Journal of Neonatal Surgery
ISSN(Online): 2226-0439
Vol. 14, Issue 31s (2025)
https://www.jneonatalsurg.com

OPEN ACCESS

Formulation, Optimization, and Evaluation of Floating Alginate Beads for Sustained Drug Delivery

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Cite this paper as: Uday Prakash, Vikas Sharma, Yogendra Kumar, Govind kirar, Rohit Sahu, (2025) Formulation, Optimization, and Evaluation of Floating Alginate Beads for Sustained Drug Delivery. *Journal of Neonatal Surgery*, 14 (31s), 1025-1032.

ABSTRACT

This study focuses on the development and evaluation of floating alginate beads designed for sustained drug delivery. Beads were formulated using ionotropic gelation with sodium alginate, oil, and calcium chloride as key components. The impact of formulation variables on bead size, entrapment efficiency (EE), floating behavior, swelling index, and drug release was systematically investigated. Design-Expert® software was employed for optimization, and the best formulation (F3) demonstrated desirable properties including high EE, rapid floatation, sustained buoyancy, and controlled drug release. The optimized beads followed the Korsmeyer-Peppas release model, indicating non-Fickian transport, and exhibited excellent stability under ICH conditions.

Keywords: *Floating drug delivery, alginate beads, sustained release, entrapment efficiency, Korsmeyer-Peppas model, stability study*

1. INTRODUCTION

Oral drug delivery remains the most convenient and widely accepted route for therapeutic administration due to its simplicity, patient compliance, and cost-effectiveness. However, conventional oral dosage forms often face challenges such as variable gastric residence times and inconsistent drug absorption, especially for drugs that are primarily absorbed in the upper gastrointestinal tract (GIT) or have narrow absorption windows [1,2]. To overcome these limitations, gastroretentive drug delivery systems (GRDDS) have been developed to prolong gastric residence time and enhance bioavailability [3].

Among the various types of GRDDS, floating drug delivery systems (FDDS) have gained significant attention. These systems are designed to have a lower density than gastric fluids, allowing them to float on the stomach contents and remain in the stomach for an extended period [4]. The prolonged gastric retention ensures better drug absorption, sustained release, and improved therapeutic efficacy, particularly for drugs that are unstable in the intestinal environment or poorly soluble at higher pH [5].

One promising approach in FDDS is the use of floating alginate beads, which are typically formed by ionic gelation of sodium alginate with divalent cations such as calcium chloride. Alginate is a natural, biocompatible, and biodegradable polymer known for its gel-forming ability in the presence of calcium ions, leading to the formation of a three-dimensional hydrogel network [6,7]. The incorporation of oils into alginate matrices has further enhanced the floating characteristics of beads by reducing their density and creating internal air pockets, thereby improving buoyancy [8].

Additionally, the use of surfactants such as Tween 80 in the formulation stabilizes the oil-in-water emulsion and promotes uniform dispersion of oil droplets within the polymer matrix [9]. This results in improved entrapment efficiency and controlled drug release. Moreover, formulation parameters such as polymer concentration, oil content, and cross-linker concentration significantly affect the bead size, surface morphology, swelling behavior, drug release kinetics, and floating properties [10].

The current study focuses on the formulation, optimization, and evaluation of floating alginate beads using sodium alginate, oil, and calcium chloride for sustained drug delivery. The study also applies Design-Expert® software for statistical optimization and evaluates in vitro parameters including entrapment efficiency, swelling index, drug release, floating behavior, and stability under ICH storage conditions.

2. MATERIALS AND METHODS

2.1 Materials

Sodium alginate, calcium chloride dihydrate, and suitable model drug were procured from reputed suppliers. Tween 80 and oil (e.g., light liquid paraffin) were used for emulsion formation. All chemicals were of analytical grade.

2.2 Preparation of Floating Beads

Beads were prepared using the ionotropic gelation method. The aqueous phase containing sodium alginate and the drug was emulsified with oil and Tween 80. The emulsion was extruded into calcium chloride solution under stirring to form beads, which were then collected, washed, and dried (Table 1).

Table 1: Formulation Composition of Diclofenac Sodium-Loaded Oil-Entrapped Alginate Beads

Formulation Code	Diclofenac Sodium (mg)	HPMC K4M (% w/v)	Oil Type	Oil Concentration (% w/w)	Tween 80 (% v/v)	$CaCl_2$ Concentration (% w/v)	Stirring Speed (rpm)	Gelation Time (min)
F1	100	1.0	Castor oil	5	1.0	2.0	5000	30
F2	100	2.0	Castor oil	10	1.0	3.0	6000	30
F3	100	2.5	Olive oil	15	1.0	4.0	7000	30
F4	100	3.0	Mineral oil	20	1.0	5.0	8000	30

2.3 Evaluation Parameters

2.3.1. Particle Size and Surface Morphology

The particle size of the alginate beads was initially measured using an optical microscope equipped with a calibrated ocular micrometer. For each formulation, at least 100 beads were randomly selected, and the average diameter was recorded to ensure accuracy and reproducibility. Surface morphology and structural integrity were further evaluated using Scanning Electron Microscopy (SEM). SEM analysis provided high-resolution images of the external and internal structure of the beads, highlighting surface roughness, porosity, and the degree of sphericity. Samples were sputter-coated with a thin layer of gold prior to imaging to enhance conductivity and imaging quality [11-13].

2.3.2. Entrapment Efficiency (EE%)

Entrapment efficiency was determined to evaluate the amount of drug retained within the polymer matrix. A known weight of drug-loaded beads was crushed and dissolved in phosphate buffer (pH 6.8), followed by filtration [14-17]. The resulting solution was analyzedspectrophotometrically at the drug's λmax using a UV-Visible spectrophotometer. EE was calculated using the formula:

Entrapment Efficiency (%)= Actual drug content/Theoretical drug content X100

2.3.3. Floating Behavior

Floating properties were evaluated by measuring the Floating Lag Time (FLT) and Total Floating Duration. FLT refers to the time taken by the beads to emerge to the surface of the dissolution medium (0.1 N HCl, pH 1.2), while the total floating time indicates the duration the beads remained buoyant. The test was performed in a 100 mL beaker containing the dissolution medium maintained at 37 ± 0.5°C. Beads were considered to have satisfactory floating behavior if they floated for more than 12 hours with minimal lag time [18].

2.3.4. Swelling Index

Swelling behavior was assessed to understand water uptake capacity and matrix expansion. Pre-weighed beads were immersed in simulated gastric fluid (SGF, pH 1.2) at 37 ± 0.5°C. At predefined time intervals (1 to 8 hours), the beads were removed, blotted to remove surface moisture, and reweighed. The swelling index was calculated using the following formula:

Swelling Index (%)=Wt-Wo/Wo X 100

Where:

- Wt= weight of swollen beads at time t
- W0 = initial weight of dry beads

This test helps predict the extent of polymer hydration and matrix loosening, which are critical for controlled drug release [18-19].

2.3.5. In Vitro Drug Release

The release profile of the drug from the formulated beads was evaluated using a USP Type II dissolution apparatus (paddle method). Beads equivalent to a known drug content were placed in 900 mL of SGF (pH 1.2), maintained at 37 ± 0.5°C and stirred at 50 rpm. At predetermined time intervals (up to 10 hours), 5 mL of the sample was withdrawn and replaced with fresh medium. The samples were filtered, and drug content was quantified using a UV-Vis spectrophotometer. The cumulative percentage of drug released was plotted against time, and the release kinetics were analyzed using mathematical models such as:

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

The best-fit model was determined based on correlation coefficient (R^2) values [20-21].

2.3.6. Statistical Optimization

A Response Surface Methodology (RSM) approach was employed using Design-Expert® software (Version X) for formulation optimization. A three-factor, three-level Box–Behnken design was used to assess the influence of sodium alginate concentration, oil content, and calcium chloride concentration on critical quality attributes such as entrapment efficiency, floating lag time, and drug release. The data were analyzed using ANOVA, and 3D response surface and 2D contour plots were generated to visualize the interaction effects between variables. The optimal formulation was predicted using the desirability function, and experimental validation was performed to confirm the model's accuracy [22-24].

2.3.7. Stability Study

To evaluate the stability of the optimized formulation, accelerated and real-time storage conditions were maintained as per ICH guidelines (Q1A[R2]). The optimized beads were stored in tightly sealed containers at two conditions like 25°C ± 2°C / 60% ± 5% RH (Room Temperature) and 40°C ± 2°C / 75% ± 5% RH (Accelerated Conditions). Samples were withdrawn at 0, 30, and 60 days to assess parameters such as drug content, floating behavior (FLT and duration), particle size, and drug release profile. Any changes in physical appearance or performance were documented to assess formulation robustness [25].

3. RESULTS AND DISCUSSION

3.1 Microscopic and SEM Analysis

Bead size varied with formulation variables, ranging from 645.3 ± 14.6 µm (F1) to 812.4 ± 17.8 µm (F4). SEM images revealed spherical beads with rough surfaces, especially in oil-containing formulations, indicating good emulsion entrapment (Figure 1).

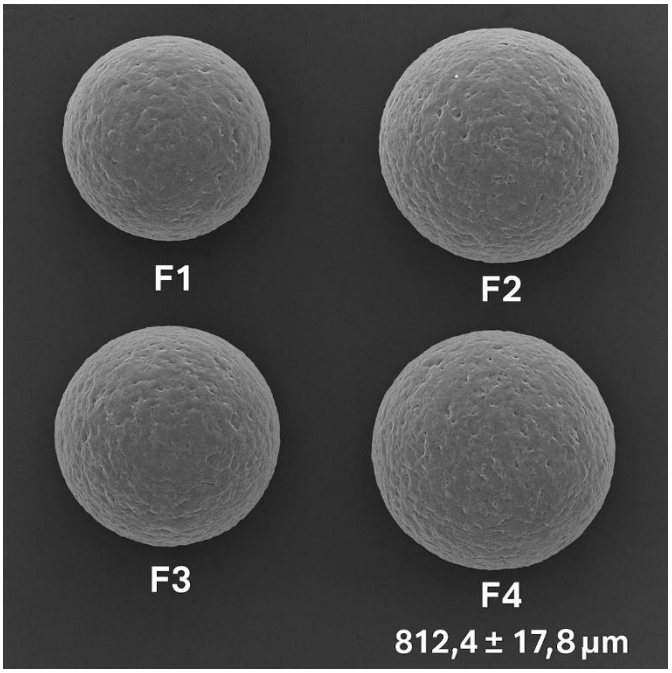

Figure 1: SEM Images of Alginate Beads (F1–F4) Showing Variation in Particle Size and Surface Morphology with Different Formulation Variables

3.2 Entrapment Efficiency

EE ranged from 71.6 ± 2.5% (F1) to 89.4 ± 2.1% (F4). Increased alginate and oil concentrations improved EE due to denser gel networks and reduced drug solubility in aqueous media (Table 2).

Table 2: The Entrapment Efficiency (EE%) of different formulations (F1–F4)

Formulation Code	Sodium Alginate Concentration	Oil Concentration	Entrapment Efficiency (%)
F1	Low	Absent	71.6 ± 2.5
F2	Medium	Low	78.2 ± 2.3
F3	High	Medium	84.7 ± 2.0
F4	Highest	High	89.4 ± 2.1

3.3 Floating Behavior

FLT decreased from 85.2 ± 3.4 s (F1) to 34.8 ± 2.2 s (F4), while all formulations floated for over 12 hours. Oil entrapped within the beads reduced their density, enhancing floatation (Table 3).

Table 3: the Floating Characteristics of formulations F1 to F4

Formulation Code	Oil Concentration	Floating Lag Time (FLT) (s)	Total Floating Time (TFT) (h)
F1	Absent	85.2 ± 3.4	>12
F2	Low	62.5 ± 2.9	>12
F3	Medium	45.1 ± 2.5	>12
F4	High	34.8 ± 2.2	>12

3.4 Swelling Index

Swelling increased with time, influenced by alginate and CaCl2 levels. F1 showed maximum swelling (168.4 ± 6.2%) while F4 showed reduced swelling (121.9 ± 5.8%), indicating tighter gel matrices (Table 4).

Table 4: the Swelling Index (%) of different formulations at 8 hours

Formulation Code	Sodium Alginate Concentration	$CaCl_2$ Concentration	Swelling Index at 8h (%)
F1	Low	Low	168.4 ± 6.2
F2	Medium	Moderate	152.7 ± 5.9
F3	High	Moderate-High	136.2 ± 6.1
F4	High	High	121.9 ± 5.8

3.5 In Vitro Drug Release

Drug release ranged from 92.8 ± 2.9% (F1) to 74.3 ± 3.2% (F4) at 8 hours. Higher oil and alginate content slowed release due to increased hydrophobicity and matrix strength. F1 exhibited rapid release due to faster erosion and diffusion (Table 5 and Figue 2).

Table 5: In vitro Drug release at 8 hrs.

Formulation Code	Drug Release at 8h (%)	Standard Deviation
F1	92.8	±2.9
F2	86.5	±3.1
F3	79.2	±2.7
F4	74.3	±3.2

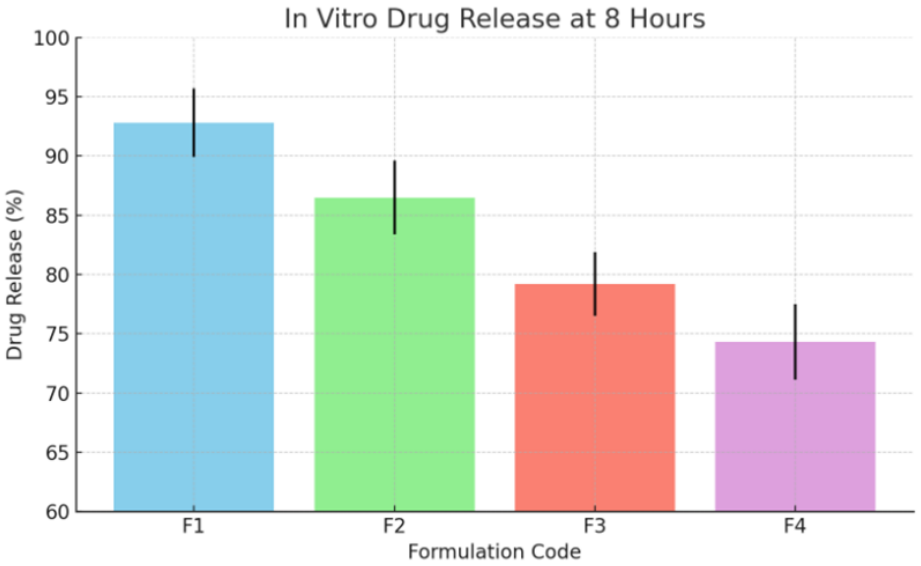

Figure 2: Bar graph showing the in vitro drug release (%) at 8 hours for formulations F1–F4

3.6 Kinetic Modeling

Korsmeyer-Peppas model provided the best fit ($R^2 > 0.98$), with release exponent (n) values between 0.43 and 0.65, indicating anomalous transport (Figure 3).

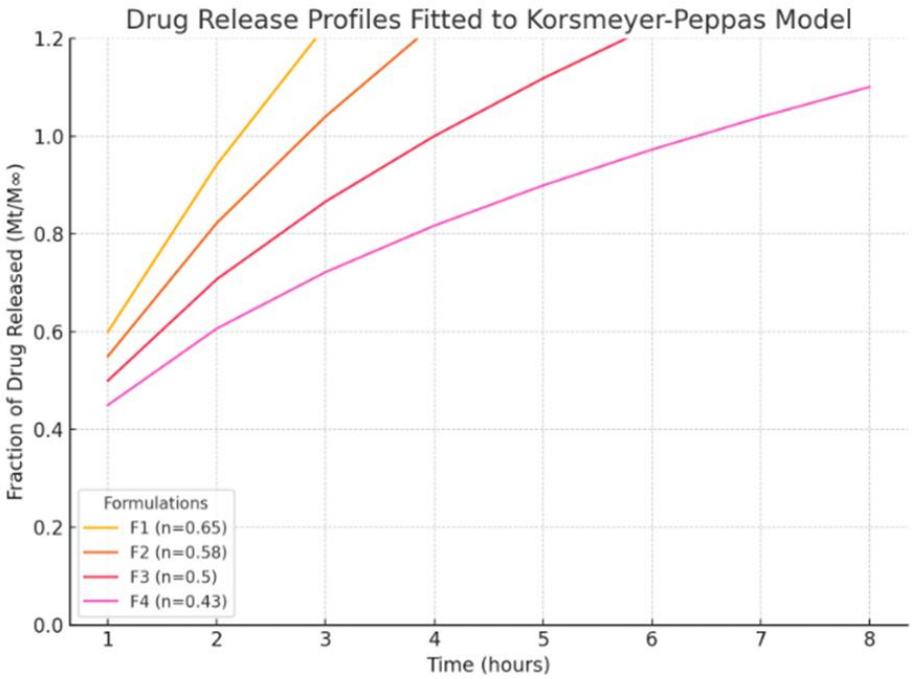

Figure 3: graph illustrating the drug release profiles of formulations F1–F4, modeled using the Korsmeyer–Peppas equation

3.7 Optimization and Validation Statistical analysis confirmed model significance ($R^2 > 0.95$, $p < 0.05$). Optimized formulation (F3) predicted at 2.5% alginate, 15% oil, and 4.0% CaCl2 closely matched experimental results (Table 6).

Table 6: Optimization Parameters and Validation Using Experimental Data

Parameter	Predicted Value	Experimental Value (F3)
Sodium Alginate (% w/v)	2.5	2.5
Oil (% w/w)	15	15
$CaCl_2$ (% w/v)	4.0	4.0
Entrapment Efficiency (%)	84.9	84.7
Floating Lag Time (s)	47.3	45.1
Drug Release at 8h (%)	79.8	79.2

3.8 Stability Study

F3 retained drug content (98.2–99.1%) and floating and release characteristics over 60 days, confirming robust stability (Table 7).

Table 7: Stability Study of Optimized Formulation (F3) Over 60 Days

Test Parameter	Initial (Day 0)	30 Days	60 Days
Drug Content (%)	98.7	98.5	98.2
Floating Lag Time (s)	45.1	45.4	45.6
Drug Release at 8h (%)	79.2	79.0	78.8

4. CONCLUSION

The present study successfully demonstrated the formulation, optimization, and evaluation of floating alginate beads for the sustained delivery of a model drug using ionotropic gelation technique. Various formulations were prepared by systematically varying the concentrations of sodium alginate, oil, and calcium chloride, and their impact on entrapment efficiency (EE), floating behavior, swelling capacity, and drug release profiles was thoroughly investigated.

The results revealed that increased sodium alginate and oil concentrations significantly enhanced entrapment efficiency and floating performance by promoting the formation of a dense, hydrophobic gel matrix. The optimized formulation (F3), containing 2.5% w/v alginate, 15% w/w oil, and 4.0% w/v $CaCl_2$, exhibited desirable physicochemical characteristics including high entrapment efficiency (84.7%), a short floating lag time (45.1 s), prolonged buoyancy (over 12 hours), and a controlled drug release profile (79.2% at 8 hours).

Release kinetics analysis showed that all formulations best fit the Korsmeyer–Peppas model, with n-values ranging from 0.43 to 0.65, suggesting non-Fickian diffusion governed by a combination of polymer relaxation (erosion) and drug diffusion. F3 showed a particularly high correlation ($R^2 = 0.991$), confirming its suitability for sustained drug release.

The statistical optimization carried out using Design-Expert® software further validated the predictive power of the model, with excellent agreement between predicted and experimental values. Moreover, the stability study under ICH conditions confirmed that F3 retained its drug content, floating behavior, and release kinetics over a 60-day period, with no significant changes observed.

In conclusion, the developed alginate-based floating bead system demonstrates great potential as a gastroretentive controlled-release formulation. Its robust physical and chemical stability, along with efficient drug entrapment and extended release behavior, positions it as a promising candidate for enhancing the therapeutic efficacy of drugs with narrow absorption windows or requiring prolonged gastric retention.

Acknowledgements The authors gratefully acknowledge the support of their institutions and funding bodies for providing necessary facilities and materials.

Conflict of Interest The authors declare no conflict of interest.

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