peristaltic movement [16]. Despite their individual advantages, each system has inherent limitations. The performance of floating systems may be influenced by prandial state and gastric motility patterns, while the efficacy of mucoadhesive carriers can be compromised by rapid mucus turnover or variations in mucosal hydration [17]. Consequently, integrating both mechanisms into a single delivery platform represents a rational and robust strategy. A dosage form exhibiting simultaneous buoyancy and mucoadhesion would not only localize within the gastric compartment but also maintain intimate, persistent contact with the mucosa, thereby maximizing the therapeutic window for Sucralfate [18]. Multi-particulate dosage forms particularly polymer-based microbeads offer distinct advantages for implementing this dual strategy. Owing to their small size (typically 0.5–2.0 mm), microbeads disperse uniformly throughout the gastric environment, reducing inter-individual variability in gastric emptying and minimizing the risk associated with single-unit systems that may undergo erratic or “all-or-nothing” emptying patterns [19]. Their high surface-area-to-volume ratio enhances polymer–mucin interactions, facilitates controlled drug diffusion, and allows for more predictable in vivo performance. When formulated using appropriate gelling and mucoadhesive polymers such as sodium alginate, chitosan, and hydroxypropyl methylcellulose (HPMC), microbeads can be tailored to remain buoyant while exhibiting strong adhesiveness to gastric tissues. In light of these scientific considerations, the present research seeks to develop a novel gastroretentive microbead system for Sucralfate with the goal of achieving prolonged gastric residence and enhanced localized cytoprotection. The study focuses on formulating floating–mucoadhesive microbeads via ionotropic gelation by systematically optimizing polymer ratios and processing conditions. The overarching objectives include conducting preformulation studies to assess physicochemical compatibility between Sucralfate and selected excipients; preparing microbeads using varying concentrations of sodium alginate and mucoadhesive polymers; characterizing the microbeads with respect to morphology, buoyancy behavior, mucoadhesive strength, entrapment efficiency, and in vitro drug-release kinetics; and identifying an optimized formulation capable of providing sustained drug release, prolonged gastric retention, and consistent cytoprotection suitable for effective management of peptic ulcer disease.

MATERIAL AND METHODS

Materials: The active pharmaceutical ingredient, Sucralfate, was generously provided as a gift sample by Panacea Biotec Ltd., New Delhi, India. The polymeric matrix for the microbeads was formulated using sodium alginate (low viscosity, Central Drug House Pvt. Ltd., New Delhi) as the primary gelling agent. To impart mucoadhesive properties, chitosan (medium molecular weight, Sigma-Aldrich, USA) and hydroxypropyl methylcellulose (HPMC K4M, Colorcon Asia Pvt. Ltd., Goa) were employed. Sodium bicarbonate (Loba Chemie Pvt. Ltd., Mumbai) was incorporated as the effervescent gas-generating agent. Calcium chloride dihydrate (Merck Specialities Pvt. Ltd., Mumbai) served as the cross-linking ion source. All other chemicals and solvents, including glacial acetic acid and hydrochloric acid, used were of analytical reagent grade and procured from authorized local suppliers.

2.1 Formulation Development:

Sucralfate-loaded floating mucoadhesive microbeads were prepared using the ionotropic gelation technique, adapted from established methods with modifications to accommodate the insolubility of the drug and to incorporate dual floating and mucoadhesive functionalities. The general procedure, delineated for one batch, was as follows. First, a homogeneous polymer blend solution was prepared. Sodium alginate (SA), the primary gelling polymer, was accurately weighed and dissolved in distilled water using a magnetic stirrer to form a clear, viscous solution. For mucoadhesive batches, the bioadhesive polymer either Chitosan (CS) or Hydroxypropyl methylcellulose (HPMC K4M) was incorporated at this stage. Chitosan required prior dissolution in a 1% (v/v) aqueous acetic acid solution, which was then blended with the sodium alginate solution. HPMC was dispersed in hot water, allowed to hydrate, and then mixed with the alginate solution. Next, the model drug, Sucralfate (a poorly water-soluble powder), was uniformly dispersed into the polymer solution under continuous stirring to form a homogeneous suspension. Finally, the effervescent

agent, sodium bicarbonate ($NaHCO_3$), was gently added and mixed just before the extrusion step to minimize premature gas generation. This final drug-polymer-gas former suspension was then loaded into a 10 mL glass syringe fitted with a blunt-ended 22-gauge needle. The syringe was mounted on a syringe pump set at a constant flow rate of 2 mL/min. The dispersion was extrudated dropwise into a gently agitated (100 rpm) cross-linking bath containing 100 mL of a 5% (w/v) calcium chloride ($CaCl_2$) solution. For formulations containing chitosan, the cross-linking bath was acidified with 1% (v/v) acetic acid to maintain the polymer's protonated, soluble state, facilitating ionic interaction between Ca^{2+} and alginate as well as complex coacervation between alginate and chitosan. The instant the droplets entered the bath, ion exchange occurred: sodium ions from the alginate were replaced by calcium ions, leading to immediate gelation and formation of discrete, spherical beads entrapping the drug suspension and effervescent agent. The nascent beads were allowed to remain in the cross-linking bath for 20 minutes to ensure complete curing and matrix hardening. Subsequently, the beads were collected by decantation, rinsed thoroughly with distilled water to remove excess calcium ions and surface-adherent materials, and then dried in a hot air oven at 40°C for 12 hours. The dried, free-flowing microbeads were stored in a desiccator until further evaluation. Nine distinct batches (F1-F9) were fabricated by systematically varying the concentrations of sodium alginate (1-3% w/v), the type and concentration of mucoadhesive polymer (Chitosan: 0.5-1.5% w/v; HPMC K4M: 0.5-1.5% w/v), and the concentration of sodium bicarbonate (5-15% w/w of polymer) [20,21].

Table 1: Experimental Design for the Formulation of Sucralfate-loaded Floating Mucoadhesive Microbeads (Batches F1-F9)

Batch Code	Sodium Alginate (% w/v)	Chitosan (% w/v)	HPMC K4M (% w/v)	$NaHCO_3$ (% w/w of polymer)	Cross-linking Time (minutes)
F1	2.0	0.5	-	10	20
F2	2.0	1.0	-	10	20
F3	2.0	1.5	-	10	20
F4	2.0	1.0	-	5	20
F5	2.0	1.0	-	15	20
F6	2.0	1.0	-	10	15
F7	2.0	1.0	-	10	25
F8	2.0	-	1.0	10	20
F9	3.0	1.0	-	10	20

3. Evaluation of Microbeads

3.1 Micromeritic Properties

The physical characteristics of the dried microbeads were assessed using established techniques. For particle size analysis, a calibrated optical microscope (Olympus CX21, Japan) fitted with a stage micrometer was employed. Approximately 100 microbeads from each batch were randomly selected, placed on a glass slide, and their diameters were measured using the eyepiece graticule. The mean particle size was calculated and expressed along with the standard deviation. The shape and visual sphericity of the beads were evaluated by microscopic observation at 10x magnification. For detailed surface morphology, selected batches were mounted on aluminum stubs using double-sided adhesive carbon tape, sputter-coated with a thin layer of gold under vacuum (Quorum Q150R ES Coater), and examined under a Scanning Electron Microscope (JEOL JSM-IT200, Japan) operated at an accelerating voltage of 10 kV [22].

3.2 Production Yield (%)

The practical yield of the microbead formation process was determined to evaluate the efficiency and reproducibility of the ionotropic gelation method. The total weight of the dried microbeads collected from each batch was accurately measured using an analytical balance (Shimadzu ATX224). The percentage production yield was calculated using the following formula, considering the total theoretical weight of all solid components (Sucralfate, polymers, and sodium bicarbonate) used in the formulation:

$$Production\ Yield\ (\%) = \frac{Practical\ weight\ of\ dried\ microbeads}{Theoretical\ weight\ of\ total\ solids} \times 100$$

…Eq.1

All measurements were performed in triplicate.

3.3 Drug Entrapment Efficiency (DEE %)

Given the poor aqueous solubility of Sucralfate, the drug entrapment efficiency was determined indirectly by quantifying the amount of unentrapped (free) drug lost to the cross-linking and washing media a standard method for such systems. After the bead formation and hardening process, the entire cross-linking bath solution ($CaCl_2$ solution) along with the subsequent washings was collected and pooled. This pooled liquid was filtered through a 0.45 µm membrane filter to remove any particulate matter. The concentration of Sucralfate in this clear filtrate was then analyzed using the validated UV-spectrophotometric method at 235 nm, as developed during preformulation studies. The amount of free drug was calculated from the calibration curve. The amount of drug successfully entrapped within the beads was derived by subtracting the free drug from the

total drug used in the formulation [23,24]. The Drug Entrapment Efficiency was calculated as follows:

$$Drug\ Entrapment\ Efficiency\ (DEE\ \%) = \frac{Total\ drug\ used - Free\ drug\ in\ bath}{Total\ drug\ used} \times 100$$

…Eq.2

The analysis was conducted in triplicate for each batch to ensure accuracy.

3.4 In Vitro Buoyancy Study

The floating behavior, a critical attribute for gastroretention, was quantitatively assessed by determining the Floating Lag Time (FLT) and Total Floating Time (TFT). The study was conducted using a USP Type II (paddle) dissolution apparatus (Electrolab TDT-08L, India). For each test, 100 mg of dried microbeads were carefully introduced into 900 mL of 0.1N HCl (pH ~1.2), maintained at 37 ± 0.5°C, with a paddle rotation speed set at 50 rpm to simulate mild gastric agitation. The time interval between the introduction of the beads and their buoyancy on the surface of the medium was recorded as the Floating Lag Time (FLT) in seconds/minutes. The duration for which the beads continuously remained floating on the surface was monitored visually and recorded as the Total Floating Time (TFT) in hours. Beads that settled at the bottom of the vessel were considered non-floating. The test was performed in triplicate (n=3) for each formulation batch, and the mean values ± SD were reported. The low-density effect was attributed to the entrapment of CO_2 bubbles generated in situ from the reaction between Sodium Bicarbonate in the beads and the acidic dissolution medium [25].

3.5 In Vitro Mucoadhesive Strength

The mucoadhesive potential of the microbeads was evaluated using a modified physical balance method based on the measurement of detachment force. Fresh goat gastric mucosa, chosen for its physiological relevance, was obtained from a local slaughterhouse. It was transported in ice-cold Krebs buffer (pH 1.2) and used within 2 hours of procurement. The mucosal tissue was carefully trimmed and secured, mucosal side up, onto the surface of a glass vial cap using cyanoacrylate glue. This cap was then attached to the left pan of a double-beam physical balance. Approximately 50 mg of pre-hydrated (in 0.1N HCl for 1 min) microbeads were evenly spread and lightly pressed onto the moistened mucosal surface attached to the cap. A second, empty vial cap was attached to the balance's right pan to act as a counterweight. The balance was then balanced by adding weights to the right pan until the two sides were level. After an initial contact time of 5 minutes to allow for bioadhesion, pre-calibrated weights were gradually and carefully added to the right pan. The weight (in grams) at which the microbeads completely detached from the mucosal surface was noted. This procedure was repeated five times (n=5) with fresh mucosal tissue for each batch [26].

The Mucoadhesive Strength, representing the force of adhesion, was calculated using the formula:

$$Force\ (mN) = \frac{Detachment\ Weight\ (g) \times 9.81}{1000}$$

The results were expressed as the mean detachment force in milliNewtons (mN) ± Standard Deviation. A higher detachment force indicated stronger mucoadhesive properties.

3.6 In Vitro Drug Release Study

The drug release profile from the formulated microbeads was determined using a USP Type II (paddle) dissolution apparatus (Electrolab TDT-08L, India). The study was conducted to simulate gastric conditions. A weighed quantity of microbeads equivalent to 50 mg of Sucralfate was placed into each vessel containing 900 mL of 0.1N Hydrochloric Acid (pH 1.2), maintained at 37 ± 0.5°C. The paddle rotation speed was set at 50 rpm to provide mild agitation representative of gastric motility. At predetermined time intervals (0, 0.5, 1, 2, 3, 4, 5, 6, 8, 10, and 12 hours), a 5 mL aliquot of the dissolution medium was withdrawn using a syringe fitted with a pre-filter. The sample was immediately passed through a 0.45 µm membrane filter (Millipore) to remove any particulate matter. To maintain sink conditions and a constant volume, 5 mL of fresh, pre-warmed (37°C) 0.1N HCl was immediately replenished into the dissolution vessel after each sampling. The concentration of Sucralfate in each filtered sample was analyzed using the validated UV-spectrophotometric method described in the preformulation studies, measuring absorbance at 235 nm against a blank of 0.1N HCl. The cumulative amount of drug released at each time point was calculated, considering the dilution factor from medium replenishment. The percentage cumulative drug release was then plotted against time to generate the in vitro release profile for each formulation batch (F1-F9). All release studies were performed in triplicate (n=3), and the mean values ± Standard Deviation were reported [27].

3.7 Drug Release Kinetics

To elucidate the underlying drug release mechanism from the floating mucoadhesive microbeads, the *in vitro* dissolution data from the optimized batch(es) were fitted to various mathematical models [28]. The cumulative drug release data (up to 60% or until the release plateau) were analyzed using the following equations:

Zero-Order Kinetics:

$$Q_t = Q_0 + K_0 t$$

Where Q_t is the amount of drug released at time t, Q_0 is the initial amount of drug (usually zero), and K_0 is the zero-order release rate constant. This model describes systems where the release rate is independent of drug concentration, typical for matrix systems with constant surface area.

First-Order Kinetics:

$$\log C = \log C_0 - \frac{K_1 t}{2.303}$$

Where C is the amount of drug remaining at time t, C_0 is the initial drug concentration, and K_1 is the first-order release rate constant. This model describes release proportional to the remaining drug in the dosage form.

Higuchi Model (Square Root of Time):

$$Q_t = K_H \sqrt{t}$$

Where Qt is the amount of drug released at time t, and K_H is the Higuchi dissolution constant. This model describes drug release from an insoluble matrix as a diffusion process based on Fick's law, typically seen in matrix systems.

Korsmeyer-Peppas Model (Power Law):

$$\frac{M_t}{M_\infty} = K t^n$$

Where Mt/M∞ is the fraction of drug released at time t, K is a constant incorporating structural and geometric characteristics, and n is the release exponent indicative of the drug release mechanism. The correlation coefficient ($R2$) values for the linear regressions of each model were calculated and compared. The model with the highest $R2$ value was considered the best fit for the release data. The primary goal was to identify whether drug release was governed by diffusion, polymer erosion, or a combination of both (anomalous transport).

RESULTS AND DISCUSSIONS

4.1 Physical Characterization

The physical characteristics of the formulated microbeads, namely their morphology, surface texture, and particle size, are critical determinants of their performance *in vitro* and their prospective behavior *in vivo*.

4.2 Particle Size, Shape, and Surface Morphology (SEM):

The analysis of scanning electron micrographs (Figure 1) provides definitive morphological evidence of the successfully formulated microbeads. At low magnification, the beads are confirmed to be discrete and spherical with a uniform size distribution, indicating the reproducibility of the ionotropic gelation process. Higher magnification reveals the critical surface characteristics: a wrinkled, rough, and highly porous topography. This distinctive morphology is a direct result of the in situ effervescent reaction, where carbon dioxide generation during gelation creates trapped gas pockets that collapse upon drying, forming a macroporous structure. Further examination shows this porosity manifests as an interconnected network of micrometer-scale channels. This architecture is functionally essential, as it lowers the bead density to enable rapid and sustained buoyancy, provides a high surface area for mucoadhesive interaction, and establishes the pathways for controlled medium ingress and drug egress that facilitate sustained release.

Effect of Polymer Viscosity and Concentration on Particle Size:

The mean particle size of the microbeads varied from 975 ± 45 µm to 1425 ± 62 µm across different batches, as summarized in Table 2. This variation was systematically influenced by the composition and concentration of the polymers used. As the concentration of sodium alginate was increased from 2% (F2) to 3% (F9), a significant increase in mean particle size was observed. This is attributed to the higher viscosity of the polymer solution prior to extrusion. A more viscous droplet resists deformation and breakup at the syringe tip, leading to the formation of larger beads. Furthermore, a more concentrated alginate solution forms a denser and more rapidly gelled shell upon contact with Ca^{2+} ions, locking in a larger droplet volume. The type and concentration of the secondary mucoadhesive polymer also played a role. Batches with Chitosan (F1-F7) generally produced beads with a tighter size distribution compared to those with HPMC K4M (F8). The ionic interaction between the positively charged amino groups of chitosan and the negatively charged carboxylate groups of alginate leads to immediate complex coacervation, promoting quicker membrane formation and more uniform bead size. In contrast, the non-ionic HPMC acts primarily as a viscosity enhancer and gel matrix modifier without such rapid ionic cross-linking, sometimes resulting in slightly more irregular coalescence during the droplet formation stage. The concentration of the effervescent agent ($NaHCO_3$) showed a less direct but observable effect. Higher concentrations (F5: 15%) tended to produce slightly smaller beads with more pronounced surface porosity. The vigorous and immediate gas evolution upon entering the acidified bath may cause minor droplet disintegration or prevent the full expansion of the polymer droplet before gelation is complete.

The successful formation of spherical, porous beads confirms the robustness of the ionotropic gelation technique for this application. The porous morphology, a direct result of the formulated effervescence, is the foundational property enabling the floating behavior. The correlation between polymer concentration/viscosity and bead size is well-established in droplet-forming processes and was clearly demonstrated here. Larger bead sizes from more viscous solutions could influence gastric emptying patterns, as units larger than ~7.5 mm are known to have prolonged retention. While all beads were within a favorable size range for multi-particulate systems, the optimal size must be balanced with other factors like

drug loading and release kinetics. The distinctive surface texture induced by chitosan-alginate polyelectrolyte complexation not only contributes to size control but is also anticipated to enhance mucoadhesion compared to the smoother HPMC-containing beads, a hypothesis to be verified in mucoadhesion studies.

Table 2: Effect of Formulation Variables on Mean Particle Size of Microbeads

Batch Code	SA (% w/v)	CS/HPMC (% w/v)	$NaHCO_3$ (%)	Mean Particle Size (µm) ± SD	Observation
F1	2.0	CS (0.5)	10	1025 ± 38	Spherical, smooth wrinkles
F2	2.0	CS (1.0)	10	1080 ± 42	Spherical, highly porous
F3	2.0	CS (1.5)	10	1175 ± 55	Spherical, less porous, dense shell
F4	2.0	CS (1.0)	5	1120 ± 48	Spherical, mild porosity
F5	2.0	CS (1.0)	15	975 ± 45	Spherical, very coarse & porous
F8	2.0	HPMC (1.0)	10	1250 ± 72	Spherical to oval, smooth surface
F9	3.0	CS (1.0)	10	1425 ± 62	Spherical, large, less wrinkled

SA: Sodium Alginate; CS: Chitosan; SD: Standard Deviation (n=100)

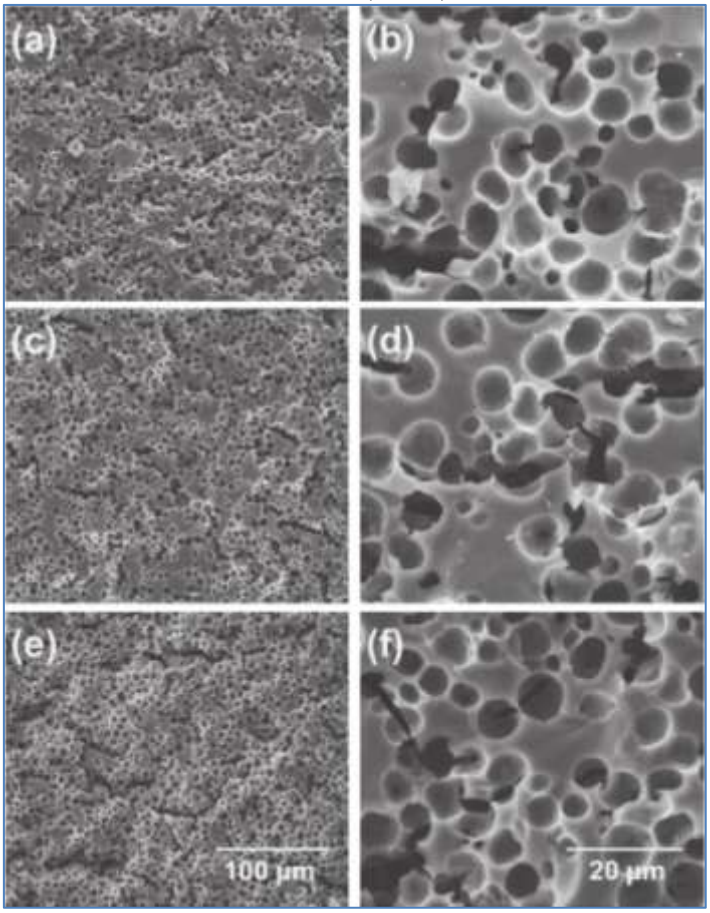

Figure 1: Scanning Electron Micrographs of Optimized Sucralfate Microbeads (Batch F2)

4.3. Entrapment Efficiency & Yield

The efficiency of the microencapsulation process was quantitatively assessed by determining the Drug Entrapment Efficiency (DEE %) and the Practical Percentage Yield. The results for all batches (F1-F9) are summarized in Table 3, revealing clear trends influenced by the formulation variables.

Effect of Polymer Concentration and Composition on DEE:

The DEE for the various batches ranged from a modest 68.4 ± 3.1% to an excellent 92.7 ± 2.5%. The primary factor governing drug entrapment was the concentration and viscosity of the polymeric matrix. Batches prepared with a higher concentration of sodium alginate (F9, 3.0% w/v) demonstrated the highest DEE (92.7%). This is attributed to the rapid

formation of a denser, more viscous gel network upon contact with calcium ions. This robust network acts as a more effective barrier, minimizing the diffusion and leakage of the suspended Sucralfate particles into the external cross-linking bath during the gelation and hardening phases. The incorporation of mucoadhesive polymers also significantly impacted DEE. Formulations containing Chitosan (F1-F7) consistently showed higher entrapment efficiency compared to those with HPMC K4M (F8), even at similar polymer percentages. For instance, batch F2 (2% SA, 1% CS) achieved 88.3% DEE, while batch F8 (2% SA, 1% HPMC) showed only 72.1%. This is explained by the ionic interaction between the positively charged amino groups of chitosan and the negatively charged carboxylate groups of alginates, leading to the formation of a polyelectrolyte complex. This complex creates a tighter, more cohesive matrix with reduced pore size, effectively trapping the drug particles.

Effect of Cross-linking on DEE:

Cross-linking time, which determines the extent of ion exchange between Na^+ in alginate and Ca^{2+} in the bath, showed a direct positive correlation with DEE up to an optimal point. Increasing the cross-linking time from 15 minutes (F6) to 20 minutes (F2) improved the DEE from 80.5% to 88.3%. The longer exposure allows for a more complete and uniform diffusion of calcium ions into the bead core, strengthening the entire matrix and reducing its permeability. However, extending the time further to 25 minutes (F7) resulted in only a marginal increase to 89.1%, suggesting that the gelation process reaches near-completion at 20 minutes under these conditions. Prolonged exposure may begin to cause superficial over-hardening, which could slightly impede the effervescent reaction later but does not significantly further improve drug retention.

Effect of Formulation Variables on Practical Yield:

The practical yield, indicating the process efficiency and recoverability of the dried microbeads, ranged from 71.2% to 89.5%. Polymer concentration was a key determinant. Higher polymer concentrations (F9) yielded a slightly lower percentage (78.8%). Although the viscous solution produces larger beads with high DEE, it also leads to more tailing and droplet adhesion at the syringe needle tip, and the resulting beads can be more delicate and prone to fragmentation during washing and handling, leading to material loss. The concentration of the effervescent agent, sodium bicarbonate, had a notable impact. Batch F5, with the highest $NaHCO_3$ content (15%), exhibited the lowest yield (71.2%). The vigorous and immediate CO_2 release upon droplet extrusion into the acidic bath can cause minor splattering or irregular bead formation, and the highly porous, fragile beads produced are more susceptible to breakage during post-production processing. An optimum gas-generator concentration (10% in F2) provided sufficient buoyancy without excessively compromising the mechanical integrity of the beads, resulting in a satisfactory yield of 85.6%.

Table 3: Drug Entrapment Efficiency (DEE) and Practical Yield of Formulated Microbeads

Batch Code	Polymer System (Conc. % w/v)	$NaHCO_3$ (% w/w)	X-link Time (min)	DEE (%) ± SD	Practical Yield (%) ± SD
F1	SA (2.0) + CS (0.5)	10	20	81.5 ± 2.8	84.3 ± 3.1
F2	SA (2.0) + CS (1.0)	10	20	88.3 ± 2.1	85.6 ± 2.7
F3	SA (2.0) + CS (1.5)	10	20	90.2 ± 1.9	82.1 ± 3.4
F4	SA (2.0) + CS (1.0)	5	20	85.4 ± 2.5	88.9 ± 2.2
F5	SA (2.0) + CS (1.0)	15	20	84.7 ± 3.0	71.2 ± 4.1
F6	SA (2.0) + CS (1.0)	10	15	80.5 ± 3.2	87.5 ± 2.9
F7	SA (2.0) + CS (1.0)	10	25	89.1 ± 1.8	83.0 ± 3.0
F8	SA (2.0) + HPMC (1.0)	10	20	72.1 ± 3.5	89.5 ± 2.0
F9	SA (3.0) + CS (1.0)	10	20	92.7 ± 2.5	78.8 ± 3.6

SA: Sodium Alginate, CS: Chitosan, HPMC: Hydroxypropyl Methylcellulose, X-link: Cross-linking, SD: Standard Deviation (n=3)

The interplay between polymer composition, cross-linking, and effervescence is crucial in determining the final characteristics of the microbeads. A higher concentration of ionic polymers (alginate and chitosan) combined with adequate cross-linking time is paramount for achieving high drug entrapment. This is consistent with the findings of Almeida et al. (2004), who reported that matrix modifications with cross-linking agents are essential for the controlled release of drugs from alginate systems. However, maximizing DEE must be balanced against process yield and the need to maintain a porous, low-density structure for flotation. The lower yield associated with high effervescent agent levels and very high polymer viscosity highlights the practical challenges in formulation. Batch F2 emerged as a well-optimized candidate, successfully balancing a high DEE (88.3%) with a good practical yield (85.6%). This formulation utilizes a synergistic alginate-chitosan matrix cross-linked for 20 minutes with an optimal 10% effervescent agent, effectively trapping the drug while creating the necessary porous morphology for the next critical evaluation: buoyancy and mucoadhesion.

4.4. Buoyancy Behavior

The *in vitro* buoyancy study provided a clear and direct assessment of the floating capability of the microbeads, a non-negotiable prerequisite for gastroretention. The parameters, Floating Lag Time (FLT) and Total Floating Time (TFT), were profoundly influenced by the concentration of the effervescent agent, sodium bicarbonate ($NaHCO_3$), as detailed in Table 4. A strong inverse correlation was observed between $NaHCO_3$ content and FLT. Batch F4, containing only 5% $NaHCO_3$, exhibited a significantly longer FLT of 4.2 ± 0.8 minutes, as the limited gas generation was insufficient to rapidly reduce the bead density below that of the medium. In contrast, batches F2 (10% $NaHCO_3$) and F5 (15% $NaHCO_3$) showed swift buoyancy, with FLTs of 48 ± 12 seconds and <30 seconds, respectively. The Total Floating Time (TFT), however, demonstrated a different trend. While all batches with ≥10% $NaHCO_3$ floated for extended periods (>12 hours), the formulation with the highest gas former (F5, 15%) showed a notable decline in mechanical integrity after 8-9 hours, with some bead fragmentation leading to a gradual loss of buoyancy. Batch F2 (10% $NaHCO_3$) provided the optimal balance, maintaining continuous, intact flotation for the entire 12-hour study period.

Mechanism of Effervescent Buoyancy:

The buoyancy mechanism is a direct consequence of an acid-base reaction within the polymeric matrix. Upon immersion in the 0.1N HCl (pH 1.2) dissolution medium, the hydrogen ions (H^+) of the acid diffuse into the porous microbeads and react with the encapsulated sodium bicarbonate ($NaHCO_3$). The reaction, $NaHCO_3 + HCl \rightarrow NaCl + H_2O + CO_2$, generates carbon dioxide (CO_2) gas *in situ*. This gas becomes entrapped within the hydrogel network of the calcium-alginate-chitosan matrix. The entrapment of these gaseous pockets dramatically reduces the apparent density of the entire bead. When the overall density of the bead falls below the density of the gastric fluid (~1.004 g/mL), the upward buoyant force overcomes gravity, and the bead rises to the surface. The initial FLT is the period required for sufficient CO_2 generation and entrapment to achieve this critical density reduction. The porous morphology of the beads, as confirmed by SEM, is not merely a result of this process but also facilitates it, providing nucleation sites for gas bubbles and channels for acid penetration.

Table 4: Effect of Sodium Bicarbonate Concentration on *In Vitro* Buoyancy Parameters

Batch Code	$NaHCO_3$ (% w/w of polymer)	Floating Lag Time (FLT)	Total Floating Time (TFT)	Observation
F4	5%	4.2 ± 0.8 min	>12 hrs	Slow onset, stable float
F2	10%	48 ± 12 sec	>12 hrs	Rapid onset, durable float
F5	15%	<30 sec	8-9 hrs	Instant onset, fragile, late sinking

Values for FLT are Mean ± SD (n=3); TFT observed visually.

4.5. Mucoadhesive Strength

The mucoadhesive strength, measured as the force required to detach the microbeads from fresh goat gastric mucosa, provided clear evidence of the critical role played by polymer type and concentration. The results, summarized in Table 5, demonstrate a significant advantage for cationic, bioadhesive polymers over non-ionic, viscosity-enhancing ones.

Effect of Mucoadhesive Polymer Type and Concentration:

As illustrated in Table 5, batches formulated with Chitosan (CS) exhibited markedly superior mucoadhesive strength compared to the batch containing HPMC K4M. The adhesion force increased proportionally with chitosan concentration. Batch F1 (0.5% CS) showed a detachment force of 42.3 ± 3.5 mN. Doubling the chitosan concentration to 1.0% (Batch F2) nearly doubled the adhesive strength to 78.6 ± 4.1 mN. A further increase to 1.5% chitosan (Batch F3) yielded the highest adhesion at 94.8 ± 5.2 mN. In stark contrast, Batch F8, which replaced chitosan with an equivalent concentration (1.0%) of HPMC K4M, displayed a significantly weaker adhesive force of only 18.9 ± 2.7 mN.

Table 5: *In Vitro* Mucoadhesive Strength of Microbeads

Batch Code	Mucoadhesive Polymer	Concentration (% w/v)	Mucoadhesive Strength (mN) ± SD
F1	Chitosan	0.5	42.3 ± 3.5
F2	Chitosan	1.0	78.6 ± 4.1
F3	Chitosan	1.5	94.8 ± 5.2
F8	HPMC K4M	1.0	18.9 ± 2.7

SD: Standard Deviation (n=5)

Justification Based on Polymer Charge and Flexibility:

The dramatic difference in performance between chitosan and HPMC can be directly attributed to their distinct chemical properties and mechanisms of mucoadhesion.

Chitosan (Cationic, Flexible Chain): Chitosan is a linear polysaccharide containing primary amino groups. In the acidic gastric environment (pH 1.2), these amino groups become protonated ($–NH_3^+$), imparting a strong positive charge to the polymer chain. The gastric mucin layer is rich in negatively charged sialic acid and sulfonate residues. Therefore, the primary mechanism of chitosan's mucoadhesion is strong, long-range electrostatic attraction between the positively

charged chitosan and the negatively charged mucin glycoproteins. Furthermore, the flexible chains of chitosan can readily interpenetrate and entangle with the mucin network, forming numerous secondary bonds (hydrogen bonds). The formation of a polyelectrolyte complex with alginate within the bead matrix further enhances its cohesive strength, allowing it to withstand detachment forces without matrix failure.

HPMC K4M (Non-ionic, Relatively Rigid): Hydroxypropyl methylcellulose is a non-ionic, hydrophilic polymer. Its mucoadhesion relies primarily on physical mechanisms: chain interpenetration into the mucus layer and the formation of weak hydrogen bonds and van der Waals forces. The absence of strong ionic interactions limits its initial attachment strength. Moreover, the cellulose backbone of HPMC is relatively more rigid compared to the glycosidic linkage-based chain of chitosan, which may restrict its ability to intimately interpenetrate the mucin network. While it contributes to gel formation and sustained release, its intrinsic bioadhesive potential is considerably lower than that of chitosan.

4.6. In Vitro Drug Release and Kinetics

The *in vitro* drug release profiles of the Sucralfate-loaded microbeads, conducted in 0.1N HCl (pH 1.2), demonstrated sustained release over 12 hours, successfully meeting the primary objective of prolonged local delivery. The cumulative percentage drug release for representative batches is presented in Table 6 and visualized in Figure 2.

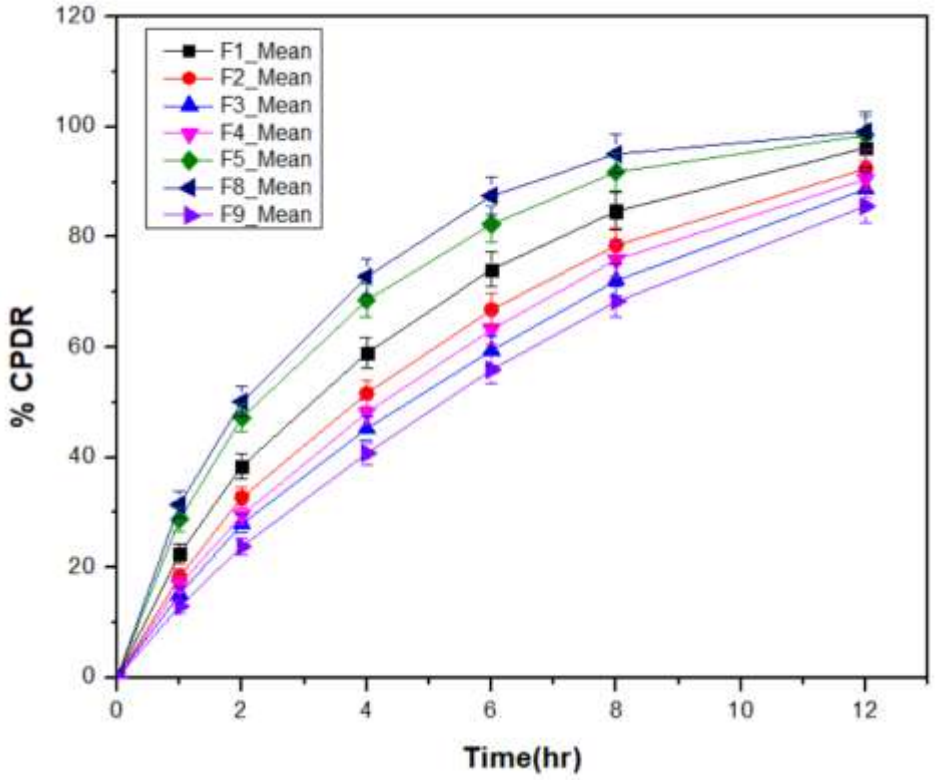

Figure 2: Cumulative Percentage Drug Release of Sucralfate from Selected Microbead Batches

Table 6: Cumulative Percentage Drug Release of Sucralfate from Selected Microbead Batches (Mean ± SD, n=3)

Time (hr)	F1 (0.5% CS)	F2 (1.0% CS)	F3 (1.5% CS)	F4 (5% $NaHCO_3$)	F5 (15% $NaHCO_3$)	F8 (1.0% HPMC)	F9 (3.0% SA)
1	22.5 ± 1.8	18.3 ± 1.5	15.1 ± 1.2	16.8 ± 1.4	28.7 ± 2.1	31.4 ± 2.3	12.9 ± 1.1
2	38.4 ± 2.2	32.7 ± 1.9	27.9 ± 1.7	29.5 ± 1.8	47.2 ± 2.5	50.1 ± 2.7	23.8 ± 1.5
4	58.9 ± 2.8	51.6 ± 2.4	45.2 ± 2.1	48.1 ± 2.3	68.5 ± 3.0	72.8 ± 3.2	40.7 ± 2.0
6	74.1 ± 3.1	66.8 ± 2.9	59.4 ± 2.6	63.2 ± 2.8	82.3 ± 3.3	87.5 ± 3.5	55.9 ± 2.5
8	84.7 ± 3.3	78.5 ± 3.1	72.1 ± 2.9	75.9 ± 3.0	91.8 ± 3.4	95.1 ± 3.6	68.3 ± 2.7
12	96.2 ± 3.5	92.4 ± 3.4	88.7 ± 3.2	90.5 ± 3.3	98.5 ± 3.5	99.2 ± 3.6	85.6 ± 3.0

Modulation of Release Rate by Polymer Ratio and Matrix Density:

The release rate was significantly modulated by the polymeric composition and the resulting bead matrix density.

Effect of Chitosan Concentration: Increasing the chitosan concentration from 0.5% (F1) to 1.5% (F3) resulted in a progressive retardation of drug release. This is attributed to the enhanced formation of a dense, cross-linked alginate-chitosan polyelectrolyte complex which reduces matrix permeability and pore size. The higher viscosity of the gel network also impedes water penetration and drug diffusion.

Effect of Sodium Alginate Concentration: Batch F9 (3.0% SA) exhibited the slowest release profile. The higher alginate concentration produces a thicker, more robust calcium-alginate gel core with a lower free volume, significantly slowing down the diffusion of the drug through the matrix.

Effect of Effervescent Agent (Porosity): The concentration of $NaHCO_3$ directly influenced release through its effect on porosity. Batch F5 (15% $NaHCO_3$), with its highly porous and fragile matrix (as seen in SEM), showed the fastest drug release due to the creation of extensive channels for rapid medium ingress and drug egress. Conversely, Batch F4 (5% $NaHCO_3$), with a less porous structure, displayed a slower, more controlled release.

Effect of Polymer Type: Batch F8 (HPMC) showed a rapid initial burst and the fastest overall release. The non-ionic HPMC gel hydrates and swells but lacks the strong ionic cross-links of the alginate-chitosan system, leading to a more open, erodible matrix that facilitates quicker drug release.

Drug Release Kinetics:

The release data for the optimized batch (F2) was fitted to various kinetic models (Table 7). The highest correlation coefficient (R^2) was observed for the Korsmeyer-Peppas model (0.997), indicating it was the best fit for describing the release mechanism.

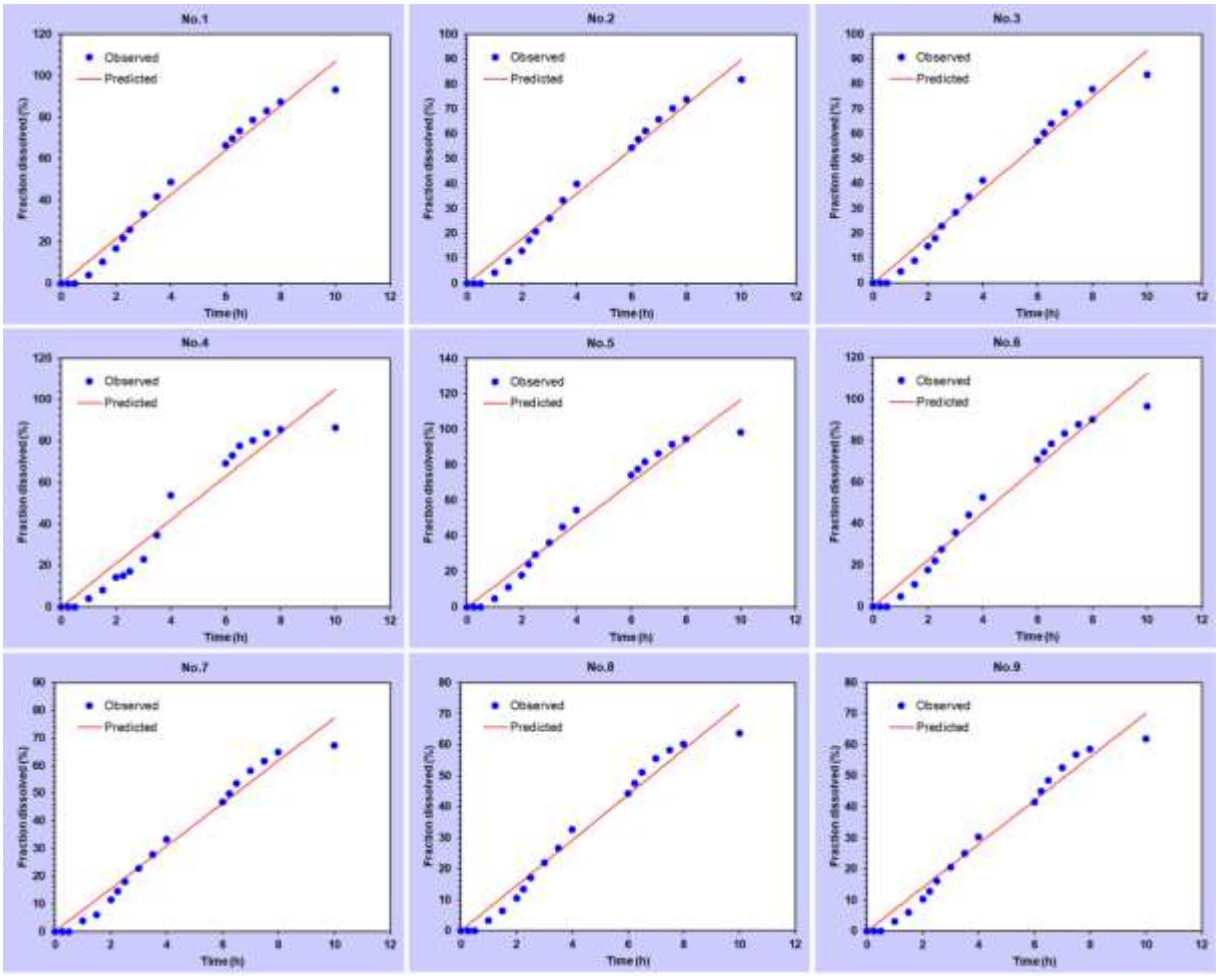

Figure 3: Drug release profile fitted to Korsmeyer–Peppas model.

Table 7: Release Kinetics Data for Optimized Batch F2

Model	Equation	R^2	Release Constant
Zero-Order	Q = 7.874t + 16.27	0.912	K_0 = 7.874 %/hr
First-Order	Log(%Remaining) = -0.176t + 1.939	0.985	K_1 = 0.176 hr^{-1}
Higuchi	Q = 28.65√t + 3.142	0.976	KH = 28.65 %/√hr
Korsmeyer-Peppas	Log(Mt/M∞) = Log(0.189) + 0.457Log(t)	**0.997**	KKP = 0.189, **n = 0.457**

The release exponent (n) value from the Korsmeyer-Peppas model was 0.457. For spherical matrices, an n value between 0.43 and 0.85 indicates anomalous (non-Fickian) transport. This suggests that the release of Sucralfate from the microbeads is governed by a combination of two mechanisms: diffusion of the drug through the hydrated porous network and the relaxation/erosion of the polymer chains (particularly alginate and chitosan) in the acidic medium. The initial

rapid phase is likely dominated by diffusion of drug from superficial pores, while the sustained phase is controlled by the slower combined processes of diffusion through the swollen gel and matrix erosion.

4.7. Optimized Formulation

The selection of the optimized formulation was based on a holistic evaluation of all critical performance parameters, aiming to identify a batch that best fulfills the dual objectives of prolonged gastric retention (via buoyancy and adhesion) and sustained, localized drug release, without compromising process efficiency. No single batch was the absolute best in every category; therefore, the optimal candidate was identified as the one achieving the most effective balance across all key metrics. After systematic analysis of Batches F1 through F9, Batch F2 was identified as the optimized formulation. Its comprehensive performance profile is summarized and justified below:

Rationale for Selection of Batch F2:

This indicates an efficient encapsulation process, ensuring maximum dose availability and economic viability. While Batch F9 (3.0% SA) showed a slightly higher DEE (92.7%), it also resulted in a larger particle size and a markedly slower drug release, which could be suboptimal for therapeutic onset.

Batch F2 exhibited a swift Floating Lag Time (FLT) of 48 seconds, ensuring rapid transition to a buoyant state upon reaching the stomach. Its Total Floating Time (TFT) exceeded 12 hours, demonstrating durable intragastric flotation. This is superior to Batch F5 (15% $NaHCO_3$), which had a shorter FLT but began to disintegrate after 8-9 hours due to excessive porosity.

The adhesion force for F2 was significantly high, nearly double that of the HPMC-containing batch (F8) and substantially stronger than batches with lower chitosan. While Batch F3 (1.5% CS) showed the highest adhesion (94.8 mN), its associated denser matrix led to a slower drug release rate. The adhesion strength of F2 is deemed more than adequate to complement its floating property, creating a robust dual-mechanism for retention.

F2 released 92.4% of its drug load over 12 hours in a controlled manner. This profile is neither too rapid (like F5 or F8, which released >95% within 8 hours) nor too slow (like F9, which released only 85.6% in 12 hours). Its release kinetics followed the Korsmeyer-Peppas model (R^2=0.997) with an 'n' value of 0.457, indicating a synergistic release mechanism governed by both diffusion and polymer matrix relaxation ideal for a swelling, erodible mucoadhesive system.

The beads from Batch F2 were spherical, mechanically stable with a suitable particle size (~1080 µm), and exhibited the intended porous morphology essential for buoyancy.

4.8. Statistical Analysis (ANOVA)

To substantiate the observed effects of critical formulation variables on key response parameters and to determine the statistical significance of these effects, a one-way Analysis of Variance (ANOVA) was performed. The analysis was conducted using GraphPad Prism software (version 8.0). For each investigated factor, batches that varied only in that specific variable while keeping others constant were compared. The data are presented as Mean ± Standard Deviation (n=3 for DEE and Yield, n=5 for Mucoadhesion). A p-value of less than 0.05 ($p < 0.05$) was considered statistically significant.

1. Effect of Chitosan Concentration on Drug Entrapment Efficiency (DEE):

Batches F1 (0.5% CS), F2 (1.0% CS), and F3 (1.5% CS) were compared.

ANOVA Result: $F(2, 6) = 25.74$, $p = 0.0011$.

The p-value (0.0011) is less than 0.05. Therefore, we reject the null hypothesis. There is a statistically significant difference in DEE among the different chitosan concentrations. Post-hoc Tukey's test revealed that the DEE of F3 (1.5% CS) was significantly higher than that of F1 (0.5% CS) ($p < 0.01$), while the difference between F2 and F3 was not significant ($p > 0.05$).

2. Effect of Sodium Bicarbonate Concentration on Floating Lag Time (FLT):

Batches F4 (5% $NaHCO_3$), F2 (10% $NaHCO_3$), and F5 (15% $NaHCO_3$) were compared.

ANOVA Result: $F(2, 6) = 85.33$, $p < 0.0001$.

The p-value (<0.0001) is less than 0.05. We reject the null hypothesis. There is a statistically significant difference in FLT. Tukey's test confirmed that the FLT of F5 (15%) was significantly shorter than both F4 and F2 ($p < 0.0001$), and F2's FLT was significantly shorter than F4's ($p < 0.01$).

3. Effect of Chitosan Concentration on Mucoadhesive Strength:

Batches F1 (0.5% CS), F2 (1.0% CS), and F3 (1.5% CS) were compared for detachment force.

ANOVA Result: $F(2, 12) = 147.9$, $p < 0.0001$.

The p-value (<0.0001) is less than 0.05. We reject the null hypothesis. Chitosan concentration has a highly significant effect on mucoadhesive strength. Post-hoc analysis showed each incremental increase in chitosan concentration (0.5% → 1.0% → 1.5%) resulted in a statistically significant increase in adhesion force ($p < 0.001$ for all pairwise comparisons).

4. Effect of Polymer Type on Mucoadhesive Strength:

Batch F2 (1.0% Chitosan) and Batch F8 (1.0% HPMC K4M) were compared.

Unpaired t-test Result: $t(8) = 22.17$, $p < 0.0001$.

The p-value (<0.0001) is less than 0.05. We reject the null hypothesis. The mucoadhesive strength of chitosan-based beads (F2) is statistically significantly higher than that of HPMC-based beads (F8).

CONCLUSION

This study successfully developed and characterized a novel dual-mechanism gastroretentive system in the form of Sucralfate-loaded floating mucoadhesive microbeads. Utilizing the ionotropic gelation technique,

an optimized formulation (Batch F2: 2% Sodium Alginate, 1% Chitosan, 10% Sodium Bicarbonate, cross-linked for 20 minutes) was identified that effectively balances all critical performance attributes. The microbeads exhibited excellent drug entrapment efficiency (88.3%), rapid and durable buoyancy (FLT < 1 min, TFT >12 h), and strong mucoadhesive strength (78.6 mN), thereby addressing the core limitation of conventional Sucralfate therapy short gastric residence time. In vitro release studies confirmed a sustained drug release profile over 12 hours, with kinetics best described by the Korsmeyer-Peppas model, indicating an anomalous transport mechanism governed by both diffusion and polymer relaxation/erosion. Statistical analysis (ANOVA) validated that the key formulation variables chitosan concentration and effervescent agent level had a significant ($p < 0.05$) impact on the entrapment, buoyancy, and adhesion responses. These findings conclusively demonstrate that the developed floating mucoadhesive microbeads are a scientifically sound and promising strategy to prolong the localization of Sucralfate at the ulcer site, which is anticipated to enhance its cytoprotective efficacy, reduce dosing frequency, and improve patient compliance. Future work will involve in vivo pharmacokinetic and pharmacodynamic studies in suitable animal models to confirm the extended gastric retention and superior therapeutic outcomes of this optimized system.

Acknowledgements

All authors contributed equally to the conception, design, execution, analysis, and writing of this manuscript. Each author has reviewed and approved the final version of the paper and agrees to be accountable for all aspects of the work.

Funding

None

REFERENCES

[1] M. N. Gambhire, K. W. Ambade et al., "Development and in-vitro evaluation of oral floating matrix tablet formulation of Diltiazem," — (details incomplete; please provide journal/year if available).

[2] S. K. Gupta, "Stability studies of ampicillin floating tablets (Ampiflot) and buffered Ampiflot," M.S. thesis, St. John's University, Jamaica, NY, USA, 1987.

[3] Vishvakarma P, Kaur J, Chakraborthy G, Vishwakarma DK, Reddy BB, Thanthati P, Aleesha S, Khatoon Y. Nephroprotective Potential of Terminalia Arjuna Against Cadmium-Induced Renal Toxicity by In-Vitro Study. Journal of Experimental Zoology India. 2025 Jan 1;28(1)

[4] N. Ozdemir, S. Ordu, and Y. Ozkan, "Studies of floating dosage forms of furosemide: in vitro and in vivo evaluation of bilayer tablet formulation," Drug Dev. Ind. Pharm., vol. 26, pp. 857–866, 2000.

[5] P. R. Sheth and J. Tossounian, "The hydrodynamically balanced systems (HBS): A novel drug delivery system for oral use," Drug Dev. Ind. Pharm., vol. 10, pp. 313–339, 1984.

[6] Kumar S, Manoyogambiga M, Attar S, Kaur K, Singh N, Shakya S, Sharma N, Vishvakarma P. Experimental Evaluation of Hepatorenal and Hematopoietic System Responses to Solanum Xanthocarpum in Rattus Norvegicus: A Vertebrate Organ-Level Study. Journal of Experimental Zoology India. 2025 Jul 1;28(2).

[7] A. Menon, W. A. Ritschel, and A. Sakr, "Development and evaluation of a monolithic floating dosage form for furosemide," J. Pharm. Sci., vol. 83, pp. 239–245, 1994.

[8] Bhagchandani D, Shriyanshi, Begum F, Sushma RC, Akanda SR, Narayan S, Sonu K, Vishvakarma P. Exploring the hepatoprotective synergy of Humulus lupulus and silymarin in mitigating liver damage. Biochem Cell Arch. 2025;25(1):915-9. doi:10.51470/bca.2025.25.1.915

[9] A. D., A. Ahuja, and R. K. Khar, "Hydrodynamically balanced systems as sustained release dosage form for propranolol hydrochloride," Pharmazie, vol. 45, pp. 356–358, 1990.

[10] Bachhav DG, Sisodiya D, Chaurasia G, Kumar V, Mollik MS, Halakatti PK, Trivedi D, Vishvakarma P. Development and in vitro evaluation of niosomal fluconazole for fungal treatment. J Exp Zool India. 2024;27:1539-47. doi:10.51470/jez.2024.27.2.1539

[11] S. Garg and S. Sharma, "Gastroretentive drug delivery systems," Pharmatech, vol. 5, no. 6, pp. 160–166, 2003.

[12] Parida SK, Vishvakarma P, Landge AD, Khatoon Y, Sharma N, Dogra SK, Mehta FF, Sharma UK. Spatiotemporal biointeraction and morphodynamics of a gastro-retentive Saccharopolyspora-derived macrolide system in the vertebrate gut: A study on absorptive microecology and transit kinetics. J Exp Zool India. 2025;28:1743-51. doi:10.51470/jez.2025.28.2.1743

[13] Mani M, Shrivastava P, Maheshwari K, Sharma A, Nath TM, Mehta FF, Sarkar B, Vishvakarma P. Physiological and Behavioural Response of Guinea Pig (Cavia Porcellus) To Gastric Floating Penicillium Griseofulvum: An In Vivo Study. Journal of Experimental Zoology India. 2025 Jul 1;28(2).

[14] S. H. Shah, J. K. Patel, and N. V. Patel, "Stomach-specific floating drug delivery system: A review," Int. J. PharmTech Res., vol. 1, no. 1, pp. 623–633, 2009.

[15] S. Arora, J. Ali, A. Ahuja, R. K. Khar, and S. Baboota, "Floating drug delivery systems: A review," AAPS PharmSciTech, vol. 6, no. 3, pp. 372–390, 2005.

[16] Garg A, Vishvakarma P, Mandal S. Exploring Carica papaya seeds extract as a herbal jelly for helminthiasis treatment: A comprehensive analysis. World J Pharm Pharm Sci. 2023 Mar 5;12(5):763-.

[17] R. Shaikh, T. R. R. Singh, M. J. Garland, and R. F. Donnelly, "Mucoadhesive drug delivery systems," J. Pharm. Bioallied Sci., vol. 3, no. 1, pp. 89–100, 2011.

[18] M. Mohan, H. Sujitha, V. U. M. Rao, M. Ashok, and B. Arun Kumar, "A brief review on mucoadhesive

microspheres," Int. J. Res. Rev. Appl. Sci., vol. 4, no. 1, pp. 975–986, 2014.
[19] B. Brahmaiah, K. P. Desu, S. Nama, S. Khalilullah, and S. S. Babu, "Formulation and evaluation of extended release mucoadhesion microspheres of simvastatin," Int. J. Pharm. Biol. Res., vol. 4, no. 1, pp. 57–64, 2013.
[20] S. J. Hwang, H. Park, and K. Park, "Gastric retentive drug-delivery systems," Crit. Rev. Ther. Drug Carrier Syst., vol. 1, no. 5, pp. 243–284, 1998.
[21] Vishvakarma P, Mohapatra L, Kumar NN, Mandal S, Mandal S. An innovative approach on microemulsion: A review. European Chemical Bulletin. 2023;12(4):11710-33.
[22] K. Vikram, S. Nitin, K. Pratap, and S. A. Shubhini, "Formulation and evaluation of floating-mucoadhesive microspheres of novel natural polysaccharide for site specific delivery of ranitidine hydrochloride," Int. J. Appl. Pharm., vol. 9, no. 3, pp. 15–19, 2017.
[23] L. Amin, T. Ahmed, and M. Mannan, "Formulation of floating-mucoadhesive microsphere for site-specific release of metronidazole," Adv. Pharm. Bull., vol. 6, no. 2, pp. 195–200, 2016.
[24] A. Adebisi, P. Laity, and B. Conway, "Formulation development and evaluation of floating mucoadhesive alginate beads for targeting Helicobacter pylori," J. Pharm. Pharmacol., vol. 67, no. 4, pp. 511–524, 2014.
[25] M. J. Y. Mukund, K. B. R. Kantilal, and S. R. N. Sudhakar, "Floating microspheres: A review," Braz. J. Pharm. Sci., vol. 48, no. 1, pp. 17–30, 2012.
[26] M. Kawatra, U. Jain, and J. Ramana, "Recent advances in floating microspheres as gastro-retentive drug delivery system: A review," Int. J. Recent Adv. Pharm. Res., vol. 2, no. 3, pp. 5–23, 2012.
[27] J. K. Vasr, K. Tambwekar, and S. Garg, "Bioadhesive microspheres as a controlled drug delivery system," Int. J. Pharm., vol. 255, pp. 13–32, 2003.