



Design of floating formulations and antiulcer activity of *Desmostachya bipinnata*

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Abstract

The study aims to design and optimize the floating formulations of the aqueous extract of *Desmostachya bipinnata* (ADB) to treat peptic ulcers. The trial concentrations of HPMC E50, HPMC K4M, and Carbopol 940 were used as factors, and floating lag time, total floating time, and % drug release at 12 h were used as responses. The formulation underwent evaluation for different parameters: aspirin-induced ulcers in rats assessed the antiulcer activity, and X-ray studies in rabbits evaluated the gastroretentive nature. The optimized formulation has shown a floating lag time of 32 s and floated in the gastric medium for more than 9 h with a maximum drug release of 93% at the end of 12 h by following the Korsmeyer-Peppas drug release mechanism. The optimized formulation has good flow properties. The FT-IR, DSC, and XRD studies show ADB and excipients didn't show any incompatibility. The formulation has shown significant antiulcer activity against aspirin-induced ulcers in rats, with an ulcer index of 3.38 ± 0.24 and inhibition of $76.67 \pm 0.56\%$. The *in vivo* X-ray imaging proved the gastric retention of the formulations for more than 8 h. The results of the formulations demonstrate the floating ability and sustained drug release of the tablet responsible for treating peptic ulcers to show a localized effect in the gastric region and to maintain the ROS levels.

Keywords antiulcer activity · design of experiment · *Desmostachya bipinnata* · floating tablets · gastric retention study

Introduction

Peptic ulcers (PU) are a significant gastrointestinal disorder that is increasingly prevalent worldwide. A pathological anomaly within the gastrointestinal tract, frequently impacting the stomach and duodenum, has been observed [1]. PU is characterized by an imbalance between the protective and

harmful factors that affect the mucosa of the upper digestive system. This condition results in damage to the lining of the system. Infection with *Helicobacter pylori* (*H. pylori*) and the overconsumption of non-steroidal anti-inflammatory drugs (NSAIDs) are the two leading causes of PU [2–4].

Proton pump inhibitors (PPIs) have been widely recognized as the most productive pharmaceutical agents for reducing gastric acid secretion. Proton pump inhibitors (PPIs) are utilized to treat severe manifestations of peptic ulcers, notably in instances characterized by bleeding, functional dyspepsia, and the eradication of *H. pylori* when combined with antibiotics. The extended use of proton pump inhibitors (PPIs) associated with acid suppression may lead to the proliferation of enteric flora in the proximal segment of the intestine. This, in turn, may increase the likelihood of pneumonia during physiological reflux and the development of parietal cell hyperplasia and gastric gland polyps. Additionally, prolonged PPI treatment may result in reduced absorption of essential nutrients such as B12 vitamins, magnesium, and calcium and an elevated risk of infection by *Clostridium*

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difficile. Furthermore, PPIs may interfere with the efficacy of certain medications, including clopidogrel and digitalis [5]. Although generally well-tolerated, these medications have adverse effects such as headache, diarrhea, nausea, drowsiness, impotence, rash, gynecomastia, dizziness, and muscle pain [2].

Several botanical remedies have been identified as potential substitutes for synthetic pharmaceuticals in managing *H. pylori* infections and mitigating and treating PUD, frequently with a reduced incidence of unfavorable outcomes. One of the plants used to treat gastrointestinal disorders is the *Desmostachya bipinnata* (Db) family, Poaceae. It is a perineal grass that commonly grows as a weed in paddy fields, also known as kusha [6], darbh [7], and dabh [8]. It is traditionally an analgesic, antipyretic, and anti-inflammatory to treat jaundice, asthma, rheumatism, and ulcers [9–12]. Many phytoconstituents are isolated from the Db, like quercetin, kaempferol, tricin, Scopoletin, Stigmasterol, Apigenin, Endoborneol, Tricyclene [11–16] and along with the isolated compounds, it also contains a small amount of saponins and volatile oils [17, 18]. The ethanolic extract of Db and its isolated compounds (Tricin and Tricin 7-glucoside) are evaluated for their antiulcer activity compared with the standard ranitidine in ethanol-induced ulcers in rats. The results show that the Db extract and the isolated compounds from the Db extract show more activity than the standard ranitidine [12]. Various studies have been conducted on the plant Db to evaluate its pharmacological activities [19].

In the present study, we are formulating the gastroretentive drug delivery systems of the aqueous extract of Db (ADB) to treat peptic ulcers. We observed the release patterns and evaluated the antiulcer activity of ADB tablets in rats and their floating behavior in rabbits.

Materials and Methods

Materials

ADB (Batch No. VH/KDGE/VHKDG41), conforming to the industrial specifications, was procured from Vital Herbs (Delhi). Quercetin was obtained from Sigma-Aldrich. Aspirin, Omeprazole, HPMC K4M, HPMC E50, and Carbopol 940 were acquired from Yarrow Chem (Mumbai). Formaldehyde, sodium hydroxide, disodium phosphate, sodium phosphate, sodium chloride, and hydrochloric acid were obtained from Loba Chem. E.D.T.A. was obtained from fisher inorganics and aromatics. Carboxymethyl cellulose was obtained from Suvindhinath laboratories. Magnesium stearate, barium sulphate, and TRIS buffer were obtained from Sisco research laboratories in Mumbai.

Formulation of gastric floating tablets

Direct compression was used to formulate ADB floating formulations. The dose of ADB was fixed at 250 mg, and as excipients, HPMC E50, HPMC K4M, and Carbopol 940 were selected [20–22]. The effervescent agent was sodium bicarbonate (NaHCO_3) [23], while the lubricant was magnesium stearate. The formulation mix was compressed into a tablet using a tablet-punching machine. The tablet's hardness was kept at 4 kg. The *in vitro* and *in vivo* characteristics of the tablet formulations were evaluated.

In vitro buoyancy determination

The tablet's buoyancy was evaluated by immersing it in 200 mL of 0.1 N HCl (pH 1.2 at 37.5°C) in a beaker [20]. Using visual observation, the floating lag time, i.e., the time required for the tablet to float on the surface of the gastric medium, and the total floating time, i.e., the total time the tablet floated on the gastric medium, were calculated [24].

In vitro drug release

The *in vitro* dissolution experiments were conducted in 900 mL of 0.1 N HCl at $37.5 \pm 0.5^\circ\text{C}$ and 50 rpm using USP Equipment II (Paddle). Five milliliters of samples were removed and replaced with the same volume of dissolving media at 1, 2, 3, 4, 5, 6, 8, 10, and 12 h. Then, test samples were diluted as required and filtered using Whatman filter paper. These materials were examined using a UV–visible spectrophotometer at 254 nm [20].

Drug release kinetics

We determined the release kinetics of the formulation based on the results of the dissolution investigation by fitting the dissolution profiles into various models. Higuchi, Korsmeyer-Peppas, first-order, and zero-order models were frequently employed model equations. DD Solver, an Excel plugin, evaluates the release kinetics [25–27].

Evaluation of pre-compression parameters

The powder blend was assessed for different parameters [28].

Bulk and tapped density

The following equations determined the bulk density and tap density by transferring 30 g of the mixture into a 250 ml dry graduated cylinder.

$$D_b = \frac{\text{Mass of powder blend (g)}}{\text{Volume of powder blend (mL)}}$$

$$D_t = \frac{\text{Mass of powder blend (g)}}{\text{Tapped volume of powder blend (mL)}}$$

D_b represents the bulk density (g/mL), and D_t represents the tapped density (g/mL).

Carr's index and Hausner's ratio

The following equations were used to calculate Carr's index and Hausner's ratio to evaluate the powder's flowability.

$$CI = \frac{D_t - D_b}{D_t} \times 100$$

$$HR = \frac{D_t}{D_b}$$

CI represents Carr's index, and HR represents Hausner's ratio.

Angle of repose

The angle of repose was computed using the fixed funnel method, in which the dimensions of the powder pile were measured after allowing 30 g of powder mass to pass through a funnel. We could determine the angle of repose by using the following equation and basing it on the diameter of the formed powder pile.

$$\tan \theta = \frac{2H}{R}$$

H – height, and R—radius of the powder pile.

Swelling studies

The tablet's swelling behavior was evaluated by weighing it (W_0) and placing it in a 200 mL container containing 0.1 N HCl. The tablet was removed at predetermined intervals of 1, 2, 3, 4, 6, 8, 10, and 12 h, and tissue paper was used to wipe off excess fluids before weighing (W_1). Then, the tablets are dried in an oven and weighed (W_2). The formula below was used to calculate the percentage of swelling index [18, 23] and erosion index [29].

$$\text{Swelling index} = \left(\frac{W_1 - W_0}{W_0} \right) \times 100$$

$$\text{Erosion index} = \left(\frac{W_0 - W_2}{W_0} \right) \times 100$$

Physicochemical characterization of gastric floating tablets

Vernier calipers were used to measure the diameter and thickness of the formulation. An electronic balance (Sartorius Lab Instruments Co., Ltd.) was used to measure the weight of the tablets. Ten tablets were used to measure each indicator, and the data were presented as an average and RSD. Fourier Transform Infrared spectroscopy (FT-IR) recorded the infrared spectra of the ADB, the optimized formulation, and the blank excipients. DSC (differential scanning calorimetry) curves were used to analyze the heating program. Samples (10 ± 0.5 mg) were placed on an aluminum plate with a flat bottom and heated in a nitrogen atmosphere from 30°C to 400°C at a rate of 10°C per minute. The X-ray diffraction (XRD) spectra of ADB, blank excipients, and the optimized formulation were measured to ascertain the compatibility of ADB with the excipients [25].

Stability studies

The tablets were maintained at a controlled temperature of $40^\circ\text{C} \pm 2^\circ\text{C}$ and a relative humidity of $75\% \pm 5\%$. The method outlined in Sect. 2.4 was utilized to investigate the drug release of the tablets in a dissolution medium with a pH of 1.2. Furthermore, an investigation was conducted to determine whether dynamic swelling and floating performance *in vitro* changed during the stability study [30].

Animals

Wistar female rats weighing 150–250 g were used in the experiment. The animals were retrieved from Manipal's central animal facility. Animal housing in laboratories was accomplished at $24 \pm 2^\circ\text{C}$, $55 \pm 5\%$ relative humidity, and a 12 h controlled light/dark cycle. Water from the tap was frequently provided along with the standard rat feed. The standards for animal care were followed regarding all rats. The Institutional Review Board authorized the use of animals in Animal Research/Studies (IAEC/KMC/83/2022).

Aspirin-induced ulcer

Animals were given a 24-h fast and unrestricted access to water. Except for the animals in group 1, all other groups received an oral dose of 150 mg/kg of body weight per day

for two days of an aspirin aqueous suspension in 1% sodium carboxymethylcellulose (CMC) after another fasting period of 12 h. There were five experimental groups, each containing six rats. In the control and disease-control groups, 1% sodium CMC solution (2 mL) was administered orally once daily for 15 days. The ADB was given to Group 3. The ADB formulation was assigned to Group 4. Group 5 (standard) received broken omeprazole tablets from a pharmacy [31].

Ulcer index

The rat stomachs were stretched out on a piece of wood, cut open along the line of greater curvature, and macroscopically

examined with the mucosal surface facing up. The frequency and severity of several sites of gross damage in the mucosa were observed under the microscope. The earlier method was used to rate the severity of damage and the formation of hemorrhages in macroscopic stomach lesions on a scale of 0 to 5 [32]. A severity factor of 0 indicates no damage, 1 indicates pinpoint erosions, 2 indicates lesions under 1 mm long, 3 indicates lesions between 1 and 2 mm long, 4 indicates lesions between 3 and 4 mm long, and 5 shows lesions longer than 4 mm long. The ulcer index (U.I.) was used to represent the average ulcer score for each animal [33].

$$\text{Ulcer Index} = \frac{\text{Ulcerated area}}{\text{Total stomach area}} \times 100$$

$$\text{Percentage inhibition} = \frac{\text{U.I of disease group} - \text{U.I of treated group}}{\text{U.I of disease group}} \times 100$$

Biochemical studies

Preparation of tissue homogenate

A 0.5 g sample of complete stomach tissue was pulverized with liquid nitrogen in a mortar for biochemical analysis. An appropriate solution, such as Tris–HCl buffer, was added to 4.5 mL of the powdered tissues. For 15 min, homogenize the mixture on ice. The homogenates' enzymatic activity was then assessed [34].

Estimation of Glutathione (G.S.H.) level

Using Sedlak and Lindsay's method, G.S.H. levels were determined [35]. The mucosal surface of the stomach was removed, weighed, and homogenized in 2 mL of 50 mM Tris–HCl, 20 mM EDTA, and 0.2 mM sucrose, pH 7.5, buffer. The mixture was precipitated by adding 25% trichloroacetic acid after centrifuging the homogenate at 4°C for 40 min at 4,000 rpm. A maximum absorption wavelength (max) of 412 nm was utilized to assess the supernatant [31].

Estimation of tissue lipid peroxidation (LPO) level

Malondialdehyde (M.D.A.), a byproduct of LPO, is quantified using the thiobarbituric acid test. The stomach tissues are homogenized in 10 mL of 100 g/L KCl. It is necessary to combine the homogenate (0.5 mL), 0.3 mL of distilled water, 0.2 mL of sodium lauryl sulphate solution diluted to 80 g/L, 1.5 mL of acetic acid solution diluted to 200 g/L, and 1.5 mL of 2-thiobarbiturate solution diluted to 8 g/L. The mixture was then incubated for another hour at 98°C. After chilling, add 5 mL of a 15:1 mixture of n-butanol and pyridine. At

4,000 rpm, the mixture is vortexed thirty minutes before the centrifugal mix. The supernatant was spectroscopically checked for M.D.A. at a wavelength of 532 nm [36].

Determination of catalase (CAT) activity

Spectrophotometry was used to calculate the catalase activity. Add the substrates (1 mM Tris EDTA, 5 mM EDTA, and 30% H₂O₂) to the supernatant samples in the cuvette to start the enzymatic reaction. H₂O₂ decomposition was monitored using a one-minute spectrometry test at 240 nm [37].

Determination of myeloperoxidase (MPO) activity

The M.P.O. activity was assessed using the Bradley *et al.* technique. The homogenized samples were centrifuged at 1500 rpm for 10 min at 4°C after three freeze–thaw cycles. To measure the M.P.O. activity of the supernatant, combine 100 mL of the supernatant with 1 mL of 1.5 mol/L o-dianisidine hydrochloride, 0.0005% w/v H₂O₂, and 1.9 mL of 10 mmol/L phosphate buffer (pH 6.0). A spectrophotometer monitored each sample's absorbance at 450 nm over time [38].

Histological studies

Following a macroscopic examination, each stomach was fixed for 24 h in a small amount of a 4% formalin solution. Various ethanol concentrations were employed to dry stomach tissue slices before embedding them in paraffin. 4 m thick paraffin slices were stained with hematoxylin and eosin. Under a microscope, a histological examination was conducted, and images were captured using a microscope camera attached to image A.R. Pro software [39, 40].

In vivo gastric retention study (X-ray imaging)

The *in vivo* buoyancy investigation was conducted using X-ray imaging (Fujifilm FCR PRIMA T) to demonstrate that formulations can be retained in the stomachs of New Zealand rabbits. The ADB in tablets was replaced with barium sulphate, a radio-opaque material, while the other elements remained the same. Three healthy New Zealand rabbits weighing between 1.8 and 2.2 kg were used in the investigation ($n=3$). Before administration, the first X-ray examination was done on the animals after a 12-h fast to ensure the stomach was free of any radiopaque material. The rabbits received gastric floating tablets and were free to drink water throughout the experiment. The X-ray machine imaged the stomach for the test tablets at 2, 4, 6, and 8 h [41, 42].

Table I Experimental Levels for the Box- Behnken Design

Factors (Polymers)	Units	Upper Limit	Lower Limit
A: HPMC E50	mg	60	120
B: HPMC K4M	mg	60	120
C: Carbopol 940	mg	30	90
Responses		Constraints	
Floating lag time	sec	Minimize	
Total floating time	h	Maximize	
Drug release at 12 h	%	Maximize	

Table II Experimental Trials Generated By the Design Expert

Run	Extract (mg)	Factors (mg)			NaHCO ₃ (mg)	Mg. Sterate (mg)	Total weight (mg)
		A: HPMC E50	B: HPMC K4M	C: Carbopol940			
1	250	120	60	60	60	5.5	555.5
2	250	90	90	60	60	5.5	555.5
3	250	60	60	60	60	4.9	494.9
4	250	90	60	30	60	4.9	494.9
5	250	60	90	30	60	4.9	494.9
6	250	90	60	90	60	5.5	555.5
7	250	60	90	90	60	5.5	555.5
8	250	120	120	60	60	6.1	616.1
9	250	60	120	60	60	5.5	555.5
10	250	90	120	90	60	6.1	616.1
11	250	90	90	60	60	5.5	555.5
12	250	90	120	30	60	5.5	555.5
13	250	90	90	60	60	5.5	555.5
14	250	90	90	60	60	5.5	555.5
15	250	90	90	60	60	5.5	555.5
16	250	120	90	90	60	6.1	616.1
17	250	120	90	30	60	5.5	555.5

Results and Discussion

Formulation of gastroretentive tablets

Preliminary trials

Quality by Design is a novel approach to drug development based on understanding the product and the development process. It is also essential to show the herbal tablet products' key quality attributes (CQA) for the product's characterization. Herbal medicines need higher therapeutic amounts than synthetic drugs because they are composed of numerous phytoconstituents and are hard to dissolve. So, optimizing the activities and parameters of herbal tablets is a significant challenge [43].

The trials were designed by Box Behnken design. The factors selected are A: HPMC E50, B: HPMCK4M, and C: Carbopol 940. The upper and lower limits for the factors (polymers) and responses to be evaluated are expressed in the Table I. The factors and the responses are evaluated using Design Expert 13 software [44]. The software has given 17 trials with varying concentrations by applying the lower and upper limits, expressed in Table II. The concentration of NaHCO₃ was fixed at 60 mg, and the magnesium stearate weight was maintained at 1% of the tablet weight.

The responses evaluated for the preliminary trials are R1: the floating lag time, R2: the total floating time, and R3: drug release after 12 h. Table III. displays the results of the experimental batches.

Table III Results of the Experimental Trials ($n=6$)

Run	Floating lag time(Sec)	Total floating time(h)	% Drug release at 12 h
1	43±3	8.5±0.2	83.68±1.15
2	54±2	9±0.3	76.58±1.26
3	32±4	9±0.5	90.27±1.62
4	42±3	9.25±0.4	84.93±1.34
5	51±5	9.5±0.3	79.79±1.91
6	51±3	9.5±0.1	79.27±1.28
7	52±2	9.5±0.2	80.02±1.26
8	51±4	9.75±0.3	79.17±1.23
9	32±3	9.75±0.6	90.18±1.45
10	50±2	9.75±0.5	79.54±1.63
11	64±4	10±0.4	70.54±1.35
12	43±1	10±0.2	83.33±1.12
13	67±2	10.2±0.3	68.64±1.82
14	56±3	10.3±0.4	74.61±1.75
15	52±5	11±0.75	77.45±1.78
16	65±4	11.3±0.5	68.66±1.85
17	56±3	11.3±0.3	75.37±1.56

Effect of factors on response R1 The coded equation generated from the obtained results by the factors is:

$$R1 = 51.00 - 4.75 * A - 5.63 * B + 11.87 * C \\ + 0.25 * AB + 0.25 * AC + 0.00 * BC \\ + 0.75 * A^2 + 1.50 * B^2 - 3.00 * C^2$$

The ANOVA results for the floating lag time are expressed in Table IV. It clearly shows that the model is significant. The perturbation graphs and the response surface graphs depicted in Fig. 1 clearly show the effect of the concentration of the factors on the floating lag time. The perturbation graphs in Fig. 1A indicate that the concentration of factors A and B shows a similar effect. In contrast, factor C shows an opposite effect to factors A and B. This could be supported by the response curves in Fig. 1B, C, and D, which state that as the concentration of factor C increases, the floating lag time rises. In the formulation, the floating lag time decreases when the concentrations of factors A and B increase.

Effect of factors on response R2 The coded equation generated from the obtained results by the factors is:

$$R2 = 9.60 - 0.4 * A + 0.54 * B + 0.83 * C \\ + 0.00 * AB - 0.18 * AC - 0.04 * BC \\ + 0.22 * A^2 + 0.20 * B^2 + 0.16 * C^2$$

The ANOVA results for the floating lag time are expressed in Table V. It clearly shows that the model is significant. The perturbation graphs and the response surface graphs in Fig. 2 clearly show the effect of the concentration of the factors on the floating lag time. The perturbation graphs in Fig. 2A indicate that the concentration of factors B and C shows a similar effect. In contrast, factor A shows

Table IV ANOVA for Response Surface Quadratic Model of Floating Lag Time

Source of variation	Sum of Squares	Degrees of freedom	Mean square	F- Value	P- Value	Degree of Significance
Model	4828.90	9	536.54	2424.05	<0.0001	Significant
A-HPMC E50	541.50	1	541.50	2446.44	<0.0001	
B-HPMC K4M	759.38	1	759.38	3430.77	<0.0001	
C-Carbopol 940	3384.38	1	3384.38	15,290.23	<0.0001	
AB	0.7500	1	0.7500	3.39	0.0733	
AC	0.7500	1	0.7500	3.39	0.0733	
BC	0.0000	1	0.0000	0.0000	1.0000	
A ²	7.11	1	7.11	32.10	<0.0001	
B ²	28.42	1	28.42	128.40	<0.0001	
C ²	113.68	1	113.68	513.61	<0.0001	
Residual	8.63	39	0.2213			
Lack of Fit	1.03	27	0.0382	0.0604	1.0000	Not Significant
Pure Error	7.60	12	0.6333			
Cor Total	4837.65	50				
Adeq Precision = 154.4297						
C.V. = 0.9289%						
R ² = 0.9982						
Adjusted R ² = 0.9978						
Predicted R ² = 0.9976						

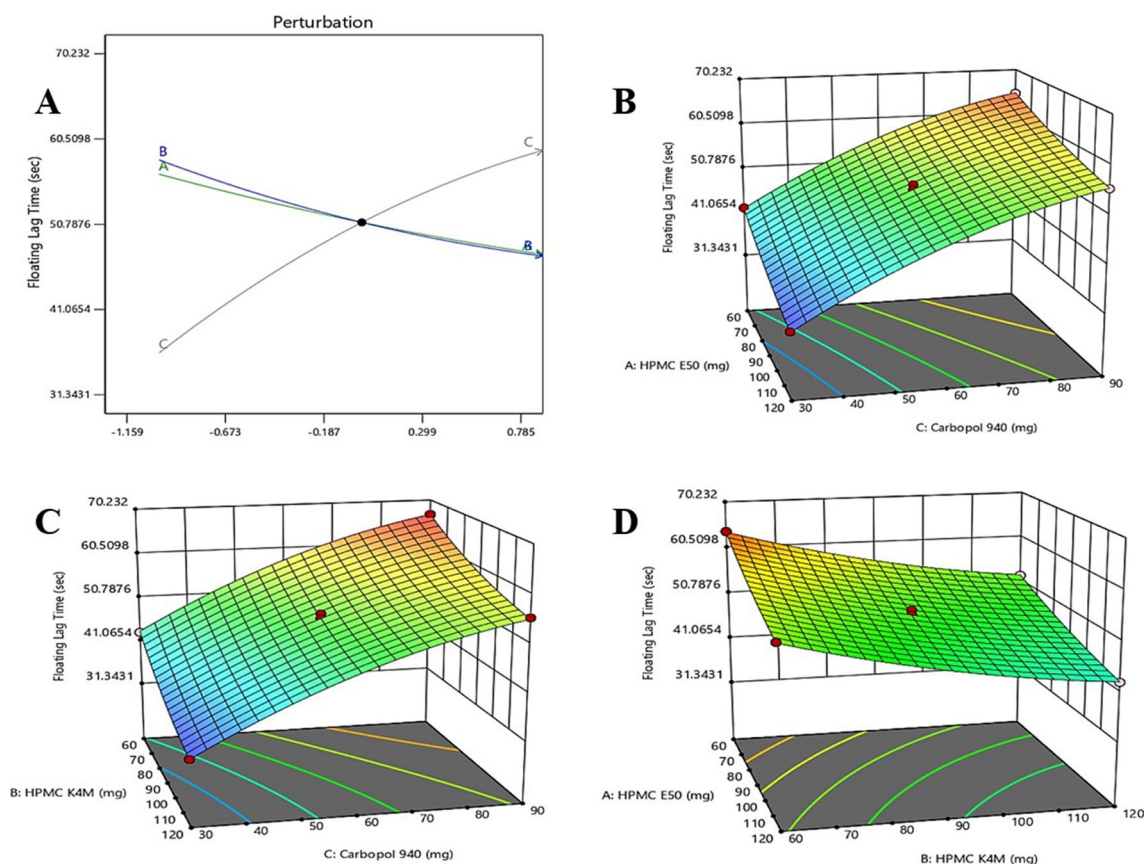


Fig. 1 Perturbation and response surface graphs for floating lag time

an opposite outcome to factors B and C. This could be supported by the response curves in Fig. 2B, C, and D, which state that as the concentration of factor A decreases, the total floating time increases. The formulation's total floating time increases when the concentrations of factors B and C increase.

Effect of factors on response R3 The coded equation generated from the obtained results by the factors is:

$$R3 = 79.64 + 2.90 * A + 3.36 * B - 7.72 * C - 0.040 * AB + 0.15 * AC + 0.058 * BC - 1.26 * A^2 - 1.41 * B^2 + 1.24 * C^2$$

The ANOVA results for drug release are expressed in Table VI. It clearly shows that the model is significant. The perturbation graphs and the response surface graphs represented in Fig. 3 clearly show the effect of the concentration of the factors on the drug release. The perturbation graphs in Fig. 3A indicate that the concentrations of factors A and B don't significantly impact drug release. Still, factor C shows a significant effect on drug release. As the concentration of

factor C increases, the drug release in the formulation shows a drastic decrease, and vice versa. This could be supported by the response curves in Fig. 3B, C, and D, which state that as the concentration of factor C decreases, the drug release increases.

Analyzing the factors for the responses depending on their concentrations clearly states that the effect of factors entirely depends on their viscosity profiles. The viscosities of factors A, B, and C are 50, 4000, and 40,000–60,000 cps, respectively. When the concentration of factor A is higher in the formulation, the total viscosity of the formulation decreases, which is responsible for the high penetration of H₂O into the formulation, which shows a decrease in floating lag time, total floating time, and an increase in drug release, or it can cause dose dumping in the gastric region as the tablet matrix is not stable. When the concentration of factor C is higher in the formulation, the total viscosity of the formulation increases too high, which is responsible for the low or minimal penetration of H₂O into the formulation, which shows a rapid increase in floating lag time, total floating time, and a decrease or prolonged drug release in the gastric region as the tablet matrix is too rigid.

Table V ANOVA for Response Surface Quadratic Model of Total Floating Time

Source of variation	Sum of Squares	Degrees of freedom	Mean square	F- Value	P- Value	Degree of Significance
Model	29.41	9	3.27	273.19	<0.0001	Significant
A-HPMC E50	3.96	1	3.96	331.13	<0.0001	
B-HPMC K4M	7.10	1	7.10	593.22	<0.0001	
C-Carbopol 940	16.34	1	16.34	1365.61	<0.0001	
AB	0.0000	1	0.0000	0.0000	1.0000	
AC	0.4219	1	0.4219	35.27	<0.0001	
BC	0.0169	1	0.0169	1.41	0.2421	
A ²	0.6160	1	0.6160	51.50	<0.0001	
B ²	0.4844	1	0.4844	40.50	<0.0001	
C ²	0.3167	1	0.3167	26.47	<0.0001	
Residual	0.4665	39	0.0120			
Lack of Fit	0.2665	27	0.0099	0.5922	0.8743	Not Significant
Pure Error	0.2000	12	0.0167			
Cor Total	29.88	50				

Adeq Precision = 53.9980
 C.V. = 1.11%
 R² = 0.9844
 Adjusted R² = 0.9808
 Predicted R² = 0.9741

Source of variation

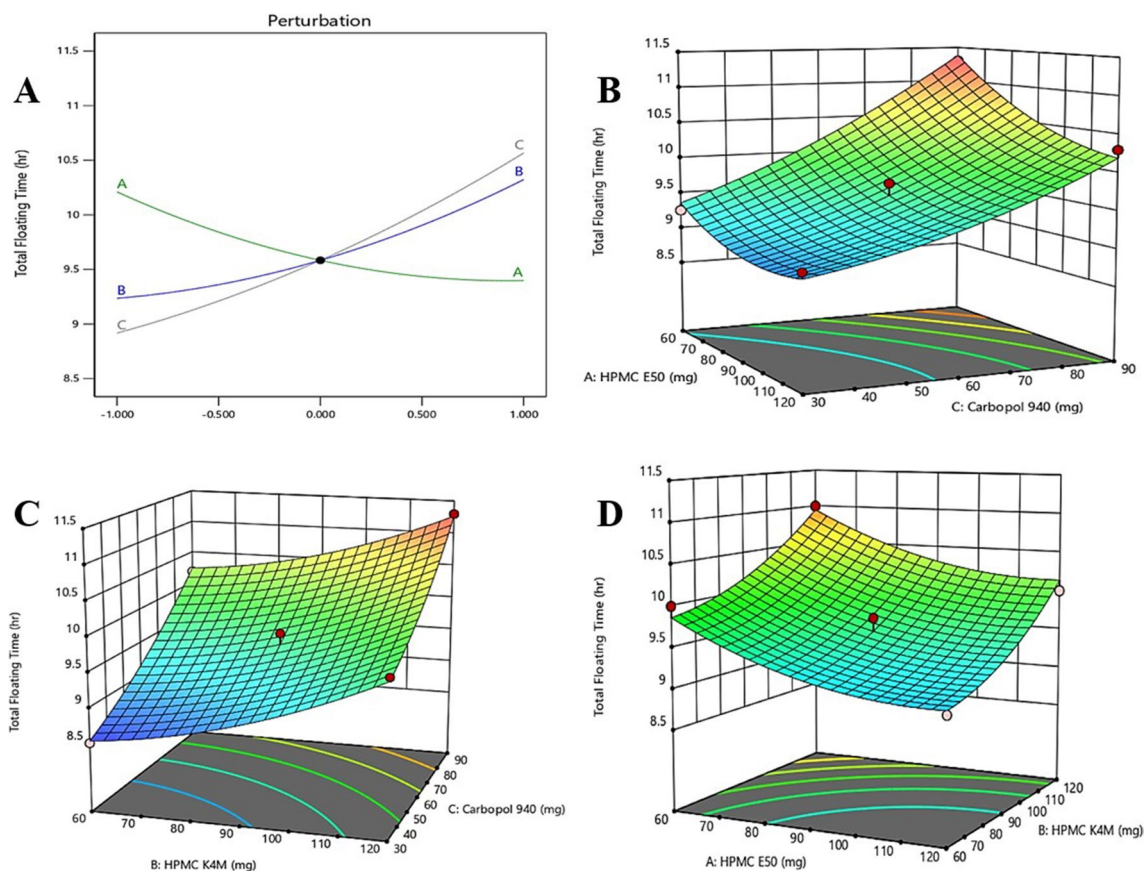
**Fig. 2** Perturbation and response surface graphs for total floating time

Table VI ANOVA for Response Surface Quadratic Model of Drug Release

	Sum of Squares	Degrees of freedom	Mean square	F- Value	P- Value	Degree of Significance
Model	1967.27	9	218.59	2718.47	<0.0001	Significant
A-HPMC E50	202.01	1	202.01	2512.37	<0.0001	
B-HPMC K4M	271.15	1	271.15	3372.22	<0.0001	
C-Carbopol 940	1431.26	1	1431.29	17,800.39	<0.0001	
AB	0.0192	1	0.0192	0.2388	0.6278	
AC	0.2791	1	0.2791	3.47	0.0700	
BC	0.0397	1	0.0397	0.4934	0.4866	
A ²	19.96	1	19.96	248.28	<0.0001	
B ²	25.01	1	25.01	311.07	<0.0001	
C ²	19.28	1	19.28	239.73	<0.0001	
Residual	3.14	39	0.0804			
Lack of Fit	1.89	27	0.0701	0.6759	0.8075	Not Significant
Pure Error	1.24	12	0.1037			
Cor Total	1970.43	50				

Adeq Precision = 161.5254
 C.V. = 0.3591%
 $R^2 = 0.9984$
 Adjusted $R^2 = 0.9980$
 Predicted $R^2 = 0.9973$

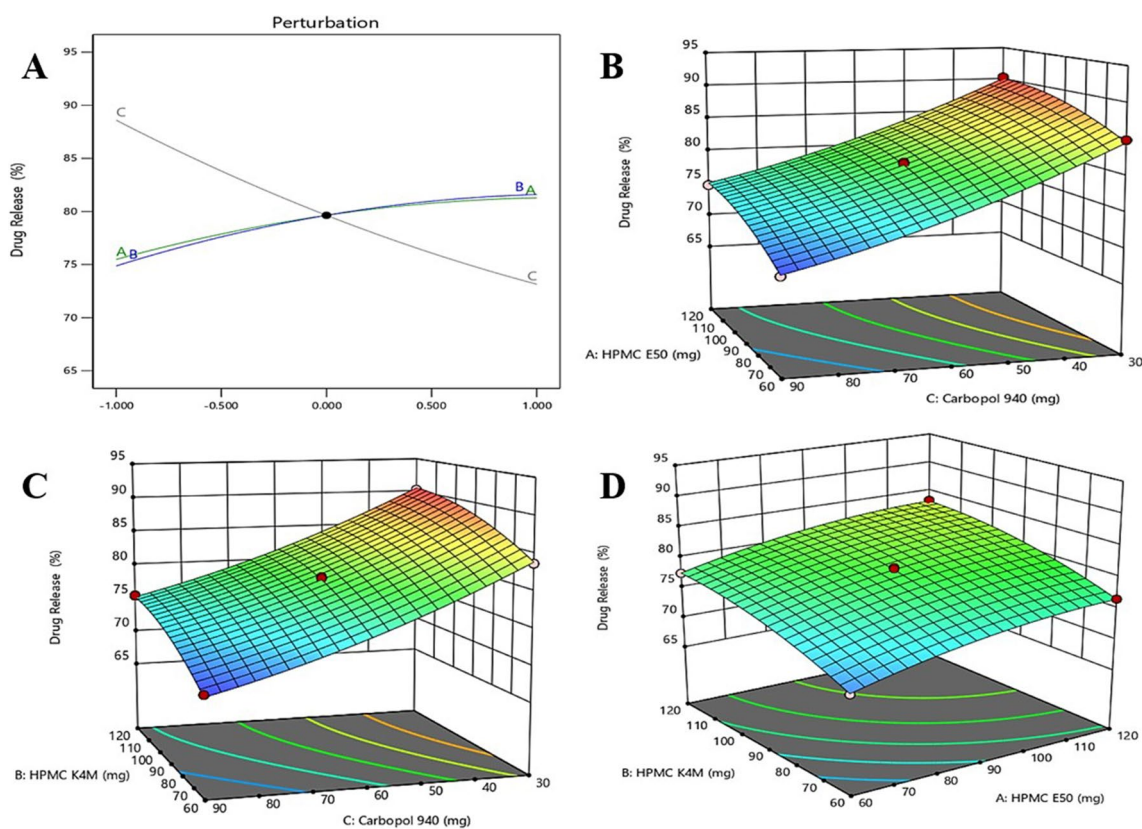
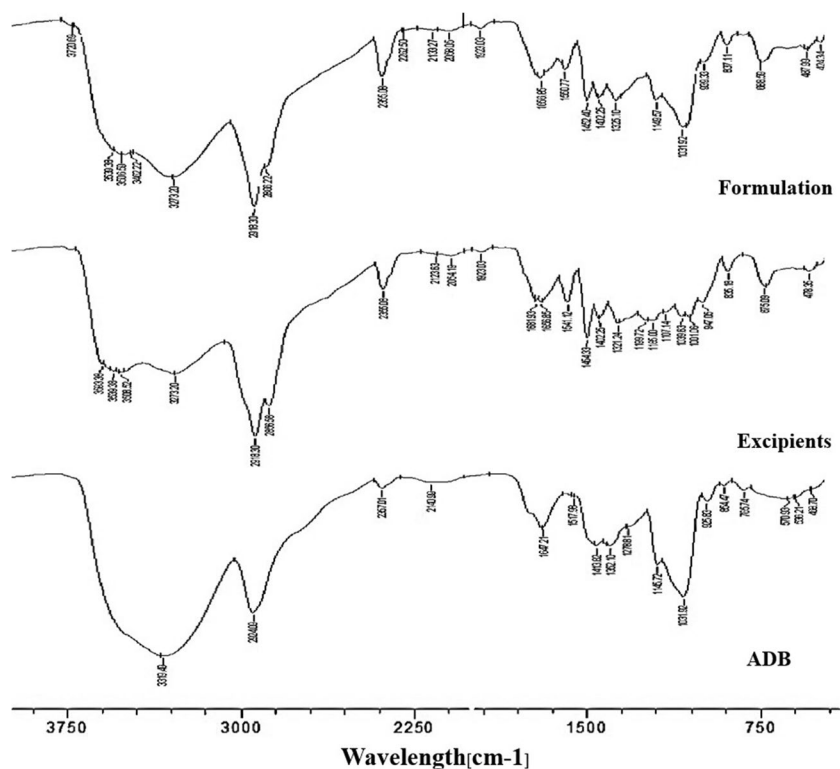
**Fig. 3** Perturbation and response surface graphs for drug release

Fig. 4 FT-IR spectra of ADB, formulation, and excipients



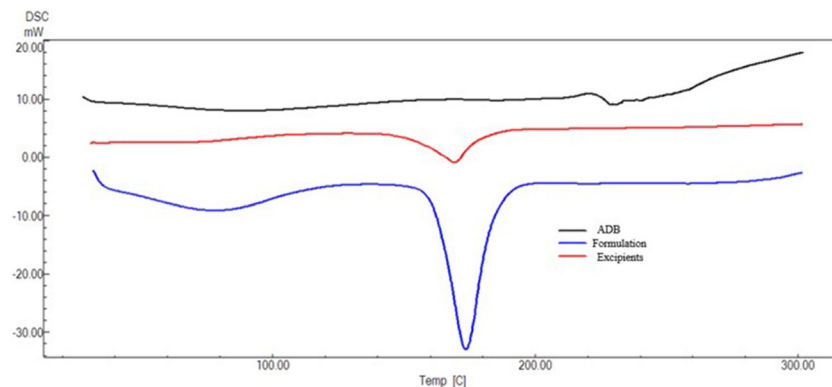
Optimizing the final formulation

The criteria selected for the optimization of the final formulation by Design Expert 13 for factors A and B are to be in range, and C should be minimized; for responses, the floating lag time and total floating time should be in range, and drug release at 12 h should be maximized. By applying the above criteria, the software has generated different solutions. The developed solution of HPMC E50–90 mg, HPMC K4M–120 mg, and Carbopol 940–30 mg with desirability 1.000 was selected as the final formulation, and post-analysis was performed on the final formulation. The pre-compression and post-compression studies were evaluated for the final formulation.

Flow properties and pre-compression parameters of the Db and excipients

Various pre-compression characteristics were examined for the mixture. The densities of the material were $0.56 \pm 0.09 \text{ g/cm}^3$ for the bulk and $0.63 \pm 0.07 \text{ g/cm}^3$ for the tapped, respectively. The inter-particle friction, possible compression bonding, and particle stability were all well represented by the HR and CI values, respectively. 31.7 ± 0.54 was the AOR. According to the AOR data, flowability was acceptable for compression. All the data before compression fell within USP guidelines.

Fig. 5 DSC thermogram of ADB, formulation, and excipients



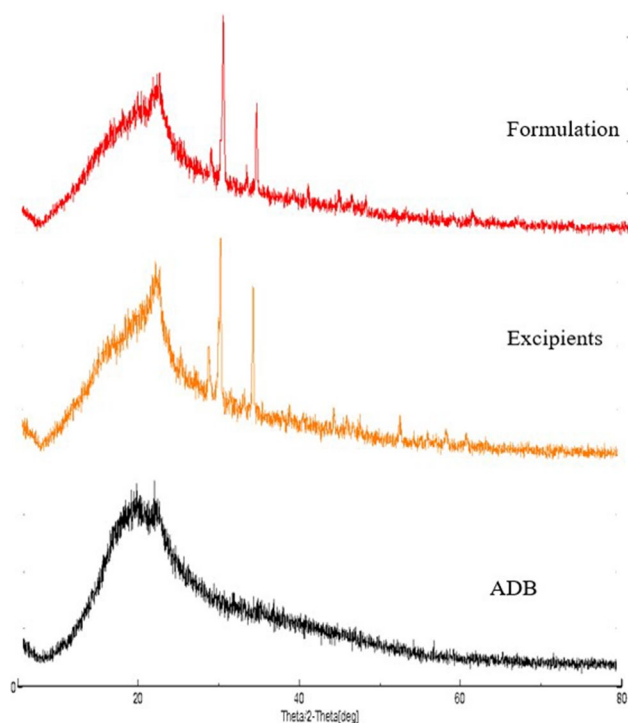


Fig. 6 XRD diffraction of ADB, formulation, and excipients

Physicochemical characteristics of the formulation

The dimensions of the formulation were 10.1 ± 0.03 mm in diameter and 4.56 ± 0.05 mm in thickness. The weight variation was 555.5 ± 0.8 mg, the hardness of the formulation was 4.5 ± 1.64 kg, and friability was $< 1\%$ ($n = 10$).

The FT-IR indicates no significant interaction between the ADB and formulation, as expressed in Fig. 4. The FT-IR of ADB exhibited peaks at $3000\text{--}2840\text{ cm}^{-1}$, $2140\text{--}2100\text{ cm}^{-1}$, and $1390\text{--}1310\text{ cm}^{-1}$, indicating the presence of the same

constituents in the formulations. The DSC thermograms and XRD diffractograms expressed in Fig. 5, 6 revealed that the ADB doesn't show any sharp peaks as it is amorphous, and the excipient mixture shows sharp peaks in both DSC and XRD. The thermogram and diffractograms of the formulation don't show any difference in the shifting of peaks, which shows the excipients and ADB are compatible.

In vitro buoyancy behavior

Figure 7 displays the effervescent behavior of the floating optimal formulation. Adding an effervescent substance can generate buoyancy more reliably than alternative methods resulting from the interaction between NaHCO_3 and gastric juice; bubbles formed on the surface when the formulation met the dissolution medium. Furthermore, the polymers expanded to cover the tablet's character in a gel. The tablets' density decreased as bubbles formed, and the formation of the gel matrix led to a mean floating lag time of 32 s. The formulation floated for nearly 9 h in the dissolution media. The optimized formulation demonstrated good floating performance.

Swelling and erosion studies

Figure 8A, B and C depicted the formulation's % drug release, swelling, and erosion profiles determined by weighing them at various intervals. As shown in Fig. 8B, the tablets expanded rapidly within the first six hours. After 6 h, however, erosion of the formulation was likely responsible for a significant drop in swelling %. After 12 h, as shown in Fig. 8C, the average degree of erosion had risen over 88%. This was supported by % drug release.

The swelling curve initially increased because the formulation swelled quicker than the matrix eroded. The

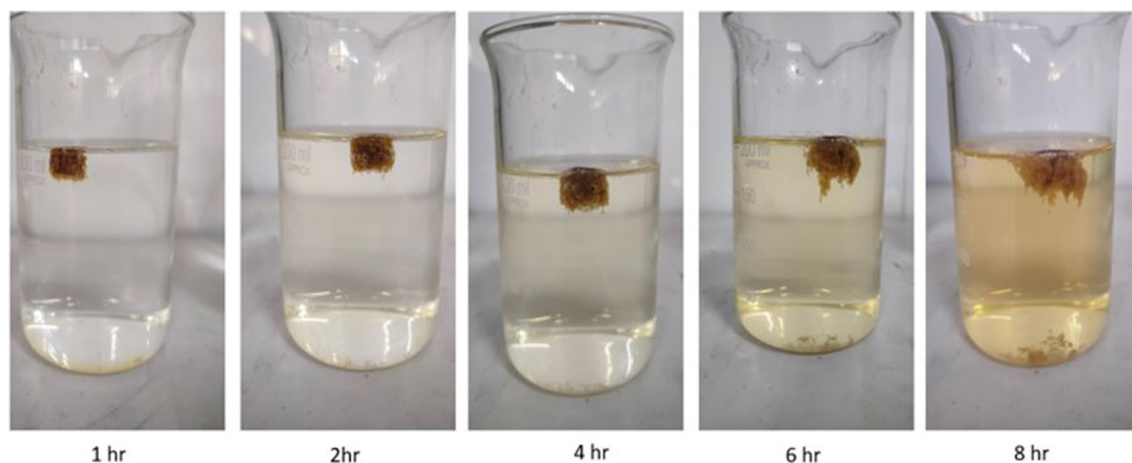


Fig. 7 Photographs of the formulation in the gastric medium at different time intervals

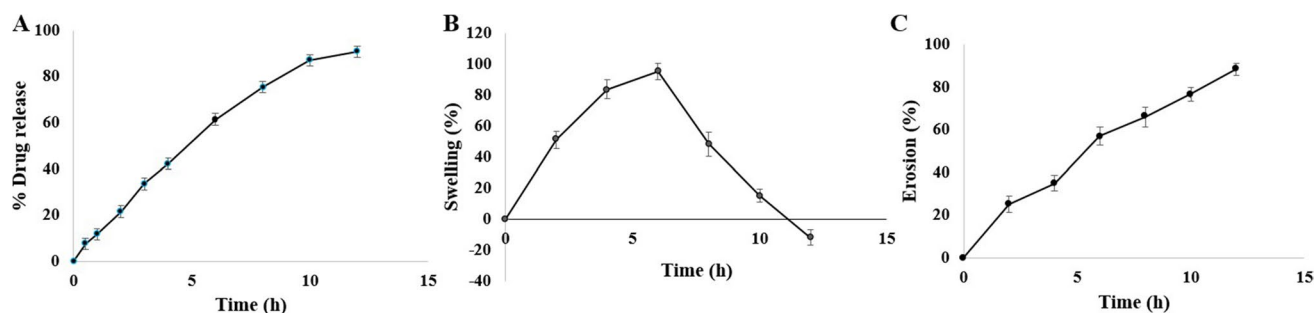


Fig. 8 **A** Drug release, **B** Swelling, and **C** Erosion % of the formulation in the gastric medium at different time intervals. Data of each formulation were presented as mean $\pm$ S.D. ($n=6$)

Table VII Mathematical Equations for Different Models

Modeling	Equation	Fit value	R ² Adjusted	AIC	MSC
Zero-order	$f = k_0 \cdot t$	$k_0 = 8.721$	0.9449	57.024	2.6700
First order	$f = 100 [1 - e^{-k_1 t}]$	$k_1 = 0.161$	0.9780	48.7577	3.5955
Higuchi	$f = k_H t^{0.5}$	$K_H = 24.625$	0.9122	61.2208	2.2107
Korsmeyer -peppas	$f = k_{kp} t^n$	$K_{kp} = 14.826$ $n = 0.756$	0.9862	45.3532	3.9738

f =amount of drug release, k_0 =reaction rate coefficient, k_1 =rate constant, K_H =dissolution constant, K_{kp} =constant depicting the experimental parameters based on geometry and dosage forms, n =release exponent, t =time

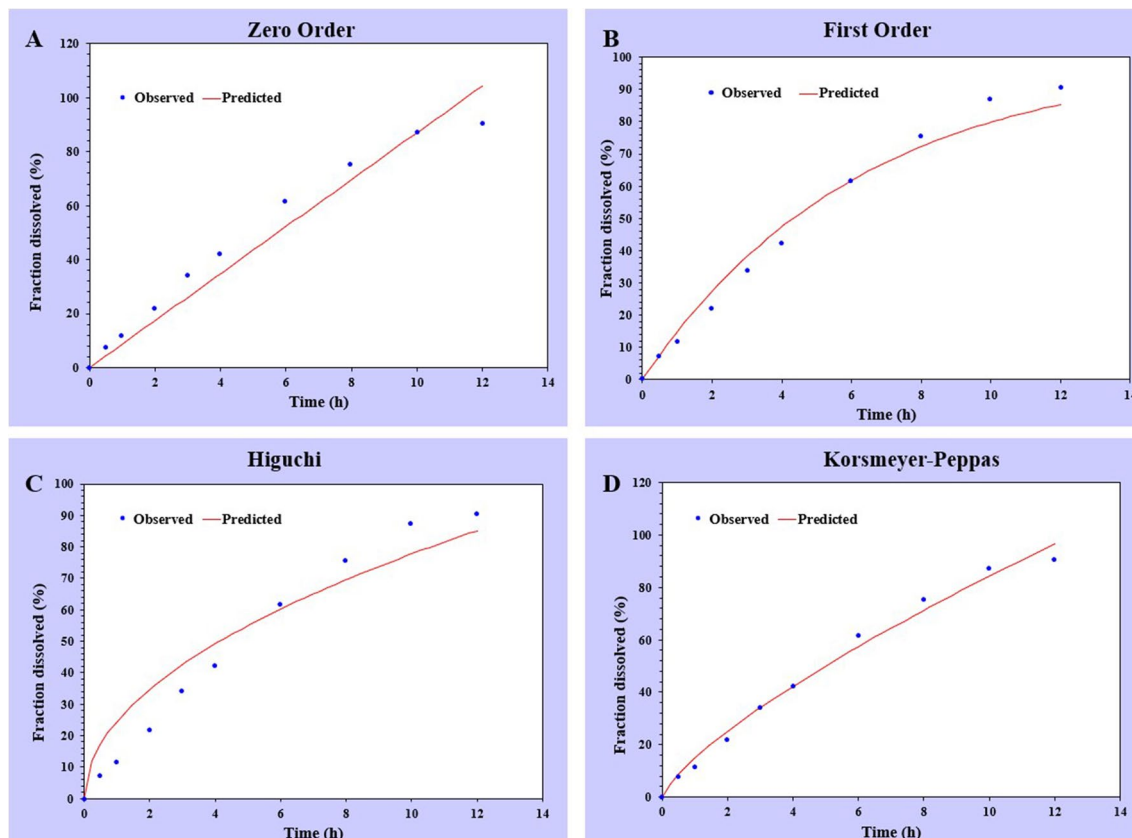


Fig. 9 Drug release kinetics profile of the final formulation

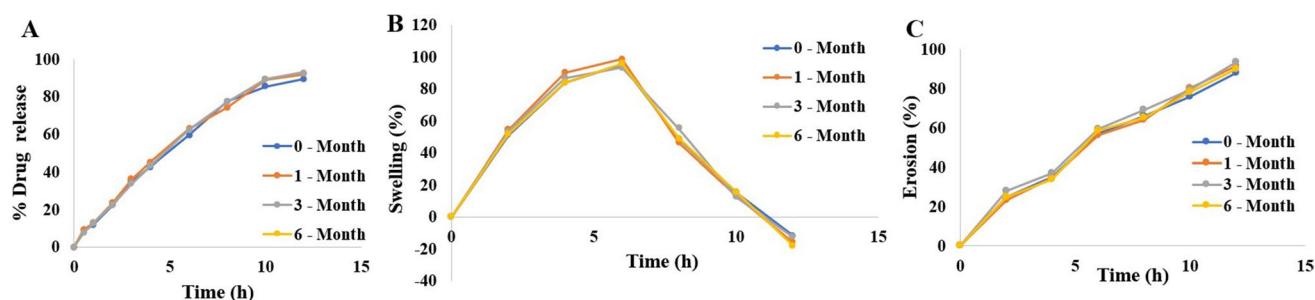


Fig. 10 Stability study: **A** Drug release, **B** Swelling, and **C** Erosion % of formulation in different time intervals

swelling of the formulation began with the diffusion of water into the formulation matrix, which then led to a progressive increase in the size of the formulation. As the experiment continued, the curve progressively declined because the swelling rate was less than the matrix erosion rate. The erosion curve continued to rise throughout the experimental phase, indicating that matrix erosion was a constant phenomenon. The findings of the swelling and erosion studies verified the formulation's release mechanism.

Drug release kinetics

A statistical software DD solver evaluated the formulation's release kinetics [45]. The release data was analyzed

using the zero order, first order, Higuchi, and Korsmeyer Peppas models. The evaluated parameters are adjusted R^2 , the Akaike Information Criterion (AIC), and the Model Selection Criterion (MSC). The R^2 is considered the primary criterion for selecting the release models. The models with small AIC and the highest MSC are considered the standard [46]. The fitted equations, the results, and the R^2 , AIC, and MSC are expressed in Table VII. and graphs in Fig. 9. By comparing the results, the formulation adheres to the predictions of Korsmeyer Peppas's model for the drug release mechanism. "n" values between 0.45 and 0.85 were obtained, indicating that drug release occurred via non-Fickian diffusion (swelling, erosion, and diffusion).

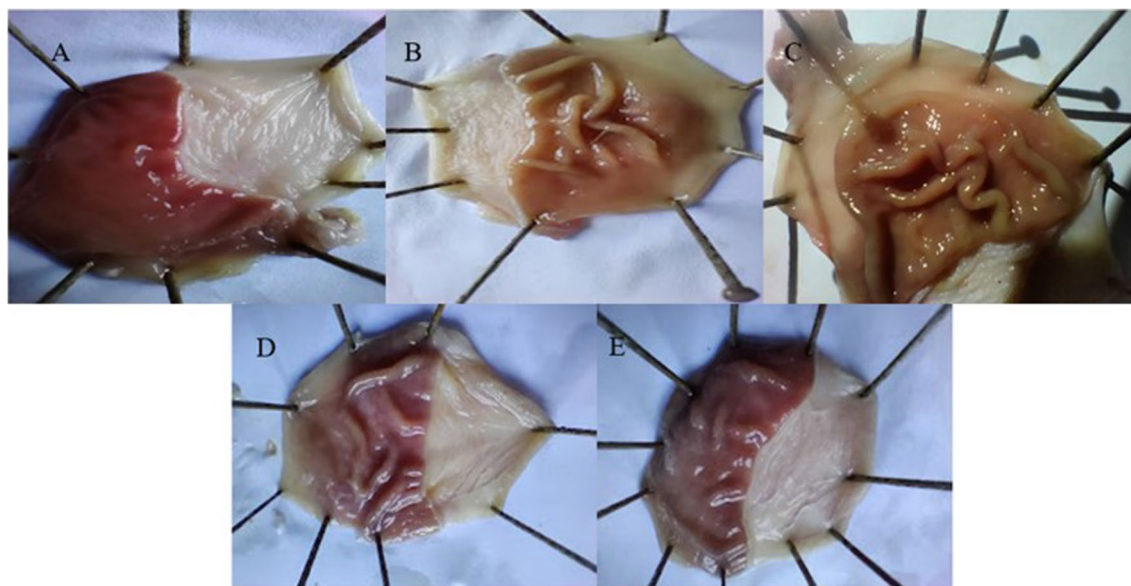


Fig. 11 The macroscopic changes discovered in the rat stomach during necropsy are depicted in representative photos. **A** The stomach mucosa in the control group was healthy and free of any visible lesions. **B** The stomach mucosa of the Aspirin group exhibited evidence of damage and inflammation. **C** Compared to the Aspirin group, the stomach mucosa of the ADB group showed mild to mod-

erate damage and inflammation. **D** Compared to the control group, the gastric mucosa of the formulation group shows no inflammation or injuries, and the tissue is similar in color to the control group. **E** Compared to the control group, the gastric mucosa of the standard group shows no inflammation injuries, and tissue is developing a similar color to the normal group

Stability studies

A stability study was conducted to examine the impact of storage on the quality of gastroretentive tablets. The findings indicated that the dissolution curve, floating and swelling performance of the tablets remained relatively stable over a six-month storage period at $40^{\circ}\text{C} \pm 2^{\circ}\text{C}$ and $75\% \pm 5\%$ relative humidity expressed in Fig. 10.

Antiulcer activity

The second most common factor in developing peptic ulcers in the upper GI tract is NSAIDs, behind *H. pylori* infection. Cyclooxygenase (COX)-1 inhibition decreases the production of cytoprotective mucosal prostaglandins and a protective bicarbonate mucus barrier in the stomach and small intestine, which causes mucosal damage [47]. The oral administration

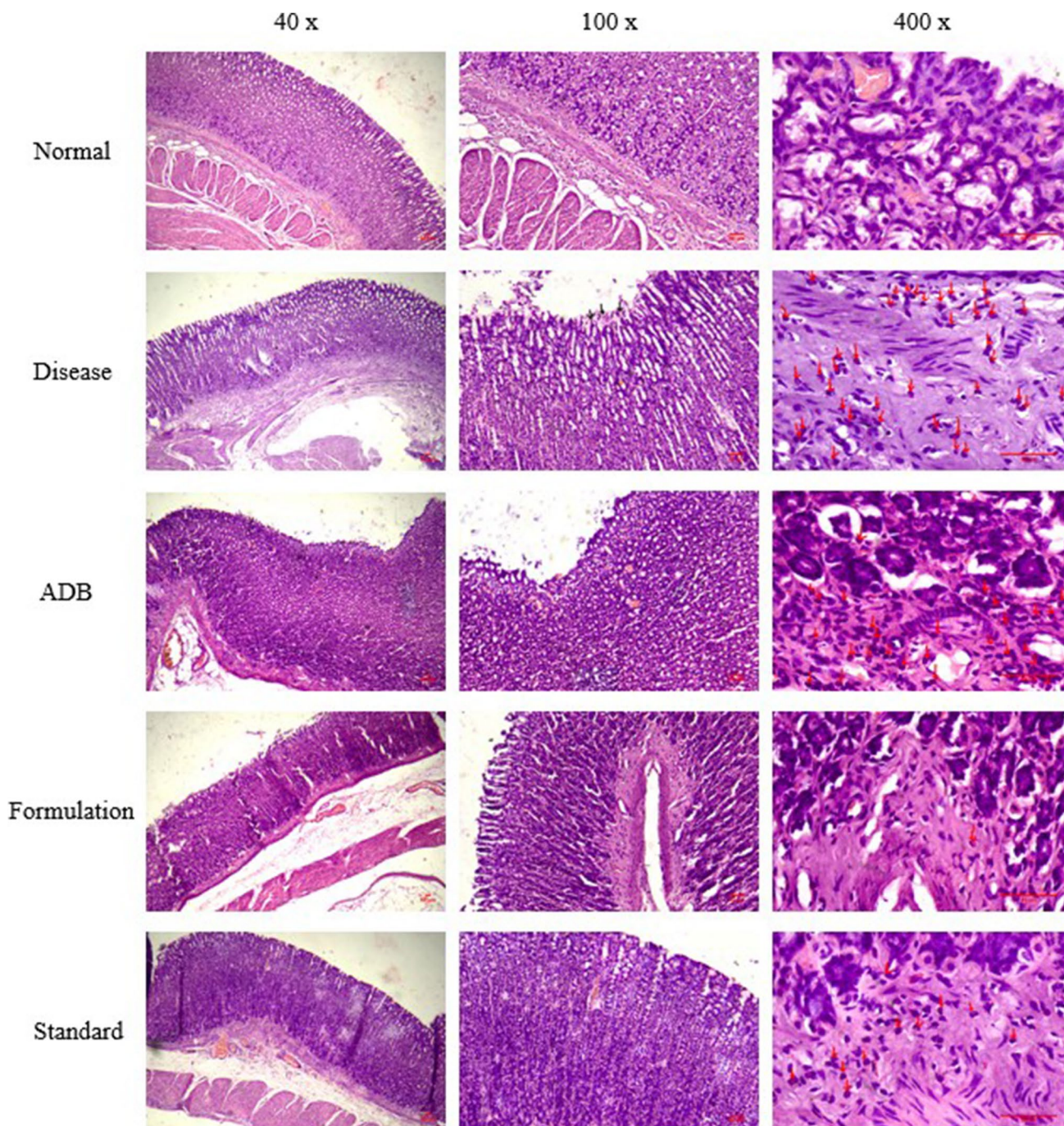


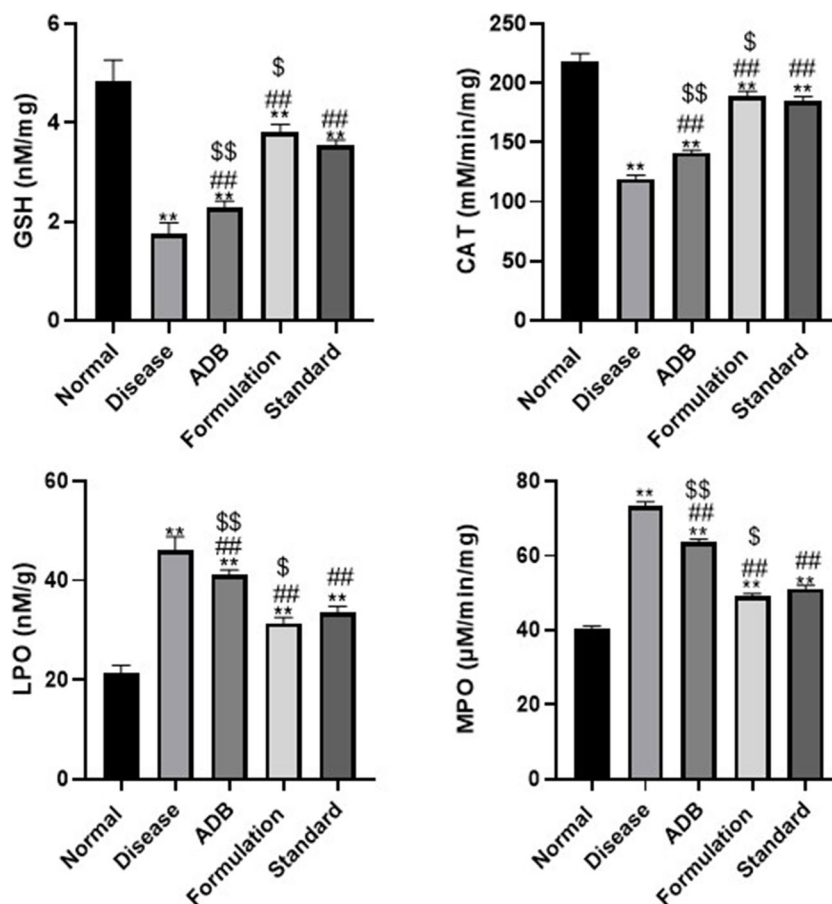
Fig. 12 Histopathological examination of H&E staining of the stomach in aspirin-induced ulcers in different animal groups with varying magnifications of 40x, 100x, 400x

of aspirin induces the ulcer by damaging the vascular endothelium, decreasing blood flow, forming obstructive microthrombi, and activating neutrophils by inhibiting prostaglandin synthesis. Macroscopic images from rat stomachs of different groups are expressed in Fig. 10. While the normal group's stomach in Fig. 11A depicts a normal gastric stomach free of inflammation and ulcer injuries, the diseased stomach in Fig. 11B appears to differ in color. It has ulcer wounds, with an ulcer index of 9.83 ± 0.34 compared to Fig. 11A. The stomachs of ADB, formulation, and standard groups are expressed in Fig. 11 C, D, E with ulcer index 7.45 ± 0.78 , 3.38 ± 0.24 , 5.64 ± 0.45 shows the decrease in inflammation when compared with the diseased stomach the ADB group stomach shows a minute decrease in inflammation with the % ulcer inhibition of 23.33 ± 0.46 but the color of the stomach remains white. Still, the stomachs of the standard and formulation groups show a decrease in pale white color. The stomach of the standard group started converting into a red color along with a reduction in inflammation with a % ulcer inhibition of 56.46 ± 0.73 . The stomach of the formulation group turned an intense red color compared to the standard group, with no signs of inflammation and a % ulcer inhibition of 76.67 ± 0.56 , representing the decrease in ulcers and inflammation and regeneration of the mucus layer. They resemble the antiulcer activity of the formulation.

Histological evaluation

Histological examination is carried out to examine the morphological changes at the cellular level. Figure 12 shows the cellular arrangement and histology of all the groups. The normal group shows the cellular arrangement without signs of inflammation or ruptures in the mucosal layer and cellular infiltration. The tissue of diseased rats shows erosion in the mucosal layer, and most of the glands in the mucosa are damaged, showing a dilated lumen and severe infiltration of acute inflammatory cells seen in the mucosa and submucosa. Compared with normal, more congested blood vessels and hemorrhagic areas are seen in the disease group. The ADB group shows a reduction in the dilation of glands, and hemorrhage is seen; severe infiltration of acute inflammatory cells is seen in mucosa and submucosa, and congested blood vessels and small areas of hemorrhage are seen. In the formulation group, the dilation of glands, hemorrhage, and inflammatory infiltration are reduced. Compared with the normal group, the standard group shows a reduction in acute inflammatory infiltration in the mucosa and submucosa. The ulcer abscess is not seen. Similar tissue architecture was seen in the formulation and standard groups compared to the normal group. This clearly shows a decrease in ulcers when treated with floating formulations.

Fig. 13 Effects of oxidative stress markers in different groups. Results are expressed as mean $\pm$ SD of 6 animals in each group for Aspirin-induced ulcers, Normal, control group; Disease, aspirin-induced ulcer group; ADB, gastric ulcer group treated with ADB; Formulation, gastric ulcer group treated with optimized formulation; Standard, gastric ulcer group treated with omeprazole; ** $P < 0.0001$ (vs Normal), ## $P < 0.0001$ (vs. Disease), \$\$ $P < 0.0001$ (vs. Standard), \$ P – nonsignificant (vs. standard) using turkey test of One way ANOVA



Biochemical studies

The GSH, LPO, CAT, and MPO values are expressed in Fig. 13. Aspirin causes gastric ulcers by inhibiting prostaglandin synthesis within the stomach tissue. In addition, it has been shown that ROS plays a crucial role in the pathogenesis of aspirin-induced mucosal injury. Reactive oxygen species (ROS), such as peroxide, superoxide, hydroxyl radicals, and peroxynitrite, are generated during normal physiological processes. In general, ROS is present in the organism at moderate concentrations. Since the G.I. tract maintains the proper balance of ROS levels, even though the body requires them for survival, too much ROS can be harmful. The results show an alteration in the enzyme levels in the gastric region induced by aspirin compared to the normal group.

Gastric ulceration necessitates neutrophil adherence to the gastric endothelium, which aspirin can promote directly through cyclooxygenase (COX)-independent mechanism that narrows microcapillaries and reduces blood supply to

the mucosa. Neutrophils in the stomach epithelia use H_2O_2 as an oxidizing agent to speed up tyrosine change to tyrosyl radicals, which cause inflammation and cell death. In line with Db's ability to lower PGE₂, our findings show that M.P.O. levels stayed the same in formulation and Omeprazole rats. Therefore, the aspirin group would have decreased neutrophil adhesion while maintaining normal mucosal blood flow. Histological results corroborate these observations, showing that the formulation was more effective than omeprazole at reducing inflammatory infiltration [48].

Ulcers cause oxidative stress in the stomach. Free radicals are byproducts of normal cellular metabolism. The release of M.D.A. results from oxidative stress, which produces free radicals. M.D.A. is a well-established marker of lipid peroxidation in stomach tissue [49]. Enzymes C.A.T. and G.S.H. protect the stomach from oxidative damage. Formulation decreases M.D.A. levels and shows an increase in the activity of antioxidant enzymes, including catalase and glutathione peroxidase, which accompanies

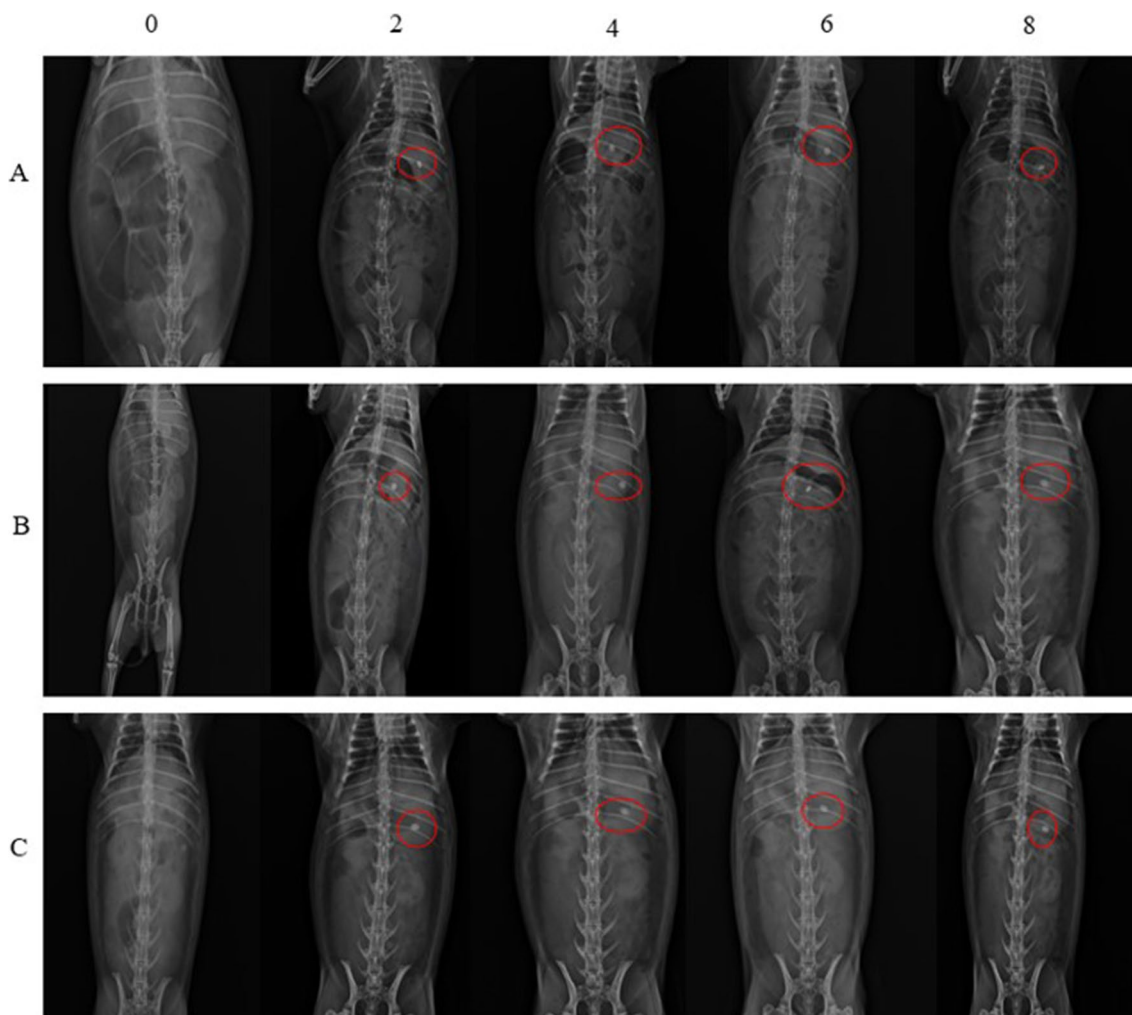


Fig. 14 X-ray imaging of floating tablets in different time intervals in three different animals represented as **A, B, C**

this decrease. This directly indicates the antioxidant potential of the formulation.

By comparing the above results expressed by the formulation with the standard omeprazole, it clearly states that the ADB used in the formulation possesses antiulcer activity because of the various classes of phytoconstituents present inside it [19]. The formulation has shown more significant antiulcer activity when compared with the ADB because the ADB, when given as a floating formulation, allows the ADB to reside in the gastric region for a more extended period with a continuous release in the target area. This results in the effective control of gastric ulcers, even when compared to the standard.

In vivo gastric retention study

X-ray imaging used barium sulphate to study the tablets' floating behavior in the gastric region [50]. The x-ray images of the rabbits taken at different time intervals are represented in Fig. 14. Before administering the tablets, the x-ray image was taken at 0 h to show the stomach doesn't contain any radio-labeled substances. Then, the radio-labeled tablets were administered to the rabbits by oral route. The X-ray images were taken at different intervals (2, 4, 6, 8 h). The tablet in the 2 h image is clear, and the shape has no disturbance. As time passed, there was a slight movement in the tablet, but the tablet didn't drown in the gastric region. However, the tablet's shape and size decrease, indicating that the tablet is releasing the barium sulphate as time passes. This shows the drug release of the tablet as time passes, and the size reduction suggests the erosion of the polymer in the gastric region at different time points. This experiment clearly shows the ability of the tablets to float in the gastric area with the help of effervescent agents and polymers to form the gel matrix.

Conclusion

The gastroretentive drug delivery systems of *Desmostachya bipinnata* extract were developed in this study. Box-Behnken design optimizes HPMC E50, HPMCK4M, and Carbopol concentrations based on the responses' floating lag time, total floating time, and drug release at 12 h. The optimized formulations exhibited a floating lag time of 32 s and floated in the gastric medium for greater than 9 h, with a maximal drug release of 93% after 12 h. Korsmeyer Peppas' model (release by diffusion and matrix erosion), substantiated by swelling and erosion studies, provided the best-fitting drug release kinetics. X-ray imaging experiments conducted on New Zealand rabbits supported the floating behavior of the formulations in the gastric region, in which the formulations floated for more than eight hours. The pharmacodynamic

activity confirms that the formulations possess significant antiulcer activity against NSAID-induced ulcers in rats compared with the standard omeprazole. Considering the above results, the prepared formulations can be used as an alternate medication to the currently available therapies for treating ulcers. The floating systems designed in the present work are well suited for herbal extracts with saponins (natural surfactants) or compounds with high solubility to restrict drug solubility in the gastric region. Further research must be done on this formulation to scale it up from laboratory to industry levels.

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Author contributions Sanjay Kumar Putta: Experimental work, Manuscript preparation

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Usha Y Nayak: Formulation studies

Sreedhara Ranganath Pai: *In vivo* studies

Raghuvier Pathuri: DOE and GraphPad analysis

Aswatha Ram HN: Guide and Correspondence

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Declarations

Conflict of interest The authors have no competing interests to declare relevant to this article's content.

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